2005

Evaluating medication utilization patterns and healthcare outcomes in patients receiving antipsychotics

Mariam K. Hassan
West Virginia University

Evaluating Medication Utilization Patterns and Healthcare Outcomes in Patients receiving Antipsychotics

Mariam K. Hassan

Dissertation submitted to the
School of Pharmacy
at West Virginia University
in partial fulfillment of the requirements
for the degree of

Doctor of Philosophy
in
Pharmaceutical Systems and Policy

S. Suresh Madhavan, M.B.A., Ph.D., Chair
Syed Islam, Ph.D.
Iftekhar Kalsekar, Ph.D.
Jan Kavookjian, M.B.A., Ph.D.
Eugene Makela, Pharm.D.
Lesley-Ann Miller, Ph.D.

Department of Pharmaceutical Systems and Policy

Morgantown, West Virginia
2005

Keywords: Antipsychotic, Schizophrenia, Bipolar Disorder, Medicaid, Adherence, Medication Utilization Pattern, Healthcare Utilization, Costs

ABSTRACT

Evaluating Medication Utilization Patterns and Healthcare Outcomes in Patients receiving Antipsychotics

Mariam K. Hassan

Several atypical antipsychotics have entered the market since the last decade. Evaluating the utilization patterns and overall cost savings generated by these expensive agents is becoming more important as their use continues to expand. Phase 1 of this study describes the patterns of antipsychotic utilization and its impact on total and mental health-related costs for schizophrenia and bipolar disorder patients in a state Medicaid program. Phase 2 of this study compares typical antipsychotics, risperidone, olanzapine, and quetiapine in terms of direct costs and utilization of healthcare services such as hospitalizations, emergency room visits, outpatient visits, psychiatric prescription use and antipsychotic therapy modifications among schizophrenia and bipolar disorder patients. A retrospective, longitudinal study design was employed and a state Medicaid claims data from January 1, 1998 to December 31, 2002 was used. Multivariate analysis was used to statistically control for various confounding factors including patient demographics, prescribing physician type, mental health diagnosis, other comorbidities, pre-index alcohol and substance abuse, pre-index concomitant medication use, and pre-index healthcare utilization. Phase 1 results revealed that a large proportion of schizophrenia and bipolar disorder patients are non-adherent to antipsychotic therapy. Schizophrenia and bipolar disorder patients who are non-adherent to antipsychotic therapy or receive antipsychotic polytherapy incurred significantly higher total and mental healthcare costs. Phase 2 results revealed that there were no significant differences in total and mental healthcare costs among schizophrenia patients initiated on any of the study antipsychotics. Bipolar disorder patients initiated on typical antipsychotics incurred higher total and mental healthcare costs as compared to patients initiated on atypicals. There were no significant differences in total and mental healthcare costs among patients initiated on any of the study atypical antipsychotics. Patients initiated on olanzapine incurred highest pharmacy costs whereas patients initiated on typical antipsychotics incurred lowest pharmacy costs. Schizophrenia and bipolar disorder patients initiated on typical antipsychotics showed significantly lower adherence and higher likelihood of modifying antipsychotic therapy as compared to atypicals.

.

ACKNOWLEDGEMENTS

First and foremost, I would like to thank Dr. Suresh Madhavan for bringing me into the research program at WVU and giving me the opportunity to learn and develop my skills in the warm, friendly and stimulating environment of our PSP department. As my dissertation chairperson, his advice, assistance and encouragement were crucial in the development and completion of this dissertation project.

I would like to thank Dr. Syed Islam for the guidance, support and invaluable learning experience I received while working with him. His insight and suggestions were very helpful throughout the course of this study. I sincerely appreciate the time and help of my committee members - Dr. Iftekhar Kalsekar, Dr. Jan Kavookjian, Dr. Eugene Makela and Dr. Lesley-Ann Miller. Their expertise and advice were essential in improving this project. I would like to thank Dr. Kitty Rajagopalan and AstraZeneca for giving the opportunity and funding support to carry out this project. I would also like to acknowledge Ms. Peggy King, Pharmacy Program Coordinator, West Virginia Bureau of Medical Services, for her support and approval to conduct this study. I want to thank Dr. Mike Smith for his informative inputs about the database use and Dr. Virginia Scott for her advice and support all through my graduate school years. I thank Kelly White and Mickey Howell for being very cooperative and helpful at all times. I also appreciate Rahul's assistance with the tables for this study.

I will always cherish the wonderful friends I made during my school years. They have filled the long years of my doctoral studies with fun, laughter and memorable moments. I would specially like to mention Vivek, Murali and Anna from the department for always being there to help, support or just hang out.

The greatest credit for this work goes to my parents for all for the attention and care they have put into my education from early on. The love, patience and encouragement from all my family members- Abba, Mummy, Nazia, Aamer and Akash has given me the strength to get to this point. The lengthy and trying phases of this work would have been difficult to overcome without the reassurance and motivation from Akash. I will always be indebted to my loving family for everything I achieve in life.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER ONE

INTRODUCTION

Schizophrenia

Schizophrenia is a complex psychiatric disorder affecting about 1.1% of the population. Despite the low prevalence of the disease, schizophrenia is the most expensive psychiatry disorder to treat (Knapp, 1997). Schizophrenia costs constitute 2.5% of total healthcare expenditures. In 1991, direct and indirect costs associated with schizophrenia were estimated to be $18.6 billion and $46.5 billion, respectively. Hospitalizations are responsible for almost 70% of costs, drug costs for almost 10%, and outpatient costs usually make up the rest of the 20% (Revicki, 1997). Annual total healthcare costs per schizophrenia patient were estimated to range between $16,000 and $57,000 in 1999 (Mauskopf, David, Grainger, & Gibson, 1999).

Bipolar Disorder

The lifetime prevalence of bipolar disorder in the US population is about 1.2% to 1.6% (Kessler et al., 1994). The estimated economic burden of the disorder is about $45 billion. The direct costs are estimated at $7.6 billion and indirect costs at $38 billion. About 60-70% of direct costs were attributable to inpatient costs (Wyatt & Henter, 1995). Medication costs constitute about 2% of direct costs. The annual medication cost per treated patient was about $548 (Wyatt et al., 1995). About 75% of bipolar patients undergo at least one hospitalization during the course of their illness (Lish, Dime-Meenan, Whybrow, Price, & Hirschfeld, 1994). About 10% of inpatient healthcare in US is utilized by bipolar patients (Narrow, Regier, Rae, Manderscheid, & Locke, 1993).

Costs for patients with bipolar disorder is higher than costs for patients treated for depression or diabetes (Simon & Unutzer, 1999).

Antipsychotic Treatment Patterns

Pharmacotherapy of schizophrenia involves use of conventional antipsychotics and relatively newer atypical antipsychotics. With the advent of newer atypical antipsychotics over the last decade, the treatment pattern of antipsychotic therapy is changing. Various studies conducted in different healthcare settings and time periods have reported this trend. A study by Williams et al using the Regenstrief Medical Record System reported only 12% atypical antipsychotic use among schizophrenia patients in 1995. About 25% of patients switched medications and 90% augmented medications during a 12-month period (Williams, Johnstone, Kesterson, Javor, & Schmetzer, 1999). A chart review of 83 outpatients showed that patients who switched antipsychotics made greater use of psychiatric services (Tempier & Pawliuk, 2003). McCombs et al used the claims data from the California Medicaid program (Medi-Cal) from 1987 to 1996 to study antipsychotics utilization patterns in terms of no drug therapy for over 1 year; delayed onset of antipsychotic drug therapy; and, switches in antipsychotic drugs within 1 year. During the time period of the study, they found that about 98% of patients were on conventional antipyschotics. About 47% of patients switched or augmented their therapy within one year. Only 11.6% of patients received continuous antipsychotic therapy for one year (McCombs, Nichol, Stimmel, Shi, & Smith, 1999b). These studies used data earlier than 1998 during which atypical antipsychotics were not widely used. Drug use pattern of antipsychotics has probably changed since this study as newer atypical antipsychotics have entered market and are being more widely used.

Until recently, atypical antipsychotics were not approved for use for bipolar patients though their use was prevalent in clinical practice (Licht et al., 1994; Shattell & Keltner, 2004). Pattern of antipsychotic use among bipolar patients has been less studied. A meta-analysis by Tohen et al revealed that about 84.7% of bipolar patients received typical antipsychotics. About 53.8% of typical antipsychotic use was as monotherapy. About 47.4% of typical antipsychotic use was as an adjunct with a mood stabilizer (Tohen et al., 2001). A study by Russo et al reported that typical antipsychotics were used by 16.4% of patients and atypical antipsychotics by 12.4% of bipolar patients between 1994 and 1998. The study also found that patients initiated on antipsychotics continued on the therapy for more than 12 months, while patients initiated on anticonvulsants or antidepressants were more likely to discontinue or switch to another medication class (Russo, Smith, Dirani, Namjoshi, & Tohen, 2002).

Antipsychotic polypharmacy

Literature reveals widespread practice of antipsychotic polypharmacy. Various studies have reported prevalence of antipsychotic polypharmacy in clinical practice despite the lack of clinical evidence supporting such practice. Analyzing prescription records of patients hospitalized between 1995 and 2000, McCue et al reported about 16% of schizophrenia patients on multiple antipsychotics. However, the study claims that polypharmacy was linked with shorter length of hospitalization and fewer adverse effects (McCue, Waheed, & Urcuyo, 2003). Procyshyn et al found that 27.5% of schizophrenic patients discharged from a tertiary psychiatric clinic were prescribed multiple antipsychotics. As compared to monotherapy, antipsychotic polytherapy was linked with greater use of anticholinergics (Procyshyn, Kennedy, Tse, & Thompson, 2001). Clark et

al reported that antipsychotic polytherapy has increased from 5.7% in 1995 to 35.6% in 1999 among schizophrenia patients (Clark, Bartels, Mellman, & Peacock, 2002). A retrospective case-control study of multiple versus single antipsychotic treatment in psychiatric inpatients revealed that multiple antipsychotic therapy is associated with more adverse effects and hospitalizations but no clinical benefit (Centorrino et al., 2004). A retrospective survey of discharge medications at a tertiary care psychiatric hospital found that antipsychotic polytherapy was very common in schizoaffective disorder (49.3%), followed by schizophrenia (44.7%), bipolar disorder (29.9%), and psychosis not otherwise specified (22.5%) (Procyshyn & Thompson, 2004). More data on polytherapy practices in bipolar disorder is lacking. More studies are needed to develop guidelines to aid clinicians and health policy decision makers regarding antipsychotic polytherapy.

Antipsychotic Use for Other Indications

Though atypicals were introduced for the management of schizophrenia, they are increasingly being used for other indications. A cross-sectional analysis of nursing home residents from Jan. 1, 1999, to Jan. 31, 2000 revealed that atypical antipsychotic were generally used in Parkinson's disease, depression, Alzheimer's disease, and non-Alzheimer dementia (Liperoti et al., 2003). Antipsychotic use has also substantially increased for attention-deficit/hyperactivity disorder, conduct disorder, and affective disorders among patients aged 2 to 18 years (Cooper, Hickson, Fuchs, Arbogast, & Ray, 2004). Though already prevalent to some extent in clinical practice, use of certain atypical antipsychotics for bipolar disorder was recently approved by FDA. However, antipyschotics use for conditions other than schizophrenia and bipolar disorders is not clearly supported by clinical studies and are not approved by FDA.

Antipsychotic Therapy and Economic Outcomes

As schizophrenia and bipolar disorders are associated with the extensive use of inpatient services, treatments that can reduce inpatient utilization may decrease the overall costs and improve the quality of life for patients, their families, and society. Though more costly than typical antipsychotics, atypical antipsychotics offer better outcomes and may be cost-effective in the long run. Despite the increase in pharmacy costs, atypicals have been shown to offset inpatient and outpatient costs as compared to typical antipsychotics (Csernansky & Schuchart, 2002; Gianfrancesco, Durkin, Mahmoud, & Wang, 2002; Gibson, Damler, Jackson, Wilder, & Ramsey, 2004; Nightengale, Garrett, Waugh, Lawrence, & Andrus, 1998).

Each atypical antipsychotic has its unique pharmacologic profile and is priced differently. However, there are very few pharmacoeconomic comparisons among the atypical antipsychotics. To date, most of the published studies have compared only risperidone and olanzapine. Relative advantage offered by one drug as compared to the other has differed depending upon study population, outcome measures, research and statistical design. A prospective observational study comparing olanzapine and risperidone showed that olanzapine had a lower risk of psychiatric hospitalization than risperidone-treated schizophrenia patients within the first year (Ascher-Svanum, Zhu, Faries, & Ernst, 2004). A retrospective analysis comparing total health care costs for patients initiated on risperidone or olanzapine between March 1997 and March 1999 reported decline in costs for risperidone-treated patients and increase in costs for olanzapine-treated patients (Fuller, Shermock, Secic, Laich, & Durkin, 2002). An analysis of Michigan Medicaid claims from January 1995 through September 1998

revealed that total costs were not significantly different between olanzapine, risperidone and haloperidol treated schizophrenia patients. However, olanzapine was associated with lower inpatient costs and risperidone was associated with greater persistence with therapy (Gibson et al., 2004). The results from the health economic data from the Risperidone Olanzapine Drug Outcomes studies in Schizophrenia (RODOS) program show that olanzapine was associated with higher total costs as compared to risperidone without any clinical benefit (Kasper, Jones, & Duchesne, 2001). A study examining inpatient data of 789 patients with schizophrenia or schizoaffective disorder initiated on risperidone or olanzapine reported higher discharge rate and lower drug costs among risperidone treated patients (Kelly, Nelson, Love, Yu, & Conley, 2001). Another study showed that patients initiated on olanzapine were prescribed anti-parkinson drugs less frequently (Zhao, 2002). Costs and utilization among patients initiated on olanzapine or risperidone between January 1, 1997 and August 31, 1998 were compared using Texas Medicaid data. Results showed no significant differences among schizophrenia-related costs but the total medical costs were lower among patients initiated in olanzapine (Rascati, Johnsrud, Crismon, Lage, & Barber, 2003).

There is only one published economic analysis that compares risperidone, olanzapine and quetiapine in real world settings. This study evaluated only the pharmacy costs in an acute care inpatient setting. The study reports lower pharmacy cost for risperidone and quetiapine as compared to olanzapine (Mladsi et al., 2004). There are no other published studies comparing quetiapine, a relatively newer atypical antipsychotic, with other atypical antipsychotics in real world settings. A clinical decision modeling study comparing atypical antipsychotics in terms of non-compliance, relapse and cost

among schizophrenia patients showed higher non- compliance, relapses, and incremental cost among risperidone and olanzapine treated patients as compared to quetiapine (Mortimer, Williams, & Meddis, 2003). The Partial Responders International schizophrenia Evaluation (PRIZE) clinical trial comparing quetiapine and haloperidol using a Markov model showed that though quetiapine has the higher acquisition cost, it can lower costs for other medications, hospitalization, and other medical services (Tilden, Aristides, Meddis, & Burns, 2002).

Literature on health care cost and utilization outcomes of antipsychotic therapy in bipolar disorder is lacking. Economic outcomes from a randomized clinical trial of olanzapine treatment in patients diagnosed with bipolar I disorder with mania showed cost saving of almost $900 per month during the 49 weeks of olanzapine therapy. These cost savings were mainly attributed to reductions in in-patient costs. Thus, it is possible that olanzapine and other atypicals may prove to be cost-effective in bipolar disorders if similar results can be shown in non-clinical trial populations (Namjoshi et al., 2002). There is only one published study comparing economic outcomes of different antipsychotics in bipolar disorder. This study reports that mental-health related costs were higher for olanzapine as compared to risperidone and quetiapine. There was no significant difference in costs between risperidone and quetiapine (Gianfrancesco, Pesa, & Wang, 2005).

STATEMENT OF PROBLEM

Several atypical antipsychotics have entered the market since the last decade. Evaluating utilization pattern and the value added to the therapy by these expensive

agents is becoming more important as their use continues to expand. There is lack of data on the population demographics, treatment patterns, utilization and costs of these newer drugs in general population. There is a need to document that antipsychotic use is not restricted to schizophrenia in clinical practice. The purpose of the present study is to link the antipsychotic therapy patterns with healthcare utilization and costs in the West Virginia Medicaid population. As previous studies have used data until 1998, there is a need for observational studies evaluating changes in utilization patterns with introduction of newer drugs.

Antipsychotic polypharmacy is prevalent in clinical practice despite the lack of scientific evidence. The practice probably results due to past experience or intuitive judgment of practicing physicians. Studying the healthcare outcomes and economic consequences of this practice can be helpful in developing guidelines for antipsychotic polypharmacy. They can also support the need for clinical trials evaluating the decision to use antipsychotic polypharmacy in some patients.

State Medicaid is the single largest payer for mental health care. In 1996, Medicaid spent about $12.6 billion on mental health care (Hogan, 1999). The burden of mental disorders such as schizophrenia and bipolar disorder is very high due to the chronic nature, hospitalizations, comorbidities and disabilities associated with these diseases. Due to very high unemployment among patients with such mental disorders, the state Medicaid bears the greatest impact of this disease (Hogan, 1998; Hogan, 1999). Atypical antipsychotics are among the ten most expensive medications for Medicaid (Clark et al., 2002). If the pharmacotherapy is effective in controlling the disease symptoms and severity, it can reduce the need for medical services and offset costs.

Though newer antipsychotics have high acquisition costs, they offer advantages in treatment such as better adherence and reduced hospitalizations. From a payer's perspective, it is important to determine which atypical antipsychotic would be most effective in reducing utilization and generating savings in total healthcare expenditures in their patient population.

Though the total medical cost is the most relevant economic outcome for formulary decision-making purposes, the differences in total cost depend upon differences in the use of inpatient services, physician services, concomitant medications, changes in treatment or treatment discontinuation rates, and relapse rates. These components of healthcare costs need to be studied to gain better understanding of costs associated with antipsychotic use. Very few studies in the literature have looked at the use of antipsychotics in bipolar disorder. This study aims to provide more information in terms of describing utilization pattern and economic comparisons of antipsychotics in bipolar disorder.

Randomized clinical trials have strict inclusion and exclusion criteria for patient enrollment. Their findings cannot be generalized to the real world settings where the patient population and treatment pattern is more diverse and complex. Use of WV Medicaid data will allow us to study our objectives in a naturalistic setting and with larger sample sizes.

CONCEPTUAL FRAMEWORK

In phase I, the study will describe different patterns of antipsychotic use in schizophrenia and bipolar disorder patients. Predictors of different pattern of use will be

determined. The effect of different patterns of use on utilization of healthcare services and costs will be evaluated. The goal of phase II is to compare risperidone, olanzapine, quetiapine and typical antipsychotics on multiple healthcare outcomes such as healthcare costs, hospitalizations, emergency room visits, outpatient visits, concomitant drug use, and adherence and persistence with the index drug,

The rationale for the use of Medicaid data, sample selection criteria, identification of study cohorts, outcomes evaluation and sample selection bias adjustment is provided below.

Selection of Database

Administrative claims database are usually large longitudinal databases developed for billing and payment purposes by the health plans. They contain medical and pharmacy claims records of the health plan subscribers that can be used for research purposes. Studies using retrospective databases use more relaxed exclusion criteria as compared to randomized clinical trials and have greater generalizability. Claims database studies are a good alternative if the relevant clinical trial has not been conducted or cannot be conducted for ethical reasons. Claims database studies are less costly and more reflective of real world setting. These databases offer large population size and can provide sufficient sample size to give adequate power to the study. They are less susceptible to Hawthorne effect (improvement of performance under observation) as the providers and patients are not contacted (Motheral & Fairman, 1997; Strom, 2005).

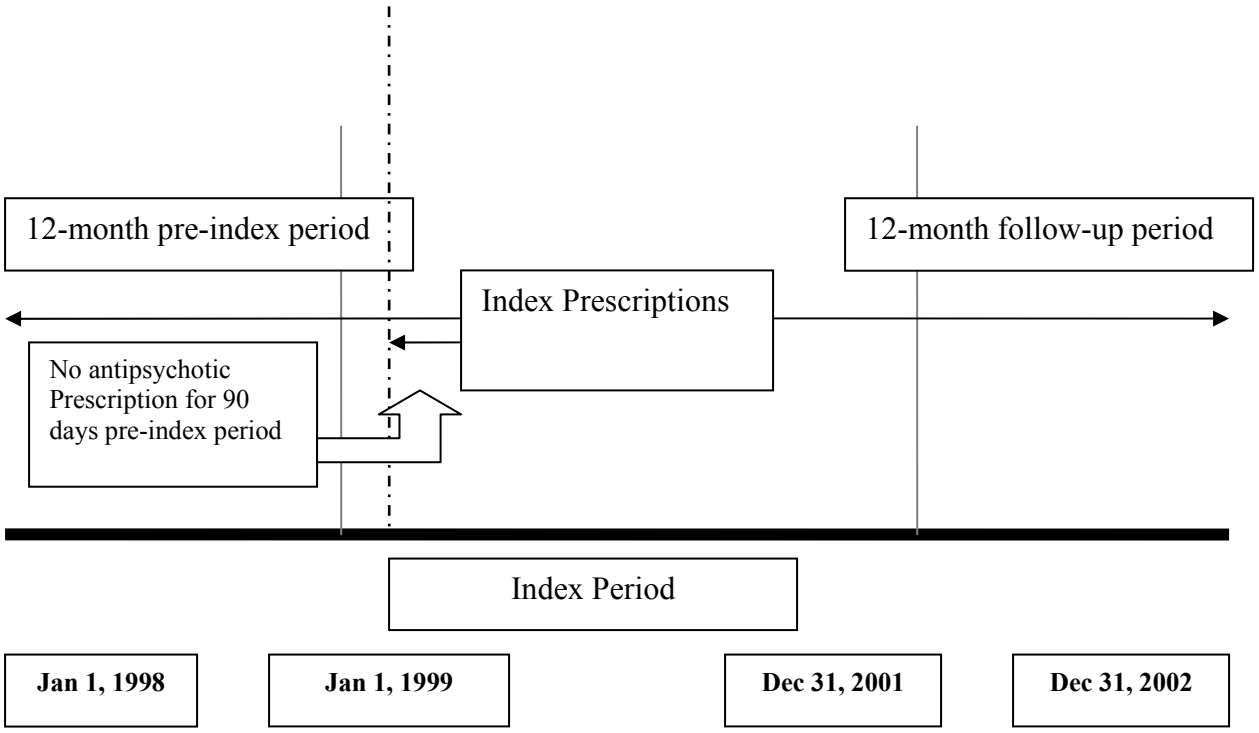
Medicaid offers comprehensive prescription and health benefits and likelihood of out-of system healthcare use among Medicaid population is rare. Due to very high unemployment rate among schizophrenia and bipolar patients, prevalence and burden of

these diseases in Medicaid is high (Hogan, 1998; Hogan, 1999). In addition, as the actual amount paid for each claim is present in the Medicaid data, it is a valuable resource to study direct costs and utilization of various healthcare components such as hospitalizations, emergency room visits, physician visits and prescriptions among schizophrenia and bipolar patients.

Sample Selection

West Virginia Medicaid maintains data on patient-level demographic information, medical and prescription drug claims for its recipients. West Virginia Medicaid data for the period January 1, 1998 to December 31, 2002 will be used for the purpose of the study. Schizophrenia and bipolar disorder patients can be identified from this data on basis of ICD-9-CM codes. All paid claims information on patients receiving at least two prescriptions of antipsychotics from January 1, 1999 to December 31, 2001 will be extracted. This period will be defined as the index period. Index date will be the first date of paid claim during the index period for the antipsychotic. Patients should have at least 12 months of continuous enrollment with the West Virginia Medicaid before and after the index date. The patients should not have any claims of an antipsychotic medication during a 90 days period before the index date to allow for a 'wash-out' period before considering the index prescription as initiation of antipsychotic therapy. Patients who were 65 years or older will be excluded as they have Medicare as their primary payer for health services. Managed care recipients will be excluded as they do not have all their utilization information in the Medicaid claims. As clozapine is indicated for treatment refractory schizophrenia, patients initiated on clozapine will be excluded. Figure 1 provides the timeframe and study design.

Figure 1: Timeframe for the study design



Phase I

Patterns of antipsychotic Use

The phase I of the study aims to evaluate the pattern of use of antipsychotic in schizophrenia and bipolar disorder patients. All prescription claims after initiation of antipsychotic will be reviewed to determine the pattern of use of antipsychotic.

The pattern of antipsychotic use in schizophrenia will be categorized into following mutually exclusive categories:

1) Antipsychotic Polytherapy (patients who are receiving two or more antipsychotics)

2) Antipsychotic Monotherapy

a) Switching (patients who change the index antipsychotic to another antipsychotic)

b) Interrupted Therapy (patients receiving less than 80% days supply of index antipsychotic in the post-index period)

c) Continuous Therapy (patients receiving at least 80% days supply of index antipsychotic in the post index period)

In addition, the pattern of antipsychotic use will also be studied in terms of:

1) Stabilization on initiating antipsychotic therapy

2) Gaps in antipsychotic therapies that indicate the missing days of antipsychotic therapy in the post-index period.

1) Stabilization on initiating antipsychotic therapy

Proportion of patients who continued on index antipsychotic beyond the trial duration (based on recommendations by the Texas Medication Algorithm Project (TMAP) guidelines) will be determined (Miller et al., 1999). This indicates that the

patients responded to the index antipsychotic therapy during the trial duration and were continued on the index antipsychotic.

TMAP guidelines recommend trial duration of 3 -10 weeks (including a week of titration to therapeutic dose) after initiation of an antipsychotic before switching antipsychotics. In this study, trial duration of 90 days after initiation of antipsychotic was selected as cut-off to classify the patients who continued on index antipsychotics for 3 months or more and the patients who changed or discontinued the index antipsychotic within 3 months. The 70 days trial duration recommended by TMAP was extended to 90 days in our study based on expert opinion estimating usual physician practices and to allow for some gaps in refills by the patient.

In addition, the pattern of antipsychotic use in bipolar disorder will be categorized into following mutually exclusive categories:

1) Antipsychotic Polytherapy (patients who are receiving two or more antipsychotics)

2) Antipsychotic Monotherapy

a) Switching (patients who change the index antipsychotic to another antipsychotic)

b) Interrupted Therapy (patients receiving less than 80% days supply of index antipsychotic in the post-index period)

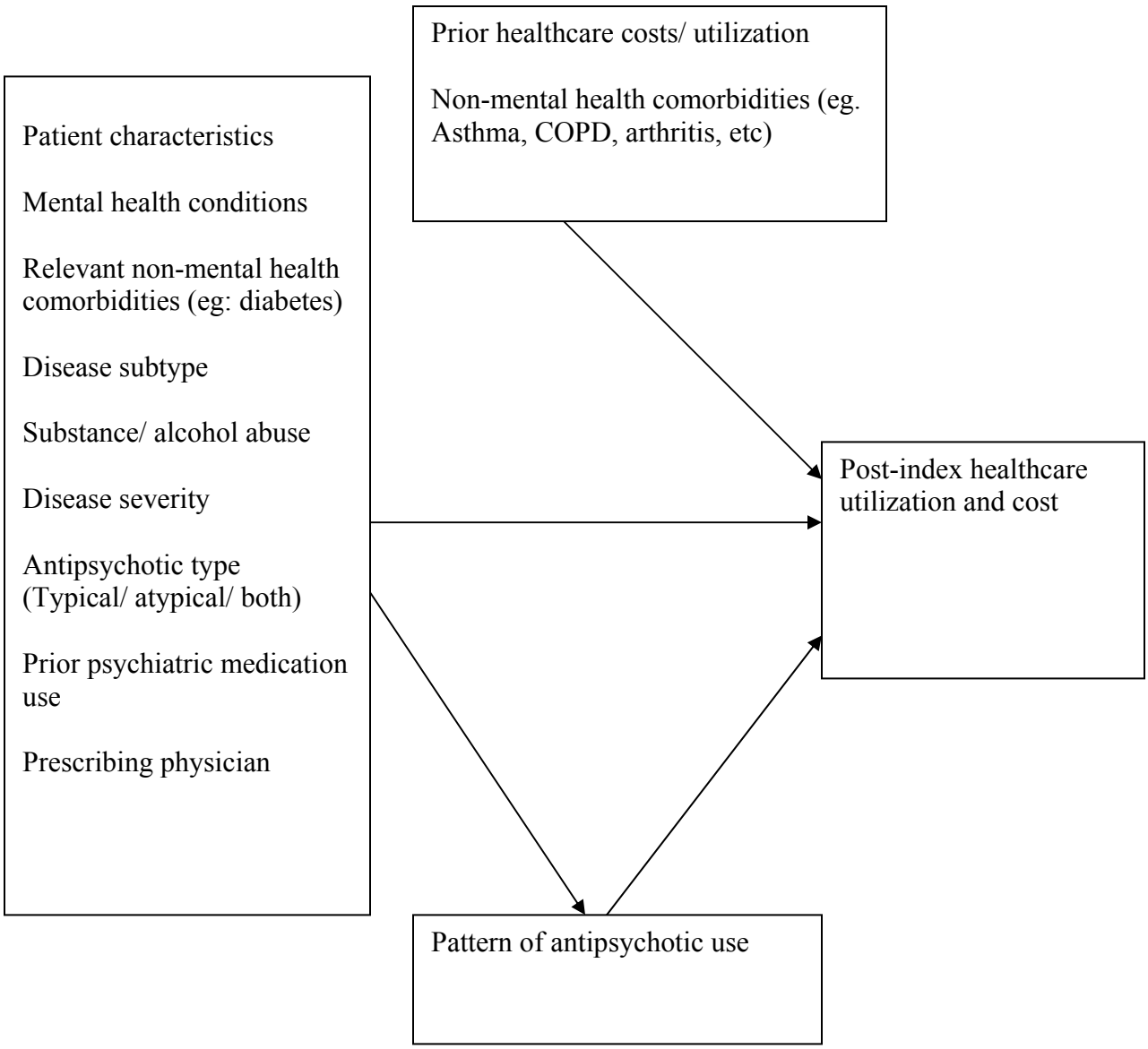
c) Continuous Therapy (patients receiving at least 80% days supply of index antipsychotic in the post index period)

Pattern of antipsychotic use will also be studied in terms of gaps in antipsychotic therapy.

