THE EFFECT OF ADJUNCTIVE PSYCHOTHERAPY ON HEALTH RELATED OUTCOMES AMONG PATIENTS WITH SCHIZOPHRENIA

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ABSTRACT

CHI-CHUAN WANG: The Effect of Adjunctive Psychotherapy on Health Related Outcomes among Patients with Schizophrenia
(Under the direction of Dr. Joel F. Farley)

Although antipsychotics have been recommended as the first-line treatment for schizophrenia, many patients are not adherent to their treatment regimens, which leads to worse treatment outcomes. As a result, psychotherapy has been suggested as an adjunctive treatment to improve patients' treatment outcomes. However, the effectiveness of psychotherapy on treatment outcomes is unclear. Therefore, the purpose of this study is to assess whether using psychotherapy in addition to pharmacotherapy improves medication persistency, reduces the risk of hospitalization, and lowers treatment costs among Medicaid populations.

2001 to 2003 Medicaid Analytic eXtract (MAX) files were used as a data source to identify patients with schizophrenia who received antipsychotic treatments. The use of psychotherapy was dichotomized as users versus non-users. Medication persistency was measured as the number of days to discontinuation after the initiation of antipsychotic use. Number of hospitalizations and treatment costs were measured as continuous variables. Factors associated with psychotherapy use were evaluated by a logistic model, and medication persistency between psychotherapy users and non-users was compared by Cox proportional-hazard regressions. Hospitalizations and treatment costs were analyzed by a hurdle model and generalized linear models respectively.

The prevalence of psychotherapy use was about 16% in this study. Older and Black patients were less likely to receive psychotherapy, while patients with comorbid depression were more likely to receive psychotherapy. We found psychotherapy only improved patients' persistency within the first two months of follow-up. The use of psychotherapy was not found to be associated with hospitalizations, but it was associated with higher treatment costs.

In conclusion, our results suggest that the rate of psychotherapy use was low and that most patients only received psychotherapy for a short period of time. These results may explain the short-term effect of psychotherapy on medication persistency as well as the null association between psychotherapy use and hospitalizations. Since the effect of psychotherapy may not appear until a patient receives sufficient psychotherapy treatment, clinicians should better incorporate psychotherapy into treatment courses. In addition, Medicaid policy makers should make sure that patients with schizophrenia have adequate access to psychotherapy in order to achieve the best treatment outcomes.

DEDICATION

This dissertation is dedicated with my love and memory to my father,

Zuo-Ci Wang

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LIST OF ABBREVIATIONS

CBT	Cognitive-Behavioral Therapy
CCI	Charlson Comorbidity Index
CI	Confidence Interval
CPT/HCPCS	Curricular Practical Training/Healthcare Common Procedure Coding System
DSM	Diagnostic and Statistical Manual
EPS	Extrapyramidal Symptoms
GLM	Generalized Linear Model
ICD	International Classification of Diseases
IL	Illinois
IV	Instrumental Variable
KS	Kansas
LATE	Local Average Treatment Effect
LR	Likelihood Ratio
MDD	Major Depressive Disorder
MEPS	Medical Expenditure Panel Survey
MN	Minnesota
MSA	Metropolitan Statistical Area
NAMCS	National Ambulatory Medical Care Survey
NC	North Carolina
OR	Odds Ratio
PDC	Proportion of Days Covered

SD	Standard Deviation
2SRI Model	Two-Stage Residual Inclusion Model

CHAPTER 1: INTRODUCTION

1.1 Overview

With the introduction of antipsychotics, especially atypical antipsychotics, patients with schizophrenia are able to better control their symptoms and thus reduce the burden of the disease. However, due to intolerable side effects and other environmental barriers, non-adherence is a common phenomenon among patients receiving antipsychotic treatments, which often leads to worse outcomes. Even for patients who are adherent to their regimen, they are likely to have some residual symptoms or experience a future relapse.[1] In order to achieve the best treatment outcomes, it is now generally agreed that psychosocial interventions should be used in combination with pharmacological treatment.[2, 3] Because there is limited information available about the effectiveness of adjunctive psychotherapy, the objective of this study is to assess whether using psychotherapy with the addition of pharmacotherapy improves patients adherence and outcomes.

1.1.1 Epidemiology of Schizophrenia

Schizophrenia affects about 24 million people in the world, and more than 50% of them do not receive appropriate treatments.[4] In the United States, the 12-month prevalence of schizophrenia was estimated to be 0.51% in 2002, with the highest prevalence in the Medicaid population (1.66%).[5] The estimated life-time incidence was 15.2 per 100,000

persons, with a wide range from 7.7 to 43 per 100,000 persons.[6] The estimations of prevalence and incidence of schizophrenia can vary by the definition of schizophrenia, study settings, and study populations.[2, 6, 7] Generally, males have a higher incidence rate than females (incidence rate ratio: 1.4).[6] Most patients with schizophrenia experience the onset of schizophrenia between ages of 16 to 30 years, with an earlier onset age among males.[2, 6, 7] In 2006, approximately 32% of patients with schizophrenia were covered by Medicaid, 22% by Medicare, and 16% by private insurance. About 30% of the patients do not have any insurance coverage.[5]

1.1.1.1 Disease Burden of Schizophrenia

Patients with schizophrenia usually have a shorter life expectancy.[2, 7, 8] Life expectancy for patients with schizophrenia is 12 to 15 years less than the general population.[2] Although suicide causes some deaths, the increased risk of mortality is mainly due to physical causes. Patients with schizophrenia often are more likely to engage in risky behaviors (e.g. poor diet, smoking, and substance abuse) and often suffer from comorbid conditions caused by medication side effects (ex. weight gain and metabolic syndrome). In addition, most patients have limited access to health care,[2, 6] which could also lead to worse health outcomes and higher risks of mortality.

Patients with schizophrenia are mentally or functionally impaired. In the U.S., schizophrenia accounts for about 20% of Social Security disability days and 20% to 30% of homelessness.[9] Because of the impairment, even though most patients want to work, only 10% to 20% of patients are employed.[1, 2] Patients may lose their self-esteem or suffer from stigma because of their disability.[10] Furthermore, schizophrenia not only affects patients

individually, it also has a significant effect on patients' families and communities. Caring for a patient with schizophrenia requires substantial time and money, and coping can be stressful. Family members may need to break their routine life, reduce their social activities, and confront stigma. It has also been found that living with the mentally ill is associated with a negative health impact for family and caregivers.[10]

Besides functional impairment, patients with schizophrenia also face a high risk of relapse. According to a review conducted by Hogarty and Ulrich in 1998, without adequate medication treatment, the relapse rate for patients with schizophrenia may be over 50%, and the risk of relapse increases with the number of subsequent relapses (up to 87% for patients with five or more previous relapse episodes).[11] With antipsychotic treatment, the annual relapse rate can be reduced to around half of the original rate, but the relapse rate is still around 40% for outpatients.[11] Wiersma et al. followed 82 patients with schizophrenia for 15 years in the Netherlands. They found that about 27% of patients experienced a complete remission over a period of 15 years, 50% of patients experienced a partial remission, and at least 10% of patients remained psychotic.[12] About two-thirds of the participants had at least one relapse, and most relapses occurred within one to two years after a patient remitted from a previous relapse.[12, 13] In addition, patients were more likely to become chronically psychotic after each subsequent relapse.[12]

Schizophrenia also creates large financial burdens on individuals and society. Despite its low prevalence, schizophrenia accounts for 2% to 3% of overall health care costs in the U.S.[9] Weiden and Olfson estimated the inpatient costs of schizophrenia relapse using the 1986 Inventory of Mental Health Organizations and General Hospital Mental Health Services data. According to their study, short-term inpatient services for multi-episode

schizophrenia patients costed approximately $2.3 billion, and average inpatient costs per patient was estimated as $9,252 (in 1993 dollars).[13] The estimated cost for rehospitalization within two years after discharge was $2 billion, with 60% ($1.2 billion) caused by a lack of narcoleptic treatment efficacy and 40% ($705 million) by non-adherence.[13] The total costs associated with schizophrenia was around $32.5 billion in 1990, with $17.3 billion in direct costs.[14] Compared to the general population, the estimated costs in 2002 for schizophrenia were $62.7 billion higher, with $22.7 billion for direct medical care costs, $32.4 billion for indirect health care costs, and $7.6 billion for indirect societal costs.[15]

1.1.1.2 The Non-adherence Problem

Because antipsychotics have been shown as the most effective way to reduce symptoms of schizophrenia, it has been recommended as the first-line treatment.[16-21] With slightly different pharmacological mechanisms (discussed in section 2.1.3), two types of antipsychotics, typical and atypical antipsychotics, have been introduced. Typical antipsychotics are usually known for the unpleasant motion side effects such as extrapyramidal symptoms, while atypical antipsychotics are often associated with weight gain and metabolic syndrome.[7, 22, 23] Because atypical antipsychotics produce fewer intolerable side effects, it is generally believed that atypical agents should be better tolerated than typical agents.

However, non-adherence is still a common phenomenon in patients with schizophrenia. The estimated adherence rate for antipsychotic treatment varies by study design and population. Generally, around 40% of patients with schizophrenia do not adhere to treatment regimens, with estimates ranging from 20% to 89%.[13, 24-28] After discharge or

therapy initiation, the adherence rate is around 50% within one year and may be as low as 25% within two years.[29] The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) also found that the all-cause discontinuation rate rises to 74% for atypical antipsychotics within 18 months.[30]

One major cause of non-adherence is intolerable side effects, such as extrapyramidal symptoms, weight gain, and glucose or lipid abnormalities.[31, 32] With the introduction of atypical antipsychotics, there is hope that patients' adherence is going to be improved because of fewer extrapyramidal side effects. Although there is evidence showing that atypical antipsychotics improve patients' adherence than the typical antipsychotics,[26] some studies do not find significant improvement on patients' adherence comparing atypical to typical antipsychotics.[24, 30, 33] Therefore, simply switching patients from typical to atypical antipsychotics may not solve the non-adherence problem.

1.1.1.3 The Role of Psychotherapy

Although the efficacy of antipsychotics is proven, it is usually not sufficient for patients to reach full remission or functional recovery with medication treatment only. The relapse rate for patients continuing with medication treatment was found to be 30% to 40% during the first year of discharge.[11] In addition, as discussed above, many patients do not follow their regimens. As a result, psychotherapy has been recommended to be applied adjunctively with pharmacotherapy to maximize the treatment effect and improve patients' functioning.[16, 18-21]

Because patients with schizophrenia often have a variety of symptoms and functional impairments, managing the disease can be complicated for both patients and clinicians, and

non-pharmacological treatment is often required. Many trials have evaluated the efficacy of different types of psychosocial interventions, but how these interventions can be applied as psychotherapy has not been standardized clinically. Psychotherapy contains a broad range of patterns from emotional consultation to behavior modification and can be provided by a variety of types of providers, such as psychiatrists, psychologists, and social workers. Even within a given type of psychotherapy, different treatment orientations and/or modalities can be applied. For example, individual psychotherapy can simply contain medication tailoring, or it can incorporate some behavioral modification techniques. Despite the heterogeneity of psychotherapy, it can be roughly categorized into three groups: individual, family, and group psychotherapy.

Even though the designs and outcomes of psychosocial interventions vary across studies, overall, evidence has shown that psychotherapy can reduce clinical symptoms and relapses, improve patients' social functioning, and reduce stress in families. Psychosocial interventions have also been shown to improve medication adherence, enhance understanding about the disease and treatment, and help patients and their family members to develop better coping strategies.[1, 34-38] In addition, psychotherapy has been suggested as a strategy to optimize treatment outcomes and reduce side effects either before or after antipsychotic switching.[39, 40] It is generally agreed that patients can benefit from adjunctive psychotherapy in addition to the standard antipsychotic treatment.[41-45]

1.1.2 Significance of the Study

Many studies have evaluated the effects of different types of psychosocial interventions at trial levels (i.e. efficacy). To the author's knowledge, no studies have

examined the effects of psychotherapy on a population basis (i.e. effectiveness). The present study fills this gap by providing real-world information regarding the utilization and the effectiveness of psychotherapy.

Few studies document the utilization patterns and factors associated with the use of psychotherapy among patients with schizophrenia at a population level.[46-48] Using 1991 Medicare claims data, Dixon et al. evaluated the costs and use of outpatient visits among Medicare-eligible patients with schizophrenia and found that individual therapy was used more often than group or family therapy.[46] The study also showed that African Americans were less likely to receive individual therapy than Caucasian patients. Patients with dual eligibility (both Medicare and Medicaid) or aged 65 or older were less likely to receive individual therapy but more likely to receive group therapy compared to those enrolled in Medicare only. When considering all psychosocial services together (individual therapy, group therapy, family therapy, and psychiatric somatotherapy), it was found that patients with a higher number of other comorbid mental conditions, drug abuse, or dually enrolled in Medicaid were more likely to receive ambulatory psychosocial services, while males, African Americans, and patients aged 65 or older were less likely to receive these services.[46]

Although outpatient psychotherapy use has been documented using a claims data set, our study can be an improvement of the previous research. Since the previous study was conducted using data in 1991, the results may be outdated. In addition, the previous study focused on Medicare population. Given that Medicare covers both the elderly and permanently disabled groups, patients in the study can have different characteristics than the general schizophrenia populations. For example, patients with schizophrenia who were older than age 65 and became eligible for Medicare were more likely to be patients who had better

controlled disease and thus live longer, while the younger patients are more likely to be those with severe symptoms and became permanently disabled. As a result, this study likely contained a highly selected group of patients with schizophrenia, which limits the generalizability. By using 2001 to 2003 Medicaid claims data, the current study provides updated information about psychotherapy use, and by constructing this study on a younger cohort covered by Medicaid, our results can be better generalized to the general schizophrenia population.

Another study evaluating guideline concordance of schizophrenia treatment found that around 37% of patients were not fully adherent to their treatments. Almost all of the patients in the study received antipsychotic treatments, and 69% of them received psychosocial treatment.[48] However, upon further examination of the different types of recommended psychotherapy, less than half of the patients received guideline recommended psychosocial treatments (e.g. percentage of patients receiving family education, individual or group therapy, or cognitive/behavioral treatment). Around 40% of patients received both pharmacotherapy and psychotherapy.[48] Given the study was conducted on 151 psychiatrist-reported patients, the generalizability is limited. In addition, the data was gathered from psychiatrists' report of treatment in the past 30 days, which may not fully capture certain services use. Our study will improve the generalizability by using a large data set and an 18-month follow-up period, which allows us to better capture the use of psychotherapy.

In addition, Olfson and colleagues conducted a study comparing the treatment patterns between schizoaffective disorder and schizophrenia among the Medicaid population. They found more than 85% of patients received antipsychotics, while only 23% of patients with schizoaffective disorder and 13% of patients with schizophrenia received psychotherapy.

The estimated medication adherence rate in this study was around 60% for both groups.[47] However, this study has a short follow-up period (6 months) and does not further distinguish the type of psychotherapy used. Our study provides a more comprehensive picture of psychotherapy use by implementing a longer follow-up period (18 months) and document the type of psychotherapy use. Instead of using a prevalent cohort as in Olfson et al.'s study, the new-user design is applied in our study, which allows us to better capture the patterns of psychotherapy use from the initiation of antipsychotic treatment to the end of 18-month follow-up. In addition, the current study has a broader array of adherence measurement (including both persistency and switching) than the previous study (which measured adherence as a dichotomous outcome), and our study evaluates mental health related hospitalizations as well as treatment costs rather than outpatient visits. Finally, the main focus of our study is to compare the health service utilization between psychotherapy users and non-users controlling for antipsychotic adherence, which is different from the purpose of Olfson et al.'s study.

As mentioned before, although the efficacy of psychosocial interventions have been evaluated, the effectiveness of these interventions remains unclear.[41] Because most studies that have examined the influence of psychotherapy on medication adherence have been conducted as clinical trials with small sample sizes, the generalizability of these results is limited. A large-scale study also allows us to generate population-level estimates of medication persistency, hospitalization rates, and mental-health related treatment costs (i.e. the effectiveness) among patients with schizophrenia. To our knowledge, this is the first study that evaluates the effectiveness of psychotherapy on antipsychotic persistency, mental-health related hospitalizations, and treatment costs. Because we are unable to extract

remission rates or disease severity information from claims, adjunctive psychotherapy is considered effective if it improves persistency, reduces hospitalization rates, or reduces treatment costs. Many studies were conducted before atypical antipsychotics were widely adopted, which entails a different practice environment than that of today. Given the change in clinical practice, it is necessary to re-evaluate the effectiveness of adjunctive psychotherapy, especially in combination with the second-generation agents. Finally, although psychotherapy is recommended as an adjunctive therapy for patients switch their medication treatments, to the authors' knowledge, the effectiveness of psychotherapy on antipsychotic switching has not been evaluated. It is therefore important to evaluate the effectiveness of psychotherapy for further evidence.

This dissertation work investigated the role of psychotherapy on medication adherence on a larger scale using Medicaid claims data. Because most studies evaluated the effectiveness of psychotherapy on clinical outcomes, little is known about the influence of psychotherapy on health care costs or service use. This study expands the existing literature by investigating the influence of psychotherapy on schizophrenic health care costs and utilization. Findings from this study can improve our understanding of the effectiveness of psychotherapy and can help to inform clinicians and policy makers about the most appropriate treatment options to use for schizophrenic patients.

1.1.3 Aims and Hypotheses

Assessing the clinical use of adjunctive psychotherapy as well as its effect on medication adherence, inpatient service utilization, and costs provides more evidence about

the effectiveness of psychotherapy. Specifically, this dissertation addresses these issues by accomplishing the following aims:

Aim 1: To describe the patterns and factors associated with the use of adjunctive psychotherapy.

Descriptive statistics was first applied to evaluate the prevalence of psychotherapy and types of psychotherapy being used. Two groups were compared: patients who received both pharmacotherapy and psychotherapy versus those who received psychotherapy only. Because our samples were composed of incident antipsychotic users (who were newly on their medication treatment), these patients were less likely to have received psychotherapy before the initiation of their pharmacological treatment. Since previous psychotherapy use may affect medication use behaviors, for the incident cohort, patients who had a record of psychotherapy use before the initiation of antipsychotic treatment were dropped. In addition to frequency and types of psychotherapy use, time of psychotherapy initiation was also evaluated during the follow-up periods. Types of psychotherapy were categorized as individual therapy, family therapy, and group therapy using the *Current Procedural Terminology* and *Healthcare Common Procedure Coding System* codes.

Patient characteristics (age, gender, and ethnicity), types of initial antipsychotic treatment (atypical/typical), and other physical as well as mental comorbid conditions were also summarized in Aim 1. Besides descriptive statistics, regression models were performed to assess factors associated with psychotherapy use, and the results were used to inform the following analyses (Aim 2 and Aim 3). Due to limited samples of adjunctive psychotherapy users, patients with different types of psychotherapy were only compared descriptively. All

psychotherapy users were combined as one group and compared with patients who did not receive psychotherapy in a logistic regression model.

Aim 2: To assess whether the use of adjunctive psychotherapy in addition to pharmacotherapy improves patients' adherence to antipsychotic treatments.

Aim 2 used medication persistency as a measure of adherence. We compared time to medication discontinuation (i.e. medication persistency) between patients who received adjunctive psychotherapy and who did not. It is hypothesized that patients who received adjunctive psychotherapy are better adherent to their treatment regimens than those who did not have any psychotherapy.

For incident antipsychotic users, survival analysis technique was performed to evaluate time from the first prescription to all-cause discontinuation or the end of follow-up. In order to best reflect a clinically meaningful discontinuation, two definitions were applied to assess medication discontinuation: a gap longer than 15 or 30 days. This study only evaluated adherence to oral antipsychotic agents but not injectable agents due to limited sample size (N=101). Patients with injectable antipsychotic agents were excluded from the analysis.

In addition to the main analysis, a sub-analysis was performed to evaluate the association between the use of psychotherapy and antipsychotic switching. It is hypothesized that patients receiving psychotherapy have a lower likelihood of medication switching. Patients were considered as switchers if they initiated a second antipsychotic agent within 30 days after the end of supply from the first antipsychotic agent. A sensitivity analysis was conducted using a 15-day window to define medication switching. A logistic regression was used to assess the likelihood of antipsychotic switching between users and non-users.

Aim 3: To assess whether receiving adjunctive psychotherapy in addition to pharmacotherapy reduces hospitalization rates and health care costs.

Aim 3 assessed the influence of using adjunctive psychotherapy on the use of inpatient services and health care costs. It is hypothesized that patients who used adjunctive psychotherapy have fewer inpatient admissions and lower total health care costs compared to those who do not receive psychotherapy. For hospitalizations, a hurdle model was applied to compare the rate of hospitalization between the two groups during the follow-up. Because the distribution of health care costs was highly skewed, a generalized linear model was used to compare total health care costs between the treatment and control groups.

In Aim 2 and Aim 3, patient characteristics can systematically differ between those who receive psychotherapy and those who do not due to observable and/or unobservable confounders. The observable confounders were adjusted by using the multiple regression techniques as addressed above. For the unobservable factors, instrumental variable (IV) technique was applied to reduce potential unobservable confounding, or the endogeneity issue, between treatment and control groups. By applying IV with a two-stage regression model, we should be able to eliminate both observed and unobserved cofounding and estimate the local average treatment effect (i.e. the "marginal patients": who can be treated with or without psychotherapy depending on their providers' preference).

1.1.4 Summary

Although not highly prevalent, schizophrenia has contributed substantial functional and financial burdens to patients and society. Because pharmacotherapy alone often has a

limited effect on functional recovery, and many patients do not adhere to their regimens, psychotherapy has been recommended as an adjunctive treatment to improve health outcomes. However, due to the lack of sufficient evidence for the effectiveness of psychotherapy, clinicians and policy makers may be reluctant to provide psychotherapy to patients, which could lead to lower quality of care.[9, 49] In contrast to previous studies, which have examined the efficacy of psychotherapy, this study evaluated the effectiveness of psychotherapy at a population level using Medicaid claims data. By contributing more evidence about the effectiveness of psychotherapy, findings from this study will help clinicians to better determine the clinical use of psychotherapy. Additionally, this study assessed treatment costs associated with the implementation of adjunctive psychotherapy. With this study being conducted based on Medicaid populations, both the effectiveness and costs information will be valuable for policy makers to better determine the allocation of resources and guide Medicaid coverage decisions.

CHAPTER 2: LITERATURE REVIEW

2.1 Schizophrenia: the Disease and the Treatments

2.1.1 Symptoms and Diagnosis of Schizophrenia

Due to the broad spectrum of symptoms and signs shared by other mental disorders, it is not easy to diagnose schizophrenia. Common signs of schizophrenia include positive (psychotic) symptoms, negative symptoms, and cognitive and/or behavioral impairments (Table 2.1).[2, 7, 17, 50, 51] Positive symptoms appear to reflect an extraction from reality, and the symptoms are usually presented in a form of false belief (delusions) or false perception (hallucinations).[7, 17, 50, 51] Negative symptoms involve loss of emotional or behavioral expressions. Three negative symptoms defining schizophrenia are immobile facial appearance (affective flattening), diminished quality and thoughts of speech (alogia), and lack of ability to initiate or follow through with plans (avolition).[7, 17, 50, 51] Cognitive/behavioral impairments include disorganized thinking, disorganized behavior, and catatonic motor behaviors.[7, 17, 50, 51] Because cognitive/behavioral impairments also appear as deviations from normal functions, these symptoms are sometimes categorized as positive symptoms.[17]

Table 2.1.Clinical Symptoms and Features of Schizophrenia

Cognitive system or subsystem	Schizophrenic symptom
	Positive
Perception	Hallucinations
Inferential thinking	Delusions
Language	Disorganised speech/formal thought disorder
Behavioural monitoring	Disorganised/bizarre/catatonic behaviour
	Negative
Conceptual fluency	Alogia
Emotional expression	Affective blunting
Experiencing pleasure	Anhedonia
Volition	Avolition

Source: Andreasen NC. Symptoms, signs, and diagnosis of schizophrenia. *Lancet.* Aug 19 1995;346(8973):477-81.

Two major diagnostic systems for schizophrenia currently used are the *International Classification of Disease, Tenth Edition* (ICD-10)[51] and the *Diagnostic and Statistical Manual, Fourth Edition, Text Revision* (DSM-IV-TR).[17] Despite some differences, the ICD and DSM have similar diagnostic criteria. Both the ICD and DSM identify similar symptoms and features for the diagnosis of schizophrenia, and both require the symptoms to be present for a long period of time to rule out temporary psychotic symptoms or conditions. In addition, to make a diagnosis of schizophrenia, both the ICD and DSM require the schizophrenic symptoms are not induced by substance abuse or other medical conditions (e.g. frontal lobe trauma or other mood disorders).[17, 50, 51] One difference between the two systems is that the ICD requires the symptoms to persist for at least one month, while the DSM requires the symptoms to be present for at least six months. Another difference is that DSM also requires social/occupational dysfunction during the onset of disturbance, while ICD does not.[17, 50, 51] Table 2.2 summarizes the diagnostic criteria from the two systems. Differential diagnosis of psychotic disorders is provided in Appendix 1, and detailed diagnostic criteria for ICD and DSM are provided in Appendices 2 and 3.

Table 2.2. ICD and DSM Diagnostic Criteria for Schizophrenia

Characteristic symptoms	Require at least two from a group of positive and negative symptoms (eg, delusions, hallucinations, formal thought disorder, affective blunting); if the symptom is considered to be typically "schizophrenic" (eg, voices commenting, thought insertion), then only one symptom is required
Deterioration in social and occupational functioning	Required by DSM but not ICD
Adequate duration	One month of characteristic symptoms in ICD; DSM adds a requirement for a total of six months, including milder prodromal or residual symptoms
Exclusions	The characteristic symptoms cannot be due to a mood disorder or to the effects of a general medical condition or a psychoactive substance (either prescribed medications or drugs of abuse)

Source: Andreasen NC. Symptoms, signs, and diagnosis of schizophrenia. *Lancet.* Aug 19 1995;346(8973):477-81.

2.1.2 Treatment Guidelines

Numerous guidelines and recommendations for schizophrenia treatments have been published in the past decade. Commonly cited practice guidelines and recommendations include the American Psychiatric Association (APA) Schizophrenia Treatment Guideline[18, 20], the Schizophrenia Patient Outcomes Research Team (PORT) Treatment Recommendations,[19, 21] and the Expert Consensus Guideline Series: Treatment of Schizophrenia.[16] Among these guidelines, the APA guideline and the PORT recommendations are synthesized based on scientific evidence, while the Expert Consensus Guideline is based on clinical experts' opinions.[52]

Both pharmacological and psychological treatments are recommended in these guidelines. Antipsychotic monotherapy is recommended as the first line treatment for schizophrenia, especially for the acute phase.[16, 18-21, 52, 53] Two common reasons for antipsychotic switching are lack of efficacy and intolerable side effects.[16, 18, 39] Switching to

another antipsychotic is recommended if patients do not respond to the treatment after maximizing the dose or after a substantial treatment period (usually 4-6 weeks of treatment).[16, 39] Long-acting injectable antipsychotics should be considered if patients do not respond will with oral antipsychotics or have poor adherence to oral agents.[16, 18-20] Combination therapy, or polypharmacy, is not considered in any of these guidelines. According to the PORT recommendations, combination of antipsychotics should only be used for a short period of time when switching medications.[16, 18-21, 52, 53]

Unlike pharmacotherapy, however, there are few details about the application of psychotherapy in a treatment course. The APA guideline recommends incorporating patient and family education into schizophrenia management. Family education is recommended for both acute and stable phases for family members to understand the disease, and for physicians to better evaluate patients' conditions through the interactions with patients' family members. Because studies have shown that psychosocial interventions are more effective in the continuation phase of treatment than the acute phase, patient level interventions, such as cognitive-behavioral psychotherapy (CBT) and social skills/employment training are recommended beginning in the stabilization phase and through the stable phase.[18, 20] The PORT recommendations also suggest that patients with schizophrenia should receive psychotherapy in addition to pharmacotherapy to improve health outcomes.[19]

Similar to the APA guideline, family interventions are recommended by the PORT group. The individual-level intervention— CBT— is recommended as an adjunctive treatment for patients with adequate pharmacotherapy in the stable phase since evidence does not show that CBT is beneficial for the acute phase.[19] Other behavioral interventions, such

as skills training, assertive community treatment, and supported employment, should also be provided, but psychoanalytic therapy, defined as "therapies that use interpretation of unconscious material and focus on transference and regression," is not recommended.[19, 21] Finally, like the other two guidelines, the Expert Consensus Guideline recommends starting patient and family education in the acute phase but initiating individual psychosocial treatments in the continuation phase.[16] However, none of these guidelines specify the modalities of psychotherapy, or how to integrate psychotherapy with pharmacotherapy into a treatment course.

2.1.3 Pharmacotherapy for Schizophrenia

As mentioned above, pharmacotherapy is recommended as the first-line treatment for schizophrenia.[16-21] Typical antipsychotics reduce positive symptoms effectively by blocking dopamine 2 (D2) receptors but often lead to side effects such as extrapyramidal symptoms (EPS) and tardive dyskinesia.[2, 7, 22, 23] In the 1990s, numerous new agents, atypical antipsychotics, with a slightly different pharmacological mechanism were developed with fewer motor side-effects. Evidence has shown that atypical antipsychotics are at least as effective for positive symptoms as typical antipsychotics, but whether atypical antipsychotics improve negative symptoms and cognitive functions is unclear.[2, 7, 22, 54-56] Although atypical antipsychotics cause fewer motor side-effects, they are associated with higher incidence of metabolic syndromes (e.g. weight gain, hypertension, and hyperlipidemia).[16-21]

While pharmacological treatment is easy to administer and reduces psychotic symptoms and signs effectively, it is not a perfect solution. Non-adherence is a common problem for pharmacological treatment. Patients may not adhere to treatment regimens due

to side effects or lack of efficacy.[11, 31, 32] Up to 50% of patients do not fully remit even with adequate pharmacotherapy and may still suffer from relapse or residual symptoms.[10-12, 58] In addition, pharmacotherapy alone does not improve cognitive and/or social functioning, which is important for patients' long-term recovery.[57] Therefore, how to improve medication adherence and functional recovery has become an important issue for patients receiving antipsychotic treatment. By studying the effect of adjunctive psychotherapy on medication adherence, this dissertation provides more information about whether use of psychotherapy improves adherence.

2.1.4 Psychotherapy for Schizophrenia

In addition to pharmacotherapy, psychotherapy has been applied as an alternative form of treatment for patients with schizophrenia. Although psychotherapy is less effective for acute symptoms of schizophrenia, it is believed that psychotherapy can improve patients' medication adherence and long-term outcomes.[57] However, because the effectiveness of psychotherapy has not been clearly demonstrated at the population level, with the introduction of antipsychotics (especially atypical antipsychotics), the use of psychotherapy has declined from 44.4% in 1996-1997 to 28.9% in 2004-2005.[58] Using Medical Expenditure Panel Survey, Olfson and Marcus also found a non-statistically significant decrease in psychotherapy use and increase in pharmacotherapy between 1997 and 2008.[59] This decline may be attributable to both the introduction of atypical antipsychotics as well as the shift in financial incentives toward prescription management in recent years.[58-60] Because of better understanding of the limitations of antipsychotic treatment in recent years, psychotherapy is now used as an adjunctive therapy with pharmacotherapy. It is hoped that

adjunctive psychotherapy will be a helpful supplement to pharmacotherapy, which creates a synergistic effect to improve patient outcomes.[45, 57]

Little is known about what affects physicians' decision about psychotherapy referral. One study assessing referral to group therapy among patients with personality disorders in Italy found no association between psychotherapy referral and patients' demographic or diagnostic factors.[61] The authors suspected that patients' negative attitude toward interpersonal interactions and physicians' stereotypes about group therapy may play a role in the decision making process.[61] Kingdon and Kirschen interviewed four psychiatrists in England reported that the most common reasons for not referring patients with schizophrenia to cognitive-behavioral therapy include a belief that patients are not likely to engage in therapy, that patients are doing well with medication treatment and do not need the therapy, and that patients refuse the referral.[62] Among non-psychiatric specialists, a lack of knowledge about the disease and psychosocial treatments is the main reason for not referral.[63, 64]

Even though many studies have evaluated the efficacy of different types of psychosocial interventions, clinically, there are no standardized interventions that have been applied as psychotherapy. Because different psychosocial interventions often focus on different domains and may be delivered by various modalities, the effects of these interventions usually vary by modalities and outcome measures. In general, patients receiving adjunctive psychotherapy have a lower risk of relapse, better adherence, and better symptom control. Among different types of psychotherapy, family therapy seems to provide the most consistent results of lowering relapse rate. Individual therapy tends to work when both behavioral and cognitive components are incorporated. Unlike family and individual

therapy, evidence for group therapy is limited, and results are often mixed. The following sections introduce common types of psychosocial interventions that may be used in combination with antipsychotics at different levels.

