Using early antipsychotic response to predict treatment outcome in patients with first-episode psychosis

USING EARLY ANTIPSYCHOTIC RESPONSE TO PREDICT

TREATMENT OUTCOME IN PATIENTS WITH FIRST-EPISODE

PSYCHOSIS

BY

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A THESIS

SUBMITTED TO THE SCHOOL OF GRADUATE STUDIES

OF MCMASTER UNIVERSITY

IN PARTIAL FULFILMENT OF THE REQUIREMENTS

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

Doctor of Philosophy (2016)   McMaster University

(MINDS Program)   Hamilton, Ontario, Canada

TITLE: Using early antipsychotic response to predict treatment

                          outcome in patients with first-episode psychosis

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NUMBER OF PAGES: xvi, 191

Dedication

This work is dedicated to my wife. You are the most generous person I know.

Abstract

Antipsychotic medications are highly effective in the treatment of patients experiencing first-episode psychosis. However, some patients do not respond to the first antipsychotic medication they are given, and may require trials of several drugs before an effective treatment is found. While antipsychotics may take months to achieve their full effect, recent evidence suggests that it is possible to predict whether a patient will respond to a particular drug by assessing early response after as little as 2 weeks of treatment. Assessing early antipsychotic response has the potential to improve treatment strategies for psychotic patients, but there is still a great deal of uncertainty about what early response can and cannot predict, and how the predictive value of early response differs among drugs and patient populations. The work presented in this thesis addresses some of the most pressing questions about early antipsychotic response in several samples of antipsychotic-naive patients with first-episode psychosis. This work demonstrates that: (1) the appropriate time point at which to assess early response differs between antipsychotic drugs; (2) early improvement in depressive and manic symptoms predicts treatment outcome, while early improvement in anxiety symptoms may not; (3) strong early response is associated with decreased rates of extrapyramidal side-effects; (4) early antipsychotic response can predict long-term treatment outcome at least 2 years after treatment initiation;

(5) the appropriate time point at which to assess early response differs in patients who receive antidepressant treatment in addition to antipsychotic treatment; (6) patients with a poor early response may benefit from being switched to another antipsychotic, particularly one with a distinct receptor binding profile. These results highlight several weaknesses of the current literature, suggesting that early antipsychotic response should be assessed differently depending on the psychiatric symptom profile of each patient and the specific medications that are being used. However, the data presented here also emphasize the potential therapeutic value of assessing early response. The ability of early response to predict treatment outcome appears to be even greater than previously thought, and understanding how to appropriately use this important assessment to guide treatment strategies may improve the efficiency and efficacy of treatment for psychotic patients.

Acknowledgements

First and foremost, thank you to Dr. Michael Mazurek for your constant support and guidance. Your knowledge of all aspects of neuroscience is amazing and invaluable. Thank you as well to Dr. Patricia Rosebush for offering so much of your time, expertise, and enthusiasm.

Many others have helped me in various stages of my research: Dr. Rebecca Anglin, Dr. Peter Margetts, Melissa McCradden, Dr. Daniel Rasmussen, Dr. Jonathan Lai, Dr. Lindsey MacGillivray, Robyn MacKenzie, Dr. Jane Foster, Dr. Ryan Van Lieshout, Dr. Kathy Murphy, and Sandra Murphy. All of you have helped to make this thesis possible.

A great deal of moral support has been provided by my wife, Nicole Robichaud, and my dog, Hudson (whether they knew it or not).

Abbreviations

AIMS: Abnormal Involuntary Movement Scale

BARS: Barnes Akathisia Rating Scale

BPRS: Brief Psychiatric Rating Scale

CATIE: Clinical Antipsychotic Trials of Intervention Effectiveness

CPZE: Chlorpromazine Equivalent Dose

DSM-V: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition

DUP: Duration of Untreated Psychosis

EPS: Extrapyramidal Side-Effects

EUFEST: European First-Episode Schizophrenia Trial

HAM-A: Hamilton Anxiety Rating Scale

HAM-D: Hamilton Depression Rating Scale

MAOI: Monoamine Oxidase Inhibitor

MSN: Medium Spiny Neuron

NPV: Negative Predictive Value

OPTiMiSE: Optimization of Treatment and Management of Schizophrenia in Europe

PANSS: Positive and Negative Syndrome Scale

PPV: Positive Predictive Value

SSRI: Selective Serotonin Reuptake Inhibitor

TCA: Tricyclic Antidepressant

YMRS: Young Mania Rating Scale

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Chapter 1

Introduction

1.1 Rationale

Antipsychotic medications are the primary treatment for patients experiencing first-episode psychosis, but some patients do not adequately respond to the first medication they are given. Despite a great deal of research, there is currently no viable method for predicting which patients will respond to which antipsychotic medications, so treatment guidelines suggest a trial-and-error method by which patients undergo a trial of one antipsychotic medication, and if it is not successful they are switched to another antipsychotic medication. Several such trials may be required before their psychotic symptoms are effectively treated. In order to reduce the length of time that patients are treated with ineffective medications, one useful approach would be to reduce the required length of each antipsychotic trial. Recent research has shown that antipsychotic treatment outcome can be predicted by early improvement within the first 2 weeks, suggesting that 2 weeks may be an adequate trial period for an initial antipsychotic before a medication switch is considered.

Early antipsychotic response has been enthusiastically embraced by researchers, but the field is very much in its infancy and many important questions have not been addressed. Differences in the predictive value of early response among patients and medications have generally been ignored. As well, it is not clear whether early response predicts long-term symptom severity or only the immediate trajectory of the initial psychotic episode. Most importantly, it is unclear whether changing treatment strategies based on early response or non-response is of any benefit. As a result, there is a great deal of information available about how to assess early antipsychotic response, but very little information about how clinicians should interpret and use this information.

The research presented in this thesis attempts to address several of the most pressing questions regarding the predictive value of early antipsychotic response in first-episode psychosis patients. By describing some of the strengths and limitations of early response, this work will provide clinicians and researchers with more information about how early response should or should not be used. The goal of this work is not to exhaustively analyze the details of early antipsychotic response, but rather to highlight limitations of early response that have been hidden by common research approaches, as well as potential benefits of assessing early response that have not yet been recognized.

1.2   Objectives

1. Chapter 3: Investigate differences in the predictive value of early response between antipsychotic medications

(a) Determine whether week 2 response predicts treatment outcome for both haloperidol and olanzapine

(b) If week 2 response is not predictive, determine whether week 3 response is a useful predictor of treatment outcome

(c) Determine whether early improvement in affective symptoms predicts treatment outcome

(d) Investigate whether switching antipsychotics in early non-responders leads to an improved treatment outcome

2. Chapter 4: Investigate the relationship between early antipsychotic response and antipsychotic-induced extrapyramidal side-effects

(a) Determine whether early response predicts the risk of developing extrapyramidal side-effects

(b) Determine whether extrapyramidal side-effects occurring early in treatment predict treatment outcome

(c) Determine whether early changes in affective symptoms predict the risk of developing extrapyramidal side-effects

3. Chapter 5: Investigate the long-term predictive value of early antipsychotic response

(a) Determine whether early improvement at week 2 or week 3 predicts treatment outcome after multiple years of antipsychotic treatment

(b) Determine whether early improvement is related to the long-term risk of extrapyramidal side-effects

    (c) Investigate whether the predictive value of early response changes depending on whether patients are switched to another antipsychotic with a different receptor binding profile

4. Chapter 6: Investigate whether early response predicts treatment outcome in patients who receive antidepressants in addition to antipsychotics

    (a) Determine whether the predictive value of early response at week 2 differs between patients who receive antidepressants and those who do not

    (b) If a difference is observed between these patient groups when early response is assessed at week 2, investigate whether this difference persists when early response is assessed at week 3

    (c) Determine whether the predictive value of early improvement in affective symptoms differs between patients who receive antidepressants and those who do not

1.3   Thesis structure

Chapter 2 of this thesis gives a broad overview of current literature relevant to the treatment of first-episode psychosis. This chapter will provide the reader with the information necessary to understand the rationale of the following chapters. Chapters 3, 4, 5, and 6 present original research, and each of these chapters is intended to stand alone as an independent publication. Consequently, each chapter includes a brief introduction describing the most relevant literature. Overlap between the content of these literature reviews and Chapter 2 has been minimized wherever possible, but certain core concepts will be reviewed in multiple chapters.

The data used in these studies are drawn from 2 main patient samples. The first sample is a group of patients admitted to hospital experiencing first-episode psychosis who were blindly randomized to treatment with olanzapine or haloperidol. Data from these patients are analyzed in chapters 3 and 5. The second sample is a larger group of patients admitted to hospital experiencing first-episode psychosis and treated naturalistically. Patients and physicians were fully aware of the treatment being given, and the choice of medication was based on patient preferences and the clinical judgment of the treating physician. Data from these patients are analyzed in chapters 4 and 6.

Contributing authors are noted for each chapter. In all cases, Sean Rasmussen is the primary author. Chapters 3, 4, 5, and 6 are in various stages of publication. However, the chapters presented here are not identical to the work published elsewhere. In general, the chapters appearing in this thesis represent a more complete record of the research conducted, without being edited or trimmed to meet specific journal requirements.

Chapter 7 provides a discussion of the data presented in the preceding chapters that ties the separate concepts together and reviews the significance of this work as a whole. Implications of this thesis for future research and clinical practice are discussed.

Chapter 2

Background

2.1 First-episode psychosis

First-episode psychosis encompasses a broad range of psychiatric diagnoses. While psychosis is often associated with schizophrenia or "schizophrenia spectrum" disorders (including schizoaffective and schizophreniform disorders), it is important to recognize that psychosis can also be caused by a number of other conditions, as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V). These conditions include affective disorders like major depression or bipolar disorder, medical conditions, or substance use. When psychosis briefly emerges for less than 1 month, often in response to a significant stressor, it is referred to as brief psychotic disorder. When delusions occur in the relative absence of other psychiatric symptoms, it is referred to as delusional disorder. The annual incidence of first-episode psychosis differs between ethnic groups and geographical regions, with estimates varying between 22 and 55 per 100 000 [189]. Schizophrenia is usually reported to be the most common individual diagnosis [13, 89, 249].

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While the criteria and labels for psychotic disorders have been somewhat fluid over time, psychosis itself is defined by several core features. The main features (at least one of which must be present for the diagnosis of schizophrenia or psychosis according to the DSM-V) are delusions, hallucinations, and disorganized thought. Delusions are fixed, false beliefs. They can take a number of forms, including persecutory, referential, grandiose, somatic, and others. The type and bizarreness of delusions differ to some extent among diagnostic categories [113]. Importantly, delusions are resistant to change, even in the face of conflicting evidence. Hallucinations are perceptual experiences that occur in the absence of external stimuli. Hallucinations can manifest in any sensory modality, but auditory hallucinations are most common [15]. Disorganized thought is generally characterized by disorganized speech. These speech abnormalities may exist on a spectrum from rapid topic switching to complete incoherence. Other common features of psychotic disorders are abnormal motor behaviour (including catatonic behaviour) and negative symptoms. Although these features are classically associated with schizophrenia, they occur in other psychotic disorders as well [90, 202, 264]. Negative symptoms include a range of features such as diminished emotional expression, avolition, alogia, and anhedonia.

It is important to specifically study patients with first-episode psychosis, as opposed to those with multiple episodes or a chronic illness. One reason for this is that patients experiencing their first psychotic episode are more responsive to antipsychotic treatment. To demonstrate this, McEvoy et al. [169] identified the "neuroleptic threshold" (the minimum antipsychotic dose at which patients develop slight rigidity) in a group of patients undergoing treatment with haloperidol. They found

that patients who were receiving antipsychotic treatment for the first time had a significantly lower neuroleptic threshold than those who had previously been exposed to an antipsychotic. Importantly, increasing the dose beyond the neuroleptic threshold did not yield increased rates of response, but did increase side-effects. Similarly, Sanger et al. [233] showed that first-episode psychosis patients treated with olanzapine experienced greater rates of response than multiple-episode patients. First-episode illness is also associated with a strong early response after only 2 weeks of treatment [238]. Another reason to specifically study first-episode psychosis patients is that they are more susceptible to antipsychotic-induced side-effects. As described above, patients undergoing antipsychotic treatment for the first time experience side-effects at a lower dose than those with previous antipsychotic exposure [169]. The study by Sanger et al. [233] also demonstrated that first-episode patients treated with haloperidol experienced more severe extrapyramidal side-effects than multiple-episode patients. Together, these studies indicate that first-episode psychosis patients are uniquely susceptible to both the therapeutic and adverse effects of antipsychotic medications.

A final reason to study first-episode psychosis patients is that the early stages of illness may represent a critical period in which treatment decisions have long-lasting consequences. Effective treatment during this early critical period appears to result in long-term benefits in functional outcomes and healthcare costs [172]. A primary goal in the treatment of first-episode psychosis is to minimize the duration of untreated illness. Reducing this treatment delay results in improved treatment outcomes [82], and the duration of untreated illness may influence whether patients experience a

trajectory of symptom deterioration or improvement as much as 4-8 years after treatment initiation [51]. The type of treatment utilized during the first psychotic episode also has long-term consequences. For example, an integrated treatment program including assertive community treatment, psychoeducational family intervention, and social skills training resulted in less severe psychotic and negative symptoms after 2 years compared to standard treatment [205]. Even 3 years after these patients transitioned from the intensive treatment program back to standard treatment, patients who underwent the integrated treatment program were living more independently [17]. These results emphasize the long-term importance of timely and effective treatment for first-episode psychosis. The long-term treatment impact, coupled with the observation that first-episode psychosis patients respond to antipsychotic treatment differently than multiple-episode patients, demonstrates the value of specifically studying this unique patient population.

2.2   Baseline predictors of treatment response

The reported response to antipsychotic treatment in first-episode psychosis patients varies among studies depending on patient characteristics and response criteria. In the McLean-Harvard First-Episode Project, which included patient with a broad spectrum of psychotic diagnoses, 77.0% of patients achieved syndromal recovery (defined as no longer meeting criteria for an ongoing episode of illness) by 6 months [273]. In the recent European First-Episode Schizophrenia Trial (EUFEST), treatment response ($\geq$50% symptom reduction) was observed in 54.8% of patients by 12 months [22]. In another study of first-episode schizophrenia patients, 80.0% of patients achieved symptom remission ($\geq$50% overall symptom reduction and psychotic

symptoms rated as no worse than "mild") within 12 months [160]. Despite these discrepancies, it is clear that a substantial proportion of patients do not experience adequate symptom improvement in response to antipsychotic treatment.

A number of factors contribute to the clinical outcome of first-episode psychosis. One particular area of interest is how the initial diagnosis predicts long-term outcome. Researchers involved in the McLean-Harvard First-Episode Project investigated this issue in 257 naturalistically-treated first-episode psychosis patients [273]. They found that among patients diagnosed with schizophrenia at the time of their initial hospitalization, only 35.7% achieved syndromal recovery after 6 months. In contrast, more than 70% of patients with non-schizophrenia diagnoses achieved syndromal recovery. Similarly, an observational study of 723 consecutive first-episode psychosis patients in Melbourne, Australia found that patients with an initial diagnosis of schizophrenia had significantly higher scores on the Brief Psychiatric Rating Scale (BPRS) than patients with affective psychosis after a follow-up period of approximately 7 years [89]. These studies are valuable because they include a broad range of psychotic diagnoses, whereas many studies of "first-episode psychosis" in fact limit their sample to only those patients with schizophrenia or schizophrenia spectrum disorders (including schizophreniform and schizoaffective disorders). However, even in these more limited samples, a diagnosis of schizophrenia seems to be associated with a worse clinical outcome [155, 178].

The studies described above suggest that an initial diagnosis of schizophrenia may have useful prognostic value, although the differences among non-schizophrenia diagnoses appear relatively minor. However, in interpreting these results, it is important to acknowledge that the initial diagnoses in first-episode psychosis patients

are often unstable. For example, in the McLean-Harvard First Episode Project mentioned above, only 74% of the initial diagnoses were maintained after 24 months [230]. Schizophrenia and bipolar disorder appear to be the most stable diagnoses [230, 242]. Even though schizophrenia itself is relatively stable, with more than 90% of patients retaining this diagnosis, a number of patients initially diagnosed with other causes of psychosis are eventually switched to a diagnosis of schizophrenia [25, 127, 209]. Among patients with psychosis caused by substance abuse or a general medical condition, approximately half evolve to schizophrenia or schizoaffective disorder [127]. As a result, studies that exclude patients with non-schizophrenia diagnoses are in fact excluding a number of patients who will eventually be given a diagnosis of schizophrenia. More broadly, it may be the case that grouping or excluding patients based on baseline diagnoses is premature, and a more informative approach may be to follow all patients presenting with first-episode psychosis regardless of their presumptive diagnosis.

Along with the initial diagnosis, a number of other factors may have prognostic significance in patients experiencing first-episode psychosis. One of the most consistently reported predictive variables, as mentioned previously, is the duration of untreated psychosis (DUP) prior to the initiation of antipsychotic therapy. For example, a study of 301 first-episode psychosis patients in Norway and Denmark demonstrated that a shorter DUP predicted a shorter time to remission and stable remission [249]. Even 10 years after the initial hospitalization, longer DUP continues to predict poor outcome [279]. The majority of studies have limited their analysis to patients with non-affective psychosis or schizophrenia spectrum disorders, and these studies also consistently report the prognostic importance of DUP [59, 167, 239, 286]. Besides

prolonged DUP, another commonly reported predictor of poor treatment response is younger age at the onset of illness [27, 49, 155, 239].

There has been a great deal of interest in determining whether baseline symptom severity can be used to predict antipsychotic response. Rather than examining all psychiatric symptoms together, many studies have attempted to categorize and group symptoms to assess whether specific symptom clusters convey different prognostic information. Particularly in schizophrenia, symptoms are commonly categorized as "positive" (for example: hallucinations, delusions, and conceptual disorganization) and "negative" (for example: blunted affect, emotional withdrawal, and social withdrawal). Interestingly, these two categories appear to have opposite influences on antipsychotic treatment response. In schizophrenic patients beginning antipsychotic treatment for the first time, more severe negative symptoms at baseline predict a poor treatment response after 6 months [195]. Similarly, in first-episode psychosis patients, more severe baseline negative symptoms continue to predict poor response 10 years after treatment initiation [279]. More severe baseline positive symptoms, on the other hand, predict a stronger treatment response in studies of first-episode schizophrenia [239, 286] or non-affective psychosis [49]. Furthermore, baseline positive symptoms are associated with early antipsychotic response after only 2 weeks of treatment in patients with schizophrenia [128, 238]. The prognostic value of baseline depressive symptoms has also been investigated. When a significant effect has been found, more severe depressive symptoms have been associated with worse treatment outcomes [220, 235, 239]. These studies suggest that distinct psychiatric symptom profiles at baseline may convey information about the nature of the underlying disease, which may in turn influence the response to antipsychotic treatment. While this

information is imprecise at best, it may nonetheless be clinically useful given the lack of other prognostic indicators available before antipsychotic treatment is initiated.

The idea that different patient characteristics at baseline may predict response to antipsychotic treatment has also been explored using pharmacogenetic approaches. Much of the research in this field has focused on polymorphisms in neurotransmitter receptors that are known to be targeted by antipsychotic drugs. For example, genetic variation in the dopamine D2 receptor has been associated with antipsychotic response in patients with schizophrenia [288], including first-episode schizophrenia [103, 146]. Downstream targets of dopamine signaling have also been implicated, including the protein kinase Akt [103]. Some efforts have been made to link specific receptors to specific symptoms. In general, polymorphisms in the dopamine receptors have been associated with improvement in positive symptoms, while polymorphisms in the serotonin receptors have been associated with improvement in negative symptoms [218, 219]. A wide range of polymorphisms associated with monoamine signaling and metabolism have been linked to antipsychotic response [10], but many of these findings have not been replicated, and should be interpreted with caution. Interestingly, genetic variation in many of the same genes has been associated with antipsychotic-induced motor side-effects. These include genes encoding the D2 and D3 receptors [70, 132], as well as the dopamine transporter [78] and 5-HT2A and 5-HT2C receptors [77]. Most of these findings are still poorly understood or unreplicated, so their clinical utility is limited. However, they suggest that in the future it may be possible to predict rates of response and optimal treatment strategies based on genetic information obtained from patients when they first present with psychosis.

A final topic that should be considered when predicting antipsychotic treatment

response based on baseline characteristics is the prodromal phase of the illness. The prodrome refers to the period of time between the first disturbances in a patient's thoughts or behaviour and the onset of clear psychosis. These early changes can include reduced concentration, reduced motivation, depressed mood, sleep disturbance, anxiety, social withdrawal, suspiciousness, and other psychiatric abnormalities, and they may last several years before a patient progresses to frank psychosis [285]. Although some prodromal symptoms are most closely associated with certain psychotic diagnoses, there is a great deal of variability, and no prodromal symptom patterns are diagnostic for any specific disorder [106]. Moreover, most patients with prodrome-like symptoms will not transition to frank psychosis, so it is difficult to study these symptoms prospectively [26]. When assessed retrospectively, however, the prodrome may provide useful prognostic information. Poor antipsychotic response is associated with a longer prodromal phase [286] and declining premorbid functioning [214]. Additionally, preventative intervention (including low-dose risperidone and cognitive behavioural therapy) in patients with prodrome-like symptoms can delay - or possibly prevent - the transition to frank psychosis [171]. While this information is non-specific, it appears that some prognostically valuable characteristics are apparent even before the first episode of psychosis. Further research is required to understand how to use this information to shape treatment strategies.

2.3   Antipsychotic drugs

Pharmacological options for the treatment of psychosis were limited until the introduction of 2 drugs: reserpine in the late 1940s and chlorpromazine in the early 1950s [210]. Early reports demonstrated that these two drugs were effective across

a range of psychiatric diagnoses, although reserpine appeared to exacerbate depression [73, 130]. Despite reserpine's efficacy, its side-effect profile limited its usefulness, and chlorpromazine subsequently became the far more influential drug. Even before the mechanism of action was discovered for chlorpromazine, a number of other antipsychotic drugs with similar mechanisms - including clozapine [92] - had been identified. In 1963, a landmark paper was published by Carlsson and Lindqvist in which they suggested that chlorpromazine and haloperidol worked via a blockade of monoaminergic receptors [35]. This suggestion marked a new stage in understanding the pathophysiology and treatment of psychosis as functions of monoamine activity [251].

With chlorpromazine as a template and monoamine receptors as a target, a host of new antipsychotic drugs were developed between 1954 and 1975 [246]. These were classified on the basis of their chemical structure into distinct categories including phenothiazines (chlorpromazine, perphenazine), thioxanthines (thiothixine), dibenzoxazepines (loxapine), dyhydroindoles (molindone), butyrophenones (haloperidol), and diphenylbutylpiperidines (pimozide) [245], but all shared a relatively high affinity for the dopamine D2 receptor [47, 182]. Several important studies demonstrated that the clinical potency of these antipsychotic drugs was associated with their dopamine antagonist activity. For example, Nyback et al. [197] found that antipsychotics increase dopamine turnover in the mouse brain, while antidepressants do not. Postsynaptically, the affinity of antipsychotic drugs for dopamine receptors correlates with their clinically effective dose [48]. While antipsychotic drugs exhibit antagonist activity at a number of receptors, results like these established inhibition of dopamine signaling as perhaps their most important mechanism of action.

The first-generation "typical" antipsychotic drugs proved to be remarkably effective at treating the core positive symptoms of psychosis, as demonstrated by a number of early placebo-controlled studies. Compared to placebo, pimozide reduces psychotic symptoms across a range of psychiatric diagnoses [110]. In schizophrenic patients with acute symptom exacerbation, chlorpromazine significantly improves conceptual disorganization, suspiciousness, and unusual thought content, while patients treated with placebo experience increasing symptom severity [248]. In a similar study, chlorpromazine was found to be superior to placebo in the treatment of of hallucinations and thought disturbance [44]. Despite the structural differences among the typical antipsychotics, they are generally similar in their ability to improve positive symptoms of psychosis as long as an appropriate dose is used [57, 115]. However, this does not imply that each individual patient will respond equally well to any typical antipsychotic medication. While any antipsychotic drug is likely to be helpful, the question of how to predict which drug will be most effective for each patient is a subject of ongoing research.