Evaluating effect of patterns of use on healthcare cost and utilization

Treatment pattern of antipsychotic therapy is changing with the introduction of newer antipsychotics. Switching between different antipsychotics is common (McCombs et al., 1999b; Tempier et al., 2003; Williams et al., 1999). Literature also reveals that there is considerable prevalence of antipsychotic polypharmacy in clinical practice settings (Clark et al., 2002; McCue et al., 2003). Various factors such as disease severity, multiple comorbidities, antipsychotic type and patient characteristics can be responsible for existence of different pattern of use for antipsychotics. Also, pattern of antipsychotic use can affect healthcare utilization and costs. It has been shown in some studies that antipsychotic polypharmacy or switching is associated with greater adverse affects, hospitalizations and psychiatric service utilization (Centorrino et al., 2004; Clark et al., 2002; McCue et al., 2003; Tempier et al., 2003). It is likely that patients with polytherapy are more severe than patients on monotherapy. Our approach is to adjust for the sample selection bias that may exist between the different patterns of use groups prior to determining the relationship between patterns of use and healthcare outcomes. Figure 2 presents the conceptual framework regarding relationship between various factors that can influence pattern of antipsychotic therapy in the post-index period. It also gives relationship between patterns of antipsychotic use, costs, and utilization.

Figure 2: Conceptual framework for Phase I



Phase II

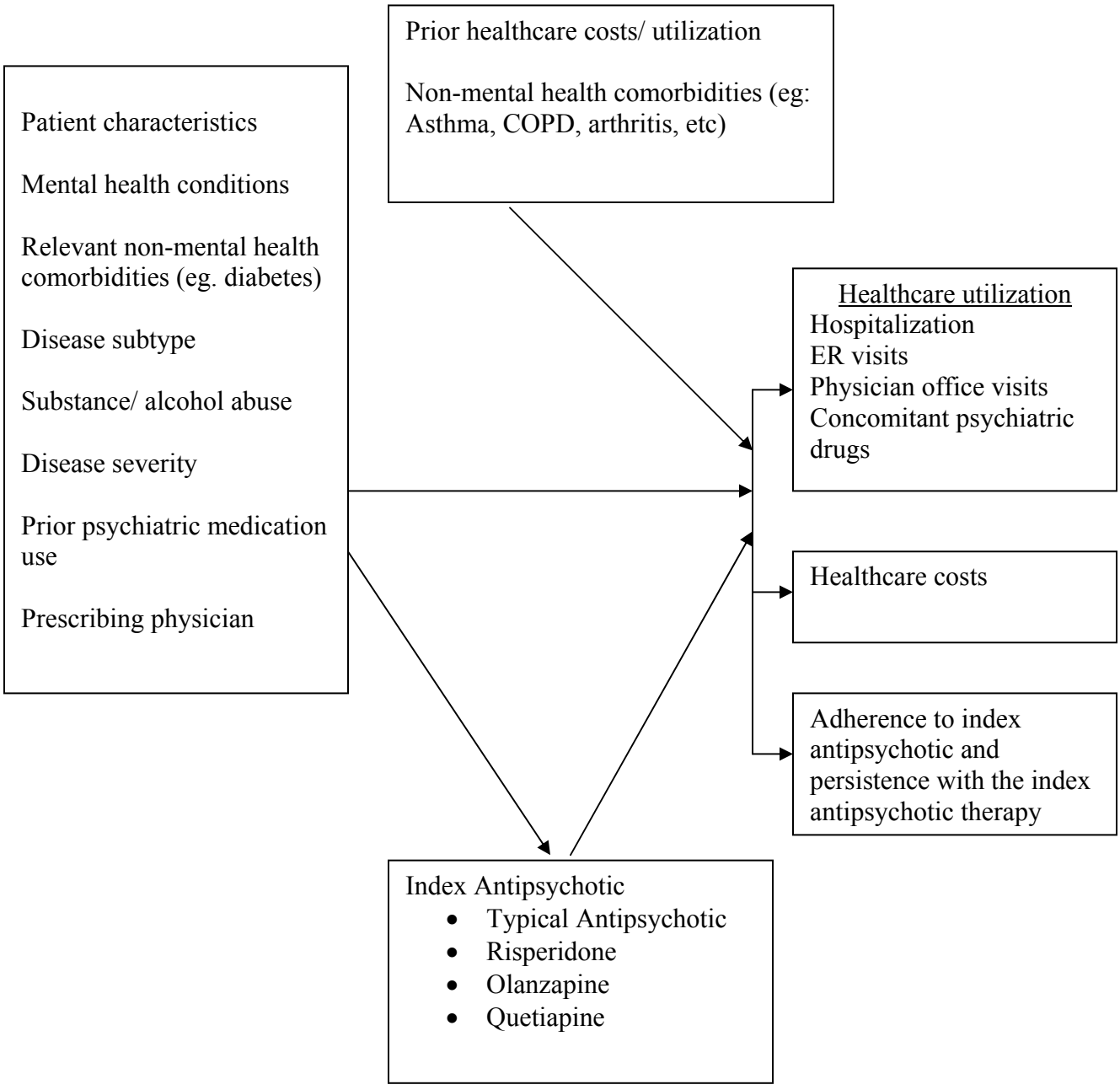
Antipsychotic therapy and healthcare utilization and outcomes

Patients will be classified into the study cohorts based on the index prescription during the index period (January 1, 1999 – December 31, 2001). The first prescription of a study medication (Risperidone, Olanzapine, Quetiapine or typical antipsychotics) during the index period will be defined as the index prescription. Intent to treat approach will be employed wherein the outcomes will be attributed to the index prescription irrespective of the medication pattern subsequent to index prescription. The affect of index antipsychotic on healthcare costs and various components of healthcare utilization such as physician visits, hospitalizations and length of stay, emergency room visits, and concomitant psychiatric prescription use will be evaluated. In addition, persistence with the index prescription and adherence to the index prescription will also be compared across the cohorts. Adherence will be measured in terms of medication possession ratio (MPR).

Multivariate regression analysis will be conducted with each of the outcome variable as dependent variable and antipsychotic type as independent variable. Various other factors that affect the outcome variables such as age, gender, prescribing physician specialty, schizophrenia/bipolar subtype, disease severity, schizophrenia/bipolar subtype, other mental illnesses, substance abuse, alcohol abuse, pre-index typical antipsychotic and other psychiatric medication use, pre-index health care costs and utilization will be controlled for in the multivariate analysis. As the assignment of patients into the index cohorts is not randomized, sample selection techniques will be

used to control for sample selection bias. Figure 3 presents the conceptual framework describing the relationship between the index antipsychotic therapy and healthcare utilization and outcomes.

Figure 3: Conceptual framework for Phase 2



Sample Selection Bias Adjustment

As there is no randomization in studies based on claims database, they are prone to selection bias. Selection bias is a systematic error associated with how the study sample is derived from study population and/or how study subjects are assigned to treatment group (Strom, 2005). If we had all variables that are associated with the likelihood of receiving certain antipsychotic, we can control for them in a multivariate regression. However, information on many relevant variables usually is not available in retrospective data. This can bias the regression coefficients in a multivariate regression model estimating affect of treatment on costs and utilization. Unobserved variables could be clinical variables needed to determine patient's severity, prescribing physician's preferences and prior experience, patient preference, and market structure forces

Heckman two-stage technique is a specialized econometric technique to control for the sample selection bias (Greene, 2000; Heckman, 1979). The main concept behind the technique is that though we cannot correct the sample, we can correct the estimation. It tries to adjust the final estimation from the regression analysis for the unobserved or omitted variables.

Heckman two-stage technique involves the following two steps:

Step 1:

The first step of the Heckman two-stage technique involves developing a selection model. The selection bias is present due to differences in certain characteristics between the study cohorts that are related to the outcome variables (cost and utilization). The selection model compares the study cohorts to determine these differences. Heckman first-stage sample selection model uses a probit model as the selection model

when there are two choices. Lee's modification of Heckman sample selection model involves use of a multinomial logit (MNL) model as the selection model when there are more than two choices (Greene, 2000).

In the selection model, the dependent variable is the choice of drug therapy (or any treatment group). The independent variables are relevant observed variables such as age, gender, race, comorbidities, physician specialty and prior medication history that can affect the choice of drug therapy. The affect of these observed variables on the choice of drug therapy is estimated using the selection model. When the affect of these observed variables on the dependent variable is removed, the remaining variation in the dependent variable is due to the unobserved variables. Therefore, the residuals of the selection model provide information on the unobserved variables and are used to calculate a covariate or a control factor that can correct for selection bias in the second-stage model.

Step 2:

The second-stage model is a multivariate regression model where the dependent variable is the study outcome such as cost and utilization. The independent variables are relevant variables that can influence cost and utilization such as patient demographics, comorbidities, prior healthcare utilization, and choice of drug therapy. The independent variables in the second-stage regression equation may overlap with those in the first-stage regression equation. In addition, the control factor calculated in the first-stage selection model to control for unobserved variables is also included as an independent variable in the second-stage regression model.

If the coefficient of the control factor in the second-stage regression model is significant, it indicates that selection bias was present and some variation in the

dependent variable is due to unobserved variables. However, the coefficient of the control factor captures the effects of unobserved variables on the outcome variables in the second-stage regression model. This results in unbiased coefficients for other independent variables in the model.

Heckman's two-stage model has been used successfully in many outcomes research studies (Crown et al., 1998; Crown, Treglia, Meneades, & White, 2001; McCollam, Lage, & Bala, 2001). Other methods such as propensity scores technique and instrumental variable can also be used to control for selection bias. However, propensity scores technique is more laborious and can reduce the sample size to matched observations. Also, it controls for only observed variables whereas Heckman two-stage technique controls for both observed and unobserved variables. The hindrance in using instrumental variable technique is to find an instrumental variable in claims database that is related to treatment choice but not to treatment outcomes (Crown et al., 1998)

STUDY OBJECTIVES

The overall goal of phase I is to study the pattern of antipsychotics use and its effects on utilization of healthcare services and expenditures. The goal of phase II is to compare risperidone, olanzapine, quetiapine and typical antipsychotics on multiple healthcare outcomes. Specific research questions necessary to achieve these goals are as follows:

Phase I

Research Question 1

To determine the annual prevalence rate of schizophrenia and bipolar disorder in West Virginia Medicaid from 1998 to 2002

Rationale: This is an exploratory question to assess prevalence rate of schizophrenia and bipolar disorder in West Virginia Medicaid from 1998 to 2002

Research Question 2

To determine the medical conditions for which antipsychotics are being prescribed in the West Virginia Medicaid population as well as describe patterns of distribution of certain demographic factors such as age, gender, and ethnicity in patients using antipsychotics.

Rationale: This is an exploratory question to assess prevalence of antipsychotic use for different medical conditions and differences in antipsychotic utilization by age, gender and ethnicity.

Research Question 3

For schizophrenia and bipolar disorder patients, determine different types of utilization pattern of antipsychotics.

Rationale: For schizophrenia and bipolar disorder patients, there is no difference in the patterns of antipsychotic utilization in terms of:

1) Polytherapy

2) Monotherapy

    a) switching

    b) interrupted therapy

    c) continuous therapy

3) Stabilization of index antipsychotic (for schizophrenia patients)

Research Question 4

For schizophrenia and bipolar disorder patients, determine the gaps between the refills of antipyschotics.

Rationale: There are no gaps in the antipsychotic therapy.

Research Question 5

For schizophrenia and bipolar disorder patients, determine predictors of different utilization patterns of antipsychotics

Null Hypothesis: There is no association between utilization patterns of antipsychotics and patient demographics, prescribing physician type, mental health diagnosis, other medical diagnosis, type of antipsychotic, year of index antipsychotic, pre-index concomitant medication use, pre-index alcohol and substance abuse and pre-index healthcare utilization.

Research Question 6

For schizophrenia and bipolar disorder patients, determine the relationship between utilization pattern of antipsychotics and total health-related healthcare costs.

Null Hypothesis: There is no association between utilization patterns of antipsychotics and total health-related healthcare utilization and costs.

Research Question 7

For schizophrenia and bipolar disorder patients, determine the relationship between utilization pattern of antipsychotics and mental health care utilization and costs.

Null Hypothesis: There is no association between utilization patterns of antipsychotics and mental health healthcare utilization and costs.

Phase II

Research Question 8

For schizophrenia and bipolar disorder patients, to compare the impact of quetiapine with risperidone, olanzapine, and typical antipsychotics on total and mental healthcare costs

Null Hypothesis: There is no association between the choice of index antipsychotic drug and total and mental healthcare costs.

Research Question 9

For schizophrenia and bipolar disorder patients, to compare the impact of quetiapine with risperidone, olanzapine, and typical antipsychotics on components of mental healthcare costs (costs associated with mental health-related inpatient, emergency room, outpatient and pharmacy services)

Null Hypothesis: There is no association between the choice of index antipsychotic drug and costs associated with mental health-related inpatient, emergency room, outpatient and pharmacy services

Research Question 10

For schizophrenia and bipolar patients, to compare the impact of quetiapine with risperidone, olanzapine, and typical antipsychotics on mental health-related healthcare hospitalizations

Null Hypothesis: There is no association between the choice of index antipsychotic drug and costs associated with mental health-related healthcare hospitalizations.

Research Question 11

For schizophrenia patients and bipolar disorder patients, to compare the impact of quetiapine with risperidone, olanzapine, and typical antipsychotics on mental healthcare-related emergency room visits

Null Hypothesis: There is no association between the choice of index antipsychotic drug and costs associated with mental healthcare-related emergency room visits.

Research Question 12

For schizophrenia and bipolar disorder patients, to compare the impact of quetiapine with risperidone, olanzapine, and typical antipsychotics on mental healthcare-related outpatient visits

Null Hypothesis: There is no association between the choice of index antipsychotic drug and costs associated with mental healthcare-related physician visits.

Research Question 13

For schizophrenia and bipolar disorder patients, to compare the impact of quetiapine with risperidone, olanzapine, and typical antipsychotics on psychiatric medication utilization

Null Hypothesis: There is no association between the choice of index antipsychotic drug and costs associated with psychiatric medication utilization.

Research Question 14

For schizophrenia and bipolar disorder patients, to compare the impact of quetiapine with risperidone, olanzapine, and typical antipsychotics on patient's adherence to the index medications in the post-index period

Null Hypothesis: There is no association between the choice of index antipsychotic drug and patient's adherence to the index medications in the post-index period.

Research Question 15

For schizophrenia and bipolar disorder patients, to compare the impact of quetiapine with risperidone, olanzapine, and typical antipsychotics on subsequent index antipsychotic therapy modification

Null Hypothesis: There is no association between the choice of index antipsychotic drug and subsequent antipsychotic switching or discontinuation.

STUDY SIGNIFICANCE

The results of this study will describe the prevalent pattern of antipsychotic drug use in the WV Medicaid and report the costs and health services utilization associated with these patterns. This can give us a picture of complex pharmacotherapy regimens that are used to manage patients in clinical practice. It will help us understand both patient behavior such as medication adherence as well as prescriber behavior in the West Virginia Medicaid program. Economic endpoints will also be relevant from a formulary decision making perspective. It can identify the consequences of inappropriate prescribing such as polytherapy that can add to the already strained Medicaid budget covering expensive antipsychotics. This study can provide the basis for need for interventions such as academic detailing and other educational programs to improve prescribing patterns.

As newer atypicals are similar in efficacy, costs associated with their use can play an important role in treatment decisions. Considering the high acquisition costs of atypical antipsychotics, it important to monitor their utilization and costs within the

system. In the proposed study, comparisons of antipsychotics will be differentiated in terms of multiple endpoints such as hospitalizations, emergency room visits, concomitant medication use, adherence and treatment discontinuation rates to give a better understanding of their impact on costs. The study will also control for selection bias to provide a better estimation of affect of choice of antipsychotics on costs and utilization. The results of this study will also be useful in understanding relatively less studied economics of antipsychotic use in bipolar disorder. These results can be useful to WV Medicaid to develop policies to provide better medication management for schizophrenia and bipolar patients.

LIMITATIONS

Use of administrative data can have certain disadvantages (Motheral et al., 1997). Inaccurate identification of diseases can occur due to errors in coding. Identification of cases in a research study solely on the basis of an outpatient visit can seriously affect the validity of study. However, hospital-based diagnoses have been shown to be very accurate (Bright, Avorn, & Everitt, 1989). A study by Schwartz et al reported that about 90-94% of cases with psychiatric diagnoses in Medicaid matched with the diagnoses in the chart demonstrating a very high reliability (Schwartz, Perlman, Paris, Schmidt, & Thornton, 1980). A study by Lurie et al validated using an inpatient claim or two outpatient claims with ICD codes for schizophrenia within past 2 years as inclusion criteria to accurately identify schizophrenics in Medicaid. They validated the diagnosis with the help of psychiatrics using DSM-III-R criteria for schizophrenia. Therefore, the inclusion criteria of an inpatient claim or two outpatient claims within past 2 years could

be used with considerable confidence in our study to identify cases of schizophrenia in the WV Medicaid population (Lurie P, Popkin M, Dysken M, & Finch M., 1992).

A claim for a prescription in the database indicates that the claim has been paid to the provider and not that medication has been taken correctly by the patient. Claims for a drug do not necessarily indicate adherence with the therapy. However, databases contain information such as date of service, amount dispensed and days of supply that can be used to calculate proxy measures for compliance. Several studies have found significant correlations between adherence measured from refill information and other methods such as self-report, pill count, and medication diary (Choo et al., 1999).

Threats to external validity are relatively lower in database studies as compared to randomized clinical trial. However, one should be careful in claiming generalizability as characteristic of study population in different databases may differ according to age, sex, race, socioeconomic status, geography, etc. Also, various factors such as co-pays, formularies, and provider access may be unique to West Virginia Medicaid. Practice patterns and costs also vary across time and geographically. Thus, findings from a study population of a certain plan may not apply to populations from other plans. Descriptive information about our study population characteristics will be given so that the readers can weigh the similarities and differences between the study population and the population in question.

Due to lack of random assignment, there may be differences between patients initiated on different therapies. Therefore, adjustments for sample selection bias are necessary. Risk adjustments are also important to control for differences between the

groups. A study by Sernyak et al validated use of sociodemographic variables, prior utilization and cost variables obtained from administrative data as risk adjusters to predict future utilization and costs. The study compared models that used administrative data alone with models that used administrative data as well as clinical data from a prospective, double-blind clinical trial. The models using combination data yielded an adjusted r-square of 0.31-0.27 that was not significantly different from adjusted r-square of 0.24-0.28 that was obtained from models that used only administrative data (Sernyak & Rosenheck, 2003). Our study will control for confounding using sociodemographics, pre-index utilization and costs as well as other variables as covariates.

CHAPTER TWO

LITERATURE REVIEW

Schizophrenia

Epidemiology and Cost

Schizophrenia is a complex psychiatric disorder affecting about 0.2% to 2% of the population. Despite the low prevalence of the disease, schizophrenia is the most expensive psychiatry disorder to treat (Knapp, 1997). The burden of disease is high due to early onset, chronic nature, hospitalizations, comorbidities and disabilities. Schizophrenia costs constitute 2.5% of total healthcare expenditures. Schizophrenic patients consume about 10% of social security benefits. About 70-80% schizophrenic patients are unemployed (Foster & Goa, 1998). In 1991, direct and indirect costs associated with schizophrenia were estimated to be $18.6 billion and $46.5 billion, respectively. Hospitalizations are responsible for almost 70% of costs, drug costs for almost 10%, and outpatient costs usually make up the rest of the 20% (Revicki, 1997). Prolonged / frequent episodes, long term hospitalization, and care in intensive community programs incur most of the direct costs. Cost of social welfare, criminal justice services and family productivity are included in the indirect costs (Revicki, 1997). Annual total healthcare costs per schizophrenia patient was estimated to range between $16,000 and $57,000 in 1999 (Mauskopf et al., 1999).

Schizophrenia symptoms usually appear in the late teens or early twenties in men and in the twenties to early thirties in women (APA, 1997; Crismon ML & Dorson PG., 1997). Prevalence is similar between the genders (APA, 1997; Crismon ML et al., 1997). The disease is chronic in nature and relapses requiring hospitalization could be frequent.

Most patients are readmitted within 3 to 5 years (APA, 1997). Risk of other medical illnesses and mortality from suicide is also high among patients with Schizophrenia (Carpenter, Jr. & Buchanan, 1994). Schizophrenic patients are at risk for substance abuse, suicide, and disability (APA, 1997). Almost 25-50% attempt suicides and almost 10% commit suicide. About 10% of disabled US population is schizophrenic (Foster et al., 1998).

Disease Description

Symptoms of schizophrenia include thought disorders, emotional changes, delusion and perception disorders (hallucinations, sensory effects), aggressive behavior, impaired judgment, ideas of reference, withdrawal from external reality, eccentric or ritualistic behavior (Crismon ML et al., 1997). A schizophrenic patient may not be able to function in society and take care of himself (Crismon ML et al., 1997). According to the American Psychiatry Association (APA) guidelines, (APA, 1997) phases of schizophrenia can be classified into: *1) Acute phase***:** The patient exhibits some of the most severe symptoms in this phase. The patient may experience hallucinations, delusions, and severely disorganized behavior and/or thinking. Prior to this phase, the individual may become more withdrawn or behave in an unusual manner. Symptoms may gradually become more severe and lead to an acute episode. An acute episode usually requires hospitalization. The duration of this phase depends on several factors including patient characteristics and environment. *2) Stabilization phase:* This phase begins as the psychotic symptoms decrease in severity and may last for 6 months or more. *3) Stable phase:* Most of the psychotic symptoms become stable in this phase.

Some idiosyncratic behaviors and nonpsychotic symptoms, such as depression, anxiety, tension, or insomnia, may still persist.

Pharmacotherapy in Schizophrenia

Schizophrenia treatment comprises of pharmacotherapy and psychosocial treatment or rehabilitation (Lehman et al., 2004b). Pharmacotherapy of schizophrenia involves use of conventional antipsychotics and relatively newer atypical antipsychotics. The typical or conventional antipsychotics include the phenothiazines (chlorpromazine, fluphenazine, mesoridazine, perphenazine, prochlorperazine, trifluoperazine, and thioridazine), butyrophenones (haloperidol), thioxanthenes (thiothixene), and dihydrolones (molindone and loxapine). Efficacy of the typical agents is due to blockade of the dopamine D_2 receptors. The blockade also is responsible for their side-effect profiles. Most of the conventional antipsychotics are comparable in efficacy. Typically, these agents decrease only the positive symptoms of schizophrenia. Depending on the extent of blockade, these agents may actually worsen negative symptoms. The common side-affects of typical antipsychotics (Crismon ML et al., 1997) are:

a. Acute extrapyramidal effects: These can lead to acute dystonia (spasm of face, neck, back muscles), Akathesia, Parkinsonism (bradykinesia, rigidity, tremor, mask face).

b. Neuroleptic malignant syndrome: These are rare but can be fatal. These are characterized by course tremor, catatonia, fluctuating vital signs, metabolic abnormalities.

c. Chronic extrapyramidal effect or tardive dyskinesia can develop during long-term treatment.

d. Autonomic effects such as antimuscarinic effects (dry mouth, constipation, difficulty urinating) *or* effects due to blockade of α1 receptors (orthostatic hypotension, sexual dysfunction).

e. Endocrine effects are responsible for hyperprolactinemia (due to dopamine receptor blockade) that can lead to galactorrhoea, amenorrhoea and gynaecomastia. Weight gain is possible due to hyperprolactinemia and 5HT blockade.

f. Psychological effects such as sedation and cognitive impairment can occur depending upon the drug.

Atypical Antipsychotics

Several atypical antipsychotics, especially effective in addressing both the negative symptoms and positive symptoms of schizophrenia, have entered the market in the last decade. For example, Clozapine (Novartis 1990), Risperidone (Janssen 1993), Olanzapine (EliLilly 1996), Quetiapine (Zeneca 1997), Ziprasidone (Pfizer 2001) and Aripiprazole (Bristol Myers Squibb 2002). These agents antagonize serotonin $5HT_{2a}$ and dopamine D_2 receptors. Therefore, there is a lower incidence of extrapyramidal side effects (Carpenter, Jr. et al., 1994). These atypical antipsychotics have high acquisition costs but are more affective in controlling positive symptoms and have more tolerable extra pyramidal symptoms profile.

Efficacy of atypical antipsychotics is comparable to typical antipsychotics for most aspects of schizophrenia (Carpenter, Jr. et al., 1994; Carpenter, Jr. et al., 1994). Atypicals have similar or slightly better global clinical efficacy for positive symptoms as compared to typical antipsychotics. They have shown better relapse prevention than typical antipsychotics in controlled trials. Clozapine, risperidone, olanzapine and

ziprasidone have been shown to be much better efficacy for negative symptoms as compared to typical antipsychotics. Quetiapine is similar to typical antipsychotic for negative symptoms. Atypical antisychotics show better efficacy than typical antipsychotics in controlling affective symptoms, depression and suicidality. Clozapine is much superior to typical antipsychotics and other atypical antipsychotics for treatment refractory patients (Carpenter, Jr. et al., 1994).

Side effect profile of atypical antipsychotics is much better than typical antipsychotics (APA, 1997; Carpenter, Jr. et al., 1994). *Acute extrapyramidal effects (EPS*) are less likely with atypical antipsychotics. *Neuroleptic malignant syndrome* is rare but can occur. *Chronic extrapyramidal effect / tardive dyskinesia* is much less likely with atypical antipsychotics. *Autonomic effects* depend upon the drug but are similar to typical antipsychotics. *Endocrine effects* such as hyperprolactinemia are less likely with typical antipsychotics. However, recent studies have shown that risk of hyperglycemia, diabetes, and hyperlipedemia may be higher in patients using antipsychotics (Koro et al., 2002; Lindenmayer et al., 2003). These effects may vary from drug to drug (Koro et al., 2002; Lindenmayer et al., 2003). Also, weight gain can be greater due to 5HT and histamine receptor blockade. *Psychological effects* such as sedation depend on drug but are similar to typicals. Impaired cognition may be less than with typical antipsychotics. Clozapine can cause blood dyscrasias (agranulocytosis) and requires white count check frequently (Amadio, Cross, & Amadio, Jr., 1997).

Antipsychotic Treatment Guidelines for Schizophrenia

The Texas Medication Algorithm Project (TMAP) has developed stepwise algorithms for schizophrenia pharmacotherapy. First published in 1999, they were updated in 2003 to include recommendations for ziprasidone and ariprazole (Miller et al., 1999; Miller, 2004). TMAP guidelines recommend using atypical antipsychotics (olanzapine/ quetiapine/ risperidone) as first-line of treatment (Miller et al., 1999). In 2003, ziprasidone and ariprazole were also included among the list of atypical antipsychotic to be used as first-line therapy (Miller, 2004). According to TMAP guidelines, duration of trial with the antipsychotic should be at least 3 weeks and at the most 10 weeks. The guidelines suggest trying the 3 atypicals in sequential order and then a typical antipsychotic before using clozapine. Monotherapy is recommended until clozapine fails. Weekly (or at least every two weeks) visits until the patient is stable is advised for outpatients who are switching antipsychotic medications. Other guidelines such as American Psychiatric Association (APA) guidelines suggest typical or atypical antipsychotics as first-line treatment whereas TMAP guidelines emphasize use of atypicals (American Psychiatric Association, 1997). However, APA guidelines do not recommend any form of polytherapy. TMAP guideline recommends polytherapy but only after a trial with clozapine fails.

Antipsychotics Utilization Patterns in Schizophrenia

Antipsychotic utilization patterns among schizophrenia patients in clinical practice can be classified into predominant categories such as polypharmacy, switching, and discontinuation.

Antipsychotic Polypharmacy

Despite the lack of controlled clinical trials evaluating efficacy of antipsychotic polypharmacy, it has considerable prevalence in clinical practice. Prevalence of antipsychotic polypharmacy has been reported to range from 6.8% to 41% in various populations. An analysis of outpatient prescriptions in Veteran Administration (VA) schizophrenia population revealed only 6.8% received polytherapy (Leslie & Rosenheck, 2001). Studies evaluating antipsychotic use among hospitalized patients have found higher rates (16% - 45%) of polytherapy (Schumacher, Makela, & Griffin, 2003; Procyshyn et al., 2001; Procyshyn et al., 2004; McCue et al., 2003). Antipsychotic polypharmacy increased from 5.7% in 1995 to 24.5% in 1999 among the New Hampshire Medicaid beneficiaries with schizophrenia (Clark et al., 2002). Prevalence of antipsychotic polypharmacy between 1998 and 2000 was about 40% in a sample of Georgia Medicaid and California Medicaid Schizophrenia patients (Ganguly, Kotzan, Miller, Kennedy, & Martin, 2004). Prevalence of antipsychotic polytherapy among Rhode Island Medicaid's elderly and disabled population was about 10% in 2003 (Kogut, Yam, & Dufresne, 2005). A retrospective review of medication information for all patients discharged from a tertiary care psychiatric facility between January 1, 2000 and December 31, 2000 revealed highest rate of antipsychotic polypharmacy among patients with schizoaffective disorder (49.3%), followed by schizophrenia (44.7%) (Procyshyn et al., 2004).