2.1.4.1 Individual-level Interventions

Individual psychotherapy can be defined as "interventions with one-to-one contact between a patient and a therapist."[65] Psychoeducation, social skill training, cognitive therapy, and cognitive-behavioral therapy (CBT) are common types of individual interventions for patients with schizophrenia. The aim of psychoeducation is to help patients to have a better understanding of their condition and treatments.[57] Although psychoeducation may reduce the fear of side effects and improve patients' confidence of treatment, it does not seem to improve medication adherence or reduce relapse rates.[27, 57, 66, 67] Psychoeducation may improve adherence in some cases, but only when it contains behavioral components and support services.[3, 68]

Cognitive therapy focuses on improving patients' information processing ability as well as recognition of their environment and dysfunctional thoughts.[69] The goal of cognitive therapy is to improve patients' insight and their medication adherence by improving their cognitive function.[43] Cognitive remediation is often achieved through repeated practice of certain tasks or techniques.[69] Although cognitive therapy seems to improve cognitive functions and reduce the severity of delusion, it does not seem to improve other clinical or functional outcomes.[43, 69] Because the focus of cognitive therapy is not on medication adherence, its effect on adherence is uncertain.[43] In addition, because the results from cognitive interventions are often not generalizable beyond the setting and the scope of the

intervention,[57, 69] cognitive therapy is often used as an integrated treatment in combination with other psychosocial interventions.[43, 69]

Another common intervention, social skill training, helps to improve patients' social behaviors and maximize their daily functioning, with a hope that social skill training will enhance patients' employment rate and their long-term outcomes. It often requires a longer training time (more than one year in some cases) to allow the positive outcomes to occur.[69] Evidence has shown that social skill training can improve patients' social adjustment and reduce clinical symptoms, but it does not reduce relapse rates nor improve quality of life.[57, 69] Whether social skill training improves adherence is still unclear.[43] Similar to psychoeducation and cognitive therapy, even though social skill training does not seem to have a significant effect on patients' health outcomes, it may play a role in an integrated psychosocial intervention, such as CBT.[57]

Like all other interventions discussed above, CBT can exist in various forms. The goal of CBT is to improve patients' perception of their symptoms and behaviors to help them better respond to changes in their environment and/or their symptoms.[43, 57] One central element of CBT is to build a strong alliance between patients and their therapists.[43, 57] To reach this goal, CBT often integrates elements from different types of psychosocial interventions, such as psychoeducation, open discussion, and other treatment modalities. By integrating these elements, CBT helps patients to explore their disease and symptoms, learn coping strategies, and receive cognitive training[43, 57] Evidence has shown that CBT can effectively reduce overall symptoms, but the effect of CBT at different disease phases still needs to be determined.[19, 43, 57] Despite limited evidence, some believe that CBT can also help to improve medication adherence and reduces relapse rates.[43] However, whether CBT

improve patients' insight remains unclear.[43, 57] After the end of the treatment, the effects of CBT may last for six months to two years.[43]

2.1.4.2 Family-level Interventions

The goal of family-level intervention is to improve family members' understanding of the disease and treatment, provide strategies for coping and disease management, and reduce stress and anxiety in the family.[1, 7, 34, 43, 57, 69] It is hoped that family therapy can reduce the rate of relapse by improving interactions between patients and their family members. Similar to individual therapy, the form and orientation of family therapy varies. For example, psychoeducation, behavioral oriented therapy, and disease/medication management can all be applied at the family level.[69] In addition to family members or key relatives, patients themselves can also be included in the treatment sessions.

Compared to standard care, family intervention has been shown to reduce relapse rates and the duration of hospitalization.[34-36, 43] It is reported that the two-year relapse rate for patients receiving family therapy ranged from 17% to 36%.[36] On average, the relapse rate for patients with family therapy is around 24%, compared to 64% for those who receive routine care.[1] Hogarty and colleagues found that family therapy successfully reduces the relapse rate during the first year (19% for the family intervention group and 41% for the drug-treated group), and the effect existed for two years (29% for the intervention group versus 62% for the comparison group).[34, 35] A similar effect was also reported in a meta-analysis conducted by Pitschel-Walz et al.[70] Their results indicated that family psychoeducation can reduce cumulative relapse and rehospitalization rates from 60% to less than 30% over two years. In addition to reducing the risks of relapse, studies have also found

that family intervention can improve medication adherence and improve patients' employment rate.[35]

Similar to certain individual interventions, the effects of family therapy may go beyond treatment duration and exist for a period of time after the end of the intervention.[57] The effect of relapse reduction from family interventions may last for one to two years, and it seems to be positively correlated with the duration of treatment.[69, 71] In general, family therapy is more effective for patients who received more than ten sessions or six months of treatment.[57]

2.1.4.3 Group-level Interventions

Group therapy allows patients and/or their family members to seek support from their peers to improve outcomes, and it can be defined by three criteria: "(1) a group of people is gathered for some therapeutic goal, (2) a professional expert leader is present to assist the group, and (3) the relationships and interactions between group members are used as tools for clarification, motivation, or behavioral change."[3, 65] Most interventions at the individual or family levels can also be applied at the group level.

Similar to some other psychological-treatment modalities, the goal of group therapy is to improve patients' social skills and recognition of stress as well as focus on social/personal adjustment and quality of life. Group therapy provides greater social support and social networking by enhancing patients' relationship with others (e.g. health care providers, family members, and other patients), which facilitates information exchange and improves self-esteem.[38] A randomized trial comparing brief group CBT versus brief group psychoeducation demonstrated the short-term effect of group CBT on readmission reduction,

but no significant difference were found regarding symptom and adherence improvement.[72] Like other psychotherapies, the effects of group-level psychotherapies vary across study designs and populations. Relatively few interventions have been conducted at the group level, and the results of group-level therapy are mixed.[57, 65, 69]

2.1.4.4 Summary

Overall, patients who receive both pharmacotherapy and psychotherapy have approximately 65% better response than those who only receive pharmacotherapy.[45] Among the different types of interventions discussed above, more trials support the efficacy of family, followed by individual therapy.[45, 73] In contrast, there is limited evidence for group therapy.[45] Regarding intervention orientations, behavioral and cognitive-oriented interventions seem to consistently produce median effect sizes across trials, while verbal therapies produce a smaller average effect size with a wider variation across different delivery methods.[45]

Given the heterogeneity of study interventions and outcome measures, there is no clear conclusion about the effect of psychotherapy on patients' health outcomes. Nevertheless, the combined use of psychotherapy and pharmacotherapy is generally considered to have additive or synergistic effects compared to psychotherapy or pharmacotherapy alone.[43, 45, 73, 74] Because most trials assessed the outcomes within one year (only few studies follow patients more than one year or up to two years), the long-term effects of psychotherapy are not clear. With an 18-month follow-up period, this dissertation provides long-term evidence of psychotherapy.

In addition to implementing different types of psychotherapy for different treatment purposes, psychotherapy can also be applied at different stages of a treatment course to provide different support. At the acute phase, psychotherapy can be used to help patients and their families to have a better understanding of the disease, recognize the necessity of medication treatment, and reduce their stress.[37] During the stabilized phase, psychotherapy should continuously emphasize the importance of treatment, help patients identify new roles, and set reasonable treatment goals.[37] Finally, at the maintenance phase, psychosocial interventions can help patients to maximize their social functioning and identify optimal coping strategies.[37] Generally, psychosocial interventions seem to be effective for treatment-resistant or for stabilized schizophrenia patients.[45, 75, 76] By examining whether adjunctive psychotherapy improve patients' adherence and reduce treatments costs, this dissertation extends our knowledge about the effectiveness of psychotherapy.

2.2 Medication Adherence

2.2.1 Definition of Medication Adherence

Medication adherence, or compliance, can be defined as "the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen".[77] It should reflect whether a patient takes medications with the right dose at the right time. There are many ways to measure adherence, such as patient or relative self-report, pill counting, and pharmacy refill records.[27] However, there are currently no standard ways to measure medication adherence. Because adherence is often not an all-or-none phenomenon, it is often difficult to have an appropriate and accurate measurement of adherence.

Many studies have evaluated medication adherence, and each has used different measurements and definitions of adherence. Studies have found low correlations between adherence measures by self-rating, significant others' rating, and pill count,[25, 27, 78] which raises questions about the validity of self-report techniques. In addition to self-report techniques, a growing method to measure medication adherence is to use pharmacy claims data.[28, 78-82] However, challenges of using claims data include how to best estimate adherence and determining the most appropriate cut point to dichotomize medication adherence.[26, 78, 83, 84] It is generally agreed that a cut point of 0.8 (or 80% of adherence) provides meaningful information to distinguish between adherent and non-adherent patients when using medication possession ratio (MPR) or proportion of days covered (PDC) as a measurement of adherence.[24, 28, 78, 80, 81] One study has also reported it is valid to select a cut-point of 0.8 to distinguish adherent versus non-adherent patients when using subsequent hospitalization as the outcome of prediction.[85]

2.2.2 Factors Associated with Medication Adherence

There are several factors associated with non-adherence. Forgetfulness is one common reason for low adherence, and many patients have indicated that a reminder would be helpful to improve their adherence.[1, 27, 86] Lack of efficacy or poor response is another reason for low adherence.[13, 87] Around 68% of patients stopped taking their medications during the first year of treatment because of loss of efficacy.[13] Intolerable side effects, such as extrapyramidal symdromes and weight gain, can also lead to non-adherence.[31, 32] Other factors that may contribute to poor adherence include shorter duration of disease, previous non-adherence, higher dose of antipsychotics, and poor alliance with therapists.[66, 87, 88]

Patients with substance abuse and lower family support were also found to be less likely to adhere to their regimens.[27, 86, 88, 89]

Although patient demographics and type of antipsychotic use are generally believed to be associated with different adherence levels, no clear associations were found between non-adherence and age, gender, ethnicity, marital status, income, or education level.[26, 27, 88] Similarly, even though there is some evidence showing that patients with weaker perceived susceptibility of relapse and hospitalization or lower perceived benefit of medication treatment are more likely to be non-adherent to their regimen, it is not without controversy.[27]

Use of atypical antipsychotics is another factor that is believed to be related to better adherence. One study found that compared to typical antipsychotic users, patients receiving atypical antipsychotics are more likely to be adherent to their medication regimen and fill their prescriptions on time.[26] However, this study did not adjust for potential confounders, and the definition of adherence was very loose (defined as PDC between 20% and 120%).[26] Despite this positive finding, another study reports an opposite finding,[81] and many studies have not found atypical antipsychotics to significantly improve adherence compared to typical antipsychotics.[24, 29, 30, 33]

Substance abuse is another factor associated with poor adherence.[27, 86-88, 90-93] A Canadian study found patients who used cannabis were 0.46 (95% CI: 0.25-0.84) times as likely to adhere to their regimen as those who did not use cannabis. However, alcohol use was not found to be significant in the adjusted model.[90] Two studies conducted using Veterans Affairs (VA) data or in VA settings reported that substance abuse or alcohol and drug problems increase the odds of poor adherence significantly.[86, 91] It has also been shown that substance abuse, including cannabis use, is a risk factor for medication discontinuation

or non-adherence among the first-episode patients.[87, 92] The hazard ratio was estimated as 2.4 (95% CI: 1.5-3.9) for non-adherence and 6.4 (95% CI: 1.2-35.6) for treatment dropout.[92] Finally, using data from the European Schizophrenia Outpatients Health Outcomes (SOHO) study, it is reported that alcohol dependence, substance abuse, and baseline adherence were all significant predictors of adherence during follow up.[93]

Poor insight or negative attitudes toward the disease and treatment are also commonly cited reasons for poor adherence.[27, 86-88, 94-98] Because insight can be measured in many different ways, different studies often have different definition of insight. Two common ways to define insight are patients' awareness of the disease or their beliefs about the treatment. A study investigating patients with schizophrenia or bipolar disorder in Taiwan found that at the baseline interview, medication adherence was only significantly associated with insight into treatment but not insight into disease.[98] However, neither of these factors were associated with adherence in the follow-up interview one year later.[98]

Since patients with schizophrenia usually have cognitive and/or behavioral problems, they may not be able to follow the treatment regimens or may not recognize the importance of their medication treatment.[24, 27, 31, 88] It is reported that patients with more severe symptoms or substance abuse are more likely to have poor insight,[87, 94, 95, 97] and that these patients may not respond as well as others to psychotherapy.[94, 95] Rittmannsberger et al. also pointed that poor insight can be either a cause or a result of non-adherence.[96] Some have proposed to use psychosocial interventions, such as cognitive-behavioral therapy, or interventions guided by the Health Belief Model to improve patients' insight.[87, 88, 98]

Factors such as disease severity, other comorbid mental conditions, and current inpatient status have also been found to have mixed effects on medication adherence.[88] No

consistent relationships have been found between medication adherence and schizophrenia subtypes and health beliefs.[27] In addition, daily dose and administrative route of antipsychotics were not found to be related to non-adherence.[26, 27] The relationship between dosage and adherence seems to be curvilinear given that low doses may lack efficacy and higher doses may produce intolerable side effect.[27] Finally, the number of adjunctive psychotropic medications was not found to be associated with adherence.[26]

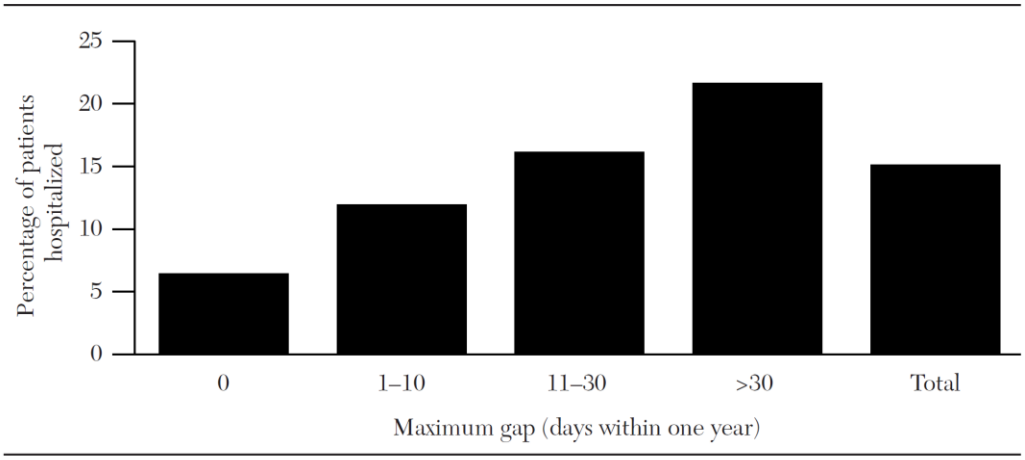
Among environmental factors, greater social support has been shown to have a positive effect on adherence.[27] Patients who receive support from relatives or friends are more likely to adhere to their antipsychotics. However, the positive effect may be diminished if the relationship between the patients and their relatives/friends is stressful.[27] Financial burdens can be another environmental barrier for adherence. Many patients discontinue their antipsychotics due to costs.[27] In addition to costs, lack of transportation or access can also lead to partial or non-adherence.[27] In this dissertation, the relationships between patients' age, gender, race, and their adherence were evaluated. We also tested whether types of initial antipsychotic received, treatment modification, and other comorbid conditions were associated with different adherence levels.

2.2.3 Outcomes Associated with Non-adherence

Patients with low adherence rates often experience negative outcomes, such as worse symptoms, lower social functioning, higher risk of relapse/hospitalization, longer hospital stay, and a higher frequency of emergency room visits.[13, 27, 28, 80-82, 89, 99-101] Using California Medicaid claims data, Weiden et al. found a "dose-response" relationship between medication gaps and risk of rehospitalization. Compared to patients without any gaps during

a one-year observation, patients with a gap of 1 to 10 days, 11 to 30 days, or more than 30 days were 1.98 (95% confidence interval, CI: 1.27-3.25), 2.81 (95% CI: 1.80-4.64), and 3.96 (95% CI: 2.54-6.50) times as likely to have at least one mental-health related rehospitalization during the follow-up period, respectively.[82] However, due to the cross-sectional design, the causal relationship between medication gaps and hospitalization was not evident. Figure 2.1 below illustrates the relationship between maximum gap days and rehospitalization.

Figure 2.1. Association between Maximum Gap Days and Percentage of Patients Rehospitalized



[a] All pairwise comparisons were siginificant at p<.005.

Source: Weiden PJ, Kozma C, Grogg A, Locklear J. Partial compliance and risk of rehospitalization among California Medicaid patients with schizophrenia. *Psychiatr Serv.* Aug 2004;55(8):886-891.

A study conducted by Weiden and Olfson , using the National Institute of Mental Health 1986 Client/Patient Sample Survey, estimated that the monthly relapse rate after hospital discharge was 3.5%, 11.0%, and 8.4% for patients who maintained their medications, who had discontinued their treatments (non-adherence), and who had their treatments

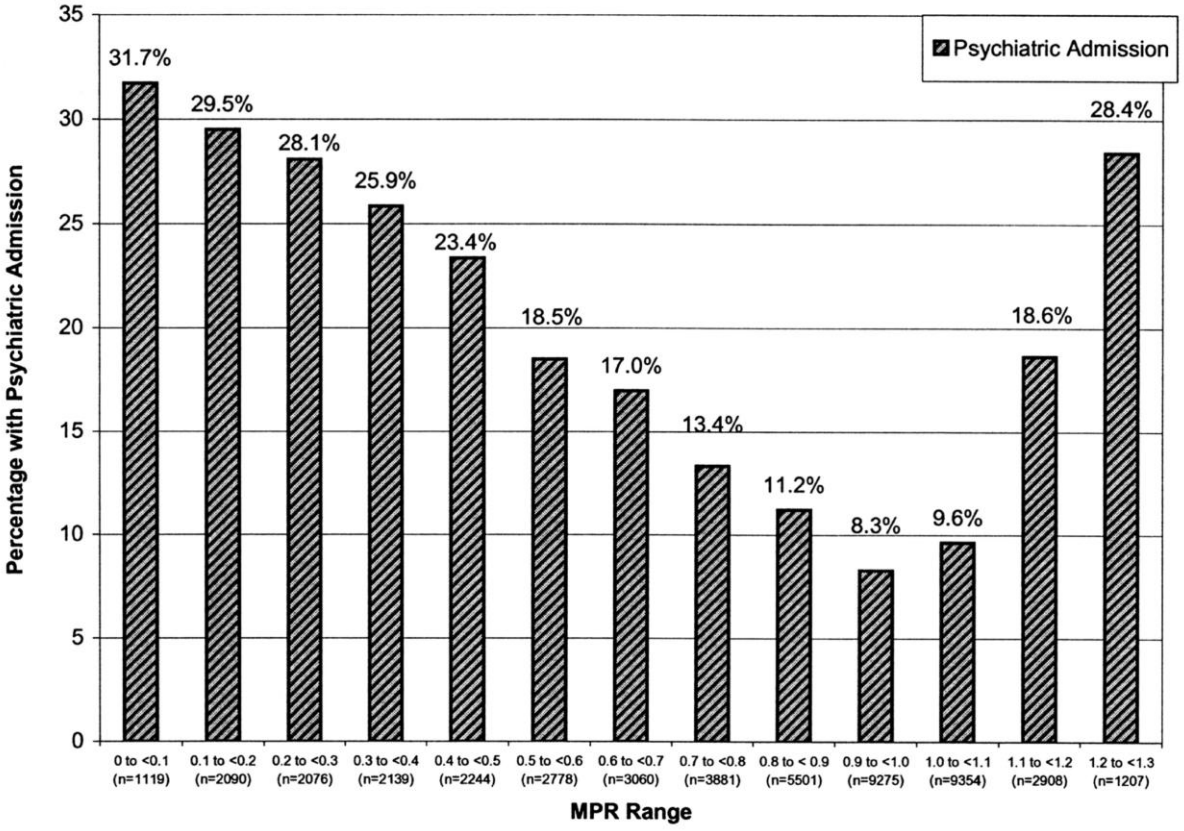
withdrawn by their clinicians, respectively.[13] Compared to the 35% rehospitalization rate for patients who are adherent to their regimen, around 50% of non-adherent patients will be rehospitalized within one year after discharge, and by the end of the second year, over 80% of the non-adherent patients will be rehospitalized (compared to the less than 60% rehospitalization rate of adherent patients).[13] It is also documented that the estimated risk of relapse for patients who withdraw from their medication treatment ranges from 60% to 80%, regardless of the duration of previous maintenance therapy.[11] Instead of measuring medication adherence and hospitalization concurrently, Valenstein et al. found poor adherence as a predictor for future hospitalization. Patients with poor adherence were 1.6 times as likely to be admitted in the following year than those who were adherent.[81]

Besides a higher risk of hospitalization, non-adherence is also related to a longer hospital stay. A study found that among patients who were admitted, those who were not adherent had more psychiatric inpatient days than those who were adherent (33 vs. 24 days, $p< 0.0001$).[81] Another study showed that the average number of inpatient days was 13.9 for patients with a 3-month gap and 3.6 for those who did not have a gap ($p<0.01$).[28] In addition, poor adherence is associated with high inpatient costs. Around 40% of the rehospitalization costs were attributable to non-adherence,[13] and the estimated amount of hospital costs was $3,400 for non-adherent patients and $1,025 to $1,799 for adherent patients.[28, 80] However, because of the higher pharmacy costs for adherent patients, even though the inpatient services costs were higher, the total costs for non-adherent patients may not be higher compared to adherent patients.[80, 101]

Although not filling a prescription on time is an issue, “excess filling” can be problematic as well. Using cumulative possession ration as an adherence measurement,

Gilmer and colleagues found that both non-adherent patients (ratio<0.8) and "excess fillers" (ratio>1.1) had a higher hospitalization rate compared to patients who were adherent (psychiatric hospitalization rate: 34.9% for non-adherent patients, 24.8% for excess fillers, and 13.5% for adherent patients).[80] Similar findings are also presented in a study conducted by Valenstein et al. They found that patients with low adherence (MPR<0.8) were 2.4 times as likely to be admitted as those who had good adherence (0.8≤MPR≤1.1), and the odds for patients who excessively filled their prescriptions (MPR>1.1) was 3.0 times the odds for those with good adherence (p< 0.0001).[81] Figure 2.2 illustrates the proportion of patients being hospitalized at different MPRs.

Figure 2.2. MPR and Percentage of Patients with a Psychiatric Admission in Fiscal Year 1999 (N= 48,148)



Source: Valenstein M, Copeland LA, Blow FC, et al. Pharmacy data identify poorly adherent patients with schizophrenia at increased risk for admission. *Med Care.* Aug 2002;40(8):630-639.

In contrast, Eaddy and colleagues did not find a higher odds of hospitalization for the "over compliant" group.[101] In their study, medication compliance was measured by the continuous, multiple interval medications available (CMA) method, and patients were categorized as partially compliant (CMA<80%), compliant (80% ≤CMA≤ 125%), and overly compliant (CMA>125%). Only the partial compliant group was found to have a higher risk of hospitalization than the compliant group (OR=1.49, p<0.001).[101] However, unlike previous studies, which included only patients with schizophrenia, this study includes both schizophrenia and bipolar populations.

In summary, poor adherence is often associated with worse symptoms and a higher risk of relapse or hospitalization. Once admitted, non-adherent patients may have a longer inpatient stay than adherent patients. Non-adherence is also associated with higher costs of inpatient services. However, due to the higher pharmacy costs for adherent patients, the total cost for non-adherent patients may not be higher. Given that non-adherence is often not attributed to a single factor, and it is not an all-or-none situation, it is necessary to study this problem from different angles and come up with multiple solutions.

2.3 Adjunctive Psychotherapy and Health Related Outcomes

2.3.1 Adjunctive Psychotherapy and Medication Adherence

Regardless of some discrepancies, it is generally believed that psychotherapy can improve medication adherence.[3, 43, 57] Compared to patients who only receive medication treatment, patients receiving interventions emphasizing medication taking behaviors are more

likely to fill their prescriptions on time.[25] However, most interventions that have successfully improved adherence contain certain behavioral changing or problem-solving components. Simply improving patients' knowledge by psychoeducation without any motivation or supportive techniques does not seem to improve adherence effectively.[3, 27, 68, 102, 103]

2.3.2 Adjunctive Psychotherapy and Hospital Utilization

Psychotherapy has been shown to effectively reduce relapse rates and risk of hospitalizations. According to a meta-analysis conducted by Mojtabai et al., the frequency of relapse was around 20% lower for patients receiving psychotherapy in addition to pharmacotherapy than those who received pharmacotherapy alone.[45] A similar result was reported in a study evaluating the effect of family intervention. A study found that the two-year relapse rate was 40% for patients receiving any form of family interventions and 75% for patients without the interventions.[36]

Among different types of interventions, family interventions have shown the most promising results in reducing the risk of relapse and hospitalization.[41, 69, 73] By improving patients and their family members' knowledge of schizophrenia and treatment, psychoeducation can have a short-term effect on reducing relapse and rehospitalization rates.[27, 66] In addition, psychotherapy may reduce inpatient days from approximately 8.5 days to 6 days.[71] Besides family therapy, individual-level interventions, especially CBT, have also been consistently shown to have positive effects on patients' symptoms and relapse rates.[41, 43, 104]

2.3.3 Adjunctive Psychotherapy and Health Care Costs

There is limited evidence for the effect of psychotherapy on treatment costs. Among the Medicare population, the mean cost per person was estimated as $411, $158, and $688 for individual, family, and group therapy in 1991, respectively.[46] A significant decrease of psychotherapy expenditures was found between 1998 and 2007 from the Medical Expenditure Panel Survey (MEPS). Annual expenditure for psychotherapy was $10.94 billion (71% of outpatient mental-health expenditure) in 1998 and was $7.17 billion (44.7% of outpatient mental-health expenditure) in 2007 ($p<0.01$).[59] Mean expenditures per psychotherapy decreased by 23% from 1997 to 2008 ($112.80 versus $94.95, $p<0.001$), and the mean expenditures for psychotherapy from Medicaid also declined by 17.3%.[59]

One review article reports that the use of psychotherapy does not significantly increase health care costs for patients with psychosis.[71] For patients who had stressful relationships their relatives, a 27% lower mean costs per patient was reported for those who received the family intervention compared to the usual care.[105] Another study found a non-significant reduction of total costs over a two-year follow-up for the intervention (CBT) group compared to the control group (treatment as usual).[106] It is believed that the increased costs of the implementation of psychosocial interventions were offset by the decreased costs of other mental-health services.[71, 105]

Although treatments costs have been evaluated in previous studies, each of them has its own limitations. With claims data, Dixon et al. is considered to have a more accurate measurement of treatment costs, but the focus of the study is on the Medicare rather than the Medicaid population.[46] As discussed previously, most patients with schizophrenia are covered under Medicaid. Patients under Medicare can be a highly selected group with

limited generalizability. The cost measurement may be less accurate for studies using MEPS because cost information in MEPS came from self-reports and imputation. In addition, rather than focusing on schizophrenia, the study using MEPS grouped schizophrenia with other psychoses (ICD-9: 297-299) together to assess costs.[59] Finally, two previous trial, one assessing the effective of family therapy for high expressed emotion families, and the other one assess the effect of CBT, were conducted with small sample sizes (N<100).[105, 106] In addition, the study evaluating CBT was conducted in United Kingdom, and instead of getting cost information directly from claims, costs were estimated based on interview information as well as external sources such Trust of the U.K. National Health Services.[106] Given the limitations of these studies, a comprehensive evaluation of treatment costs associated with psychotherapy use in the United States is needed. This dissertation improves the accuracy of diagnosis and cost information using Medicaid claims, and with a larger sample size, our results are more generalizable, especially to the Medicaid population.

2.4 Conceptual Framework

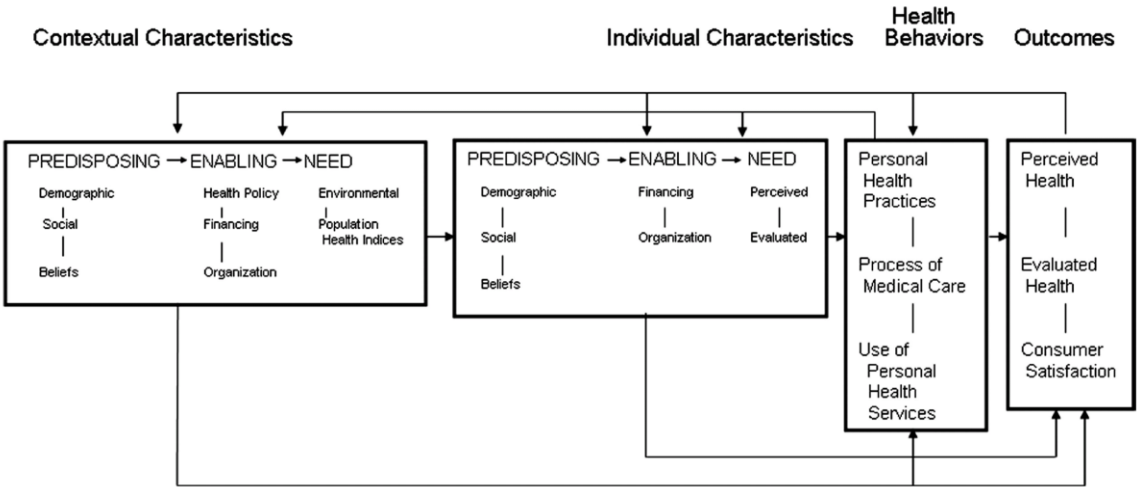
The following sections describe the conceptual framework that is used to guide this dissertation. The proposed framework is based on Andersen's Behavioral model with modifications of some key components.

2.4.1 Andersen's Behavioral Model of Health Services Use

Andersen's Behavioral Model of Health Service Use was first developed in the late 1960s to assess families' use of health care, to evaluate access to health care, and to help develop policies that improve equitable access.[107] It was developed to both predict and

explain health service use.[107] Since the development of the initial model, it has been revised several times. In the 1990s, the model incorporated health outcomes and revealed dynamic and recursive relationships among outcomes, health behavior, and population charactersitcs.[83, 84] The most recent revision of the model was in 2008. In addition to individual characteristics, the model emphasizes contextual characteristics, such as organization, community, and provider-relevant factors (Figure 2.3).[108]

Figure 2.3. Andersen's Behavioral Model of Health Service Use



Source: Andersen RM. National health surveys and the behavioral model of health services use. *Med Care.* Jul 2008;46(7):647-653.

Three components from this model were used to guide the conceptual framework in this dissertation: individual characteristics, health behaviors, and health outcomes. Under the individual characteristics, predisposing characteristics are factors that exist before the onset of the disease, which explain the likelihood of health service use.[107, 109, 110] Such factors include demographics (age, gender, race), social structure (education, occupation, ethnicity), and health beliefs (attitudes, values, knowledge).[107, 110] Because social structure and health

belief factors are unavailable in a claims dataset, this dissertation includes only age, gender, and race as predisposing variables.