Despite their effectiveness at treating positive symptoms, typical antipsychotics have long been recognized to suffer from a variety of shortcomings. For example, typical antipsychotics appear to be relatively ineffective in the treatment of negative symptoms associated with schizophrenia [36, 67]. While some have argued that typical antipsychotics (particularly pimozide) do in fact improve negative symptoms, this effect is less robust and less frequently reported than improvement in positive symptoms [177]. In addition, typical antipsychotics do little to ameliorate the substantial cognitive deficits that often accompany schizophrenia [37]. Typical antipsychotics by themselves also do not consistently improve depressive symptoms

[186]. Because depressive symptoms have a strong negative influence on the quality of life of schizophrenic patients [101, 211], it is important to effectively manage them. Typical antipsychotics proved to be effective against some symptoms, but not others, prompting continued research investigating new strategies for antipsychotic treatment.

Another concern with typical antipsychotics was their propensity to cause extrapyramidal side-effects (EPS). Briefly, EPS are a diverse group of movement disorders including parkinsonism, akathisia, dystonia, and dyskinesia, several of which may be present simultaneously in any given patient. Multiple systematic reviews of first-episode psychosis patients have suggested that EPS are more common in patients treated with typical antipsychotics than those treated with second-generation "atypical" antipsychotics [80, 287]. In the recent EUFEST study of first-episode psychosis patients, haloperidol was more prone to causing EPS than the atypical antipsychotics that were investigated [229]. This is particularly concerning in first-episode psychosis patients, who are especially susceptible to EPS [169, 233]. Along with being uncomfortable and distressing, EPS are an important factor leading to treatment discontinuation [107, 157, 181], so avoiding them is likely to be beneficial in the treatment of psychotic patients. Therefore, the perceived association between typical antipsychotics and EPS is often cited as a shortcoming of these drugs.

Clozapine was introduced to the United States in 1990, and was closely followed by a number of other antipsychotic drugs categorized as "atypical" [246]. With the introduction of atypical antipsychotics, there was initial hope that the major concerns associated with typical antipsychotics had been addressed. For example, early

observations indicated that atypical antipsychotics were more effective than typical antipsychotics for the treatment of negative and depressive symptoms associated with schizophrenia [20, 161, 185]. The atypical antipsychotics also appeared to have a greater effect on cognitive deficits than typical antipsychotics [121, 175]. Finally, early reports suggested that atypical antipsychotics produced EPS no more frequently than placebo at therapeutic doses [21, 201]. In fact, a lack of EPS was considered a defining characteristic of atypical antipsychotics [107].

The mechanism by which atypical antipsychotics achieved their apparent therapeutic advantage was unknown. One approach to investigating this question was to examine the affinity of the drugs for various receptors. Atypical antipsychotics tend to have a lower affinity for D2 receptors and a greater affinity for other receptors involved in serotonergic, adrenergic, cholinergic, and histaminergic signaling [47, 182]. One popular theory suggested that a high affinity for the 5-HT2A receptor relative to the affinity for the D2 receptor accounted for the advantages of atypical antipsychotics [174]. However, various studies have also implicated other serotonin receptors, dopamine receptors, adrenergic receptors, and muscarinic receptors [32, 97]. While all of these theories have some compelling supporting evidence, none fully explain the proposed advantages of atypical antipsychotics. Moreover, it has been argued that appropriate D2 receptor modulation by itself is necessary and sufficient to achieve atypical antipsychotic activity [116]. Antagonists that rapidly dissociate from the D2 receptor may permit signaling from surges of endogenous dopamine, thereby minimizing antipsychotic-induced side-effects and accounting for atypical antipsychotic activity [117].

Research into the mechanisms of antipsychotic atypicality has been hampered

to some extent by a lack of clear information about advantages and defining criteria of atypical antipsychotics. Despite early enthusiasm, more recent studies have shown that many of the advantages of atypical antipsychotics may not be as great as originally suggested. For example, an early study of antipsychotic-naive patients demonstrated that risperidone in fact produces EPS at a rate similar to the typical antipsychotic haloperidol [223]. As early as 2003, a meta-analysis comparing atypical antipsychotics with low-potency typical antipsychotics (unlike the high-potency drug haloperidol, which is commonly used as a comparator) found that most atypical drugs did not have an advantage with respect to EPS risk [148]. The atypical antipsychotics that showed some advantage were clozapine and - to a lesser extent - olanzapine. Subsequent large-scale, multi-centre trials have continued to show that the advantage of atypical antipsychotics over typical antipsychotics regarding EPS risk may be small or non-existent [111, 181, 224]. This work suggests that the distinct receptor binding profiles of atypical antipsychotics do not necessarily lead to less severe motor side-effects, and calls into question the use of this criterion as a defining characteristic of the atypical antipsychotic class.

There have also been several studies showing that atypical antipsychotics are no more effective than typical antipsychotics in the treatment of negative symptoms or depressive symptoms [111, 151, 224]. Other findings to the contrary may have been influenced by the use of very high doses of haloperidol as the typical comparator [20, 162]. However, reports on this topic are inconsistent, and interpretation of results is hampered by variability in outcome measures and study populations [30, 166, 215]. Regarding cognitive function, a consistent benefit of atypical antipsychotics over typical antipsychotics has not been demonstrated [123, 281]. Although an advantage

has been found for olanzapine versus haloperidol in first-episode psychosis patients, the difference is small [122]. When choosing between antipsychotic drugs, it is also important to recognize the increased incidence of metabolic side-effects associated with atypical antipsychotics, including obesity, dyslipidemia, and insulin resistance [247]. These side-effects are particularly common with olanzapine [83, 161, 224, 247].

While most atypical antipsychotics have demonstrated few advantages over typical antipsychotics, clozapine continues to stand apart. It has shown superior efficacy compared to most other antipsychotics (typical or atypical), particularly in treatment-resistant schizophrenic patients [153, 170, 248]. Clozapine is also associated with less severe EPS than other antipsychotics [148, 153]. Unfortunately, clozapine carries a high risk for metabolic dysfunction as well as other potentially life-threatening side-effects including agranulocytosis and myocarditis [104, 179]. These serious adverse reactions limit clozapine's use as a first line agent, so it is only recommended after patients have already failed trials of other antipsychotics [14, 152].

Because D2 antagonists have generally failed to produce meaningful improvements in the treatment of psychosis since the introduction of the first antipsychotics, ongoing research is investigating potential new mechanisms of antipsychotic action. Aripiprazole was the first D2 partial agonist approved for clinical use, and studies have reported encouraging results regarding its efficacy and side-effect profile [56]. Partial agonists work by stimulating the target receptor, but at a lower level than the endogenous ligand. Therefore, some dopamine signaling is maintained even at very high levels of D2 receptor occupancy. Several other D2 partial agonists are currently under development [136]. Allosteric modulation of D2 receptors is also being investigated as a potential antipsychotic mechanism [18]. Drugs utilizing this mechanism

may be more tolerable at high doses, since their activity is dependent on endogenous dopamine signaling [45]. Despite the recognized importance of the D2 receptor, a number of drugs are also being investigated that act primarily on serotonin, glutamate, and acetylcholine receptors as well as a number of other targets [136]. More work is required before it can be determined whether these strategies are useful in clinical populations.

Overall, atypical antipsychotics as a class have shown only marginal improvement over typical antipsychotics in the management of schizophrenia. No medication has emerged as superior to the rest, and there is no clear first-line treatment [152]. There is also no currently available method to individualize the choice of antipsychotic for each specific patient, although pharmacogenetic strategies have shown some promise [10, 218]. In first-episode psychosis patients, physicians are limited to a trial-and-error approach in which they may have to attempt treatment with several antipsychotics before an effective strategy is found [142, 152]. The efficiency of such an approach may be improved either by optimizing the choice of the initial antipsychotic or by shortening the necessary length of each antipsychotic trial, so that less time passes before a successful drug is identified.

2.4   Pathophysiology of psychosis

The dopaminergic antipsychotics approved to date have often been developed based on the fortuitous success of earlier drugs, rather than a true understanding of the pathophysiological mechanisms being targeted [246]. This approach may have contributed to the emphasis on dopamine signaling that is central to the action of existing antipsychotics. It could be argued that a broader understanding of the mechanisms

of psychosis would lead to improved treatment strategies beyond dopamine antagonism. Additionally, a better understanding of the role of aberrant dopamine signaling within the context of other abnormalities in psychotic patients may enable physicians to use existing antipsychotic drugs more effectively. In this section, several theories and areas of research regarding the pathophysiology of psychosis are outlined.

Because so much of our understanding of psychosis is based on dopamine signaling, it is important to understand the major dopamine signaling pathways in the brain. Dopamine systems are numerous and complex, but the pathways that appear to be most relevant to schizophrenia and psychosis project to the striatum, limbic regions, and cortex [54, 176]. The mesolimbic pathway projects from the ventral tegmental area in the midbrain to the nucleus accumbens and other limbic structures [176, 187]. Mesocortical projections also originate from the ventral tegmental area, but terminate in the cortex (including the frontal cortex as well as the limbic regions of the cingulate gyrus, entorhinal cortex, and hippocampus) [176, 187]. There is substantial overlap between these two pathways projecting from the ventral tegmantal area, and they are sometimes discussed as one major pathway with multiple branches [187]. Finally, the nigrostriatal pathway projects from the substantia nigra pars compacta to the striatum [176, 187]. In all of these pathways, dopamine acts on presynaptic or postsynaptic G-protein coupled receptors to stimulate signal transduction (in the case of D1 and D5 receptors) or inhibit signal transduction (in the case of D2, D3, and D4 receptors) by increasing or decreasing cAMP production [94, 105]. A final pathway that should be mentioned is the tuberoinfundibular pathway projecting from the arcuate nucleus of the hypothalamus to the median eminance, where it regulates prolactin secretion from the pituitary [176]. Inhibition of this pathway is responsible

for the hyperprolactinemia caused by many antipsychotic drugs.

The importance of dopamine in psychosis can be illustrated by three major categories of evidence. The first type of evidence is the importance of dopamine antagonism in the treatment of psychosis. As mentioned previously, it has been shown that the clinical potency of antipsychotic drugs is correlated with their affinity for dopamine receptors [48]. Subsequent studies have clarified some details of this relationship. In PET studies of schizophrenic patients, improvements in psychiatric symptoms are correlated with D2 receptor occupancy in the striatum [196]. Specifically, D2 receptor occupancy of at least 65% is required for most patients to achieve satisfactory antipsychotic treatment response [118]. Binding of D2 receptors outside the striatum may be less important for the action of antipsychotic drugs, and striatal D2 binding is mostly closely related to positive symptom improvement [5]. Despite this close relationship between striatal D2 receptor binding and positive symptoms, it must be noted that some patients fail to achieve adequate symptom improvement despite high D2 receptor occupancy [5, 118, 196]. Thus, the importance of D2 antagonism does not exclude the potential for other therapeutic mechanisms.

A second line of evidence connecting dopamine to psychosis is the ability of dopamine agonists to worsen psychotic symptoms. Stimulants that increase dopamine release can cause or exacerbate psychotic symptoms, especially in schizophrenic patients [159]. Additionally, use of prescription stimulants is associated with an earlier onset of psychosis in psychotic patients [188]. Other substances associated with the onset of psychotic symptoms, including ketamine and cannabinoids, also increase dopamine release [40, 124]. These studies suggest that increasing dopamine release pharmacologically can cause or worsen psychotic symptoms, or even induce the onset

of a chronic psychotic illness. However, these substances have complex actions across a number of brain systems, so they do not exclusively implicate dopamine.

A third type of evidence demonstrating the importance of dopamine is the presence of dopamine signaling abnormalities in psychotic patients. Dopamine synthesis and availability in striatal dopaminergic neurons are increased in these patients [98, 99]. Furthermore, the degree to which dopamine synthesis is increased correlates with the severity of psychotic symptoms [100]. This increased dopamine synthesis is coupled with increased dopamine release in response to amphetamine [24], increased D2 receptor density [143], and increased baseline occupancy of D2 receptors [1]. These findings all link excess striatal dopamine to psychosis. Other symptoms associated with psychosis may also be related to underlying dopamine abnormalities. For example, poor cognitive function in schizophrenic patients is correlated with increased prefrontal D1 receptor availability, which is consistent with a response to reduced prefrontal dopamine activity [2]. The link between dopamine and psychosis is clear. However, a number of questions remain to be answered regarding the exact nature and regional specificity of dopamine abnormalities. As well, prominent dopamine abnormalities do not rule out the presence of other contributing or even primary pathophysiological mechanisms.

The pool of data describing dopamine abnormalities in schizophrenia has been compiled into several versions of the "dopamine hypothesis of schizophrenia." The earliest descriptions of the dopamine hypothesis suggested that schizophrenia - or at least some aspects of it - were due to excess dopamine activity [176]. After a considerable amount of research, a major revision to the dopamine theory was described in 1991 [54]. This version suggested that negative symptoms were in fact related to

prefrontal hypodopaminergia, and this deficit led to subcortical hyperdopaminergia, which was in turn responsible for positive symptoms. A recent description of the dopamine theory illustrates the importance of multiple genetic and environmental insults interacting to cause dysregulation of presynaptic dopamine synthesis and release [98]. This version of the theory also suggests that dopamine dysregulation is primarily responsible for positive psychotic symptoms, while the explanation for other aspects of schizophrenia remains unclear. Perhaps most interestingly, this theory provides a hypothetical framework linking dopamine dysregulation to the experience of hallucinations and delusions. The authors highlight dopamine's role in mediating the attribution of salience to external stimuli and internal experiences [98, 116]. When dopamine is dysregulated, salience may be assigned to otherwise unremarkable experiences, and the individual's cognitive efforts to make sense of this abnormal salience provide the basis for hallucinations and delusions. The event is filtered through an individual's own experience and cultural context, so each individual's psychosis is unique despite a shared underlying pathophysiology. Although it is difficult to prove, this theory may provide a useful framework for investigating the role of dopamine in psychosis.

Dysfunctional glutamate signaling is also strongly implicated in schizophrenia and psychosis. The importance of this neurotransmitter system is demonstrated by the ability of NMDA receptor antagonists such as ketamine and phencyclidine (PCP) to induce positive, negative, and cognitive symptoms similar to those seen in schizophrenia [66]. A number of antipsychotic medications are capable of ameliorating these effects, suggesting that their effect on glutamate transmission may be a component of their therapeutic mechanism [182]. The glutamate theory and the dopamine theory

of psychosis are not mutually exclusive, due to the extensive interactions between the two systems. Ketamine increases amphetamine-induced striatal dopamine release [124, 144], while excess D2 stimulation inhibits subcortical glutamate transmission [144]. Therefore, either system may be the source of the primary abnormality, or both systems may be affected secondary to another insult.

One influential theory contends that schizophrenia and its associated symptoms have their origin in neurodevelopment [65, 158]. Several lines of evidence support this theory. Firstly, obstetric and perinatal complications are associated with an increased risk of schizophrenia [65]. Also, a number of important genetic risk factors for schizophrenia, for example *NRG1* and *DISC1*, are involved in neuronal development, maturation, and synapse formation [216, 225]. Schizophrenic patients experience progressive brain structural abnormalities that are present even before the onset of psychosis [225]. Along with gross structural changes, there is evidence of disrupted white matter integrity [65] that is present even in high-risk patients who have not yet experienced a psychotic episode [96]. Finally, cytoarchitectural abnormalities are present in the brains of schizophrenic patients that are suggestive of disordered neuronal migration [225]. These changes may be responsible for the behavioural and cognitive abnormalities observed in schizophrenic patients long before their first psychotic episode [216]. Over time, genetic and environmental insults, including social stressors, may accumulate and lead through a number of possible pathways to dopamine dysregulation and psychosis [26].

A number of other abnormalities may contribute to the pathophysiology of psychosis. For example, cortisol has a role in the regulation of dopamine signaling, and

there is some evidence of hypercortisolemia in schizophrenic patients [275]. Supporting this theory is the observation that patients with hypercortisolemia due to pituitary or adrenal tumours can experience psychosis [190, 217]. Others have suggested that the primary abnormality in schizophrenia may occur in parvalbumin-positive interneurons, which are important for the synchronization of neural activity [193]. Whatever the initial abnormality may be, it seems clear that a number of possible etiologies for psychosis could eventually converge on a final common pathway of excess striatal dopamine. Treating this final common pathway using D2 antagonists has proved relatively effective, but understanding the upstream causes of the dopamine abnormality may eventually improve the ability of physicians to individualize treatment strategies and predict patient outcomes.

2.5   Pathophysiology of extrapyramidal side-effects

While D2 antagonism has so far proved proved to be crucial in the treatment of psychosis, it also leads to extrapyramidal side-effects (EPS). As mentioned previously, EPS may lead to treatment discontinuation [107, 157, 181], and are of particular concern in first-episode psychosis patients [169, 233]. Understanding the pathophysiological mechanisms leading to EPS may help to illustrate the links between EPS and psychosis. For example, it may be possible to predict a patient's EPS risk based on the nature or severity of their psychiatric symptoms, or their likelihood of achieving treatment response based on the occurrence of EPS. Unfortunately, the pathophysiology of EPS is not well understood, but this section will review some of the existing evidence.

The circuitry of the basal ganglia is central to our current understanding of EPS,

and has been thoroughly described in several recent reviews [34, 138]. Briefly, cortical glutamatergic inputs synapse on medium spiny neurons (MSNs) in the striatum. MSNs can be roughly categorized into two groups. "Direct pathway" MSNs project to the globus pallidus pars interna and the substantia nigra pars reticulata, the output structures of the basal ganglia. These projections are GABAergic, so they inhibit basal ganglia output. This in turn leads to disinhibition of thalamocortical projections and activation of behavioural output (for example, a specific movement). "Indirect pathway" MSNs project to the globus pallidus pars externa, then to the subthalamic nucleus, and finally to the basal ganglia output structures. The net effect of this pathway is to inhibit thalamocortical projections, thereby inhibiting behavioural output. Both types of MSNs are affected by dopamine inputs. Direct pathway MSNs primarily express excitatory D1 receptors, while indirect pathway MSNs primarily express inhibitory D2 receptors. In either case, the effect of dopamine is to stimulate behavioural output.

The importance of the dopamine D2 receptor in EPS has been highlighted by PET studies. There appears to be a "therapeutic window" between 60-80% D2 occupancy in which antipsychotic treatment is therapeutically effective, but above 80% occupancy the risk of EPS increases dramatically for both typical and atypical antipsychotic drugs [116, 118, 198]. However, this value is somewhat variable depending on the specific antipsychotic involved. For example, aripiprazole, which acts as a D2 partial agonist, may show minimal EPS even with D2 occupancy of 90% or higher [284]. While most studies investigate D2 binding in the striatum, D2 autoreceptor binding in the substantia nigra has also been associated with EPS [274]. In addition, there is evidence of genetic susceptibility to EPS [133]. In particular, studies have

associated D2 receptor gene polymorphisms with increased EPS risk [78, 88, 132].

While it is clear that the D2 receptor is related to the pathophysiology of EPS, the precise mechanism of this connection is unknown. What is certain is that the D2 receptor is not the only important component. At the genetic level, polymorphisms in the serotonin 5-HT2A and 2C receptors have also been associated with EPS [10, 77], along with polymorphisms in metabolic enzymes [10], multidrug resistance protein 1 [112], and the dopamine D3 receptor [70]. The D3 receptor may be especially important, as antipsychotic treatment does not result in significant D3 blockade, and may in fact cause D3 upregulation [183]. Any upregulation of D3 availability could promote EPS, since there is evidence that D3 antagonism might protect against EPS [76, 79].

Since dystonia is often the earliest extrapyramidal motor disturbance to occur during antipsychotic treatment [93], it is informative to consider the proposed mechanisms of this symptom. Early theories suggested that after substantial D2 receptor blockade, a compensatory "supersensitivity" was established by increasing postsynaptic D2 receptor expression and presynaptic dopamine release [131]. It was thought that when antipsychotic drug levels fell and D2 blockade decreased, the dopamine supersensitivity resulted in elevated dopamine signaling, causing dystonia [93, 228]. However, this theory cannot explain L-DOPA-responsive dystonia occurring in hypodopaminergic patients [199], and also struggles to explain tardive EPS that are associated with antipsychotic treatment [206]. In general, the idea that dopamine blockade leads to a lack of movement while excess dopamine leads to increased movement seems too simplistic to explain the variety of antipsychotic-induced EPS.

The mechanism by which altered dopamine signaling leads to dystonia or other

EPS may involve disrupted communication between the direct and indirect pathways, including direct connections between MSNs and connections mediated by striatal interneurons. It has been suggested that coordinated activity between these pathways is required for appropriate selection of behavioural outputs, and dopamine plays a crucial role in this coordination [34]. Within the globus pallidus pars externa, bridging collaterals connect MSNs of the direct and indirect pathways. The density of these collaterals is regulated by D2 stimulation, such that 2 weeks of haloperidol administration significantly decreases the number of collaterals and promotes motor activity in animal models [38]. A number of collaterals also exist among MSNs within the striatum, both within and between pathways [263]. Dopamine depletion leads to a reduction in these collaterals [263], likely regulated at least in part by D2 receptor activity [141]. This loss of lateral inhibitory connections is one possible mechanism by which the activity of MSNs becomes pathologically synchronous when dopamine signaling is disrupted [72]. The loss of communication between MSNs may prevent the selective activation of appropriate behavioural outputs based on cortical input, instead leading to disorganized, unpurposeful, or involuntary movement.

Striatal output is also coordinated by several types of interneurons that are regulated by dopamine activity. D2 receptor agonism inhibits cholinergic neurons, while D2 blockade using haloperidol increases striatal acetylcholine release [55]. Increased cholinergic stimulation has been strongly associated with EPS [207]. In addition to modifying activity of striatal projection neurons [34, 139], acetylcholine regulates multiple subtypes of GABAergic interneurons [163, 269]. Of particular interest, acetylcholine release excites parvalbumin-positive fast-spiking GABAergic interneurons, which are connected by gap junctions and lead to powerful feedforward inhibition

of MSNs [163, 270]. These neurons may have a role in the selective activation of behavioural outputs [16]. Dopamine depletion induces rapid plasticity in parvalbumin-positive interneurons whereby they dramatically increase their innervation of medium spiny neurons in the indirect pathway, leading to increased synchrony of MSN firing [72].

Interneurons expressing somatostatin, neuropeptide Y, and nitric oxide synthase are also under cholinergic [138] and dopaminergic [232] control. Nitric oxide release from these neurons in the striatum appears to increase the sensitivity of dopaminergic neurons in the substantia nigra, enhancing dopamine release [278]. This enhanced sensitivity, coupled with a lack of D2 autoreceptor stimulation on dopaminergic neurons themselves, could contribute to the increased dopamine turnover seen as a result of antipsychotic treatment [184]. This in turn could lead to dopaminergic neuron down-regulation and parkinsonian symptoms that persist even after antipsychotic medication is discontinued [156, 168, 173]. Indeed, SPECT studies have found nigrostriatal dopaminergic neuron abnormalities in patients with antipsychotic-induced parkinsonism [272] and tardive dyskinesia [243].

Long-term synaptic plasticity in the striatum is also highly dependent upon dopaminergic and cholinergic signaling. Stimulation of D2 receptors enhances production and release of endocannabinoids from postsynaptic MSNs, which induces long-term depression at excitatory presynaptic terminals [139]. This effect has been hypothesized to result from D2-mediated inhibition of cholinergic interneurons, which in turn disinhibits postsynaptic MSNs and enhances endocannabinoid release [277]. Administration of D2 antagonists blocks this form of long-term depression [277]. Conversely, increased acetylcholine release causes long-term potentiation at corticostriatal synapses

through M1 muscarinic receptor activation [33, 207]. Disrupting long-term plasticity may be one way in which antipsychotic use interferes with normal striatal function, potentially leading to EPS.