As each atypical antipsychotic has a unique receptor profile, there may be theoretical rationale in combining these medications to manage symptoms for some patients. Physician surveys have revealed that the most common reason cited for

prescribing polytherapy was to reduce the positive symptoms. In many cases, physicians have stated that addition of another antipsychotic was intended to be transitional but continued because of patient's preference or improvement in symptoms (Sernyak & Rosenheck, 2004; Tapp et al., 2003). A physician survey by Schumacher and colleagues reported therapy augmentation as the most common rationale for polytherapy. However, majority of the patients treated by these physicians had not received a trial of atypical or typical monotherapy or clozapine before receiving polytherapy (Schumacher et al., 2003). Case reports and retrospective charts reviews evaluating antipsychotic polypharmacy do not provide any conclusive information regarding efficacy and adverse effects of this practice (Freudenreich & Goff, 2002). One open prospective trial reported increased risk of mortality during 10-year follow-up period among schizophrenia patients on antipsychotic polytherapy (Waddington, Youssef, & Kinsella, 1998). The difference in mortality rates may be due to selective prescription of antipsychotic polypharmacy to more severe patients.

There are very few studies evaluating economic consequences of antipsychotic polytherapy. Majority of these studies are restricted to inpatient settings. McCue and colleagues used hospital records of an inpatient psychiatry facility to compare schizophrenia patients who were discharged in the year 1995 to schizophrenia patients who were discharged in 2000. They reported that no patients discharged in 1995 received polytherapy whereas 15.9% of patients discharged in 2000 received polytherapy. They also report lesser adverse drug reactions and shorter length of hospital stay among patients discharged in 2000. As they examined cross-sectional data in 1995 and 2000, we cannot make inference regarding association of polypharmacy with decreased adverse

drug reactions and length of stay. Prescribing practices for schizophrenia has changed considerably between 1995 and 2000 due to greater use of atypical antipsychotics. Fewer adverse effects may be attributed to fewer EPS side-effects with the atypicals. A retrospective review of medications prescribed during discharge from a tertiary psychiatry facility to non-elderly patients between November 1, 1996 and October 31, 1998 revealed that 27.5% were discharged on antipsychotic polypharmacy. Despite a small sample size of the study (N = 229), antipsychotic polytherapy was significantly associated with greater use of anticholinergics compared to monotherapy (Procyshyn et al., 2001). Centorrino and colleagues used a case-control study design to compare polypharmacy with monotherapy using inpatient records of psychiatric patients. Seventy patients receiving 2 or more antipsychotics for at least 3 consecutive days were identified as cases and matched with 70 patients who received only one antipsychotic. Cases and controls were matched on gender, age, psychiatric disorder (schizophrenia/ bipolar disorder/ or other disorders) and illness severity. The analysis revealed that although there were similar clinical improvements in both groups, patients on polytherapy had 55% longer length of stay and 56% higher risk of adverse effects than patients on monotherapy (Centorrino et al., 2004).

Antipsychotic Switching and Discontinuation

Pharmacotherapy of schizophrenia often requires switching between the medications (Bogan, Shellhorn, Brown, McDanald, & Suppes, 2000; Burns, Chabannes, & Demyttenaere, 2002; Menzin, Boulanger, Friedman, Mackell, & Lloyd, 2003). Switching can occur if there is inadequate control of positive symptoms, residual negative symptoms such as apathy and mood symptoms. Atypical antipychotics are

better at controlling mood symptoms like depression. Atypicals also have fewer pyramidal side-effects compared to conventional antipsychotics. Therefore, many patients can be switched to atypicals. Introduction of new atypical drugs in market can lead to switches from previously used drugs. Prescriber may switch drug if the patient relapses despite compliance. However, weight gain and high cost of atypical drugs can also lead to non-compliance(1999).

Non-compliance is a critical problem with antipsychotic therapy. Non-compliance is mainly a result of disabling adverse effects such as extrapyramidal symptoms (EPS) that can offset the benefits of the therapy (Van Putten, 1974). EPS symptoms include muscular rigidity and cramping, tremors, gait disturbances, drooling, agitation, and involuntary abnormal movements of the lips, tongue, and facial muscles. Other adverse effects such as gynecomastia, galactorrhea, amenorrhea and impotence that are related to elevated prolactin concentrations also reduce compliance (Hamner, Arvanitis, Miller, Link, & Hong, 1996). About 50% of schizophrenic patients who discontinue their antipsychotic therapy relapse within a year (Pigott et al., 2003). Non-compliance is also responsible for repeated hospitalizations also known as "revolving door syndrome" among schizophrenics (Haywood et al., 1995). About 37% of direct costs within 2 years of discharge after first hospitalization results due to non-compliance (Weiden & Olfson, 1995). Because of better side-effect profile, atypical antipyschotics have shown better compliance and are recommended as the first-line treatment for schizophrenia. About 30% of patients relapse with typical antipychotics whereas about 20% of patients relapse with atypical antipsychotics (Weiden, Aquila, & Standard, 1996).

Patient non-compliance due to disease nature and side-effects of medications can result in high discontinuation rates. Increasing patient persistence with the given antipsychotic therapy is a challenge for health care providers. In addition, about 5%-25% of schizophrenia patients are treatment refractory (Brenner et al., 1990). The physician's attempts to control symptoms in these patients can lead to varying patterns of antipsychotic use.

In 1995, Williams and colleagues studied use of antipsychotic in an outpatient patient population with schizophrenia using Regenstrief Medical Record System. Out of 316 study sample, about 88% received typical and 12% received atypical antipsychotic. About 71.5% of patients received only antipsychotic whereas about 25% of patients switched to another antipsychotic during the 1-year follow-up period. About 30% of patients received continuous antipsychotic treatment for one year. About 67.1% of patients had a gap of 1-11 months in their antipsychotic therapy. Factors associated with continuous use of antipsychotics in this patient population were not investigated (Williams et al., 1999). A study by Al-Zakwani and colleagues followed 469 managed care plan enrollees who were initiated on antipsychotics irrespective of mental health diagnosis for one year. Patients were initiated on antipsychotic between 1999 and 2000. About 81.8% received atypical and 18.2% received typical antipsychotic. The proportion of patients who switched from atypical antipsychotics (18.2%) was not significantly different from proportion of patients who switched from typical antipsychotics (12.9%) (Al Zakwani et al., 2003).

There are two studies investigating various types of antipsychotic utilization patterns in schizophrenia patient population predominantly on typical antipsychotics.

McCombs and colleagues used administrative claims data from the California Medicaid program (Medi-Cal) to study utilization pattern of antipsychotics from 1987 to 1996. A total of 2,655 schizophrenia patients were identified between 1987 and 1996. During the time period of the study, they found that about 98% of patients were on conventional antipyschotics. About 47% of patients switched or augmented their therapy within one year. Only 11.6% of patients received continuous antipsychotic therapy for one year. The average duration of antipsychotic therapy was 142 days. They also reported that factors such as increasing age, manic disorder, major depression, bipolar disorder and non-organic psychosis are associated with switching (McCombs et al., 1999b). A cost analysis of association between these patterns of use and healthcare costs revealed that antipsychotic switching can increase the annual total cost by $9,719 (McCombs et al., 2000). However, as 98% of their patient population was on typical antipsychotics, these factors do not provide information on switching from atypical therapy.

Loosbrook and colleagues used an employer claims database to study utilization pattern of antipsychotics and associated costs with utilization patterns during the year 1997 (Loosbrock, Zhao, Johnstone, & Morris, 2003). The study reports about 26% of schizophrenia patients received no antipsychotic therapy, 52% received only one antipsychotic, 13% switched, 7% augmented with additional antipsychotic, and 2% received more than one antipsychotics at the beginning of the year. Regression analysis, adjusting for various covariates such as age, gender, schizophrenia subtype, comorbidities, and prior costs, revealed that antipsychotic switching and augmentation can increase the total cost by $4,706 and $4,244, respectively.

None of the above studies adjusted for selection bias that may exist among patients who follow different patterns of utilization. Majority of antipsychotic use was of typicals as the most recent data used was upto 1997.

Bipolar Disorder

Epidemiology and Cost

Bipolar disorder, also referred to as manic depressive illness, is characterized by periodic episodes ranging from mania (e.g. euphoria, grandiosity, impulsivity, excessive libido) to the depression (e.g. depression, anxiety, violence, suicidal thoughts and activity). Psychotic symptoms such as delusions and hallucinations are also common in case of acute mania (Perry, Tarrier, Morriss, McCarthy, & Limb, 1999; APA, 1994). The lifetime prevalence of bipolar disorder in the US population is about 1.2% to 1.6% (Kessler et al., 1994). The estimated economic burden of the disorder is about $45 billion. The direct costs are estimated at $7.6 billion and indirect costs at $38 billion. About 60-70% of direct costs were attributable to inpatient costs (Wyatt et al., 1995). Medication costs constitute about 2% of direct costs. The annual medication cost per treated patient was about $548 (Wyatt et al., 1995). About 75% of bipolar patients undergo at least one hospitalization during the course of their illness (Lish et al., 1994). About 10% of inpatient healthcare in US is utilized by bipolar patients (Narrow et al., 1993). Costs for patients with bipolar disorder is higher than costs for patients treated for depression or diabetes (Simon et al., 1999). Also, the disorder is the sixth leading cause of disability in the world (Jenkins, 1997). The chronic relapsing nature of the bipolar disorder impairs psychosocial functioning and ability to work in patients (Goldberg, Harrow, & Grossman, 1995). About 50% of patients are unable to live independently or

retain employment (Levine, Chengappa, Brar, Gershon, & Kupfer, 2001). Among employed bipolar patients, the employment does not match the educational level attained by these patients before the onset of the disease (Tse & Walsh, 2001).

About 20% of severely mentally ill patients have diagnosis of bipolar (Clark et al., 1998). The prevalence of bipolar disorder is similar among adolescents and adults and between genders (Lewinsohn, Klein, & Seeley, 1995; Weissman et al., 1996). Mean age of onset is 18 years for bipolar I and 22 years for bipolar II (Weissman et al., 1988). The rate of mortality among untreated bipolar disorder patients is about 19% and is comparable to heart disease and cancer patients (Hopkins & Gelenberg, 1994). Suicide rates are about 11-15% (Hilty, Brady, & Hales, 1999; Shepherd & Hill, 1996). Commonly prevalent comorbidities among bipolar patients are alcohol and drug abuse, anxiety and personality disorders (Shepherd et al., 1996; Strakowski et al., 1998; Strakowski & DelBello, 2000).

Disease Description

The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (*DSM-IV*) classifies bipolar disorder into: bipolar I, bipolar II and cyclothymia (APA, 1994). Bipolar I disorder is characterized by manic-depressive episodes of duration greater than 1 week. Manic episode is characterized by feelings of self-importance, elation, talkativeness, increased sociability, irritability, impatience, hyperactivity, and a decreased need for sleep. Mixed states consisting of manic or hypomanic (milder form of mania) episodes and depressive episodes can also occur in bipolar I patients. Bipolar II disorder is characterized by major depressive episodes along with episodes of hypomania. Patients with bipolar depression show retarded mental and physical processes, extreme

fatigue, and hypersomnia. Bipolar depression may be difficult to distinguish from a unipolar major depressive episode. Cyclothymia refers to less severe but multiple episodes of hypomania and depression. DSM also defines a phenomenon of rapid cycling in bipolar episodes where manic and depressive episodes alternate at least 4 times in 12 months. Studies have reported about 34-61% relapse rates among patients receiving treatment (Bowden, 2000; Harrow, Goldberg, Grossman, & Meltzer, 1990; O'Connell, Mayo, Flatow, Cuthbertson, & O'Brien, 1991).

Pharmacotherapy in Bipolar Disorder

Treatment for bipolar disorder aims to stabilize mood and alleviate mania or depression. Although mood stabilizer such as lithium has been recommended as the first-line treatment for bipolar disorder, about 42-62% of patients are resistant to lithium (Solomon, Keitner, Miller, Shea, & Keller, 1995). About 80% of patients with mixed and rapid cycling bipolar disorder are resistant to lithium (Tohen & Zarate, Jr., 1998). There are problems with lithium treatment like its toxic doses are close to its therapeutic range. Common side-effects of lithium are tremor, gastrointestinal irritation, cognitive dulling, and renal, thyroid and cardiovascular side-effects on prolonged use. Early discontinuation of lithium therapy is common (Moller & Nasrallah, 2003). Other medications recommended for bipolar treatment include anticonvulsants, antipsychotics, and antidepressants. Anticonvulsants such as divalproex and carbamazepine are used for acute treatment and long term maintenance therapy (Moller et al., 2003). Antidepressants are recommended as an adjunct with mood stabilizer in severely depressed and suicidal patients (Bottlender, Rudolf, Strauss, & Moller, 2001). Use of antidepressants is risky as they may induce mania or rapid cycling (Moller et al., 2003).

Antipsychotics have been recommended as an adjunct to a mood stabilizer in US for bipolar disorder with resistant mania, psychoses, agitation and insomnia (Sachs, Printz, Kahn, Carpenter, & Docherty, 2000). However, monotherapy with antipsychotics has been used as first-line treatment for severe and hospitalized bipolar patients in Europe (Moller et al., 2003). Typical antipsychotics show similar efficacy to lithium for treating mania but may fail to prevent or may induce depression (McElroy, Keck, Jr., & Strakowski, 1996). Also, the risk of tardive dyskinesia with typical antipsychotics can lead to non-compliance and relapse (Moller et al., 2003). Recent studies have shown efficacy of atypical antipsychotics in treating both manic and depressive symptoms in bipolar patients with and without psychoses (Frye et al., 1998; Sanger et al., 2003; Shattell et al., 2004; Strakowski, Del Bello, Adler, & Keck, Jr., 2003). Use of olanzapine was recommended as an alternative to lithium or divalproex for acute mania by Texas Medication Algorithm (Suppes et al., 2003). Though Olanzapine, quetiapine, risperidone, ziprasidone and ariprazole were recently approved by FDA for use in bipolar disorder (Shattell et al., 2004; Perlis, 2005), the use of antipsychotics to treat mania has been widely prevalent in clinical practice (Licht et al., 1994).

Treatment Guidelines for Bipolar Disorder

Treatment guidelines for bipolar disorder differ between different committees such as TMAP, APA or expert consensus guidelines and according to bipolar subtype. In general, monotherapy with lithium, divalproex sodium or atypical antipsychotic is recommended as first-line treatment for mania or hypomania. In case of partial response or non-response, combination of mood stabilizer or anticonvulsant or atypical antipsychotic is usually advised (Fountoulakis et al., 2005). TMAP guidelines

recommend monotherapy with lithium or divalproex or atypical antipsychotic as first-line treatment. APA guidelines recommend use of lithium or a combination of mood stabilizer with an atypical antipsychotic as the first-line therapy. For bipolar depression with psychosis, atypical antipsychotic is required as an alternative to electroconvulsive therapy (ECT) (Perlis, 2005).

Antipsychotic Utilization Pattern in Bipolar Disorder

There are very few studies investigating pattern of use of antipsychotics among bipolar patients. However, majority of studies looking at pharmacotherapy patterns in bipolar disorder have reported considerable prevalence of antipsychotic use as monotherapy and in combination with mood stabilizers among bipolar patients.

A meta-analysis of 16 studies published between 1980 and 1999 showed that use of typical antipsychotic was common in bipolar patients. About 84.7% of bipolar patients received typical antipsychotics. About 53.8% of typical antipsychotic use was as monotherapy whereas about 47.4% of typical antipsychotic use was in combination with a mood stabilizer (Tohen et al., 2001). A study by Russo and colleagues studied pattern of pharmacotherapy in bipolar disorder between 1994 and 1998 using a privately insured managed care patients. The study reports that out of 3,057 bipolar patients, 78% were using lithium or valproate, 16.4% were using typical antipsychotics, 12.4% were using atypical antipsychotics and 74% were using antidepressants. As the drug categories were not mutually exclusive, patients could be on all or any of these medications. Patients who initiated on lithium or valproate, antipsychotics, antidepressants or anticonvulsants were followed for one year to study patterns of continuous or discontinuous use, and switch. However, results of logistic regression analysis showed that patients initiated on

antipsychotics were more likely to use them for 12 months or more compared to patients initiated on lithium/ valproate. As compared to lithium/valproate, patients initiated on antidepressants were more likely to switch and patients initiated on anticonvulsants were more likely to discontinue medications. Proportion of patients initiated on each drug category was not reported (Russo et al., 2002).

Craig and colleagues examined patterns of medication use among first-admission bipolar disorder patients between 1989 and 1995. A sample of 155 patients was followed for 24 months. Medication use and clinical assessments were observed at baseline, 6-month and 24-month time period. Early and regular use of lithium/ valproate or carbamazepine was associated with better Global Assessment of Functioning (GAF) scores and lesser time in remission. The study reported that antipsychotic use was associated with poor clinical outcomes in these patients (Craig et al., 2004). It is possible that more severe bipolar patients may be receiving antipsychotics. Also, most patients in the study received typical antipsychotics

Procyshyn and colleagues conducted a retrospective review of medication information for all patients discharged from a tertiary care psychiatric facility between January 1, 2000 and December 31, 2000. They found a 29.9% prevalence of antipsychotic polypharmacy among bipolar disorder (Procyshyn et al., 2004).

Antipsychotic Use for Other Indications

Few studies have reported us of antipsychotics for other indications. Liperotti and colleagues used a cross-sectional data between January 1, 1999 and January 31, 2000 from 1,732 nursing homes from 5 US states. They reported that atypical antipsychotic use was associated with Parkinson's disease, depression, Alzheimer's disease, and non-

Alzheimer dementia (Liperoti et al., 2003). Cooper and colleagues used Tennessee's Medicaid managed care data to study the use of antipsychotics among patients aged 2 to 18 years (Cooper et al., 2004). They report that antipsychotic use among children has increased almost 2-5 folds in attention-deficit/hyperactivity disorder, and affective disorders between 1996 and 2001. Other than schizophrenia, antipsychotics were also used in acute psychotic reaction and autism. A retrospective chart review of 2000 charts to determine atypical antipsychotic use as augmentation agent to antidepressants in treatment-resistant major depression patients captured 49 cases (Barbee, Conrad, & Jamhour, 2004).

Antipsychotics use for conditions other than schizophrenia and bipolar disorders is still under investigation in clinical trials and is not approved by FDA (Shelton, 2003; Ostroff & Nelson, 1999; Kaplan, 2000). However, prevalence of antipsychotic use in other conditions is present in clinical practice and needs to be documented.

Antipsychotic Therapy and Economic Outcomes in Schizophrenia

Pharmacoeconomic studies in schizophrenia focus on testing the hypothesis that atypical antipsychotics will decrease utilization of healthcare services leading to reduction in overall treatment costs and improve patient outcomes. Most pharmacoeconomic evaluations focus on comparing total healthcare costs, which are definitely an important endpoint from formulary decision-making perspective.

Atypical antipsychotics have been shown to offset inpatient and outpatient costs as compared to typical antipsychotics. However, they are also responsible for considerable proportion of pharmacy or formulary costs (Csernansky et al., 2002;

Gianfrancesco et al., 2002; Gibson et al., 2004; Nightengale et al., 1998). The challenge for healthcare policymakers is to determine the degree to which benefits of antipsychotic overweigh their high acquisition costs. Pharmacoeconomic comparisons between atypical antipsychotics have reported varying results depending upon study population, outcome measures, research and statistical design. Most of the comparisons are between risperidone and olanzapine and have total treatment costs or inpatient drug costs as outcome measure.

A retrospective database study using an employer claims database from 1994 to 1999 compared one-year treatment outcomes between olanzapine and risperidone (Zhao, 2004). The outcomes measures were duration of therapy and direct healthcare costs. Results of multiple regression analysis show that the patients initiated on olanzapine (n = 142) had significantly lower costs compared to patients initiated on risperidone (n=431). The average duration of therapy was also longer with olanzapine compared to risperidone. Another study by Rascati and colleagues also reported that average duration of therapy was longer with olanzapine compared to risperidone based on analysis of Texas Medicaid data from 1996 to 1999. However, risperidone has lower total medical costs compared to olanzapine (Rascati et al., 2003). Better medication adherence for olanzapine was also reported by Gibson and colleagues in their analysis of Michigan Medicaid data from 1995 to 1998. Olanzapine cohort had about 60% adherence compared to risperidone cohort with 54% adherence. Though there were no significant differences in total healthcare costs across the cohorts, exclusion of index medication costs resulted in significantly lower total costs for olanzapine cohort compared to risperidone (Gibson et al., 2004). The differences in pharmacy costs may be attributed to

higher acquisition costs of olanzapine (Procyshyn & Zerjav, 1998; Byerly et al., 2003; Voris & Glazer, 1999) or better adherence resulting greater utilization of index drug. A prospective observational study comparing olanzapine and risperidone showed that olanzapine had lesser psychiatric hospitalization than risperidone-treated schizophrenia patients within one year period (Ascher-Svanum et al., 2004).

There are other studies that report cost savings with risperidone, especially for inpatient drug costs. The Risperidone Olanzapine Drug Outcomes studies in Schizophrenia (RODOS) used retrospective chart reviews of hospitalized patients (N = 1,901) from nine countries. The outcomes measures were utilization and costs of inpatient drugs among patients using olanzapine (n = 977) or risperidone (n = 924). The average total inpatient drug costs were greater for olanzapine compared to risperidone ($297 vs. $159). This difference was attributed to longer duration of use for olanzapine compared to risperidone. However, after adjusting for baseline difference and comparing the costs on daily basis, olanzapine group still showed significantly higher inpatient costs compared to risperidone (Kasper et al., 2001). Similar results regarding inpatient drug costs were also reported by Kelly and colleagues in their study examining inpatient data of 789 patients with schizophrenia or schizoaffective disorder initiated on risperidone or olanzapine between July 1997 and June 1998. Daily drug costs was lower among risperidone treated patients ($6.42) compared to olanzapine patients ($12.29). In addition, they reported higher discharge rate after 30 days of treatment among risperidone patients (45%) compared to olanzapine patients (32%) (Kelly et al., 2001).

Another study evaluating antipsychotic costs, psychiatric inpatient and outpatient costs among schizophrenia patients initiated on risperidone and olanzapine concluded

that though there are no significant differences in inpatient and outpatient costs among patients initiated on risperidone or olanzapine, it is more economic to prescribe risperidone due to its lower drug acquisition costs (Byerly et al., 2003). The study was conducted using VA data among hospitalized patients who were initiated on risperidone (n = 23) or olanzapine (n = 47) after November 4, 1996 and had continuous therapy with the index drug for 9 months after initiation. The cost of index antipsychotic, psychiatric hospitalizations and outpatient care after 9 months of initiation were the outcome measures. Major limitation of this study is its limited sample size and lack of adjustment in cost comparisons for patient demographics or disease severity.

There is only one published study that includes quetiapine among head-to-head comparisons of atypical antipsychotics. This study has examined total pharmacy costs in acute care inpatient medical facilities using retrospective chart reviews. The study sample consisted of patients hospitalized between May 1, 1998 and June 30, 2000 and discharged within 30 days after admission (N = 327). Patients initiated on risperidone (n = 120), olanzapine (n = 153) and quetiapine (n = 54) within 7 days of hospital admissions were categorized in study drug groups. After adjusting for selection bias using propensity scoring methodology, the study reported that average daily pharmacy cost during the inpatient stay was $4.35 less for risperidone and $1.41 less for quetiapine compared to olanzapine (Mladsi et al., 2004). As the study includes patients who were discharged within 30 days of hospitalizations, the results apply only to those patients who respond to the treatment. Due to this inclusion criteria, discharge rate and length of hospital stay cannot be compared. Other outcome measures such as total inpatient costs

were not reported. Also, there was no information or control for extent of use of other concomitant medications.

Most studies in literature have reported total costs or inpatient drug costs as outcome measures. Except for the study by Mladsi and colleagues, none of the studies have controlled for selection bias or included quetiapine in their cost comparisons. Though Mladsi and colleagues included quetiapine in their analysis, their evaluation was restricted to only pharmacy costs in an inpatient setting (Mladsi et al., 2004).

Other than curtailing costs, effectiveness of antipsychotic in improving adherence and persistence with therapy, preventing hospitalization and emergency room visits and decreasing concomitant usage of other medications is also important. Non-adherence to therapy has been shown to be major predictor of hospitalizations. Patients who are partially compliant or interrupt their antipsychotic therapy have 2-4 times greater risk of hospitalization (Weiden et al., 1995; Eaddy, Grogg, & Locklear, 2005). Hospitalization costs represent about one-third to two-third of total healthcare costs for schizophrenia patients. Persistence with initial therapy can also play an important role in cost savings. If patients are less likely to respond upon initiation on certain antipsychotic, it is possible there is greater likelihood of future hospitalizations and emergency care in these patients. Switching to other antipsychotics will be associated with additional expenses due to non-response to earlier treatment. Therefore, implications of antipsychotic treatment on utilization such as adherence, persistence, emergency room visits, hospitalizations, and outpatient visits also need to be considered while evaluating antipsychotic therapy.

Antipsychotic Therapy and Economic Outcomes in Bipolar Disorder

Addition of atypicals antipsychotics is a significant advance in bipolar disorder pharmacotherapy. However, economic evaluation studies of antipsychotic use in bipolar disorder are limited. There were only two randomized controlled trials and one retrospective database study comparing economic outcomes of atypical antipsychotic therapy in bipolar disorder.

A randomized controlled trial conducted by Namjoshi and collegues (Namjoshi et al., 2002) evaluated the cost-effectiveness of olanzapine among patients diagnosed with bipolar I disorder exhibiting manic or mixed episodes. The duration of follow-up consisted of a 3-week acute phase followed by a 49-week open label extension. During the 49-week open label extension, inpatient costs reduced by $900 per month among patients treated with olanzapine. Another randomized control trial by Revicki and colleagues (Revicki, Paramore, Sommerville, Swann, & Zajecka, 2003) compared divalproex and olanzapine among 120 patients with bipolar disorder Type I who were hospitalized for an acute manic episode. Patients were recruited from 21 U.S. clinical centers and randomly assigned to the divalproex or olanzapine group (N = 63 divalproex, N = 57 olanzapine). These patients were then followed in hospitals for 21 days. Patients showing clinical improvement after 21 days of therapy were further followed for 12 weeks. The study only compared 12-week outpatient cost for these patients. The divalproex group showed significantly lower outpatient costs ($541) as compared to olanzapine patients ($1080).

Namjoshi and colleagues (Namjoshi et al., 2002) reported savings due to reduction in hospitalization whereas Revicki and colleagues (Revicki et al., 2003)

reported savings in outpatient medical costs. Also, it should be noted that in the study by Revicki and colleagues, outpatient costs were compared for divalproex and olanzapine for hospitalized bipolar patients who had shown clinical improvement on their respective therapy after 21 days. Thus, it is possible that the impact of increased cost and utilization by patients not showing clinical improvement or showing deterioration due to pharmacotherapy has not been captured in this evaluation.

Gianfrancesco and colleagues used a commercial health plan's administrative data to compare mental health costs associated with risperidone, olanzapine and quetiapine treatment in bipolar disorder patients (Gianfrancesco et al., 2005). They identified treatment episodes with any of the study antipsychotics during a time period of January 1999 and April 2002. A total of 7,518 treatment episodes (29% associated with risperidone, 30.3% associated with olanzapine and 25.7% associated with quetiapine) were identified. The unit of analysis was an antipsychotic treatment episode. Total mental healthcare costs for each treatment episode were the billed charges for mental healthcare services incurred during the treatment episode. Controlling for factors such as patient demographics, bipolar subtype, prior healthcare charges, treatment length and substance abuse, the study reports that risperidone and quetiapine incurred about $84 and $76 lesser mental-health related charges per patient per month compared to olanzapine. There was no significant difference in costs between risperidone and quetiapine (Gianfrancesco et al., 2005).

This study has certain limitations. The study has compared only mental-health costs incurred between the initiation of therapy and discontinuation with the therapy. Patients may discontinue treatment due to treatment failure or adverse affects of the

therapy. Costs associated with this treatment failure would be incurred in the post-discontinuation phase. In addition, it is not possible to identify discontinuation of a treatment if it occurs during the hospitalization. Therefore, costs associated with this hospitalization may not be included in the total costs associated with the antipsychotic used in the episode. Also, if the same patient has multiple episodes, it is possible that this patient is more severe or treatment refractory. As this person has not stabilized on earlier antipsychotic therapy, he or she may incur higher costs when initiated on another antipsychotic in the next episode. It is also likely that such patients would be initiated on newer drugs in later episodes. Therefore, treatment episodes with newer may have higher costs due to inclusion of more severe patients. The study does not control for selection bias or for the use of mood stabilizers along with the antipsychotic therapy.

CHAPTER THREE

METHODOLOGY

An overview of antipsychotic therapy for schizophrenia and bipolar population has been provided in the previous chapters. Rationale for using Medicaid data, sample selection criteria, identification of cohorts, outcomes evaluation and sample selection bias adjustment has been explained under the conceptual framework section in chapter one. This chapter focuses on describing the data source, selection criteria, variable definitions, study design and statistical methodology.

Data source

West Virginia Medicaid Claims Data

The West Virginia Medicaid Program (WVMP) is managed by the Bureau for Medical Services of the West Virginia Department of Health and Human Resources. It is responsible for providing health care coverage to poor and disabled individuals. The West Virginia Medicaid Bureau currently contracts with ACS, Inc (based in Atlanta,, GA) to serve as its claims processor. ACS maintains and operates the Medicaid Management Information Systems (MMIS), which processes provider claims and payments. MMIS data comprises of 3 files - provider files, recipient files, and claims (medical and pharmacy) files. The following is a description of these files and the specific fields (variables) contained in each file.