Enabling resources are the "means" that are available for individuals to use health services.[107, 109, 110] These factors refer to the availability of health services. Enabling resources include personal resources (income, health insurance, and regular source of care) and community resources (rural/urban residential area, provider types, and facilities). Although the patients in this study are all Medicaid beneficiaries, their health utilization may still be affected by different reimbursement methods. In this study, a rural/urban indicator and an indicator for different coverage policies in different states (Illinois, Kansas, Minnesota, and North Carolina) are classified as enabling factors.

The third component under patient characteristics is need. This factor describes the "illness level" of an individual and is the most immediate cause of health service use.[109, 110] Both patients' self-perceived need and clinically evaluated need are included under this component.[107, 110] Notice that in the latest revised model, perceived and evaluated health are also identified as health outcomes and can affect individual characteristics (especially the "need" component) and health behaviors.[108] In this study, patients' need is assessed by comorbid physical and mental conditions.

In addition to patient characteristics, several variables in this study are considered as health behaviors in the model. Personal health practices (e.g. diet and exercise), process of medical care (e.g. counseling and prescriptions), and use of personal health services (e.g. physician visits and hospital services) are three components under health behaviors.[108] These variables may interact with one another and influence health outcomes. One dependent variable in this study, medication adherence, is considered as a process of medical care factor.

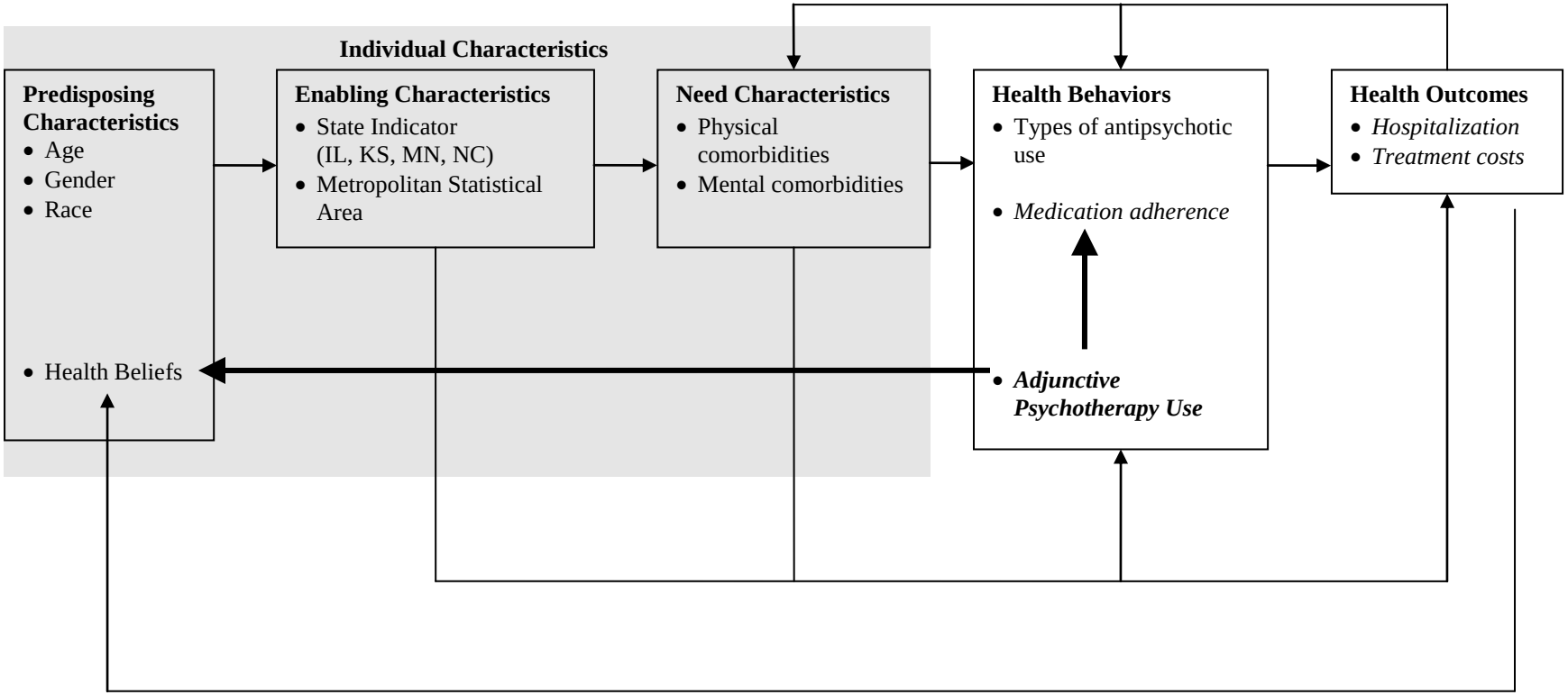
Another dependent variable, hospitalization, is considered as use of health services under health behaviors. Independent variables, such as use of psychotherapy and types of antipsychotic used, can be list as factors under process of medical care and use of personal health services.

Finally, although the predisposing, enabling, and need factors are all important components of the determination of health service use, it is important to know that those factors may have different explanatory power when different types of services are evaluated. According to Andersen, because hospital services are often received for more serious problems, it is expected that predisposing and need characteristics are the primary explanation factors.[107, 108] In contrast, ambulatory physician services are expected to be explained by all three components of patient characteristics, because conditions leading to physician services are often less serious and demanding.[107, 108]

2.4.2 Proposed Conceptual Framework

The proposed conceptual framework for this dissertation is based on Andersen's Behavioral Model of Health Services Use. As mentioned previously, three key components (individual characteristics, health behaviors, and health outcomes) are used to guide this study. Figure 2.4 shows the conceptual framework for this dissertation.

Figure 2.4. Proposed Conceptual Framework



Following Andersen's model, health behavior and health outcomes are determined by patients' predisposing (age, gender, race), enabling (state indicator, metropolitan statistical area), and need (physical and mental comorbidities) characteristics. In addition to social-demographic factors, health belief is also placed as one of the predisposing factors according to Andersen's model. Unlike Andersen's model, which lists health status and patient satisfaction as health outcomes, this proposed model considers health behavior (medication adherence) and use of health services (type of antipsychotic use and use of adjunctive psychotherapy) as "health behaviors", while hospitalization and treatment costs are considered as "health outcomes".

In addition, the synthesized model incorporates two feedback loops from health outcomes to health behaviors and patients' need. It is assumed that patients' health behaviors will change after experiencing certain health outcomes. For example, a patient may become more adherent to his/her regimen after experiencing a hospitalization event. A patient's health status may also change after receiving certain inpatient services (e.g. a patient may receive more intensive treatment and become healthier/sicker after discharge). Besides indirect effects, it is also assumed that enabling and need characteristics have a direct effect on health behaviors and health outcomes. For instance, different states may have different policies, and patients living in different states may have different levels of access to health care services. Need is assumed to directly affect health outcomes because a patient can experience an outcome (ex. hospitalization) regardless of his/her health behaviors (ex. adherence or non-adherence) if the patient's condition becomes more severe. Lastly, health outcomes are assumed to influence health beliefs directly. Patients may have different health

beliefs after experiencing certain health outcomes. For instance, a patient may perceive antipsychotics as being ineffective after being hospitalized several times.

The key independent variable, use of adjunctive psychotherapy, is considered as a factor under health behaviors. The assumption is that adjunctive psychotherapy changes patients' health beliefs by improving patients and/or their family members' attitude toward the disease and treatment. Psychotherapy can also affect patients' medication use behaviors (i.e. adherence) if it contains behavioral modification components or focuses on adherence improvement. Although it can be argued that health beliefs may have a direct influence on health behaviors and outcomes, based on the Andersen Model, health beliefs do not affect health behavior or outcomes directly. Therefore, in the proposed model, health beliefs can only affect health behaviors and outcomes through enabling and need factors.

CHAPTER 3: METHODS

3.1 Data Source and Aims

Data for this study were obtained from the 2001 to 2003 Medicaid Analytic eXtract (MAX) files. The person-level data contain records for individuals who were enrolled in Medicaid at least one day during the year, including demographic information (e.g. date of birth, gender, race), enrollment status, health service utilization, and treatment costs. Prescription drug information, such as prescription filling date, days supply, and payment, were identified from the claims.[111] Four states were included for analyses: Illinois, Kansas, Minnesota, and North Carolina. These four states were chosen because to the author's knowledge, they did not have any major pharmaceutical policy change (such as prior authorization or number of prescription restricted) that could affect antipsychotic use and adherence during 2001 to 2003. In addition, because the use of psychotherapy has declined in recent years, using 2001 to 2003 data may allow us to identify a larger sample of psychotherapy users. Data from these states were used to accomplish the following aims:

Aim 1: To describe the patterns and factors associated with the use of adjunctive psychotherapy.

Descriptive statistics were first applied to evaluate the prevalence of psychotherapy and types of psychotherapy being used. Frequency and percentage of psychotherapy use were reported. In addition to the patterns of psychotherapy use, patient characteristics were

compared across two groups (patients with both pharmacotherapy and psychotherapy versus patients with pharmacotherapy alone). A logistic regression was performed to assess factors associated with psychotherapy use.

Aim 2: To assess whether the use of adjunctive psychotherapy in combination with pharmacotherapy improves patients' adherence to antipsychotic treatments.

Survival analyses were performed to assess time to treatment discontinuation (a gap excess 15 or 30 days) among the new antipsychotic users. In addition, a sub-analysis was conducted to assess the likelihood of medication switching between psychotherapy users and non-users.

Aim 3: To assess whether receiving adjunctive psychotherapy in combination with pharmacotherapy reduces hospitalization rates and health care costs.

Due to a high proportion of zeros, a two-part count model (a hurdle model) was applied to evaluate the rate of hospitalizations between the two groups during follow-up. With non-normally distributed health care costs, generalized linear models were used to compare health care costs between psychotherapy users and non-users.

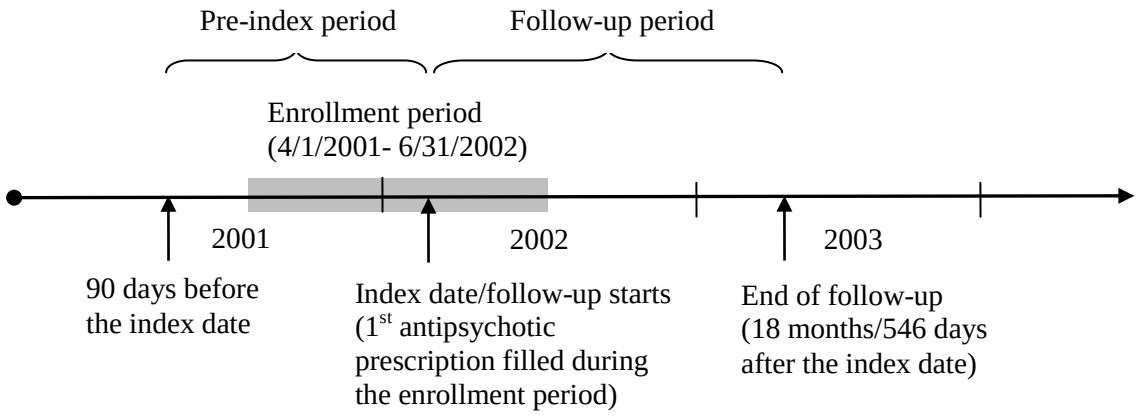
3.2 Study Design and Sample

This study constructed a posttest-only design with nonequivalent groups using 2001 to 2003 Medicaid claims data. The study sample included patients who had been diagnosed with schizophrenia and who had at least one antipsychotic prescribed during the enrollment period. Because antipsychotics could also be used to treat bipolar disorder, patients

diagnosed with bipolar disorders at any time during the study period were excluded to reduce confounding. In addition, to avoid dual eligibility and to best capture health utilization, patients were excluded if they were younger than 18 or older than 62 years old in 2001.

Figure 3.1 describes the timeframe applied to Aim 2 and Aim 3. Patients with schizophrenia were identified using the *International Classification of Disease, Ninth version, Clinical Modification* (ICD-9-CM) code of 295.xx. To be included, a patient was required to have at least one inpatient or two outpatient diagnoses of schizophrenia any time during the study period. Each patient was assigned an index-date, which is the date of their first antipsychotic prescription filled during the enrollment period (April 1st, 2001 to June 31st, 2002). A pre-index (or "screening") period was assigned as 90 days before the index date, which was used to assess patients' history of medication and health service use. All patients were followed for 18 months (or 546 days) after the index date. Specific inclusion/exclusion criteria are described in the following section.

Figure 3.1. Study Design and Timeframe



Inclusion/Exclusion Criteria for Incident Antipsychotic Users

This study investigated the effectiveness of psychotherapy using an incident cohort design (i.e. new-user design). Using an incident cohort can eliminate some biases introduced by prevalent cohorts. First, the new-user design eliminates the "healthy user" effect.[112] In this case, to be included as a prevalent case, a patient has to have at least one record of antipsychotic use during the pre-index period. Therefore, we are more likely to include patients who are already stable (or better adherent) on their medications than those who are not. This phenomenon not only leads to a selection bias but also confounds our results by patients' immortal time (in this case, time that by definition, a patient has to stay on treatment). In addition, the use of a treatment often co-varies with factors associated with the treatment itself.[112] For example, the use of adjunctive psychotherapy is likely to be affected by previous adherence or outcomes. A patient may receive psychotherapy because of his/her poor adherence. The new-user design eliminates these two problems by implementing a washout period which "washes out" the history of previous medication use behaviors and by measuring the baseline characteristics prior to the implement of the treatment.[112] Incident cases (new antipsychotic users), were identified following the inclusion/exclusion criteria described below.

<u>Inclusion criteria:</u>

1. Patients with at least one inpatient or two outpatient diagnoses of schizophrenia (ICD-9-CM: 295.xx) any time during the study period.

2. Patients with no antipsychotic filled records during the "pre-index" period (90 days before the index date), and at least one antipsychotic filled during the enrollment period.
3. Patients were required to have continuous eligibility from the pre-index period (three months before the index date) to the end of follow-up period (546 days after the index date).

Exclusion criteria:

1. Because antipsychotics could also be used to treat bipolar disorder, to reduce confounding by other indication, patients with a bipolar diagnosis (see Table 3.1 for ICD-9 Codes) at any time during the study period were excluded.

Table 3.1. ICD-9 Codes for Bipolar Disorder

Diagnosis	ICD-9-CM codes
Bipolar I	296.0, 296.1, 296.4-296.7
Bipolar II	296.89
Bipolar Unspecified	296.80
Cyclothymic Disorder	301.13

2. Patients younger than age of 18 or older than age of 62 years in 2001 were excluded. Because this study focuses on adults with schizophrenia, we excluded patients younger than 18 years old. To fully capture health care utilization under Medicaid, we excluded those who would turn 65 years old and become eligible for Medicare during the study period.
3. To best capture patients' medication/health service utilization, patients who ever enrolled in a managed care plan or without full Medicaid benefits were excluded.

4. Patients with a record of a long-term care facility stay at any time during the study were excluded due to potential incomplete pharmacy records,.
5. Patients who were hospitalized in the pre-index period were excluded because these patients were more likely to have more serious symptoms or to be treatment resistant compared to other patients.
6. Patients with a record of psychotherapy in the pre-index period were excluded because previous psychotherapy might affect their medication use behaviors and thus confound our results.
7. Patients with a claim of injection or long-acting antipsychotics, such as haloperidol decanoate or fluphenazine decanoate, were excluded because these patients might have different characteristics (i.e. non-adherent to oral agents or treatment resistant)[16, 18-20] or potential inconsistent records of days supply.[80-82]

3.3 Measurements

3.3.1 Psychotherapy

The use of adjunctive psychotherapy served as the dependent variable for Aim 1 and key independent variable for Aim 2 and 3 (Table 3.3), and it was measured during the follow-up period. Psychotherapy use was defined as a dichotomous variable to indicate whether a patient ever received psychotherapy (yes/no). Due to limited sample sizes, our analyses were not stratified by the type of psychotherapy.

The use of psychotherapy was identified by the *Current Procedural Terminology* and *Healthcare Common Procedure Coding System* codes (CPT/HCPCS). Codes included in this study are 90804-90809 and 90875 (individual psychotherapy), 90846-90847 and 90849

(family psychotherapy), and 90853 as well as 90857 (group therapy). Notice that 90849 "multiple-family group psychotherapy" was categorized as family therapy here. A sensitivity analysis was conducted to check how the results would change if 90849 is categorized as group therapy. Interactive psychotherapy and psychoanalysis are not included in this study because interactive psychotherapy is often used in children, and psychoanalysis is not recommended by the guidelines.

3.3.2 Dependent variables for Aim 2 and 3

The dependent variables for Aim 2 and Aim 3 are medication adherence (Aim 2), hospitalizations, and treatment costs (Aim 3). The following sections describe the measurements for medication adherence, hospitalizations, and treatment costs.

3.3.2.1 Medication Adherence and Switching

Medication Adherence

Medication adherence was assessed as "time to all-cause medication discontinuation." Number of days to discontinuation was calculated for each patient. Although Cramer and colleagues have argued that medication adherence and medication persistency should be better defined and distinguished,[77] in this dissertation, medication persistency is considered as one component of adherence. Measuring medication persistency as a function of gaps between refills has been recommended by Sikka et al., for its ability to reflect medication continuity and suitability for survival analysis.[84] Medication discontinuation is defined as a gap of 30 days or more between medication refills. This definition is chosen based on the findings that a gap longer than 30 days increased the hazard of hospitalization by 50%,[113] and

around 90% of rehospitalized patients had a gap of 30 (or more) days prior to their rehospitalization.[28] Because there is currently no standard definition of medication discontinuation, to best reveal different scenarios of discontinuation and provide clinically meaningful information, a sensitivity analysis using a gap of 15 days or more was also be conducted.[82, 84, 113] A 15-day gap is chosen because studies have shown that even a 10-day gap could be associated with a higher risk of hospitalization,[82, 113] and it is also recommended to define a gap (15 days) as half of the days supply (30 days).[84]

Antipsychotic Switching

The other dependent variable in Aim 2 was antipsychotic switching, measured as a binary variable which indicates whether a patient ever switched antipsychotics during the follow-up. Based on a review, medication switching is often defined as using a different drug within a period of time after the initial treatment was filled.[114] However, different studies usually apply different timeframe, and some of them may use additional criteria to define switching.[115-118] In this study, switching was defined as initiating a different antipsychotic agent within 30 days after the end of the previous supply. We choose to define switching as initiating a second drug after finishing the first drug supply because this approach allowed us to clearly separate switching from potential augmenting, defined as initiating a second drug before finishing the previous supply (see section 3.3.3 for details). In addition, a sensitivity analysis was conducted using a 15-day window to define medication switching.

3.3.2.2 Hospitalizations

Hospitalizations were measured as the number of mental-health related inpatient admissions during follow-up. Using Weiden and colleagues' definition,[82] mental-health related hospitalization was defined as having an inpatient record with a primary diagnosis code of schizophrenia, depression, anxiety, other psychoses, or dementia (Table 3.2). The broad definition of mental-health related hospitalization allows us to capture all possible admissions associated with the index diagnosis of schizophrenia.[82] This definition has been widely used in other studies as well.[85, 113, 119]

Table 3.2. ICD-9 Codes for Mental-Health Related Hospitalizations

Diagnosis	ICD-9-CM codes
Schizophrenia	295
Depression	296.2, 296.3, 296.9, 300.4, 309.0, 311
Anxiety	300.0, 300.2, 300.3, 306.9, 308, 309.2, 309.4, 309.9
Other psychoses	297, 298, 299, 300.1, 302.8, 307.9
Dementia	290, 291.2, 310.9, 331.0

Source: Weiden PJ, Kozma C, Grogg A, Locklear J. Partial compliance and risk of rehospitalization among California Medicaid patients with schizophrenia. *Psychiatr Serv.* Aug 2004;55(8):886-91.

3.3.2.3 Treatment Costs

Treatment costs were measured as inpatient costs, outpatient costs, pharmacy costs, and total costs. Inpatient costs were calculated as the total amount paid by Medicaid for mental-health related hospitalizations. Outpatient costs included Medicaid payment for mental-health related visits and outpatient medical services, which were identified from outpatient claims with the ICD-9 codes presented in Table 3.2. Pharmacy costs included all antipsychotic medications paid by Medicaid. Finally, total costs were calculated as the sum of inpatient, outpatient, and pharmacy costs. Because patients' out-of-pocket costs are

usually low for Medicaid beneficiaries, the focus is on payer's costs in this study. All costs were adjusted to 2003 dollars using the U.S. Annual Consumer Price Index, Medical Care component.[120] The dependent variables and key independent variable were summarized in Table 3.3.

Table 3.3. Summary of the Dependent Variables and Key Independent Variable

	Variable	Description	Type
Dependent Variables for Aim 2 and 3			
Aim 2	Adherence	Time to all-cause discontinuation (number of days)	Continuous
Aim 2	Switching	Whether a patient had switched antipsychotic during the follow-up	Dichotomous (yes/no)
Aim 3	Hospitalizations	Rate of hospitalization during the follow-up period (number of hospitalization/person-time)	Count
Aim 3	Treatment Costs	Sum of Medicaid payment for mental-health related inpatient, outpatient, and antipsychotics	Continuous
Key Independent Variable (Dependent variable for Aim 1)			
All Aims	Use of Adjunctive Psychotherapy	Receiving psychotherapy during the follow-up period	Dichotomous (yes/no)

3.3.3 Other adjusted variables

According to the proposed conceptual framework, several other factors may also affect the use of psychotherapy and/or the outcomes of interest. Therefore, it is important to adjust these factors in our analyses. Table 3.4 below describes other adjusted variables based on the proposed conceptual framework and aims.

Table 3.4. Description of Other Adjusted Variables

	Variable	Description	Type
Other Independent Variables			
	Predisposing Characteristics		
All Aims	Age	Age in 2001	Categorical (18-35, 36-50, >50)
	Gender	Gender	Binary (Male/Female)
	Race	Race/ethnicity	Categorical (White, Black, Other)
	Enabling Characteristics		
All Aims	State indicator	An indicator of different states (a proxy to control for different policies in different state)	Categorical (IL, KS, MN, NC)
	Metropolitan Statistical Area (MSA)	Indicates whether an Medicaid enrollee lives in a MSA	Binary (MSA: yes/no)
	Need Characteristics		
All Aims	Comorbidities	Physical: measured by Charlson Comorbidity Index	Continuous
		Mental: dummies for depression, alcohol/substance abuse, and other psychosis	Binary (yes/no)
	Health Behavior		
	Type of Initial antipsychotic Treatment	Type of the first antipsychotic filled	Binary (Atypical/Typical)
Aim 2&3	Treatment Modification	An indicator for medication modification (either medication switching, augmenting, or both)	Binary (yes/no)
Aim 3	Adherence	Antipsychotic adherence during the follow-up, measured by PDC	Binary (Adherence: PDC≥0.8; non-adherence: PDC<0.8)

Age was measured as the year of age in 2001. We found no significant differences coding either age as a continuous or categorical variable. Therefore, age was categorized into three groups (age from 18 to 35, 36 to 50, and older than 50 years old) to get a more meaningful estimates between age groups. In addition to the percentage of patients in different age groups, mean age was also reported in the descriptive statistical table.

Race was categorized as White, Black, and others. Black race was coded as an independent category because a previous study has shown that African Americans were less likely to receive psychotherapy than Causation patients.[46] We separated other races from White and Black because patients with different races may have different perception of schizophrenia and its treatment. However, due to small sample sizes, we grouped other race (including Asian, Hispanic, Pacific Islanders, and patients with multiple races) into one category.

Because different states usually have different Medicaid policies, it is important to control for effects that are attributable to different benefit designs. Small variation was found in the four states in this study, Illinois, Kansas, Minnesota, and North Carolina, in terms of physician and psychologist services. In 2003, all of the four states covered physician services, and two of them covered psychologist services (Illinois and North Carolina did not cover psychologist services). The copayment for physician and psychologist visits ranged from $1 to $3. Illinois and Minnesota generally did not restrict the number of physician and psychologist visits. In Kansas, patients were limited to 12 office visits and 32 hours of psychotherapy per year, and North Carolina covered up to 24 ambulatory visits per year.[121]

Coverage for mental health/substance abuse rehabilitation and non-hospital public/mental health clinic services was similar across the four states. All four states covered mental health/substance abuse rehabilitation as well as non-hospital public/mental health clinic services as of January 2003, and most of them did not limit the service or varied by different level of care. Kansas limited substance abuse service to three treatment episodes over a lifetime, and North Carolina required prior approval if patients have more than eight outpatient psychiatric visits. Regarding non-hospital public/mental health clinic services,

Kansas required a $3 copayment per visit and limited coverage to 40 hours of group or family therapy per year and 200 hours of psychotherapy and substance abuse services lifetime. Public health clinic visits were not covered in Kansas, and patients in North Carolina were restricted to 24 ambulatory public health clinic visits per year (in limits with other specified practitioners).[121]

All four states covered outpatient hospital services in 2003. Kansas required a $3 copayment for a non-emergency visit, and non-emergency visits counted toward the physician visit limit. North Carolina required $3 per visit with a prior approval requirement for eight or more outpatient psychiatric visits, and the number of non-emergency visits per year was limited to 24 (alone with limits for other specified practitioners). The copayment for a non-emergency visit in ER was $6 in Minnesota.[121]

In terms of prescription drugs, all four states provided prescription drug coverage, and the copayment per prescription ranged from $1 to $3 in 2003. Most states did not limit the number of prescriptions covered per month, except for North Carolina (a limit of six prescriptions per month).[121] Table 3.5 summarizes different coverage under these four states.

Table 3.5. Summary of State Coverage for Mental-Health Related Services

States / Coverage	Illinois	Kansas	Minnesota	North Carolina
Physician Services (Coverage Limitations and Prior Authorization Requirement)	$2/visit	$2/visit (12 office visits/year, 1 inpatient hospital visit/day, 1 office consultation/ 2 months, 1 inpatient hospital consultation /10 days)	$ 3/visit for non preventative service except mental health	$3/visit (24 ambulatory visit/year included in limits with other specified practitioners)
Psychologist Services (Coverage Limitations)	Not covered	$3/office visit (32 hours psychotherapy/year in combination with other providers)	Covered, with no specified copayment or coverage limitations	Not covered
Mental Health and Substance Abuse Rehabilitation Services	Covered, with no specified copayment (Limits for substance abuse services vary by established levels of care)	Covered, with no specified copayment (Services limited to substance abuse and 3 treatments episode/lifetime)	Covered, with no specified copayment (Mental health service and visit limits vary)	Covered, with no specified copayment (Prior authorization was required if more than 8 psychiatric visits)
Non-Hospital Public/Mental Health Clinic Services	Covered, with no specified copayment or coverage limitations	$3/visit (32 hours individual psych therapy/year, 40 hours group or family therapy/year, psych therapy and substance abuse	$3/visit for non-preventive services except mental health	Covered, with no specified copayment (Limited to 24 ambulatory visits/year to Public Health Clinic included in limits

		services limited to 200 hours/lifetime, Public Health Clinics not covered)		with other specified practitioners. Prior authorization was required if more than 8 psychiatric visits)
Outpatient Hospital Services	Covered, with no specified copayment or coverage limitations	$3/non-emergency visit (Non-emergency visits count toward physician visit limit, rehab must be restorative)	$6/ non-emergency visit in ER	$3/visit (24 non-emergency visits/year included in limits with other specified practitioners. Prior authorization was required if more than 8 psychiatric visits)
Prescription Drugs	$3/brand Rx, $1/generic Rx	$3/Rx	Covered, with no specified copayment (Prior authorization was required for non-preferred and brand Rx when generic available)	$3/brand Rx, $1/generic Rx (6 Rx/month, Rx must be generic unless dispense as written)

Source: The Henry J. Kaiser Family Foundation. Medicaid Benefits: Online Database. http://medicaidbenefits.kff.org/index.jsp. Accessed Aug. 15, 2010.

Metropolitan Statistical Areas (MSAs) were identified using the 2009 list of metropolitan and micropolitan statistical areas defined by the U.S. Office of Management and Budget (OMB). A MSA contains a core urban area with at least 50,000 or more people and its adjacent areas that are highly integrated with the core urban area.[122] State and county codes were used to generate the Federal Information Processing Standard (FIPS) codes which allowed us to identify counties listed under a MSA in the Medicaid data.[122, 123]

Comorbidities were also adjusted because comorbid conditions are likely to affect both treatment plans (i.e. the use of psychotherapy) and health outcomes (i.e. hospitalizations and treatment costs). In this study, we used two approaches to measure physical and mental comorbid conditions. Physical comorbidities were measured by Charlson Comorbidity Index (Deyo and Quan's version)[124-126], while mental comorbidities were adjusted using disease-specific indicators for common comorbid mental conditions of schizophrenia (depression, alcohol/substance abuse, anxiety, and other psychoses). Charlson Comorbidity Index (CCI) adjusts the risk of mortality by weighting selected conditions.[124] Each patient got a summary score (Charlson comorbidity scores) based on the number and severity of his/her comorbid conditions.

Charlson Comorbidity Index is chosen over other commonly used comorbidity indexes (such as the Elixhauser Index and Chronic Disease Score) for several reasons. Unlike Elixhauser Index, which does not weight different comorbidities and keeps them separately, CCI assigns weights to different conditions based on the risk of inpatient mortality, which should better reflect a patient's overall disease severity. In addition, because the Elixhauser Index includes several mental conditions (alcohol abuse, drug abuse, psychoses, and depression) that are not counted in CCI, using the Elixhauser Index will

prohibit us from separating the effects of these selected mental comorbidities from other physical comorbidities. Since the outcomes of interest in this study are all mental-health related, the effect of these mental comorbidities may be different from physical comorbidities, and it may be inappropriate to count a mental condition the same as a physical condition. Finally, CCI is considered more stable than Chronic Disease Score because Chronic Disease Score uses pharmacy records for risk adjustment, which is more dynamic then diagnosis codes. As a result, CCI was chosen over the Chronic Disease Score and the Elixhauser Index.

Charlson Comorbidity Index was first developed and designed for medical records. Deyo et al. adapted it for administrative dataset research using ICD-9-CM diagnosis codes.[125] Their codes were then updated by Quan and colleagues.[126] Table 3.6 shows the ICD-9-CM codes for comorbid conditions.

Table 3.6. ICD-9CM codes of Charlson Comorbidity Index

Conditions	ICD-9CM
Myocardial infarct	410, 412
Congestive heart failure	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4-425.9, 428
Peripheral vascular disease	093.0,437.3, 440-441, 443.1-443.9, 47.1, 557.1, 557.9, V43.4
Cerebrovascular disease	362.34, 430-438
Dementia	290, 294.1, 331.2
Chronic pulmonary disease	416.8, 416.9, 490-505, 506.4, 508.1, 508.8
Rheumatic Disease	446.5, 710.0-710.4, 714.0-714.2, 714.8, 725
Peptic ulcer disease	531-534
Mild liver disease	070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 570-571, 573.3, 573.4, 573.8, 573.9, V42.7

Diabetes	250
Hemiplegia or paraplegia	334.1, 342-343, 344.0-344.6, 344.9
Renal disease	403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 582, 583.0-583.7, 585-586, 588.0, V42.0, V45.1, V56.0
Any malignancy, including lymphoma and leukemia, except malignant neoplasm of skin	140-172, 174-195.8, 200-208, 238.6
Moderate or severe liver disease	456.0-456.2, 572.2-572.8
Metastatic solid tumor	196-199
AIDS	042-044

Source: Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care.* Nov 2005; 43(11):1130-9.