In summary, although striatal circuitry is still incompletely understood, it appears plausible that impaired dopaminergic signaling does not simply lead to a lack of motor activity, but rather to a variety of disruptions in normal striatal circuitry. These disruptions may impair the ability of the striatum to adjust its responses to cortical inputs, selectively stimulate an appropriate behavioural response while inhibiting competing signals, and form a coordinated output signal. This may result in a lack of movement when cortical input fails to coalesce into a coordinated motor output. It may also lead to excess movement due to aberrant responses to cortical inputs and poorly functioning inhibitory circuits within the striatum.

It is interesting to compare this model of EPS to the salience model of psychosis mentioned previously [98, 116]. Just as the striatal abnormalities outlined here provide possible mechanisms for the inappropriate activation of motor signals, they also suggest plausible mechanisms by which the striatum could assign abnormal salience (both increased and decreased) to other types of cortical input. When inputs are sensory, cognitive, or emotional in nature, striatal dysfunction may lead to hallucinations, delusions, and negative symptoms. When inputs are motor in nature, striatal dysfunction may lead to extrapyramidal syndromes. This would suggest that there is a shared pathophysiology for motor disturbances and psychosis. In support of this notion is the observation that many first-episode psychosis patients experience extrapyramidal syndromes even before receiving antipsychotic treatment [95, 204], and these motor disturbances have been associated with affective symptoms [42],

cognitive dysfunction [52], and negative symptoms [39]. Furthermore, extrapyramidal syndromes in antipsychotic-naive patients sometimes resolve with antipsychotic treatment [134]. The close association between extrapyramidal syndromes and psychotic symptoms suggests that a patient's psychiatric symptom profile and response to treatment may help predict his risk of EPS.

2.6   The role of antidepressants

A major question in the treatment of first-episode psychosis is how to most effectively manage depressive symptoms. Because affective disorders are a common cause of psychosis, this issue affects a large proportion of first-episode psychosis patients. In the McLean-Harvard First-Episode Project, bipolar disorder and major depressive disorder with psychotic features together accounted for 66.9% of primary diagnoses in first-episode psychosis patients [273]. In the Cavan-Monaghan First Episode Psychosis Study, these two diagnoses accounted for 38% of patients at their first presentation, while schizophrenia accounted for 21.4% [127]. Among women, major depressive disorder with psychotic features was the most common diagnosis [127]. However, even among patients with schizophrenia, depressive symptoms are common [31]. These symptoms are especially common in first-episode patients [63].

Not only are depressive symptoms common in psychotic patients, they also have a profound influence on treatment outcome and quality of life. In patients with chronic schizophrenia, depressive symptoms are more closely related to subjective quality of life than psychotic or negative symptoms [101, 211]. Depressive symptoms are also associated with worse treatment response in first-episode schizophrenia [220, 239] and chronic schizophrenia [191]. Additionally, depressed first-episode schizophrenia

patients show significantly less insight into their illness and significantly more sui-cidality than non-depressed patients [220]. Partially as a result of suicide, higher mortality rates have been found in patients with major depressive disorder with psy-chotic features than patients with other psychotic diagnoses [127]. Currently, a great deal of emphasis is placed on treating positive psychotic symptoms in first-episode psychosis patients. However, these data suggest that treating depressive symptoms may be at least as important with respect to long-term patient outcomes.

One possible approach to treating depressive symptoms in psychotic patients is to use an antidepressant drug in addition to an antipsychotic. Recent treatment guide-lines cautiously suggest that this strategy may be helpful in patients with persistent depressive symptoms, although the authors acknowledge that existing evidence in this field is not strong [14, 29, 84, 152]. Despite the weakness of current evidence, physicians commonly prescribe antipsychotics and antidepressants together. In one study of patients with schizophrenia spectrum disorders, 28.5% had prescriptions for both an antidepressant and an antipsychotic [222]. From 1996 to 2005, the number of first-episode schizophrenia patients who received an antidepressant increased dra-matically [194]. Antidepressant and antipsychotic co-treatment is also an increasingly common strategy in bipolar disorder [19]. There appears to be a discrepancy between the frequency of antidepressant use in practice and the strength of evidence-based recommendations, highlighting the need for more research investigating this type of polypharmacy.

Like antipsychotics, antidepressants have a number of proposed mechanisms of action. In general, these drugs act to increase transmission of the monoamines sero-tonin, norepinephrine, or dopamine. Monoamine oxidase inhibitors (MAOIs) block

the metabolism of these neurotransmitters, while tricyclic antidepressants (TCAs) block the reuptake of serotonin and norepinephrine by their respective transporters [71, 252]. TCAs also act as antagonists at several serotonergic, cholinergic, adrenergic, and histaminic receptors [71]. Selective serotonin reuptake inhibitors (SSRIs) are relatively more specific for the serotonin transporter [253, 276], and other antidepressants act on monoamine receptors and transporters with varying specificity [252]. However, it is far from certain that these primary mechanisms lead directly to the therapeutic effect of antidepressants. Various theories have suggested that the antidepressant effect requires downstream changes in monoamine receptor activity [253, 276], neurogenesis [234], glucocorticoid signaling [9], or pro-inflammatory cytokines [81, 140]. Whatever the final mechanism of action may be, it is clear that antidepressants act on many of the same neurotransmitter systems as antipsychotics. Additionally, antidepressant drugs affect the clearance rate of antipsychotics [53]. At this time, it is unclear precisely how these interactions between antipsychotics and antidepressants manifest clinically.

One area that has received a great deal of attention is the use of antidepressants to treat negative symptoms in schizophrenic patients. Several meta-analyses have suggested that antidepressants in conjunction with antipsychotics are more effective than antipsychotics alone [227, 250]. However, others have reported that antidepressant augmentation does not improve the treatment of negative symptoms [67, 102]. It is unclear to what extent this relationship is influenced by the specific antidepressant and antipsychotic drugs being used. For the treatment of depressive symptoms in schizophrenia, there appears to be a small advantage for adjunctive antidepressant medication over antipsychotic monotherapy [271, 280], but this result is not found in

some studies [102]. Intriguingly, one study reported that augmenting typical antipsychotics with the antidepressant mirtazapine significantly improved the treatment of negative as well as positive symptoms [108], but this result has not been replicated by other groups. In patients with major depressive disorder with psychotic features, antidepressant and antipsychotic co-treatment appears to be superior to monotherapy with either type of medication, although only a limited number of drug combinations have been studied [64, 226]. Since different antipsychotics have demonstrated varying efficacy against depressive symptoms [20, 161], they may also interact differently with antidepressants. Unfortunately, all of these studies investigated patients with chronic illnesses, so it is even less clear how antidepressants and antipsychotics interact in first-episode psychosis patients.

Antidepressants and antipsychotics may interact not only through their therapeutic effect, but also through their side-effects. EPS similar to those observed with antipsychotic treatment have also been associated with antidepressants, particularly SSRIs [87, 164]. The risk of EPS may be slightly elevated in patients receiving antidepressant and antipsychotic medications together [240], but the evidence in this area is not strong. EPS and other side-effects [23] clearly show that antidepressant medication is not without potential drawbacks, and should not be implemented carelessly. Since first-episode psychosis patients are especially prone to EPS [169, 233], the association between antidepressants and EPS may be of particular importance in this patient population. A great deal of research is still required to understand how antidepressants and antipsychotics interact, how they should be used in psychotic patients, and how response to this treatment combination should be monitored.

2.7   Early antipsychotic response

Early studies of dopamine antagonists suggested that their antipsychotic effect took 3-4 weeks to become apparent, while for the first 2 weeks there was no advantage over placebo [50, 109]. This observation cast some doubt upon the dopamine hypothesis of schizophrenia, as it was unclear why the antipsychotic effect should lag so far behind the blockade of dopamine receptors. One explanation for the delayed onset of antipsychotic activity was the "depolarization block" of dopaminergic neurons [75]. Proponents of this theory reported that acute administration of antipsychotic drugs to rodents increased the firing of dopaminergic neurons. However, when the drugs were administered daily for 21 days, the activity of dopaminergic neurons was reduced below control levels. It was hypothesized that the onset of this depolarization block was responsible for the antipsychotic effect of dopamine antagonists. Based on the delayed onset of antipsychotic action, treatment guidelines suggested that patients should remain on their initial antipsychotic for at least 6 weeks before it was deemed ineffective and a medication switch was considered [145].

More recently, large studies and meta-analyses have rejected the delayed onset of antipsychotic action entirely. In a meta-analysis of 7450 patients with schizophrenia and schizoaffective disorder, a substantial improvement in psychotic symptoms was observed in the first week of treatment, even after the effect of placebo treatment was removed [3]. In fact, it appears that more improvement occurs during weeks 1-2 than during weeks 3-4 [3, 149], and most of the improvement achieved after 1 year is already apparent by week 4 [149]. Even within the first 24 hours of treatment, antipsychotic treatment is superior to placebo with respect to improvement in psychotic symptoms [119]. The concept of delayed onset may have resulted from a lack of power in early

studies. Although patients treated with antipsychotics improved more than patients treated with placebo during the first week, small studies that were only powered to detect differences of 25-30% would not have found a significant difference until weeks 3-4 [4]. These early studies were not assessing the onset of antipsychotic action, but rather the time until a large portion of the final antipsychotic effect was achieved.

If early response to antipsychotics only reflects a portion of the final treatment outcome, is it still clinically informative? Many studies have now demonstrated that early partial antipsychotic response is a valuable predictor of treatment outcome. In patients with schizophrenia spectrum disorders, 20% improvement on the Positive and Negative Syndrome Scale (PANSS) or Brief Psychiatric Rating Scale (BPRS) at week 2 of treatment predicts response after 3 months [128] or 6 months [7]. In patients with first-episode schizophrenia, partial response at week 2 predicts response and remission at hospital discharge [239] or at week 12 [255]. Various improvement thresholds and time points have been examined. For example, some studies have reported that non-response at week 1 is a robust predictor of non-response at week 4 [46], or that 30% improvement at week 2 should be used as a threshold for predicting eventual response and remission [237]. The optimal threshold for early improvement is likely to differ dramatically among patient populations, and may be as high as 60% in first-episode psychosis patients [237]. A recent meta-analysis including 9460 patients found that patients who failed to achieve 20% improvement after 2 weeks were unlikely to respond later, and the authors suggest that these patient may benefit from a treatment change [231]. If it can be demonstrated that an early treatment change after 2 weeks is beneficial in early non-responders, the length of time that patients spend being treated with ineffective drugs could be reduced dramatically.

While the issue of early antipsychotic switching is central to the importance of assessing early response, this topic has received surprisingly little attention. In one study by Kinon et al. [129], early risperidone non-responders (less than 20% PANSS improvement after 2 weeks) were randomized to continue on risperidone or switch to olanzapine. There was a small but significant advantage in symptom improvement after 12 weeks for patients who switched drugs. This study is important in that it demonstrates the clinical utility of assessing and acting upon early antipsychotic response, but it is limited in several ways. First, it describes patients switching from risperidone to olanzapine, but not from olanzapine to risperidone. Therefore, the results could simply reflect an advantage of olanzapine in this patient sample, rather than a benefit from switching. Second, the patients were mainly chronic schizophrenia patients who had received prior antipsychotic treatment, so the results are not necessarily informative for the treatment of first-episode psychosis patients. A similar study investigated early non-responders to olanzapine or risperidone who were randomized to be switched to the other drug or to receive augmentation with the other drug [86]. The study found no advantages for any group with respect to symptom improvement after 12 weeks, but very small sample sizes and the lack of a control group that remained on the initial treatment regimen make these results difficult to interpret. Two trials investigating the efficacy of antipsychotic switching - the SWITCH study and the OPTiMiSE study - may shed more light on this issue when their results are published. Until it is demonstrated that altering treatment strategies based on early non-response is beneficial, the clinical value of assessing early response at all is uncertain.

Another important question is whether the expected time course of early response

varies among antipsychotic drugs. Leucht and Zhao [147] investigated this issue in a pooled analysis of several trials studying asenapine, olanzapine, risperidone, and haloperidol. They found that early improvement at week 2 predicted treatment response at week 6 for all drugs except olanzapine. One possible explanation for these results is that olanzapine has a more gradual onset of therapeutic action than other drugs, limiting the predictive value of 2 week responses. This interpretation is supported by Hatta et al. [85], who compared risperidone and olanzapine and found that, while risperidone non-response could be accurately predicted by 2 weeks, a significant response to olanzapine often did not occur until 4 weeks. As well, a recent meta-analysis found that response to clozapine continued for at least 6 weeks, whereas response to other antipsychotics plateaued at 3-4 weeks [258]. The authors reasonably suggest that this could be due to the gradual titration of clozapine dose, but it is also interesting to note that clozapine and olanzapine share a relatively low affinity for the D2 receptor [97]. Furthermore, clozapine and olanzapine have the lowest rates of EPS [148] and the highest rates of metabolic side-effects [247]. It is unclear which features of these two drugs contribute to their clinical similarity, but it is possible that these shared features also lead to a gradual onset of therapeutic action, such that early response at 2 weeks is a poor predictor of treatment outcome. Unfortunately, most studies of early antipsychotic response have not investigated differences between antipsychotic drugs, so these results have yet to be replicated in prospective trials and a number of questions still remain.

While it is clear that early antipsychotic response has the potential to predict long-term treatment efficacy, it is not yet known whether early response can predict the risk of EPS. Several studies have examined this issue and found conflicting results.

One study found that early response or non-response to risperidone did not predict the risk of EPS during 12 weeks of treatment [129]. Another study found that early non-response to haloperidol or olanzapine was associated with more severe parkinsonism, but this difference did not emerge until 10 weeks [255]. Finally, in patients receiving naturalistic treatment, less EPS within the first 2 weeks of treatment was associated with stronger early response at 2 weeks, but the long-term predictive value of this finding was not assessed [238]. Part of the explanation for these conflicting results may be the pooling of data from patients treated with different antipsychotics, which may have different rates of EPS and different early response trajectories. An even more important problem may be that most of the patients included in these studies were chronic schizophrenia patients with a great deal of prior antipsychotic exposure. A study investigating first-episode, antipsychotic-naive patients may be more informative, since these patients are more sensitive to both the therapeutic effect and side-effects of antipsychotic drugs [60, 169, 233, 238].

Another issue currently under investigation is the role of affective symptoms in predicting long-term treatment response. As discussed previously, depressive symptoms at baseline may predict a worse treatment response [220, 235, 239]. However, it may also be helpful to determine whether early improvement in affective symptoms could assist in the prediction of long-term outcomes. Recent studies investigating this issue have found encouraging results. For example, in schizophrenic patients treated with quetiapine, early improvement in depressive symptoms within the first 3 days of treatment predicts remission after 4 weeks [43]. Early improvement in manic symptoms within 1 week also predicts response after 3 weeks in bipolar patients experiencing manic or mixed episodes [261]. In bipolar patients experiencing depressive

episodes, early improvement in depressive symptoms predicts eventual treatment response [125]. These studies suggest that early improvement in affective symptoms should be specifically examined in first-episode psychosis patients in order to predict treatment outcomes.

Since antidepressants are frequently used in psychotic patients [194, 222], it is also important to understand how early response to antidepressant treatment predicts long-term outcomes. Although several landmark studies initially suggested that there was a delayed onset to the therapeutic action of antidepressants [212, 213], more recent analyses have found that the antidepressant response actually begins within the first week of treatment [203, 265]. Moreover, it appears that early response within the first two weeks is a strong predictor of long-term antidepressant treatment outcome [120, 259, 260]. Unfortunately, there is no information currently available about the predictive value of early response to antidepressant/antipsychotic combination therapy. Because these medications influence many of the same neurotransmitter systems - often in opposite directions - it is possible that the trajectory of treatment response is altered when they are administered together.

One weakness of the existing literature on early antipsychotic response that has not yet been discussed is the lack of long-term follow-up. The predictive value of antipsychotic response at week 2 has only been convincingly demonstrated up to 3-6 months following treatment initiation [7, 129]. One 18 month study reported that the advantage of early responders over non-responders only remained significant until week 44 [154], which casts doubt on the long-term value of assessing early response. However, as with most studies, these results were based on patients with prior antipsychotic exposure, so it is not clear whether the initial symptom severity

represents a true baseline or whether the symptom change during the first two weeks can truly be interpreted as "early antipsychotic response." It is possible that for antipsychotic-naive patients, the predictive value of early response would be more robust.

2.8   Summary

The existing literature makes it clear that a major goal in the treatment of first-episode psychosis should be the rapid resolution of psychotic symptoms. Affective symptoms also play an important role in patient well-being, so every effort should be made to target them as well. Unfortunately, despite a great deal of work, no clear first-line antipsychotic (or even class of antipsychotics) has yet been identified. As a result, physicians are generally limited to a trial-and-error approach to finding the most effective drug. For patients who do not respond to their first antipsychotic medication, this can lead to a lengthy delay in the effective treatment of their symptoms.

Assessing early antipsychotic response may be useful in improving the efficiency of the trial-and-error approach. Rather than waiting until week 6 of treatment, an antipsychotic switch could be initiated as early as week 2 based on early non-response. This treatment approach is promising, but has not yet been thoroughly investigated. Assessing early response may also prove useful for predicting the risk of EPS. Since there appears to be substantial overlap in the physiological mechanisms of antipsychotic response and EPS, early response patterns may allow physicians to predict the long-term risk of EPS and adjust the treatment strategy accordingly.

Many of the details of early antipsychotic response have yet to be investigated. How does early response differ among antipsychotics? How does early response change

when multiple drugs are used together? Do baseline symptoms or psychiatric diagnoses affect early response? Can early response predict side-effects? Does the predictive value of early response persist throughout long-term antipsychotic treatment? What is the best treatment approach in patients who experience early non-response? When these questions are answered in antipsychotic-naive samples, physicians will better understand how to use early response to guide clinical decisions in the treatment of first-episode psychosis patients.

Chapter 3

The predictive value of early treatment response in antipsychotic-naive patients with first-episode psychosis: haloperidol versus olanzapine

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Abstract

Background: It has been proposed that early response to antipsychotic drugs can predict treatment outcome for psychotic patients. However, recent evidence suggests that this may not be the case for patients treated with olanzapine. Furthermore, it is unclear whether improvement in affective symptoms that often accompany psychosis can be predicted based on early response. In this study, we assessed the predictive value of early response to olanzapine or haloperidol at multiple time points.

Methods: We examined a cohort of 94 antipsychotic-naive inpatients with first-episode psychosis randomized to treatment with haloperidol or olanzapine. All patients were assessed at baseline and twice weekly thereafter using the Brief Psychiatric Rating Scale (BPRS), Hamilton Depression Rating Scale (HAM-D), Hamilton Anxiety Rating Scale (HAM-A), and Young Mania Rating Scale (YMRS). Regression analyses were used to determine whether improvements on these measures at week 2 or week 3 predicted improvements at hospital discharge. A follow-up analysis was conducted to determine whether non-response at week 2 or week 3 was associated with a beneficial effect of switching antipsychotic medications.

Results: Response to antipsychotic treatment was early and robust in both groups, with the majority of patients experiencing $\geq$50% BPRS improvement at week 2 and $\geq$75% improvement at hospital discharge. In the haloperidol group, week 2 improvement was associated with improvement at discharge for BPRS total ($p<.001$), BPRS psychotic symptom subscale ($p=.016$), HAM-D ($p<.001$), and YMRS scores ($p=.011$), though

not HAM-A scores. In the olanzapine group, week 2 improvement was only predictive of improvement at discharge for HAM-D scores ($p=.019$). Week 3 improvement in the olanzapine group did predict improvement at discharge for BPRS total ($p<.001$), BPRS psychotic symptom subscale ($p=.009$), HAM-D ($p=.001$), and YMRS scores ($p=.001$), but not HAM-A scores. Olanzapine non-responders ($<50\%$ BPRS total score reduction) at week 2 who switched medications did not differ at discharge from those who stayed on olanzapine. However, olanzapine non-responders at week 3 who switched medications did experience more improvement at discharge on BPRS total score ($p=.020$) than patients who stayed on olanzapine.

Conclusion: Response at week 2 was predictive of response at discharge for patients treated with haloperidol. For patients treated with olanzapine, response at discharge could not be predicted until week 3 of treatment. Additionally, patients who would benefit from having olanzapine switched to another antipsychotic could be identified by week 3, but not by week 2. These results suggest that a 2 week trial of haloperidol may be sufficient before considering switching drugs due to non-response, while a 3 week trial may be required for olanzapine.

3.1   Introduction

Antipsychotic drugs are the mainstay of treatment for psychosis, but their mechanism of action is still incompletely understood. Early theories suggested that there was a "delayed onset" of antipsychotic action, whereby the therapeutic effect would not become apparent for several weeks after initiation of treatment. Based on preclinical models, this delayed onset was thought to reflect a depolarization block of dopaminergic neurons observed after 3 weeks of antipsychotic administration [75]. As a result, antipsychotic trials of at least 6 weeks were suggested before efficacy of the drug could be properly evaluated [145].

In the last decade, however, it has become increasingly apparent that the therapeutic action of antipsychotics actually begins much earlier in the course of treatment, with the greatest improvement occurring in the first 2 weeks [3, 4]. This suggests that antipsychotic effectiveness could be assessed soon after treatment initiation, without the need for extended 6-week trials. Subsequent studies have confirmed that early response (usually defined as decreased scores on the Brief Psychiatric Rating Scale [BPRS] or Positive and Negative Syndrome Scale [PANSS] 2 weeks after starting treatment) can be used to accurately predict which patients will eventually achieve adequate symptom improvement [7, 11, 46, 128, 239]. Although the clinical utility of this information has not yet been extensively tested, there is some evidence that identifying patients with a poor 2-week response and immediately switching them to another antipsychotic may improve treatment outcome [129].

Recent studies have reported that the predictive value of early response may not be equally applicable to all antipsychotic drugs. Hatta et al. [85] found that early non-response at 2 weeks robustly predicted non-response at 4 weeks for patients

treated with risperidone, but not for those receiving olanzapine. Similarly, Leucht et al. [147] found that early response at 2 weeks predicted response at 6 weeks for patients treated with asenapine, risperidone, haloperidol, or placebo, but not olanzapine. These studies suggest that olanzapine response at 2 weeks may not reliably predict response at later time points. It is not known whether olanzapine response at 3 weeks (or later) would provide sufficient predictive value. It is also unclear why olanzapine might perform differently than other antipsychotics. Furthermore, interpretation of these results is complicated by the fact that many of the patients studied were not antipsychotic-naive. Since patients with prior antipsychotic exposure are often less responsive to antipsychotic treatment [60, 169], an investigation of exclusively antipsychotic-naive patients might provide clearer information about early olanzapine response.

Another area of uncertainty is the role of affective symptomatology in early antipsychotic response. Depression and anxiety are associated with positive symptoms in schizophrenia and schizophreniform disorder [63, 192], and depressive symptoms at baseline may predict a poorer treatment response [191, 220, 235]. Moreover, early improvement in depressive symptoms has been reported to predict eventual remission in patients with schizophrenia [43]. Additionally, in patients with bipolar I disorder receiving antipsychotic treatment, early improvement in psychotic or manic symptoms predicts eventual manic episode remission [126, 261]. These studies suggest that early changes in affective symptomatology may predict treatment outcome in patients undergoing antipsychotic treatment, but these relationships have not yet been fully explored. Again, it is difficult to interpret the results of many of these

studies because of the lack of antipsychotic-naive patients. Without assessing patients prior to any antipsychotic exposure, it is unclear whether the initial assessment represents a true "baseline." As a result, early improvements from baseline may not accurately represent initial responses to antipsychotic treatment. Unfortunately, antipsychotic-naive populations are rare; even in major randomized controlled trials of first-episode psychosis patients, a majority of patients typically have some prior antipsychotic exposure [114, 241].

While early antipsychotic response has emerged as a powerful predictor of treatment outcome, several uncertainties remain. In particular, it is important to clarify the predictive value of early response to olanzapine at multiple time points. Additionally, it is unclear whether improvement on concurrent symptoms of depression, anxiety, or mania can be predicted to the same extent based on early response. We investigated these issues in a sample of antipsychotic-naive patients admitted to hospital for first-episode psychosis.

3.2 Methods

3.2.1 Study design

All patients admitted to the inpatient psychiatry service at one hospital in Hamilton, Ontario over a three-year period were assessed for eligibility. To be considered eligible, patients had to be experiencing their first episode of psychosis and must have had no prior antipsychotic exposure. Patients were not excluded based on age, DSM diagnosis, or other criteria. Eligible patients received a complete description of the study before they or their substitute decision-makers were given the opportunity to

provide written informed consent. All study protocols were approved by the McMaster University Research Ethics Board.