The provider file contains specific information regarding all health care providers who are eligible to deliver services to Medicaid recipients. This information includes a provider number, specialty and Medicaid eligibility related information. The recipient file includes information such as Medicaid number, eligibility begin date, eligibility end

date, gender, and race. The claims file stores detailed information specific to processed claims. The medical claim file contains information, such as invoice type, provider number, recipient number, International Classification of Disease 9th edition (ICD-9) code of diagnosis for which the service was provided, Common Procedural Terminology (CPT) code for procedures and services provided, Diagnostic Related Group (DRG) codes, date claim was submitted, date of adjudication, through-date of service, coordination of benefit code, primary carrier code, and total amount paid. The pharmacy claim file contains information such as number of days supply, metric quantity, National Drug Classification (NDC) code, generic code, therapeutic class code, refill number, provider ID number, and amount paid.

Permission to use the WV Medicaid data was obtained from the West Virginia Medicaid Bureau. The approval to conduct the study was obtained from the Institutional Review Board (IRB). The data was stored and analyzed according to the Health Insurance Portability and Accountability Act (HIPAA) standards.

Data extraction and cleaning

The West Virginia University's Rational Drug Therapy Program (RDTP) stores the West Virginia Medicaid data obtained from ACS, Inc on its server. The data needed for this study was downloaded from the server using Access and converted to SAS datasets. The extracted data was then put through cleaning and classification processes to obtain the final dataset.

The WV Medicaid organizes all its medical claims into two separate files: the outpatient claims file and the ER/ hospitalization claims file. The ER/ hospitalization claims file contains ER and hospitalization claims as well as some outpatient claims. All

claims from the ER/ hospitalization file having DRG greater than 0 were classified as hospitalization claims. Revenue codes and hospitalization extract indicator variable indicating ER visit were used to identify ER visit. All claims occurring on the same day as ER visit were classified into ER file. ER visits leading to hospitalization were considered as hospitalization events. Therefore, ER claims that had same date as hospitalization claims were transferred to hospitalization file. Remaining claims in the ER/ hospitalization were identified as outpatient claims and transferred to the outpatient file. The WV Medicaid's outpatient file also contained few ER claims. These claims were identified on the basis on CPT codes (99281-99285) and transferred to the ER file. In addition, duplicate claims in the medical and pharmacy files (identified by presence of subsequent negative claims) were deleted.

Study population

West Virginia Medicaid claims data for the period January 1st 1998 to December 31st 2002 was extracted for the purpose of the study. All patient-level demographic data as well as paid claims information on type of service, date of service, amount billed, length of service, and prescription drug claims were reviewed. Patients who were 65 years or older were excluded as they have Medicare as their primary payer for health services. Only patients less than or of 64 years of age are included to avoid including those patients who would become eligible for Medicare during the period of follow-up after being initially present. Managed care recipients also do not have all their utilization information in the Medicaid claims and were excluded.

The index period for the study ranged from January 1st 1999 – December 31st 2001, to allow for 12 pre-index and 12 post-index months. From the prescription claims

data, all paid claims information on patients receiving at least two prescriptions of antipsychotics between January 1st, 1999 and December 31st 2001 was extracted. The first date of paid claim for an antipsychotic during the index period was considered as the index prescription. The selection criteria used to derive the final study sample for the study are listed below:

Selection Criteria

- At least two prescriptions of antipsychotics between January 1st, 1999 and December 31st, 2001
- Patients who were 65 years or older were excluded as they have Medicare as their primary payer for health services
- At least 12 months of continuous enrollment with the West Virginia Medicaid before and after the index date
- Managed care recipients were excluded as they do not have all their utilization information in the Medicaid claims.
- No claims of an antipsychotic medication during a 90 days period before the index date to indicate the index prescription is an initiation of antipsychotic therapy.
- Patients initiated on clozapine were excluded. As clozapine is indicated for treatment refractory schizophrenia, patients initiated on clozapine are more likely to be more severe or inappropriately initiated on clozapine. In addition, patients initiated on ziprasidone will excluded as it was introduced towards the end of our index period in 2001 and will probably have very small sample size.

Identification of schizophrenia and bipolar disorder patients

Schizophrenia patients will be identified by at least 1 inpatient or 2-outpatient diagnosis of schizophrenia. Schizophrenia or Schizoaffective disorder diagnosis will be defined on the basis of International Classification of Diseases (9^{th} Edition) (ICD-9-CM) code of 295.00 – 295.99. This algorithm to identify schizophrenia patients in Medicaid has been validated in a study by Lurie and colleagues (Lurie P et al., 1992). Based on a study by Unutzer and colleagues validating identification of bipolar disorder patients in a large HMO population, bipolar disorder patients will be identified by at least 2 or more paid claims with ICD-9-CM diagnosis for 296.00-296.19, 296.40-296.89 (Simon et al., 1999).

Measurement of cost

Total health care costs will include costs associated with both medical and mental conditions. Mental health-related costs will be identified by claims associated with diagnosis of a mental health disorder (ICD-9-CM codes 290.xx – 316.xx) or CPT codes for psychiatric services (90801-90899) and psychiatric medications. Health care costs will be categorized into inpatient, ER, outpatient, and pharmacy cost. As one-year pre-index and post-index costs will be compared for patients initiated on antipsychotics anytime during the index period, all costs will be adjusted to 2002 US dollars using the medical care and prescription price index.

Measurement of mental health-related variables

Psychotherapy utilization will be identified using CPT codes (90804-90829) or CPT codes (90846-90853). Many psychiatric patients also receive medication management (identified by CPT code 90862) that includes prescribing, recommendations

for use, and review of medication with no more than minimal medical psychotherapy. Electroconvulsive therapy will be identified using CPT codes (90870-90871). All hospitalization, ER visits, and physician office visits associated with a diagnosis of a mental health disorder (ICD-9-CM codes 290.xx – 316.xx) will be categorized as mental-health-related utilization. Psychiatric medications utilization will be categorized into different classes such as mood stabilizers, antidepressants, antipsychotics, anxiolytics/hypnotics/sedatives, antiparkinsons, anticholinergics, benzodiazepines and other psychiatric drugs. Drugs from each of the above class will be identified from the pharmacy claims data using the NDC codes. The provider identifier associated with the index prescription claim will be used to determine if the prescribing physician was a psychiatrist or a non-psychiatrist. Various pre-index utilization variables such as pre-index ER visits, pre-index hospitalizations, pre-index physician visits, number of psychotherapy visits, number of medication management visits, and pre-index period psychiatric medication use of mood stabilizers, antipsychotics, antidepressants and benzodiazepines will be used to control for confoundings in the multivariate analysis.

Patient demographics

The Medicaid recipient data file contained information on the patient's date of birth, gender, race and county of residence. The patient's age was obtained by calculating the difference between the recipient's date of birth and the date of index prescription. As the proportion of non-Caucasian population in WV is very less, the patients were classified as Caucasians and non-Caucasians. Patient's county of residence was classified as metropolitan and non-metropolitan by using the Rural-urban Continuum Codes. The Rural-urban Continuum Codes were developed by the standard Office of

Management and Budget (OMB) to differentiate metropolitan and non-metropolitan counties based on size, degree or urbanization and proximity to metro areas (Rural Urban Continuum codes, 2003).

Co-morbidities

It is important to control for baseline co morbid conditions that may be present among patients initiated on antipsychotics. Presence of specific mental health conditions such as major depression, mild to moderate depression, attention deficit disorder, non-schizophrenia psychosis, other affective disorders, anxiety, personality disorder, dementia, and autism in the pre-index period will be determined on the basis of ICD-9-CM codes. Conditions such as arrhythmia, diabetes, hypertension, and arrhythmia that have been associated with the use of antipsychotic will also be determined from the pre-index claims. Alcohol and substance abuse is also a common co-morbid condition among schizophrenia patients and can be identified on basis of ICD-9-codes (291, 292, 303, 304, 305.0-305.03, 305.2-305.9) from claims data. Suicide attempts recorded in the claims data in form of ICD-9-CM code (E950-E959) will also be identified. In addition, Charlson co-morbidity index will also be used to measure co morbidity. Charlson co-morbidity index is sum of the severity weights ranging from 1 to 6 that were calculated on the basis of relative risks of mortality and assigned to 19 co-morbid conditions. This index was adapted by Deyo and colleagues for use with ICD-9-CM codes from administrative claims data to predict resource utilization (Deyo, Cherkin, & Ciol, 1992). Deyo's adaptation of Charlson co-morbidity index will be used to control for severity of other medical conditions while predicting cost and utilization.

Phase 1

Research Question 1

To determine the annual prevalence rate of schizophrenia and bipolar disorder in West Virginia Medicaid from 1998 to 2002

The number of patients identified with the diagnosis of schizophrenia or bipolar disorder based on ICD-9 claims from the Medical claims file will be used as the numerator in the prevalence rate calculations. The denominator will be the number of people eligible under the WV Medicaid for that year. The number of people eligible under the WV Medicaid was derived from the Health Care Financing Administration (HCFA) 2082 Reports. The eligible population consists of people who have paid claims in the Medicaid claims data as well as people who have never used/claimed any Medicaid services but were eligible for them.

Research Question 2

To determine the medical conditions among the patients initiated on antipsychotics during the study period in the West Virginia Medicaid population as well as describe patterns of distribution of certain demographic factors such as age, gender, and ethnicity in these patients

Identifying Mental Health Comorbidities

A patient will coded to be under mental health conditions listed below on the basis of ICD-9-CM diagnosis for that condition in the medical claims data during the pre-index period or the index date.

- Major Depression: At least 2 or more paid claims with ICD-9-CM diagnosis for 296.20-296.39.

- Mild to Moderate Depression: At least 2 or more paid claims with ICD-9-CM diagnosis for 300.40-300.49, 311, 309.0 and 309.1.
- Attention-Deficit Disorder: At least 2 or more paid claims with ICD-9-CM diagnosis for 314.00, 314.01 and 314.0
- Non-schizophrenia Psychosis: At least 2 or more paid claims with ICD-9-CM diagnosis for 291.00-294.99
- Other Affective Disorders: At least 2 or more paid claims with ICD-9-CM diagnosis for 296, 296.0, 296.9, 296.90 and 296.99
- Anxiety: At least 2 or more paid claims with ICD-9-CM diagnosis for 297.00-297.00-297.99, 300.00-300.39, 300.5-300.99
- Personality Disorder: At least 2 or more paid claims with ICD-9-CM diagnosis for 301.00-301.99
- Dementia: At least 2 or more paid claims with ICD-9-CM diagnosis for 290.00-290.99
- Autism: At least 2 or more paid claims with ICD-9-CM diagnosis for 299.0, 299.00 and 299.01
- Other Mental Health diagnosis: At least 2 or more paid claims with ICD-9-CM diagnosis for 302.00-302.99, 306.00-308.99, 309.2-310.99, 311.1-313.99, 314.2-314.99, 316.00-316.99
- Multiple Categories: 2 or more of above categories

Frequencies will be calculated to estimate proportion of patients initiated on antipsychotics under each mental health diagnostic category. Patient population will be categorized on basis of age into two groups: less than 18 years and 18 years.

Demographic characteristics of patients under each diagnostic category will be presented in terms of age (mean, median), gender (frequency N, %), and race (frequency N, %). In this exploratory analysis, the patients may suffer from multiple mental health conditions. Therefore, initiation of antipsychotic cannot be assumed to be indicated for the given mental health condition. However, proportion of patients within each mental health condition who did not have any other psychiatric co-morbidity will be reported.

Research Question 3

For schizophrenia and bipolar disorder patients, determine different types of utilization pattern of antipsychotics.

Patients would be classified into schizophrenia and bipolar disorder disease category based on ICD-9-CM diagnosis code. For schizophrenia, only patients 18 years or above will be used. For bipolar disorder, patient population will be categorized on basis of age into two groups: less than 18 years and 18 years or above. All prescription claims after initiation of antipsychotic will be reviewed to determine the pattern of use of antipsychotic.

A) Pattern of antipsychotic use among schizophrenia and bipolar patients will be described in terms of:

1) Antipsychotic Polytherapy: Polytherapy refers to a situation when a second antipsychotic is started within 15 days of the index antipsychotics and both medications were refilled at least once. Patients can be initiated on polytherapy or can switch to polytherapy in course of treatment.

2) Antipsychotic Monotherapy: Use of only one antipsychotic at a time in the course of treatment is defined as antipsychotic monotherapy. Antipsychotic monotherapy will be classified into the following types:

a) Switching: Switching refers to a situation when the index antipsychotic is changed to another antipsychotic. Antipsychotic switching will be defined as starting a different antipsychotic after the date of the index fill while not obtaining a refill for the index antipsychotic.

Patient using the same index antipsychotic throughout the 12-month post-index period will be classified as:

b) Interrupted Therapy: Patients receiving less than 80% of total days of supply of medications during the 12-month post-index period.

c) Continuous Therapy: Patients receiving greater or equal to 80% of the total days of supply of medications during the 12-month post-index period

B) Schizophrenia patients initiated on index antipsychotic therapy will be categorized into:

1. Patients who continued on index antipsychotic prescription for 3 or more months
2. Patients who changed or discontinued index antipsychotic prescription within 3 months

Research Question 4

For schizophrenia and bipolar disorder patients, determine the gaps between the refills of antipsychotics.

Gaps between the refills will be defined as number of days between the depletion date of one prescription and fill date of the subsequent prescription of the antipsychotic.

The depletion date of a prescription will be calculated as claims fill date plus days of supply. The longest continuous gap between refills for each patient will be reported in terms of mean (±SD) and median gap. Also, treatment gap categories will be created depending upon the length of the gaps. Percentage distribution of patients across the treatment gap categories will be reported.

Research Question 5

For schizophrenia and bipolar disorder patients, determine predictors of patterns of use.

Multinomial logistic regressions will be used to determine predictors of pattern of antipsychotic use among schizophrenia and bipolar patients. The dependent variable will have four mutually exclusive categories: polytherapy, switching, interrupted therapy and continuous therapy. Various predictors considered in the model would be: patient demographics (age, gender, and race), prescribing physician type, schizophrenia or bipolar subtype, other medical/mental diagnosis during the pre-index period, type of index antipsychotic, year of index antipsychotic, pre-index alcohol and substance abuse and pre-index healthcare utilization. Separate analysis will be conducted for schizophrenia and bipolar patients. Disease severity will be controlled using pre-index concomitant psychiatric medication use, mental-health related ER or physician visits, and schizophrenia or bipolar disorder-related hospitalization as covariates in regression models.

Pattern of antipsychotic use (polytherapy, switching, interrupted therapy, continuous therapy) = constant + $\beta 1$ demographics + $\beta 2$ physician type + $\beta 3$ co morbidities + $\beta 4$ disease subtype + $\beta 5$ pre-index utilization + $\beta 6$ index antipsychotic type + error term

Research Question 6

For schizophrenia and bipolar disorder patients, determine the relationship between utilization pattern of antipsychotics and total health care costs.

Heckman-2 stage technique will be used to control for observed and unobserved differences between patients having different pattern of use. The first-stage selection model will be similar to multinomial regression model in research question 5.

First-stage selection model:

Pattern of antipsychotic use (polytherapy, switching, interrupted therapy, continuous therapy) = constant + β1 demographics + β2 physician type + β3 co morbidities associated with treatment + β4 disease subtype + β5 pre-index utilization + β6 index antipsychotic type + error term

Continuous therapy will be used as reference category for all comparisons in the multinomial logistic models. The selection factor obtained from these models will be used as a covariate in the second stage regression models.

The dependent variable in the second-stage regression will be cost. As cost is usually skewed, it will be log transformed. Control variables in the second stage regression include: age, gender, Charlson Comorbidity Index, schizophrenia/ bipolar subtype, alcohol and substance abuse, psychiatrist prescriber, pre-index mental-health care cost, type of index prescription, use of concomitant psychiatric medications, year of index prescription, pattern of antipsychotic use and selection factor.

Second-stage selection model:

Log(Cost) = constant + β1 demographics + β2 physician type + β3 Charlson comorbidity index + β4 disease subtype + β5 pre-index utilization + β6 index antipsychotic type + β7 pattern of antipsychotic use + β8 selection factor + error term

Separate models will be created for schizophrenia and bipolar disorder patients.

Research Question 7

For schizophrenia and bipolar disorder patients, determine the relationship between utilization pattern of antipsychotics and mental health care utilization and costs.

Mental health-related costs will be identified by claims associated with diagnosis of a mental health disorder (ICD-9-CM codes 290.xx – 316.xx) or CPT codes for psychiatric services (90801-90899) and psychiatric medications. The first stage multinomial logistic regression model will be same as that used in research question 6. The second stage OLS regression models will have log transformed mental health-related costs as dependent variable. Separate models will be created for schizophrenia and bipolar disorder patients.

Phase 2

Cohort Selection

Patients were classified into the study cohorts based on the index prescription during the index period (January 1st 1999 –December 31st 2001). The first prescription of a study medication (Risperidone, Olanzapine, Quetiapine, or typical antipsychotics) during the index period was defined as the index prescription. Patients initiated on any other antipsychotics or multiple antipsychotics will be excluded from the analysis.

Study Cohorts

The study participants were divided into following 4 study cohorts based on atypical antipsychotic therapy:

- Cohort 1. Patients initiated on Risperidone
- Cohort 2. Patients initiated on Olanzapine
- Cohort 3. Patients initiated on Quetiapine
- Cohort 4. Patients initiated any typical antipsychotic (chlorpromazine, haloperidol, thioridazine, fluphenazine and others).

Intent to treat approach will be employed wherein the outcomes will be attributed to the index prescription irrespective of the medication pattern subsequent to index prescription.

Reference Cohort

Quetiapine was selected as the reference antipsychotic cohort for statistical analysis for following reasons:

- Quetiapine cohort was the most recent atypical antipsychotic cohort in our study with adequate sample size. As the index period for this study was between January 1st 1999 and December 31st 2001, there were not sufficient numbers of patients initiated on ziprasidone during this period to provide adequate sample size for statistical analyis.
- Economic evaluations comparing quetiapine to other antipsychotics were lacking in the published literature.

Research Question 8

For schizophrenia and bipolar disorder patients, to compare the impact of quetiapine with risperidone, olanzapine, and typical antipsychotics on total and mental healthcare costs

Cost data will be collected for each of the study participants in the pre- and post index phase. Mental health-related utilization will be identified by claims associated with diagnosis of a mental health disorder (ICD-9-CM codes 290.xx – 316.xx) or CPT codes for psychiatric services (90801-90899) and psychiatric medications. Total health care costs will include all costs for medical and mental conditions.

Univariate analysis will describe resource costs of care: 1) in the pre-index period, and 2) in the post-index period. The Wilcoxon rank sum tests (equivalent to Mann-Whitney U test) were used to measure between-cohort differences. The Wilcoxon rank sum test is a non parametric alternative to two sample t test that can be used to compare differences between cohorts for non-normal data.

Next, multivariate regression techniques, controlling for specific covariates, will be used to evaluate the association between type of atypical antipsychotic therapy used and post-index cost. Age, gender, prescribing physician specialty, index year, schizophrenia/bipolar subtype, substance and alcohol abuse, Charlson Comorbidity Score, pre-index cost and utilization, and concomitant medication use would be considered as covariates. Sample selection models will be used to adjust for sample selection bias due to treatment selection. The first stage sample selection model will be a multinomial logistic regression model predicting choice of index antipsychotic therapy.

Index antipsychotic selection (quetiapine, risperidone, olanzapine, typical antipsychotic). = constant + $\beta 1$ demographics + $\beta 2$ physician type + $\beta 3$ co-morbidities + $\beta 4$ disease subtype + $\beta 5$ pre-index utilization + error term

The selection factor obtained from these models will be used as a covariate in the second stage regression models.

Log(Cost) = constant + β1 demographics + β2 physician type + β3 co-morbidities/ Charlson comorbidity index + β4 disease subtype + β5 pre-index utilization + β6 index antipsychotic type + β8 selection factor + error term

Quetiapine will be used as reference category for all comparisons in the multinomial logistic models and regression models. Separate analysis will be conducted for schizophrenia and bipolar disorder patients. For each disease group, separate models will developed for mental health-related and total healthcare cost.

Research Question 9

For schizophrenia and bipolar disorder patients, to compare the impact of quetiapine with risperidone, olanzapine, and typical antipsychotics on components of mental healthcare costs (costs associated with mental health-related inpatient, emergency room, outpatient and pharmacy services)

Univariate analysis will describe resource costs of care: 1) in the pre-index period, and 2) in the post-index period. Univariate comparisons for the differences in mental health-related inpatient, emergency room, outpatient and pharmacy costs between the index drug cohorts will be conducted using the Wilcoxon rank sum tests.

A 2-part model will be used to establish relationship between drug therapy patterns and mental health related cost categories like ED and inpatient that are likely to have zero values for some patients. The first part will consist of a logistic regression for each dependent variable (ED and inpatient) to distinguish between patients having no cost and any cost. The second part will be a multiple regression analysis conducted among the patients who have incurred greater than zero cost during the follow-up period.

Part 1:

Any Cost (0/ greater than 0) = constant + β1 demographics + β2 physician type + β3 Charlson comorbidity index + β4 disease subtype + β5 pre-index utilization + β6 index antipsychotic type + β7 pattern of antipsychotic use + β8 selection factor + error term

Part 2:

Log(Cost) = constant + β1 demographics + β2 physician type + β3 Charlson comorbidity index + β4 disease subtype + β5 pre-index utilization + β6 index antipsychotic type + β7 pattern of antipsychotic use + β8 selection factor + error term

For dependent variables like total mental health-related costs, outpatient and pharmacy cost category that are not likely to have zero costs, multiple regression analysis will be used.

Treatment severity will be controlled using pre-index concomitant psychiatric medication use and other mental-health related healthcare utilization as covariates in regression models. Control variables in the study will include: age, gender, Charlson Comorbidity Index, schizophrenia/ bipolar subtype, alcohol and substance abuse, psychiatrist prescriber, pre-index mental- health care cost and utilization, use of concomitant psychiatric medications, and year of index prescription. As the cost data is skewed, log transformations will be used to normalize the data.

Research Question 10

For schizophrenia and bipolar patients, to compare the impact of quetiapine with risperidone, olanzapine, and typical antipsychotics on mental health-related healthcare hospitalizations

Univariate analysis will describe number of inpatient visits and length of inpatient visits: 1) in the pre-index period, and 2) in the post-index period. The Wilcoxon rank sum tests were used to measure between-cohort differences.

Hospitalization rates calculated as the percent of patients who were hospitalized with a psychiatric diagnosis during the pre and post index period will be analyzed using Mantel-Haenszel test. Mantel-Haenszel test is used to compare proportion of people between two groups.

Time to hospitalization will be defined as the number of days from the index date to the first hospitalization. As this is time-to-event data, survival analysis procedures will be used for analysis. Kaplan Meier survival curves will be used for univariate analysis. The relative hazard of hospitalization over a follow-up period will be analyzed using Cox proportional model that will control for confounding variables.

Time to first hospitalization = constant + $\beta 1$ demographics + $\beta 2$ physician type + $\beta 3$ Charlson comorbidity index + $\beta 4$ disease subtype + $\beta 5$ pre-index utilization + $\beta 6$ index antipsychotic type + $\beta 7$ pattern of antipsychotic use + $\beta 8$ selection factor + error term

Poisson regression analysis will be used for multivariate comparison of the number of inpatient visits among different cohorts.

Separate analysis will be conducted for schizophrenia and bipolar disorder patients.

Research Question 11

For schizophrenia patients and bipolar disorder patients, to compare the impact of quetiapine with risperidone, olanzapine, and typical antipsychotics on mental healthcare-related emergency room visits

Univariate analysis will describe ER visits: 1) in the pre-index period, and 2) in the post-index period. The Wilcoxon tests will be used to measure between-cohort differences.

ER visit rate is calculated as the percent of patients who were admitted with a psychiatric diagnosis during the pre and post index period and will be analyzed using Mantel-Haenszel test.

Time to ER visit will be defined as the number of days from the index date to the first ER visit. The relative hazard (or incidence rate) of ER visit over a follow-up period will be analyzed using Cox proportional model.

Poisson regression analysis will be conducted to compare the number of ER visits among different cohorts.

Control variables in the study will include: age, gender, prescribing physician specialty, index year, adherence to index medication, schizophrenia/bipolar subtype, Charlson Comorbidity Score, pre-index psychiatric ER visits, substance abuse, alcohol abuse, and concomitant medication use.

Separate analysis will be conducted for schizophrenia and bipolar disorder patients.

Research Question 12

For schizophrenia and bipolar disorder patients, to compare the impact of quetiapine with risperidone, olanzapine, and typical antipsychotics on mental healthcare-related outpatient visits

Univariate analysis will describe total and mental health-related physician visits, psychotherapy sessions and specific medication management psychotherapy in terms of:

1) in the pre-index period, and 2) in the post-index period. The Wilcoxon rank sum tests will be used to measure between-cohort differences.

Poisson regression analysis will be conducted to compare the number of mental health-related physician visits among different cohorts.

Control variables in the study will include: age, gender, prescribing physician specialty, index year, schizophrenia/bipolar subtype, Charlson Comorbidity Score, pre-index physician visits, substance abuse, alcohol abuse, and concomitant medication use.

Separate analysis will be conducted for schizophrenia and bipolar disorder patients.

Research Question 13

For schizophrenia and bipolar disorder patients, to compare the impact of quetiapine with risperidone, olanzapine, and typical antipsychotics on psychiatric medication utilization

Use of concomitant medications will be categorized into following classes: Mood stabilizers, antidepressants, Anxiolytics/Hypnotics/Sedatives, antiparkinsons, anticholinergics, antipsychotics (pre-index use), clozapine and benzodiazepine.

Proportions of patients from each cohort using concomitant medications will be compared using Mantel-Haenszel test.

Separate analysis will be conducted for schizophrenia and bipolar disorder patients.

Research Question 14

For schizophrenia and bipolar disorder patients, to compare the impact of quetiapine with risperidone, olanzapine, and typical antipsychotics on patient's adherence to the index medications in the post-index period

Adherence with the index therapy will be compared in terms of Medication possession ratio (MPR)

$$MPR = \frac{\text{the total days supplied for the index drug}}{\text{total days from index date to the date of last prescription of index drug + days supplied on last claim}}$$

Medicaid prescription claims data does not record claims of medications administered to patients in an inpatient setting. To adjust for this absence of record while calculating days of supply of index antipsychotic, the number of days of hospitalizations was added to the days supply of drugs for the index antipsychotic if the admit and discharge dates of the hospitalization occurred between the first fill date and end of follow up period for that index antipsychotic.

Ordinary Least Squares (OLS) regression models will be used determine the impact of choice of index antipsychotic drug on MPR. Age, gender, prescribing physician specialty, index year, schizophrenia/bipolar subtype, Charlson Comorbidity Score, schizophrenia/bipolar subtype, other mental illnesses, psychiatric hospitalization, psychiatric ER visit, substance abuse, alcohol abuse, and concomitant medication use would be considered as covariates. Separate analysis will be conducted for schizophrenia and bipolar disorder patients.

Research Question 15

For schizophrenia and bipolar disorder patients, to compare the impact of quetiapine with risperidone, olanzapine, and typical antipsychotics on subsequent index antipsychotic therapy modification

Persistence or time until treatment change

Persistence or time until treatment change will be defined as the total days from the index prescription fill date until the occurrence of a filled prescription for any other index or a non-index antipsychotic or until discontinuation of therapy with the index drug.

The relative hazard of discontinuation or switch

The relative hazard of discontinuation or switch over a follow-up period will be analyzed using Cox proportional hazard model. Age, gender, prescribing physician specialty, index year, adherence to index medication, schizophrenia/bipolar subtype, Charleston Comorbidity Score, schizophrenia/bipolar subtype, other mental illnesses, psychiatric hospitalization, psychiatric ER visit, substance abuse, alcohol abuse, concomitant medication use, and time from date of market availability to index date would be considered as covariates. Separate analysis will be conducted for schizophrenia and bipolar disorder patients.

CHAPTER FOUR

RESULTS AND DISCUSSION

The previous chapter described study objectives and methodology. This chapter presents results and discussion for each of the study objectives. The results and discussion for schizophrenia and bipolar disorder are presented together under each research question. The results are classified into phase 1 and phase 2.

Table 1 presents the number of eligible study participants after applying each inclusion and exclusion criterion. A total of 5,297 patients were initiated on antipsychotic medications between the index period January 1st, 1999 and December 31st, 2001 in the WV Medicaid. Patients with diagnosis of schizophrenia and bipolar disorder were identified using the specified criteria. A total of 1,036 patients with schizophrenia and 832 patients with bipolar disorder were initiated on antipsychotics during the study index period. Power analysis carried out for the resulting sample size revealed greater than 80% power for the univaraite and multivariate analysis proposed in this study.