Although CCI provides a good adjustment for physical comorbidities, it does not adjust for mental conditions. Since this study examines health related outcomes among schizophrenia patients, it is important to adjust for common mental comorbidities in this group. We therefore include four dummies to indicate whether a patient had depression, alcohol/substance abuse, anxiety, or other psychoses. Codes used to identify depression and other psychoses were adopted from Weiden et al.,[82] which were the same ICD-9-CM codes used to identify psychiatric hospitalizations. For alcohol/substance abuse, we used the ICD-9-CM codes proposed by Elixhauser and Quan.[126, 127] Comorbid conditions were measured at baseline using the pre-index period to screen for comorbidities. Table 3.7 shows the ICD-9-CM codes used to identify mental comorbidities.

Table 3.7. ICD-9-CM Codes for Mental Comorbidities

Diagnosis	ICD-9-CM codes
Depression	296.2, 296.3, 296.9, 300.4, 309.0, 311
Substance Abuse (Alcohol/Drug Abuse)	Alcohol abuse: 265.2, 291.1-291.3, 291.5-291.9, 303.0, 303.9, 305.0, 357.5, 425.5, 535.3, 571.0-571.3, V11.3 Drug abuse : 292, 304, 305.2-305.9, V65.42
Anxiety	300.0, 300.2, 300.3, 306.9, 308, 309.2, 309.4, 309.9
Other psychoses (including dementia)	290, 291.2, 297, 298, 299, 300.1, 302.8, 307.9, 310.9, 331.0

Source: Weiden PJ, Kozma C, Grogg A, Locklear J. Partial compliance and risk of rehospitalization among California Medicaid patients with schizophrenia. *Psychiatr Serv.* Aug 2004;55(8):886-91.

Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care.* Nov 2005; 43(11):1130-9.

Another covariate controlled in this study was type of antipsychotic use because it could be associated with the use of psychotherapy as well as the outcomes of interest. Instead of measuring the type of antipsychotic use during the follow-up period, we chose to use the type of initial antipsychotic treatment as an indicator for type of antipsychotic use. Using the initial treatment assignment allowed us to assess the baseline antipsychotic assignment which occurred before or with the first psychotherapy. Because many patients with schizophrenia switch or use different types of antipsychotic concurrently, this intent-to-treat approach not only avoids the crossover and the endogeneity issues between the type of antipsychotic received and psychotherapy used during the follow-up, but also provides a clearer temporal association between the antipsychotic assignment and psychotherapy use.

Medication adherence during the follow-up period was measured as proportion of days covered (PDC), defined as the proportion of days a patient had prescribed medications available during the follow-up period. PDC has been found to have the highest predictive validity for hospitalization among patients with diabetes[128] and has been used to assess

antipsychotic adherence among patients with schizophrenia in previous studies.[119, 129] A study comparing eight different adherence measures, using Arkansas Medicaid claims data, found that PDC is one of the best predictors of all-cause and mental-health related hospitalization.[119] In addition, unlike medication possession ratio, which may overestimate medication adherence, PDC provides a more conservative estimate of adherence. PDC is therefore recommended as an adherence measure, especially when multiple drugs in a class are prescribed concurrently.[129] Specifically, the formula used to calculate PDC is:

$$\text{PDC} = \left(\frac{\text{Total days supply in the follow-up period}}{\text{Total number of days in the follow-up period}}\right) \text{x } 100\%, \text{ capped at } 1^{[83, 119]}$$

In this study, a cut-point of 80% was used to categorize full adherence (PDC$\geqq$80%) versus non-adherence (PDC<80%). As discussed in section 2.2.1, PDC$\geqq$80% has been considered as a valid cut-point to distinguish adherence versus non-adherence,[24, 28, 78, 80, 81] and it has also been adopted by several other studies.[24, 28, 78, 80, 81] Instead of predict mean adherence (PDC score), dichotomizing adherence allows us to predicting the probability of non-adherence given a set of characteristics of a patient, which is more clinically meaningful.

Two special cases need to be considered when calculating PDC: polypharmacy and switching. For patients who were on multiple antipsychotics, a given day was considered as covered if at least one antipsychotic was available on that day. In other words, all follow-up days with at least one antipsychotic available were counted in the numerator of PDC. For patients switching antipsychotics, if there was no gap before the switching occurred, the days covered by the new agent were treated as the days covered by the old agent and were counted

cumulatively in the numerator. Gaps due to switching (i.e. patients start a new agent after the gap) are not counted in the numerator because the Expert Consensus Guideline does not recommend a gap before the initiation of the new agent.[16, 130] Therefore, regardless of the initiation of a new agent, any given day was counted in the numerator of PDC as long as there was at least one antipsychotic agent available, and this calculation was consistently applied across all situations.

In addition to PDC, an indicator of medication modification was also added to the regression models in Aim 3. As discussed previously, PDC is capped at one and only count the proportion of days covered by antipsychotics. Therefore, PDC does not count any potential switching or augmenting of antipsychotics that may affect the use of psychotherapy as well as outcomes of interests (hospitalizations and treatment costs). To better capture the potential medication switching or augmenting, another dummy variable was added in Aim 3 to indicate whether a patient had modified his/her treatment regimen during the follow-up. A patient was considered as having modified his/her antipsychotic treatment if he/she had switched or augmented his/her antipsychotics during the follow-up period. Antipsychotic switching was defined as having a different antipsychotic refilled within a 30 or 15-day window after the end of the previous antipsychotic supply (section 3.3.2.1). In contrast to switching, medication augmenting was measured as an initiation of a different antipsychotic refilled before the end of the last antipsychotic supply. By combining these two indicators together, the treatment modification dummy should be able to capture all the potential switching, augmenting, or concurrent use of antipsychotics.

3.3.3.1 Independent variables for Aim 1

Aim 1 evaluated patterns and predictors of adjunctive psychotherapy use (yes versus no). The covariates included in the model for Aim 1 were: age, gender, race, states, MSA, comorbidities, and types of initial antipsychotic treatment. According to the proposed conceptual model, age, gender, and race were considered as predisposing factors. State indicator, which captured the effects of different policies among states, and MSA, which captured the effect of being in different geographic areas (rural versus urban), were considered as enabling factors. Comorbidities (both physical and mental) were classified as need factors.

Because some health behaviors can affect the use of psychotherapy during the follow-up period (as discussed in section 2.4.2), type of initial antipsychotic use (atypical versus typical) were also included in the model for Aim 1. Hypothetical associations between each independent variable and psychotherapy use are summarized in Table 3.8.

Table 3.8. Hypothetical Associations between Independent and Dependent Variables for Aim 1

	Use of adjunctive psychotherapy
Older age	-
Female gender	??
Race – nonwhite	-
State	??
MSA	+
Higher number of comorbidities - Physical	+ or no difference
Higher number of comorbidities - Mental	+
Type of initial antipsychotic use - Typical	+

(+) positive association, (-) negative association, (??) cannot be determined

3.3.3.2 Independent variables for Aim 2

Aim 2 assessed the association between psychotherapy use and antipsychotic adherence (time to discontinuation and antipsychotic switching). Age, gender, and race were included as predisposing characteristics. State and MSA indicators were classified as enabling factors. Physical and mental comorbidities were included as need characteristics. Type of initial antipsychotic used was included in the model as a health behavioral factor that may affect both psychotherapy use and patients' adherence levels. Table 3.9 summarizes the relationships between the independent and dependent variables for Aim 2.

Table 3.9. Hypothetical Associations between Independent and Dependent Variables for Aim 2

	Use of adjunctive psychotherapy	Adherence	Switching
Use of adjunctive psychotherapy		**+**	**-**
Older age	-	+ or no difference	+ or no difference
Female gender	??	+ or no difference	+ or no difference
Race – nonwhite	-	- or no difference	+ or no difference
State	??	??	??
MSA	+	+	??
Higher number of comorbidities – Physical	+ or no difference	- or no difference	No difference
Higher number of comorbidities – Mental	+	-	+
Types of initial antipsychotics - Typical	+	-	+

(+) positive association, (-) negative association, (??) cannot be determined

3.3.3.3 Independent variables for Aim 3

Hospitalizations

Aim 3 first examined the association between the use of adjunctive psychotherapy and the risk of hospitalization. Age, gender, and race were classified as predisposing factors. State and MSA were classified as enabling factors for inpatient service use. Similar to Aim 1 and Aim 2, need characteristics was measured by comorbidities, and type of initial antipsychotic treatment was considered as a health behavioral factor.

In addition, adherence and an indicator of treatment modification during the follow-up were also included as health behavior factors in Aim 3 because the occurrence of hospitalization should be related to the concurrent medication using behaviors in the same period of time. Table 3.10 describes the relationships between the independent and dependent variables for the hospitalization model in Aim 3.

Table 3.10. Hypothetical Associations between Independent and Dependent Variables for the Hospitalization Model in Aim 3

	Use of adjunctive psychotherapy	Psychiatric hospitalization
Use of adjunctive psychotherapy		**-**
Older age	-	+
Female gender	??	- or no difference
Race – nonwhite	-	+
State	??	??
MSA	+	??
Higher number of comorbidities – physical	+ or no difference	+ or no difference
Higher number of comorbidities – mental	+	+
Types of initial antipsychotics - Typical	+	+
Better adherence during the follow-up	-	-
Modified antipsychotic treatments during the follow-up	+	+

(+) positive association, (-) negative association, (??) cannot be determined

Treatment Costs

Regarding the cost model, age, gender, and race were considered as patient characteristics that could affect the use of adjunctive psychotherapy as well as treatment costs. Similar to previous aims, state and MSA indicators were included in the model as enabling factors. Because treatment costs were assessed from a payer's perspective (Medicaid payment), and different states could have different reimbursement rates, we controlled for the state level effects. Compare to patients living in a non-MSA, patients who lived in a MSA may have higher outpatient and medication costs because they have better access to health care and thus have a higher utilization rate of outpatient and pharmacy services. However, patients living in a MSA may not have higher inpatient costs than patients lived in a non-MSA if patients lived in a MSA can better control for their conditions with better access to outpatient services.

Physical and mental comorbidities were also included in the model as need factors that could also affect both psychotherapy use and treatment costs. Type of initial antipsychotic use was included because it was directly associated with treatment costs. In addition, medication adherence during the follow-up was included in the model because whether a patient adhered to his/her treatment could have a direct effect on health service utilization, which affected treatment costs. Similar to the hospitalization model, an indicator of treatment modification was included in the cost model given that changes in regimens was directly associated with antipsychotic costs and could be indirectly associated with other treatment costs. Table 3.11 summarizes the relationships between the independent and dependent variables for the cost model in Aim 3.

Table 3.11. Hypothetical Associations between Independent and Dependent Variables for the Treatment Cost Model in Aim 3

	Use of adjunctive psychotherapy	Inpatient Costs	Outpatient Cost	Medication Costs	Total Costs
Use of adjunctive psychotherapy		-	+	+	- or no difference
Older age	??	+	+	?? or no difference	+
Female gender	??	??	+ or no difference	?? or no difference	?? or no difference
Race – nonwhite	-	+	-	-	??
State	??	??	??	??	??
MSA	+	-	+	+	+
Higher number of comorbidities – physical	+ or no difference	+ or no difference	+	+	+
Higher number of comorbidities – mental	+	+	+	+	+
Type of initial antipsychotics - Typical	+	+	+	- or No difference	+
Better adherence during the follow-up	-	-	- or no difference	+	??
Treatment modification during the follow-up	+	+	+/-	-	+

(+) positive association, (-) negative association, (??) cannot be determined

3.4 Statistical Analysis by Aims

This section explains the analytical plans by Aims. Data construction, logistic regressions, and survival analysis were performed using SAS 9.2 (Cary, NC). Hurdle models, generalized linear models, instrumental variable analyses, and bootsratp were performed using STATA 10 (College Station, TX). Statistical significance was determined as alpha less than 0.05 using two-sided tests.

3.4.1 Aim 1: To describe the patterns and factors associated with the use of adjunctive psychotherapy.

Aim 1 began with comparisons of two groups: 1) patients with both pharmacotherapy and psychotherapy and 2) patients with pharmacotherapy only. Patient characteristics and other clinical factors were summarized for these two groups. Due to insufficient sample size, our analyses were not further stratified by type of psychotherapy use.

To better understand at what treatment stage patients initiated their psychotherapy, time of psychotherapy initiation was evaluated. Incidence of different types of psychotherapy was summarized with frequency and percentage over a three-month interval (i.e. every three months in the follow-up period). Time of psychotherapy initiation was reported as number and percentage of patients newly initiated on psychotherapy during each of the three-month intervals.

For unadjusted statistical tests, *t*-tests and Chi-square tests were used to compare the distributions of continuous and categorical variables between the psychotherapy users and non-users. For the adjusted analysis, a multiple logistic regression was used to identify factors associated with the use of psychotherapy (dichotomized as yes/no) during the follow-up. The model for Aim 1 is:

$$\begin{aligned}\text{Logistic}(\text{Psychotherapy use}) &= \beta_0 + \beta\ \ (\text{Age}) + \beta_2(\text{Gender}) + \beta_3(\text{Race}) + \beta_4(\text{State}) + \beta_5(\text{MSA}) \\ &+ \beta_6(\text{Physical comorbidities}) + \beta_7(\text{Mental comorbidities}) + \varepsilon\end{aligned}$$

Age: a vector of age between 18 and 35, 36-50, and >50 years old as in 2001
Gender: a vector of male and female gender
Race: a vector of White, Black, and Other race

State: a vector of state indicators (IL, KS, MN, NC)
MSA: a vector of MSA versus non-MSA
Physical comorbidities: a scalar of Charlson Comorbidity Score
Mental comorbidities: a set of scalar indicating whether a patient had specified mental comorbidities (depression, alcohol abuse, drug abuse, anxiety, dementia, other psychosis)

3.4.2 Aim 2: To assess whether the use of adjunctive psychotherapy in combination with pharmacotherapy improves patients' adherence to antipsychotic treatments.

H2.1: Among new antipsychotic users, patients who receive adjunctive psychotherapy stay on medication treatment longer than patients who do not receive psychotherapy.

H2.2 Patients receiving adjunctive psychotherapy are less likely to switch antipsychotics than patients without adjunctive psychotherapy.

Given that medication adherence was measured as number of days to antipsychotic discontinuation, a Cox proportional-hazard model was used to assess time to discontinuation. Because medication switching was a dichotomous variable, a logistic regression was used to assess the likelihood of switching. Patients who were hospitalized before their discontinuation will be treated as censored cases at the time of hospitalization.

Because the Cox proportional-hazard model assumes proportional hazard between the two groups, we first tested this assumption by plotting the log of cumulative hazard for each of the two groups. In addition, an interaction term of time and psychotherapy use and log time [psychotherapy*log(t)] was added to the Cox model to check the proportional hazard assumption. Since the interaction term was statistically significant, which meant the

proportional hazard assumption was violated, the interaction term was kept in the Cox model to allow the hazard to be non-proportional over time.

A lotgistic regression was used to assess medication switching, measured as ever switch versus never switch during the follow-up. In addition to the original definition of switching (defined as an initiation of a different antipsychotic during a 30 or 15-day window after the end of the last supply), two sensitivities analyses were conducted using different definitions of switching. In addition to the originally defined switchers, patients who initiated a second antipsychotic agent before the end of the last supply and never went back to use their first antipsychotic agent were also defined as switchers in the first sensitivity analysis. However, because it was difficult to distinguish switching from augmenting in patients with multiple switching on one or more antipsychotics, among patients who filled a second antipsychotic drug before the end of the last supply of the initial antipsychotic, only patients who switched antipsychotic once were re-coded as switchers in the first sensitivity analysis model. In the second sensitivity analysis, treatment modification (including both augmenting and switching) was used as the dependent variable instead of medication switching. Although treatment modification includes both augmenting and switching, this variable should capture all of the switching activities which allows us to assess the effect of psychotherapy on medication switching (especially patients with multiple switching) from a different angle. Models used to assess Aim 2 are:

Cox(Time to discontinuation, Time to switching)

$$= \beta_0 + \beta_1(\text{Psychotherapy}) + \beta_2(\text{Age}) + \beta_3(\text{Gender}) + \beta_4(\text{Race}) + \beta_5(\text{State})$$
$$+ \beta_6(\text{MSA}) + \beta_7(\text{Physical comorbidities}) + \beta_8(\text{Mental comorbidities})$$
$$+ \beta_9(\text{Type of antipsychotics}) + \beta_{10}(\text{psychotherapy} * \log(t)) + \varepsilon$$

Logistic(Switching)

$$= \beta_0 + \beta_1(\text{Psychotherapy}) + \beta_2(\text{Age}) + \beta_3(\text{Gender}) + \beta_4(\text{Race}) + \beta_5(\text{State})$$
$$+ \beta_6(\text{MSA}) + \beta_7(\text{Physical comorbidities}) + \beta_8(\text{Mental comorbidities})$$
$$+ \beta_9(\text{Type of initial antipsychotic treatment}) + \varepsilon$$

Psychotherapy: an indicator of psychotherapy use
Age: a vector of age between 18 and 35, 36-50, and >50 years old as in 2001
Gender: a vector of male and female gender
Race: a vector of White, Black, and Other race
State: a vector of state indicators (IL, KS, MN, NC)
MSA: a vector of MSA versus non-MSA
Physical comorbidities: a scalar of Charlson Comorbidity Index
Mental comorbidities: a set of vectors indicating whether a patient had specified mental comorbidities (depression, alcohol abuse, drug abuse, anxiety, dementia, other psychosis)
Type of initial antipsychotic treatment: a vector of the type of antipsychotics a patient initially received (atypical versus typical)

3.4.3 Aim 3: To assess whether receiving adjunctive psychotherapy in combination with pharmacotherapy reduces total health care costs and hospitalization rates.

H3.1: Patients receiving adjunctive psychotherapy have a lower rate of hospitalizations than patients who do not receive psychotherapy.

H3.2: Patients receiving adjunctive psychotherapy have lower inpatient and total costs, but higher outpatient and pharmacy costs compared to those who do not receive psychotherapy.

As described in section 3.3.2.2, hospitalization was measured as the number of hospitalizations during the follow-up period, and a hurdle model was used to compare the hospitalization rates between the two groups. For the cost analyses, a generalized linear model (GLM) was applied because the distribution of treatment costs was highly skewed. The link function of the GLM model was chosen based on tests of normality. Each dependent variable was transformed by different functional forms (e.g. log transformation or power transformation), and normality tests were then performed to assess whether the transformed dependent variable was normally distributed. If the distribution of dependent variable was close to normal, the transformational form was selected as the link function. The distribution was tested using a modified Park test proposed by Manning and Mullahy.[131]

Due to the high proportion of zero inpatient costs, a two-part model was applied to compare the inpatient costs between psychotherapy users and non-users. The first part of the model was a logistic regression which predicted the probability of having non-zero inpatient costs, and the second part was a GLM with a gamma distribution and a log link function. For outpatient costs, a GLM model with gamma distribution and a log link function was applied, and models with gamma distribution and power link function were applied to medication costs and total treatment costs models.

In addition, the predicted values from each of the outcome models were calculated and reported. The incremental costs for psychotherapy users versus non-users were also calculated. For two-part models (hospitalizations and inpatient costs), the expected values

from the first-part, the second-part, and two parts combined were all reported. The unconditional expected values from the two-part models were calculated as (the predicted probability from the first-part model)*(the expected number from the second-part model). A bootstrap program with 1,000 replications was then used to calculate the bias corrected 95% confidence intervals. The model used to assess hospitalization rate is:

$$\begin{aligned}\text{Hurdle (Hospitalizations)} &= \beta_0 + \beta_1(\text{Psychotherapy}) + \beta_2(\text{Age}) + \beta_3(\text{Gender}) + \beta_4(\text{Race}) + \beta_5(\text{State}) \\ &+ \beta_6(\text{MSA}) + \beta_7(\text{Physical comorbidities}) + \beta_8(\text{Mental comorbidities}) \\ &+ \beta_9(\text{Type of Initial Antipsychotic Treatment}) \\ &+ \beta_{10}(\text{Adherence}) + \beta_{11}(\text{Treatment modification}) + \varepsilon\end{aligned}$$

The model used to assess treatment costs is:

$$\begin{aligned}\text{GLM(Costs)} &= \beta_0 + \beta_1(\text{Psychotherapy}) + \beta_2(\text{Age}) + \beta_3(\text{Gender}) + \beta_4(\text{Race}) + \beta_5(\text{State}) \\ &+ \beta_6(\text{MSA}) + \beta_7(\text{Physical comorbidities}) + \beta_8(\text{Mental comorbidities}) \\ &+ \beta_9(\text{Type of initial antipsychotic treatment}) + \beta_{10}(\text{Adherence}) \\ &+ \beta_{11}(\text{Treatment modification}) + \varepsilon\end{aligned}$$

Psychotherapy: an indicator of psychotherapy use
Age: a vector of age between 18 and 35, 36-50, and >50 years old as in 2001
Gender: a vector of male and female gender
Race: a vector of White, Black, and Other race
State: a vector of state indicators (IL, KS, MN, NC)
MSA: a vector of MSA versus non-MSA
Physical comorbidities: a scalar of Charlson Comorbidity Index

Mental comorbidities: a set of vectors indicating whether a patient had specified mental comorbidities (depression, alcohol abuse, drug abuse, anxiety, dementia, other psychosis)

Type of initial antipsychotic treatment: a vector of the type of antipsychotics a patient initially received (atypical versus typical)

Adherence: a vector indicating whether PDC ≥ 0.8 during the follow-up period

3.5 Methodological Issues

In a randomized trial, study subjects are randomly assigned to either treatment or control groups, which ensures the balance of all observed and unobserved covariates between the two groups. In an observational study, however, study subjects are often not randomly assigned to receive treatments, which can lead to systematic differences between groups. If such differences are associated with both the treatment assignment and the outcome of interest, estimates can be biased. Since the study subjects in this dissertation are not randomly assigned to receive adjunctive psychotherapy, it is important to adjust for systematic differences between the two groups.

In this study, we adjust the observed imbalanced factors by multivariate regression models. However, this study may still suffer from confounding bias due to unobserved or un-measurable factors. Disease severity may be one of the un-measurable confounding factors in this study. Patients with more severe symptoms may be more likely to receive psychotherapy and more likely to be hospitalized. In this case, failing to adjust for disease severity will bias the estimate upward and towards the null. Unobservable confounding variables can also lead to an endogeneity problem. Without observing disease severity, a physician may assign a patient to psychotherapy based on his/her risk of hospitalization. As

a result, the use of psychotherapy and hospitalization are jointly determined, which can also result in biased estimates.

One way to address the unobserved confounding and endogeneity issues is to use an instrumental variable (IV) to estimate the effect of adjunctive psychotherapy. Instrumental variables create a pseudo-randomization situation by inducing variation in the treatment, and this technique adjusts for both observable and unobservable confounders. With the balance of all observed and unobserved covariates, the local average treatment effect can be assessed with an IV.[132-134] However, a strong instrument relies on two assumptions: 1) the instrument is strongly associated with the treatment, and 2) the instrument does not have an effect on the outcome of interest other than through the treatment.[132-135]

Given the two critical assumptions of instrumental variables, it is usually hard to identify potential instruments that are strong enough and meet both criteria for successful IV estimates. Another method to reduce confounding by indication is through the propensity score method. Propensity score is a summary score describing the likelihood of a patient receiving treatment based on observed covariates.[134, 136, 137] Grouping patients in the treatment and control groups by propensity score will balance the distribution of observed covariates. For this to be true, a propensity score model must include all covariates that are associated with both the treatment and outcomes (i.e. confounders).[133]

Similar to the IV approach, results from the propensity score matching may not be generalizable to the entire population because patients with extreme scores will not have comparable partners in the other group. As a result, findings can only be generalized to patients represented in both groups.[137] Because of the assumption that treatment is assigned based only on observed factors, the magnitude of bias due to omitted variables can be similar

to multiple regression adjustment.[134] However, a propensity score model suffers less from misspecification than a multiple regression model given that there is no restriction on the number of covariates in the propensity score model.[133, 134]

In addition to the propensity score approach, fixed-effect modeling can be another way to reduce treatment selection. Using repeated observations, a fixed-effect model differences out the time-invariant effects (both measurable and un-measurable), and it compares patients who ever switched psychotherapy use (either from no psychotherapy to have psychotherapy, or the other way around) to those who never or always have psychotherapy at different time points. To get a causal effect from a fixed-effect model, two conditions need to be held: 1) sufficient within group variation and 2) the switching between receiving and non-receiving psychotherapy is random (conditional on the covariates and un-measurable fixed effects).[138] A fixed-effect estimation will be biased if the unmeasured effects are time-variant (such as disease severity) or if measurement error occurs. With claims data, our measurement bias should be small, or at least, consistent over time. With consistent measurement errors, results from a fixed-effect model should not suffer from attenuation bias because the measurement errors will be differenced out.

In this dissertation, IV technique was used to eliminate the potential confounding from both observable and unobservable factors. Propensity scores and fixed-effect techniques were not applied because of two reasons. First, the results with propensity score technique should be similar to the results from the multiple regression models because this technique only deals with observable confounders. The results from this study, however, should be mostly threatened by unobservable confounders. Second, because one of our outcomes (i.e. hospitalizations) is rare, there may not be enough within variations for fixed-

effect estimates. Given all the concerns above, IV was chosen over the propensity score and fixed-effect methods.

3.6 Instrumental Variable Analysis

3.6.1 Instrumental Variables

Two variables that may induce the variation in psychotherapy use but are not directly associated with adherence and hospitalization were considered as potential instruments in this study: 1) whether a provider provided psychotherapy to the schizophrenia patient seen prior to the current patient, and 2) whether a patient has seen a provider who provided psychotherapy to patients with major depressive disorder (MDD). Both of these IVs are trying to capture the underlying providers' preference.

According to Brookhart and his colleagues' work, providers' preference of treatment can be measured as the treatment assignment (yes/no) for a patient who is most recent prior to the next patient's treatment.[135, 139] Based on this idea, we constructed a variable which measures whether a patient received psychotherapy as a preference indicator of psychotherapy use for the next patient. For this variable to hold as a valid IV, two assumptions must be true: 1) physicians' choice of treatment must be directly associated with the assignment of psychotherapy, and 2) treatment choice is unrelated to the treatment outcomes except through psychotherapy use. Patients without sufficient information to construct an IV were excluded from the IV analysis. The final sample sizes for each instrument are summarized in Table 3.12 below.

Table 3.12. Sample Sizes for Each Instrumental Variable

	Psychotherapy		
Instrumental Variables	**Users**	**Non-Users**	**Total**
Psychotherapy use for the last patient seen by the same provider	585	2,818	3,403
Psychotherapy use for MDD patients seen by the same provider	585	2,814	3,399

The validity of using physicians' prescribing preference as an instrument has been proven in two of Brookhart's previous studies. One assessed the association between the types of antipsychotic use and short-term mortality, and another one evaluated the relationship between the use of COX-2 inhibitors and gastrointestinal complications.[135, 139] In both cases, physicians' preference served as a good instrument because physicians' choice of treatment can directly affect the medication assignment, but it is unlikely that physicians' preference will affect patients' morbidity or mortality rates.

In our case, a physician's preference of psychotherapy use should directly associate with the use of psychotherapy. Since atypical antipsychotics are recommended as the first-line treatment for schizophrenia patients, whether a physician preferred to use adjunctive psychotherapy should not affect his/her decision on medication treatment. Therefore, the preference of psychotherapy use is unlikely related to patients' adherence other than through the actual use of psychotherapy.

The other IV constructed in this study is whether a patient has ever seen a provider who ever provided psychotherapy for his/her patients with major depressed disorder. Providing psychotherapy to MDD patients is used as an indicator of psychotherapy preference. A provider was considered as preferring psychotherapy use if he/she ever provided psychotherapy to his/her MDD patients. The assumption is that if a patient has seen

a provider providing psychotherapy to his/her patients with MDD at any time during the study period, the patient should be more likely to receive psychotherapy for that provider, and whether psychotherapy is provided to MDD patients should not be related to our outcomes of interest, which are medication adherence, hospitalizations, and treatment costs among patients with schizophrenia.

3.6.2 Two-Stage Residual Inclusion Model and Specification Tests

Instead of using two-stage predictor substitution, we implemented two-stage residual inclusion (2SRI) models because the traditional linear IV method could be biased in non-linear settings, and this bias would not attenuate even with a large sample size.[140, 141] Because a regular second-stage model did not account for the uncertainty carried from the first-stage predictions, the 95% confidence interval generated from the second-stage model was narrower than it should be. We therefore used bootstrap to calculate the 95% confidence intervals to account for this under-estimation of confidence intervals. As mentioned above, two instruments were constructed in this study: 1) whether a patient's provider had provided psychotherapy for the previous patient seen by the same provider and 2) whether a patient had ever seen a provider who ever provided psychotherapy for his/her patients with MDD at anytime during the study. Both IVs were dichotomous as yes (IV= 1) versus no (IV= 0).

Three specification tests were performed to test the validity of our IVs with respect to different outcomes (medication persistency, hospitalizations, and treatment costs). We first tested the strength of each IV by checking the z-statistics in the first-stage logistic regression model. In a linear regression model, an IV is considered to be strongly associated with psychotherapy use if the coefficient in the regression model is significant and the F-statistic

is large (F-statistic> 10). Because we used a logistic regression as our first-stage model, instead of checking the F-statistics, we used a Wald test to evaluate the strength of our IVs. After running the first-stage model, we first checked the z-statistic and p-value of the instrument provided by the logistic regression output. A Wald test was then performed to further test the strength of the instrument by checking the chi-square statistic and p-value from the test result. Each instrument was first tested separately, and the strength of the two instruments was then tested jointly.

With the over-identification situation, we were able to test whether our IVs were validly excluded from the second-stage model (no direct or indirect associations between the IVs and outcomes other than through psychotherapy) using a Hausman over-identification test.[142] If no test results could be obtained from a Hausman test due to non-inversable matrix or negative chi-square statistic, a Chow test was then used to compare the differences in coefficients between the two compared models. In addition to Hausman tests, likelihood ratio (LR) tests were also performed to check the exclusion criteria of our IVs. However, because LR tests evaluate all the IVs jointly, we can only conclude that not all of our IVs are validly excluded from the second-stage equation if we reject the null that all IVs are jointly excluded from the second-stage model, but we are unable to determine which IV is more valid. Therefore, this test served as a second check of our IV selection for the Hausman test results.

Lastly, we used a Hausman test to check whether psychotherapy was endogeneous which could make the model become inconsistent.[142] Similarly, if no test results could be obtained from the Hausman test, a Chow test was then used to check the endogeneity of psychotherapy use. In addition, an alternative test of endogeneity was performed. This test

utilized the second-stage regression model, which included both the actual psychotherapy use variable and the predicted residuals from the first-stage, to test the endogeneity of psychotherapy use. The null hypothesis is that psychotherapy use is exogeneous, and hence, the predicted residuals should not have any explanatory power in the second-stage regression. Therefore, finding the predicted residuals significant and rejecting the null would indicate that psychotherapy use is endogeneous.[143]

Results from the final endogeneity test, however, were only used as a reference for several reasons. First, as addressed above, Hausman tests may not be able to provide valid results given the non-inversable matrix or negative chi-square statistic problems. Although a Chow test can be applied as an alternative of the Hausman test, a valid conclusion of endogeneity may not be reached by comparing the coefficients manually. In addition, given the high variances of a 2SRI model, we may not have enough power to reject the null hypothesis of exogeneity. Finally, even with the rejection of null, it is still unclear that whether this rejection is caused by the endogeneity of psychotherapy, or by other factors such as incorrect functional forms or measurement errors in psychotherapy. Since the endogeneity tests are inconclusive, whether the use of adjunctive psychotherapy was endogeneous was mainly determined by assumptions, not by the test results. We assumed that all of our dependent variables were endogeneous and conducted IV estimations. The results from the specification tests and IV models are discussed in the following sections.