Patients entering the study were assessed at admission before any treatment was initiated. They were subsequently blindly randomized to receive either haloperidol or olanzapine. Olanzapine treatment began at 5 mg/day. The daily dose was adjusted in 2.5 mg increments/decrements as clinically indicated by clinicians blinded to the treatment assignment. Haloperidol treatment began at 2 mg/day, and the dose was adjusted in 1 mg increments/decrements. Supplementary medications (for example, benzodiazepines or anticholinergic medications) were permitted in accordance with usual clinical care. In cases where changing antipsychotic medications was deemed necessary due to intolerable side-effects or perceived treatment ineffectiveness, both the patient and physician were unblinded to the treatment condition, but patients continued to be assessed until the study endpoint.

3.2.2   Assessments

Upon admission, demographic information was collected along with each patient's psychiatric and medical history. Complete assessments were conducted at baseline and twice a week thereafter until discharge from hospital. The lowest scores recorded during each week were used for the analysis. Hospital discharge was used as the study endpoint.

Overall illness severity was assessed using the Brief Psychiatric Rating Scale (BPRS). Affective symptoms were assessed using the Hamilton Depression Rating Scale (HAM-D), Hamilton Anxiety Rating Scale (HAM-A), and the Young Mania

Rating Scale (YMRS). To specifically evaluate psychosis, a BPRS psychotic symptom subscale was calculated from the sum of scores on conceptual disorganization, suspiciousness, hallucinations, and unusual thought content. Since akathisia may influence anxiety scores, akathisia was also assessed using the Barnes Akathisia Rating Scale (BARS). Assessments were conducted by physicians or a research nurse blinded to the treatment condition.

3.2.3   Statistical analysis

Along with total scores for each psychiatric measure at each time point, percent improvement from baseline was calculated. Since BPRS items are scored from 1 to 7, the minimum score (18) was subtracted from the total score to calculate percentages. Linear regression accounting for age and sex was used to determine whether improvement at week 2 or week 3 predicted improvement at discharge. This analysis was conducted separately for each psychiatric measure of interest. Percent improvement on the BPRS total score at hospital discharge was used as the primary outcome measure.

Akathisia was determined to be present if patients scored at least "mild" (2) on the BARS global assessment item. In a secondary analysis, the presence of akathisia at hospital discharge was included in regression models assessing the predictive value of early improvement on the HAM-A. Since akathisia is often interpreted as anxiety, this analysis was intended to determine the extent to which akathisia influenced the final assessment of HAM-A improvement.

To directly compare treatment groups, independent t-tests were used for continuous variables and Fisher's exact test was used for categorical variables. To assess

dose changes over the course of treatment, we used repeated-measures ANOVA with Bonferroni-corrected post-hoc testing.

Initially, a modified intention-to-treat analysis was conducted for all patients who had complete BPRS information at baseline, week 2, and discharge. However, due to a large group of patients treated with olanzapine who switched drugs during their hospital stay (see results section), we also conducted a per-protocol analysis investigating only the patients who did not switch medications before discharge.

In previous studies, early improvement and eventual treatment response have been dichotomized using thresholds of 20% and 50% BPRS improvement respectively [231]. We applied these thresholds to patients in our sample in order to calculate the sensitivity (probability that a non-responder at discharge was a non-responder at week 2), specificity (probability that a responder at discharge was a responder at week 2), positive predictive value (PPV, probability that a non-responder at week 2 was a non-responder at discharge) and negative predictive value (NPV, probability that a responder at week 2 was a responder at discharge). Following the example of Samara et al. [231], this analysis emphasizes the identification of non-responders, since these are the patients who may benefit from a change of treatment.

Given the large number of patients who switched from olanzapine to other drugs, we conducted a post hoc analysis to determine whether patients with a poor early response who eventually switched medications experienced more symptom improvement than those who remained on the randomized drug throughout their hospital stay. First, patients who failed to reach 50% BPRS total score reduction (the treatment response definition recommended by Leucht et al. [150]) by week 2 were identified.

We used this higher threshold of treatment response because the normal early response threshold of 20% improvement identified very few non-responders and showed poor predictive value. Within this group, independent t-tests were used to compare improvement on the BPRS total score at discharge between patients who remained on the randomized drug and patients who switched medications. Next, we conducted an identical analysis for patients who failed to reach 50% BPRS total score reduction at week 3. We hypothesized that this later cut-off point could better identify patients who would benefit from switching olanzapine to another antipsychotic medication.

3.3   Results

3.3.1   Patient baseline characteristics

We identified 125 patients who met inclusion criteria, 13 of whom declined participation in the study. The remaining 112 patients were randomized to treatment with olanzapine (n=58) or haloperidol (n=54). Of these remaining patients, 11 (8 olanzapine and 3 haloperidol) were missing data at discharge, and 7 (4 olanzapine and 3 haloperidol) were missing data at week 2 or were discharged before week 2. These patients were excluded from the analysis. Baseline information for the remaining 94 patients is presented in Table 3.1. There were no significant differences between treatment groups at baseline.

3.3.2   Treatment response

The lengths of hospitalization for patients treated with olanzapine (mean=32.89 days, SEM=2.78) and haloperidol (mean=32.58 days, SEM=2.55) were not significantly

Table 3.1: Treatment group characteristics at baseline

	Olanzapine (n=46)	Haloperidol (n=48)	p
Age (years)	30.02 (1.36)	29.98 (1.59)	.984
Sex			.664
Male	32	31	
Female	14	17	
Diagnosis			.711
Manic (bipolar)	21	29	
Delusional disorder	6	5	
Schizophrenia	7	4	
Atypical psychosis	4	4	
Major depression with psychosis	4	2	
Other	4	4	
Current smoker			.680
Yes	24	22	
No	22	26	
Symptom duration (weeks)	39.34 (12.50)	43.39 (11.22)	.856

Continuous variables are presented as: mean (SEM)

different (p=.935). A number of patients were also treated with lithium during their hospitalization (20 in the olanzapine group and 26 in the haloperidol group), but the proportion of patients receiving lithium did not differ between groups (Fisher's p=.312). Patients in both groups experienced dramatic symptom improvement, with the majority showing a decrease in BPRS total score of at least 50% at week 2. By discharge, 89% of patients experienced a reduction in BPRS total score of at least 50% (see Table 3.2).

Repeated measures ANOVA demonstrated significant changes in dose over time both for patients treated with olanzapine (p<.001) and those treated with haloperidol (p=.033). Follow-up testing with a Bonferroni correction showed that olanzapine doses increased from week 1 to weeks 3 and 4. In contrast, haloperidol doses decreased from week 3 to week 4 (see Figure 3.1).

Baseline scores for each psychiatric measure along with improvements at week

Table 3.2: Number of patients experiencing different levels of BPRS improvement at week 2 and at hospital discharge

		<0%	0 to <25%	25 to <50%	50 to <75%	75 to 100%
Week 2	Olanzapine (n=46)	2 (4)	8 (17)	8 (17)	18 (39)	10 (22)
	Haloperidol (n=48)	1 (2)	3 (6)	9 (19)	18 (38)	17 (35)
Discharge	Olanzapine	0 (0)	2 (4)	3 (7)	9 (20)	32 (70)
	Haloperidol	0 (0)	1 (2)	4 (8)	10 (21)	33 (69)

Values within parentheses represent percentages
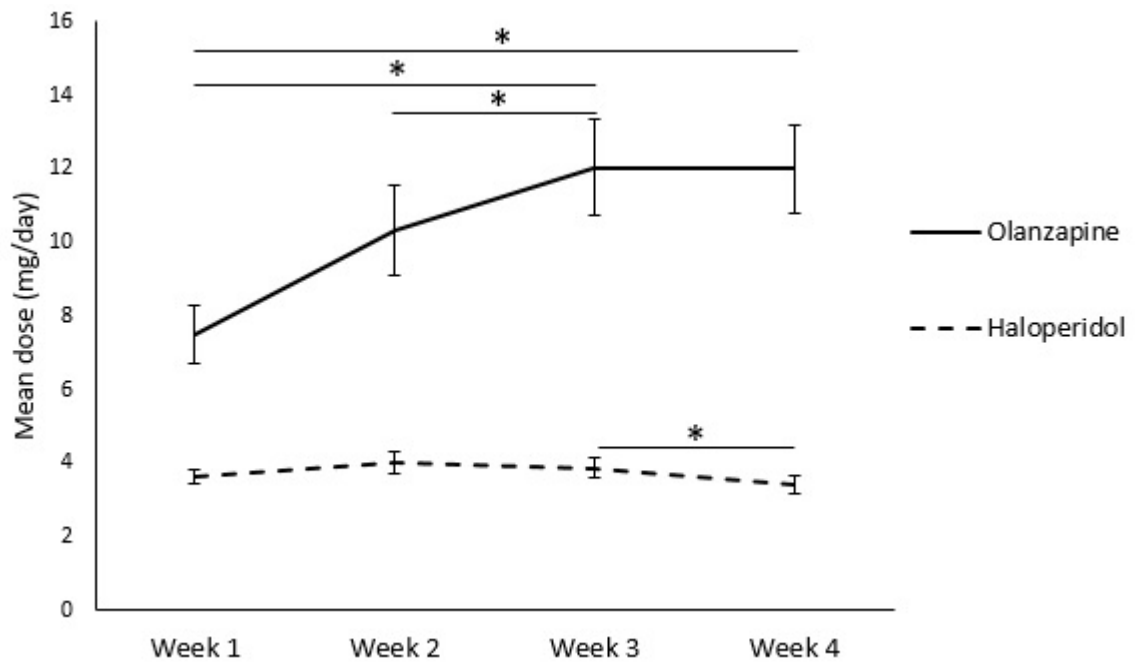
Figure 3.1: Mean daily dose by week.
*: $p<.05$, Bonferroni correction

2 and at hospital discharge are presented in Table 3.3. Patients in both groups showed high levels of affective symptomatology at baseline, particularly as measured by the HAM-D and YMRS. HAM-A scores at baseline were marginally higher in the olanzapine group than in the haloperidol group. However, the *p*-values in Table 3.3 are not corrected in any way for multiple comparisons.

3.3.3 Predictive value of early response

For each outcome measure, linear regression was used to determine whether the percent improvement at week 2 predicted the percent improvement at discharge. Age and sex were included in all regression models. Results from these analyses are shown in Table 3.4. For patients treated with haloperidol, improvement at week 2 predicted improvement at discharge for the BPRS total, BPRS psychotic symptom subscale, HAM-D, HAM-A, and YMRS scores. For patients treated with olanzapine, improvement at week 2 predicted improvement at discharge only for HAM-D scores. The addition of lithium use as a predictor did not significantly contribute to any regression model. Nor did lithium use predict week 2 response in either treatment group.

These results are consistent with the hypothesis that early response is a poor predictor of treatment outcome for patients treated with olanzapine. However, this interpretation must be viewed in the context of increasing olanzapine doses from week 1 to week 4 (see Figure 3.1). It is possible that changing doses altered treatment response trajectories, interfering with the predictive value of early response. However, the interaction term between dose change and week 2 response was not a significant predictor of BPRS improvement at hospital discharge (B=-0.014, R^2=.346, *p*=.366), suggesting that changing doses did not significantly alter the predictive value of week

Table 3.3: Comparison of treatment response between olanzapine and haloperidol groups

		Baseline	% Improvement at week 2	% Improvement at discharge
BPRS total	Olanzapine (n=46)	49.61 (1.37)	52.49 (4.47)	79.48 (3.38)
	Haloperidol (n=48)	49.48 (1.24)	61.02 (3.95)	78.87 (3.06)
	p	.944	.155	.893
BPRS psychotic	Olanzapine	16.59 (0.55)	50.17 (5.42)	84.62 (3.29)
	Haloperidol	17.17 (0.48)	59.98 (4.38)	85.94 (2.58)
	p	.427	.162	.753
HAM-D	Olanzapine	26.24 (0.89)	65.46 (4.39)	84.21 (2.53)
	Haloperidol	23.75 (1.36)	65.26 (3.57)	78.35 (3.89)
	p	.130	.971	.216
HAM-A	Olanzapine	14.15 (0.80)	64.90 (5.24)	84.26 (2.57)
	Haloperidol	11.77 (0.85)	64.28 (5.62)	84.98 (3.90)
	p	**.044**	.937	.878
YMRS	Olanzapine	22.24 (1.41)	47.13 (5.24)	82.03 (3.61)
	Haloperidol	21.67 (1.20)	46.80 (5.75)	82.96 (3.13)
	p	.756	.966	.847

Data are presented as: mean (SEM)

p-values describe t-tests comparing olanzapine and haloperidol groups

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Table 3.4: Predictive value of improvement at week 2 for improvement at discharge (all patients)

	Measure	B	R^2	p
Olanzapine (n=46)	BPRS total	0.123	.054	.293
	BPRS psychotic	0.106	.094	.256
	HAM-D	0.186	.121	**.034**
	HAM-A	0.068	.075	.364
	YMRS	0.072	.025	.531
Haloperidol (n=48)	BPRS total	0.420	.293	**<.001**
	BPRS psychotic	0.238	.179	**.006**
	HAM-D	0.611	.356	**<.001**
	HAM-A	0.234	.131	**.025**
	YMRS	0.203	.152	**.010**

2 response in patients treated with olanzapine.

Another source of concern when interpreting the data was that a number of patients (14 olanzapine and 5 haloperidol) switched antipsychotic medications before they were discharged from hospital. In the olanzapine group, 12 patients switched because olanzapine was perceived to be ineffective, 1 switched because of side-effects, and 1 switched for unknown reasons. In the haloperidol group, 1 patient switched because of ineffectiveness, 3 switched because of side-effects, and 1 switched for unknown reasons. To determine whether these patients reduced the apparent predictive value of early response in the intention-to-treat analysis, we conducted a per-protocol analysis investigating only those patients who remained on the randomized drug throughout their hospital stay. As before, linear regression was used to determine whether improvement at week 2 predicted improvement at discharge for each psychiatric measure. This analysis is presented in Table 3.5. For patients treated with olanzapine, a trend towards significance emerged for the BPRS total score, but the results were otherwise similar to the previous analysis. Surprisingly, HAM-A improvement at week 2 did

Table 3.5: Predictive value of improvement at week 2 for improvement at discharge (patients who remained on randomized antipsychotic)

	Measure	B	R^2	p
Olanzapine (n=32)	BPRS total	0.323	.120	.071
	BPRS psychotic	0.117	.096	.401
	HAM-D	0.266	.203	**.019**
	HAM-A	0.155	.154	.202
	YMRS	0.097	.020	.513
Haloperidol (n=43)	BPRS total	0.387	.273	**<.001**
	BPRS psychotic	0.228	.157	**.016**
	HAM-D	0.672	.401	**<.001**
	HAM-A	0.091	.053	.282
	YMRS	0.211	.160	**.011**

not predict HAM-A improvement at discharge for patients in either treatment group.

Next, we assessed whether improvement at week 3 predicted improvement at hospital discharge. This analysis was conducted for all patients assessed at week 3 (Table 3.6) and for only those patients who remained on the randomized drug throughout hospitalization (Table 3.7). Improvement at week 3 predicted improvement at discharge for all measures except the HAM-A in both treatment groups. Fewer patients were included in this analysis because several were discharged before week 3, and therefore had no week 3 scores.

To determine whether akathisia played a role in the poor predictive value of early HAM-A improvement, we included the presence of akathisia in a secondary analysis of all patients who remained on the randomized drug throughout their hospitalization. A total of 8 patients in this group were experiencing akathisia at the time of their discharge (3 treated with olanzapine and 5 treated with haloperidol). In a regression analysis including HAM-A improvement at week 2, age, sex, and akathisia at discharge, akathisia emerged as a significant predictor of less HAM-A improvement

Table 3.6: Predictive value of improvement at week 3 for improvement at discharge (all patients)

	Measure	B	R^2	p
Olanzapine (n=41)	BPRS total	0.312	.144	**.032**
	BPRS psychotic	0.234	.151	.063
	HAM-D	0.313	.161	**.019**
	HAM-A	0.014	.035	.912
	YMRS	0.330	.164	**.016**
Haloperidol (n=47)	BPRS total	0.390	.320	**<.001**
	BPRS psychotic	0.251	.169	**.010**
	HAM-D	0.563	.689	**<.001**
	HAM-A	0.158	.091	.090
	YMRS	0.286	.200	**.003**

Table 3.7: Predictive value of improvement at week 3 for improvement at discharge (patients who remained on randomized antipsychotic)

	Measure	B	R^2	p
Olanzapine (n=28)	BPRS total	0.816	.526	**<.001**
	BPRS psychotic	0.439	.323	**.009**
	HAM-D	0.585	.380	**.001**
	HAM-A	0.186	.121	.339
	YMRS	0.640	.369	**.001**
Haloperidol (n=42)	BPRS total	0.354	.271	**.001**
	BPRS psychotic	0.236	.156	**.025**
	HAM-D	0.564	.709	**<.001**
	HAM-A	0.102	.074	.156
	YMRS	0.276	.185	**.007**

at discharge (B=-21.383, R^2=.166, p=.002). Additionally, HAM-A improvement at week 2 reached trend-level significance in this model (p=.090).

3.3.4   Predictive performance of standard response criteria

We evaluated the ability of early non-response (less than 20% BPRS improvement) at week 2 to predict non-response (less than 50% BPRS improvement) at hospital discharge. The number of patients meeting these criteria are outlined in Table 3.8. The great majority of patients in both groups were responders at week 2 and at hospital discharge. For patients treated with olanzapine, early non-response predicted non-response at hospital discharge with a sensitivity of 0.00 and a specificity of 0.85 (PPV=0.00, NPV=0.88). For patients treated with haloperidol, early non-response predicted non-response at hospital discharge with a sensitivity of 0.40 and a specificity of 0.95 (PPV=0.50, NPV=0.93). These results indicate that an early response threshold of 20% improvement does not adequately identify patients who will experience a poor treatment response. Moreover, the low number of non-responders at hospital discharge suggests that 50% improvement is too conservative as a threshold for treatment response among patients who have been evaluated before receiving any antipsychotic medication.

3.3.5   Effect of switching antipsychotics

Since a large group of patients switched from olanzapine to other antipsychotic drugs, we took advantage of the opportunity to investigate which patients were most likely to benefit from antipsychotic switching. Specifically, we attempted to determine how early in treatment it was possible to predict which patients would benefit from

Table 3.8: Predictive performance of standard response criteria

		≥50% BPRS improvement at discharge	<50% BPRS improvement at discharge
Olanzapine (n=46)	≥20% BPRS improvement at week 2	35	5
	<20% BPRS improvement at week 2	6	0
Haloperidol (n=48)	≥20% BPRS improvement at week 2	41	3
	<20% BPRS improvement at week 2	2	2

changing olanzapine to another medication. First, we identified 18 patients treated with olanzapine who failed to achieve a 50% reduction in the BPRS total score at week 2 (non-responders at week 2). This cut-off point included 10 patients who remained on olanzapine and 8 patients who eventually switched medications (5 to haloperidol, 2 to risperidone, and 1 to loxapine). Within this group of non-responders, we compared improvement on the BPRS total score at discharge between patients who switched medications and those who remained on olanzapine. The week 2 non-responders who switched from olanzapine to another medication did not experience more improvement at discharge than patients who remained on olanzapine (see Figure 3.2).

Next, we investigated whether non-response at week 3 would be a better predictor of the effectiveness of switching antipsychotics. We identified 12 patients treated with olanzapine who failed to achieve 50% BPRS total score reduction at week 3. Of these patients, 5 remained on olanzapine throughout their hospitalization, while 7 switched medications (6 to haloperidol, and 1 to risperidone). As shown in Figure 3.2, week 3 non-responders who switched from olanzapine to other antipsychotics experienced more improvement at discharge on the BPRS total score than those who remained on olanzapine (p=.020). These patients switched medications between day 21 and day 31 of treatment (mean=27 days).

The analyses described in Figure 3.2 were also conducted for patients treated with haloperidol. However, only a single week 2 non-responder and 2 week 3 non-responders eventually switched medications. The patients who switched medications did not experience significantly more improvement than the patients who stayed on haloperidol.
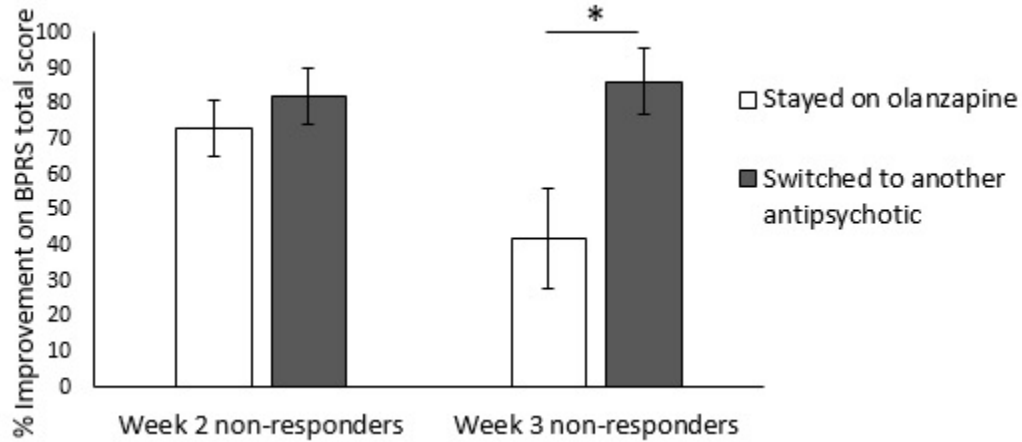
Figure 3.2: BPRS total score improvement at discharge in early olanzapine non-responders.
*: $p<.05$

3.4 Discussion

In this study, we investigated the predictive value of early treatment response in a group of antipsychotic-naive patients with first-episode psychosis. Three main findings emerged. First, early response at week 2 predicted treatment outcome at hospital discharge for patients treated with haloperidol, but not for patients treated with olanzapine. Second, early response at week 3 predicted treatment outcome for patients treated with haloperidol or olanzapine. Third, patients who would benefit from switching olanzapine to another antipsychotic could be identified as early as week 3. Overall, these data indicate that a brief 2 week trial of haloperidol may be sufficient to predict longer term treatment effectiveness, while a 3 week trial may be required for olanzapine. An extended 4-6 week trial is likely not necessary for either drug.

One important aspect of these results is the extent to which treatment response in our patient sample differed from treatment responses reported in previous studies of

schizophrenic patients. In previous studies, 22-46% of patients have been identified as early responders based on an improvement threshold of 20% at week 2 [11, 128, 147]. In the current study, 93.3% of patients achieved the same improvement threshold. Because our patients were assessed prior to any antipsychotic exposure, this difference is not necessarily surprising. However, it does highlight the unique characteristics of these patients, and suggests that a strong response should be expected when patients with first-episode psychosis begin antipsychotic treatment for the first time.

These results build upon the studies by Leucht et al. [147] and Hatta et al. [85] demonstrating that early response to olanzapine does not strongly predict treatment outcome. The study by Leucht et al. [147] is a thorough post-hoc analysis of a large number of patients, but all of the patients had prior antipsychotic exposure. The study by Hatta et al. [85] compared patients treated with risperidone and olanzapine, and included a number of antipsychotic-naive patients. However, the proportion of antipsychotic-naive patients in the olanzapine group (36%) was significantly lower than in the risperidone group (61%). Direct comparison between these groups was therefore difficult, since antipsychotic response has been shown to be greater in previously antipsychotic-naive patients [60, 169]. By investigating only antipsychotic-naive patients in the current study, we eliminate the confounding effect of prior antipsychotic exposure and clarify previous results. Notably, our results indicate that 20% improvement at week 2 is not an appropriate definition of early response in antipsychotic-nave patients. The most useful threshold likely depends on a number of baseline factors as well as the treatment strategy and long-term goals, and will require a great deal of future research to accurately identify.