Table 1: Application of the selection criteria and the resulting sample size

Selection Criteria	*Sample Size N*
1. At least 2 antipsychotic Rx during the index period (January 1st 1999 –December 31st 2001)	22,577
2. Less than or equal to 64 years of age	16,698
3. At least 12 months of continuous pre and post enrollment	11,021
4. Excluding managed care recipients	10,193
5. No claims of an antipsychotic during a 90 days period before the index date	5,384
6. Excluding patients initiated on clozapine	5,366
7. Excluding patients initiated on ziprasidone	5,297
Final Sample	**5,297**
8. Identification of schizophrenia patients (18 years and older)	**1,036**
9. Identification of bipolar disorder patients	**832**

PHASE 1

Results for research objective 1

To determine the annual prevalence rate of schizophrenia and bipolar disorder in West Virginia Medicaid from 1998 to 2002

To calculate the annual prevalence rate of schizophrenia and bipolar disorder patients, all patients with diagnosis of schizophrenia or bipolar disorder during the year (not just patients initiated on antipsychotics) were identified as numerator. The denominator was the number of people eligible under the WV Medicaid for that year. Tables 2a and 2b present annual prevalence rates for schizophrenia and bipolar disorder in the WV Medicaid population for the years 1998-2002. Total annual prevalence of schizophrenia ranged from 0.9% to 1.5% between the year 1998 and 2002 among WV Medicaid eligible population. Total annual prevalence of bipolar disorder ranged from 0.6% to 1.7% between the year 1998 and 2002 among WV Medicaid eligible population. Annual prevalence of bipolar disorder among patients between 20 and 64 years of age increased from 1.3% in 1998 to 3.2% in 2002. Annual prevalence of bipolar disorder among patients less than 14 years of age was 0.02%-0.03% and patients between 14 and 20 years of age was 0.08%-1.7%.

Table 2a: Annual prevalence rate for schizophrenia in the WV Medicaid (1998-2002)

	2002		*2001*		*2000*		*1999**		*1998*	
	N[b]	***PR [95% CI]***	***N[b]***	***PR [95% CI]***	***N[b]***	***PR [95% CI]***	***N[b]***	***PR [95% CI]***	***N[b]***	***PR [95% CI]***
Age Category										
Up to or equal to 14 years	27	0.17 [0.10, 0.23]	23	0.24 [0.14, 0.34]	34	0.23 [0.15, 0.31]	77	-	99	0.59 [0.48, 0.71]
Greater than 14 to 20 years	110	2.74 [2.23, 3.25]	112	2.91 [2.37, 3.45]	142	3.68 [3.07, 4.28]	114	-	124	2.89 [2.38, 3.40]
Greater than 20 to 64 years	4,110	32.47 [31.47, 33.46]	3,995	32.03 [31.03, 33.02]	4,001	32.12 [31.12, 33.11]	3,154	-	2,854	21.98 [21.18, 22.79]
Total (less than or equal to 64 years population)	4,247	12.93 [12.54, 13.32]	4,130	15.91 [15.42, 16.39]	4,177	13.43 [13.02, 13.83]	3,345	9.71 [9.38, 10.03]	3,077	9.07 [8.75, 9.39]

N[b] = Number of patients with diagnosis of schizophrenia in the given one year period
PR = Prevalence Rate per 1,000 WV eligible patients in the given one year period
*classification of number of people eligible for WV Medicaid based on age category was not available for 1999.

Table 2b: Annual prevalence rate for bipolar disorder in the WV Medicaid (1998-2002)

	2002		*2001*		*2000*		*1999**		*1998*	
	Nb	***PR [95% CI]***	***N[b]***	***PR [95% CI]***	***N[b]***	***PR [95% CI]***	***N[b]***	***PR [95% CI]***	***N[b]***	***PR [95% CI]***
Age Category										
Up to or equal to 14 years	571	3.53 [3.24, 3.82]	367	3.81 [3.42, 4.19]	479	3.24 [2.95, 3.53]	339	-	260	1.56 [1.37, 1.75]
Greater than 14 to 20 years	689	17.15 [15.87, 18.43]	630	16.38 [15.10, 17.66]	593	1,5.35 [14.11, 16.58]	451	-	347	8.08 [7.23, 8.93]
Greater than 20 to 64 years	4,125	32.59 [31.59, 33.58]	3,525	28.26 [27.33, 29.19]	3,473	27.88 [26.95, 28.81]	2,243	-	1,723	13.27 [12.64, 13.90]
Total (less than or equal to 64 years population)	5,385	16.39 [15.96, 16.83]	4,522	17.42 [16.91, 17.92]	4,545	14.61 [14.19, 15.03]	3,033	8.80 [8.49, 9.11]	2,330	6.87 [6.59, 7.15]

N[b] = Number of patients with diagnosis of schizophrenia in the given one year period
PR = Prevalence Rate per 1,000 WV eligible patients in the given one year period
*classification of number of people eligible for WV Medicaid based on age category was not available for 1999.

Discussion for research objective 1

Information regarding prevalence of schizophrenia and bipolar disorder in WV Medicaid is important from a health services planning perspective. Although it has been suggested that the prevalence of these mental health disorders may be higher in low income populations, information regarding prevalence of schizophrenia and bipolar disorder in Medicaid systems is lacking in literature(Scott, 1993; Goldner, Jones, & Waraich, 2003).

Based on a survey of 20,291 adults by National Institute of Mental Health Epidemiologic Catchment Area Program, one-year prevalence rate of schizophrenia in 1993 was reported to be 1.1% (Regier et al., 1993). Our study reports similar prevalence rates of schizophrenia (0.9% - 1.5%) from 1998 to 2002 in the WV Medicaid population. The rates of prevalence of both schizophrenia and bipolar disorder show steady increase from 1998 to 2002 in WV Medicaid, except for the year 2001. The higher prevalence rates in the year 2001 compared to 2002 was due to decrease in the denominator i.e. the number of people eligible under the WV Medicaid during the year 2001.

Prevalence of bipolar disorder has been estimated to range between 1% and 2% in different studies. The Epidemiologic Catchment Area (ECA) survey reported lifetime prevalence of 1.3% whereas the National Comorbidity survey has reported lifetime prevalence of 1.6% (Bebbington & Ramana, 1995; Kessler et al., 1994). A survey of representative sample of adult US population in 2000 revealed a very high prevalence rate of 3.7% for bipolar disorder (Hirschfeld RMA, Calabrese JR, & Weissman M, 2005). Our study also found that the prevalence rate of bipolar disorder had increased to 3.2% in 2002 among adults. The prevalence rates in our study may differ from other studies as it

was calculated based on the presence of disease specific ICD-9-CM codes in the administrative data whereas other studies have reported the prevalence rates based on community surveys. The WV Medicaid patient population differs from the patient population used in other studies due to over representation of low-income and women population.

Results for research objective 2

To determine the medical conditions for which antipsychotics are being prescribed in the West Virginia Medicaid population as well as describe patterns of distribution of certain demographic factors such as age, gender, and ethnicity in patients using antipsychotics.

Tables 3a, 3b and 3c present results of an analysis to determine the mental health conditions as well as describe patterns of distribution of certain demographic factors such as age, gender, and ethnicity in patients who were initiated on antipsychotics in the West Virginia Medicaid population during the study period.

In this analysis, the patients may suffer from multiple mental health conditions. Therefore, initiation of an antipsychotic medication cannot be assumed to be indicated for the given mental health condition. However, the tables also provide information on proportion of patients within each mental health condition who did not have any other psychiatric co-morbidity. Disease conditions such as autism, non-schizophrenia psychosis, major depression, and attention-deficit disorders are of particular interest as considerable proportion of patients initiated on antipsychotics during the study period in these disease conditions do not have any other mental health co-morbidities.

Table 3a: Exploratory analysis of mental health conditions among patients who were initiated on antipsychotics in the West Virginia Medicaid population during the study period

	Attention-Deficit Disorder N = 472		*Major Depression N = 1,112*		*Mild to Moderate Depression N = 665*	
	Less than 18 years n = 104	*18 years and above n = 368*	*Less than 18 years n= 212*	*18 years and above n= 900*	*Less than 18 years n= 145*	*18 years and above n = 520*
No other psychiatric co-morbidities	25 (22.0%)	95 (25.8%)	56 (26.4%)	242 (26.9%)	21 (14.5%)	59 (11.3%)
Age in years (mean/std, median)	14.1/2.7, 15.0	33.5/10.4, 32.5	11.6/3.4, 12.0	42.2/11.6, 42.0	12.1/3.4, 13.0	41.2/11.1, 41.0
Gender						
Males	65 (62.5%)	159 (43.2%)	141 (66.5%)	361 (40.1%)	87 (60.0%)	208 (40.0%)
Females	37 (35.6%)	207 (56.3%)	69 (32.6%)	532 (59.1%)	53 (36.5%)	309 (59.4%)
Missing	2 (1.9%)	2 (0.5%)	2 (0.9%)	7 (0.8%)	5 (3.5%)	3 (0.6%)
Race						
Caucasians	94 (90.5%)	340 (92.4%)	196 (92.5%)	842 (93.6%)	133 (91.7%)	480 (7.7%)
Others	10 (9.5%)	28 (7.6%)	16 (7.5%)	58 (6.4%)	12 (8.3%)	40 (92.3%)
Index Drug Category						
Typical Antipsychotics	11 * (10.6%)	95 * (25.8%)	18 * (8.5%)	278 * (30.9%)	13 * (9.0%)	158 * (30.4%)

Table 3a: Exploratory analysis of mental health conditions among patients who were initiated on antipsychotics in the West Virginia Medicaid population during the study period (contd.)

	Attention-Deficit Disorder N = 472		*Major Depression N = 1,112*		*Mild to Moderate Depression N = 665*	
	Less than 18 years n = 104	*18 years and above n = 368*	*Less than 18 years n= 212*	*18 years and above n= 900*	*Less than 18 years n= 145*	*18 years and above n = 520*
Risperidone	53 * (51.0%)	82 * (22.3%)	139 * (65.6%)	180 * (20.0%)	77 * (53.1%)	112 * (21.5%)
Olanzapine	30 * (28.9%)	132 * (35.9%)	44 * (20.8%)	300 * (33.3%)	41 * (28.3%)	177 * (34.0%)
Quetiapine	9 * (8.7%)	54 * (14.7%)	9 * (4.3%)	132 * (14.7%)	13 * (9.0%)	68 * (13.1%)
Combination	1 (1.0%)	5 (1.4%)	2 (0.9%)	10 (1.1%)	1 (.7%)	5 (1.0%)

* Results of chi-square analysis indicate significant differences between the index drug category within the respective age groups at $p < 0.05$

Table 3b: Exploratory analysis of mental health conditions among patients who were initiated on antipsychotics in the West Virginia Medicaid population during the study period

	Anxiety N = 837		*Personality Disorder N = 284*		*Autism N = 51*	
	Less than 18 years n = 170	*18 years and above n = 667*	*Less than 18 years n = 55*	*18 years and above n = 299*	*Less than 18 years n = 7*	*18 years and above n= 44*
No other psychiatric co-morbidities	33 (19.4%)	115 (17.2%)	1 (1.8%)	10 (3.3%)	5 (71.4%)	26 (59.1%)
Age in years (mean/std, median)	11.4/3.4, 11.0	42.3/10.9, 42.0	11.9/3.4, 13.0	41.5/11.8, 41.0	13.4/1.7, 13.0	37.4/11.4, 36.0
Gender						
Males	119 (70.0%)	259 (38.8%)	31 (56.3%)	110 (36.7%)	6 (85.7%)	17 (38.6%)
Females	49 (28.8%)	400 (59.9%)	22 (40.0%)	188 (62.8%)	1 (14.3%)	27 (61.4%)
Missing	2 (1.1%)	8 (1.2%)	2 (3.6)	1 (0.3%)	-	-
Race						
Caucasians	155 (91.2%)	618 (92.6%)	53 (96.4%)	281 (93.9%)	6 (85.7%)	40 (90.9%)
Others	15 (8.8%)	49 (7.4%)	2 (3.6%)	18 (6.1%)	1 (14.3%)	4 (9.1%)
Index drug Category						
Typical Antipsychotic	12 (7.0%)	225 * (33.7%)	2 (3.6%)	88* (29.4%)	1 (14.2%)	13 (29.5%)

Table 3b: Exploratory analysis of mental health conditions among patients who were initiated on antipsychotics in the West Virginia Medicaid population during the study period (contd.)

	Anxiety N = 837		*Personality Disorder N = 284*		*Autism N = 51*	
	Less than 18 years n = 170	*18 years and above n = 667*	*Less than 18 years n = 55*	*18 years and above n = 299*	*Less than 18 years n = 7*	*18 years and above n= 44*
Risperidone	107 * (62.9%)	121 * (18.3%)	32 (58.1%)	62* (20.7%)	3 (42.8%)	8 (18.1%)
Olanzapine	38 * (22.3%)	225 * (33.7%)	13 (23.6%)	109 * (36.4%)	2 (28.5%)	16 (36.3%)
Quetiapine	12 (7.0%)	89 * (13.3%)	5 (9.0%)	37* (12.3%)	1 (14.2%)	7 (15.9%)
Combination	1 (0.8%)	7 (1.0%)	3 (5.4%)	3 (1.0%)	-	-

* Results of chi-square analysis indicate significant differences between the index drug category within the respective age groups at $p < 0.05$

Table 3c: Exploratory analysis of mental health conditions among patients who were initiated on antipsychotics in the West Virginia Medicaid population during the study period

	Dementia N = 27		*Non-schizophrenia Psychosis N = 220*	
	Less than 18 years n = 10	*Less than 18 years n = 56*	*Less than 18 years n = 56*	*18 years and above n = 692*
No other psychiatric co-morbidities	1 (10.0%)	18 (32.1%)	18 (32.1%)	-
Age in years (mean/std, median)	13.5/3.5, 14.5	12.2/3.1, 12.0	12.2/3.1, 12.0	37.3/ 11.2, 37.0
Gender				
Males	7 (70.0%)	34 (60.7%)	34 (60.7%)	280 (40.5%)
Females	3 (30.0%)	21 (37.5%)	21 (37.5%)	405 (58.5%)
Missing	-	1 (1.8%)	1 (1.8%)	7 (1.0%)
Race				
Caucasians	10 (100.0%)	50 (89.2%)	50 (89.2%)	635 (91.8%)
Others	-	6 (10.8%)	6 (10.8%)	57 (8.2%)
Index Drug Category				
Typical Antipsychotics	-	4 (7.2%)	4 (7.2%)	182 * (26.3%)

Table 3c: Exploratory analysis of mental health conditions among patients who were initiated on antipsychotics in the West Virginia Medicaid population during the study period (contd.)

	Dementia N = 27		*Non-schizophrenia Psychosis N = 220*	
	Less than 18 years n = 10	*Less than 18 years n = 56*	*Less than 18 years n = 56*	*18 years and above n = 692*
Risperidone	5 (50.0%)	31 (55.3%)	31 (55.3%)	142 * (20.5%)
Olanzapine	4 (40.0%)	14 (25.0%)	14 (25.0%)	252 * (36.4%)
Quetiapine	1 (10.0%)	7 (12.5%)	7 (12.5%)	110 * (15.9%)
Combination	-	-	-	6 (0.9%)

* Results of chi-square analysis indicate significant differences between the index drug category within the respective age groups at $p < 0.05$

For example, a total of 1,112 patients who were initiated on antipsychotics between 1999 and 2001 had major depression. Of these, about 26% did not have diagnosis of any other mental health disorder (except major depression) in the 12-month pre-index period suggesting that initiation of antipsychotic may have been for major depression. Similarly, more than 50% of patients with autism who were initiated on antipsychotics did not have any other co-morbidities.

For most mental health conditions (non-schizophrenic psychosis, attention deficit disorder, major depression , mild to moderate, depression, anxiety, other mental health disorders), higher proportion of patients *who are less than 18 years of age* were initiated on *risperidone* compared to any other antipsychotic.

For most mental health conditions (non-schizophrenic psychosis, attention deficit disorder, major depression , mild to moderate, depression, anxiety, personality disorder, other affective disorders, autism, other mental health disorders), higher proportion of patients *who are 18 years or older* were initiated on *olanzapine* compared to any other antipsychotic. Results of Chi-square analysis are not presented for cohorts with inadequate sample size.

Discussion for research objective 2

The results of our study indicate that a significant proportion of patients were probably initiated on antipsychotic therapy for off-label indications such as autism, non-schizophrenia psychosis, major depression and attention-deficit disorders. A study by Cooper and colleagues reported that greater numbers of adolescents are being initiated on atypical antipsychotics for conditions such as attention-deficit/hyperactivity disorder, conduct disorder, and affective disorders (Cooper et al., 2004). Other studies have also

reported incidences of off-label antipsychotic use for depression, attention-deficit/hyperactivity disorder, affective disorders, and autism (Barbee et al., 2004; Cooper et al., 2004; Liperoti et al., 2003). These results suggest that the prevalence of antipsychotic use in other conditions is present in clinical practice even though clinical evidence regarding risks and benefits of this practice is lacking. It is likely that antipsychotics are being used concomitantly along with other psychotropic medications indicated with these conditions.

It is important to study whether the use of antipsychotics adds any therapeutic benefit to the traditional treatment of conditions that are not yet indicated for antipsychotic use. Physicians involved in treating patients using antipsychotics can provide more information regarding outcomes of this practice. Pharmacists should be made aware of increasing use of antipsychotics for other indications and encouraged to monitor these patients regularly.

Results for research objective 3

For schizophrenia and bipolar disorder patients, determine different types of utilization pattern of antipsychotics.

Schizophrenia

Table 4a describes the patterns of antipsychotic use in the 12-month follow-up period among schizophrenia patients who are greater than 18 years of age. The patterns of antipsychotic use were classified into mutually exclusive categories: 1) initial polytherapy, 2) later polytherapy, 3) switch, 4) interrupted, and 5) continuous therapy. Results of chi-square analysis revealed that there are significantly different patterns of antipsychotic use prevalent in the schizophrenia population.

About 3.6% of patients were initiated on polytherapy (i.e received a combination of two or more antipsychotics). About 8.4% of patients switched to polytherapy during the course of their treatment. Therefore, our study population showed 12.0% of patients on polytherapy during the 12-month period after initiation of antipsychotic treatment. The remaining 88.0% of patients received antipsychotic monotherapy during the 12-month period after initiation of antipsychotic treatment.

About 12.7% of patients switched from the index antipsychotic to another antipsychotic. A large proportion of our study population (56.8%) received less than 80% days supply of index antipsychotic in the 12-month post index period or interrupted therapy. About 18.5% of patients received continuous therapy, i.e. they received at least 80% days supply of index antipsychotic in the 12-month post index period.

Table 4b provides the proportion of patients who continued on index antipsychotic of three or more months (trial duration based on recommendations by the Texas Medication Algorithm Project (TMAP) guidelines). About 77.3% of patients continued on index antipsychotic prescription for 3 or more months. About 22.7% of patients changed or discontinued index antipsychotic prescription within 3 months. The average duration of index antipsychotic use was 242.1 ($\pm$136.9) days.

Table 4a: Pattern of antipsychotic use in the 12-month follow-up period among Schizophrenia patients (18 years and above)

Pattern of antipsychotic use	*Number of Patients (%) N=1,036*
Antipsychotic Polytherapy	
Initial Polytherapy	37 (3.6%)
Later Polytherapy	87 (8.4%)
Antipsychotic Monotherapy	
Switch	132 (12.7%)
Interrupted	588 (56.8%)
Continuous	192 (18.5%)

Table 4b: Duration of index antipsychotic prescription use among schizophrenia patients

	N = 999*
Duration of index antipsychotic use in days	
Mean (±std)	242.1 (±136.9)
Median	293.0
Patients who continued on index antipsychotic prescription for 3 or more months n (%)	772 (77.3%)
Patients who changed or discontinued index antipsychotic prescription within 3 months n (%)	227 (22.7%)

* thirty seven patients initiated on polytherapy were deleted from this analysis.

Bipolar Disorder

Table 5 describes the patterns of antipsychotic use in the 12-month follow-up period among bipolar patients. Results of chi-square analysis revealed that there are significantly different patterns of antipsychotic use prevalent among bipolar disorder patients who are18 years and older and less than 18 years. Initiation on antipsychotic polytherapy was seen in only 0.8% of bipolar patients. About 7.2% of 18 years and older patients and about 10.1% of less than 18 years old patients switched to polytherapy during course of their treatment.

About 13.3% of patients switched from index antipsychotic use to another antipsychotic. About 56.3% of 18 years and older patients and about 66.9% of less than 18 years old patients had received interrupted therapy. About 21.6% of 18 years and older patients and about 12.2% of less than 18 years old patients received antipsychotic adherent therapy during the post-index period.

Table 5: Pattern of antipsychotic use in the 12-month follow-up period among bipolar disorder patients

	18 years and above n=684	*Less than 18 years n=148*	*Total N = 832*
Antipsychotic Polytherapy			
Initial Polytherapy	6 (0.9%)	1 (0.7%)	7 (0.8%)
Later Polytherapy	49 (7.2%)	15 (10.1%)	64 (7.7%)
Antipsychotic Monotherapy			
Switch	96 (14.0%)	15 (10.1%)	111 (13.3%)
Interrupted	385 (56.3%)	99 (66.9%)	484 (58.2%)
Continuous	148 (21.6%)	18 (12.2%)	166 (20.0%)

Discussion for research objective 3

Schizophrenia

Our study reports about 12.0% overall polytherapy among schizophrenia patients initiated on antipsychotics between 1999 and 2001 in the WV Medicaid. Varying rates of polytherapy have been found in published literature depending upon study population, data used, the year of study, and definitions of polytherapy. Most studies based on outpatient prescription use report lower rates of polytherapy compared to studies based on inpatient prescription use indicating that the practice of antipsychotic polytherapy is more prevalent during inpatient treatment. A study by Loosbrock and colleagues conducted using am employer claims data from 1997 reported similar polytherapy rates as our study (Loosbrock et al., 2003). They found that about 2% of patients had been initiated on polytherapy and 7% patients had switched to polytherapy during one-year follow-up period. About 6.8% antipsychotic polytherapy was reported among schizophrenia patients from Veteran Administration in 1999(Leslie et al., 2001). Prevalence of antipsychotic polytherapy among Rhode Island Medicaid's elderly and disabled population was about 10% in 2003 (Kogut et al., 2005). Clark and colleagues report increasing rates of polytherapy from 5.7% in 1995 to 24.5% in 1999 among schizophrenia patients in the New Hampshire Medicaid(Clark et al., 2002). Ganguly and colleagues have reported about 40% antipsychotic polytherapy between 1998 and 2000 in the Georgia Medicaid and California Medicaid Schizophrenia patients (Ganguly et al., 2004). This is the highest prevalence of polytherapy reported based on an outpatient prescription record. It may be due to identification of polytherapy based on an episode of polytherapy anytime between 1998 and 2000. Studies evaluating antipsychotics using

inpatient prescription records have found rates of polytherapy between 16% to 45% (Schumacher et al., 2003; Procyshyn et al., 2001; Procyshyn et al., 2004; McCue et al., 2003).

The rate of switching in the 12-month post-index period after initiation on antipsychotic was 12.7% in our study. Loosbrock and colleagues found about 13% rates of switching in 1997 among schizophrenia patients from an employer based claims data (Loosbrock et al., 2003). Williams and colleagues have reported a 25% rate of switching observed in an indigent Indianapolis community patients who were initiated on antipsychotics in 1995 (Williams et al., 1999). As majority of their patient population (88%) were on typical antipsychotics, it is possible that rates of switching increased as the use of atypical became more widespread. McComb and colleagues have reported a 47% rate of switching to another antipsychotic or augmenting with another antipsychotic in the California Medicaid population between 1987 and 1996 (McCombs et al., 1999b). The higher rate of switching in their study can be attributed to the episode of care methodology and possible differential rates of switching occurring between 1987 and 1996. In addition, about 98% of their study population was on typical antipsychotics.

Only 18.5% of schizophrenia patients in our study received continuous index antipsychotic therapy. The rate of continuous therapy in our study is comparable to 11.6% of patients in the McComb study of California Medicaid patients (McCombs et al., 1999b). Medication adherence is usually low in the schizophrenia population due to reasons such as impaired awareness of disease, alcohol and substance abuse, and medication side-effects (Lacro, Dunn, Dolder, Leckband, & Jeste, 2002; Hudson et al., 2004; Van Putten, 1974). The 71% monotherapy found in our study is similar to 71.5%

reported by William and colleagues and higher than the 52% reported by Loosbrock and colleagues (Williams et al., 1999; Loosbrock et al., 2003). Loosbrock and colleagues also reported in their study that 67.1% of patients received interrupted therapy with gaps of 1 to 11 months. Our study defines interrupted therapy in terms of patients who have received less than 80% days supply of index antipsychotic in the 12-month post index period. This definition accounts for non-adherence to therapy due to large continuous gaps in the therapy or some intermittent missed days of therapy. We found 56.8% patients having interrupted therapy according to our definition. In general, the differences in the patterns of use across the study can be due to the differences in study methodology and definition of the pattern, year of study and proportion of patients on typical antipsychotics.

Bipolar Disorder

Our study reports 7.7% prevalence of antipsychotic polypharmacy among patients initiated on antipsychotics during the index period 1999-2001. A retrospective review of psychiatric medications among patients discharged from a tertiary care psychiatric facility had revealed 29.9% rate of antipsychotic polytherapy among bipolar patients (Procyshyn et al., 2004). Compared to our study, antipsychotic polypharmacy rates may have been higher among patients discharged from hospital due to disease severity. Higher rates antipsychotic polypharmacy were also reported by studies based on inpatient prescription use among schizophrenia patients(Schumacher et al., 2003; Procyshyn et al., 2001; Procyshyn et al., 2004; McCue et al., 2003).

Rates of interrupted therapy were similar among schizophrenia (56.8%) and adult bipolar disorder (56.3%) patients. As in schizophrenia population, non-adherence is a

major problem with bipolar disorder patients (Keck, Jr., McElroy, Strakowski, Bourne, & West, 1997). Prevalence of substance abuse disorder and denial of disease condition have been cited as the reasons for non-adherence among bipolar disorder patients (Keck, Jr. et al., 1997; Lacro et al., 2002; Scott & Pope, 2002). Though adherence to antipsychotics has not been studied in previous studies, the rate of partial or total non-adherence with mood stabilizers was reported to be about 51% in bipolar disorder population (Keck, Jr. et al., 1997). About one in three patients with bipolar disorder take less than 30 percent of their medication (Scott et al., 2002). However, the rate of interrupted therapy was much higher among bipolar disorder patients less than 18 years of age. Since antipsychotics were not approved by the FDA for bipolar disorder at the time of study, it is possible that physicians were wary of using antipsychotics for extended periods in children and were using them for short periods to control symptoms.

Results for the research objective 4

For schizophrenia and bipolar disorder patients, determine the gaps between the refills of antipsychotics.

Schizophrenia

Table 6 describes treatment gaps among schizophrenia patients in terms of the longest continuous gap between refills of antipsychotics for each patient. About 27.5% of patients had no gaps greater than 15 days between refills of antipsychotic therapy. About 60.9% of patients had at least 1 gap of greater than 30 days. About 30.4% of patients had at least 1 gap of greater than 90 days between refills of antipsychotics. Average duration of the longest gap was 72.2 ($\pm$ 75.6) days.

Bipolar Disorder

Table 7 describes treatment gaps among schizophrenia patients in terms of the longest continuous gap between refills of antipsychotics for each patient. About 26.8% of 18 years and older bipolar disorder patients and about 37.2% of less than 18 years old bipolar disorder patients had no gaps greater than 15 days between refills of antipsychotic therapy. About 23.8% of 18 years and older bipolar disorder patients and about 17.6% of less than 18 years old bipolar disorder patients had at least 1 gap of greater than 90 days between refills of antipsychotics. Average duration of the longest gap was 64.1 ($\pm$ 71.3) days for patients 18 years or older and 48 ($\pm$ 63.9) days for patients less than 18 years of age.

Table 6: Study of antipsychotic treatment gaps among schizophrenia patients (18 years and above)

Duration of gap* in days	***N = 1,036***
Mean (±std) Median	72.2 (±75.6) 48.0
Up to or equal to 15 days	285 (27.5%)
Greater than 15 days to 30 days	121 (11.7%)
Greater than 30 days to 60 days	188 (18.2%)
Greater than 60 days to 90 days	127 (12.3%)
Greater than 90 days	315 (30.4%)

* The longest continuous gap between refills for each patient

Table 7: Study of antipsychotic treatment gaps among bipolar disorder patients

Duration of gap* in days	***18 years and above n=684***	***Less than 18 years n=148***	***Total N = 832***
Mean (±std) Median	64.1 (±71.3) 37.0	48.0 (±63.9) 26.0	61.2 (±70.3) 33.0
Up to or equal to 15 days	183 (26.8%)	55 (37.2%)	194 (28.6%)
Greater than 15 days to 30 days	117 (17.1%)	31 (20.9%)	148 (17.8%)
Greater than 30 days to 60 days	137 (20.0%)	27 (18.2%)	164 (19.7%)
Greater than 60 days to 90 days	84 (12.2%)	9 (6.08%)	93 (11.2%)
Greater than 90 days	163 (23.8%)	26 (17.6%)	189 (22.7%)

* The longest continuous gap between refills for each patient

Discussion for the research objective 4

Schizophrenia

Gaps in the antipsychotic therapy are a measure of compliance or adherence to therapy. Poor adherence to antipsychotic therapy among schizophrenia patients can be attributed to the nature of disease as well as side-effects to the antipsychotic therapy. Large gaps in antipsychotic therapy as found in our study have also been observed in other published studies. McCombs and colleagues have noted "drug holidays" among schizophrenia patients with only 11.6% of patients received uninterrupted antipsychotic therapy. About 30.7% of a treated sample of 2,010 patients had gaps larger than 90 days (McCombs, Nichol, Stimmel, Shi, & Smith, 1999a). Mojtabai and colleagues report that about 51% of patients discharged from hospital had gaps of greater than 30 days in antipsychotic treatment within a year(Mojtabai et al., 2002). Weiden and colleagues found gaps of greater than 30 days among 25.97% of patients in California Medicaid (Weiden, Kozma, Grogg, & Locklear, 2004).