3.6.3 IV Limitations

Several limitations should be noticed when interpreting the results of IV estimates. First, the IV estimates are consistent when our instruments are strongly correlated with the

explanatory variable (i.e. psychotherapy use) and uncorrelated with the un-measurable confounders (i.e. IVs are not correlated with the unmeasurable confounders). However, if the associations between our instruments and the explanatory variable are not strong, the results from our IV models can be in efficient and biased.[143, 144] Since the test results showed that the two IVs were both strongly associated with psychotherapy use, weak instruments should not be a concern.

Second, although we were able to perform tests for the exclusion restriction criterion with the overidentification situation, whether these IVs are truly uncorrelated with the outcomes other than through psychotherapy use cannot be tested. Our IV estimates can still be biased if the instruments are correlated with the outcomes.[145] For example, patients with more severe conditions may be more likely to be referred to a provider who provides psychotherapy. In this situation, provider preference is linked to disease severity and thus indirectly correlates with outcomes. As aforementioned, some common reasons for not referring patients to psychotherapy include 1) providers' belief that patients are unlikely to engage in psychotherapy, 2) patients are doing well with pharmacotherapy and therefore do not need psychotherapy, 3) patient refuse, and 4) providers' lack of knowledge about psychotherapy.[61-64]

In the first situation, patients who are not referred to psychotherapy may be sicker because they are less likely to engage in psychotherapy, while in the second situation, patients who do not receive psychotherapy may be healthier because healthier patients are more likely to be well controlled by medication only. In the third situation, however, both healthier and sicker patients can refuse to use psychotherapy for different concerns. Sicker patients may lack of insight and thus refuse the treatment, whereas healthier patients may be

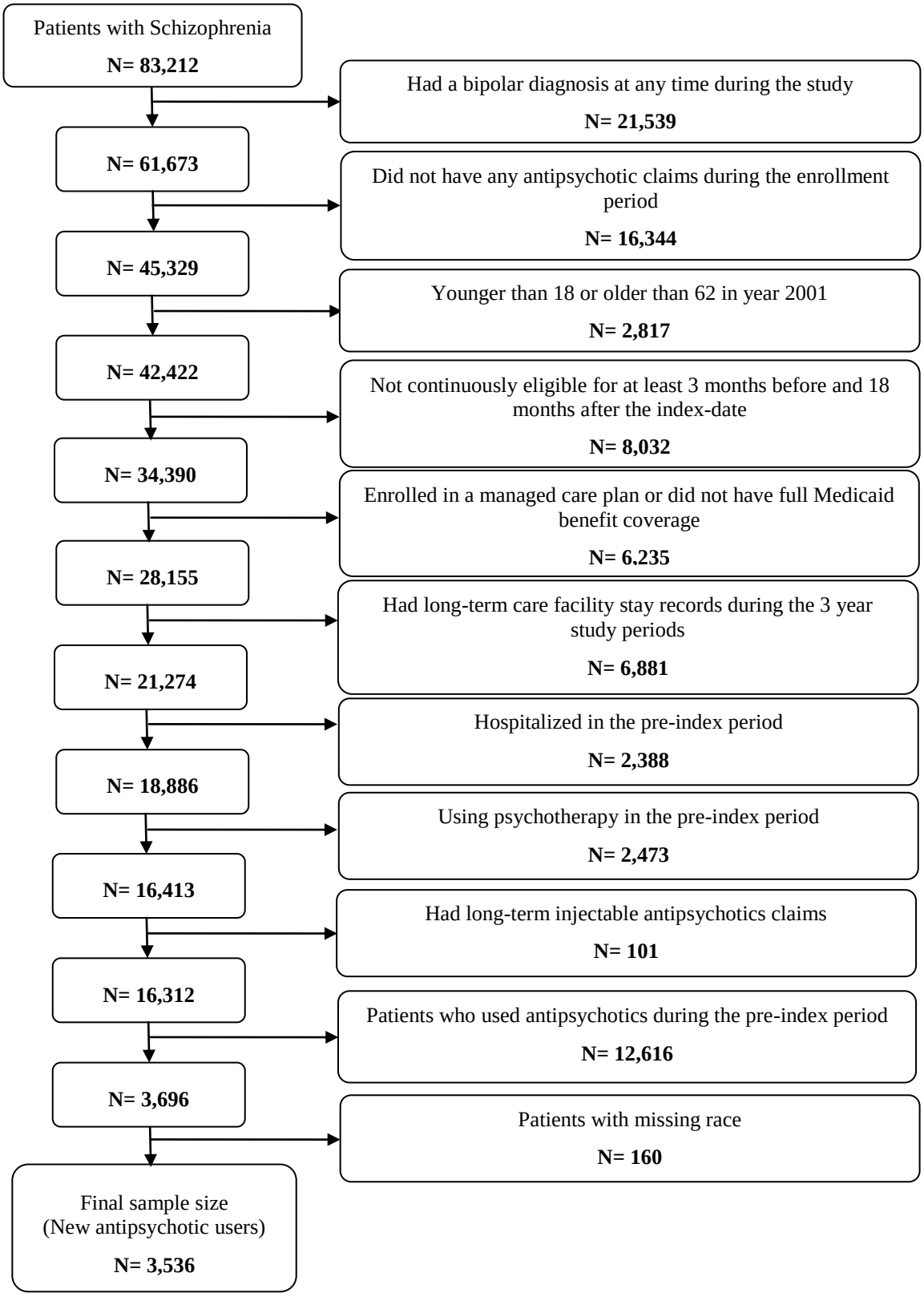
concerned about the time taken for the treatment and believe that they can do well simply by medication treatment. In the last situation, if a provider does not have enough knowledge about psychotherapy and hence does not provide it to his/her patients, there should be no selection problem because all patients will not receive psychotherapy regardless of their disease severity.

In addition to provider referral, patients may actively seek psychotherapy. Patients who seek psychotherapy should be relatively healthy and have some knowledge about psychotherapy. Therefore, given all of the hypothetical situations and considerations above, the problem that our IVs are correlated with the outcomes of interest through un-measurable disease severity should be minor. Nevertheless, if our IVs are actually correlated with the second-stage residuals through unobservable confounders, such as disease severity or physician practice patterns, the results from the IV models are biased. Finally, because IV estimates require two-stage modeling, the insignificant findings can simply be due to the nature of wide confidence intervals caused by the two-stage estimation.

CHAPTER 4: RESULTS

Using Medicaid data from four states (IL, KS, MN, NC), our initial sample included 84,180 patients with at least two outpatient or one inpatient diagnoses of schizophrenia. After applying all the inclusion/exclusion criteria, there were 3,696 patients included in this study. We further excluded 160 patients with missing race. The final sample size for this study was 3,536 with 606 (17.14%) patients as psychotherapy users and 2,930 (82.86%) as non-users (Figure 4.1). The following sections describe the results by Aims.

Figure 4.1. Sample Size Flow Chart



4.1 Aim 1: To describe the patterns and factors associated with the use of adjunctive psychotherapy

Aim 1 begins with descriptive statistics to summarize patient characteristics and patterns of psychotherapy use. The sensitivity analysis showed that there was no difference to code 90849 either as group therapy or family therapy. Because of insufficient sample size ($N_{individual\ therapy}$= 555, $N_{family\ therapy}$= 16, $N_{group\ therapy}$=83), no formal statistical tests were performed to test the differences among different types of psychotherapy. Patient characteristics were only compared descriptively across three different types of psychotherapy. A logistic regression was used to assess factors associated with psychotherapy use.

Table 4.1 summarizes the characteristics of adjunctive psychotherapy users and non-users. Compared to the non-psychotherapy users, psychotherapy users tended to be younger (mean age: 39.61 for users vs. 41.20 for non-users, $p<0.01$), more likely to be White (43.23% of users vs. 37.58% of non-users, $p<0.01$), and less likely to live in a metropolitan statistical area (71.29% vs. 75.70, $p<0.01$). Psychotherapy users were more likely to have depression (20.63% vs. 11.40%, $p<0.01$), anxiety (6.77% vs. 4.37%, $p=0.01$), and other psychoses (11.55% vs. 8.63%, $p=0.02$). In addition, a higher proportion of psychotherapy users received atypical antipsychotics as their initial treatment (88.28% vs. 85.02%, $p=0.04$).

On average, psychotherapy users had 5.41 [Standard Deviation (SD)= 8.25] psychotherapy visits, and the average number of days between the first psychotherapy visit and last psychotherapy visit was 161.29 days (SD= 170.32). However, the distributions for both the number of psychotherapy visits as well as the duration of psychotherapy were highly skewed. More than 50% of the psychotherapy users had less than five psychotherapy visits,

and around 40% of the psychotherapy users had all of their treatment sessions within the first 40 days (results not shown here).

A higher percentage of psychotherapy users were adherent to their regimens than non-users (29.04% vs. 22.49%, p<0.01). Compared to non-users, a higher percentage of psychotherapy users had switched their antipsychotics (21.45% vs. 15.19% in a 15-day window, p<0.01; 27.89% vs. 19.52% in a 30-day window, p<0.01) or augmented their antipsychotic treatment (39.11% vs. 29.32%, p<0.01) at sometime during follow-up. When considering switching or augmenting together, a higher proportion of psychotherapy users were found to have modified their treatment regimens (i.e. either switched or augmented their medications).

Table 4.1. Patient Characteristics of Psychotherapy Users and Non-Users

	Adjunctive Psychotherapy Users	Non-users	
	N= 606	N= 2,930	
	%	%	P-value
Baseline Characteristics			
Age, Mean(SD)	39.61(10.98)	41.20(10.23)	<0.01
Age Group			<0.01
18-35	35.81	27.71	
36-50	46.20	53.38	
>50	17.99	18.91	
Gender			0.16
Male	54.62	57.71	
Female	45.38	42.29	
Race			<0.01
White	43.23	37.58	
Black	49.01	56.28	
Other	7.76	6.14	
State			0.35
IL	35.64	39.18	
KS	8.91	7.71	
MN	10.56	10.65	

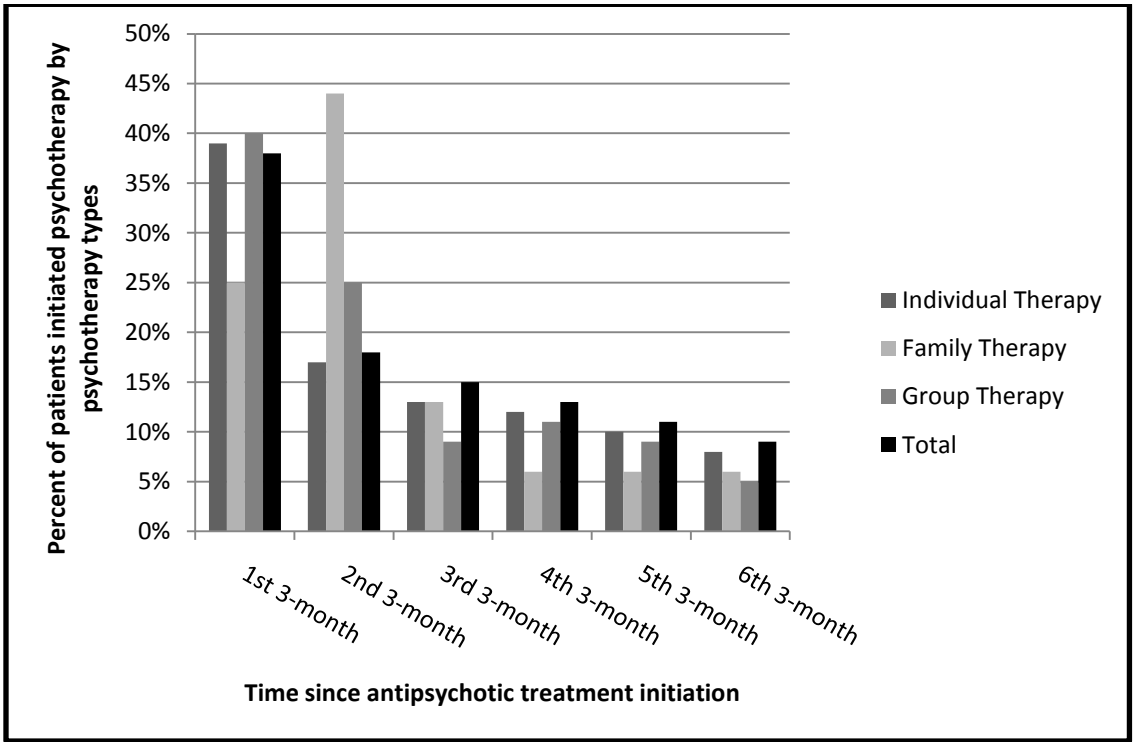
NC	44.88	42.46	
MSA			<0.01
Yes	71.29	75.70	
No	28.71	24.30	
Charlson Score, Mean(SD)	0.19(0.60)	0.18(0.60)	0.71
Mental Comorbidities			
Depression	20.63	11.40	<0.01
Substance Abuse	8.25	8.02	0.85
Anxiety	6.77	4.37	0.01
Other Psychoses	11.55	8.63	0.02
Type of Initial Treatment			0.04
Atypical	88.28	85.02	
Typical	11.72	14.98	
Characteristics Measured During the Follow Up			
Number of Psychotherapy Visits, Mean(SD)	5.41(8.25)	N/A	
Duration of Psychotherapy (Days)†, Mean(SD)	161.29(170.32)	N/A	
Adherence			<0.01
Yes	29.04	22.49	
No	70.96	77.51	
Medication Augmentation	39.11	29.32	<0.01
Treatment modification- switching in 15 days or augmentation	41.75	31.88	<0.01
Treatment modification- switching in 30 days or augmentation	43.56	33.41	<0.01

SD: Standard Devisation; IL: Illinois, KS: Kansas, MN: Minnesota, NC: North Carolina; MSA: Metorpolitan Statistical Area; PDC: Proportion of Days Covered; N/A: Not Applicable

† Duration of psychotherapy was defined as the number of days between the first psychotherapy visit to the last psychotherapy visit

We next evaluated when patients began to use psychotherapy after the initiation of their pharmacotherapy. Figure 4.2 shows the percentage of patients who initiated different types of psychotherapy by a 3-month interval. About 40% of the patients initiated their psychotherapy in the first three months after antipsychotic treatment initiation. The rate of all types of psychotherapy use dropped to 18% during month three to month six, and it then gradually declined through the end of the follow-up period.

Figure 4.2. Percent of Patients Initiated Psychotherapy at Different Intervals



In terms of the type of initial psychotherapy, among the 606 psychotherapy users, 540 of them began with individual therapy, 8 of them began with family therapy, and 58 of them started with group therapy. Most patients used only one type of psychotherapy. Nine patients received both individual and family therapy, 37 patients received individual and group therapy, and one patient received all three types of psychotherapy.

Because the three types of psychotherapy had relatively small sample sizes and were not mutually exclusive, we collapsed all three different types of psychotherapy into one group (as psychotherapy users) for the subsequent analyses. Results from the logistic regression are summarized in Table 4.2. Consistent with our hypotheses, older patients were less likely to use psychotherapy than younger patients (Odds Ratio $[OR]_{Age\ 36\text{-}50}$= 0.69, 95% Confidence Interval $[CI]_{Age\ 36\text{-}50}$= 0.56-0.84; $OR_{Age>50}$= 0.73, 95% $CI_{Age>50}$= 0.56-0.95), and

Black patients were less likely to receive adjunctive psychotherapy than White patients (OR= 0.75, 95% CI= 0.62-0.92). Unlike the original hypothesis, we did not find patients living in a metropolitan area to be more likely to receive psychotherapy. Patients with comorbid depression were more likely to receive psychotherapy (OR= 1.86, 95% CI= 1.47-2.36) then patients without depression, which was consistent with our original hypothesis. Finally, we did not find patients initiating with typical antipsychotic to be more likely to receive psychotherapy as we originally hypothesized.

Table 4.2. Factors Associated with Adjunctive Psychotherapy Use ($N= 3,536$; $N_{user}= 606$, $N_{non\text{-}user}= 2,930$)

	OR	95% CI
Age Group		
18-35	*Reference*	-
36-50	0.69**	(0.56-0.84)
>50	0.73*	(0.56-0.95)
Gender		
Male	*Reference*	-
Female	1.12	(0.95-1.35)
Race		
White	*Reference*	-
Black	0.76**	(0.62-0.93)
Other	1.05	(0.74-1.51)
State		
IL	*Reference*	-
KS	1.18	(0.83-1.68)
MN	0.96	(0.70-1.32)
NC	1.20	(0.98-1.49)
MSA		
Yes	*Reference*	-
No	1.17	(0.95-1.45)
Charlson Score	1.01	(0.86-1.17)
Mental Comorbidities		
Depression	1.86**	(1.47-2.36)
Substance Abuse	0.98	(0.71-1.36)
Anxiety	1.28	(0.88-1.87)

Other Psychoses	1.33	(1.00-1.77)
Type of Initial Treatment		
Atypical	*Reference*	-
Typical	0.86	(0.65-1.13)

OR: Odds Ratio; CI: Confidence Interval; SD: Standard Devisation; IL: Illinois, KS: Kansas, MN: Minnesota, NC: North Carolina; MSA: Metorpolitan Statistical Area; PDC: Proportion of Days Covered, measured in the follow-up period
* p<0.05
** p<0.01

4.2 Aim 2: To assess whether the use of adjunctive psychotherapy in combination with pharmacotherapy improves patients' adherence to antipsychotic treatments

Two dependent variables were evaluated in Aim 2: medication persistency and medication switching. Medication persistency was measured as time to all-cause discontinuation which was defined as a gap greater than 30 days (or greater than 15 days for the sensitivity analysis). Medication switching was defined as an initiation of a different antipsychotic agent within 30 days (or 15 days for the sensitivity analysis) after the end of the last supply, and the variable was dichotomous (ever switch versus never switch). Cox proportional-hazard models were used to compare the discontinuation rates between psychotherapy users and non-users, and logistic regressions were used to assess the likelihood of switching between the two groups.

4.2.1 Medication Persistency

Table 4.3 shows the unadjusted outcomes for Aim 2. Results from t-tests showed that medication persistence was similar for psychotherapy users and non-users using either a gap in excess of 30 days (214 versus 220 days) or 15 days (159 versus 163 days) definition.

Results from chi-square tests indicated a higher percentage of patients receiving psychotherapy had switched their antipsychotics in either a 30-day (27.89% versus 19.52%, $p<0.01$) or 15-day (21.45% versus 15.19%, $p<0.01$) window.

Table 4.3. Unadjusted Results for Outcomes in Aim 2- Medication Discontinuation and Switching

	Adjunctive Psychotherapy		
	Users	Non-users	
	N= 606	N= 2,930	
	%	%	P-value
Number of Days to a Gap >30 days, Mean(SD)	220.9(220.0)	214.8(225.5)	0.54
Number of Days to a Gap >15 days, Mean(SD)	159.4(192.2)	163.1(203.4)	0.68
Medication Switch – 30-day Window	27.89	19.52	<0.01
Medication Switch – 15-day Window	21.45	15.19	<0.01

The unadjusted survival curves for the psychotherapy users and non-users are presented in Figure 4.3 and Figure 4.4 for a 30-day and 15-day gap definition, respectively. Using a 30-day or a 15-day gap to define discontinuation did not seem to greatly alter the results, and Log-Rank tests results indicated that there were no significant differences between the two groups using either definition ($p=0.41$ for a 30-day gap definition, and $p= 0.94$ for a 15-day gap definition). In both graphs, we can see a sharp drop followed by a gradual decrease in survival rate around day 30. The gradual decrease before the sharp drop reflects the immortal time because by definition, patients are unable to discontinue their medications before the end of their first antipsychotic supply which is often 30 days. The two graphs also show that psychotherapy users had better persistency in the beginning of the follow-up, but they also had a higher rate of discontinuation over time.

Figure 4.3. Survival Curves for A 30-day Gap Discontinuation

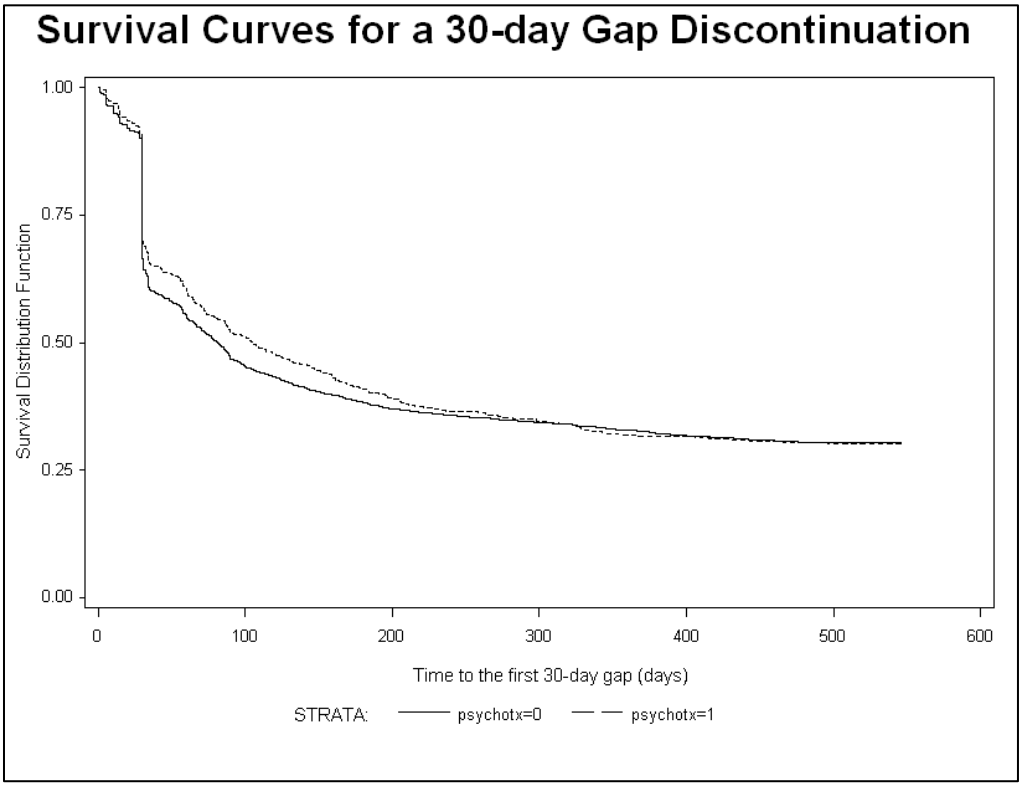
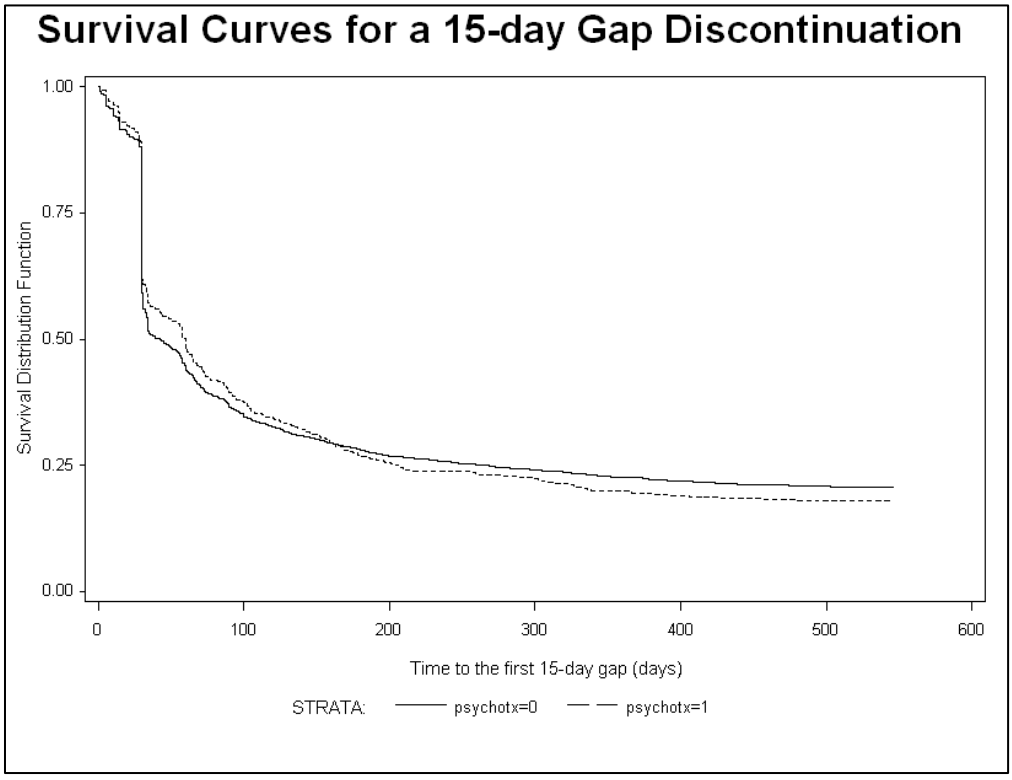


Figure 4.4. Survival Curves for a 15-day Gap Discontinuation



Results from Cox proportional-hazard models are presented in Table 4.4. In the main analysis (discontinuation defined as having a gap in excess of 30 days), we found that patients who received psychotherapy were less likely to discontinue their treatment than patients who did not receive psychotherapy (β= -0.593, p< 0.01), but this protective effect diminished and patients with psychotherapy became less persistent over time ($\beta_{Interaction}$ = 0.154, p< 0.01). Compared to White patients, non-white patients were more likely to experience a discontinuation (β_{Black}= 0.389, p< 0.01; $\beta_{Other\ race}$= 0.308, p< 0.01). Patients living in North Carolina were more likely to discontinue antipsychotics than patients in Illinois (β= 0.651, p= 0.02). In addition, patients with typical antipsychotics as their initial treatment were also more likely to discontinue their treatment than patients who had begun their treatment with atypical antipsychotics (β= 0.651, p< 0.01). Interestingly, patients who had modified their treatment were less likely to experience a gap longer than 30 days compared to patients who did not modify their treatment (β= -0.197, p< 0.01).

The sensitivity analysis (discontinuation defined as having a gap in excess of 15 days) showed similar results as the main analysis (Table 4.4). Patients with psychotherapy were less likely to discontinue their regimens than patients without psychotherapy (β= -0.701, p< 0.01), but the interaction terms indicated this protective effect decreased over time (β= 0.194, p< 0.01). Patients who were Black or another race were also more likely to discontinue their treatment than White patients (β_{Balck}= 0.306, p< 0.01; $\beta_{Other\ race}$= 0.247, p< 0.01). We also found that patients living in rural areas were more likely to have a gap in excess of 15 days than patients living in urban areas (β= 0.114, p= 0.02). Similar to the main analysis, patients initiated with typical antipsychotics were more likely to experience a discontinuation (β=

0.547, p< 0.01), and patients who had modified their regimens were less likely to discontinue their treatment (β= -0.114, p< 0.01).

Table 4.4 Results from Cox Proportional-Hazard Models of Time to Discontinuation (N= 3,536; N_{user}= 606, $N_{non-user}$= 2,930)

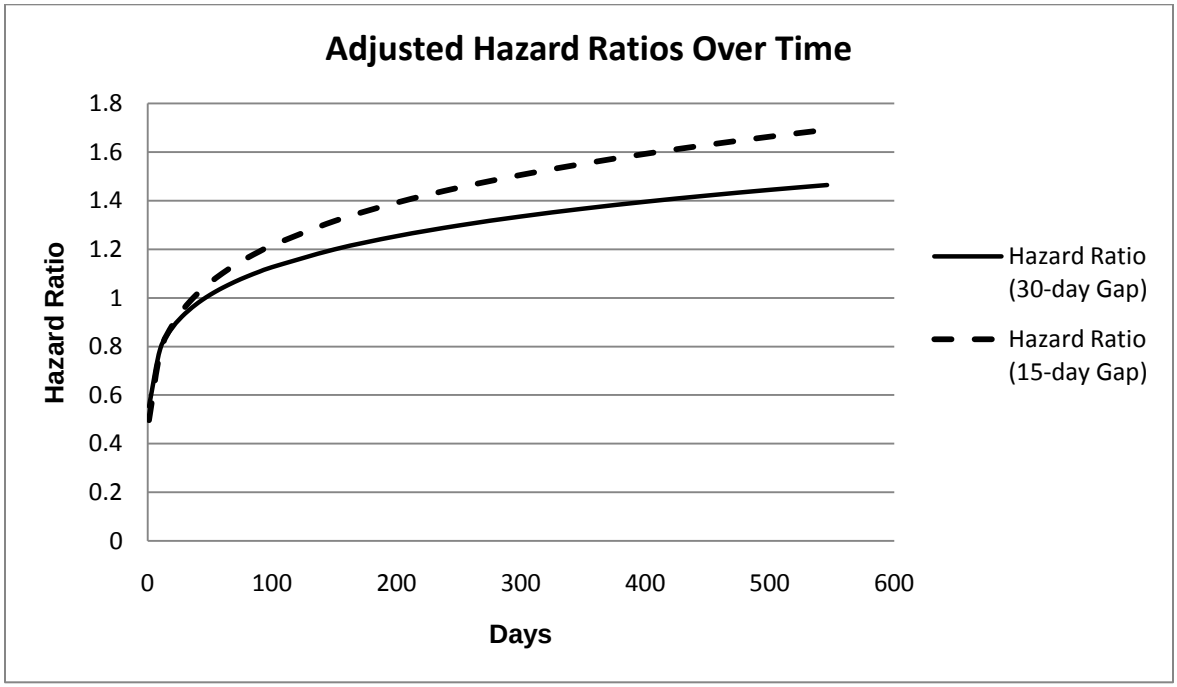
	A Gap > 30 Days		A Gap > 15 Days	
	β	SE	β	SE
Psychotherapy Use	-0.593**	0.217	-0.701**	0.206
Age Group				
18-35	*Reference*	-	*Reference*	-
36-50	0.018	0.048	0.015	0.045
>50	-0.019	0.064	-0.034	0.059
Gender				
Male	*Reference*	-	*Reference*	-
Female	-0.038	0.043	-0.011	0.040
Race				
White	*Reference*	-	*Reference*	-
Black	0.389**	0.047	0.306**	0.044
Other	0.308**	0.089	0.247**	0.083
State				
IL	*Reference*	-		
KS	0.052	0.083	0.011	0.077
MN	-0.017	0.077	-0.063	0.070
NC	0.117*	0.048	0.017	0.045
MSA				
Yes	*Reference*	-	*Reference*	-
No	0.094	0.050	0.114*	0.047
Charlson Score	0.011	0.036	0.002	0.035
Mental Comorbidities				
Depression	-0.099	0.065	-0.056	0.061
Substance Abuse	-0.040	0.076	-0.070	0.072
Anxiety	0.009	0.100	-0.022	0.093
Other Psychoses	-0.090	0.072	-0.102	0.068
Initial Treatment				
Atypical	*Reference*	-	*Reference*	-
Typical	0.651**	0.055	0.547**	0.054
Treatment Modification[†]	-0.197**	0.044	-0.114**	0.041
Interaction Term[‡]	0.154**	0.053	0.195**	0.052

SE: Standard Error; IL: Illinois, KS: Kansas, MN: Minnesota, NC: North Carolina; MSA: Metorpolitan Statistical Area; PDC: Proportion of Days Covered

† Treatment modification includes both medication switching and augmenting
‡ Because the proportional hazard assumption was not met, an interaction term [psychotherapy use*log(number of days to the 1st 15-day gap)] was added to release the assumption
* p<0.05
** p<0.01

Because the model indicated that the hazard ratio changed over time, the adjusted results of the estimated hazard ratios for discontinuation at different time points is presented in Figure 4.5 below. We can see that at the beginning of the follow-up, patients with psychotherapy are about 50% less likely to discontinue the treatment than patients without psychotherapy (hazard ratio ≈ 0.5 when $t \rightarrow 0$). The protection effect then diminishes around day 50 (where the hazard ratio cross one), and after day 50, patients with psychotherapy become more likely to discontinue their treatment than patients without psychotherapy. By the end of the follow-up, patients who received psychotherapy are over 1.4 times as likely to discontinue their antipsychotic treatment as patients who did not receive psychotherapy using a 30-day gap definition; the hazard ratio is over 1.6 when using a 15-day gap definition.