The issue of prior antipsychotic exposure is not simply a matter of experimental

validity, but has important clinical implications. In patients who have previously received antipsychotic medication, the choice of subsequent antipsychotics will be guided by their response to the first drug [29, 152]. However, no such information is available for antipsychotic-naive patients, so it is in these patients that the predictive value of early response is most useful in guiding clinical decisions.

In contrast to the results of Leucht et al. [147] and Hatta et al. [85], several prior studies investigating olanzapine have found that early response predicts treatment outcome. However, some of these studies define "early response" as occurring at week 4, which supports our finding that a prognostically important olanzapine response occurs between 2-4 weeks [12, 283]. Other studies do not specifically report differences between olanzapine and other antipsychotics in the analysis [7, 128, 255]. Our study suggests that if data from these studies were stratified by treatment, olanzapine would differ from the other antipsychotics.

A secondary goal of the present study was to assess the predictive value of early improvement in affective symptoms. Predicting improvement in affective symptoms may be especially important in patients suffering from bipolar disorder. While a number of patients in our sample were also treated with lithium, early response to antipsychotic monotherapy is emerging as an important predictor of treatment outcomes in bipolar patients [125, 126, 261]. In the current results, it is interesting to note that early improvement in depressive symptoms during olanzapine treatment predicted treatment outcome even when early improvement in psychotic symptoms did not. Therefore, if management of depressive symptoms is a primary treatment goal, assessing olanzapine response at week 2 (or earlier) may be prognostically valuable.

Effective alleviation of affective symptomatology accompanying psychosis has profound implications for long-term patient outcomes in schizophrenia. Depression and anxiety symptoms reportedly influence quality of life in schizophrenic patients even more strongly than psychotic symptoms [101, 211]. In our study, both olanzapine and haloperidol provided rapid amelioration of depression and anxiety symptoms, with >60% improvement at week 2 and >75% improvement at discharge. Unfortunately, the current data suggest that predicting improvement in anxiety based on early antipsychotic response may be difficult. This may be due in part to akathisia influencing scores on measures of anxiety.

There are several potential limitations to this study. First, the increasing mean olanzapine dose over the course of treatment must temper our interpretation of the results. While our analysis suggests that increasing olanzapine doses did not significantly interfere with the predictive value of week 2 response, it is difficult to completely rule out this possiblity. A cautious interpretation of our results would be that any predictive value of week 2 olanzapine response is sensitive to dose changes. It is worth noting, however, that both previous studies reporting poor predictive value for early olanzapine response used a higher initial dose of 10 mg/day [85, 147], further suggesting that the lack of predictive value for week 2 olanzapine response is unlikely to be explained by dosing issues.

It should also be highlighted that our patient sample differs from those of most other studies in the field. Along with being exclusively antipsychotic-naive, these patients had a wide range of psychiatric diagnoses, including a large number of patients with bipolar disorder. Our approach, which was intended to provide a naturalistic sample of all first-episode psychosis inpatients treated with antipsychotics, is in line

with recent recommendations that studies not be limited by specific DSM diagnoses [200]. This inevitably limits our ability to compare our results to those of previous studies.

Our analysis of patients who switched medications was limited to a post-hoc analysis, since the decision to switch medications was based on the clinical judgment of the treating physician. Furthermore, switching medications did not occur at a consistent time point for all patients. Our analysis suggests that patients who would benefit from having olanzapine switched to another medication can be identified as early as week 3 of treatment, but future studies specifically assessing the effect of switching drugs after the week 3 assessment will help to clarify this finding.

Early response is a powerful prognostic indicator that has the potential to improve antipsychotic treatment, particularly for patients with no prior antipsychotic exposure. The current results demonstrate that the appropriate time at which to assess early response differs depending on the specific antipsychotic being used. Additionally, these data suggest that the value of assessing early response differs depending on the symptoms being targeted. Future research will be required to determine whether these principles can be incorporated into an effective treatment strategy, allowing physicians to arrive at the optimal treatment for psychotic patients as quickly as possible.

Chapter 4

The relationship between early antipsychotic response and antipsychotic-induced extrapyramidal side-effects

Sean A. Rasmussen, Patricia I. Rosebush, Michael F. Mazurek

Abstract

Background: Early response to antipsychotic medication within 2 weeks of initiating treatment can predict psychiatric outcomes. However, it is unclear whether early response is also predictive of extrapyramidal side-effects (EPS) associated with antipsychotic medications. In this study, we investigated whether early response predicts EPS risk and whether early EPS predict psychiatric outcomes.

Methods: We investigated 199 consecutive antipsychotic-naive first-episode psychosis patients naturalistically treated with haloperidol. Patients were assessed at baseline and weekly after treatment initiation using the Brief Psychiatric Rating Scale (BPRS), Hamilton Depression Rating Scale (HAM-D), and Hamilton Anxiety Rating Scale (HAM-A). Dystonia, parkinsonism, akathisia, and dyskinesia were also assessed weekly using standardized rating scales. Regression analyses were used to determine whether early response at week 2 of treatment predicted the incidence of EPS, and whether EPS occurring before week 2 predicted psychiatric symptom severity at discharge from hospital.

Results: Greater BPRS percent improvement at week 2 predicted a decreased risk of EPS ($p=.004$), even in patients who did not show any EPS within the first 2 weeks of treatment ($p=.005$). For specific EPS, early response predicted a decreased incidence of parkinsonism ($p=.028$) and dyskinesia ($p=.025$), but not akathisia ($p=.492$) or dystonia ($p=.944$). HAM-D and HAM-A improvement at week 2 did not predict EPS, although there was a trend towards significance for HAM-D improvement

($p=.094$). Additionally, EPS were not predicted by the maximum antipsychotic dose received during hospitalization. Early EPS did not predict improvement at discharge on the BPRS ($p=.879$), HAM-D ($p=.205$), or HAM-A ($p=.428$).

Conclusion: These results indicate that early antipsychotic response is valuable not only for predicting psychiatric outcomes, but also for predicting the risk of EPS. This information has the potential to guide clinical decision making in order to minimize the incidence of these distressing side-effects.

4.1   Introduction

Recent work investigating antipsychotic drugs has consistently demonstrated that early response within 2 weeks of initiating treatment can predict longer term treatment outcomes [147, 239, 255]. This finding has raised the possibility that patients who fail to respond to a particular medication after 2 weeks may benefit from immediately switching to another antipsychotic [129], although few studies have directly tested such an approach. While a great deal of evidence has accumulated with respect to predicting improvements in psychiatric symptoms, less is known about the relationship between early response and antipsychotic-induced extrapyramidal side-effects (EPS), particularly in patients beginning antipsychotic treatment for the first time. These side-effects constitute an important aspect of treatment outcome, and the ability to predict them based on early antipsychotic response would enhance physicians' ability to rapidly and effectively treat psychotic patients. Furthermore, since EPS often occur early in treatment [74, 229], it is of some interest to determine whether these "early EPS" predict any aspect of treatment outcome.

EPS are a diverse group of movement disorders that frequently occur in patients treated with antipsychotic drugs, commonly categorized as dystonia, parkinsonism, akathisia, and dyskinesia. In the CATIE schizophrenia trial, 12-month event rates of parkinsonism and akathisia were 37-44% and 26-35% respectively, while 12-month event rates for dyskinesia were lower at 8-12% [181]. Dystonic reactions are rarely reported in major trials of patients with prior antipsychotic exposure like the CATIE schizophrenia trial, but studies of antipsychotic-naive patients have reported incidences of dystonia from 15-37% [8, 20, 223]. These distressing side-effects impair

multiple aspects of patient functioning [262], and akathisia in particular has been associated with depression and suicidality [135, 244]. Moreover, EPS are an important cause of treatment discontinuation [157, 181]. Preventing and ameliorating these side-effects are crucial aspects of antipsychotic treatment, so being able to predict EPS based on early antipsychotic response may be an important tool for optimizing treatment of psychotic patients, particularly those experiencing first-episode psychosis. For instance, patients suspected to be at high risk for EPS may benefit from being treated with particular antipsychotic drugs, lower antipsychotic doses, or prophylactic anticholinergic medication, thereby minimizing EPS and maximizing treatment compliance.

There is considerable overlap between the pharmacological mechanisms of antipsychotic response and EPS. Most notably, dopamine D2 receptor occupancy is critically implicated in both improvement of psychiatric symptoms and development of EPS [5, 118]. D2 receptor gene polymorphisms have also been associated with EPS risk [78, 132] and antipsychotic efficacy [10, 218]. A number of other other receptors and neurotransmitter systems are implicated in antipsychotic action and EPS development, and overall it is clear that psychosis and EPS have some degree of shared pathophysiology. As a result of this shared pathophysiology, it is possible that early changes in psychiatric symptoms could predict changes in motor symptoms, or that early changes in motor symptoms could predict changes in psychiatric symptoms.

Several previous papers have taken preliminary steps towards describing the relationship between early antipsychotic response and EPS. For example, Kinon et al. [129] found that early response or non-response to risperidone (using a cutoff

value of $\geq 20\%$ Positive And Negative Syndrome Scale [PANSS] total score reduction) did not predict the incidence of akathisia or parkinsonism in a 12-week study period. Switching early non-responders to olanzapine did result in a decreased frequency of dyskinesia, but this may have been unrelated to early non-response, and merely a result of switching medications. Schennach-Wolff et al. [238] found that early non-response was associated with more EPS occurring within the first 2 weeks of treatment, but did not investigate whether this association persisted beyond the early treatment period. Finally, Stauffer et al. [255] reported that both early responders and early non-responders experienced parkinsonism early in treatment, but these symptoms eventually improved for early responders, resulting in more parkinsonism in early non-responders by weeks 10-12 of treatment. This is a compelling result, but interpreting it is difficult because analyses in the study included pooled data from patients treated with olanzapine or haloperidol. Recent results from our group and others [85, 147] have suggested that early response to olanzapine does not have the same predictive value as early response to other antipsychotics. As such, olanzapine early responders may not be equivalent to haloperidol early responders. Furthermore, none of these earlier studies specifically investigated patients with no previous antipsychotic exposure. Since these patients appear to be at higher risk of antipsychotic-induced EPS [169, 233], it is of particular interest to predict and prevent EPS for them.

There is a somewhat larger body of literature concerning the ability of EPS occurring during treatment to predict psychiatric outcomes. In general, the development of EPS during treatment is associated with a worse clinical outcome [41, 62]. In particular, antipsychotic-induced parkinsonism seems to predict less improvement of

psychiatric symptoms, while other EPS may have poorer predictive value [221]. However, other studies have failed to find this association between EPS and psychiatric outcomes [7, 129, 134].

To take full advantage of the predictive value of antipsychotic-induced EPS, it would be informative to specifically investigate EPS occurring early in treatment, and some studies have addressed this issue. Schennach-Wolff et al. [238] found that less EPS within the first 2 weeks of treatment predicted greater antipsychotic response at 2 weeks. However, this analysis did not distinguish between different types of EPS or assess whether the predictive value of early EPS persisted beyond week 2. In a separate analysis, Schennach-Wolff et al. [239] found that schizophrenia patients who achieved remission by week 8 of antipsychotic treatment experienced less EPS during the first week of treatment. As before, this analysis did not distinguish between different types of EPS. Furthermore, it is possible that EPS occurring during the first 2 weeks of treatment would be more informative than EPS only in the first week, since 2 weeks is the time point most often used to assess early antipsychotic response [129, 147, 239, 255]. Collectively, these studies suggest that EPS early in treatment may predict treatment outcomes, but it is unclear which specific side-effects may be most informative, and what time point would provide the most useful information for guiding clinical management decisions.

Another issue of interest is whether affective symptoms accompanying psychosis are associated with EPS risk. Some studies have found that patients with prominent affective symptoms are more likely to experience antipsychotic-induced EPS [58] or spontaneous parkinsonism prior to antipsychotic treatment [42]. However, others have found that depression in schizophrenic patients is associated with akathisia but

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not other EPS [165], or that there is a negative correlation between parkinsonism and depression [229]. These studies suggest a relationship between affective symptoms and EPS in psychotic patients, but once again the exact nature of that relationship is unclear. The existence of this relationship raises the question of whether early improvement in affective symptoms following antipsychotic treatment might assist in predicting EPS risk.

Early antipsychotic response has emerged as a reliable and clinically valuable predictor of psychiatric outcomes, but little is known about whether it can also predict the risk of side-effects. In the current study, we address this issue in a sample of antipsychotic-naive first-episode psychosis patients treated with haloperidol. We further investigate the relationship between psychiatric symptoms and EPS by determining whether early improvement in affective symptoms predicts EPS risk, or whether EPS occurring within the first 2 weeks of treatment predict longer term outcomes. As the value of assessing early response becomes better recognized, we hope to clarify which signs and symptoms at this time point provide the most clinical utility, allowing physicians to optimize treatment for psychotic patients.

4.2   Methods

4.2.1   Study design

From 1989 to 2002, all first-episode psychosis patients admitted to our adult psychiatric inpatient service were prospectively studied to assess psychiatric outcomes and

neurologic side-effects. At the time of the study, this unit was one of 3 university-affiliated acute-care facilities in Hamilton, Ontario, which collectively served a catchment area of approximately 500 000 people. Upon admission to hospital, patients or substitute decision makers gave informed consent, and patients were fully assessed before any antipsychotic treatment was initiated.

For the current analysis, we identified those patients who were antipsychotic-naive upon admission and treated with haloperidol for at least 75% of their hospitalization. Patients were not selected based on their specific psychiatric diagnosis. Supplementary medications were used in accordance with normal clinical care. Anticholinergic medications were used to treat emergent EPS, but were not given prophylactically.

4.2.2   Assessments

Patients were assessed at admission, weekly throughout their hospital stay, and at hospital discharge. These assessments were conducted by a psychiatrist (P.R.), a neurologist (M.M.), or a research nurse. Psychiatric symptomatology was quantified using the Brief Psychiatric Rating Scale (BPRS), Hamilton Depression Rating Scale (HAM-D), and Hamilton Anxiety Rating Scale (HAM-A).

Acute dystonia was diagnosed if a patient experienced a sustained muscle contraction that required immediate treatment with benztropine.

Akathisia was assessed using the Barnes Akathisia Rating Scale (BARS). A global clinical impression of "mild" (2) was regarded as the cutoff point for the presence of akathisia.

Our parkinsonism scale was adapted from the motor examination section of the United Parkinson's Disease Rating Scale, including items measuring facial and vocal

expression, tremor, rigidity, bradykinesia (formally assessed using an alternate motion rate task), gait (including slowing, shuffling, arm swing, and turning), and writing. Each item was scored from 0 ("normal") to 4 ("severely impaired"). Based on these assessments, a global clinical impression of parkinsonism was scored from 1 ("no parkinsonism") to 4 ("severe parkinsonism"). Patients with a global impression score of 2 ("mild parkinsonism") or greater were considered to have parkinsonism.

Dyskinesia was assessed using the Abnormal Involuntary Movement Scale (AIMS). Patients met diagnostic criteria for dyskinesia if they scored "moderate" (3) for movements of one body part, or "mild" (2) for movements of 2 or more body parts.

Inter-rater reliability among the investigators for these EPS rating scales has been reported previously [223], with intraclass correlation coefficients of 0.80-0.91.

4.2.3   Statistical analysis

The analysis was designed to answer two main questions. First, does early antipsychotic response predict EPS risk? Second, do EPS occurring early in treatment predict treatment outcomes? Secondary analyses were also conducted to determine the roles of specific types of EPS and affective symptoms.

We calculated percent improvement on psychiatric scales by subtracting the week 2 or discharge score from the baseline score, and dividing by the baseline score. Since the minimum score on the BPRS is 18, we subtracted 18 from the raw scores before making this calculation.

Binary logistic regression was used to determine whether early BPRS improvement at week 2 predicted EPS. BPRS improvement was used as a continuous variable, without setting specific criteria for response or non-response. The presence of any

EPS at any point during hospitalization was the primary outcome measure. Age, sex, length of hospital stay, and maximum antipsychotic dose were included in the regression models. Patients with missing BPRS scores at the relevant time points were not included in this analysis. Secondary analyses were conducted using specific EPS (dystonia, parkinsonism, akathisia, or dyskinesia) as outcome measures. We also conducted a separate analysis excluding patients who experienced EPS within the first 2 weeks of treatment to determine whether early BPRS improvement in this subgroup predicted EPS beginning at later time points.

To assess the predictive power of early improvement in affective symptoms, percent improvement on HAM-D or HAM-A scores at week 2 was substituted for BPRS improvement in the regression models described above. Again, patients with missing HAM-D or HAM-A scores at the relevant time points were not included in these analyses.

The second major question we hoped to answer was whether EPS occurring early in treatment (by week 2) predicted treatment outcome. We investigated this possibility using linear regression with BPRS percent improvement at hospital discharge as the primary outcome measure. The presence of any EPS within 2 weeks of treatment initiation was included as a predictor variable, along with age, sex, length of hospital stay, and maximum antipsychotic dose. In secondary analyses, specific EPS were used as predictor variables, and HAM-D and HAM-A improvements were used as outcome variables.

To compare patients included in the analysis to patients excluded because of missing BPRS scores, we used independent t-tests for continuous variables and Fisher's exact test for categorical variables.

4.3   Results

4.3.1   Patients and treatment

A total of 199 antipsychotic-naive patients treated with haloperidol participated in the study. Of these patients, 63 were missing BPRS assessments at week 2, and were not included in the analyses of early response. Additionally, 41 patients were missing BPRS assessments at discharge, and were not included in analyses of psychiatric outcome. Characteristics of the patient sample are presented in Table 4.1. Comparisons are presented between patients with complete BPRS information and patients with missing BPRS information (either at week 2 or at discharge). No significant differences emerged between groups, although there was a trend towards a sex difference.

A number of patients treated with antipsychotics also received other medications during their hospital stay. In total, 63.5% used antiparkinsonian agents, 34.2% used lithium, 87.8% used benzodiazepines, 28.3% used antidepressants, and 13.6% used beta-blockers. Rates of supplementary medication use did not significantly differ between patients with missing BPRS scores and those with complete BPRS information. Additionally, 15.6% of patients used an antipsychotic other than haloperidol at some point during their hospitalization.

The majority of patients experienced >50% BPRS improvement at week 2 and >75% improvement at hospital discharge (see Table 4.2). Mean BPRS improvement was 55.6% (SEM=3.33) at week 2 and 76.6% (SEM=2.06) at hospital discharge. Patients also showed dramatic improvement on measures of affective symptomatology. At week 2, mean improvement on the HAM-D was 46.0% (SEM=5.26) and

Table 4.1: Sample characteristics

	Total (n=199)	Complete BPRS (n=115)	Missing BPRS (n=84)	p
Age (years)	40.52 (1.41)	42.49 (1.85)	37.82 (2.14)	.101
Sex				.062
Male	100	51	49	
Female	99	64	35	
Diagnosis				.288
Manic (bipolar)	55	28	27	
Delusional disorder	36	25	11	
Major depression with psychosis	34	21	13	
Schizophrenia	33	18	15	
Schizoaffective disorder	8	5	3	
Atypical psychosis	5	4	1	
Other	28	14	14	
Baseline BPRS	48.92 (0.83)	47.91 (1.08)	50.30 (1.28)	.155
Symptom duration (weeks)	25.32 (3.53)	25.71 (5.15)	24.80 (4.53)	.899
Length of hospitalization (days)	34.58 (1.48)	33.14 (1.69)	36.56 (2.64)	.255
Mean antipsychotic dose (CPZE)	200.67 (8.41)	200.80 (11.47)	200.50 (12.35)	.986

Continuous variables are presented as: mean (SEM)

CPZE: chlorpromazine equivalent dose in mg/day

p-values describe comparisons between groups with complete and missing BPRS information

Table 4.2: Number of patients experiencing different levels of BPRS improvement at week 2 and hospital discharge

	<0%	0 to <25%	25 to <50%	50 to <75%	75 to 100%
Week 2 (n=136)	8 (5.9)	13 (9.6)	28 (20.6)	40 (29.4)	47 (34.6)
Discharge (n=158)	2 (1.3)	5 (3.2)	14 (8.9)	37 (23.4)	100 (63.3)

Values within parentheses represent percentages.

mean improvement on the HAM-A was 45.0% (SEM=6.59). At hospital discharge, mean improvement on the HAM-D was 71.0% (SEM=4.16) and mean improvement on the HAM-A was 70.4% (SEM=4.36). This resulted in mean raw scores of 4.41 (SEM=0.41) on the HAM-D and 3.29 (SEM=0.38) on the HAM-A at hospital discharge.

Rates of EPS occurring during hospitalization are presented in Table 4.3. Of the 159 patients who experienced some form of EPS, 130 experienced EPS within the first 2 weeks of treatment. Among patients with no EPS during the first 2 weeks, 29 went on to experience EPS beginning later in treatment. Rates of EPS were not affected by the use of lithium, but they were somewhat higher in patients who used an antidepressant in addition to haloperidol during their hospitalization (Fisher's exact $p=.048$).

4.3.2   Early response

The first issue we investigated was whether early antipsychotic response (measured by BPRS percent improvement at week 2) predicted the occurrence of EPS at any point during hospitalization. A logistic regression model including BPRS improvement at week 2, age, sex, length of hospitalization, and maximum antipsychotic dose revealed that greater antipsychotic response at week 2 was associated with decreased rates

Table 4.3: Incidence of EPS during hospitalization in all patients and the subgroup of patients with no EPS by week 2 of treatment

	Any EPS	Akathisia	Parkinsonism	Dystonia	Dyskinesia
All patients (n=199)	159 (79.9)	108 (54.3)	100 (50.3)	73 (36.7)	20 (10.8)
No EPS by week 2 (n=69)	29 (42.0)	19 (27.5)	22 (31.9)	6 (8.7)	5 (7.2)

Values within parentheses represent percentages.

of EPS (Exp(B)=0.971, p=.004). To determine whether early response continued to predict EPS that began after week 2 of treatment, we performed an identical analysis excluding all patients with EPS occurring within the first 2 weeks. In this model, greater BPRS improvement at week 2 remained a significant predictor of reduced EPS (Exp(B)=0.960, p=.005). This result indicates that greater early response continues to be associated with reduced EPS risk even in patients who have not experienced EPS by week 2 of treatment. Maximum antipsychotic dose was not a significant predictor of EPS in either of these regression models. The addition of antidepressant use as a predictor in these models did not significantly contribute to the models' predictive value or affect the predictive value of early response. When we repeated this analysis excluding patients who received any antipsychotic other than haloperidol, strong early response continued to predict decreased rates of EPS (Exp(B)=0.970, p=.006), even when we additionally excluded all patients with EPS occurring within the first 2 weeks (Exp(B)=0.962, p=.014).