Bipolar Disorder

Our study found large gaps in antipsychotic therapy were present among bipolar disorder patients as well as schizophrenia patients. Though few studies have reported the problem of non-adherence to mood stabilizer therapy in bipolar disorder patients, gaps in the therapy or adherence to antipsychotic therapy has not been explored. Gaps in antipsychotic therapy among bipolar disorder patients may be due to drug side-effects, patient denial of illness and alcohol and substance abuse (Keck, Jr. et al., 1997; Lacro et al., 2002; Scott et al., 2002).

Results for research objective 5

For schizophrenia and bipolar disorder patients, determine predictors of different utilization patterns of antipsychotics

Schizophrenia

Table 8 presents the results of the multinomial logistic model predicting factors associated with patterns of antipsychotic use among schizophrenia patients. Alcohol and substance abuse, and use of typical antipsychotics as index prescription showed significant association with all patterns of antipsychotic use. In addition, Schizophrenia subtypes, diagnosis of major depression, prescription of mood stabilizers, antidepressants and antipsychotics in the pre-index period were also significantly associated with certain patterns of antipsychotic use.

Patients having diagnosis of alcohol and substance abuse were almost 2 times more likely to show either interrupted therapy, switching or polytherapy pattern than continuous therapy pattern. Patients showing mixed diagnosis of schizophrenia and schizoaffective disorders were almost 2 times more likely to show continuous therapy rather than switching or polytherapy. Patients having major depression were 2.3 times more likely to receive polytherapy rather than continuous monotherapy.

Compared to patients initiated on quetiapine, patients initiated on typical antipsychotic were about 5 times more likely to receive interrupted antipsychotic therapy, about 1.1 times more likely to switch, and about 5.6 times more likely to receive polytherapy.

Table 8: Multinomial logistic regression model determining predictors of pattern of antipsychotic use among schizophrenia patients (first-stage sample selection model)

	Interrupted vs. Adherent		*Switching vs. Adherent*		*Polytherapy vs. Adherent*	
	Coefficient	***t-ratio***	***Coefficient***	***t-ratio***	***Coefficient***	***t-ratio***
Demographic characteristics						
Age (in years)	-0.009	-1.192	-0.021	1.926	0.001	0.15
Males (ref: females)	0.008	0.627	0.751	0.047	0.005	0.246
Whites (ref: non-whites)	0.007	0.024	0.293	0.675	-0.111	-0.273
Metro (ref: non-metro)	0.068	0.291	-0.424	1.408	-0.215	-0.697
Prescribing physician type						
Psychiatric prescriber	-0.001	-1.871	-0.008	-1.647	-0.005	-1.501
Schizophrenia subtype (ref: only schizophrenia)						
Schizoaffective disorder	0.219	0.867	0.0844	0.268	-0.384	-1.127
Both schizoaffective disorder and schizophrenia	0.162	0.646	-0.777	- 2.309*	-0.965	-2.647*
Pre-index co-morbidities						
Diabetes	0.493	1.464	0.349	0.793	-0.183	-0.357
Hyperlipidemia	0.021	0.057	-0.349	-0.65	0.099	0.162
Hypertension	0.122	0.454	0.331	0.949	-0.489	-1.113
Alcohol and substance abuse	0.686	2.676*	0.701	2.193*	0.873	2.614*
Bipolar disorder	0.547	1.931	0.313	0.873	0.293	0.724
Major depression	0.195	0.749	0.437	1.348	0.834	2.382*
Anxiety disorder	-0.164	-0.639	-0.178	-0.532	-0.305	-0.802
Personality disorder	-0.160	-0.532	0.086	0.232	-0.120	-0.279
Non-specified psychosis	-0.647	-1.497	-1.382	-1.923	-1.182	-1.731
Other affective psychosis	-0.797	-1.381	-0.461	-0.597	-1.312	-1.111

Table 8: Multinomial logistic regression model determining predictors of pattern of antipsychotic use among schizophrenia patients (first-stage sample selection model) (contd.)

	Interrupted vs. Adherent		*Switching vs. Adherent*		*Polytherapy vs. Adherent*	
	Coefficient	***t-ratio***	***Coefficient***	***t-ratio***	***Coefficient***	***t-ratio***
Attention deficit disorders	-0.669	-1.238	-0.217	-0.322	-0.056	-0.072
Mild to moderate depression	0.240	0.786	0.351	0.923	0.143	0.325
Pre-index healthcare utilization and cost						
Number of pre-index mental-health related ER visits/ hospitalizations	0.005	1.558	-0.005	-1.066	-0.002	-0.476
Number of pre-index mental-health related physician visits	-0.129	-1.345	0.084	0.856	0.062	0.59
Number of psychotherapy visits	0.008	0.398	-0.038	-0.689	0.018	0.645
Number of medication management visits	0.009	0.3	-0.043	-1.012	-0.037	-0.784
Year of index prescription (ref: 1999)						
• 2000	0.209	0.868	0.217	0.675	-0.251	-0.684
• 2001	0.190	0.71	0.105	0.286	-0.023	-0.058
Pre-index period psychiatric medication use (days of supply)						
Mood stabilizers	-0.341	-2.542*	-0.869	-0.107	-0.000	-0.128
Anticholinergics	-0.017	-1.386	-0.003	-0.584	0.002	0.303
Anxiolytics/hypnotics/ sedatives	0.004	0.25	0.001	1.004	0.007	0.338
Antipsychotics	-0.125	-2.314*	-0.003	-1.007	-0.006	-0.227
Antidepressants	-0.003	-0.489	0.322	2.656*	-0.003	-0.332
Benzodiazepines	-0.003	-0.422	-0.001	-1.27	0.001	1.597
Antiparkinsons	0.006	0.245	0.003	1.08	0.005	0.142

Table 8: Multinomial logistic regression model determining predictors of pattern of antipsychotic use among schizophrenia patients (first-stage sample selection model) (contd.)

	Interrupted vs. Adherent		*Switching vs. Adherent*		*Polytherapy vs. Adherent*	
	Coefficient	***t-ratio***	***Coefficient***	***t-ratio***	***Coefficient***	***t-ratio***
Index prescription (ref: quetiapine)						
Risperidone	0.309	1.09	0.144	0.364	0.819	1.580
Olanzapine	0.025	0.102	0.218	0.422	0.543	1.130
Typicals	1.628	5.112*	0.108	2.567*	1.730	3.289*

*significant at $p<0.05$

Model fit statistics:

Pseudo R-square = 13.1%, ***-2 Log Likelihood*** = 1034.62; χ^2= 314.49; p= 0.00

Bipolar Disorder

Table 9 presents the results of the multinomial logistic model predicting factors associated with patterns of antipsychotic use among bipolar disorder patients. Compared to bipolar disorder patients who were less than 18 years of age, bipolar disorder patients who were 18 years or older were almost 2 times less likely to have adherent index antipsychotic therapy. Patients having psychiatric prescriber for the index prescription were 1.22 times less likely to have interrupted therapy. Patients having diagnosis of alcohol and substance abuse were almost 2.3 times more likely to show interrupted therapy, 2.8 times more likely to switch, and 2.7 times more likely to have polytherapy pattern than continuous therapy pattern. Patients using mood stabilizers in the pre-index period were 1.3 times more likely to have adherent antipsychotic therapy. Patients initiated on typicals were 1.86 times more likely to have interrupted antipsychotic therapy.

Patients having mixed bipolar disorder patients were almost 2 times less likely to switch. Patients who have used antidepressants in the pre-index period were almost 1.2 times more likely to switch index antipsychotic therapy. Patients who have used typical antipsychotics were almost 1.13 times more likely to switch index antipsychotic therapy.

Patients who have major depression are 2.5 times more likely to receive polytherapy. Patients who have anxiety are 2.8 times less likely to receive polytherapy. Patients receiving typical antipsychotics were 3.3 times more likely to receive polytherapy.

Table 9: Multinomial logistic regression model determining predictors of pattern of antipsychotic use among bipolar disorder patients (first-stage sample selection model)

	Interrupted vs. Adherent		*Switching vs. Adherent*		*Polytherapy vs. Adherent*	
	Coefficient	***t-ratio***	***Coefficient***	***t-ratio***	***Coefficient***	***t-ratio***
Demographic characteristics						
Age (in years)	-0.007	-0.730	-0.019	-1.53	0.014	0.956
18 years or above (ref: less than 18 years)	0.719	2.371*	-0.338	-0.845	-0.810	-1.942
Males (ref: females)	0.002	1.417	0.001	0.554	0.108	0.379
Whites (ref: non-whites)	-0.041	-0.117	0.224	0.462	0.200	0.356
Metro (ref: non-metro)	0.146	0.541	-0.347	-1.007	-0.232	-0.596
Prescribing physician type						
Psychiatric prescriber	-0.200	-2.212*	-0.001	-1.036	-0.001	-1.563
Bipolar Subtype (ref: bipolar disorder I)						
Bipolar disorder II	0.318	1.095	0.181	0.509	-0.144	-0.346
Mixed	0.260	0.923	-0.742	-2.015*	-0.769	-1.824
Pre-index co-morbidities						
Diabetes	0.409	1.124	0.259	0.533	-0.782	-1.094
Hyperlipidemia	-0.002	-0.005	-0.616	-1.005	0.153	0.199
Hypertension	0.144	0.496	0.331	0.883	-0.315	-0.608
Alcohol and substance abuse	0.877	2.916*	1.033	2.867*	1.010	2.380*
Bipolar disorder	0.520	1.656	0.060	0.147	0.076	0.148
Major depression	0.356	1.234	0.529	1.49	0.925	2.151*
Anxiety disorder	-0.366	-1.273	-0.190	-0.517	-1.058	-1.966*
Personality disorder	-0.091	-0.273	0.066	0.16	-0.227	-0.416
Non-specified psychosis	-0.634	-1.248	-1.175	-1.501	-0.378	-0.506
Other affective psychosis	-0.788	-1.194	0.003	0.003	-28.058	0.000

Table 9: Multinomial logistic regression model determining predictors of pattern of antipsychotic use among bipolar disorder patients (first-stage sample selection model) (contd.)

	Interrupted vs. Adherent		*Switching vs. Adherent*		*Polytherapy vs. Adherent*	
	Coefficient	***t-ratio***	***Coefficient***	***t-ratio***	***Coefficient***	***t-ratio***
Attention deficit disorders	-0.682	-1.237	-0.285	-0.415	0.133	0.162
Mild to moderate depression	0.148	0.448	0.240	0.58	-0.015	-0.028
Number of pre-index mental-health related ER visits/ hospitalizations	0.001	1.534	-0.001	-1.18	0.000	-0.224
Number of pre-index mental-health related physician visits	-0.095	-0.886	0.105	0.958	0.124	1.040
Number of psychotherapy visits	-0.019	-0.764	-0.048	-0.789	-0.105	-0.244
Number of medication management visits	0.050	1.461	-0.072	-1.408	-0.177	-0.357
Year of index prescription (ref: 1999)						
• 2000	0.056	0.213	0.123	0.354	0.000	-0.414
• 2001	0.025	0.084	-0.016	-0.041	0.006	0.928
Pre-index period psychiatric medication use (days of supply)						
Mood stabilizers	-0.320	-3.041*	0.000	0.137	0.003	1.250
Anticholinergics	-0.007	-1.298	-0.005	-0.708	0.001	0.248
Anxiolytics/hypnotics/ sedatives	0.001	0.464	0.002	1.04	-0.002	-1.787
Antipsychotics	-0.106	-2.293*	-0.005	-1.327	0.001	1.053
Antidepressants	-0.001	-1.219	0.202	2.442*	0.000	-0.028
Benzodiazepines	-0.656	-0.079	-0.001	-1.266	0.017	0.575
Antiparkinsons	-0.001	-0.207	-0.671	-0.016	-0.012	-0.208

Table 9: Multinomial logistic regression model determining predictors of pattern of antipsychotic use among bipolar disorder patients (first-stage sample selection model) (contd.)

	Interrupted vs. Adherent		*Switching vs. Adherent*		*Polytherapy vs. Adherent*	
	Coefficient	***t-ratio***	***Coefficient***		***Coefficient***	***t-ratio***
Index prescription (ref: quetiapine)						
Risperidone	-0.001	-1.589	-0.001	-1.751	-0.002	-1.237
Olanzapine	-0.001	-1.719	0.000	-1.368	-0.002	-1.536
Typicals	0.620	3.132*	0.13	2.461*	1.210	2.075*

* significant at $p < 0.05$

Model fit statistics:

Pseudo R-square = 13.67%
-2 Log Likelihood = 801.14; $\chi^{2} =$ 253.90; p= 0.00

Discussion for research objective 5

Schizophrenia

Alcohol and substance abuse is a common co morbidity among schizophrenia patients (APA, 1997). Our study found that alcohol and substance abuse was a significant predictor of interrupted therapy, switching, and polytherapy. Other studies have also reported association of substance abuse with non-adherence with medications (Hudson et al., 2004; Hunt, Bergen, & Bashir, 2002; Kashner et al., 1991; Kamali et al., 2001). A study of barriers to medication adherence among schizophrenia patients reported patients with substance and alcohol abuse were 3.24 times more likely to be non-compliant with the medications (Hudson et al., 2004). As management of disease condition may be difficult in these patients, physicians may resort to switching or polytherapy to treat patients. As use of alcohol and drugs are strictly contraindicated with use of psychotropic medications, the patients may choose to stop taking medications and take alcohol or drugs.

Patients with mixed diagnosis of both schizophrenia and schizoaffective disorder may be showing range of symptoms. Physicians may be attempting to control the symptoms by changing or augmenting antipsychotic therapy. According to our study results, patients with major depression were 2.3 times more likely to receive polytherapy. A study by McCombs and colleagues also reported about 1.9 times greater likelihood of switching or polytherapy among schizophrenia patients with diagnosis of major depression (McCombs et al., 1999a). Polytherapy may have been used in these patients

to manage greater exacerbation of disease symptoms due to presence of an additional mental illness.

Compared to patients initiated on quetiapine, patients initiated on typical antipsychotic had a high likelihood of interrupted antipsychotic therapy, switching and polytherapy. Typical antipsychotics have been associated with poor adherence due to disabling adverse effects such as extrapyramidal symptoms (EPS) (Van Putten, 1974). Studies have reported poorer adherence rates with typical antipsychotics (50.1%) compared to atypical antipsychotics (54.9%) (Dolder, Lacro, Dunn, & Jeste, 2002). Menzin and colleagues found that schizophrenia patients on atypical antipsychotics in the California Medicaid population were less likely to switch (OR = 0.37) than typical antipsychotics in 1997(Menzin et al., 2003). Compared with quetiapine, olanzapine and risperidone did not show any significant difference in the likelihood of interrupted therapy, switching, and polytherapy. Though few studies have reported better persistence with index antipsychotic for olanzapine with respect to risperidone (Gibson et al., 2004), no studies have compared the typical and atypical antipsychotics in terms of continuous, interrupted, switching and polytherapy patterns.

Bipolar Disorder

As among schizophrenia patients, we found alcohol and substance abuse was a significant predictor of interrupted therapy, switching or polytherapy among bipolar patients. Prevalence of alcohol and substance abuse is about 40% to 60% among bipolar disorder patients (Salloum & Thase, 2000). Other studies have also reported association of alcohol and substance abuse with medication non-adherence, especially in schizophrenia population (Keck, Jr. et al., 1997).

Patterns of antipsychotic therapy are relatively less studied among bipolar disorder patients. Common factors associated with non-adherence to mood-stabilizers medications among bipolar disorder are mania, personality disorders, alcohol and substance abuse, and denial of disorder or need for treatment (Keck, Jr. et al., 1997; Loosbrock et al., 2003; Maarbjerg, Aagaard, & Vestergaard, 1988; Schumann, Lenz, Berghofer, & Muller-Oerlinghausen, 1999). In our study, factors such as disease subtype, use of mood stabilizers , antidepressants, and typical antipsychotics, alcohol and substance abuse were common predictors of patterns of antipsychotic use among bipolar and schizophrenia patients.

The significant association of use of typical antipsychotics with interrupted therapy and switching may be due to side-effects. Use of mood-stabilizers was associated with decreased likelihood of receiving interrupted therapy. Presence of major depression was linked with greater likelihood of receiving polytherapy. Major depression was also associated with polytherapy among schizophrenia patients in our study as well as in the McCombs study (McCombs et al., 1999a).

Results for research objective 6

For schizophrenia and bipolar disorder patients, determine the relationship between utilization pattern of antipsychotics and total health-related healthcare costs.

The objective was to determine the effect of pattern of antipsychotic use on total healthcare costs among schizophrenia and bipolar patients. The results of univariate analysis show that the post-index total healthcare costs was significantly less for the continuous therapy group compared to the interrupted, switch and polytherapy group. Multivariate analysis was conducted to test this difference after controlling for patient

demographics, disease severity, co morbidities and prior utilization of healthcare services. An important step of this analysis was to adjust for the sample selection bias between patients showing different patterns of antipsychotic utilization. In the first step of the analysis, a multinomial logistic regression analysis was carried out using various explanatory variables such as patient demographics, co morbidities and healthcare utilization variables. This model was same as the model provided in the table 8 for schizophrenia patients and table 9 for bipolar disorder patients. This model allowed for calculation of Inverse Mills Ratio (IMR) to adjust for sample selection bias in the second step regression models. Individual contrasts were carried out to obtain IMR for continuous vs. interrupted therapy, continuous vs. switching therapy, and continuous vs. polytherapy.

In the second step of the analysis, multivariate regression models were used to investigate association of different patterns of antipsychotic use with total healthcare costs. Three semi-log OLS regressions were developed to compare costs associated with interrupted therapy, switching and polytherapy with adherent therapy. IMRs calculated from the first stage regression models were added as a covariate in the second stage regression models to adjust and test for sample selection bias. The models were further tested for appropriate specifications. It is possible that multicollinarity resulting due to inclusion of IMR in the model may be inflating the standard errors. Therefore, a semi-log OLS model was developed without including the IMR and the output was compared with the outputs of regression models that included IMR.

The univariate analysis for total and mental healthcare costs for schizophrenia patients are presented in table 10. The second stage regression models for total and

mental healthcare costs for schizophrenia patients are presented in the tables 11 and 12, respectively.

The univariate analysis for total and mental healthcare costs for bipolar disorder patients are presented in table 13. The second stage regression models for total and mental healthcare costs for bipolar disorder patients are presented in the tables 14 and 15, respectively.

Schizophrenia

The results of univariate analysis presented in table 10 show that the post-index total healthcare costs was significantly less for the continuous therapy group ($19,960 ± $32,312) compared to the switching ($21,595 ± $24,595) and polytherapy ($27,741 ± 35,334) group. The multivariate analyses of total costs are presented in tables 11a-11c. The results of multivariate analysis presented in table 11a show that patients receiving interrupted index antipsychotic therapy incur 7.89% higher total healthcare costs than patients receiving continuous antipsychotic therapy. After controlling for confounding variables, there were no significant differences among patients receiving continuous antipsychotic therapy and patients switching from index antipsychotic therapy (table 11b). Table 11c shows that patients receiving polytherapy incur 28.40% higher total costs than patients receiving continuous index antipsychotic therapy. Also, IMR was not significant in all the models indicating possible absence of selection bias between patients on different patterns of antipsychotic use cohorts.

Bipolar disorder

The results of univariate analysis presented in table 13 show that the post-index total healthcare costs was significantly less for the continuous therapy group ($18,383 ±

$30,283) as compared to the interrupted ($20,486 ± $21,513), switching ($20,104 ± $23,116) and polytherapy ($26,972 ± 32,885) groups. The results of multivariate analysis presented in table 14a show that patients receiving interrupted index antipsychotic therapy incur 1.5% higher total healthcare costs than patients receiving continuous antipsychotic therapy. Table 14b shows that patients switching from index antipsychotic to monotherapy with another antipsychotic incur 17.0% higher total costs than patients receiving continuous index antipsychotic therapy. Table 14c shows that patients receiving polytherapy incur 37.71% higher total costs than patients receiving continuous index antipsychotic therapy.

Results for research objective 7

For schizophrenia and bipolar disorder patients, determine the relationship between utilization pattern of antipsychotics and mental health care utilization and costs.

Schizophrenia

The results of univariate analysis presented in table 10 show that the post-index mental healthcare costs was significantly less for the continuous therapy group ($18,383 ± $30,283) compared to the interrupted ($12,482 ± $24,195), switching ($17,890 ± $18,330) and polytherapy ($21,006 ± $35,334) groups. The multivariate results in table 12a show that after controlling for confounding variables, patients receiving interrupted index antipsychotic therapy incur 3.44% higher mental healthcare costs than patients receiving continuous antipsychotic therapy. After controlling for confounding variables, there were no significant differences among patients receiving continuous antipsychotic therapy and patients switching from index antipsychotic therapy (table 12b). Table 12c

shows that patients receiving polytherapy incur 12.74% higher mental health care costs than patients receiving continuous index antipsychotic therapy.

Bipolar

The results of univariate analysis presented in table 13 show that the post-index mental healthcare costs was significantly less for the continuous therapy group ($18,383 ± $30,283) as compared to the interrupted ($11,134 ± $21,901), switching ($17,890 ± $18,330) and polytherapy ($16,470 ± $15,258) group. The multivariate results in table 15a show that after controlling for confounding variables, patients receiving interrupted index antipsychotic therapy incur 7.03% higher total healthcare costs than patients receiving continuous antipsychotic therapy. After controlling for confounding variables, there were no significant differences among patients receiving continuous antipsychotic therapy and patients switching from index antipsychotic therapy (table 15b). Table 15c shows that patients receiving polytherapy incur 16.18% higher total costs than patients receiving continuous index antipsychotic therapy.

Discussion for research objective 6 and 7

Schizophrenia and bipolar disorder

Our results show that significant increase in total and mental costs is associated with different patterns of antipsychotic use. Other studies have also found that non-adherent patients are more costly than adherent patients. A study by Knapp and colleagues conducted among adults living in institutions in the UK reported that non-adherent patients incurred an additional £5000 in total costs than adherent patients (Knapp, King, Pugner, & Lapuerta, 2004). Eaddy and colleagues report 54.5% increase in inpatient costs among partially adherent patients (Eaddy et al., 2005). Gilmer and

colleagues found that non-adherent patients incur almost 3 times higher inpatient cost than adherent patients in a California Medicaid population. Risk of hospitalization has also been shown to increase with increasing gaps in therapy (Weiden et al., 2004; Gilmer et al., 2004). Literature on association of pattern of medication use with healthcare costs and utilization are relatively rare in bipolar disorder. Studies have shown that the risk of relapse resulting in hospitalizations increases after discontinuing lithium treatment in bipolar disorder patients (Schou, 1997; Suppes, Baldessarini, Faedda, & Tohen, 1991). Our study demonstrates that patients with non-adherent or interrupted antipsychotic therapy are more likely to incur higher costs.

Our results show that switching from index antipsychotic to another antipsychotic was associated with significant increase in cost for bipolar disorder patients but not for schizophrenia patients. Other studies in literature have suggested that switching can increase costs as it usually occurs when a patient fails the previous treatment or experiences severe side-effects (McCombs et al., 2000; Loosbrock et al., 2003). McCombs and colleagues reported that antipsychotic switching can increase the annual total cost by $9,719 (McCombs et al., 2000). However, they combined the cost of switching to antipsychotic monotherapy or polytherapy in their analysis which could have overestimated the increase in total costs. Loosberg and colleagues also found an increase of $4,706 associated switching antipsychotics(Loosbrock et al., 2003). As the data used in above two studies is prior to 1997 and a large proportion of the study population was on typical antipsychotics, it is likely that increase in cost was mainly due to switching from typical to atypical antipsychotics, which are more costly. Switching antipsychotics is advocated by the treatment guidelines when patient fails to respond or

stabilize on current medications and may lead to finding the appropriate medication regimen for the patients.

Significantly greater increase in total and mental costs was associated with polytherapy for schizophrenia and bipolar disorder patients. Results are similar to those observed in the Loosbrock study that evaluated total costs differences between schizophrenia patients on polytherapy and monotherapy. The study reported that schizophrenia patients on polytherapy incurred an additional $4,244 in total costs as compared to schizophrenia patients on monotherapy. However, it should be noted that in our study comparisons are being made between polytherapy and adherent or continuous monotherapy.

Antipsychotic polytherapy has been associated with increased risk of adverse effects and hospitalization (Centorrino et al., 2004). Utilization of anticholinergics among patients on antipsychotics was significantly higher as compared to monotherapy (Procyshyn et al., 2001). The cost of adverse reactions as well as that of utilization of additional drug may be driving the cost of polytherapy higher. It is also likely that the patients on polytherapy are more severe or treatment refractory and are utilizing more healthcare services. However, results were significant after controlling for the severity and selection bias for these patients using pre-index comorbidities and utilization-related factors.

Table 10: Total and mental healthcare costs associated with the different antipsychotic utilization patterns among schizophrenia patients

	Continuous N = 192	*Interrupted N = 588*	*Switch N =132*	*Polytherapy N = 124*
Total Healthcare Cost				
Mean (±std)				
Pre-index	$13,157[I] (±$27,855)	$10,521[C] (±$16,613)	$13,336 (±$21,517)	$12,267 (±$13,244)
Post-index	$19,960[SP] (±$32,312)	$20,486 (±$21,513)	$21,595[C] (±$24,226)	$27,741[C] (±$35,334)
Mental Healthcare Cost				
Mean (±std)				
Pre-index	$8,513[I] (±$24,121)	$6,168[C] (±$9,761)	$8,764 (±$11,778)	$8,641 (±$11,583)
Post-index	$12,482[ISP] (±$24,195)	$17,890[C] (±$18,330)	$15,049[C] (±$16,957)	$21,006[C] (±$35,334)

[I] Significant difference between continuous (c) and interrupted cohorts at $p<0.05$
[S] Significant difference between continuous (c) and switch cohorts at $p<0.05$
[P] Significant difference between continuous (c) and polytherapy cohorts at $p<0.05$

Table 11a: Ordinary Least Squares (OLS) regression model for the impact pattern of antipsychotic use on total healthcare cost among schizophrenia patients (second stage sample selection models): Interrupted vs. Adherent therapy

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Demographic characteristics				
Age (in years)	0.005	0.003	1.376	0.169
Males (ref: females)	0.571	0.000	0.211	0.833
Whites (ref: non-whites)	0.120	0.104	1.155	0.248
Metro (ref: non-metro)	-0.152	0.091	-1.669	0.095
Prescribing physician type				
Psychiatric prescriber	0.798	0.000	0.719	0.472
Schizophrenia subtype (ref: only schizophrenia)				
Schizoaffective disorder	0.069	0.096	0.709	0.478
Both schizoaffective disorder and schizophrenia	-0.124	0.113	-1.095	0.274
Pre-index co-morbidities				
Charlson Comorbidity Index	0.215	0.030	7.208	0.000
Alcohol and substance abuse	0.294	0.107	2.731	0.006
Bipolar disorder	0.103	0.128	0.804	0.422
Major depression	0.055	0.112	0.493	0.622
Other mental comorbidities	0.015	0.088	0.171	0.865
Pre-index healthcare utilization and cost				
Pre-index total health related cost	0.129	0.023	5.683	0.000
Pre-index total health related ER visits	0.081	0.092	0.880	0.379
Pre-index total health related hospitalizations	0.187	0.112	1.667	0.096
Pre-index total health related physician visits	0.005	0.005	1.006	0.315

Table 11a: Ordinary Least Squares (OLS) regression model: Interrupted vs. Adherent therapy (contd.)

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Year of index prescription (ref: 1999)				
• 2000	-0.010	0.117	-0.088	0.930
• 2001	-0.438	0.120	-3.656	0.000
Pre-index period psychiatric medication use (days of supply)				
Mood stabilizers	0.021	0.010	1.966	0.049
Antipsychotics	-0.002	0.001	-1.710	0.087
Antidepressants	0.282	0.083	3.404	0.001
Benzodiazepines	0.082	0.082	1.002	0.317
Index prescription (ref: quetiapine)				
Risperidone	-0.865	0.904	-0.958	0.338
Olanzapine	-0.666	0.000	-0.606	0.544
Typicals	0.020	0.852	-1.556	0.120
Interrupted (ref: Adherent)	0.078	0.466	2.314	0.021
Inverse Mills Ratio	0.403	0.280	1.441	0.150

Model fit statistics:

Adjusted R-square = 29.58% , ***F*** = 13.59 , ***p*** = 0.00

Table 11b: Ordinary Least Squares (OLS) regression model for the impact pattern of antipsychotic use on total healthcare cost among schizophrenia patients (second stage sample selection models): Switching vs. adherent therapy

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Demographic characteristics				
Age (in years)	0.012	0.004	2.663	0.008
Males (ref: females)	-0.834	0.001	-0.153	0.879
Whites (ref: non-whites)	0.338	0.190	1.783	0.076
Metro (ref: non-metro)	-0.036	0.136	-0.265	0.791
Prescribing physician type				
Psychiatric prescriber	0.277	0.000	0.202	0.840
Schizophrenia subtype (ref: only schizophrenia)				
Schizoaffective disorder	-0.001	0.134	-0.006	0.995
Both schizoaffective disorder and schizophrenia	-0.108	0.149	-0.721	0.471
Charlson Comorbidity Index	0.130	0.039	3.320	0.001
Pre-index co-morbidities				
Alcohol and substance abuse	0.254	0.137	1.855	0.065
Bipolar disorder	0.088	0.166	0.530	0.597
Major depression	-0.169	0.136	-1.238	0.217
Other mental comorbidities	0.152	0.120	1.270	0.205
Pre-index healthcare utilization and cost				
Pre-index total health related cost	0.128	0.034	3.735	0.000
Pre-index total health related ER visits	-0.121	0.125	-0.962	0.337
Pre-index total health related hospitalizations	-0.105	0.155	-0.679	0.498
Pre-index total health related physician visits	0.002	0.006	0.292	0.770

Table 11b: Ordinary Least Squares (OLS) regression model: Switching vs. adherent therapy (contd.)