Figure 4.5. Adjusted Estimated Hazard Ratios over the Follow-Up Period



4.2.2 Medication Switching

Table 4.5 shows factors associated with medication switching within 30 or 15 days of the end of the last supply. In contrast to our hypothesis, we found that patients receiving psychotherapy were more likely to switch medications in both our main and sensitivity analyses. In our main analysis (a 30-day switching window), patients who used psychotherapy were more likely to switch to another antipsychotic agent than patients who did not use psychotherapy (OR=1.57, 95% CI=1.29-1.93). Compared to patients aged 18 to 35 years old, patients who were over 50 years old were less likely to switch antipsychotics (OR=0.69, 95% CI=0.53-0.90). The sensitivity analysis using a 15-day window definition showed the similar results as the main analysis. Patients receiving psychotherapy were more likely to switch antipsychotics than patients not receiving psychotherapy (OR=1.52, 95%

CI=1.22-1.90), and patients older than age 50 were less likely to switch antipsychotics than patients aged between 18 and 35 (OR=0.73, 95% CI=0.55-0.98, Table 4.5).

Table 4.5. Logistic Regression Results – Medication Switching
(N= 3,536; N_{user}= 606, $N_{non\text{-}user}$= 2,930)

	Within a 30-day window		Within a 15-day window	
	OR	95% CI	OR	95% CI
Psychotherapy Use	1.57**	(1.29-1.93)	1.52**	(1.22-1.90)
Age Group				
18-35	*Reference*	-	Reference	-
36-50	0.94	(0.78-1.13)	1.04	(0.85-1.28)
>50	0.69**	(0.53-0.90)	0.73*	(0.55-0.98)
Gender				
Male	*Reference*	-	Reference	-
Female	0.88	(0.74-1.05)	0.93	(0.77-1.13)
Race				
White	*Reference*	-	Reference	-
Black	0.88	(0.73-0.95)	0.80*	(0.66-0.98)
Other	1.30	(0.93-1.81)	1.23	(0.86-1.77)
State				
IL	*Reference*	-	Reference	-
KS	1.02	(0.74-1.41)	1.03	(0.72-1.47)
MN	0.71*	(0.52-0.97)	0.83	(0.60-1.15)
NC	0.97	(0.80-1.18)	1.08	(0.88-1.34)
MSA				
Yes	*Reference*	-	Reference	-
No	1.07	(0.87-1.30)	0.98	(0.79-1.23)
Charlson Score	0.93	(0.80-1.09)	0.97	(0.82-1.14)
Mental Comorbidities				
Depression	0.83	(0.64-1.07)	0.81	(0.61-1.08)
Substance Abuse	0.93	(0.68-1.26)	0.96	(0.69-1.35)
Anxiety	1.19	(0.82-1.72)	0.97	(0.63-1.49)
Other Psychoses	1.20	(0.91-1.57)	1.21	(0.90-1.63)
Type of Initial Treatment				
Atypical	*Reference*	-	Reference	-
Typical	0.85	(0.66-1.09)	0.94	(0.72-1.23)

OR: Odds Ratio; CI: Confidence Interval; SD: Standard Devisation; IL: Illinois, KS: Kansas, MN: Minnesota, NC: North Carolina; MSA: Metorpolitan Statistical Area; PDC: Proportion of Days Covered
* p<0.05
** p<0.01

As mentioned previously, because medication switching was defined as an initiation of a second agent after the end of the previous supply, patients who switched antipsychotic before the end of their last supply were not considered as switchers nor included in the regression model. Two sensitivity analyses were conducted to evaluate the use of psychotherapy on medication switching using different definitions of switching (regression outputs in Appendixes 6 and 7). Although the odds ratios estimated in the sensitivity analyses were slightly smaller (OR ≈ 1.50 in all sensitivity models) than the odd ratios estimated in the original models, both of our sensitivity models showed that the use of psychotherapy was significantly associated with a higher chance of medication switching. Therefore, regardless of which definition of switching we used, all of our results indicated that psychotherapy use was associated with about a 50% increase in medication switching than non-users.

4.3 Aim 3: To assess whether receiving adjunctive psychotherapy in combination with pharmacotherapy reduces total health care costs and hospitalization rates

Two types of outcomes were assessed in Aim 3: mental-health related hospitalizations and treatment costs. Hospitalizations were measured as number of hospitalizations during follow-up. Because of a high proportion of zeros, hospitalizations were evaluated by a hurdle model. Treatment costs were broken into four parts: inpatient, outpatient, pharmacy, and total costs. A two-part model with GLM as the second part was applied to assess the inpatient costs. All other cost variables were assessed by GLMs.

4.3.1 Hospitalizations

Table 4.6 shows the descriptive statistics of number of mental-health related hospitalizations and treatment costs. Approximately 17% of the patients had been hospitalized. On average, psychotherapy users had a higher mean number of hospitalizations than non-users in the entire study sample (0.38 vs. 0.23, $p<0.01$), or among patients who had be admitted at least once (1.70 vs. 1.42, $p< 0.01$). The maximum number of hospitalizations was eight, and the median number of hospitalizations among patients who had been admitted was one.

Table 4.6 also shows that psychotherapy users tended to have higher inpatient costs than non-users, which is contrary to our original hypothesis. The higher inpatient costs can be caused by treatment and selection bias. Selection may occur because patients with more severe mental-health conditions are more likely to use psychotherapy, and they are also more likely to be hospitalized. Once they are hospitalized, these patients may require more inpatient care due to the severity of their conditions.

As we expected, the average outpatient treatment costs were also found to be higher for psychotherapy users than non-users. Since psychotherapy users received additional outpatient services (i.e. adjunctive psychotherapy) than non-users, it is not surprising that they had higher outpatient costs. In addition, as addressed above, patients with psychotherapy may be sicker and therefore require more outpatient services, which increased the costs.

The unadjusted finding that psychotherapy users had higher antipsychotic costs was consistent with our original hypothesis. The higher costs of antipsychotics may due to the higher rate of medication switching among the psychotherapy users. Finally, with higher

inpatient, outpatient, and antipsychotic costs, the average total costs for psychotherapy users were significantly higher for non-users.

Table 4.6. Descriptive Statistics of Outcomes in Aim 3 – Mental Health Related Hospitalizations and Treatment Costs

	Adjunctive Psychotherapy Users	Non-users	
	N= 606	N= 2,930	
	Mean(SD)	Mean(SD)	P-value
Number of mental-health related hospitalizations for all patients	0.38(0.87)	0.23(0.62)	<0.01
Number of mental-health related hospitalizations among patients admitted at least once	1.70(1.07)	1.42(0.83)	<0.01
Treatment Costs			
Inpatient	2043.9(7899.5)	725.2(3046.6)	<0.01
Outpatient	6203.4(15299.5)	3885.1(8611.3)	<0.01
Medication - Antipsychotics	3638.1(5073.8)	2592.0(3625.1)	<0.01
Total	11885.4(21327.7)	7202.3(10786.2)	<0.01

SD: Standard Deviation

Adjusted results of the comparison of number of hospitalizations between psychotherapy users and non-users are presented in Table 4.7. The first part of the Hurdle model (logistic regression) indicates that patients with psychotherapy were 30% more likely to have a mental-health related hospitalization than patients without psychotherapy during the follow-up period (OR= 1.30, 95% CI= 1.03-1.62). Patients aged between 36 and 50, and patients over 50 years old were 0.64 (95% CI= 0.53-0.79) and 0.41 (95% CI= 0.30-0.56) times as likely to be hospitalized as patients who were 18 to 35 years old, respectively. Compared to patients living in Illinois, patients living in Kansas or North Carolina were less likely to be hospitalized (OR_{KS}= 0.48, 95% CI= 0.31-0.74; OR_{NC}= 0.75, 95% CI= 0.60-0.92). Having comorbid depression increased the odds of hospitalization by a factor of 1.67 (95% CI= 1.29-2.16), and having other comorbid psychoses increased the odds by 1.45 times (95%

CI= 1.08-1.95). Interestingly, patients who had begun with typical antipsychotics were less likely to be hospitalized than patients beginning with atypical antipsychotics (OR= 0.68, 95% CI= 0.50-0.92). Patients who were adherent to their antipsychotic treatment were also less likely to be hospitalized than patients who were not adherent (OR= 0.72, 95% CI= 0.57-0.90). Finally, patients who had switched or augmented their antipsychotic treatments were more likely to experience a mental-health related hospitalization than those who did not modify their treatment regimens (OR= 3.42, 95% CI= 2.82-4.14).

According to the second part of the Hurdle model (a zero-truncated model), the use of psychotherapy was not associated with the number of hospitalizations among those who had been admitted at least once. However, the interaction term of psychotherapy and adherence indicated that the number of hospitalizations for patients who used psychotherapy and had better adherence was estimated as 0.60 [exp(0.30-0.74+0.86-0.93)= 0.60] times the average number of hospitalizations for other patients. Among those who had been admitted at least once, the number of hospitalizations for patients in North Carolina was 0.68 [exp(-0.39)= 0.68] times the number of hospitalizations for patients in Illinois. Patients who were adherent to their regimens were associated with a 52% [exp(-0.74)= 0.48] decrease in the number of hospitalizations compared to non-adherent patients. Having treatment modification increased the number of hospitalizations by a factor of 1.58 [exp(0.46)= 1.58].

Table 4.7. Results from the Hurdle Model– Number of Hospitalizations ($N= 3,536$; $N_{user}= 606$, $N_{non\text{-}user}= 2,930$)

	Part 1: Logistic Regression		Part 2: Zero-Truncated Model	
	OR	95% CI	β	95% CI
Psychotherapy Use	1.30*	(1.03, 1.62)	0.30	(-0.56, 0.66)
Age Group				
18-35	*Reference*	-	*Reference*	-
36-50	0.64**	(0.53, 0.79)	-0.23	(-0.53, 0.08)
>50	0.41**	(0.30, 0.56)	-0.44	(-0.95, 0.08)
Gender				
Male	*Reference*	-	*Reference*	-
Female	1.19	(0.98, 1.43)	0.12	(-0.18, 0.42)
Race				
White	*Reference*	-	*Reference*	-
Black	1.02	(0.83, 1.26)	0.21	(-0.11, 0.53)
Other	1.10	(0.76, 1.59)	-0.06	(-0.57, 0.45)
State				
IL	*Reference*	-	*Reference*	-
KS	0.48**	(0.31, 0.74)	-0.06	(-0.63, 0.52)
MN	0.73	(0.52, 1.03)	-0.02	(-0.56, 0.52)
NC	0.75*	(0.60, 0.92)	-0.39*	(-0.73, -0.06)
MSA				
Yes	*Reference*	-	*Reference*	-
No	0.93	(0.74, 1.18)	0.04	(-0.32, 0.40)
Charlson Score	1.10	(0.96, 1.26)	-0.20	(-0.47, 0.08)
Mental Comorbidities				
Depression	1.67**	(1.29, 2.16)	0.18	(-0.15, 0.50)
Substance Abuse	1.26	(0.92, 1.72)	-0.15	(-0.64, 0.35)
Anxiety	1.16	(0.77, 1.73)	0.13	(-0.49, 0.74)
Other Psychoses	1.45*	(1.08, 1.95)	0.13	(-0.27, 0.53)
Initial Treatment				
Atypical	*Reference*	-	*Reference*	-
Typical	0.68*	(0.50, 0.92)	0.08	(-0.50, 0.66)
Adherence				
Yes	0.72**	(0.57, 0.90)	-0.74**	(-1.21, -0.28)
No	*Reference*	-	*Reference*	-
Treatment Modification[†]	3.42**	(2.84, 4.12)	0.46**	(0.15, 0.77)
Psychotherapy*Adherence	N/A	-	0.86*	(0.15, 1.58)
Constant	N/A	-	-0.93**	(-1.59, -0.27)

OR: Odds Ratio; CI: Confidence Interval; IRR: Incidence Rate Ratio; IL: Illinois, KS: Kansas, MN: Minnesota, NC: North Carolina; MSA: Metorpolitan Statistical Area; PDC: Proportion of Days Covered; N/A: Not Applicable

† Treatment modification was defined as having either switched antipsychotics within a 30-day window or augmented treatment at anytime during the follow-up period
*p<0.05
**p<0.01

The predicted probabilities of hospitalization and number of hospitalizations are presented in Table 4.8. The average predicted probability of hospitalization was 0.17 (SD= 0.11), and the predicted probabilities of hospitalization were 0.20 (SD= 0.12) and 0.17 (SD= 0.11) for psychotherapy users and non-users respectively. The incremental effect of adjunctive psychotherapy on the probability of hospitalization was estimated as 0.03 (SD= 0.02). Consistent with the logistic regression results reported in Table 4.7 ($OR_{psychotherapy}$= 1.30, 95% CI= 1.03-1.62), this incremental effect is marginally significant.

Based on the second part of the Hurdle model, the mean predicted number of hospitalizations (conditional on at least on admission) was 0.40 (SD= 0.20) for the 18-month follow-up period. The average number of hospitalizations was 0.50 (SD= 0.22) for psychotherapy users and 0.40 (SD= 0.17) for non-users. By subtracting the two numbers, the incremental effect of psychotherapy on hospitalizations was calculated as 0.13 (SD= 0.06), and this effect was statistically significant.

Table 4.8. Predicted Values of Hospitalizations from the Hurdle Model

	Mean	SD	Min	Max
Part 1- Predicted Probabilities of non-zero hospitalizations				
Predicted probability for all patients	0.17	0.11	0.02	0.66
Predicted probability (set psychotherapy= 1)	0.20	0.12	0.03	0.71
Predicted probability (set psychotherapy= 0)	0.17	0.11	0.02	0.66
Incremental effect of psychotherapy on hospitalization probability	0.03	0.02	0.01	0.06
Part 2- Predicted Number of Hospitalizations (Conditional on at least one admission)				
Predicted number of hospitalizations for all patients	0.40	0.20	0.03	1.42

Predicted number of hospitalizations (psychotherapy= 1)	0.50	0.22	0.04	1.42
Predicted number of hospitalizations (psychotherapy= 0)	0.40	0.17	0.03	1.05
Incremental effect of psychotherapy on number of hospitalizations	0.13	0.06	0.01	0.37

SD: Standard Deviation

The unconditional predicted values of hospitalizations are presented below in Table 4.9. After combining the two parts of the Hurdle model, the mean unconditional predicted number of hospitalizations was 0.08 (95% CI= 0.04-0.12) with the original characteristics of the population. With psychotherapy, patients were expected to have 0.13 (95% CI= 0.06-0.20) hospitalizations during the follow-up, and the expected number of hospitalizations was 0.07 (95% CI= 0.03-0.10) without psychotherapy. The incremental number of hospitalizations was calculated as 0.07 for psychotherapy users, and the effect was marginally significant (95% CI= 0.01-0.12).

Table 4.9. Predicted Number of Hospitalizations from the Hurdle Model (Unconditional)

	Mean	Bootstrap 95% CI
Predicted number of hospitalizations for all patients	0.08	(0.04-0.12)
Predicted number of hospitalizations (psychotherapy= 1)	0.13	(0.06-0.20)
Predicted number of hospitalizations (psychotherapy= 0)	0.07	(0.03-0.10)
Incremental effect of psychotherapy on number of hospitalizations	0.07	(0.01-0.12)

CI: Confidence Interval

4.3.2 Treatment Costs – Inpatient Costs

The predicted values from the two-part model are summarized in Table 4.10. Because the first-part model evaluated the probability of having non-zero inpatient costs, which was identical as the first-part of the hospitalization model, the predicted values were

identical as the first-part predicted probabilities in Table 4.8. Therefore, we only presented the predicted values from the second-part of the inpatients cost model, and the predicted values from the first-part inpatient cost model were skipped here.

Based the second part of the model (conditional on at least one admission), the average inpatient costs were calculated as $4,727.13 (SD= $2,931.73) for the entire population. With adjunctive psychotherapy, the expected inpatient costs were $9,094.51 (SD= $3,896.60), and the expected inpatient costs were $3,851.38 (SD= $1,650.14) without psychotherapy. The conditional incremental costs among patients who had been hospitalized were estimated as $5,243.14 (SD= $2,246.45) for patients with psychotherapy.

Table 4.10. Predicted Inpatient Treatment Costs from the Second-part Model† (Conditional on at least on admission, $)

	Mean	SD	Min	Max
Predicted inpatient costs for all patients	4,727.13	2,931.73	876.21	29,695.67
Predicted inpatient costs (psychotherapy= 1)	9,094.51	3,896.60	2,069.05	32,322.85
Predicted inpatient costs (psychotherapy= 0)	3,851.38	1,650.14	876.21	13,688.19
Incremental effect of psychotherapy on inpatient costs	5,243.14	2,246.45	1,192.84	18,634.66

SD: Standard Deviation

† All costs are presented in 2003 dollars

Table 4.11 shows the unconditional predicted inpatient treatment costs. After combining the two parts of the model, the average inpatient treatment costs were calculated as $956.75 (95% CI= $834.95-$1,114.79) for the study samples. The estimated inpatient costs for patients with psychotherapy were $2,004.25 (95% CI= $1,529.33-$2,673.67), and the expected inpatient costs for patients without psychotherapy were $714.11 (95% CI= $607.92-$821.38). Finally, the use of psychotherapy was associated with a $1,290.13

increase in inpatient treatment costs, which was significantly different from zero (95% CI= $803.35-$1,927.39).

Table 4.11. Predicted Inpatient Treatment Costs† (Unconditional, $)

	Mean	Bootstrap 95% CI	
Predicted inpatient costs for all patients	956.75	834.95	1,114.79
Predicted inpatient costs (psychotherapy= 1)	2,004.25	1,529.33	2,673.67
Predicted inpatient costs (psychotherapy= 0)	714.11	607.92	821.38
Incremental effect of psychotherapy on inpatient costs	1,290.13	803.35	1,927.39

CI: Confidence Interval

† All costs are presented in 2003 dollars

Finally, Table 4.12 shows the regression outputs from the two-part inpatient cost model. Because there were two patients who had been admitted but with zero inpatient costs, the odd ratios estimated in the first-part model here were slightly different from the odds ratios in the first-part hospitalization model. Based on the second-part model, the use of psychotherapy was associated with a 136% [exp(0.86)= 2.36] increase in inpatient costs among patient who had been admitted. The inpatient costs for black patients were 1.58 [exp(0.46)= 1.58] times the inpatient costs of white patients, and the inpatient costs for patients with other races were 1.46 [exp(0.38)= 1.46] times the costs of white patients. The inpatients costs for patients in Kansas were 1.46 [exp(0.38)= 1.46] times the costs for patients in Illinois , and the inpatient costs in North Carolina were 0.69 [exp(-0.38)= 0.69] times the costs in Illinois. Having other psychoses increased the inpatient costs by a factor of 1.42 [exp(0.35)= 1.42], while being adherent to the regimens decreased the inpatient costs by a factor of 0.72 [exp(-0.33)= 0.72]. Patients who had modified their treatments had 27% higher inpatient costs than patients who had not modified their treatments [exp(0.24)= 1.27].

Table 4.12. Results from the Two-Part Model- Inpatient Treatment Costs (N= 3,536; N_{user}= 606, $N_{non-user}$= 2,930)

	Part 1: Logistic Regression		Part 2: GLM Model‡	
	OR	**95% CI**	**β**	**Robust SE**
Psychotherapy Use	1.27*	(1.01-1.59)	0.86**	0.12
Age Group				
18-35	*Reference*	-	*Reference*	-
36-50	0.64**	(0.53-0.79)	-0.05	0.11
>50	0.41**	(0.31-0.56)	-0.27	0.16
Gender				
Male	*Reference*	-	*Reference*	-
Female	1.18	(0.97-1.42)	0.13	0.10
Race				
White	*Reference*	-	*Reference*	-
Black	1.01	(0.82-1.24)	0.46**	0.11
Other	1.10	(0.76-1.59)	0.38*	0.18
State				
IL	*Reference*	-	*Reference*	-
KS	0.47**	(0.31-0.73)	-0.41	0.21
MN	0.69*	(0.49-0.98)	0.38*	0.18
NC	0.75*	(0.60-0.92)	-0.38**	0.11
MSA				
Yes	*Reference*	-	*Reference*	-
No	0.94	(0.74-1.18)	-0.21	0.13
Charlson Score	1.10	(0.96-1.26)	-0.03	0.08
Mental Comorbidities				
Depression	1.64**	(1.26-2.12)	-0.10	0.12
Substance Abuse	1.26	(0.92-1.73)	-0.11	0.16
Anxiety	1.16	(0.78-1.74)	-0.35	0.19
Other Psychoses	1.43*	(1.06-1.92)	0.35*	0.17
Initial Treatment				
Atypical	*Reference*	-	*Reference*	-
Typical	0.68*	(0.50-0.92)	-0.15	0.20
Adherence				
Yes	0.71**	(0.57-0.89)	-0.33**	0.11
No	*Reference*	-	*Reference*	-
Treatment Modification†	3.45**	(2.85-4.18)	0.24*	0.10
Constant	N/A	-	8.14**	0.15

OR: Odds Ratio; SE: Standard Error; IL: Illinois, KS: Kansas, MN: Minnesota, NC: North Carolina; MSA: Metorpolitan Statistical Area; PDC: Proportion of Days Covered; N/A: Not Applicable

† Treatment modification was defined as having either switched antipsychotics within a 30-day window or augmented treatment at anytime during the follow-up period
‡ Generalized Linear Model with a log link function and gamma distribution
*p<0.05
**p<0.01

4.3.3 Treatment Costs – Outpatient Costs

The predicted costs for mental-health related outpatient services are presented in Table 4.13 below. The mean predicted outpatient costs were $4,301.83 (SD= $2,479.07). The expected population-level outpatient costs for psychotherapy users were $5,562.95 (SD= $2,851.42), and the population-level outpatient costs for non-psychotherapy users were estimated as $4,022.85 (SD= $2,219.49). By subtracting the two numbers, we found that the incremental outpatient costs for psychotherapy use were $1,540.10 (SD= $633.40).

Table 4.13. Predicted Outpatient Treatment Costs† ($)

	Mean	SD	Min	Max
Predicted outpatient costs for all patients	4,301.83	2,479.07	848.92	21,663.16
Predicted outpatient costs (psychotherapy= 1)	5,562.95	2,851.42	1,325.41	27,484.68
Predicted outpatient costs (psychotherapy= 0)	4,022.85	2,219.49	848.92	21,663.16
Incremental effect of psychotherapy on outpatient costs	1,540.10	633.40	476.49	5,821.52

SD: Standard Deviation
† All costs are presented in 2003 dollars

Outputs from the outpatient cost model are presented in Table 4.14. The outpatient costs for patients with psychotherapy were 1.43 [exp(0.36)= 1.43] times the outpatient costs for non-psychotherapy users. The outpatient costs for patients living in Kansas were 1.99 [exp(0.69)= 1.99] times the outpatient costs for patients living in Illinois, while the outpatient costs for patients in North Carolina were 0.77 [exp(-0.26)= 0.77] times the outpatient costs

for patients in Illinois. Interestingly, patients with comorbid anxiety had 30% [exp(-0.35)= 0.70] lower outpatient costs than patients without comorbid anxiety, but patients with other comorbid psychoses had 35% [exp(0.30)= 1.35] higher outpatient costs than patients without other comorbid psychoses. Compared to patients who had begun with atypical antipsychotics, patients beginning with typical antipsychotics had 95% [exp(0.67)= 1.95] higher outpatient costs. The outpatient costs for patient who were adherent to their treatments were 1.87 times the outpatient costs for patients who were not adherent. Finally, the outpatient costs for patients who had modified their regimens were 1.57 [exp(0.45)= 1.57] times the outpatients costs for patients who did not modify their regimens.

Table 4.14. Results from the GLM Model[‡]- Outpatient Costs
(N= 3,536; N_{user}= 606, $N_{non\text{-}user}$= 2,930)

	β	Robust SE
Psychotherapy Use	0.36*	0.13
Age Group		
18-35	*Reference*	-
36-50	-0.14	0.09
>50	-0.20	0.12
Gender		
Male	*Reference*	-
Female	-0.02	0.08
Race		
White	*Reference*	-
Black	0.11	0.09
Other	-0.22	0.14
State		
IL	*Reference*	-
KS	0.69**	0.14
MN	0.17	0.12
NC	-0.26*	0.09
MSA		
Yes	*Reference*	-

No	0.15	0.08
Charlson Score	-0.01	0.06
Mental Comorbidities		
Depression	0.07	0.10
Substance Abuse	0.05	0.13
Anxiety	-0.35*	0.15
Other Psychoses	0.30*	0.12
Initial Treatment		
Atypical	*Reference*	-
Typical	0.67**	0.12
Adherence		
Yes	0.63**	0.09
No	*Reference*	-
Treatment Modification†	0.45**	0.08
Constant	4.80**	0.13

SE: Standard Error; IL: Illinois, KS: Kansas, MN: Minnesota, NC: North Carolina;
MSA: Metorpolitan Statistical Area; PDC: Proportion of Days Covered
† Treatment modification was defined as having either switched antipsychotics within a 30-day window or augmented treatment at anytime during the follow-up period
‡ Generalized Linear Model with a log link function and gamma distribution
*p<0.05
**p<0.01

4.3.4 Treatment Costs – Antipsychotic Costs

Table 4.15 below summarizes the predicted costs for antipsychotics. The average predicted antipsychotic costs were $2,861.89 (SD= $2,454.39). The predicted antipsychotic costs for psychotherapy users at the population level were $3,166.64 (SD= $2,630.32), and the predicted antipsychotic costs for non-users at the population level were $2,788.41 (SD= $2,380.67). The expected incremental antipsychotic costs for psychotherapy use were calculated as $378.23 with a standard deviation of $250.28.

Table 4.15. Predicted Antipsychotic Drug Costs† ($)

	Mean	SD	Min	Max
Predicted antipsychotic costs for all patients	2,861.89	2,454.39	350.08	12,838.91
Predicted antipsychotic costs (with psychotherapy)	3,166.64	2,630.32	427.79	12,838.91
Predicted antipsychotic costs (without psychotherapy)	2,788.41	2,380.67	350.08	11,611.01
Incremental effect of psychotherapy on antipsychotic costs	378.23	250.28	77.71	1,227.90

SD: Standard Deviation

† All costs are presented in 2003 dollars

Table 4.16 shows the results of Medicaid payments for antipsychotics. According to the results from the GLM model, antipsychotic costs for psychotherapy users were 1.14 [exp(0.13)= 1.14] times the costs for non-users. Compared to patients aged between 18 and 35 years old, the costs of antipsychotics were 15% [exp(-0.16)= 0.85] lower for patients aged between 36 and 50 years old and 27% [exp(-0.31)= 0.73] lower for patients aged 51 and older. The costs for female were 14% [exp(-0.15)= 0.86] less than the costs for males. Black patients and patients with other races had 12% [exp(-0.13)= 0.88] and 17% [exp(-0.19)= 0.83] lower antipsychotic costs than white patients. Patients living in North Carolina had 10% [exp(-0.10)= 0.90] lower antipsychotic costs than patients living in Illinois. Patients who initiated with typical psychotherapy had 46% [exp(-0.62)= 0.54] lower antipsychotic costs than patients starting with atypical antipsychotics. Being adherent increased the antipsychotic costs by a factor of 3.10 [exp(1.13)= 3.10], and treatment modification increased the costs by a factor of 2.03 [exp(0.71)= 2.03].

Table 4.16. Results from the GLM Model[‡]- Antispsychotic Costs (N= 3,536; N_{user}= 606, $N_{non-user}$= 2,930)

	β	Robust SE
Psychotherapy Use	0.13*	0.05
Age Group		
18-35	*Reference*	-
36-50	-0.16**	0.05
>50	-0.31**	0.06
Gender		
Male	*Reference*	-
Female	-0.15**	0.04
Race		
White	*Reference*	-
Black	-0.13**	0.04
Other	-0.19*	0.07
State		
IL	*Reference*	-
KS	0.10	0.07
MN	0.10	0.06
NC	-0.10*	0.05
MSA		
Yes	*Reference*	-
No	0.03	0.05
Charlson Score	0.06	0.03
Mental Comorbidities		
Depression	-0.01	0.05
Substance Abuse	-0.08	0.07
Anxiety	-0.08	0.13
Other Psychoses	0.02	0.06
Initial Treatment		
Atypical	*Reference*	-
Typical	-0.62**	0.06
Adherence		
Yes	1.13**	0.04
No	*Reference*	-
Treatment Modification[†]	0.71**	0.04
Constant	4.53**	0.06

SE: Standard Error; IL: Illinois, KS: Kansas, MN: Minnesota, NC: North Carolina; MSA: Metorpolitan Statistical Area; PDC: Proportion of Days Covered

† Treatment modification was defined as having either switched antipsychotics within a 30-day window or augmented treatment at anytime during the follow-up period
‡ Generalized Linear Model with a power link function and gamma distribution
*p<0.05
**p<0.01

4.3.5 Treatment Costs – Total Costs

The predicted total treatment costs were presented in Table 4.17. The average predicted total treatment costs over the follow-up period were $8,049.17 (SD= $4,726.79). The expected total costs at the population level were $10,303.54 (SD= $5,395.86) for psychotherapy users and $7,534.33 (SD= $4,225.91) for non-users. The incremental total costs for psychotherapy users were estimated as $2,769.21 (SD= $1,171.82). Table 4.18 summarizes the incremental costs for different types of services.

Table 4.17. Predicted Total Treatment Costs† ($)

	Mean	SD	Min	Max
Predicted total costs for all patients	8,049.17	4,726.79	2,085.33	37,436.99
Predicted total costs (psychotherapy= 1)	10,303.54	5,395.86	3,139.39	37,436.99
Predicted total costs (psychotherapy= 0)	7,534.33	4,225.91	2,085.33	29,296.59
Incremental effect of psychotherapy on total costs	2,769.21	1,171.82	1,054.06	8,140.40

SD: Standard Deviation
† All costs are presented in 2003 dollars

Table 4.18. Summary of the Predicted Incremental Costs for Different Types of Services† ($)

	Mean	SD
Incremental Costs- Inpatient Costs	1,290.13	284.78‡
Incremental Costs- Outpatient Costs	1,540.10	633.40
Incremental Costs- Antipsychotic Costs	378.23	250.28
Incremental Costs- Total Costs	2,769.21	1,171.82

SD: Standard Deviation

† All costs are presented in 2003 dollars
‡ Bootstrap standard error

Finally, the regression outputs for total treatment costs (sum of inpatient, outpatient, and antipsychotic costs) are shown in Table 4.19. The use of psychotherapy was associated with an increase in total treatment costs by a factor of 1.48 [exp(0.39)= 1.48]. Compared to patients who were 18 to 35 years old, the total treatment costs were 18% [exp(-0.20)= 0.82] lower for patients aged between 36 and 50 and 30% [exp(-0.36)= 0.70] lower for patients over 50. Compared to patients in Illinois, the total costs were 46% [exp(0.38)= 1.46] higher for patients in Kansas and 29% [exp(-0.34)= 0.71] lower for patients in North Carolina. Having other comorbid psychoses was associated with a 1.35 [exp(0.30)= 1.35] times increase in total costs. The total costs for patients having typical antipsychotics as their initial treatment were 1.30 [exp(0.26)= 1.30] times the total costs for patients having atypical antipsychotics as their initial treatment. Being adherent to antipsychotic treatments was associated with an increase in total costs by a factor of 2.27 [exp(0.82)= 2.27], and having modified the treatment during the follow-up was associated with an increase in total costs by a factor of 2.05 [exp(0.72)= 2.05].