In secondary analyses, we used specific EPS as outcome measures. These analyses demonstrated that greater BPRS improvement at week 2 was associated with a decreased incidence of parkinsonism (Exp(B)=0.987, p=.028) and dyskinesia (Exp(B)=0.985, p=.025), but not dystonia (Exp(B)=1.000, p=.944) or akathisia (Exp(B)=0.996, p=.492). Maximum antipsychotic dose was not a significant predictor of EPS in any of these models. Comparisons of early improvement between patients who experienced EPS and those who did not are illustrated in Figure 4.1. The p-values in Figure 4.1 describe simple t-tests comparing patients with and without EPS. Increasing age was associated with decreased rates of dystonia (Exp(B)=0.958, p<.001) and akathisia (Exp(B)=0.964, p=.001).
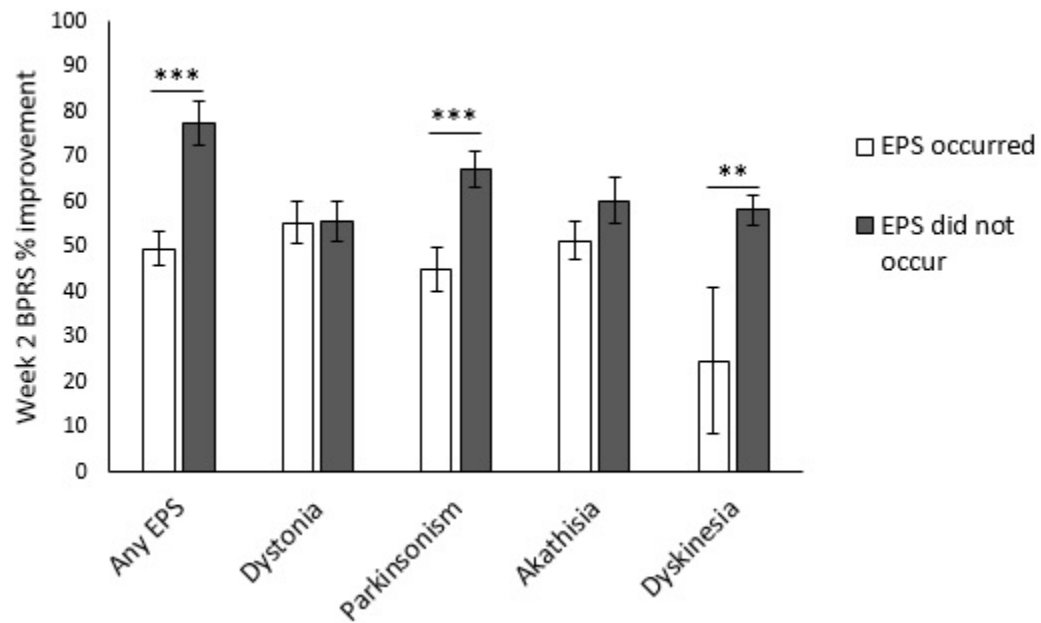
Figure 4.1: Early antipsychotic response in patients with or without EPS during hospitalization.
**: $p<.01$, ***: $p<.001$
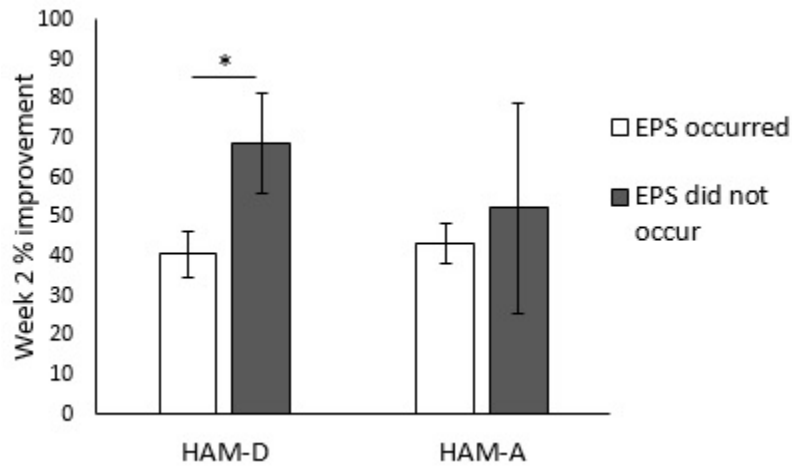
Figure 4.2: Early HAM-D and HAM-A improvement in patients with or without EPS during hospitalization.
*: $p<.05$

4.3.3 Early improvement in affective symptoms

We next assessed whether early improvement in HAM-D and HAM-A scores predicted EPS risk. The logistic regression model indicated that HAM-A improvement at week 2 did not predict risk of EPS during hospitalization (Exp(B)=1.000, $p=.975$). There was a trend towards significance for the predictive value of early HAM-D improvement (Exp(B)=0.988, $p=.094$). Early HAM-D and HAM-A improvements are compared between patients with and without EPS in Figure 4.2. Again, the p-values in Figure 4.2 describe t-tests comparing patients with and without EPS, not accounting for any other variables. With this simpler statistical approach, HAM-D improvement was significantly greater in patients without EPS, but this comparison should be interpreted conservatively. Neither HAM-D nor HAM-A early improvement predicted the incidence of dystonia, parkinsonism, akathisia, or dyskinesia specifically.
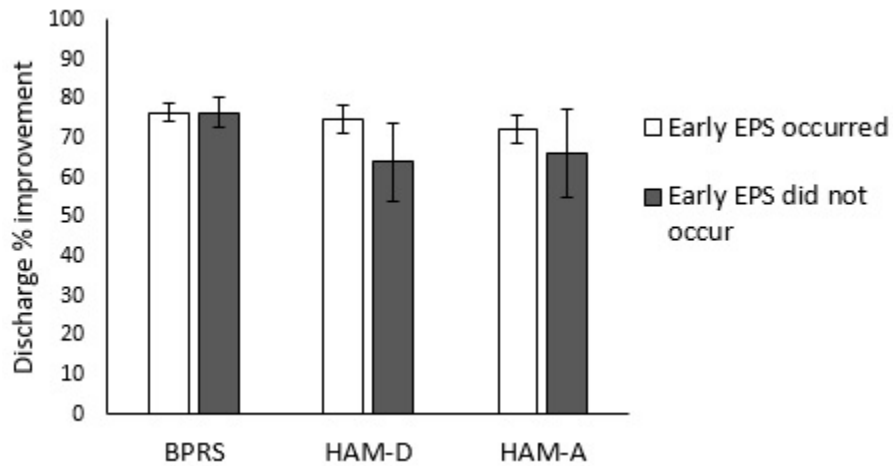
Figure 4.3: Improvement at hospital discharge in patients with or without EPS occurring within 2 weeks of starting antipsychotic treatment.

4.3.4   Early EPS

The second major issue we investigated was whether EPS specifically occurring early in treatment predicted psychiatric outcomes. The regression model indicated that the presence of any EPS by week 2 did not significantly predict BPRS percent improvement at hospital discharge (B=0.660, R^2=.068, p=.879). Similarly, early EPS did not predict HAM-D improvement (B=11.364, R^2=.048, p=.205) or HAM-A improvement (B=7.295, R^2=.108, p=.428). Improvement on psychiatric rating scales at hospital discharge is compared between patients with and without early EPS in Figure 4.3. Specific EPS occurring within the first 2 weeks of treatment also did not predict treatment outcome.

4.4   Discussion

In this study, we investigated two main issues: whether early response was associated with EPS risk, and whether early EPS predicted treatment outcomes. Most patients experienced dramatic symptom improvement, reflecting the striking effectiveness of antipsychotic medication in this patient population. We found that a greater early antipsychotic response was associated with a decreased incidence of EPS, particularly parkinsonism and dyskinesia. Importantly, this predictive value continued to apply to EPS that began after 2 weeks of treatment. We also found that dystonia and akathisia were more common in younger patients. Early HAM-A improvement did not predict EPS, but there was a non-significant trend suggesting that greater HAM-D improvement at week 2 was associated with a decreased incidence of EPS. Finally, EPS occurring within the first 2 weeks of treatment did not predict improvement on psychiatric rating scales at hospital discharge.

One possible interpretation of these results is that patients who experienced a poor early treatment response were subsequently treated with higher antipsychotic doses and developed EPS as a result. However, maximum antipsychotic dose was not a significant predictor of EPS in any regression analysis we conducted. This suggests that the relationship between early antipsychotic response and EPS reflects some aspect of the underlying illness rather than the specific treatment regimen.

Earlier work has associated poor clinical response with EPS [41, 62]. However, no previous studies have demonstrated that early antipsychotic response can predict a variety of EPS occurring later in treatment, thereby providing useful prognostic information that could guide clinical decision-making. For instance, patients at high risk may benefit from the use of prophylactic anticholinergic medication even if they

have not yet exhibited any signs of EPS by week 2 of treatment. The clinical utility of such an approach should be evaluated in future research.

A unique advantage of the current study is the use of an entirely antipsychotic-naive patient sample. While others have taken steps towards describing the relationship between early antipsychotic response and EPS risk [129, 238, 255], these studies primarily investigated patients with prior antipsychotic exposure. The use of antipsychotic-naive patients is important for several reasons. First, antipsychotic-induced EPS appear to be more common in first-episode psychosis patients and those with no prior antipsychotic exposure [169, 233], so it is in this population that assessing EPS risk is most relevant. Second, in patients with prior antipsychotic exposure, treatment decisions will be guided by their experience with previous antipsychotics. In antipsychotic-naive patients, no such experience is available, so the prognostic value of early antipsychotic response is more valuable. Third, in patients who have been treated with antipsychotics before the first study assessment, it is unclear whether a true "baseline" has been established. This lack of a baseline limits the interpretation of early treatment response. The lack of antipsychotic-naive patients may help to explain the conflicting results of earlier studies [129, 255].

Given the relationship between early response and EPS that we observed, it is somewhat surprising that early EPS did not predict treatment outcome. The existing literature is divided on this issue, with some studies reporting a relationship between EPS and treatment outcome [41, 239] and others failing to find any relationship [7, 134]. It is unclear whether these differing results reflect distinct patient populations, antipsychotic treatment regimens, or strategies for the management of EPS themselves. While EPS occurring early in treatment should undoubtedly be

closely monitored, the current data suggest that they do not necessarily predict a worse psychiatric prognosis.

The generalizability of the current results is limited to some extent by the fact that every patient was treated with haloperidol. This approach was chosen to limit the variability associated with different antipsychotic drugs, and because haloperidol was the antipsychotic most used in our study population during the time period in which these data were collected. However, since the predictive value of early response appears to differ between antipsychotics [85, 147], it is unclear to what extent the results observed here can be applied to patients treated with other drugs. The rates of EPS observed in the current study may also be affected by the frequent use of non-antipsychotic medications including anticholinergic drugs and benzodiazepines. Although anticholinergic medications were not given prophylactically, if they were given to treat emergent parkinsonism they could still affect subsequent EPS. Similarly, benzodiazepines given for other reasons may reduce the apparent incidence of antipsychotic-induced EPS. Future research may be required to understand whether the use of these supplementary medications interacts with the predictive value of early antipsychotic response, but the current results have the strength of external validity, and can likely be applied to many psychiatric populations where the use of supplementary medications is common.

Overall, this study of antipsychotic-naive, first-episode psychosis patients naturalistically treated with haloperidol further demonstrates the value of assessing early response after 2 weeks of treatment. In addition to predicting psychiatric outcomes, early response also provides clinically useful information about the risk of EPS, even

in patients who do not exhibit these side-effects within the first 2 weeks of treatment. This information has the potential to guide clinical decision-making in order to minimize the incidence of EPS in patients treated with antipsychotic medications.

Chapter 5

Can early antipsychotic response predict long-term treatment outcome?

Sean A. Rasmussen, Patricia I. Rosebush, Michael F. Mazurek

Abstract

Background: Early response within 2-4 weeks of beginning antipsychotic treatment is a powerful predictor of treatment outcomes in patients with first-episode psychosis. However, it is unclear whether this predictive value applies only to the acute treatment period or if it persists throughout long-term antipsychotic treatment, especially when the antipsychotic medication is changed during the treatment period.

Methods: We conducted follow-up assessments of 64 patients with first-episode psychosis an average of 25 months after they began antipsychotic treatment. Patients were initially randomized to receive either haloperidol or olanzapine, but their treatment after the acute hospitalization period was not controlled. The primary outcome measure was percent improvement on the Brief Psychiatric Rating Scale (BPRS) total score from baseline before patients received any antipsychotic medication. Patients were also assessed using the Hamilton Depression Rating Scale, Hamilton Anxiety Rating Scale, and Young Mania Rating Scale. Regression analyses were used to determine whether early response at 2 or 3 weeks predicted sustained response at long-term follow-up. We conducted secondary analyses to determine whether the predictive value of early response changed depending on whether patients were still being treated with an antipsychotic medication of the same class as their randomized medication. Finally, we assessed whether early response predicted rates of extrapyramidal side-effects (EPS) at long-term follow-up.

Results: Both treatment groups experienced a dramatic response to

antipsychotic medication that was generally sustained at the long-term follow-up assessment. Early response to haloperidol at 2 weeks predicted BPRS improvement on long-term follow-up whether patients were, at that time, being treated with a typical (p=.038) or an atypical (p=.011) antipsychotic drug. Early response to olanzapine at 3 weeks predicted improvement on follow-up when patients were still being treated with an atypical antipsychotic (p=.021), but not when they had been switched to a typical antipsychotic (p=.201). Olanzapine response at 2 weeks did not predict long-term outcome regardless of the antipsychotic treatment at follow-up. Rates of EPS did not differ between treatment groups. Early response did not predict rates of EPS at follow-up in the haloperidol or olanzapine groups.

Conclusion: These results demonstrate the long-term prognostic value of assessing early response to antipsychotic medication. Importantly, early response to haloperidol continued to predict long-term outcome regardless of whether patients switched antipsychotics or not. This was not the case for patients treated with olanzapine, suggesting that early olanzapine non-responders may experience more benefit from switching to an antipsychotic drug of a different class.

5.1   Introduction

Antipsychotic drugs have long been the cornerstone of pharmacological treatment for patients presenting with psychosis. Recently, early antipsychotic response - usually defined as improvement in psychiatric symptoms within 2 weeks of initiating treatment - has emerged as a strong predictor of eventual treatment outcome [128, 147]. However, the predictive value of early response has only been consistently demonstrated for treatment periods of 3-6 months [7, 129], with one study suggesting that strong early response may not predict better outcomes after 40 weeks of treatment [154]. Several studies have found that early antipsychotic response predicts symptomatic remission over a longer follow-up period of 2-4 years [59, 61], but these studies assessed early treatment response at 6 weeks rather than 2 weeks, which is not as useful with respect to optimizing antipsychotic treatment strategies as quickly as possible. While early antipsychotic response has the potential to predict treatment outcome in patients with first-episode psychosis, it remains an open question whether this predictive value persists over long-term treatment or whether it is only relevant to the initial acute treatment period. In this study, we investigate whether 2-3 week response to haloperidol or olanzapine predicts long-term treatment outcomes.

Other than early response, duration of untreated psychosis (DUP) is perhaps the most consistently reported predictor of longer-term response to antipsychotic treatment [59, 61, 160, 286]. In fact, a longer DUP continues to predict poor treatment outcomes even 10 years after the initial presentation of first-episode psychosis [279]. These results underscore the long-term importance of rapidly initiating effective treatment of psychotic symptoms. A number of other predictors of treatment outcome

have also been reported in the literature. More severe psychotic or positive symptoms at baseline appear to predict a favourable treatment outcome [49, 239], while negative and depressive symptoms at baseline may predict a poor treatment outcome [69, 235, 279]. Similarly, poor premorbid functioning [49, 214, 279] or antipsychotic-induced extrapyramidal side-effects (EPS) [41, 62, 221] predict a worse treatment outcome. While all of these factors are prognostically important, they do little to recommend the use of one antipsychotic over another.

Most research to date has focused on predicting therapeutic outcomes, with less attention to whether baseline clinical variables or early antipsychotic response can predict antipsychotic-induced side-effects. EPS are associated with specific genetic polymorphisms in dopamine receptors [70, 132] and dopamine receptor occupancy during antipsychotic treatment [118, 282], and it is possible that these same variables may influence the clinical response to antipsychotic medication. Several studies have reported that EPS are associated with a poor treatment response [41, 62]. Additionally, early antipsychotic response has been associated with reduced frequency of EPS occurring within the first 2 weeks of treatment [238] and less severe parkinsonism at week 12 of treatment [255], but the long-term predictive value of early response is unknown. It is possible that patients with a poor early antipsychotic response are more prone to EPS simply because their antipsychotic dosage is more likely to be subsequently increased. Besides poor early response, other variables associated with more EPS include affective symptoms [58, 244] and poor premorbid functioning [95]. Tardive dyskinesia is predicted by a longer duration of treatment, more severe psychiatric symptoms, and - most robustly - other EPS occurring earlier in treatment [180, 266, 267]. Once these side-effects have emerged, they can be persistent [268],

highlighting the importance of predicting and preventing their initial occurrence.

While the studies listed above provide valuable information about the likelihood of achieving a satisfactory treatment response or experiencing EPS, they are often limited due to a short follow-up period or a lack of antipsychotic-naive patients at baseline. Particularly when evaluating the predictive value of early response, it is useful to assess patients prior to any antipsychotic exposure. This allows a true baseline to be established so that subsequent assessments of symptom improvement are accurate.

Another issue that has not been thoroughly studied is the influence of switching antipsychotics on prognosis. If early non-response predicts that a patient will experience a poor long-term treatment outcome, does switching that patient to a different antipsychotic drug improve their outcome? Results from our group (Chapter 3) and others [6, 129] suggest that switching antipsychotics can improve treatment outcome in early non-responders. However, studies have suggested that the effect may be small, such that most early non-responders still experience a poor treatment outcome even after switching antipsychotics [6, 129]. Neither of these studies specifically investigated antipsychotic-naive patients or provided data on long-term follow-up. Moreover, these studies investigated patients switching between risperidone and olanzapine, both of which have high affinity for serotonin receptors [97], whereas treatment guidelines recommend switching to an antipsychotic with a substantially different receptor binding profile [152]. We have revisited the issue by looking at longer-term follow-up in patients who were at some point switched from a typical to an atypical antipsychotic or vice versa.

In the current study, we provide 1-3 year follow-up information on a sample of

first-episode psychosis patients who were assessed prior to any antipsychotic exposure and randomized to treatment with haloperidol or olanzapine. We investigated whether long-term treatment response or EPS during this follow-up period can be predicted based on early response. We also conducted a secondary analysis to determine whether this predictive value is affected by switching to an antipsychotic drug of a different class between the initial treatment period and the follow-up assessment.

5.2   Methods

5.2.1   Study design

We conducted a follow-up assessment of patients who were originally involved in a randomized controlled trial comparing treatment with olanzapine vs. haloperidol (see Chapter 3). All patients were initially hospitalized for first-episode psychosis, and were antipsychotic-naive at the time of their first assessment. The study was designed to investigate a naturalistic sample of all first-episode psychosis patients treated with antipsychotics, so patients were not excluded based on age, specific DSM diagnosis, or other criteria. While patients were initially randomized to receive either olanzapine or haloperidol, their treatment after the initial hospitalization was not systematically controlled. All patients were assessed twice weekly during their initial hospitalization, allowing us to determine the early response to antipsychotic treatment.

Patients were contacted and asked to participate in the follow-up assessment, which took place 1-3 years after their hospitalization for first-episode psychosis. All patients or substitute decision makers received a complete description of the study protocol and gave written informed consent, and all procedures were approved by the

McMaster University Research Ethics Board.

5.2.2 Assessments

During the assessment, information about current medications was gathered and a trained rater administered several psychiatric rating scales. These included the Brief Psychiatric Rating Scale (BPRS), Hamilton Depression Rating Scale (HAM-D), Hamilton Anxiety Rating Scale (HAM-A), and Young Mania Rating Scale (YMRS). In addition, a psychotic symptom subscale was calculated from the BPRS using the sum of scores on the following items: conceptual disorganization, suspiciousness, hallucinatory behaviour, and unusual thought content.

With respect to EPS, dystonia was diagnosed if a patient experienced sustained muscle contraction in one or more body parts that required treatment with benztropine. Akathisia was assessed using the Barnes Akathisia Rating Scale (BARS). Akathisia was considered to be present if a patients scored at least 2 (mild) on the global clinical assessment item of the BARS. Our parkinsonism scale was adapted from the motor examination section of the United Parkinson's Disease Rating Scale, and included assessments of facial and vocal expression, tremor, rigidity, bradykinesia, gait abnormalities, and writing. Based on these assessments, a global clinical impression of parkinsonism was scored from 1 (no parkinsonism) to 4 (severe parkinsonism). Parkinsonism was considered to be present if patients scored at least 2 (mild) on the global item. Dyskinesia was assessed using the Abnormal Involuntary Movement Scale (AIMS). Dyskinesia was considered to be present if a patient scored 3 (moderate) for movements of one body part, or 2 (mild) for movements in 2 or more body parts.

All assessments and rating scales administered at follow-up were identical to those administered during the initial hospitalization.

5.2.3   Statistical analysis

Improvements on the BPRS, HAM-D, HAM-A, YMRS, and BPRS psychotic symptom subscale were calculated as a percent improvement from baseline (prior to any antipsychotic treatment). For the BPRS total score and psychotic symptom subscale, the minimum score (18 and 4 respectively) was subtracted from the raw score before percent improvement was calculated. Independent samples t-tests were used to compare scores on the psychiatric rating scales and other continuous variables between the haloperidol and olanzapine treatment groups. Fisher's exact test was used to compare categorical variables such as rates of EPS between treatment groups.

The primary outcome measure was percent improvement on the BPRS total score at 1-3 year follow-up relative to baseline. A linear regression model including age, sex, and week 2 BPRS percent improvement was used to determine whether early improvement predicted antipsychotic response at long-term follow-up. Patients randomized to treatment with haloperidol or olanzapine were analyzed separately on an intention-to-treat basis. Secondary analyses were conducted using early improvement on the HAM-D, HAM-A, YMRS, and BPRS psychotic symptom subscale to determine whether early improvements on these measures predicted psychiatric outcomes (evaluated using the same measures) at 1-3 year follow-up. Since previous studies from our group have suggested that early response to olanzapine has better predictive value when assessed at 3 weeks rather than 2 weeks, we also investigated symptom improvement at this later time point as a predictor variable.

The second major question we investigated was whether the predictive value of early response changed depending on whether participants were switched to another class of antipsychotic between their initial randomization and the follow-up assessment. Patients were divided into two groups: those who were being treated with the same class of antipsychotic (typical or atypical) as when they were first randomized; and those who had been switched to a different class of antipsychotic. Patients who were not being treated with an antipsychotic at the follow-up assessment or who admitted to being non-compliant with their medication were not included in this analysis. The regression analyses described above were conducted separately for these two groups of patients to determine whether early BPRS improvement predicted sustained BPRS improvement at long-term follow-up.

The last major issue we investigated was whether EPS occurring at long-term follow-up could be predicted based on early BPRS improvement. We conducted binary logistic regression analyses with dyskinesia, akathisia, parkinsonism, dystonia, or any EPS at follow-up as outcome variables. Early improvement on the BPRS total score at 2 weeks (or 3 weeks for patients randomized to olanzapine treatment) was included as predictor variables along with age and sex. Overall rates of EPS during hospitalization or at follow-up were also compared between patients initially treated with haloperidol and those treated with olanzapine.

5.3 Results

5.3.1 Sample characteristics and treatment response at 1-3 year follow-up

Of the 94 patients included in the original study, 64 participated in the follow-up assessment. The other 30 patients either declined to participate or were lost to follow-up. Characteristics of this sample are described in Table 5.1. Note that the "olanzapine" and "haloperidol" groups refer to the original randomization of these patients, and do not reflect their medication at the time of follow-up. Similarly, the diagnoses listed in Table 5.1 are the diagnoses given during the initial hospitalization. The assessment was conducted an average of 2 years after each patient's initial hospitalization, although the exact time period ranged from 14-36 months. The two treatment groups did not differ in the severity of psychiatric symptoms.