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Year of index prescription (ref: 1999)				
• 2000	0.209	0.149	1.399	0.163
• 2001	-0.124	0.142	-0.874	0.383
Pre-index period psychiatric medication use (days of supply)				
Mood stabilizers	0.021	0.000	2.971	0.003
Antipsychotics	-0.001	0.001	-0.421	0.674
Antidepressants	0.039	0.116	0.335	0.738
Benzodiazepines	0.110	0.108	1.012	0.312
Index prescription (ref: quetiapine)				
Risperidone	0.001	0.000	1.149	0.252
Olanzapine	0.001	0.000	0.839	0.402
Typicals	-0.020	0.000	-2.429	0.016
Switch (ref: Adherent)	0.559	0.331	1.688	0.092
Inverse Mills Ratio	-0.262	0.209	-1.253	0.211

Model fit statistics:

Adjusted R-square = 23.4%, ***F*** = 4.84, p = 0.00

Table 11c: Ordinary Least Squares (OLS) regression model for the impact pattern of antipsychotic use on total healthcare cost among schizophrenia patients (second stage sample selection models): Polytherapy vs. adherent therapy

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Demographic characteristics				
Age (in years)	0.010	0.005	2.007	0.046
Males (ref: females)	-0.002	0.000	-4.055	0.000
Whites (ref: non-whites)	0.502	0.181	2.778	0.006
Metro (ref: non-metro)	0.002	0.136	0.017	0.987
Prescribing physician type				
Psychiatric prescriber	0.000	0.000	-1.406	0.161
Schizophrenia subtype (ref: only schizophrenia)				
Schizoaffective disorder	0.049	0.148	0.330	0.742
Both schizoaffective disorder and schizophrenia	-0.458	0.171	-2.687	0.008
Charlson Comorbidity Index	0.117	0.047	2.513	0.013
Pre-index co-morbidities				
Alcohol and substance abuse	0.440	0.155	2.842	0.005
Bipolar disorder	0.272	0.195	1.396	0.164
Major depression	0.133	0.159	0.838	0.403
Other mental comorbidities	0.171	0.140	1.222	0.223
Pre-index healthcare utilization and cost				
Pre-index total health related cost	0.107	0.022	4.861	0.000
Pre-index total health related ER visits	-0.125	0.120	-1.040	0.299
Pre-index total health related hospitalizations	-0.041	0.180	-0.228	0.820
Pre-index total health related physician visits	0.012	0.009	1.293	0.197

Table 11c: Ordinary Least Squares (OLS) regression model: Polytherapy vs. adherent therapy (contd.)

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Year of index prescription (ref: 1999)				
• 2000	0.000	0.157	0.001	0.999
• 2001	-0.281	0.162	-1.734	0.084
Pre-index period psychiatric medication use (days of supply)				
Mood stabilizers	0.211	0.000	3.487	0.001
Antipsychotics	-0.001	0.001	-1.457	0.146
Antidepressants	0.073	0.127	0.572	0.568
Benzodiazepines	0.075	0.120	0.627	0.531
Index prescription (ref: quetiapine)				
Risperidone	0.133	0.000	1.338	0.182
Olanzapine	0.078	0.000	0.989	0.324
Typicals	0.026	0.000	2.935	0.004
Polytherapy (ref: Adherent)	0.252	0.483	0.523	0.015
Inverse Mills Ratio	0.466	0.285	1.633	0.104

Model fit statistics:

Adjusted R-square = 28.6%, $F = 5.87$, $p = 0.00$

Table 12a: Ordinary Least Squares (OLS) regression model for the impact pattern of antipsychotic use on mental healthcare cost among schizophrenia patients (second stage sample selection models): Interrupted vs. adherent therapy

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Demographic characteristics				
Age (in years)	0.002	0.004	0.498	0.619
Males (ref: females)	0.002	0.000	3.337	0.001
Whites (ref: non-whites)	0.092	0.121	0.762	0.446
Metro (ref: non-metro)	-0.141	0.100	-1.400	0.162
Prescribing physician type				
Psychiatric prescriber	0.000	0.000	1.655	0.098
Schizophrenia subtype (ref: only schizophrenia)				
Schizoaffective disorder	0.094	0.106	0.889	0.374
Both schizoaffective disorder and schizophrenia	-0.423	0.122	-3.464	0.001
Charlson Comorbidity Index	0.053	0.045	1.184	0.236
Pre-index co-morbidities				
Alcohol and substance abuse	0.369	0.132	2.808	0.005
Bipolar disorder	0.112	0.149	0.754	0.451
Major depression	0.118	0.122	0.962	0.336
Other mental comorbidities	0.013	0.099	0.132	0.895
Pre-index healthcare utilization and cost				
Pre-index mental-health related cost	0.192	0.093	2.069	0.039
Pre-index mental-health related ER visits	-0.032	0.129	-0.244	0.807
Pre-index mental-health related hospitalizations	0.306	0.103	2.960	0.003
Pre-index mental-health related physician visits	0.379	0.139	2.726	0.006

Table 12a: Ordinary Least Squares (OLS) regression model: Interrupted vs. adherent therapy (contd.)

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Year of index prescription (ref: 1999)				
• 2000	-0.021	0.126	-0.163	0.870
• 2001	-0.334	0.133	-2.520	0.012
Pre-index period psychiatric medication use (days of supply)				
Mood stabilizers	0.051	0.000	2.472	0.014
Antipsychotics	0.001	0.002	0.450	0.653
Antidepressants	0.419	0.227	1.848	0.065
Benzodiazepines	-0.582	0.529	-1.100	0.271
Index prescription (ref: quetiapine)				
Risperidone	0.735	0.000	0.709	0.478
Olanzapine	0.024	0.000	2.985	0.303
Typicals	-0.033	0.995	-3.344	0.001
Interrupted (ref: Adherent)	0.034	0.015	2.318	0.020
Inverse Mills Ratio	0.038	0.322	0.118	0.906

Model fit statistics:

Adjusted R-square = 26.79%, ***F*** = 11.26, ***p*** = 0.00

Table 12b: Ordinary Least Squares (OLS) regression model for the impact pattern of antipsychotic use on mental healthcare cost among schizophrenia patients (second stage sample selection models): Switch vs. adherent therapy

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Demographic characteristics				
Age (in years)	0.014	0.004	3.167	0.002
Males (ref: females)	0.001	0.000	1.591	0.113
Whites (ref: non-whites)	0.373	0.217	1.719	0.087
Metro (ref: non-metro)	0.008	0.140	0.056	0.955
Prescribing physician type				
Psychiatric prescriber	0.000	0.000	-1.075	0.283
Schizophrenia subtype (ref: only schizophrenia)				
Schizoaffective disorder	0.169	0.147	1.149	0.252
Both schizoaffective disorder and schizophrenia	-0.166	0.136	-1.218	0.224
Charlson Comorbidity Index	-0.019	0.049	-0.391	0.696
Pre-index co-morbidities				
Alcohol and substance abuse	0.274	0.151	1.810	0.071
Bipolar disorder	0.130	0.161	0.809	0.419
Major depression	-0.237	0.144	-1.648	0.100
Other mental comorbidities	0.033	0.125	0.263	0.793
Pre-index healthcare utilization and cost				
Pre-index mental-health related cost	0.042	0.017	2.495	0.013
Pre-index mental-health related ER visits	-0.243	0.153	-1.592	0.113
Pre-index mental-health related hospitalizations	0.054	0.124	0.431	0.667
Pre-index mental-health related physician visits	0.433	0.065	6.680	0.000

Table 12b: Ordinary Least Squares (OLS) regression model: Switch vs. adherent therapy (contd.)

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Year of index prescription (ref: 1999)				
• 2000	0.204	0.154	1.327	0.186
• 2001	-0.122	0.131	-0.925	0.356
Pre-index period psychiatric medication use (days of supply)				
Mood stabilizers	0.001	0.000	2.532	0.012
Antipsychotics	-0.001	0.002	-0.557	0.578
Antidepressants	0.357	0.296	1.205	0.229
Benzodiazepines	-0.014	0.109	-0.130	0.896
Index prescription (ref: quetiapine)				
Risperidone	0.020	0.000	1.382	0.168
Olanzapine	0.054	0.000	1.440	0.151
Typicals	-0.020	0.000	-3.105	0.002
Switch (ref: Adherent)	0.432	0.364	1.188	0.236
Inverse Mills Ratio	-0.181	0.225	-0.804	0.422

Model fit statistics:

Adjusted R-square = 23.3%, F = 4.65, p = 0.00

Table 12c: Ordinary Least Squares (OLS) regression model for the impact pattern of antipsychotic use on mental healthcare cost among schizophrenia patients (second stage sample selection models): Polytherapy vs. adherent therapy

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Demographic characteristics				
Age (in years)	0.012	0.005	2.495	0.013
Males (ref: females)	-0.001	0.001	-0.592	0.554
Whites (ref: non-whites)	0.361	0.203	1.775	0.070
Metro (ref: non-metro)	-0.029	0.133	-0.216	0.829
Prescribing physician type				
Psychiatric prescriber	0.000	0.000	-1.498	0.135
Schizophrenia subtype (ref: only schizophrenia)				
Schizoaffective disorder	0.120	0.146	0.826	0.409
Both schizoaffective disorder and schizophrenia	-0.554	0.164	-3.369	0.000
Charlson Comorbidity Index	-0.020	0.057	-0.357	0.721
Pre-index co-morbidities				
Alcohol and substance abuse	0.471	0.166	2.830	0.005
Bipolar disorder	0.381	0.199	1.916	0.056
Major depression	0.028	0.172	0.162	0.871
Other mental comorbidities	0.151	0.144	1.047	0.295
Pre-index healthcare utilization and cost				
Pre-index mental-health related cost	0.058	0.017	3.339	0.001
Pre-index mental-health related ER visits	0.058	0.152	0.381	0.703
Pre-index mental-health related hospitalizations	-0.137	0.129	-1.059	0.290
Pre-index mental-health related physician visits	0.058	0.518	0.112	0.911

Table 12c: Ordinary Least Squares (OLS) regression model: Polytherapy vs. adherent therapy (contd.)

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Year of index prescription (ref: 1999)				
• 2000	0.114	0.164	0.695	0.487
• 2001	-0.180	0.149	-1.211	0.220
Pre-index period psychiatric medication use (days of supply)				
Mood stabilizers	0.021	0.000	1.787	0.070
Antipsychotics	-0.001	0.001	-1.173	0.241
Antidepressants	0.104	0.132	0.787	0.431
Benzodiazepines	-0.071	0.123	-0.572	0.567
Index prescription (ref: quetiapine)				
Risperidone	0.030	0.000	1.452	0.147
Olanzapine	0.034	0.000	1.683	0.093
Typicals	-0.095	0.000	-3.013	0.002
Polytherapy (ref: Adherent)	0.128	0.045	2.833	0.005
Inverse Mills Ratio	0.349	0.306	1.139	0.256

Model fit statistics:

Adjusted R-square = 28.8%, $F = 5.57$, $p = 0.00$

Table 13: Total and mental healthcare costs associated with the different antipsychotic utilization patterns among bipolar disorder patients

	Continuous N = 166	*Interrupted N = 484*	*Switch N =111*	*Polytherapy N = 64*
Total Healthcare Cost				
Mean (±std)				
Pre-index	$12,220 (±$26,609)	$10,521 (±$16,613)	$12,630 (±$20,699)	$10,664 (±$9,695)
Post-index	$18,383 [P] (±$30,283)	$20,486 [C] (±$21,513)	$20,104 [C] (±$23,116)	$26,972 [C] (±$32,885)
Mental Healthcare Cost				
Mean (±std)				
Pre-index	$7,389 [I] (±$21,824)	$6,168 [C] (±$9,761)	$7,652 (±$10,565)	$6,243 (±$7,247)
Post-index	$11,134 [I P] (±$21,901)	$17,890 [C] (±$18,330)	$12,758 (±$15,133)	$16,470 [C] (±$15,258)

[I] Significant difference between continuous (c) and interrupted cohorts at $p<0.05$
[S] Significant difference between continuous (c) and switch cohorts at $p<0.05$
[P] Significant difference between continuous (c) and polytherapy cohorts at $p<0.05$

Table 14a: Ordinary Least Squares (OLS) regression model for the impact pattern of antipsychotic use on total healthcare cost among bipolar disorder patients (second stage sample selection models): Interrupted vs. adherent therapy

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Age (in years)	0.006	0.004	1.575	0.115
18 years or above (ref: less than 18 years)	0.398	0.140	1.135	0.344
Males (ref: females)	0.512	0.000	0.015	0.988
Whites (ref: non-whites)	0.253	0.121	2.090	0.037
Metro (ref: non-metro)	-0.134	0.104	-1.278	0.201
Psychiatric prescriber	0.000	0.000	1.014	0.311
Bipolar Subtype (ref: bipolar disorder I)				
Bipolar disorder II	0.130	0.111	1.165	0.244
Mixed	-0.084	0.127	-0.657	0.511
Pre-index co-morbidities				
Charlson Comorbidity Index	0.213	0.032	6.744	0.000
Alcohol and substance abuse	0.309	0.126	2.449	0.014
Bipolar disorder	0.010	0.140	0.072	0.943
Major depression	0.113	0.123	0.919	0.358
Other mental comorbidities	0.056	0.096	0.584	0.559
Pre-index mental-health related cost	0.137	0.024	5.778	0.000
Pre-index mental-health related ER visits	0.042	0.099	0.428	0.669
Pre-index mental-health related hospitalizations	0.158	0.122	1.294	0.196
Pre-index mental-health related physician visits	0.007	0.006	1.289	0.197
Year of index prescription (ref: 1999)				
• 2000	-0.001	0.126	-0.010	0.992
• 2001	-0.481	0.129	-3.712	0.000

Table 14a: Ordinary Least Squares (OLS) regression model: Interrupted vs. adherent therapy (contd.)

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Pre-index period psychiatric medication use (days of supply)				
Mood stabilizers	0.001	0.000	1.613	0.107
Antipsychotics	-0.002	0.002	-1.282	0.200
Antidepressants	0.262	0.090	2.927	0.003
Benzodiazepines	0.052	0.090	0.583	0.560
Index prescription (ref: quetiapine)				
Risperidone	-0.951	0.000	-0.919	0.358
Olanzapine	-0.997	0.000	-0.794	0.427
Typicals	0.000	0.917	-1.687	0.092
Interrupted (ref: Adherent)	0.016	0.451	2.126	0.034
Inverse Mills Ratio	-0.295	0.271	-1.088	0.276

Model fit statistics:

Adjusted R-square = 30.20%, F = 23.45, p = 0.000

Table 14b: Ordinary Least Squares (OLS) regression model for the impact pattern of antipsychotic use on total healthcare cost among bipolar disorder patients (second stage sample selection models): Switching vs. adherent therapy

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Demographic characteristics				
Age (in years)	0.011	0.005	2.251	0.025
18 years or above (ref: less than 18 years)	0.568	0.130	1.135	0.524
Males (ref: females)	0.000	0.001	-0.183	0.855
Whites (ref: non-whites)	0.423	0.218	1.942	0.053
Metro (ref: non-metro)	-0.164	0.144	-1.141	0.255
Prescribing physician type				
Psychiatric prescriber	-0.170	0.000	-0.012	0.990
Bipolar Subtype (ref: bipolar disorder I)				
Bipolar disorder II	-0.049	0.150	-0.324	0.746
Mixed	-0.167	0.158	-1.057	0.292
Pre-index co-morbidities				
Charlson Comorbidity Index	0.125	0.041	3.070	0.002
Alcohol and substance abuse	0.185	0.161	1.151	0.251
Bipolar disorder	0.112	0.189	0.593	0.553
Major depression	-0.228	0.155	-1.475	0.141
Other mental comorbidities	0.173	0.128	1.353	0.177
Pre-index mental-health related cost	0.123	0.031	3.963	0.000
Pre-index mental-health related ER visits	-0.105	0.129	-0.811	0.418
Pre-index mental-health related hospitalizations	-0.178	0.156	-1.144	0.254
Pre-index mental-health related physician visits	0.007	0.007	0.958	0.339
Year of index prescription (ref: 1999)				
• 2000	0.197	0.160	1.237	0.217
• 2001	-0.150	0.153	-0.978	0.329

Table 14b: Ordinary Least Squares (OLS) regression model: Switching vs. adherent therapy (contd.)

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Pre-index period psychiatric medication use (days of supply)				
Mood stabilizers	0.001	0.000	2.477	0.014
Antipsychotics	-0.001	0.001	-0.819	0.414
Antidepressants	0.097	0.118	0.821	0.412
Benzodiazepines	0.016	0.116	0.140	0.889
Index prescription (ref: quetiapine)				
Risperidone	0.631	0.000	0.532	0.596
Olanzapine	0.830	0.000	0.629	0.530
Typicals	0.030	0.000	2.451	0.015
Switch (ref: Adherent)	0.163	0.373	2.517	0.030
Inverse Mills Ratio	-0.293	0.235	-1.245	0.214

Model fit statistics:

Adjusted R-square = 23.45%, F = 4.13, p = 0.000

Table 14c: Ordinary Least Squares (OLS) regression model for the impact pattern of antipsychotic use on total healthcare cost among bipolar disorder patients (second stage sample selection models): Polytherapy vs. adherent therapy

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Demographic characteristics				
Age (in years)	0.011	0.006	1.905	0.058
18 years or above (ref: less than 18 years)	0.244	0.135	1.156	0.444
Males (ref: females)	-0.001	0.001	-1.999	0.047
Whites (ref: non-whites)	0.604	0.223	2.712	0.007
Metro (ref: non-metro)	0.062	0.162	0.380	0.705
Prescribing physician type				
Psychiatric prescriber	0.020	0.010	-1.193	0.234
Bipolar Subtype (ref: bipolar disorder I)				
Bipolar disorder II	0.087	0.167	0.519	0.605
Mixed	-0.344	0.192	-1.798	0.074
Pre-index co-morbidities				
Charlson Comorbidity Index	0.115	0.057	2.018	0.045
Alcohol and substance abuse	0.376	0.166	2.263	0.025
Bipolar disorder	0.154	0.190	0.810	0.419
Major depression	0.066	0.172	0.383	0.702
Other mental comorbidities	0.202	0.153	1.318	0.189
Pre-index mental-health related cost	0.108	0.025	4.366	0.000
Pre-index mental-health related ER visits	-0.118	0.137	-0.859	0.391
Pre-index mental-health related hospitalizations	-0.056	0.213	-0.263	0.793
Pre-index mental-health related physician visits	0.016	0.011	1.480	0.140
Year of index prescription (ref: 1999)				
• 2000	0.027	0.180	0.152	0.879

Table 14c: Ordinary Least Squares (OLS) regression model: Polytherapy vs. adherent therapy (contd.)

	Beta	*S.E*	*t-statistic*	*Significance (p)*
• 2001	-0.345	0.184	-1.876	0.062
Pre-index period psychiatric medication use (days of supply)				
Mood stabilizers	0.021	0.000	2.305	0.022
Antipsychotics	-0.001	0.001	-1.350	0.179
Antidepressants	0.111	0.148	0.752	0.453
Benzodiazepines	-0.055	0.138	-0.399	0.690
Index prescription (ref: quetiapine)				
Risperidone	0.002	0.020	1.402	0.162
Olanzapine	0.002	0.001	1.057	0.292
Typicals	0.036	0.010	2.452	0.021
Polytherapy (ref: Adherent)	0.320	0.504	2.154	0.007
Inverse Mills Ratio	-0.298	0.309	-0.963	0.337

Model fit statistics:

Adjusted R-square = 25.7%, $F = 4.02$, $p = 0.000$

Table 15a: Ordinary Least Squares (OLS) regression model for the impact pattern of antipsychotic use on mental healthcare cost among bipolar disorder patients (second stage sample selection models): Interrupted vs. adherent therapy

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Demographic characteristics				
Age (in years)	0.002	0.004	0.418	0.676
18 years or above (ref: less than 18 years)	0.543	0.342	1.360	0.561
Males (ref: females)	0.002	0.001	3.898	0.000
Whites (ref: non-whites)	0.163	0.139	1.174	0.241
Metro (ref: non-metro)	-0.073	0.115	-0.638	0.524
Psychiatric prescriber	0.000	0.000	2.007	0.045
Bipolar Subtype (ref: bipolar disorder I)				
Bipolar disorder II	0.047	0.124	0.378	0.706
Mixed	-0.408	0.136	-2.999	0.003
Pre-index co-morbidities				
Charlson Comorbidity Index	0.066	0.047	1.391	0.164
Alcohol and substance abuse	0.381	0.156	2.441	0.015
Bipolar disorder	0.059	0.158	0.371	0.711
Major depression	0.198	0.129	1.527	0.127
Other mental comorbidities	0.016	0.107	0.153	0.879
Pre-index mental-health related cost	0.030	0.015	1.965	0.050
Pre-index mental-health related ER visits	-0.020	0.141	-0.141	0.888
Pre-index mental-health related hospitalizations	0.319	0.111	2.884	0.004
Pre-index mental-health related physician visits	0.364	0.151	2.414	0.016
Year of index prescription (ref: 1999)				
• 2000	-0.059	0.134	-0.438	0.661
• 2001	-0.420	0.143	-2.947	0.003

Table 15a: Ordinary Least Squares (OLS) regression model: Interrupted vs. adherent therapy (contd.)

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Pre-index period psychiatric medication use (days of supply)				
Mood stabilizers	0.051	0.000	2.217	0.027
Antipsychotics	0.001	0.002	0.557	0.578
Antidepressants	0.245	0.250	0.981	0.327
Benzodiazepines	0.213	0.103	2.075	0.038
Index prescription (ref: quetiapine)				
Risperidone	0.000	0.000	1.233	0.218
Olanzapine	0.001	0.000	1.139	0.072
Typicals	0.041	0.000	3.317	0.001
Interrupted (ref: Adherent)	0.069	0.503	2.330	0.015
Inverse Mills Ratio	-0.103	0.305	-0.336	0.737

Model fit statistics:

Adjusted R-square = 28.18%, F = 10.43, p = 0.000

Table 15b: Ordinary Least Squares (OLS) regression model for the impact pattern of antipsychotic use on mental healthcare cost among bipolar disorder patients (second stage sample selection models): Switch vs. adherent therapy

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Demographic characteristics				
Age (in years)	0.012	0.005	2.514	0.013
18 years or above (ref: less than 18 years)	0.348	0.341	1.432	0.356
Males (ref: females)	0.001	0.000	1.674	0.095
Whites (ref: non-whites)	0.435	0.249	1.750	0.081
Metro (ref: non-metro)	-0.039	0.142	-0.272	0.786
Psychiatric prescriber	0.000	0.000	-1.058	0.291
Bipolar Subtype (ref: bipolar disorder I)				
Bipolar disorder II	0.075	0.158	0.474	0.636
Mixed	-0.205	0.149	-1.375	0.170
Pre-index co-morbidities				
Charlson Comorbidity Index	-0.018	0.049	-0.358	0.720
Alcohol and substance abuse	0.201	0.182	1.101	0.272
Bipolar disorder	0.079	0.161	0.492	0.623
Major depression	-0.229	0.136	-1.684	0.093
Other mental comorbidities	0.009	0.128	0.070	0.944
Pre-index mental-health related cost	0.041	0.016	2.502	0.013
Pre-index mental-health related ER visits	-0.259	0.160	-1.617	0.107
Pre-index mental-health related hospitalizations	0.068	0.127	0.535	0.593
Pre-index mental-health related physician visits	0.519	0.070	7.457	0.000
Year of index prescription (ref: 1999)				
• 2000	0.162	0.162	0.997	0.320
• 2001	-0.209	0.130	-1.603	0.110

Table 15b: Ordinary Least Squares (OLS) regression model: Switch vs. adherent therapy (contd.)

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Pre-index period psychiatric medication use (days of supply)				
Mood stabilizers	0.001	0.000	2.253	0.025
Antipsychotics	-0.002	0.002	-0.889	0.375
Antidepressants	0.208	0.334	0.622	0.535
Benzodiazepines	-0.090	0.116	-0.769	0.443
Index prescription (ref: quetiapine)				
Risperidone	0.040	0.000	1.172	0.242
Olanzapine	0.021	0.000	1.344	0.180
Typicals	0.040	0.000	2.753	0.006
Switch (ref: Adherent)	0.517	0.402	1.286	0.200
Inverse Mills Ratio	-0.322	0.242	-1.332	0.184

Model fit statistics:

Adjusted R-square = 25.90%, F = 4.57, p = 0.000

Table 15c: Ordinary Least Squares (OLS) regression model for the impact pattern of antipsychotic use on mental healthcare cost among bipolar disorder patients (second stage sample selection models): Polytherapy vs. adherent therapy

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Demographic characteristics				
Age (in years)	0.012	0.005	2.219	0.028
18 years or above (ref: less than 18 years)	0.345	0.432	2.265	0.044
Males (ref: females)	0.002	0.001	2.760	0.006
Whites (ref: non-whites)	0.445	0.282	1.580	0.116
Metro (ref: non-metro)	0.079	0.156	0.507	0.613
Psychiatric prescriber	0.000	0.000	-1.667	0.097
Bipolar Subtype (ref: bipolar disorder I)				
Bipolar disorder II	0.163	0.161	1.010	0.314
Mixed	-0.434	0.174	-2.497	0.013
Pre-index co-morbidities				
Charlson Comorbidity Index	0.038	0.051	0.739	0.461
Alcohol and substance abuse	0.432	0.186	2.316	0.022
Bipolar disorder	0.290	0.173	1.669	0.097
Major depression	-0.023	0.170	-0.133	0.895
Other mental comorbidities	0.137	0.157	0.872	0.384
Pre-index mental-health related cost	0.044	0.016	2.686	0.008
Pre-index mental-health related ER visits	0.110	0.166	0.661	0.510
Pre-index mental-health related hospitalizations	-0.073	0.138	-0.528	0.598
Pre-index mental-health related physician visits	0.116	0.043	2.689	0.008
Year of index prescription (ref: 1999)				
• 2000	0.108	0.184	0.586	0.558
• 2001	-0.285	0.154	-1.848	0.066

Table 15c: Ordinary Least Squares (OLS) regression model: Polytherapy vs. adherent therapy (contd.)

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Pre-index period psychiatric medication use (days of supply)				
Mood stabilizers	0.004	0.020	0.732	0.465
Antipsychotics	-0.002	0.001	-1.300	0.195
Antidepressants	0.059	0.157	0.377	0.707
Benzodiazepines	-0.127	0.146	-0.871	0.385
Index prescription (ref: quetiapine)				
Risperidone	0.031	0.023	1.688	0.093
Olanzapine	0.050	0.017	2.029	0.084
Typicals	0.032	0.000	2.293	0.023
Polytherapy (ref: Adherent)	0.153	0.503	2.304	0.002
Inverse Mills Ratio	-0.168	0.298	-0.561	0.575

Model fit statistics:

Adjusted R-square = 26.91%, F = 4.22, p = 0.000

PHASE 2 - Results

Schizophrenia patients initiated on multiple antipsychotics (n = 37) were excluded from the analysis in the phase 2. This resulted in sample size of 999 schizophrenia patients. Schizophrenia patients initiated on study antipsychotics were divided into the following study cohorts based on the first prescription of the index antipsychotic:

- Patients initiated on olanzapine: 346 (34.63%)
- Patients initiated on risperidone: 201 (20.12%)
- Patients initiated on quetiapine: 149 (14.91%)
- Patients initiated on typical antipsychotics: 303 (30.33%)

There were 7 bipolar disorder patients who were initiated on multiple antipsychotics. After excluding these patients, the resulting sample size of bipolar disorder patients was 825. Bipolar disorder patients initiated on study antipsychotics were divided into the following study cohorts based on the first prescription of the index antipsychotic:

- Patients initiated on olanzapine: 283 (34.30%)
- Patients initiated on risperidone: 231 (28.00%)
- Patients initiated on quetiapine: 106 (12.85%)
- Patients initiated on typical antipsychotics: 205 (24.85%)

Demographic characteristics of patients initiated on antipsychotics

Schizophrenia

Table 16 provides information on demographic characteristics and co-morbidities among schizophrenia patients initiated on antipsychotics. Wilcoxon rank sum test was

used to compare continuous variables like age and Charlson comorbidity index. Chi-square analysis was used to compare the categorical variables.

Patients initiated on quetiapine did not differ significantly from patients initiated on other antipsychotics based on age, gender and race. Significantly higher proportion of patients initiated on quetiapine (79.2%) were from non-metro areas compared to patients initiated on olanzapine (66.8%) and typical antipsychotics (67.7%). In addition, significantly higher proportion of patients initiated on quetiapine (68.3%) had a psychiatric prescriber for the index prescription compared to patients initiated on olanzapine (55.7%), risperidone (55.3%), and typical antipsychotic (42.5%).

Significantly higher proportion of patients initiated on quetiapine showed 'dual diagnosis' (claims associated with both diagnosis in the 12-months pre-index period) of schizophrenia and schizoaffective disorder (57.7%) as compared to initiated olanzapine (39.6%), risperidone (37.3%) and typical antipsychotics (31.3%). There were significantly a higher proportion of patients with alcohol and substance abuse in the quetiapine cohort (24.8%) as compared to the risperidone (14.9%) cohort. There was significantly greater proportion of patients with mild to moderate depression among the quetiapine cohort (13.4%) as compared to the typical antipsychotic cohort (7.6%).