Table 4.19. Results from the GLM Model‡- Total Treatment Costs (N= 3,536; N_{user}= 606, $N_{non\text{-}user}$= 2,930)

	β	Robust SE
Psychotherapy Use	0.39**	0.10
Age Group		
18-35	*Reference*	-
36-50	-0.20*	0.07
>50	-0.36**	0.09
Gender		
Male	*Reference*	-
Female	0.05	0.06

Race		
White	*Reference*	-
Black	0.04	0.07
Other	-0.19	0.11
State		
IL	*Reference*	-
KS	0.38**	0.13
MN	0.12	0.10
NC	-0.34**	0.07
MSA		
Yes	*Reference*	-
No	0.08	0.07
Charlson Score	0.02	0.05
Mental Comorbidities		
Depression	0.11	0.08
Substance Abuse	0.01	0.10
Anxiety	-0.22	0.17
Other Psychoses	0.30**	0.10
Initial Treatment		
Atypical	*Reference*	-
Typical	0.26*	0.11
Adherence		
Yes	0.82**	0.06
No	*Reference*	-
Treatment Modification†	0.72**	0.06
Constant	5.58**	0.10

SE: Standard Error; IL: Illinois, KS: Kansas, MN: Minnesota, NC: North Carolina;
MSA: Metorpolitan Statistical Area; PDC: Proportion of Days Covered
† Treatment modification was defined as having either switched antipsychotics within a 30-day window or augmented treatment at anytime during the follow-up period
‡ Generalized Linear Model with a power link function and gamma distribution
*p<0.05
**p<0.01

4.4 Results from Instrumental Variable Estimations

Around 4% of the final sample did not have enough information to construct an instrumental variable and therefore was excluded in the IV analyses (psychotherapy use for

MDD patients: 137 missing; psychotherapy use for the previous patient: 133 missing). When test the two IVs separately in the first-stage logistic regression, the results indicated that both of our IVs were strongly associated with psychotherapy use (psychotherapy use for MDD patients, z= 7.69, p< 0.001; chi-square = 59.15, p< 0.001; psychotherapy use for the previous patient z= 14.84, p< 0.001; chi- square= 220.24, p< 0.001). When both IVs were included in the first-stage regression model, both of our IVs were still significantly associated with psychotherapy use although the strength of psychotherapy use for MDD patients became weaker (z= 2.44, p< 0.015 for psychotherapy use for MDD patients; z= 12.29, p< 0.001 for psychotherapy use for the previous patient). The Wald test result showed that the two IVs were jointly significant in the first-stage model (chi-square= 218.96, p<0.001). Since both IVs seemed to be strongly associated with the use of psychotherapy, the IV selection was then mainly based on the exclusion restriction criterion. Table 4.20 summarizes the IV selection for each dependent variable based on the results of Hausman tests, and the specification tests results are shown in Appendix 5.

Table 4.20. IV Selection for Each Dependent Variable

	Psychotherapy use for MDD patients	Psychotherapy use for the previous patient
Medication discontinuation		X
Medication Switching	X	X
Hospitalizations		
part 1 model		X
part 2 model		X
Inpatient costs		
part 1 model		X
part 2 model	X	X
Outpatient costs		X
Prescription drug costs	X	X
Total costs		X

Notice that except for four dependent variables: medication switching, the second part of the hospitalizations, the second part of the inpatient costs, and total treatment costs, at least one IV can be considered as valid instrument for all other dependent variables using Hausman tests. Because of negative chi-squared statistics, whether the two IVs meet the exclusion restriction from Hausman tests was unable to be determined for these four outcome models. The decision of including both IVs in these two models was instead based on the results from Chow tests as well as the LR test which indicated that both IVs should be validly excluded from the second-stage model. While for the second-part hospitalization model and total cost model, we only included the use of psychotherapy for the previous patient in the model because the LR tests reject the null that both IVs were validly excluded from the second-stage of the IV model. Since the first-stage test showed that the use of psychotherapy for the previous patient was a stronger IV than psychotherapy use for MDD patients, only the use of psychotherapy for the previous patient was used as an IV in the second-stage model.

Finally, because the Hausman test for the endogeneity of psychotherapy did not provide valid test results for all of the outcome models, using a formal test to check whether psychotherapy was endogeneous was not feasible. Therefore, the use of adjunctive psychotherapy was assumed to be endogeneous with respect to all of the outcomes, and IV estimates were constructed for all the outcome models. The results from the naïve regression models and IV models are summarized in Table 4.21.

Table 4.21. Point Estimates and Confidence Intervals of Adjunctive Psychotherapy Use

	Original Model		IV model	
	β	95% CI	β	Bootstrap 95% CI
Medication discontinuation†	-0.59*	(-1.02, -0.17)	-0.53*	(-0.97, -0.07)
Medication switching†	0.45*	(0.25, 0.66)	0.48*	(0.20, 0.69)
Hospitalizations				
part 1 model	0.26*	(0.03, 0.48)	0.23	(-0.07, 0.49)
part 2 model	0.30	(-0.56, 0.66)	0.13	(-0.55, 0.44)
Inpatient costs				
part 1 model	0.24*	(0.01, 0.47)	0.23	(-0.08, 0.49)
part 2 model	0.86*	(0.62, 1.09)	0.72*	(0.28, 0.96)
Outpatient costs	0.36*	(0.10, 0.62)	0.42*	(0.14, 0.73)
Antipsychotic costs	0.13*	(0.04, 0.23)	0.37*	(0.06, 0.68)
Total costs	0.39*	(0.19, 0.59)	0.42*	(0.14, 0.73)

CI: Confidence Interval
† Both medication persistency and medication switching were measured using a 30-day gap/window definition
* Significant at $\alpha = 0.05$ level

In Table 4.21, we can see that the point estimates of psychotherapy use do not change much after applying the IV technique. The effect of psychotherapy on most outcome variables increased in the IV models compared to the estimates in the naïve models with the exception of coefficients in the discontinuation, hospitalization, and inpatient cost models. Use of adjunctive psychotherapy significantly decreased the likelihood of discontinuation at the beginning of the follow-up. Unlike the results from the naïve regressions, psychotherapy use did not significantly increase the likelihood of hospitalization. However, according to the second-stage IV inpatient cost model, among patients who had been admitted, the use of psychotherapy led to an 2.05 [exp(0.72)= 2.05] times increase in inpatient costs. After combining both parts of the inpatient cost models and calculating the unconditional incremental costs, we found patients with psychotherapy still had significantly higher inpatient costs (mean incremental cost= $1,045.43, 95% CI= $513.63-$1,652.30) although

this result was slightly lower than the result from the original model without IVs (mean = $1,390.13, 95% CI= $803.35-$1,927.39).

Similar to the naïve estimates, results from the IV model indicated that the use of adjunctive psychotherapy increased outpatient costs by 52% [exp(0.42)= 1.52]. After accounting for the potential endogeneity, the IV estimates showed that psychotherapy use caused a 45% [exp(0.37)= 1.45] increase in antipsychotic costs compared to a 14% [exp(0.13)= 1.14] increase from the naïve estimate. Finally, the IV estimate suggested that psychotherapy increased the total treatment costs by a factor of 1.52 [exp(0.42)= 1.52] which was slightly higher than the naïve estimate [exp(0.39)= 1.48].

When comparing the IV estimates to the naïve estimates, it is important to know that IV provides the local average treatment effect (LATE), which estimates the effect of psychotherapy on marginal patients (i.e. patients can be treated either with or without psychotherapy), while the naïve model estimates average treatment effect as the difference between the average treatment effect as treated and the average treatment effect as non-treated, which compares the effect of psychotherapy between those who received it versus who did not.[145-147] Therefore, the differences between IV estimates and naïve estimates may be caused by different populations being used for the estimations, and both estimates could be accurate. On the other side, since 1) the naïve models could suffer from un-measurable confounding (as discussed in section 3.5), and 2) our IVs could still be correlated with the outcomes through unobservable routes (as discussed in section 3.6.3) and thus bias the IV results, it is possible that both our naïve estimates and IV estimates are biased.

Finally, except for the second-part of the hospitalization model, outpatient costs, and total treatment costs, most of our results failed to reject the null hypothesis that the use of

psychotherapy was exogeneous. This indicates that the use of psychotherapy may not be endogeneous with respect to most of our outcomes. However, as discussed before, the exogeneity test is inconclusive. We may fail to reject the null because of weak or invalid instruments. Given the high variance in the second-stage model, we often fail to reject the null because of low power. Even if the null hypothesis is rejected, it can be caused by measurement errors or incorrect functional form. As a result, failing to reject the null does not conclude the exogeneity of psychotherapy use. We should treat these test results as references, and keep in mind that the use of psychotherapy can still be endogeneous.

4.5 Summary

In summary, only a few patients (17%) received psychotherapy during the 18-month follow-up period, and most patients had a relatively short treatment duration for psychotherapy (mean psychotherapy visits= 5.4 and mean treatment duration= 160 days). Our naïve estimates showed that the use of adjunctive psychotherapy was associated with better antipsychotic persistency at the beginning of the follow-up. However, this protective effect diminished within the first two months of follow-up, and patients with psychotherapy became less persistent than patients without psychotherapy after the first two months. Patients with adjunctive psychotherapy were also found to be more likely to switch their antipsychotics and had higher treatment costs. However, we found the use of adjunctive psychotherapy was associated with a small but significant increase in hospitalizations.

Consistent with our naïve estimates, the IV estimates showed that patients receiving psychotherapy had significantly better persistency at the beginning of the follow-up. Patients with psychotherapy were still found to be more likely to switch medications, and they had

higher outpatient, pharmacy, and total treatment costs compared to patients without psychotherapy. In contrast, results from IV models did not show that the use of adjunctive psychotherapy leads to a higher risk of hospitalization. If our IVs are strong and truly valid, we can conclude that the use of adjunctive psychotherapy increase patients' persistency and treatment costs, but it does not significantly increase the risk of hospitalization.

CHAPTER 5: DISCUSSION

To the author's knowledge, this is the first study looking at the effectiveness of adjunctive psychotherapy among patients with schizophrenia among Medicaid populations. The results showed that only 17% of patients received adjunctive psychotherapy during the 18-month follow-up period, and individual therapy was the most common type of psychotherapy. Compared to patients receiving pharmacotherapy alone, patients with adjunctive psychotherapy had better medication persistency in the first two months of the follow-up, but they became less persistent after the first two months. Patients with adjunctive psychotherapy were also found to have a higher number of hospitalizations and treatment costs than patients without psychotherapy. However, the IV results indicated that the use of psychotherapy did not lead to a higher risk of hospitalization nor higher inpatient treatment costs. The following sections discuss the results in detail by each aim.

5.1 Discussion of results by Aims

5.1.1 Aim 1: Patterns and predictors of adjunctive psychotherapy use

The 18-month prevalence of adjunctive psychotherapy use was estimated to be 17% in this study, which is similar to the six-month prevalence (16%) calculated from Olfson and colleagues' previous work.[47] Although the follow-up period is longer in our study, given that most patients initiated their psychotherapy in the first six months of the follow-up period, we

should capture most psychotherapy users in the first six months of the follow-up. Therefore, the prevalence estimated in this study is consistent with the prevalence estimated in Olfson et al.'s study which was also conducted among Medicaid populations.[47]

Interestingly, the estimated 18-month prevalence in this study is comparable to the prevalence estimated in a previous study using National Ambulatory Medical Care Survey (NAMCS),[58] but it is much lower than the prevalence estimated in another study using Medical Expenditure Panel Survey (MEPS).[59] The prevalence of psychotherapy use among patients with schizophrenia in the study using NAMCS was 14.3% in 2004-2005, and the prevalence of psychotherapy use for schizophrenia patients was estimated as 74.4% in 2007 in the study using MEPS. Both studies used a questionnaire which asked whether a patient was provided psychotherapy or counseling during a visit (defined as verbal interactions between patients and providers), and the broad definition of psychotherapy can include services that are not reimbursed by the third party. With a broad definition of psychotherapy, the low prevalence estimated in the study using NAMCS may indicate that psychotherapy is under-utilized in patients with schizophrenia.

On the other hand, the high prevalence estimated in the study using MEPS may show that most patients with schizophrenia received certain types of psychosocial treatment or counseling during their visits, which may not be captured in the claims. However, the higher prevalence estimated in the study using MEPS may also due to an even broader definition of psychotherapy, and the fact that the study population includes both schizophrenia as well as other related disorders. Finally, because NAMCS surveyed physicians, they may provide more accurate responses about psychotherapy use since physicians should better understand the definition of psychotherapy. Since MEPS surveyed patients, they may potentially

misclassify medication education or counseling as psychotherapy. Moreover, because MEPS only surveyed one adult per household, the person being surveyed may misrepresent the satiation of health service utilization for other family members. Both situations could lead to an overestimation of psychotherapy use.

In addition, using NAMCS, Mojtabai et al. also found a higher percentage of patients covered under Medicaid or managed care did not receive psychotherapy during a visit, while a higher percentage of patients who paid themselves for psychotherapy during a visit received psychotherapy.[58] Our study may underestimate the prevalence of psychotherapy use since we are unable to capture the psychotherapy visits that were paid by patients' out-of-pocket costs. However, given that our study samples are all Medicaid beneficiaries, it is less likely that patients paid on their own for psychotherapy.

In the previous study, fewer patients had a visit that involved psychotherapy if there were medications prescribed on that visit.[58] Since our study population consists of Medicaid patients with antipsychotic treatment, the prevalence of psychotherapy use in our study may be lower than the general schizophrenia population. The lower psychotherapy visits rate among patients under Medicaid can be the result of financial considerations as well as the shift towards managed care.[58-60] Although antipsychotic agents were not specified as the medication prescribed during the visit in Mojtabai et al.'s study,[58] for patients with schizophrenia, it is likely that antipsychotics were prescribed in a visit. Since the effectiveness of psychotherapy remains unclear, patients and/or physicians may prefer pharmacotherapy over psychotherapy, which explains the lower rate of psychotherapy use among patients receiving medication treatment.[58] Finally, the low rate of psychotherapy use may come from the fact that most treatment for schizophrenia patients focus on clinical and

functional improvement, with little attention being paid to patients' humanistic needs (e.g. friendship and self-confidence).[38]

Similar to the findings in two previous studies,[46, 58] our descriptive statistics show that adjunctive psychotherapy users tend to be younger, White, and have comorbid depression, anxiety, or other psychoses. The descriptive results also show that patients receiving psychotherapy are more likely to come from rural areas and have atypical antipsychotics as their initial treatment. However, in the adjusted model, only comorbid depression was significantly associated with psychotherapy use, and rural/urban residency and type of initial treatment became insignificant.

The finding that younger patients are more likely to receive psychotherapy might be due to the fact that the onset of schizophrenia usually occurs between ages of 16 and 30.[2, 6, 7] Patients who are diagnosed with schizophrenia at an elderly age may have different characteristics than younger patients and therefore have different treatment needs, which decreases the use of psychotherapy for older patients. In addition, because we used a three-month washout period to screen new users, some of our patients may not be true new users and have a history of medication use prior to the three-month window. This "pseudo new user" phenomenon may be more likely to occur among older patients. If older patients in this study are actually prevalent users rather than new users, they are more likely to be stabilized with their treatments, and therefore, may not need additional psychosocial treatments. We may not find this difference if we had a longer wash-out period to identify true new users among the elder patients.

The fact that non-white populations are less likely to receive psychotherapy than White populations may indicate that these populations are under served, especially the Black

population. Although we are unable to assess the severity of schizophrenia, our results show that patients with additional mental health conditions are more likely to receive psychotherapy, which may indicate that patients with worse mental-health status are more likely to receive psychotherapy. Similar to the previous finding,[46] we found high percentages of atypical antipsychotic use in both groups. Since atypical antipsychotics are recommended as the first line treatment choice, the high proportion of antipsychotic use is concordant with guidelines.[16-21]

Regarding the type of psychotherapy used, consistent with Dixson et al.'s study,[46] individual therapy was found to be the most prevalent type of adjunctive psychotherapy used, followed by group therapy; family therapy was the least prevalent type of psychotherapy among the three. This finding suggests that family therapy may be underutilized since more evidence supports the efficacy of family therapy over the other two types of psychotherapy.[45, 73] In addition, family therapy has been recommended by most guidelines as an adjunctive psychosocial treatment, especially for the acute phase.[17-20] With a cohort of schizophrenia patients who are newly treated with antipsychotic treatments, the prevalence of family therapy is lower than we expected.

When looking at the time of psychotherapy initiation over a three-month interval, we found that most patients initiated their psychotherapy during the first three to six months after their antipsychotic initiation, and that the rate of psychotherapy initiation declined over time. Since the first three to six months of antipsychotic initiation may be the acute phase of schizophrenia, it is reasonable that more patients initiate their adjunctive psychosocial treatment during their early acute phase rather than the later maintenance phase. However, even in the first three months of the follow-up, the initiation rate for all types of

psychotherapy was still below 40%. As discussed previously, psychotherapy, especially family therapy, is recommended to be used during the acute phase to improve patients and their families' understanding of disease and treatments.[17-20] Even in the stabilizing or maintenance phase, other types of cognitive or behavioral treatments (e.g. individual psychotherapy) are still recommended.[16, 18, 20] Therefore, our findings reveal that most schizophrenia patients do not receive adequate psychotherapy, which could affect their physical and functional recovery.

5.1.2 Aim 2: The effect of adjunctive psychotherapy use on medication persistency and switching

5.1.2.1 Medication Persistency

Results from the survival analyses showed that patients receiving psychotherapy were less likely to discontinue their medication treatment initially. This protective effect, however, diminished during the first two months of the follow-up, and patients with psychotherapy became more likely to discontinue their treatment after the first two months of the follow-up. Given the average number of psychotherapy visits in this study is 5.4, if we assume patients have an average of one visit per week, their psychotherapy is likely to be ended around the fifth or sixth week following their initial psychosocial treatment. Additionally, we found that around 40% of patients received their first psychotherapy treatment session within the first three months of pharmacotherapy initiation, and most patients had all of their psychotherapy visits within the first 40 days in Aim 1. The finding in Aim 2 that psychotherapy users were more persistent in the first 60 days of the follow-up may reflect the effect of psychotherapy when patients are regularly receiving psychosocial treatments.

After the first two months, patients may complete their five or six psychosocial treatment sessions and no longer have psychotherapy. Since patients receiving psychotherapy often have worse mental health conditions (as shown in the descriptive statistic results), they could be less adherent to their regimens than their non-psychotherapy receiving counterparts. This may explain the increased hazard of medication discontinuation for the psychotherapy group after the first two months of the follow-up. Therefore, our result from the survival analysis may indicate that 1) psychotherapy is effective when continuously used, and 2) once patients stop psychotherapy, the effect of psychotherapy lasts only for a short period of time.

The result that patients with psychotherapy had better adherence in the first two months may be also explained by other services provided to the patients that could not be captured in the claims data. As discussed in section 5.1.1, a previous study using MEPS found a high proportion of patients had mental-health related psychotherapy or counseling services during an outpatient visit in 2007.[59] Since the definition of psychotherapy in this previous study was "a treatment technique for certain forms of mental disorders relying principally on talk/conversation between the mental health professional and the patient", many of these services can be an informal treatment and thus do not show up in the claims. Given that the patients in our study are new antipsychotic users, they may receive more psychosocial interventions or counseling services that cannot be identified in the claims at the beginning of their antipsychotic treatment, which also explains the better persistency in the first three months of the follow-up.

In addition, the short effect of psychotherapy on medication persistency may simply be due to the underuse of psychotherapy since the effect of psychotherapy usually appears

after patients received a minimum number of treatments.[57, 148] For example, it is suggested that patients need to attend at least ten treatment sessions for psychotherapy in order for psychotherapy to be effective.[57, 148] It is reported that only attending one session of treatment may worsen medication adherence.[38] Therefore, the patients in our study may not receive enough treatment sessions to make a clinically significant improvement.

Another potential explanation of the lack of effectiveness of psychotherapy after the first two months is that since more than 70% of the first-episode patients will achieve a full remission in the first three to four months,[17, 18] psychotherapy initiated after the first three months may have different focus from medication use and therefore has limited effect on medication persistency.

In addition to the effectiveness of psychotherapy use, we found that non-white patients were more likely to stop taking their medications. This may be caused by a lack of access to health care or by different cultural backgrounds, which lead to different perceptions of disease and treatment. We also found that patients living in North Carolina were more likely to discontinue their antipsychotic treatment compared to patients in Illinois, when using a gap excess of 30 days to define discontinuation. However, this effect is not significant when using a gap greater than 15 days to define discontinuation. The slightly higher rate of 30-day discontinuation in North Carolina might be due to the monthly prescription cap (6 prescriptions per month) as in 2003.

Another interesting finding in the Cox model is that patients who had modified their antipsychotic treatment were less likely to experience a discontinuation. This result may indicate that patients receiving psychotherapy have more chances to provide feedback on

their conditions or treatments to their health care professionals, and therefore, the clinicians can better adjust their regimens, which improves persistency.

5.1.2.2 Medication Switching

The logistic regression models showed that patients with psychotherapy were more likely to switch their antipsychotics using either a 30-day or 15-day window to define switching, and this result remained unchanged in the IV model with a 30-day switching window. Because the use of psychotherapy and medication switching were measured during the same period of time, the results from the naïve model can only be interpreted as an association, not causation. However, our IV results still indicate the use of psychotherapy leads to a higher probability of antipsychotic switching. Since the use of psychotherapy is recommended before and after a change in antipsychotics,[39, 40] to facilitate switching, physicians may be more likely to provide psychotherapy to their patients before changing patients' antipsychotics. Therefore, our findings may indicate that most patients were receiving psychotherapy before antipsychotic switching, rather than indicating that the use of psychotherapy increases the risk of medication switching.

Similar to the previous discussion in section 5.1.1.1, another potential explanation of the higher chance of switching could be that patients with psychotherapy may have more chances to interact with health care professionals, which provides them more opportunities to discuss the effectiveness of their current medication treatment. As a result, a physician may be more likely to be aware of problems associated with medication treatment for patients with psychotherapy and hence switch these patients to another antipsychotic agent. In this case, the use of psychotherapy serves as a channel for patients to reveal their problems with

antipsychotic treatment, and the higher chance of medication switching can be viewed as a positive outcome. When we consider medication persistency and switching together, the better medication persistency among patients with psychotherapy may be due to the fact that patients using psychotherapy were more likely to switch to a suitable antipsychotic agent.

5.1.3 Aim 3: The effect of adjunctive psychotherapy use on hospitalizations and treatment costs

5.1.3.1 Hospitalizations

Without an IV, the naïve hurdle model showed that the use of psychotherapy was associated with a small but significantly higher chance (3%) of being hospitalized, but it did not significantly affect the number of hospitalizations among patients who had been admitted at least once. One possible explanation of this result is unobservable confounding. For example, patients with worse mental-health status may be more likely to receive psychotherapy and also have a higher rate of hospitalizations. On the other hand, patients who used psychotherapy may have more chance to interact with their health care providers, and the higher frequency of provider-patient interactions may allow the clinicians to better detect health problems or identify symptoms early on. This closer monitoring may also lead to a higher rate of hospitalizations. In this case, however, a higher hospitalization rate may be a positive outcome since patients' problem can be identified early on and receive necessary treatment.

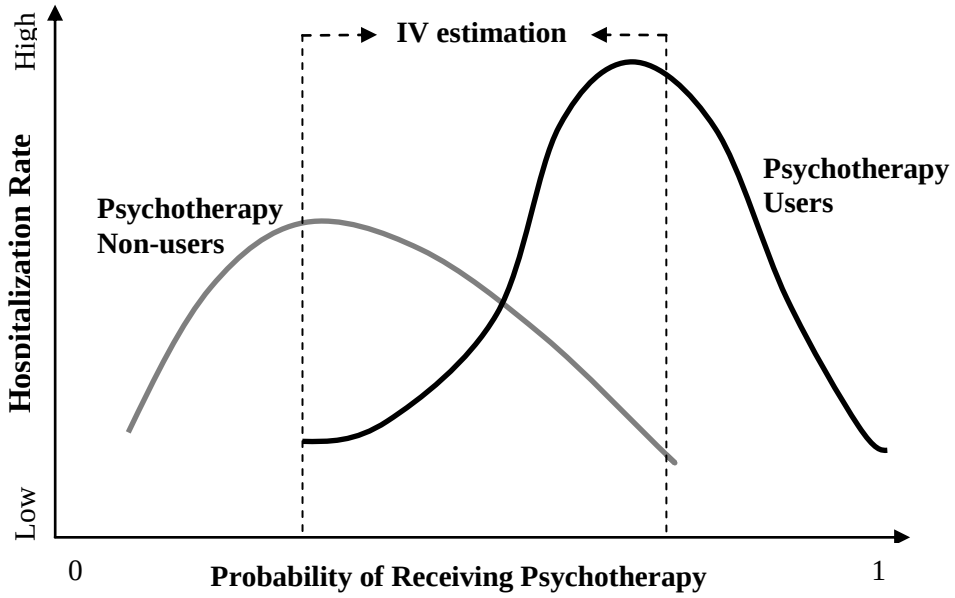
After applying IVs to adjust for un-measurable confounding, we did not find psychotherapy to significantly increase the risk of hospitalization, nor the number of admissions. With the "natural experiment" situation created by IV techniques, the results

from IV models should not be biased by un-measurable confounding and therefore can be interpreted as causal relationships. If our IVs are truly valid, we can conclude that psychotherapy does not significantly increase the rate of hospitalizations.

Another possible explanation of the difference between the naïve estimates and IV estimates is that without the IVs, we estimate the effect of psychotherapy on hospitalizations for the entire population, while with the IVs, we only estimate the local average treatment effect, which gives us the average effect of psychotherapy among marginal patients (i.e. patients' use of psychotherapy is dependent on provider's preference).[145-147] Figure 5.1 below shows a graphic illustration of the populations used for the naïve and IV estimations.

Since patients who will always (or never) be treated with psychotherapy may have different characteristics and different severities than patients who can be treated with or without psychotherapy (i.e. marginal patients), these non-marginal patients may have different patterns of inpatient service utilization. For example, patients who will always be treated with psychotherapy may have worse underlying mental-health status and hence have a higher chance to be admitted; while patients who will never be treated with psychotherapy may be much healthier and thus have a lower chance of hospitalization. As a result, the true effect of psychotherapy can be biased, or masked, by underlying heterogeneity between the psychotherapy users and non-users. Excluding these extreme patients and only looking at marginal patients will help to eliminate this "treatment selection" or confounding by indication issue and make the two groups more comparable. Therefore, the IV results should be a better reference for clinicians when determining whether to provide psychotherapy to a marginal patient.

Figure 5.1. Populations Used for Naïve versus IV Estimations



Interestingly, using typical antipsychotics as the initial treatment was found to be associated with a lower chance of hospitalization, which is contrary to the original hypothesis. Since typical antipsychotics are often used as the second-line treatment, we expected patients receiving typical antipsychotics to have worse symptoms and therefore more likely to be hospitalized. A possible explanation of this finding is that we may have some prevalent antipsychotic users in our study sample, as discussed in section 5.1.1. With only a short washout period, patients who had typical antipsychotics as their initial treatment are likely to have a history of antipsychotic treatment and get stabilized with their treatment. If patients using typical antipsychotics are more likely to be prevalent users and stabilized in their treatment, it is plausible that they are less likely to be hospitalized.

Even if our sample contains only new users, patients who started with typical antipsychotics can have very different characteristics since atypical antipsychotics are

recommended as the first line treatment. Patients initiated with typical antipsychotics may have more severe symptoms and may skip their treatments or regular check-ups. Therefore, these patients may be less willing to receive treatment and under-utilize inpatient services, which leads to a lower probability of hospitalization. On the other side, patients with less severe symptoms may begin with typical antipsychotics since these agents are often cheaper than the atypical agents and can still control for patients' conditions. If this is the case, patients initiating with typical antipsychotics should have a lower risk of hospitalization given the lower severity of their disease.

In addition, our results suggest that patients living in Kansas and North Carolina were less likely to be hospitalized compared to patients in Illinois, but among those who had been admitted, patients in North Carolina seemed to have a lower number of hospitalizations than patients in Illinois. Given the limited information available, we did not find notable difference in terms of mental-health related hospitalization services among these states (only North Carolina was found to require prior authorization for mental-health related inpatient services[149]). Nevertheless, without specific information about cost sharing or reimbursement rate for inpatient services, it is hard to determine whether the lower rate of hospitalization was due to different coverage among these states.

5.1.3.2 Treatment Costs – Inpatient Costs

Results from the naïve two-part model for inpatient costs showed that the use of psychotherapy was associated with a higher likelihood of non-zero inpatient costs as well as higher average inpatient costs among those who had been admitted. As discussed in section 5.1.3.1, our findings suggested that patients receiving psychotherapy had a higher number of

expected hospitalizations. Not surprisingly, the findings from the inpatient cost model correspond with the hospitalization model, given that the higher inpatient treatment costs can be viewed as a consequence of the higher hospitalization rate.

Unlike the results from the naïve models, results from the IV models did not show psychotherapy use increased the likelihood of positive inpatient costs, but psychotherapy use still led to significantly higher inpatient costs. Since patients receiving psychotherapy tend to have more comorbid mental conditions and thus may have worse mental-health status at baseline, once hospitalized, these patients may require more intensive care which leads to higher inpatient costs.

5.1.3.3 Treatment Costs – Outpatient Costs

Results from both the original regression and IV regression indicated that the use of adjunctive psychotherapy increased outpatient costs. The average incremental outpatient costs was $1,540 for patients receiving psychotherapy in the 18-month period, which was around $86 per month. Since adjunctive psychotherapy is an additional service, it is expected that patients using adjunctive psychotherapy had higher outpatient costs. In addition, given that our descriptive results showed that patients using psychotherapy were more likely to have other comorbid mental conditions, psychotherapy users may be sicker than non-users. Therefore, other than psychotherapy, these patients may generally have a higher utilization rate of the outpatient services, which raises their outpatient costs.

Another interesting finding is that patients with comorbid anxiety had significant lower outpatient costs compared to patients without comorbid anxiety, which is contrary to a general expectation. This finding may be the results of the modeling given that comorbid

anxiety was not found to be significantly associated with outpatient costs when a log link was used instead of a power link in the model. Since there is no clinically plausible explanation of the lower costs for patients with comorbid anxiety, the significant finding from the original GLM may simply be caused by the particulars of our modeling and is not a true effect.

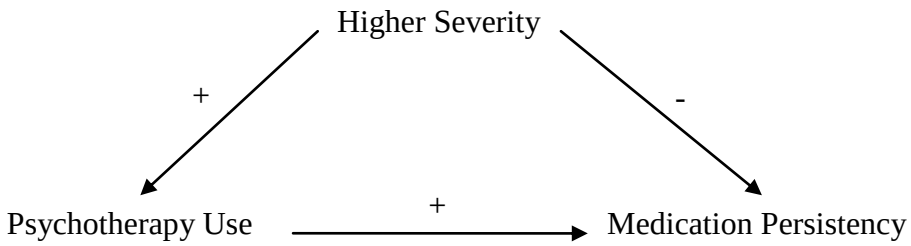
5.1.3.4 Treatment Costs – Antipsychotic Costs

The result from the naïve GLM showed that patients with psychotherapy had 14% higher antipsychotic costs than patients without psychotherapy, and this effect became even larger (a 45% increase in antipsychotic costs) after adjusting for unobservable confounders with IVs. The higher antipsychotic costs caused by psychotherapy use may indicate that the use of psychotherapy improves medication adherence and hence increases the medication costs. Given the result in Aim 2 that patients with psychotherapy had better persistency in the first two months of their antipsychotic treatment, it is possible that the higher antipsychotic costs came from the better adherence among patients receiving psychotherapy.