Details of baseline symptom severity and early treatment response in this patient sample have been reported previously (see Chapter 3). A brief summary of the overall treatment response in each group is given in Table 5.2. Both groups demonstrated dramatic symptom improvement during the early treatment period, with the majority of patients experiencing greater than 50% BPRS improvement at week 2. This early treatment response was generally sustained on long term follow-up, at which point the majority of patients experienced greater than 75% BPRS improvement. One patient in the olanzapine group was missing their week 3 assessment. BPRS percent improvement was somewhat greater in the haloperidol group than in the olanzapine group at week 2, but was similar at week 3 and at follow-up (Figure 5.1). There was no significant difference among diagnostic categories with respect to BPRS total

Table 5.1: Sample characteristics at follow-up

	Olanzapine (n=32)	Haloperidol (n=32)	p
Age at hospitalization (years)	30.28 (1.42)	28.56 (1.68)	.437
Sex			1.000
Male	21	22	
Female	11	10	
Diagnosis			.154
Manic (bipolar)	12	19	
Schizophrenia	8	1	
Delusional disorder	3	2	
Atypical psychosis	4	4	
Major depression with psychosis	3	3	
Other	2	3	
Months since first admission	24.53 (0.76)	24.69 (0.82)	.890
Psychiatric symptom severity			
BPRS total	27.84 (2.16)	25.81 (1.38)	.431
HAM-D	7.59 (1.64)	6.91 (1.41)	.751
HAM-A	4.88 (1.14)	5.38 (1.11)	.754
YMRS	7.13 (2.22)	5.78 (1.50)	.617
BPRS psychotic subscale	7.69 (1.06)	6.63 (0.67)	.401

Continuous variables are presented as: mean (SEM)
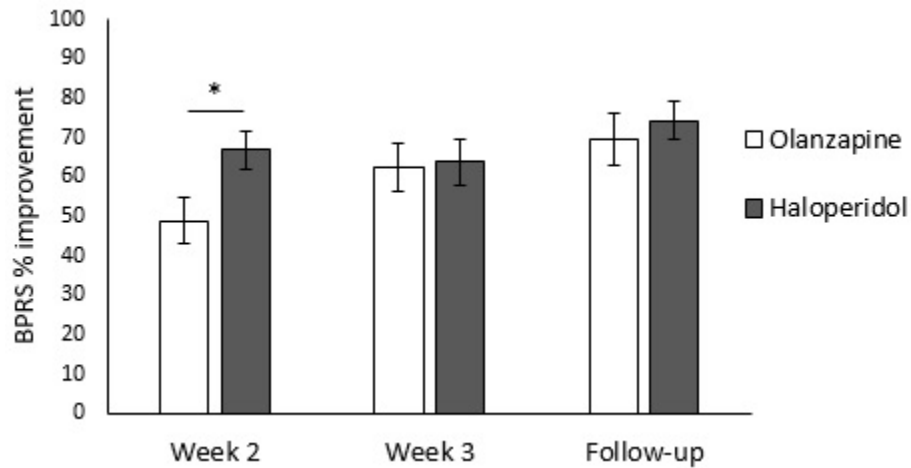
Figure 5.1: BPRS improvement during hospitalization and at long-term follow-up in groups initially randomized to treatment with olanzapine or haloperidol.
*: $p < .05$

percent improvement at follow-up ($p = .199$).

5.3.2   Predictive value of early response

Regression analyses accounting for age and sex were conducted to determine whether early improvement at week 2 of treatment predicted clinical status at 1-3 year follow-up. This analysis is presented in Table 5.3. For patients initially treated with haloperidol, percent improvement at 2 weeks predicted percent improvement at follow-up for the BPRS total score, BPRS psychotic symptom subscale, and the HAM-D. YMRS scores showed trend-level significance. For patients treated with olanzapine, week 2 improvement did not predict improvement at follow-up on any measure. We also assessed week 3 percent improvement as a predictor of treatment response at follow-up for patients treated with olanzapine (Table 5.4). Unexpectedly, early improvement still did not emerge as a significant predictor.

Table 5.2: Number of patients experiencing different levels of BPRS improvement

		<0%	0 to <25%	25 to <50%	50 to <75%	75 to 100%
Week 2	Olanzapine (n=32)	2 (6)	7 (22)	5 (16)	11 (34)	7 (22)
	Haloperidol (n=32)	1 (3)	1 (3)	5 (16)	10 (31)	15 (47)
Week 3	Olanzapine (n=31)	2 (7)	0 (0)	8 (26)	7 (23)	14 (45)
	Haloperidol (n=32)	3 (9)	0 (0)	7 (22)	6 (19)	16 (50)
Follow-up	Olanzapine (n=32)	2 (6)	2 (6)	4 (13)	4 (13)	20 (63)
	Haloperidol (n=32)	0 (0)	2 (6)	5 (16)	3 (9)	22 (69)

Values within parentheses represent percentages.

Table 5.3: Predictive value of improvement at week 2 for improvement at follow-up

	Measure	B	R^2	p
Olanzapine (n=32)	BPRS total	-0.074	.096	.726
	BPRS psychotic	-0.132	.116	.539
	HAM-D	0.003	.084	.989
	HAM-A	0.024	.037	.942
	YMRS	-0.010	.123	.967
Haloperidol (n=32)	BPRS total	0.584	.331	**.002**
	BPRS psychotic	0.656	.405	**<.001**
	HAM-D	0.602	.196	**.039**
	HAM-A	0.252	.063	.258
	YMRS	0.399	.131	.092

Table 5.4: Predictive value of improvement at week 3 for improvement at follow-up in patients treated with olanzapine

Measure	B	R^2	p
BPRS total	0.132	.109	.541
BPRS psychotic	-0.022	.097	.931
HAM-D	0.298	.167	.144
HAM-A	0.187	.046	.520
YMRS	0.077	.122	.733

5.3.3   The effect of switching antipsychotic drug class

Antipsychotic medications being used at the follow-up assessment are described in Table 5.5. We hypothesized that the poor predictive value of early olanzapine response may be related to the large proportion of patients who were no longer being treated with their randomized study drug at the follow-up assessment. To investigate whether switching to an antipsychotic drug of a different class affected the predictive value of early response, we conducted separate analyses for patients being treated with typical and atypical antipsychotics at the follow-up assessment (see Table 5.6). Patients who were not taking any antipsychotic medication at their follow-up assessment were not included in these analyses. For patients initially treated with haloperidol, week 2 percent improvement predicted percent improvement on the BPRS total score at follow-up regardless of whether they were treated with a typical or atypical antipsychotic. For patients initially treated with olanzapine, week 2 percent improvement did not predict percent improvement at follow-up regardless of whether they were treated with a typical or atypical antipsychotic. Week 3 olanzapine response predicted percent improvement at follow-up only when patients were still being treated with an atypical antipsychotic, but not if they had switched to a typical antipsychotic 5.7. This suggests that, for example, a patient who experienced minimal early improvement in response to olanzapine might go on to experience dramatic symptom improvement if they were switched to haloperidol.

5.3.4   Extrapyramidal side-effects

Rates of EPS did not differ between treatment groups during hospitalization or at follow-up (Table 5.8). The majority of patients in both treatment groups experienced

Table 5.5: Antipsychotics being used at 1-3 year follow-up for patients initially randomized to receive olanzapine or haloperidol

	Olanzapine (n=32)	Haloperidol (n=32)
Haloperidol	3	6
Loxapine	4	3
Fluphenazine	1	0
Olanzapine	6	2
Risperidone	5	3
Quetiapine	0	2
Clozapine	3	4
Risperidone + quetiapine	0	1
Olanzapine + clozapine	1	0
None	9	11

Table 5.6: The predictive value of week 2 antipsychotic response in patients being treated with typical or atypical antipsychotic drugs at follow-up

Randomized drug	Drug class at follow-up	Measure	B	R^2	p
Olanzapine	Typical (n=8)	BPRS total	-0.407	.478	.252
	Atypical (n=15)	BPRS total	0.137	.102	.526
Haloperidol	Typical (n=9)	BPRS total	0.759	.654	**.038**
	Atypical (n=12)	BPRS total	0.529	.734	**.011**

Table 5.7: The predictive value of week 3 olanzapine response in patients being treated with typical or atypical antipsychotic drugs at follow-up

Drug class at follow-up	Measure	B	R^2	p
Typical (n=8)	BPRS total	-0.506	.523	.201
Atypical (n=14)	BPRS total	0.424	.446	**.021**

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Table 5.8: Number of patients experiencing EPS during hospitalization and at follow-up

		Olanzapine (n=32)	Haloperidol (n=32)	p
Hospitalization	Any EPS	18	22	.439
	Dyskinesia	3	1	.613
	Akathisia	14	16	.802
	Parkinsonism	7	14	.109
	Dystonia	2	6	.257
Follow-up	Any EPS	8	8	1.000
	Dyskinesia	3	2	1.000
	Akathisia	4	2	.672
	Parkinsonism	3	4	.708
	Dystonia	1	0	1.000

EPS during their initial hospitalization, and 25% were experiencing EPS during their follow-up assessment. Early response was examined as a predictor of EPS at follow-up. Based on earlier results, week 2 BPRS improvement was used as a predictor for the haloperidol group and week 3 BPRS improvement was used for the olanzapine group. As shown in Table 5.9, early response did not predict the occurrence of EPS at follow-up in either treatment group.

5.4   Discussion

In this study, we investigated long-term treatment outcomes in a group of antipsychotic-naive patients with first-episode psychosis randomized to treatment with olanzapine or haloperidol. At the 2 year follow-up assessment, we observed dramatic symptom improvement from baseline in both treatment groups. For patients randomized to olanzapine, long-term clinical outcome could be predicted by the degree of early improvement at week 3, but only when patients were still being treated with olanzapine

Table 5.9: The predictive value of early response for EPS at follow-up

		Exp(B)	p
Olanzapine (n=31)	Any EPS	0.974	.072
	Dyskinesia	1.011	.640
	Akathisia	0.862	.138
	Parkinsonism	1.017	.521
	Dystonia	0.506	.996
Haloperidol (n=32)	Any EPS	1.010	.605
	Dyskinesia	0.989	.729
	Akathisia	0.977	.404
	Parkinsonism	1.047	.188
	Dystonia	-	-

or another atypical antipsychotic. For patients randomized to haloperidol, treatment response at 2 year follow-up could be predicted by early improvement at week 2 regardless of whether patients switched to another class of antipsychotic or not. Rates of EPS did not differ between groups, and EPS at follow-up were not predicted by early response in either treatment group.

Treatment outcomes and side-effects were not significantly different between groups. This is consistent with earlier studies demonstrating minimal differences between antipsychotic classes with respect to efficacy in treating psychosis [161] or rates of EPS [181]. However, the current results suggest that the long-term predictive value of early response differs between haloperidol and olanzapine, which may be particularly important for patients who do not show a satisfactory early response to antipsychotic treatment.

The association between early response and long-term outcome suggests that patients who respond poorly during the first 2-3 weeks of treatment will continue to show a poor response even after prolonged antipsychotic treatment. Previous studies have suggested that these early non-responders may benefit from being immediately

switched to another antipsychotic drug [129]. The current results support this suggestion by demonstrating that a poor early olanzapine response does not necessarily predict a poor long-term treatment outcome if patients are switched to a typical antipsychotic. This result allows for the possibility that early olanzapine non-responders may still show a satisfactory long-term response if they are switched to another antipsychotic, and reinforces recommendations that the initial antipsychotic should be switched to a drug with a distinct receptor binding profile [152]. However, our analysis is limited by the small number of patients who switched from olanzapine to a typical antipsychotic, so the non-significant relationship between early response and long-term response in these patients should be interpreted conservatively.

The more surprising result to emerge from these data is that early haloperidol response predicted long-term outcomes even when haloperidol-treated patients were switched to an atypical antipsychotic. While this does not imply that early haloperidol non-responders will not gain any benefit from switching antipsychotics, it does suggest that their early non-response will always remain relevant to long-term prognosis. It is unclear why haloperidol might perform differently than olanzapine in this respect. Once could speculate that since haloperidol has a relatively specific affinity for the dopamine D2 receptor [47, 97], which appears to be important to the mechanism of action of all antipsychotics [116], its efficacy might generalize to some extent to all other antipsychotics. Olanzapine, on the other hand, has relatively greater affinity for receptors of other neurotransmitters [47, 97]. Although the therapeutic importance of these other neurotransmitter systems is not well described, it is possible that olanzapine's mechanism of action relies on them to some extent, and therefore its efficacy may not generalize to other antipsychotics with distinct receptor binding

profiles.

Our analysis is limited by the grouping of antipsychotics into "typical" and "atypical" classes. Particularly within the group of atypical antipsychotics, there is considerable heterogeneity, such that grouping all of these drugs together is somewhat arbitrary. Rather than examining antipsychotic drugs by class, a more clinically informative (though possibly prohibitively complex) approach would be to examine the efficacy of switching to specific drugs following early non-response to specific first-line agents. Several earlier studies have utilized simplified versions of this approach and found that patients who discontinue a typical antipsychotic may benefit more from switching to olanzapine or quetiapine than to risperidone [257], while patients who discontinue an atypical antipsychotic may benefit more from switching to olanzapine or risperidone than to quetiapine or ziprasidone [256]. Clozapine is likely to be the most effective option [170], but this efficacy must be balanced against its risk of serious side-effects. While these studies are informative, they do not utilize early response as a predictor or as a tool for clinical decision making. Data has begun to accumulate to answer the question of whether early non-responders should be switched to another antipsychotic. However, the answer to this question is less useful without knowing *which* antipsychotic these patients should be switched to. Investigating this second issue is considerably more complex, but it is necessary in order to optimize the treatment of patients with first-episode psychosis.

Overall, these results demonstrate the lasting prognostic value of early antipsychotic response throughout multiple years of antipsychotic treatment. While the optimal time point at which to assess early response may differ between haloperidol and olanzapine, this assessment has long-term importance for both medications. These

results also make some predictions about the effectiveness of antipsychotic switch-ing, but ultimately much more research is required in order to develop treatment strategies for patients who do not show an early response to their initial antipsy-chotic. Without understanding which drug early non-responders should be switched to, it appears possible that these patients would see minimal benefit from the switch, thereby prolonging ineffective treatment.

Chapter 6

Predicting outcome in patients with first-episode psychosis treated concurrently with antipsychotic and antidepressant medications

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Abstract

Background: Many patients with first-episode psychosis experience prominent affective symptoms, and one strategy for treating these symptoms is to add antidepressant medications to ongoing antipsychotic treatment. Currently, there is limited evidence guiding the use of antidepressants in these patients. In particular, it is unclear whether early response after 2 weeks of antipsychotic/antidepressant treatment is a valuable predictor of treatment outcome.

Methods: In this observational study we investigated 115 antipsychotic-naive patients with first-episode psychosis throughout their initial hospitalization. All patients were treated with haloperidol. Within this sample, 33 patients received antidepressant medication, while 82 did not. Linear regression was used to determine whether early improvement on the Brief Psychiatric Rating Scale (BPRS) at week 2 or week 3 predicted improvement at hospital discharge, and whether this predictive value differed between treatment groups. In secondary analyses, we assessed whether early improvement on the Hamilton Depression Rating Scale (HAM-D) or Hamilton Anxiety Rating Scale (HAM-A) predicted improvement on these measures at hospital discharge. We also assessed whether the use of an antidepressant affected treatment outcome in the entire patient sample or in a subset with at least moderate depression at baseline.

Results: Most patients experienced dramatic improvement in psychiatric symptomatology, and the degree of improvement was not affected by the use of antidepressant medication. For patients who did not receive

antidepressant medication, week 2 BPRS improvement was a significant predictor of BPRS improvement at hospital discharge ($p<.001$). However, for patients who were treated with an antidepressant, week 2 BPRS improvement did not predict improvement at hospital discharge ($p=.618$). BPRS improvement at week 3 predicted improvement at hospital discharge whether patients were treated with an antidepressant ($p=.004$) or not ($p<.001$). Week 2 HAM-D improvement predicted HAM-D improvement at hospital discharge in patients who did not receive antidepressant medication ($p<.001$), but it did not predict treatment outcome in patients who received antidepressant medication ($p=.247$). The predictive value of early HAM-A improvement did not significantly differ between treatment groups.

Conclusion: It may be difficult to predict treatment outcome based on week 2 response in patients treated concurrently with antipsychotic and antidepressant medications. This disadvantage must be weighed against the limited clinical benefits of antidepressant use in patients with first-episode psychosis.

6.1   Introduction

First-episode psychosis is often accompanied by depression and anxiety. These symptoms are not restricted to specifically "affective" causes of psychosis (such as bipolar disorder or depression with psychotic features), but are also common in patients who are eventually found to have a schizophrenic illness [31]. Depression or anxiety can have a severe impact on the quality of life of patients with schizophrenia or other psychotic illnesses [101, 211], so physicians rightly place great emphasis on treating these symptoms. However, little evidence is currently available to guide the management of affective symptoms, particularly in patients experiencing their first episode of psychosis. One particularly important question is whether patients should receive an antidepressant medication in addition to antipsychotic treatment. To shed light on this issue, we investigated the potential to predict treatment outcomes in patients treated with a combination of antipsychotic and antidepressant medications based on their early response to treatment after 2 weeks.

The majority of research on antidepressants in schizophrenia has focused on their ability to improve persistent negative symptoms in chronic illness [227, 250]. It has even been reported that antidepressant augmentation improves positive and negative symptoms [108], although this finding has not been replicated by other groups. Results in this area are encouraging, but some researchers have suggested that the benefits of antidepressants are not large enough to be clinically meaningful [67]. Although there is overlap between negative symptoms and depression, it is important to examine depression as a unique entity. Regarding depressive symptoms specifically, some studies have shown that antidepressant augmentation is beneficial [271, 280],

while others have not shown any effect [102]. Studies in this field have mainly investigated patients with chronic schizophrenia, so it is unknown whether antidepressant augmentation is of any benefit in patients with first-episode psychosis.

Arguing against the use of antidepressants is the observation that many antipsychotics have shown efficacy in alleviating depressive symptoms [151, 186]. Even outside of schizophrenia, antipsychotic monotherapy has emerged as a viable treatment option in patients suffering from bipolar depression [68] or mania [126, 261]. Therefore, it is possible that antipsychotic treatment alone may be sufficient to treat affective symptoms in many patients, and antidepressant medication may be unnecessary. Additionally, there are some reports that antidepressant use in acutely psychotic patients may actually exacerbate psychosis [28, 137], prompting recommendations that antidepressant use should be delayed until active psychosis is controlled [208].

In general, treatment guidelines suggest that antidepressant treatment may be useful in schizophrenic patients with persistent depressive and negative symptoms, but further research is required in the area [14, 152]. Much less is known about the usefulness of antidepressants in first-episode psychosis patients. Despite the lack of concrete data, there is evidence that the use of antidepressants in first-episode schizophrenia patients is increasing [194]. The treatment of major depression with psychotic features has not been studied as thoroughly as the treatment of schizophrenia, but recent research has suggested that a combination of antidepressant and antipsychotic medications is most effective [64, 226]. Given these recommendations, it is important to understand how to evaluate treatment efficacy and predict outcomes in patients treated with antipsychotic/antidepressant combination therapy so that treatment strategies can be altered and optimized appropriately for each individual

patient.

The most useful predictor of outcomes in patients treated with antipsychotics appears to be early treatment response after approximately 2 weeks [128, 147]. Early non-responders are unlikely to ever achieve a satisfactory treatment response, so it may be beneficial to immediately switch them to another antipsychotic drug [129]. Similarly, it has become clear that the response to antidepressant medications can occur within the first 1-2 weeks of treatment [203, 265], and that early response or non-response can predict later treatment outcomes [120, 259, 260]. While these results have tremendous potential to shape treatment strategies, they have focused on patients treated with either antipsychotics or antidepressants, and have not examined patients treated with antipsychotic/antidepressant combination therapy. It is unknown whether early response can predict treatment outcomes in this important patient population.

In this observational study, we attempted to clarify whether antidepressant use in patients with first-episode psychosis alters the predictive value of early antipsychotic response. We chose to limit the analysis to patients treated primarily with haloperidol because there is evidence that different antipsychotics may have different antidepressive effects [186], and haloperidol was the most commonly used antipsychotic during the study period.

6.2   Methods

6.2.1   Study design

This was an observational study assessing consecutive patients who were admitted to hospital with first-episode psychosis between 1989-2002. During this period, all consenting patients admitted to the adult psychiatric inpatient service at one hospital in Hamilton, Ontario were prospectively followed to evaluate psychiatric outcomes. At the time of the study, our inpatient service was one of three university-affiliated facilities serving a catchment area of approximately 500 000. Patients were admitted to these facilities from a central emergency service based on bed availability. Upon hospital admission, patients and substitute decision makers were given a full description of the study and signed written informed consent. The only exclusion criterion was prior antipsychotic exposure. The patient sample and treatment protocol were naturalistic, and patients were not excluded from the study based on age, presumptive DSM diagnosis, or other factors. Complete assessments of each patient were conducted weekly until their discharge from hospital.

For the current study, we identified patients who were treated with haloperidol during their hospital stay. The use of antidepressants and other medications was permitted in accordance with usual clinical care. Patients were grouped according to whether or not they received an antidepressant medication in addition to an antipsychotic.

6.2.2   Assessments

Patients were assessed upon hospital admission, weekly throughout their hospital stay, and at hospital discharge. Overall psychiatric symptomatology was assessed using the Brief Psychiatric Rating Scale (BPRS). Affective symptoms were assessed using the Hamilton Depression Rating Scale (HAM-D) and the Hamilton Anxiety Rating Scale (HAM-A). At the first assessment, demographic information was also collected along with a complete medical and social history. The assessments were conducted by a psychiatrist (P.R.), a neurologist (M.M.), or a trained research nurse.

6.2.3   Statistical analysis

Baseline differences between the groups with or without antidepressant augmentation were compared using independent t-tests for continuous variables and Fisher's exact tests for categorical variables. We assessed whether the addition of antidepressant medication altered treatment outcome in patients with moderate depression at baseline (corresponding to a baseline HAM-D score of at least 17 [289]). Within this group, we used independent t-tests to compare percent improvement at hospital discharge on the BPRS, HAM-D, and HAM-A between patients who received antidepressant medication and those who did not.

To determine whether antidepressant use altered the predictive value of early antipsychotic response, we used linear regression accounting for age and sex. Percent improvement on the BPRS total score from baseline to hospital discharge was used as the primary outcome variable. The minimum BPRS score (18) was subtracted from the raw score to calculate percentages. Patients who were missing BPRS scores at week 2 or at discharge were excluded from the analysis. The regression analyses

were conducted in two steps. The first step included BPRS percent improvement at week 2 and antidepressant use as predictor variables (along with age and sex). The second step included the product term of week 2 BPRS percent improvement and antidepressant use to determine whether there was an interaction between these two variables. For this analysis, patients who did not receive antidepressant treatment were scored "0" while those who did receive antidepressant treatment were scored "1." All continuous variables were centered before being used in interaction analyses.

When a significant interaction was found between early response and antidepressant use, we assessed the two treatment groups independently to evaluate the predictive value of early response. Within each group, we used age, sex, and week 2 BPRS percent improvement as predictors in a linear regression model with BPRS percent improvement at hospital discharge as the outcome variable.

In secondary analyses, improvements on the HAM-D and HAM-A were used as outcome variables, and improvements on these measures at week 2 were used as predictor variables in place of the BPRS. The rest of the analyses were identical to that described above. Additionally, the predictive value of week 3 BPRS improvement was evaluated as before to determine whether this time point was more useful than week 2 for predicting treatment outcome.

Because the two groups differed in baseline symptom severity (especially with respect to HAM-D scores, see Table 6.1), we assessed whether baseline symptoms could influence the predictive value of early response regardless of antidepressant use. A regression analysis was run including age, sex, baseline BPRS score, week 2 BPRS improvement, and the product term of baseline BPRS and week 2 BPRS improvement. BPRS improvement at hospital discharge was used as the outcome

measure. Identical analyses were run using the baseline HAM-A or HAM-D score in place of the baseline BPRS score.

Finally, we conducted a brief descriptive analysis of patients who experienced increased BPRS scores at week 2 to determine whether antidepressant use in patients with first-episode psychosis might sometimes exacerbate psychiatric symptomatology.

6.3 Results

6.3.1 Patients and treatment

During the study period, we identified 201 previously antipsychotic-naive patients who were treated with haloperidol. Of these patients, 86 did not have BPRS assessments at week 2 or at hospital discharge, and could not be analyzed. In the final sample of 115 patients, 33 received antidepressant medication during their hospitalization, while 82 did not. 17 patients were treated with tricyclic antidepressants, and 16 were treated with selective serotonin reuptake inhibitors. Characteristics of the patient sample are presented in Table 6.1. Unsurprisingly, the two groups differed on baseline affective symptom severity and the distribution of psychiatric diagnoses.

6.3.2 Overall symptom severity

The majority of patients in both groups experienced $\geq 50\%$ BPRS improvement at week 2 and $\geq 75\%$ BPRS improvement at hospital discharge (Table 6.2). At week 2, BPRS improvement was significantly less in patients who received antidepressant treatment (mean=43.51%, SEM=9.41) than in patients who did not (mean=62.20%,

Table 6.1: Sample characteristics

	No antidepressant (n=82)	Antidepressant (n=33)	p
Age (years)	40.61 (1.99)	47.15 (4.07)	.155
Sex			1.000
Male	36	15	
Female	46	18	
Diagnosis			<.001
Manic (bipolar)	28	0	
Delusional disorder	18	7	
Major depression with psychosis	3	18	
Schizophrenia	16	2	
Schizoaffective disorder	5	0	
Atypical psychosis	4	0	
Other	8	6	
Baseline BPRS	49.18 (1.29)	44.76 (1.90)	.064
Baseline HAM-D	17.23 (1.04)	25.16 (1.48)	<.001
Baseline HAM-A	11.35 (0.94)	15.62 (1.25)	.014
Untreated symptom duration (weeks)	25.31 (6.71)	26.61 (7.43)	.908
Length of hospitalization (days)	32.02 (2.05)	35.91 (2.91)	.299

Continuous variables are presented as: mean (SEM)
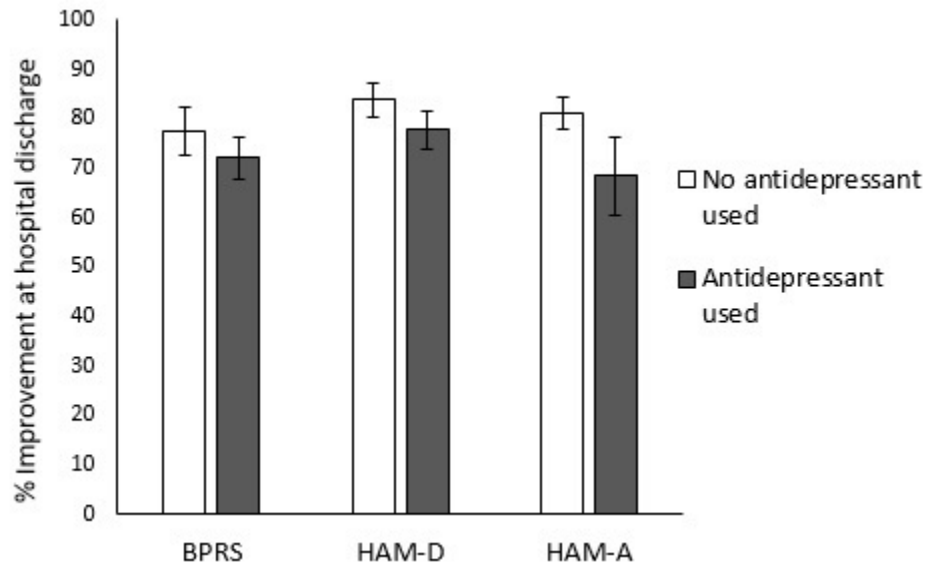
Figure 6.1: Improvement at hospital discharge in patients with at least moderate depression at baseline.

SEM=3.53, p=.024). However, at hospital discharge there was no significant difference in BPRS improvement between patients who received antidepressant treatment (mean=73.67%, SEM=3.45) and those who did not (mean=78.04%, SEM=3.22, p=.431). There were no significant differences in symptom improvement at week 2 or hospital discharge between patients with a primary diagnosis of major depressive disorder and those with other diagnoses.

Among patients with moderate depression at baseline (HAM-D $\geq$17), we assessed whether the addition of antidepressant medication had any influence on improvement at hospital discharge. This analysis included 26 patients who were treated with an antidepressant and 39 who were not. As shown in Figure 6.1, no significant differences were observed.

Table 6.2: Number of patients experiencing different levels of BPRS improvement at week 2 and hospital discharge

		<0%	0 to <25%	25 to <50%	50 to <75%	75 to 100%
Week 2	Antipsychotic only (n=82)	3 (3.7)	8 (9.8)	15 (18.3)	20 (24.4)	36 (43.9)
	Antipsychotic/antidepressant (n=33)	4 (12.1)	3 (9.1)	7 (21.2)	11 (33.3)	8 (24.2)
Discharge	Antipsychotic only	2 (2.4)	3 (3.7)	6 (7.3)	15 (18.3)	56 (68.3)
	Antipsychotic/antidepressant	0 (0.0)	1 (3.0)	3 (9.1)	10 (30.3)	19 (57.6)

Values within parentheses represent percentages.

Table 6.3: Interaction between antidepressant use and early BPRS improvement at week 2 predicting BPRS improvement at hospital discharge

Regression model	Variable	B	R^2	p
Step 1	Week 2 BPRS % improvement	0.224	.160	**<.001**
	Antidepressant use	0.074		.989
Step 2	Week 2 BPRS % improvement	0.425	.228	**<.001**
	Antidepressant use	-1.266		.810
	Interaction	-0.371		**.003**

6.3.3   Early response

We investigated the relationship between early response, antidepressant use, and treatment outcome using linear regression models that also accounted for age and sex. Results from this analysis are shown in Table 6.3. Week 2 BPRS improvement was a significant predictor of BPRS improvement at hospital discharge, but there was a significant interaction between week 2 BPRS improvement and antidepressant use, indicating that the predictive value of early response changed depending on whether patients received antidepressant medication.

We analyzed the two groups separately, and found that week 2 improvement was a significant predictor of improvement at hospital discharge for patients who did not receive antidepressant medication (B=0.408, R^2=.272, p<.001). However, for patients who received antidepressant medication, week 2 BPRS improvement did not predict improvement at hospital discharge (B=0.035, R^2=.020, p=.618).

We also investigated the predictive value of week 3 BPRS improvement. As shown in Table 6.4, BPRS improvement at week 3 was a significant predictor of BPRS improvement at hospital discharge, and this did not change depending on whether patients were treated with antidepressants. When the treatment groups were analyzed separately, week 3 BPRS improvement was a significant predictor of BPRS

Table 6.4: Interaction between antidepressant use and early BPRS improvement at week 3 predicting BPRS improvement at hospital discharge

Regression model	Variable	B	R^2	p
Step 1	Week 3 BPRS % improvement	0.555	.508	<**.001**
	Antidepressant use	-1.052		.863
Step 2	Week 3 BPRS % improvement	0.606	.523	<**.001**
	Antidepressant use	-0.337		.956
	Interaction	-0.251		.173

improvement at hospital discharge for patients who were treated with an antidepressant (B=0.355, R^2=.477, p=.004) and for those who were not (B=0.606, R^2=.527, p<.001).

6.3.4   Affective symptoms

In secondary analyses, we investigated the relationship between early improvement in affective symptoms and antidepressant use. The analysis of HAM-D improvement is presented in Table 6.5. As before, this analysis showed that early improvement on the HAM-D predicted HAM-D improvement at hospital discharge, but that this predictive value was affected by the use of antidepressants. We analyzed the two treatment groups separately and found that early HAM-D improvement predicted treatment outcome in patients who did not receive antidepressant treatment (B=0.740, R^2=.535, p<.001), but not in those who received antidepressant treatment (B=0.118, R^2=.222, p=.247)

We also investigated the predictive value of early improvement in HAM-A scores (Table 6.6). Early HAM-A improvement predicted HAM-A improvement at hospital discharge, but the interaction with antidepressant use was not significant.

Table 6.5: Interaction between antidepressant use and early HAM-D improvement predicting HAM-D improvement at hospital discharge

Regression model	Variable	B	R^2	p
Step 1	Week 2 HAM-D % improvement	0.664	.491	**<.001**
	Antidepressant use	7.680		.429
Step 2	Week 2 HAM-D % improvement	0.718	.519	**<.001**
	Antidepressant use	11.844		.221
	Interaction	-0.571		**.020**

Table 6.6: Interaction between antidepressant use and early HAM-A improvement predicting HAM-A improvement at hospital discharge

Regression model	Variable	B	R^2	p
Step 1	Week 2 HAM-A % improvement	0.436	.362	**<.001**
	Antidepressant use	1.300		.903
Step 2	Week 2 HAM-A % improvement	0.457	.369	**<.001**
	Antidepressant use	1.868		.862
	Interaction	-0.214		.361

6.3.5   Influence of baseline symptom severity

Because the treatment groups differed on baseline symptomatology, we assessed whether baseline symptom severity interacted with early response in the prediction of treatment outcome. Separate regression analyses demonstrated no significant interactions between week 2 BPRS percent improvement and baseline BPRS score (B=-0.002, R^2=.178, p=.810) or baseline HAM-A score (B=-0.013, R^2=.141, p=.183). However, there was a significant interaction between baseline HAM-D score and week 2 BPRS percent improvement (B=-0.014, R^2=.180, p=.047), suggesting that higher baseline HAM-D scores were associated with a weaker relationship between BPRS improvement at week 2 and at hospital discharge. BPRS percent improvement at hospital discharge was used as the outcome measure in all of these regression models.

6.3.6   Patients who experienced worsening psychiatric symptomatology at week 2

We investigated whether any acutely psychotic patients in this sample experienced worsening psychiatric symptomatology during concurrent treatment with antipsychotic and antidepressant medications. We identified 7 patients in total who experienced increased BPRS scores at week 2, 4 of whom were receiving antidepressant medication (Table 6.7). Interestingly, all 4 of these patients showed remarkable improvement at hospital discharge despite their striking deterioration early in treatment. Patients like these clearly contribute to the poor predictive value of week 2 response in the group receiving antidepressant medication. Unfortunately, it is not clear from these data whether the increasing severity of psychiatric symptoms in these patients was directly caused by the use of antidepressant treatment.

6.4   Discussion

In this study, we evaluated the predictive value of early antipsychotic response in first-episode psychosis patients who also received antidepressant medication. Early response after 2 weeks of treatment was a poor predictor of treatment outcome at hospital discharge in these patients. However, treatment outcome could be predicted by improvement at week 3. In patients who did not receive antidepressant medication, early antipsychotic response at week 2 was a robust predictor of treatment outcome. This difference between groups was apparent whether we examined overall psychiatric symptom severity or depressive symptoms specifically. The addition of antidepressant medication did not alter psychiatric outcome in these patients, even

Table 6.7: Hospital course of patients who experienced worsening BPRS scores at week 2

Case	Antidepressant used	Day antidepressant started	Measure	Baseline score	Week 2 score	Discharge score
1	TCA	4	BPRS	43	59	20
			HAM-D	38	26	0
2	TCA	10	BPRS	36	61	23
			HAM-D	22	21	5
3	TCA	1	BPRS	43	45	27
			HAM-D	-	23	10
4	SSRI	1	BPRS	33	50	20
			HAM-D	15	19	0
5	None	-	BPRS	41	45	27
			HAM-D	13	-	-
6	None	-	BPRS	35	38	31
			HAM-D	11	12	5
7	None	-	BPRS	37	42	48
			HAM-D	3	11	13

TCA: Tricyclic Antidepressant, SSRI: Selective Serotonin Reuptake Inhibitor

when we restricted the sample to only those patients with at least moderate depression at baseline. However, given the observational nature of the study, this result should be interpreted conservatively.

As clinical studies continue to demonstrate the predictive value of early antipsychotic response, it may become more common for physicians to re-evaluate antipsychotic treatment plans after 2 weeks. If patients show a poor response to antipsychotic treatment during this time, they could benefit from immediately being switched to a different antipsychotic drug [129]. However, it will be important to identify subgroups of patients for whom this is a less effective strategy. The current results suggest that patients being treated with both antipsychotic and antidepressant drugs may be one such subgroup. If early response is a poor predictor of treatment outcome in these patients, then it may be prudent to persist longer with the initial treatment plan before switching medications. Alternatively, an effective strategy may be to treat patients with only an antipsychotic for the first 2 weeks, at which point early antipsychotic response could be assessed. If depressive symptoms had not shown substantial improvement by week 2, an antidepressant could be added. This strategy of antidepressant treatment following poor early antipsychotic response is consistent with recent treatment guidelines [14, 152]. Avoiding the early use of antidepressants is even more appealing in light of the current results showing that antidepressant treatment is not associated with improved outcome and may lead to early symptom worsening in a small subset of patients. It was not clear in our patients whether early symptom worsening was specifically caused by antidepressant use, but given previous reports of this phenomenon [28, 137], the possibility should be considered.

The major findings of this study build upon earlier results in the field. In an analysis of response trajectories in schizophrenic patients, Stauffer et al. [254] found that patients with a delayed response or an unsustained early response had more severe depressive symptoms at baseline. This finding suggests that early response would be a poor predictor of treatment outcome in those patients, but it is unclear to what extent the response trajectories described in schizophrenic patients apply to other psychotic diagnoses. Additionally, it is unclear whether the poor predictive value of early response is due to depressive symptomatology, antidepressant medication itself, or a combination of these factors.

This uncertainty highlights one of the major difficulties in interpreting the current results. Due to the observational study design, the two treatment groups were composed of fundamentally distinct patient populations at baseline. The distribution of primary diagnoses is especially notable, in that almost every patient diagnosed with schizophrenia or a manic episode of bipolar disorder did not receive an antidepressant. This approach allows us to describe the utility of assessing early response in patients treated with antidepressants and antipsychotics in a clinical setting. However, it does not allow us to determine whether the poor predictive value we observed was due to antidepressant treatment or due to patient characteristics (for example, higher HAM-D scores at baseline). Since early response to antidepressant monotherapy is a valuable predictor of treatment outcome [120, 259, 260], it would be surprising if antidepressant augmentation was solely responsible for undermining the predictive value of early antipsychotic response in the current study.

This study suggests that early antipsychotic response at week 2 may not be a useful predictor of treatment outcome in patients with first-episode psychosis who are

judged clinically to require adjunctive treatment with an antidepressant. While the precise mechanism of this finding remains unclear, it may be prudent for physicians to wait at least 3 weeks before they deem their initial treatment strategy ineffective, or to avoid the use of antidepressants completely during the early treatment of first-episode psychosis. Further research is required to understand the extent to which this finding is related to the treatment protocol (including different combinations of antipsychotics and antidepressants) or baseline patient characteristics.

Chapter 7

Discussion

The assessment of early antipsychotic response is the best tool currently available for predicting treatment outcome in patients with first-episode psychosis. Despite its clear clinical utility, there are many uncertainties about what early response can and cannot predict, and how it should be appropriately used in clinical settings. The objective of the preceding chapters has been to raise - and begin to answer - several important questions about early antipsychotic response. First, how does the predictive value of early response differ among antipsychotic drugs? Second, can early response also predict changes in affective symptoms that accompany psychosis? Third, is early response related to the side effects of antipsychotic drugs as well as the therapeutic effect? Fourth, for how long does the predictive value of early response persist? Fifth, does the utility of early antipsychotic response change when patients are also taking other medications? Sixth, does the utility of early antipsychotic response differ depending on a patient's symptoms at baseline? Seventh, does the appropriate time at which to assess early response change depending on the specific medications that a patient is receiving? Eighth, and perhaps most importantly, how

should a patient's treatment change if he is identified as an early non-responder? While the data presented here have not provided exhaustive answers, they have shed some light on all these issues.

The results presented in Chapter 3 suggest that the appropriate time point at which to assess early response differs between antipsychotic drugs. In addition, it appears that early improvements in depressive and manic symptoms have good predictive value, while early improvements in anxiety symptoms do not. Chapter 4 indicates that poor early antipsychotic response is associated with an increased risk of EPS, but early EPS do not necessarily predict eventual treatment outcome. Chapter 5 demonstrates the long-term predictive value of early response up to approximately 2 years after the initiation of antipsychotic treatment. Chapter 6 suggests that the predictive value of early response at week 2 is poor in patients who receive both antidepressant and antipsychotic treatment. However, week 3 response was a significant predictor of treatment outcome in these patients. Our studies were not specifically designed to address the issue of antipsychotic switching, but they nevertheless provided some compelling results on this subject. Our exploratory analyses suggest that patients with a poor early response benefit from being switched to another antipsychotic (Chapter 3), and the long-term benefits appear to be greatest when they are switched to an antipsychotic with a different receptor binding profile (Chapter 5). The data in Chapter 3 build upon previous results demonstrating the poor predictive value of olanzapine response at week 2 [85, 147], but the main results of the other chapters are being demonstrated here for the first time. These studies are the first to assess the value of switching antipsychotics based on early response in patients with first-episode psychosis.

The patient samples included in these studies differ from those of previous studies in two important ways. First, we included patients with any psychotic diagnosis, rather than limiting the samples to only those patients with schizophrenia, schizoaffective, or schizophreniform disorder. This approach provides a clinically representative sample, and also acknowledges the diagnostic uncertainty and instability associated with first-episode psychosis [127, 230, 242]. Second, we included only patients who were antipsychotic-naive when they entered the study. Unlike the approach of studies that permit brief (or extended) prior antipsychotic exposure, our approach allows us to establish a true baseline to which early response can be compared. Additionally, patients experiencing their first antipsychotic exposure are both more responsive to treatment and more susceptible to EPS [60, 169], so it is useful to specifically study this population. The unique characteristics of these patients are made clear in Chapter 3, where we demonstrate that the standard response criteria widely used in other studies are unable to identify non-responders in our patient sample.

Our analytical approach also differed from previous studies. Earlier studies have dichotomized antipsychotic response using consensus-based thresholds to identify responders and non-responders [147, 231]. Since these thresholds are generally based on chronic schizophrenia patients with prior antipsychotic exposure, they are not appropriate for our sample. Instead, we treated symptom improvement in response to antipsychotic treatment as a continuous variable. Similar to previous studies, we focused our analysis on overall psychiatric symptom severity (assessed by the BPRS in our case). However, we also included measures of affective symptomatology. These measures - particularly the HAM-D - appear to convey useful prognostic information.

Some previous studies have attempted to control or account for the influence of

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other prognostic factors such as substance use disorders, treatment adherence, and psychiatric diagnosis, to the extent that such control is possible. While all of these factors are known to predict various aspects of treatment outcome, they may be impossible to accurately evaluate in patients experiencing first-episode psychosis. This is a weakness of many methods for predicting treatment outcome, but may in fact be a strength of early antipsychotic response. Variables that impact long-term treatment response may reasonably be expected to impact early response as well, such that early response "captures" the influence of these variables even when they cannot be accurately assessed. In cases where a history of substance abuse or a precise DSM diagnosis cannot be ascertained, early antipsychotic response still provides useful prognostic information. The previous chapters provide highly generalizable results by not excluding or categorizing patients based on these other prognostic factors. However, future studies focused on describing mechanistic explanations for antipsychotic response may benefit from identifying the influence of early response independent of other prognostic variables.

The results of these studies have several implications for how future research on early antipsychotic response should be conducted. First, future studies may benefit from including measures of affective symptomatology. Affective symptom severity is an important aspect of treatment outcome, and our results suggest that early HAM-D improvement may have long-term predictive value even when early BPRS improvement does not.

Second, it is clear that the thresholds of 20% and 50% improvement to define early improvement and treatment response respectively should not be applied to all patients. Just as these values were not appropriate for the patients in our studies,

there are undoubtedly other subsets of psychotic patients for whom different thresholds are required. Our results suggest that early response may be influenced by the use of specific antipsychotic medications, other medications being taken concurrently, baseline symptom profile, or prior antipsychotic exposure. Others have reported that early response is affected by baseline positive symptoms, illness duration, and early EPS [238]. The currently popular approach of attempting to define a single threshold for all psychotic patients is laudable in its attempt to provide simple, clinically useful information, but it may not reflect the complexity of the issue at hand.

Third, future studies should avoid pooling data from patients receiving different antipsychotic medications as previous studies have [7, 128, 255], since it is becoming increasingly clear that early response differs between drugs. One particularly relevant example is the upcoming SWITCH study [91]. This study identifies early non-responders to olanzapine or amisulpride at 2 weeks and randomizes them to either remain on their initial antipsychotic or switch to the other antipsychotic. When the results are published, they will be the most definitive answer yet provided about whether early antipsychotic switching benefits early non-responders. However, the apparently poor predictive value of early olanzapine response at week 2 has profound implications for how the results of the SWITCH study are interpreted.

The results of the studies presented here also provide some guidance on the clinical management of patients with first-episode psychosis. Above all, the current data emphasize the importance of assessing early antipsychotic response. By demonstrating that the predictive value of early response extends for multiple years after treatment initiation and can also be applied to EPS, we have increased the usefulness of this assessment. Future research is required to understand how best to manage early

non-responders, but at the very least this information allows patients and physicians to better understand the future trajectory of psychotic illnesses and prepare for the most likely outcomes. However, our results also suggest the use of caution when interpreting early response. We have identified multiple groups of patients for whom antipsychotic response at 2 weeks does not predict treatment outcome, and other similar groups will likely be identified by future research. Until the variables affecting early response are described in much more detail, there is room for optimism even in the face of early non-response.

There is still some disagreement in the literature about the use of week 2 response to assess early improvement. For example, Schennach et al. [236] argue that long-term outcome after 1 year of treatment in first-episode schizophrenia patients is better predicted by week 6 response. The authors suggest that patients who are assessed for early response before week 6 may be subjected to "an unnecessary change of treatment." However, the authors do not actually conduct any analysis of drug switching, and they do not weigh the cost of unnecessary drug changes against the cost of undergoing prolonged treatment with an ineffective antipsychotic medication. It is self-evident that waiting longer after the initiation of antipsychotic treatment before assessing early improvement will yield better long-term predictive value, but the cost of this waiting period is significant, and must be factored into the calculation. Unfortunately, the cost of waiting to assess early response has not been quantified, and neither has the benefit of early antipsychotic switching. Until these values are clarified, it will be difficult to place sensitivity and specificity analyses of early response thresholds into any meaningful context. Put another way, it is not yet clear how the benefit of identifying non-responders (and presumably switching them to

another medication) compares to the cost of failing to identify non-responders (and subjecting them to a longer period of ineffective treatment) or incorrectly identifying non-responders (and unnecessarily switching their medications early in treatment). Therefore, it is impossible to know how to correctly value sensitivity and specificity in the establishment of early response times and thresholds.

It should be noted that antipsychotic switching is not the only available option for early non-responders. Studies have investigated the efficacy of high-dose strategies [6] and antipsychotic combinations [86] in patients who do not respond to their initial antipsychotic treatment. Results in these studies have been modest, but somewhat encouraging. Antipsychotic switching seems to be the most desirable option in order to avoid the side-effects associated with high-dose antipsychotics and long-term polypharmacy, but the relative merit of these different approaches is worth exploring.

There are several limitations to the studies presented in the preceding chapters, most of which have been discussed previously. However, two broad limitations are particularly important in the interpretation of the current results, and deserve special mention. The first is that, although we demonstrate that the standard early response threshold of 20% improvement is not appropriate in our patient sample, we do not propose alternative, more useful thresholds. There are two reasons for this. First, the appropriate threshold value likely varies among patients depending on a number of baseline variables that are not yet understood. Second, without knowing how patients stand to benefit from being identified as non-responders, it is not clear how sensitive the early response threshold should be. Because we do not provide a categorical system for dividing patients into groups of responders and non-responders, there is no simple way for clinicians to apply the current results to their patients. However, since

the optimal treatment approach for early non-responders has not yet been described, it is not clear how clinicians would use this information anyway. Our results suggest that switching antipsychotics based on early non-response would be helpful, but this answer is far from conclusive. In addition, it may be the case that patients with different degrees of early response would benefit from different treatment approaches (for example, dose increases for moderate responders versus drug switching for poor responders). Ongoing research should continue to explore these relationships before fixating on a method of dichotomizing patients into groups of responders and non-responders.

The second major limitation of the current results is that we do not provide a true explanation for treatment response. Although we explore the ways in which early response predicts treatment outcome, we certainly do not suggest a causal link between these two variables. Rather, it seems most likely that both early response and treatment outcome could be predicted based on some combination of underlying patient characteristics. However, despite a great deal of effort, these characteristics have not yet been fully described. In this sense, predicting treatment outcome based on early response is inherently an imperfect method, akin to looking at shadows of the variables that have a *direct* impact on antipsychotic response. Early response is important only to the extent that it is the best option currently available. If further research were to discover a method of predicting which patients would respond to which antipsychotic drugs before treatment initiation, it would immediately render the assessment of early response obsolete. Unfortunately for patients with first-episode psychosis, such a discovery does not appear to be imminent.

Since the introduction of chlorpromazine, the treatment of psychosis has been

marked by slow, incremental steps forward (and occasionally backward). Similarly, the research presented here does not revolutionize the treatment of psychotic patients. Until the mechanisms of psychosis and antipsychotic treatment are understood, perhaps the best we can hope for is to reduce the length of time that patients spend receiving ineffective medication. Assessing early antipsychotic response is the best method for achieving this goal, and improving our understanding of how to use this method will undoubtedly improve clinical treatment strategies. By investigating the limits of what early antipsychotic response is capable of predicting, this thesis represents another incremental step toward the effective treatment of patients with psychosis.

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