The larger effect observed in the IV models may be explained by potential confounding by indication (i.e. disease severity). As described in Figure 5.2 below, without adjusting for disease severity, which is an unobservable confounder in our naïve model, our results could be biased towards the null. In contrast, the IV model should adjust for this potential confounding, and therefore, the result from our IV analysis should not suffer from the downward bias. This may explain the larger effect we observed in the IV model than the original model. Lastly, we found that psychotherapy users were more likely to switch

medications in Aim 2. The higher costs of antipsychotics may also be attributable to the higher rate of antipsychotic switching or treatment modifications in the psychotherapy users.

Figure 5.2. Confounding by Disease Severity



5.1.3.5 Treatment Costs – Total Costs

Unlike previous studies,[105, 106] this study did not find the use of psychotherapy to decrease total treatment costs. Instead, both our naïve and IV models showed that patients with psychotherapy had higher total treatment costs compared to patients without psychotherapy. The different findings could come from the fact that the previous two studies are both trials, and patients in these trials are required to attend treatment sessions regularly; while in this current study, we evaluate the real world phenomenon where patients often do not or cannot attend treatment sessions regularly. In addition, in the trials, the study samples were more homogeneous, and the intervention often focused on one particular issue, which could make the effect of psychotherapy more appealling. Because both trials focused on patients with some cumbersome problems (ex. acute symptoms, stressful relationships with family members), given the regression to the mean phenomenon, it might be easier to find the intervention effective. In contrast, our study did not select patients by disease severity or

other clinical factors and thus included average patients, which may make it harder to find a significant effect of psychotherapy. Finally, although each study included slightly different mental-health services to calculate treatment costs, the major cause of different findings may come from the different ways to estimate costs. The two previous studies used information from interview and external references as their major sources for cost estimation, while our study gathered cost information directly from administrative claims records. As a result, our cost estimates should be more accurate than the two previous trials.

The original hypothesis assumes that the use of psychotherapy will increase patients' outpatient and medication costs, but this increase will be compensated by the decrease in patients' inpatient costs. In contrast to the original hypothesis, findings from the current study do not show the use of psychotherapy reduces any components (inpatient, outpatient, and antipsychotic costs) of the total treatment cost. Since the expected inpatient, outpatient, and antipsychotic costs are all higher, it is not surprising to find higher total treatment costs for patients receiving psychotherapy. Therefore, from a payer's perspective (especially Medicaid), the use of adjunctive psychotherapy will increase the cost of treatment for patients with schizophrenia.

5.1.4 Implication

Overall, we found low prevalence of adjunctive psychotherapy use among patients with schizophrenia. Most patients initiated their psychotherapy during the first three to six months of the beginning of antipsychotic treatment and received psychotherapy only for a short period of time. Individual therapy was the most prevalent type of psychotherapy being used, with family therapy as the least prevalent type. Given that more evidence has support

the efficacy of family therapy than the other two types of psychotherapy,[45, 73] and family therapy has been recommended in both the acute phase through the stable phase,[16, 18-20] clinicians should consider incorporating family therapy in the early treatment stage and encourage patients to consistently attend treatment sessions.

As addressed in Chapter 2, common reasons for not referring patients to psychotherapy include physicians or patients' lack of knowledge about the effectiveness of psychotherapy. To improve the use of psychotherapy, in addition to further study the effectiveness of psychotherapy, evidence related to psychotherapy should also be disseminated to clinicians and patients through treatment guidelines or patient education. Patients may refuse to participate in psychotherapy because they do not know what psychotherapy is or do not think it is helpful, and patients with different races/ethnicities may have different perceptions about schizophrenia and its treatment. For these reasons, we may encourage patients to participate in psychotherapy by improving patient and their relatives' understanding about psychotherapy and emphasize the benefits that psychotherapy could bring.

In addition, patients may be reluctant to use psychotherapy because it requires extra time or efforts to participate in a treatment session. This may also explain the exceptionally low rate of family therapy since family therapy requires both patients and their family members' participation. To increase the utilization of psychotherapy, we suggest moving psychotherapy from clinics to home-based or community-based environment to increase the accessibility and convenience of psychosocial treatment.

Our findings also suggested that the use of adjunctive psychotherapy improved patients' medication persistency for a short period of time, but we did not find the use of

psychotherapy helped to reduce treatment costs. The short effect of psychotherapy may come from the fact that most patients only had five to six psychotherapy visits during the 18-month follow-up period, and the overall prevalence of psychotherapy use was low. As discussed in Chapter 2, the effect of psychotherapy may not be significant or clinically meaningful until a patient received a minimum number of psychosocial treatments (at least ten sessions or six months of treatment in the case of family therapy).[57, 148] Therefore, as revealed by the study findings, the underuse of psychotherapy may not help to improve patients' treatment outcomes but simply increase the treatment costs.

Although we did not find a significant protective effect of psychotherapy use on most of our outcomes in this study, the effect of psychotherapy on other clinical outcomes should not be overlooked. For example, evidence has shown that psychotherapy can help to reduce the stress in patients' families, improve their cognitive function, and reduce the severity of symptoms, which are all valuable outcomes that cannot be assessed in a claim database.[43, 57, 69] In addition, because we were unable to measure remission rates or disease severity using a claims dataset, in this study, psychotherapy was considered to be effective if it helps to reduce hospitalizations or treatment costs. Given that pharmacotherapy and psychotherapy often have different treatment effects and goals, it is hard to find a common outcome that can be used to compare the effect between these two types of therapy fairly. The outcomes we chose in the present study may be more suitable for pharmacotherapy evaluation rather than psychotherapy effectiveness evaluation. In addition, the use of adjunctive psychotherapy can serve as a channel for patients to provide feedback on their medication treatment, which allows clinicians to better evaluate patients' conditions and change patients' treatment plans. Therefore, when treating patients with schizophrenia, it is important for clinicians to consider

both physical and functional recovery and provide both pharmacotherapy as well as psychotherapy to patients.

Given that our cost analysis was conducted from a payer's perspective, even though we found the use of psychotherapy increased the treatment costs for schizophrenia paid directly by Medicaid, psychotherapy may be cost-effective from the societal perspective. As mentioned before, schizophrenia accounts for about 20% of Social Security disability days and 20% to 30% of homelessness,[9] and most patients are unemployed.[1, 2] If adjunctive psychotherapy can help patients achieve better cognitive and functional recovery, it may help to reduce some of the societal costs (e.g. homeless, unemployment, care givers' time and efforts). As a result, when considering both direct and indirect costs associated with schizophrenia, the use of adjunctive psychotherapy may actually help to reduce the disease burden on society.

In addition, evidence has shown that the use of psychotherapy has declined over time.[58, 59] Concordant with that trend, this study found a low use rate of psychotherapy. As discussed above, the under use of psychotherapy may be caused by several reasons such as lack of clear evidence to support the effectiveness of psychotherapy, physicians' or patients' lack of knowledge about psychotherapy, or the extra time and efforts required by psychotherapy. However, another component that could largely influence the use of psychotherapy is insurance coverage. In addition to financial disincentives and the move toward managed care,[58-60] many plans may only cover certain types of psychosocial treatments or have limited psychotherapy coverage, which restricts patients' access to psychotherapy. For example, in Table 3.5, we can see that both Kansas and North Carolina have limited the number of mental-health ambulatory visits, and both Illinois and North

Carolina did not cover psychologist services. Therefore, Medicaid policy makers should consider providing more generous coverage which allows patients to have sufficient psychotherapy visits and be benefit from psychosocial treatment.

Another way to improve the use of psychotherapy is to encourage professionals other than psychiatrists, such as nurses, psychologists, and social workers, to provide psychotherapy. Allowing these professionals to provide psychotherapy under psychiatrists' supervision may not only help to reduce psychiatrists' burden, but also provide some flexibility of psychotherapy since these professional psychotherapy providers may be more flexible to provide psychotherapy as home-based or community-based interventions. Instead of directly providing psychotherapy to patients, a psychiatrist can supervise the treatment plan. With less time and efforts from psychiatrists, involving other professionals to provide psychotherapy may also help to reduce the costs of psychotherapy.

Finally, our study did not find psychotherapy helps to reduce hospitalizations or reduce treatment costs but it may have limited effect on adherence improvement. These results may suggest psychotherapy is ineffective. Therefore, clinicians may still need to carefully monitor the treatment outcomes even when a patient is receiving adjunctive psychotherapy.

In summary, this study found that psychotherapy is underutilized among patients with schizophrenia. Although we did not find a significant benefit of using psychotherapy in respect to hospitalization and treatment costs, our results suggested that psychotherapy may help to improve patients' medication persistency. Since psychotherapy has been shown to be beneficial for patients and recommended by treatment guidelines,[16-21] clinicians and policy

makers should increase the availability of psychotherapy for patients with schizophrenia to help them reach the best treatment outcomes.

5.2 Study Limitations

There are several limitations in this study. First, this study is conducted on Medicaid claims data. Therefore, the results may not be generalizable to privately insured or uninsured populations. Second, even though we adjust for several demographic and clinical factors, there could still be un-measureable variables that could affect our outcomes of interest, such as income and disease severity. Since our study population contains only Medicaid beneficiaries, patients in our study should have similar incomes. Without being able to measure disease severity, our results can be biased. In general, omitting disease severity will bias our results toward the null for outcomes such as adherence and hospitalization/inpatient costs, while the results may be biased away from the null for outcomes like outpatient or antipsychotic costs. To solve the unobservable confounding issue, we applied IV methods, and the results from the IV models should not be biased from the un-measurable confounders.

In addition, because we are unable to capture patients' actual medication taking behaviors using pharmacy claims, it is assumed that patients take all of their medications once they filled a prescription. In the survival analysis, a 15 or 30 day gap may not be able to best capture patients' medication-taking behaviors. An exploratory analysis conducted by Valenstein et al. showed that among those with poor adherence, 13% of them did not have a contiguous gap longer than one month, which indicates that they may take fewer medications than prescribed or have several short gaps over time.[81]

Due to small sample sizes, we are unable to differentiate the type of psychotherapy or detail the components of a psychotherapy visit from administrative claims. Given that different types of psychotherapy often apply different modalities and have different orientations, our results could bias toward the null if certain types of psychotherapy are less effective than others in respect to the outcomes in this study. Additionally, both the use of psychotherapy and the outcomes of interest (adherence, hospitalizations, and treatment costs) are assessed at the same period of time, which makes the temporality between the treatment assigned and outcomes less clear. Nevertheless, this temporality issue should also be eliminated with IV estimations.

As aforementioned, another limitation in this study is the short washout period. With only a three-month washout period, some patients identified in this study can be actually prevalent users who had a history of antipsychotic use three months ago.[150] Assuming prevalent antipsychotic users were less likely to receive psychotherapy because their condition has been stabilized. This "pseudo-new users" phenomenon could bias our results up or down depending on the association between the confounder (i.e. pseudo-new users) and psychotherapy use as well as the association between the confounder and the outcomes. Generally, this should bias our results toward the null. Finally, using a claims data set, we are unable to assess the effect of psychotherapy on patients' perceptions (ex. changes in insights or self-efficacy), behaviors, or symptom severity (ex. the positive and negative syndrome score), which are also important treatment outcomes.

Finally, our results may be confounded by selection effect. Given the descriptive results that patients using psychotherapy were more likely to have other mental comorbidities, patients with psychotherapy may be sicker than patients without psychotherapy. The

imbalance of disease severity between the two groups could bias our results. If the true effect of psychotherapy is positive or null, the adverse selection situation (i.e. sicker patients were more likely to use psychotherapy) in this study can bias our results toward negative. (e.g. psychotherapy use results in poor adherence).

5.3 Future Research

This study expands the existing literature by evaluating the effectiveness of adjunctive psychotherapy among Medicaid patients with schizophrenia. It improves our epidemiological knowledge of psychotherapy use as well as the effect of psychotherapy use on patients' clinical and economic outcomes. However, with only limited evidence about the effectiveness of psychotherapy, many questions are still waiting to be answered. Since there are no clear guidelines about how psychotherapy should be incorporated in a treatment course. One important step will be to clarify the effect of different types of psychosocial interventions and standardize them into a psychotherapy treatment course which can be applied clinically. In addition, it will also be important to identify outcomes that are clinically assessable and meaningful for clinicians to evaluate the effectiveness of psychotherapy. Given the cross-sectional design of the current study, a future study should employ a longitudinal design with a longer wash-out period to further clarify the causal relationship between the use of psychotherapy and treatment outcomes. With limited sample sizes, we were unable to examine the effectiveness by different types of psychotherapy. A future study can advance our knowledge by comparing the effectiveness across different types of psychotherapy. Finally, even though our study showed that psychotherapy may have limited effect on patients' adherence, hospitalization rates, and treatment costs, future

research should consider examining the effect of psychotherapy on other types of outcomes, such as patients' insight/perception, symptom improvement, or functional status, to provide a more comprehensive picture of the effectiveness of psychotherapy.

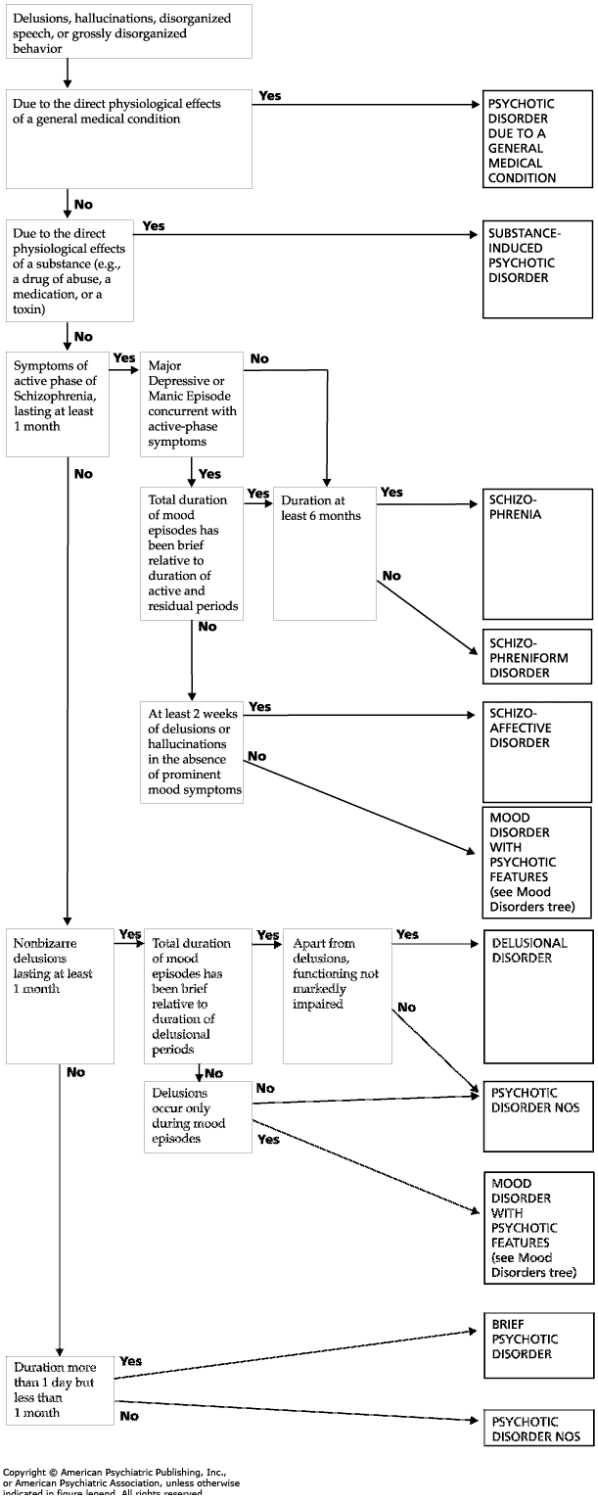
5.4 Conclusion

In conclusion, the rate of psychotherapy use was found to be low in this study. Although the use of adjunctive psychotherapy was associated with higher treatment costs, it also seemed to improve patients' medication persistency for a short period of time. To maximize the treatment effect, it takes not only pharmacotherapy to reduce the symptoms, but also psychosocial treatment to improve patients' adherence and functional recovery.

Our study showed that psychotherapy was underutilized, and states with more restrictive policies seemed to have lower utilization rates of psychotherapy. To allow patients receiving adequate psychosocial treatment to benefit from this treatment, we suggest policy makers in Medicaid consider reducing restrictions of psychotherapy to improve access to these services. Although we did not find significant benefits of psychotherapy use regarding inpatient admission reduction or cost saving, we found psychotherapy may help to improve patients' medication persistency especially when patients attend the treatment sessions regularly. Clinicians may consider providing psychotherapy to help patients better adhere to their treatment regimens. Psychotherapy may also be used to improve patients and their family members' understanding about the disease and treatment, or serve as a channel for patients and providers to better communicate the treatment effect.

APPENDIX

Appendix 1. Differential Diagnosis of Psychotic Disorders



Source: American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-IV-TR.Washington, DC: American Psychiatric Association; 2000.

Appendix 2. ICD-10 Diagnostic Criteria for Schizophrenia

Diagnostic symptom groups:

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

Diagnostic guidelines:

- A minimum of one very clear symptom (and usually two or more if less clear-cut) belonging to any one of the groups listed as (a) to (d) above, or symptoms from at least two of the groups referred to as (e) to (h);
- Symptoms have been clearly present for most of the time *during a period of 1 month or more*.
- Symptoms (i) in the above list applies only to the diagnosis of Simple Schizophrenia, and a duration of at least one year is required.
- The diagnosis of schizophrenia should not be made in the presence of extensive depressive or manic symptoms unless it is clear that schizophrenic symptoms antedated the affective disturbance, and schizophrenia should not be diagnosed in the presence of overt brain disease or during states of drug intoxication or withdrawal.
- If both schizophrenic and affective symptoms develop together and are evenly balanced, the diagnosis of schizoaffective disorder should be made, even if the schizophrenic symptoms by themselves would have justified the diagnosis of schizophrenia.

Source: World Health Organization. The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines Geneva: World Health Organization; 1992.

Appendix 3. DSM-IV Diagnostic Criteria for Schizophrenia

A. Characteristic symptoms: Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated):
   1. delusions
   2. hallucinations
   3. disorganized speech (e.g., frequent derailment or incoherence)
   4. grossly disorganized or catatonic behavior
   5. negative symptoms, i.e., affective flattening, alogia, or avolition

Note: Only once Criteria A symptom is required if delusions are bizarre or hallucinations consist of a voice keeping up a running commentary on the person's behavior or thoughts, or two or more voices conversing with each other.

B. Social/occupational dysfunction: For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations, or self-care are markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, failure to achieve expected level of interpersonal, academic, or occupational achievement).

C. Duration: Continuous signs of the disturbance persist for at least 6 months. This 6-months period must include at least 1month of symptoms (or less if successfully treated) that meet Criteria A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms.
   During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or two or more symptoms listed in Criteria A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).

D. Schizoaffective and Mood Disorder exclusion: Schizoaffective Disorder and Mood Disorder With Psychotic Features have been ruled out because either (1) on Major Depressive, manic, or Mixed Episodes have occurred concurrently with the active-phase symptoms; or (2) if mood episodes have occurred during active-phase symptoms, their total duration has been brief relative to the duration of the active and residual periods.

E. Substance/general medical condition exclusion: The disturbance is not due to the direct Physical effect of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

F. Relationship to a Pervasive Developmental Disorder: If there is a history of Autistic Disorder or another Pervasive Development Disorder, the additional diagnosis of Schizophrenia is made only if prominent delusions or hallucinations are also present for at least a month (or less if successfully treated).

Source: American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-IV-TR Washington, DC: American Psychiatric Association; 2000.

Appendix 4. UNC IRB Approval

THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL

Subject: IRB Notice
Sender: IRB <irb_no_reply@mailserv.grad.unc.edu>
Recipient: cc_wang@unc.edu <cc_wang@unc.edu>
Copy: jffarley@email.unc.edu <jffarley@email.unc.edu>
Date: 24.08.2010 16:19

To: Chi-Chuan Wang
School of Pharmacy
CB: 7573

From: Biomedical IRB

Date: 8/24/2010

RE: Determination that Research or Research-Like Activity does not require IRB Approval
Study #: 10-1463

Study Title: The Effect of Adjunctive Psychotherapy on Health Related Outcomes among Patients with Schizophrenia

This submission was reviewed by the above-referenced IRB. The IRB has determined that this submission does not constitute human subjects research as defined under federal regulations [45 CFR 46.102 (d or f) and 21 CFR 56.102(c)(e)(l)] and does not require IRB approval.

Study Description:

Purpose: To document the patterns of adjunctive psychotherapy and to investigate the role of psychotherapy on anti-psychotic adherence, hospitalization, and treatment costs. Participants: Medicaid beneficiaries with schizophrenia in Illinois, Kansas, Minnesota, North Carolina, and Vermont (year 2001-2003). Procedures: The study will be conducted using a de-identified Medicaid claims datasets. A retrospective study design and statistical analyses will be performed to evaluate the effect of adjunctive psychotherapy on patients' outcomes.

If your study protocol changes in such a way that this determination will no longer apply, you should contact the above IRB before making the changes.

CC:
Joel Farley, School Of Pharmacy

IRB Informational Message—please do not use email REPLY to this address

Appendix 5. Patient Characteristics by Type of Adjunctive Psychotherapy

	Individual Therapy	Family Therapy	Group Therapy
	N= 555	N= 16	N= 83
	%	%	%
Baseline Characteristics			
Age, Mean(SD)	39.54(10.95)	31.88(11.45)	40.70(11.04)
Age Group			
18-35	36.40	56.25	31.33
36-50	45.41	43.75	50.60
>50	18.20	0.00	18.07
Gender			
Male	53.87	68.75	59.04
Female	46.13	31.25	40.96
Race			
White	44.32	43.75	36.14
Black	47.93	37.50	55.42
Other	7.75	18.75	8.43
State			
IL	34.95	31.25	36.14
KS	9.37	12.50	8.43
MN	11.35	25.00	6.02
NC	44.32	31.25	49.40
MSA			
Yes	70.99	68.75	74.70
No	29.01	31.25	25.30
Charlson Score, Mean(SD)	0.19(0.56)	0.06(0.25)	0.16(0.71)
Mental Comorbidities			
Depression	20.72	12.50	26.51
Substance Abuse	7.57	6.25	16.87
Anxiety	6.85	6.25	7.23
Other Psychoses	8.69	18.75	8.43
Type of Initial Treatment			
Atypical	89.01	81.25	86.75
Typical	10.99	18.75	13.25
Characteristics Measured During Follow Up			
Adherence			
Yes	30.45	50.00	25.30
No	69.55	50.00	74.70
Medication Switch – 30-day Window	28.29	31.25	33.73
Medication Switch – 15-day Window	21.80	12.50	28.92
Medication Augmentation	38.92	50.00	49.40

Treatment modification- switching in 15 days or augmentation	41.62	50.00	51.81
Treatment modification- switching in 30 days or augmentation	43.42	56.25	53.01

SD: Standard Devisation; IL: Illinois, KS: Kansas, MN: Minnesota, NC: North Carolina; MSA: Metorpolitan Statistical Area; PDC: Proportion of Days Covered

Appendix 6. Aim 2 Sensitivity Analysis- Medication Switching†
(N= 3,536; N_{user}= 606, $N_{non-user}$= 2,930)

	Within a 30-day window		Within a 15-day window	
	OR	95% CI	OR	95% CI
Psychotherapy Use	1.47**	(1.22-1.77)	1.49**	(1.23-1.81)
Age Group				
18-35	*Reference*	-	*Reference*	-
36-50	0.91	(0.77-1.08)	0.95	(0.79-1.12)
>50	0.74**	(0.59-0.93)	0.75*	(0.59-0.95)
Gender				
Male	*Reference*	-	*Reference*	-
Female	0.94	(0.81-1.10)	1.03	(0.88-1.20)
Race				
White	*Reference*	-	*Reference*	-
Black	1.02	(0.87-1.20)	1.03	(0.87-1.22)
Other	1.17	(0.86-1.59)	1.13	(0.82-1.55)
State				
IL	*Reference*	-	*Reference*	-
KS	1.03	(0.77-1.38)	1.04	(0.77-1.42)
MN	0.76*	(0.58-0.99)	0.84	(0.63-1.10)
NC	1.02	(0.86-1.21)	1.07	(0.90-1.28)
MSA				
Yes	*Reference*	-	*Reference*	-
No	0.97	(0.81-1.17)	0.97	(0.80-1.16)
Charlson Score	0.95	(0.84-1.08)	0.96	(0.84-1.10)
Mental Comorbidities				
Depression	1.01	(0.81-1.27)	0.99	(0.79-1.24)
Substance Abuse	1.04	(0.79-1.36)	1.04	(0.79-1.37)
Anxiety	1.42*	(1.02-1.98)	1.37	(0.98-1.92)
Other Psychoses	1.12	(0.87-1.43)	1.13	(0.87-1.46)
Type of Initial Treatment				
Atypical	*Reference*	-	*Reference*	-
Typical	0.88	(0.71-1.09)	0.93	(0.75-1.17)

OR: Odds Ratio; CI: Confidence Interval; SD: Standard Devisation; IL: Illinois, KS: Kansas, MN: Minnesota, NC: North Carolina; MSA: Metorpolitan Statistical Area; PDC: Proportion of Days Covered

† In additional to the original switchers, the switching group here included patients who filled another antipsychotic before the end of the previous supply and never went back to the previous drug (only switch once)

* p<0.05

** p<0.01

Appendix 7. Aim 2 Sensitivity Analysis- Medication Modification†

	Within a 30-day window		Within a 15-day window	
	OR	95% CI	OR	95% CI
Psychotherapy Use	1.49**	(1.25-1.79)	1.50**	(1.25-1.79)
Age Group				
18-35	*Reference*	-	*Reference*	-
36-50	0.85	(0.72-1.00)	0.87	(0.74-1.02)
>50	0.67**	(0.54-0.84)	0.69**	(0.56-0.87)
Gender				
Male	*Reference*	-	*Reference*	-
Female	0.98	(0.84-1.13)	0.99	(0.86-1.15)
Race				
White	*Reference*	-	*Reference*	-
Black	0.97	(0.83-1.13)	0.98	(0.84-1.15)
Other	1.15	(0.86-1.55)	1.08	(0.80-1.46)
State				
IL	*Reference*	-	*Reference*	-
KS	1.07	(0.81-1.42)	1.08	(0.81-1.44)
MN	0.87	(0.68-1.12)	0.95	(0.74-1.22)
NC	1.07	(0.91-1.26)	1.10	(0.93-1.30)
MSA				
Yes	*Reference*	-	*Reference*	-
No	1.03	(0.87-1.23)	1.05	(0.88-1.24)
Charlson Score	0.91	(0.80-1.03)	0.91	(0.80-1.04)
Mental Comorbidities				
Depression	0.95	(0.76-1.17)	0.93	(0.75-1.15)
Substance Abuse	1.01	(0.78-1.31)	1.00	(0.77-1.30)
Anxiety	1.33	(0.97-1.84)	1.24	(0.89-1.72)
Other Psychoses	1.15	(0.91-1.46)	1.15	(0.91-1.47)
Type of Initial Treatment				
Atypical	*Reference*	-	*Reference*	-
Typical	0.86	(0.70-1.06)	0.88	(0.71-1.09)

OR: Odds Ratio; CI: Confidence Interval; SD: Standard Devisation; IL: Illinois, KS: Kansas, MN: Minnesota, NC: North Carolina; MSA: Metorpolitan Statistical Area; PDC: Proportion of Days Covered

† The dependent variable was treatment modification with a 30-day or 15-day switching window

* p<0.05

** p<0.01

Appendix 8. Specification Test Results for IVs

			Psychotherapy Use for the previous patient	Psychotherapy Use for a MDD patient seen by the same provider	Two IVs Jointly
Test of Strength[†]	Z-statistic (p-value)		14.84 (p< 0.001)	7.69 (p< 0.001)	N/A
	Chi-square statistic (p-value)		220.24 p< 0.001	59.15 (p< 0.001)	218.96 p<0.001
Exclusion Restriction	Hausman Test[‡]	Survival Analysis	Chi-square= 0.89, p= 1.00	Negative chi-square	N/A
		Medication Switching*	Negative chi-square	Negative chi-square	N/A
		Hospitalizations Part 1 Model	Chi-square= 2.47, p= 1.00	Negative chi-square	N/A
		Hospitalizations Part 2 Model	Chi-square= 1.30, p= 1.00	Chi-square= 1.72, p= 1.00	N/A
		Inpatient Cost Part 1 Model	Chi-square= 2.54, p= 1.00	Negative chi-square	N/A
		Inpatient Cost Part 2 Model	Negative chi-square	Negative chi-square	N/A
		Outpatient Costs	Chi-square= 0.84, p= 1.00	Chi-square= 0.82, p= 1.00	N/A
		Antipsychotic Costs	Chi-square= 1.37, p= 1.00	Chi-square= 17.77, p= 0.47	N/A
		Total Costs	Negative chi-square	Negative chi-square	N/A
	LR Test[+]	Survival Analysis	N/A	N/A	LR Chi-square= 1.09, p= 0.30
		Medication Switching	N/A	N/A	LR Chi-square= 3.54, p= 0.06
		Hospitalizations Part 1 Model	N/A	N/A	LR Chi-square= 19.94, p< 0.01
		Hospitalizations Part 2 Model	N/A	N/A	LR Chi-square= 7.38, p= 0.02
		Inpatient Cost Part 1 Model	N/A	N/A	LR Chi-square= 19.87, p< 0.01
		Inpatient Cost Part 2 Model	N/A	N/A	LR Chi-square= -0.19, p=1.00
		Outpatient Costs	N/A	N/A	LR Chi-square= 53.85, p< 0.01

		Antipsychotic Costs	N/A	N/A	LR Chi-square= 1.87, p= 0.17
		Total Costs	N/A	N/A	LR Chi-square= 9.84, p< 0.01
Test of Endogeneity	Hausman Test[§]	Survival Analysis	Negative Chi-square	-	-
		Medication Switching	-	-	Negative Chi-square
		Hospitalizations Part 1 Model	Negative Chi-square	-	-
		Hospitalizations Part 2 Model	-	-	Chi-square= 2.19, p=1.00
		Inpatient Cost Part 1 Model	Negative Chi-square	-	-
		Inpatient Cost Part 2 Model	-	-	Negative Chi-square
		Outpatient Costs	-	-	Negative Chi-square
		Antipsychotic Costs	-	-	Negative Chi-square
		Total Costs			Negative Chi-square
	Alternative Test for Endogeneity[¶]	Survival Analysis	p= 0.13	-	-
		Medication Switching	-	-	p= 0.40
		Hospitalizations Part 1 Model	p= 0.95	-	-
		Hospitalizations Part 2 Model	p= 0.01	-	-
		Inpatient Cost Part 1 Model	p= 0.93	-	-
		Inpatient Cost Part 2 Model	-	-	p= 0.11
		Outpatient Costs	p= 0.04	-	-
		Antipsychotic Costs	-	-	p= 0.20
		Total Costs	p= 0.03	-	-

LR Test: Likelihood Ratio Test; N/A: Not Applicable

† H_0: IV is not associated with psychotherapy use

‡ H_0: Assume the model including one IV is valid and will be consistent while the model including both IVs will be efficient

+ H_0: Both IVs are valid and jointly uncorrelated with the second-stage model residuals
§ H_0: Assume the model without IVs is consistent while the model including IVs is efficient
¶ H_0: The use of psychotherapy is exogeneous and thus IVs do not have any explanatory power
* Both IVs were included in the medication switching model based on the results from Chow tests

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