Bipolar Disorder

Table 17 provides information on demographic characteristics and co-morbidities among schizophrenia patients initiated on antipsychotics. Significantly greater proportions of patients initiated on quetiapine (90.6%) were 18 years or older compared to patients initiated on risperidone (63.2%). Significantly higher proportion of patients

initiated on quetiapine (84.0%) were from non-metro areas compared to patients initiated on olanzapine (70.6%), risperidone (71.8%) and typical antipsychotics (73.6%). There were no significant differences between the patients initiated on quetiapine and other antipsychotics based on gender and race. Significantly higher proportion of patients initiated on quetiapine (65.2%) had a psychiatric prescriber for index prescription as compared to patients initiated on typical antipsychotic (34.0%).

A significantly higher proportion of patients initiated on quetiapine showed a mixed diagnosis (68.9%) as compared to patients initiated olanzapine (48.1%), risperidone (32.5%) or typical antipsychotics (46.3%). There was significantly a higher proportion of patients with alcohol and substance abuse in the quetiapine cohort (21.6%) as compared to the risperidone (15.2%) cohort. There was significantly a lesser proportion of patients with major depression in the quetiapine cohort (13.3%) as compared to the olanzapine (35.8%), risperidone (29.4%) or typical antipsychotics (21.3%) cohorts. Also, there were significantly lesser proportion of patients with mild to moderate depression, anxiety and personality disorder in the quetiapine cohort as compared to the other antipsychotic cohorts.

Table 16: Demographic characteristics of schizophrenia patients (18 years and older) who were initiated on study antipsychotics between January 1, 1999 and December 31, 2001 (N = 999)

	Olanzapine N = 346	*Risperidone N = 201*	*Quetiapine N = 149*	*Typical N = 303*
Demographics				
Age in years (Mean/±SD)	40.0 (±11.8)	38.8 (±14.2)	41.0 (±11.5)	43.9(±11.0)
Gender				
Females	188 (54.34%)	106 (53.00%)	89 (60.54%)	166 (55.15%)
Males	158 (45.66%)	94 [Q] (47.00%)	58 (39.46%)	135 (44.85%)
Race				
Caucasians	322 (93.06%)	182 (90.55%)	137 (91.95%)	260 (85.81%)
Others	24 (6.94%)	19 (9.45%)	12 (8.05%)	43 (14.19%)
Residence				
Metro	115 [Q] (33.24%)	48 (23.88%)	31 [OT] (20.81%)	98 [Q] (32.34%)
Non-Metro	231 [Q] (66.76%)	153 (76.12%)	118 [OT] (79.19%)	205 [Q] (67.66%)
Prescriber type				
Psychiatric	167 [Q] (55.67%)	87 [Q] (55.06%)	84 [ORT] (68.29%)	94 [Q] (42.53%)
Non-Psychiatric	133 [Q] (44.33%)	71 [Q] (44.94%)	39 [ORT] (31.97%)	127 [Q] (57.47%)
Year of Index Prescription				
1999	176 [Q] (50.87%)	105 [Q] (52.24%)	54 [ORT] (36.24%)	219 [Q] (72.28%)
2000	98 (28.32%)	59 (29.35%)	50 [T] (33.56%)	55 [Q] (18.15%)
2001	72 [Q] (20.81%)	37 [Q] (18.41%)	45 [ORT] (30.20%)	29 [Q] (9.57%)
Schizophrenia	129 (37.28%)	71 (35.32%)	31 (20.81%)	150 (49.50%)

Table 16: Demographic characteristics of schizophrenia patients (18 years and older) who were initiated on study antipsychotics between January 1, 1999 and December 31, 2001 (N = 999) (contd.)

	Olanzapine N = 346	*Risperidone N = 201*	*Quetiapine N = 149*	*Typical N = 303*
Schizophrenia Subtype				
Schizoaffective Disoders	80 (23.12%)	55 (27.36%)	32 (21.48%)	58 (19.14%)
Mixed diagnosis	137 [Q] (39.60%)	75 [Q] (37.31%)	86 [ORT] (57.72%)	95 [Q] (31.35%)
Co-morbidities				
Alcohol and substance abuse	77 (22.25%)	30 [Q] (14.93%)	37 [R] (24.83%)	70 (23.10%)
Bipolar disorder	51 (14.74%)	28 (13.93%)	27 (18.12%)	36 (11.88%)
Major Depression	80 (23.12%)	33 (16.42%)	27 (18.12%)	38 (12.54%)
Mild to Moderate Depression	55 (15.90%)	29 (14.43%)	20 [T] (13.42%)	23 [Q] (7.59%)
Anxiety	72 (20.81%)	26 (12.94%)	28 (18.79%)	43 (14.19%)
Personality Disorder	40 (11.56%)	20 (9.95%)	18 (12.08%)	26 (8.58%)
Non-Schizophrenia Disorder	19 (5.49%)	7 (3.48%)	3 (2.01%)	8 (2.64%)
Other Affective Disorders	7 (2.02%)	5 (2.49%)	4 (2.68%)	2 (0.66%)
Attention deficit Disorder	8 (2.31%)	13 (6.47%)	3 (2.01%)	5 (1.65%)
Diabetes	31 (8.96%)	21 (10.45%)	15 (10.07%)	40 (13.20%)
Hyperlipedemia	24 (6.94%)	9 (4.48%)	16 (10.74%)	22 (7.26%)
Hypertension	59 (17.05%)	35 (17.41%)	35 (23.49%)	49 (16.17%)

Table 16: Demographic characteristics of schizophrenia patients (18 years and older) who were initiated on study antipsychotics between January 1, 1999 and December 31, 2001 (N = 999) (contd.)

	Olanzapine N = 346	***Risperidone N = 201***	***Quetiapine N = 149***	***Typical N = 303***
Charlson Comorbidity Index	0.4 (1.1)	0.5 (1.4)	0.5 (0.9)	0.7 (1.6)

[O] Significant difference between quetiapine and olanzapine cohorts at $p<0.05$
[R] Significant difference between quetiapine and risperidone cohorts at $p<0.05$
[T] Significant difference between quetiapine and typicals cohorts at $p<0.05$

Table 17*:* Demographic characteristics of bipolar disorder patients who were initiated on study antipsychotics between January 1, 1999 and December 31, 2001 (N = 825)

	Olanzapine N = 283	*Risperidone N = 231*	*Quetiapine N = 106*	*Typical N = 205*
Age category				
18 years or above	239 (84.5%)	146[Q] (63.2%)	96[R] (90.6%)	197 (96.1%)
Age in years (Mean±SD)	39.9 (±11.0)	41.5 (±12.7)	40.5 (±10.7)	43.0 (±11.5)
Less than 18 years	44 (15.5%)	85[Q] (36.8%)	10[R] (9.4%)	8 (3.9%)
Age in years (Mean/±SD)	12.8(±3.3)	11.1(±3.4)	14.2(±2.9)	13.1(±2.7)
Gender				
Females	156 (55.1%)	123 (53.2%)	61 (57.5%)	116 (56.6%)
Males	127 (44.8%)	107 (46.3%)	44 (41.5%)	87 (42.4%)
Race				
Caucasians	264 (93.3%)	210 (90.9%)	97 (91.5%)	181 (88.4%)
Others	19 (6.7%)	21 (9.0%)	9 (8.5%)	24 (11.7%)
Residence				
Metro	83[Q] (29.3%)	65[Q] (28.1%)	17[ORT] (16.0%)	54[Q] (26.3%)
Non-Metro	200[Q] (70.6%)	166[Q] (71.8%)	89[ORT] (84.0%)	151[Q] (73.6%)
Prescriber type				
Psychiatric	135 (60.0%)	103 (59.5%)	60[T] (65.2%)	54[Q] (34.0%)
Non-Psychiatric	90 (40.0%)	70 (40.5%)	32[T] (34.9%)	105[Q] (66.0%)

Table 17: Demographic characteristics of bipolar disorder patients who were initiated on study antipsychotics between January 1, 1999 and December 31, 2001 (N = 825) (contd.)

	Olanzapine N = 283	*Risperidone N = 231*	*Quetiapine N = 106*	*Typical N = 205*
Year of Index Prescription				
1999	137 [Q] (48.4%)	124 [Q] (53.7%)	36 [ORT] (34.0%)	140 [Q] (68.3%)
2000	83 [Q] (29.3%)	65 [Q] (28.1%)	36 (34.0%)	45 [Q] (21.9%)
2001	63 [Q] (22.3%)	42 [Q] (18.2%)	34 [ORT] (32.1%)	20 [Q] (9.8%)
Bipolar Disorder Subtype				
Bipolar 1	91 [Q] (32.2%)	89 [Q] (38.5%)	13 [ORT] (12.3%)	79 [Q] (38.5%)
Bipolar 2	56 (19.8%)	67 (29.0%)	20 (18.9%)	31 (15.1%)
Mixed	136 [Q] (48.1%)	75 [Q] (32.5%)	73 [ORT] (68.9%)	95 [Q] (46.3%)
Co-morbidities				
Alcohol and substance abuse	27 (25.5%)	35 [Q] (15.2%)	61 [R] (21.6%)	42 (20.5%)
Schizophrenia	51 (14.74%)	28 (13.93%)	27 (18.12%)	36 (11.88%)
Major Depression	67 [Q] (35.8%)	55 [Q] (29.4%)	25 [ORT] (13.3%)	40 (21.3%)
Mild to Moderate Depression	62 [Q] (36.2%)	51 [Q] (29.8%)	21 [ORT] (12.2%)	37 (21.6%)
Anxiety	71 [Q] (39.2%)	46 [Q] (25.4%)	13 [ORT] (7.1%)	51 [Q] (28.1%)
Personality Disorder	43 [Q] (34.9%)	32 [Q] (26.0%)	15 [ORT] (12.2%)	33 [Q] (26.8%)
Non-Schizophrenia Disorder	8 (24.2%)	8 (24.2%)	6 (18.1%)	11 (33.3%)
Other Affective Disorders	9 (31.0%)	8 (27.5%)	3 (10.3%)	9 (31.0%)

Table 17: Demographic characteristics of bipolar disorder patients who were initiated on study antipsychotics between January 1, 1999 and December 31, 2001 (N = 825) (contd.)

	Olanzapine N = 283	***Risperidone N = 231***	***Quetiapine N = 106***	***Typical N = 205***
Attention deficit Disorder	39 (34.2%)	34 (29.8%)	17 (14.9%)	24 (21.0%)
Diabetes	25 (8.8%)	24 (10.4%)	9 (8.5%)	28 (13.6%)
Hyperlipidemia	17 (6.0%)	14 (6.0%)	9 (8.5%)	19 (9.3%)
Hypertension	47 (16.6%)	42 (18.2%)	24 (22.6%)	40 (19.5%)
Charlson Comorbidity Index	0.52 (1.1)	0.54 (1.5)	0.59 (0.9)	0.9 (1.9)

[O] Significant difference between quetiapine and olanzapine cohorts at $p<0.05$
[R] Significant difference between quetiapine and risperidone cohorts at $p<0.05$
[T] Significant difference between quetiapine and typicals cohorts at $p<0.05$

Results for research objective 8

For schizophrenia and bipolar disorder patients, to compare the impact of quetiapine with risperidone, olanzapine, and typical antipsychotics on total and mental healthcare costs

Schizophrenia

Results for univariate analysis comparing differences in total and mental costs between each of the index antipsychotics are reported in table 18. There were no significant differences in total healthcare costs of quetiapine cohort compared to other index antipsychotic cohorts. Total post-index mental health-related costs for quetiapine ($15,318 ± $20,343) were significantly lesser compared to olanzapine ($17,919 ± $25,660) and typical cohorts ($18,342 ± $26,730).

It is possible that various factors such as patient demographics, comorbidities, disease severity, or sample selection bias could have confounded the results of univariate analysis. Therefore, a multivariate analysis controlling for various confounders was conducted to determine the impact of index antipsychotic use on total healthcare costs.

The first step involved developing a multinomial logistic regression model predicting treatment selection. This model allowed for calculation of Inverse Mills Ratio (IMR) to adjust for sample selection bias in the second step regression models. Individual contrasts were carried out to obtain IMR for quetiapine vs. olanzapine, quetiapine vs. risperidone, and quetiapine vs. typicals. The results of this multinomial logistic regression model are presented in table 19.

In the second step of the analysis, three semi-log OLS regressions were developed to compare costs associated with olanzapine, risperidone and typical with quetiapine

therapy. IMRs calculated from the first stage regression models were added as a covariate in the second stage regression models to adjust and test for sample selection bias. The second stage regression models are presented in tables 20a to 21c. Variables were dropped from the model if data was sparse for a variable. Certain variables such as pre-index ECT, pre-index clozapine use, pre-index suicides, and pre-index arrhythmia were dropped due to sparse data. Variables were also dropped from the model if they were highly collinear with other variables. Variance inflation factors were less than 3. Wherever needed, White's correction for heteroskedasity was used.

Table 18: Healthcare costs comparison among schizophrenia patients: (Quetiapine versus other antipsychotics)

	Olanzapine N = 346	*Risperidone N = 201*	*Quetiapine N = 149*	*Typical N = 303*
	Total health-related Costs			
Total Mean (±std)				
Pre-index	$11,644 (±$18,638)	$14,486 (±$31,387)	$10,433 (±$11,451)	$9,908 (±$12,021)
Post-index	$17,919 (±$25,660)	$19,488 (±$31,858)	$15,318 (±$20,343)	$18,342 (±$26,730)
	Mental health-related Costs			
Total Mental Health-related Mean (±std)				
Pre-index	$7,342 (±$10,432)	$8,946 (±$24,339)	$6,965 (±$9,881)	$5,630 (±$8,429)
Post-index	$12,281[Q] (±$20,602)	$11,147 (±$16,709)	$9,638[TO] (±$12,893)	$10,265[Q] (±$18,717)
Inpatient Mean (±std)				
Pre-index	$4,476 (±$8,465)	$4,832 (±$22,435)	$4,478[T] (±$7,980)	$2,684[Q] (±$6,221)
Post-index	$4,813 (±$11,309)	$4,274 (±$11,285)	$4,865 [T] (±$11,332)	$5,418 [Q] (±$15,787)
Outpatient Mean (±std)				
Pre-index	$2,343 (±$4,877)	$3,583 (±$9,096)	$2,021 (±$4,795)	$2,469 (±$4,718)
Post-index	$4,136[Q] (±$16,349)	$4247 (±$10,209)	$2,071[O] (±$3,479)	$3,218 (±$5,652)
ER Mean (±std)				
Pre-index	$143 ($501)	$114 ($399)	$98[T] ($241)	$54[Q] ($224)
Post-index	$259 ($1,396)	$152 [Q] ($415)	$231 [R] ($539)	$207 ($546)

Table 18: Healthcare costs comparison among schizophrenia patients: (Quetiapine versus other antipsychotics) (contd.)

	Olanzapine N = 346	*Risperidone N = 201*	*Quetiapine N = 149*	*Typical N = 303*
Prescription Mean (±std)				
Pre-index	$379 ($658)	$416 ($698)	$367 ($590)	$421 ($800)
Post-index	$3,072[Q] ($2,285)	$2,473 ($2,071)	$2,470[OT] ($1,789)	$1,421[Q] ($1,898)

[O] Significant difference between quetiapine and olanzapine cohorts at $p<0.05$
[R] Significant difference between quetiapine and risperidone cohorts at $p<0.05$
[T] Significant difference between quetiapine and typicals cohorts at $p<0.05$

Table 19: Multinomial logistic regression model determining predictors of index antipsychotic use among schizophrenia patients (first-stage sample selection model)

	Olanzapine vs. Quetiapine		*Risperidone vs. Quetiapine*		*Typicals vs. Quetiapine*	
	Coefficient	***t-ratio***	***Coefficient***	***t-ratio***	***Coefficient***	***t-ratio***
Demographic characteristics						
Age (in years)	0.004	0.418	-0.004	-0.324	0.033	3.161*
Males (ref: females)	0.088	0.581	0.002	1.204	0.001	0.877
Whites (ref: non-whites)	0.230	0.592	-0.069	-0.168	-0.413	-1.069
Metro (ref: non-metro)	0.211	0.710	-0.435	-1.335	-0.044	-0.141
Prescribing physician type						
Psychiatric prescriber	-0.001*	-3.805*	-0.001	-3.908*	-0.001	-3.95*
Schizophrenia subtype (ref: only schizophrenia)						
Schizoaffective disorder	-0.402	-1.303	-0.248	-0.746	-0.860	-2.619*
Both schizoaffective disorder and schizophrenia	-0.709	-2.289*	-1.105	-3.284*	-1.152	-3.532*
Pre-index co-morbidities						
Diabetes	0.123	0.321	0.418	1.001	0.627	1.604
Hyperlipidemia	-0.395	-1.021	-0.906	-1.879	-0.105	-0.256
Hypertension	-0.242	-0.837	0.078	0.240	-0.133	-0.420
Alcohol and substance abuse	-0.402	-1.571	-0.868	-2.859*	-0.068	-0.250
Bipolar disorder	-0.277	-0.942	-0.347	-1.033	-0.054	-0.166
Major depression	0.307	1.097	-0.064	-0.199	0.012	0.037
Anxiety disorder	-0.081	-0.287	-0.525	-1.560	-0.090	-0.286
Personality disorder	0.024	0.070	-0.257	-0.670	-0.331	-0.887
Non-specified psychosis	0.931	1.384	0.925	1.227	0.312	0.418
Other affective psychosis	-0.477	-0.685	-0.122	-0.161	-0.866	-0.936

Table 19: Multinomial logistic regression model determining predictors of index antipsychotic use among schizophrenia patients (first-stage sample selection model) (contd.)

	Olanzapine vs. Quetiapine		*Risperidone vs. Quetiapine*		*Typicals vs. Quetiapine*	
	Coefficient	***t-ratio***	***Coefficient***	***t-ratio***	***Coefficient***	***t-ratio***
Attention deficit disorders	-0.041	-0.055	1.082	1.504	0.653	0.803
Mild to moderate depression	0.110	0.336	0.415	1.142	-0.217	-0.575
Pre-index healthcare utilization and cost						
Number of pre-index mental-health related ER visits	0.000	1.196	0.000	1.111	0.184	0.045
Number of pre-index mental-health related hospitalizations	0.064	0.574	-0.025	-0.199	-0.176	-1.287
Number of psychotherapy visits	0.014	0.651	-0.019	-0.558	-0.001	-0.050
Number of medication management visits	-0.064	-2.024*	-0.047	-1.285	-0.095	-2.509*
Year of index prescription (ref: 1999)						
• 2000	-0.102	-0.371	0.364	1.169	-0.524	-1.760
• 2001	-0.312	-1.051	0.054	0.158	-1.130	-3.326*
Pre-index period psychiatric medication use (days of supply)						
Mood stabilizers	0.001	0.710	0.000	0.125	-0.002	-1.991
Anticholinergics	-0.005	-1.131	-0.021	-1.547	-0.010	-1.214
Anxiolytics/hypnotics/ sedatives	0.001	0.755	0.002	1.015	0.001	0.802
Antipsychotics	-0.001	-0.101	0.018	3.077*	0.0164*	2.937*
Antidepressants	0.000	0.268	0.000	-0.542	-0.001	-1.086
Benzodiazepines	-0.002	-2.829*	-0.002	-1.860	-0.002	-2.046*
Antiparkinsons	-0.002	-0.756	-0.006	-1.466	0.001	0.243

*significant at $p<0.05$

Model fit statistics:

Pseudo R-square = 12.43%

-2 Log Likelihood = 1128.21; χ^2 = 331.90; p= 0.00

Table 20a: Ordinary Least Squares (OLS) regression model for the impact of index antipsychotic on total healthcare cost among schizophrenia patients (second stage sample selection models): Olanzapine vs. quetiapine

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Demographic characteristics				
Age (in years)	0.005	0.004	1.386	0.166
Males (ref: females)	-0.979	0.001	-0.130	0.896
Whites (ref: non-whites)	0.089	0.161	0.552	0.582
Metro (ref: non-metro)	0.005	0.114	0.044	0.965
Prescribing physician type				
Psychiatric prescriber	0.000	0.000	2.702	0.007
Schizophrenia subtype (ref: only schizophrenia)				
Schizoaffective disorder	-0.064	0.120	-0.536	0.592
Both schizoaffective disorder and schizophrenia	-0.112	0.137	-0.817	0.414
Pre-index co-morbidities				
Charlson Comorbidity Index	0.150	0.045	3.341	0.001
Alcohol and substance abuse	0.257	0.103	2.492	0.013
Bipolar disorder	0.206	0.135	1.527	0.128
Major depression	-0.016	0.108	-0.144	0.886
Other mental comorbidities	-0.020	0.100	-0.201	0.841
Pre-index healthcare utilization and cost				
Pre-index total health related cost	0.174	0.032	5.413	0.000
Pre-index total health related ER visits	-0.121	0.128	-0.941	0.347
Pre-index total health related hospitalizations	0.006	0.108	0.051	0.960
Pre-index total health related physician visits	0.005	0.006	0.786	0.432
Year of index prescription (ref: 1999)				
• 2000	-0.093	0.117	-0.795	0.427
• 2001	-0.278	0.137	-2.034	0.043

Table 20a: Ordinary Least Squares (OLS) regression model for the impact of index antipsychotic on total healthcare cost among schizophrenia patients (second stage sample selection models): Olanzapine vs. quetiapine (contd.)

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Antipsychotics	0.003	0.002	1.739	0.083
Antidepressants	0.000	0.000	1.001	0.317
Benzodiazepines	0.179	0.104	1.717	0.087
Index prescription (ref: quetiapine)				
Olanzapine	0.499	0.442	1.129	0.259
Inverse Mills Ratio	-0.211	0.267	-0.787	0.432

Model fit statistics:

Adjusted R-square = 22.14% , **F** = 6.85 , **p** = 0.00

Table 20b: Ordinary Least Squares (OLS) regression model for the impact of index antipsychotic on total healthcare cost among schizophrenia patients (second stage sample selection models): Risperidone vs. quetiapine

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Demographic characteristics				
Age (in years)	0.012	0.005	2.403	0.017
Males (ref: females)	0.000	0.001	0.363	0.717
Whites (ref: non-whites)	0.360	0.192	1.878	0.061
Metro (ref: non-metro)	-0.119	0.148	-0.805	0.422
Prescribing physician type				
Psychiatric prescriber	0.000	0.000	1.184	0.238
Schizophrenia subtype (ref: only schizophrenia)				
Schizoaffective disorder	0.077	0.153	0.505	0.614
Both schizoaffective disorder and schizophrenia	-0.242	0.182	-1.332	0.184
Pre-index co-morbidities				
Charlson Comorbidity Index	0.162	0.050	3.219	0.001
Alcohol and substance abuse	0.346	0.160	2.170	0.031
Bipolar disorder	0.229	0.171	1.336	0.183
Major depression	-0.009	0.150	-0.057	0.954
Other mental comorbidities	-0.100	0.131	-0.764	0.446
Pre-index healthcare utilization and cost				
Pre-index total health related cost	0.091	0.021	4.295	0.000
Pre-index total health related ER visits	0.211	0.166	1.272	0.204
Pre-index total health related hospitalizations	-0.012	0.130	-0.092	0.927
Pre-index total health related physician visits	0.004	0.009	0.422	0.673
Year of index prescription (ref: 1999)				
• 2000	-0.199	0.153	-1.295	0.196
• 2001	-0.506	0.177	-2.859	0.005

Table 20b: Ordinary Least Squares (OLS) regression model for the impact of index antipsychotic on total healthcare cost among schizophrenia patients (second stage sample selection models): Risperidone vs. quetiapine (contd.)

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Pre-index period psychiatric medication use (days of supply)				
Mood stabilizers	0.001	0.000	2.834	0.005
Antipsychotics	-0.001	0.002	-0.666	0.506
Antidepressants	0.001	0.000	2.197	0.029
Benzodiazepines	0.100	0.133	0.752	0.453
Index prescription (ref: quetiapine)				
Risperidone	0.207	0.394	0.526	0.599
Inverse Mills Ratio	-0.040	0.246	-0.161	0.873

Model fit statistics:

Adjusted R-square = 27.5% , **F** = 6.52, **p** = 0.00

Table 20c: Ordinary Least Squares (OLS) regression model for the impact of index antipsychotic on total healthcare cost among schizophrenia patients (second stage sample selection models): Typicals vs. quetiapine

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Demographic characteristics				
Age (in years)	0.004	0.005	0.700	0.485
Males (ref: females)	0.000	0.001	0.440	0.661
Whites (ref: non-whites)	0.166	0.163	1.021	0.308
Metro (ref: non-metro)	-0.228	0.140	-1.626	0.105
Prescribing physician type				
Psychiatric prescriber	0.000	0.000	1.428	0.154
Schizophrenia subtype (ref: only schizophrenia)				
Schizoaffective disorder	0.152	0.164	0.929	0.354
Both schizoaffective disorder and schizophrenia	-0.076	0.177	-0.426	0.670
Pre-index co-morbidities				
Charlson Comorbidity Index	0.208	0.045	4.631	0.000
Alcohol and substance abuse	0.255	0.133	1.913	0.057
Bipolar disorder	-0.107	0.184	-0.580	0.562
Major depression	0.071	0.154	0.463	0.644
Other mental comorbidities	0.188	0.133	1.416	0.157
Pre-index healthcare utilization and cost				
Pre-index total health related cost	0.238	0.053	4.478	0.000
Pre-index total health related ER visits	0.291	0.184	1.581	0.115
Pre-index total health related hospitalizations	0.146	0.153	0.957	0.339
Pre-index total health related physician visits	0.000	0.009	0.030	0.976
Year of index prescription (ref: 1999)				
• 2000	-0.064	0.173	-0.369	0.712
• 2001	-0.311	0.227	-1.370	0.172

Table 20c: Ordinary Least Squares (OLS) regression model for the impact of index antipsychotic on total healthcare cost among schizophrenia patients (second stage sample selection models): Typicals vs. quetiapine (contd.)

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Mood stabilizers	0.021	0.000	2.153	0.032
Antipsychotics	-0.011	0.001	-0.441	0.659
Antidepressants	0.000	0.000	0.853	0.394
Benzodiazepines	0.171	0.135	1.268	0.205
Index prescription (ref: quetiapine)				
Typical	-0.355	0.000	-0.077	0.939
Inverse Mills Ratio	-0.004	0.279	-0.016	0.987

Model fit statistics:

Adjusted R-square = 27.92%, F = 8.28, p = 0.00

Table 21a: Ordinary Least Squares (OLS) regression model for the impact of index antipsychotic on mental healthcare cost among schizophrenia patients (second stage sample selection models): Olanzapine vs. quetiapine

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Demographic characteristics				
Age (in years)	0.004	0.004	1.035	0.301
Males (ref: females)	0.001	0.001	1.235	0.218
Whites (ref: non-whites)	0.173	0.175	0.991	0.322
Metro (ref: non-metro)	-0.092	0.124	-0.739	0.460
Prescribing physician type				
Psychiatric prescriber	0.000	0.000	2.592	0.010
Schizophrenia subtype (ref: only schizophrenia)				
Schizoaffective disorder	-0.101	0.130	-0.773	0.440
Both schizoaffective disorder and schizophrenia	-0.337	0.150	-2.251	0.025
Pre-index co-morbidities				
Charlson Comorbidity Index	0.108	0.047	2.301	0.022
Alcohol and substance abuse	0.365	0.112	3.256	0.001
Bipolar disorder	0.095	0.147	0.647	0.518
Major depression	0.041	0.117	0.345	0.730
Other mental comorbidities	0.053	0.109	0.488	0.626
Pre-index healthcare utilization and cost				
Pre-index mental-health related cost	0.071	0.016	4.533	0.000
Pre-index mental-health related ER visits	-0.212	0.135	-1.568	0.118
Pre-index mental-health related hospitalizations	0.202	0.112	1.798	0.073
Pre-index mental-health related physician visits	-0.024	0.027	-0.894	0.372
Year of index prescription (ref: 1999)				
• 2000	-0.035	0.127	-0.272	0.786
• 2001	-0.180	0.147	-1.223	0.222

Table 21a: Ordinary Least Squares (OLS) regression model for the impact of index antipsychotic on mental healthcare cost among schizophrenia patients (second stage sample selection models): Olanzapine vs. quetiapine (contd.)

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Pre-index period psychiatric medication use (days of supply)				
Mood stabilizers	0.001	0.000	1.472	0.142
Antipsychotics	0.004	0.002	1.870	0.062
Antidepressants	0.000	0.000	1.207	0.228
Benzodiazepines	0.126	0.114	1.104	0.270
Index prescription (ref: quetiapine)				
Olanzapine	0.482	0.478	1.008	0.314
Inverse Mills Ratio	-0.169	0.290	-0.583	0.560

Model fit statistics:

Adjusted R-square = 19.97%, **F** = 6.14, **p** = 0.00

Table 21b: Ordinary Least Squares (OLS) regression model for the impact of index antipsychotic on mental healthcare cost among schizophrenia patients (second stage sample selection models): Risperidone vs. quetiapine

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Demographic characteristics				
Age (in years)	0.011	0.005	1.966	0.050
Males (ref: females)	0.001	0.001	0.986	0.325
Whites (ref: non-whites)	0.304	0.218	1.393	0.165
Metro (ref: non-metro)	-0.150	0.167	-0.901	0.368
Prescribing physician type				
Psychiatric prescriber	0.000	0.000	1.645	0.101
Schizophrenia subtype (ref: only schizophrenia)				
Schizoaffective disorder	-0.059	0.174	-0.340	0.734
Both schizoaffective disorder and schizophrenia	-0.465	0.206	-2.255	0.025
Pre-index co-morbidities				
Charlson Comorbidity Index	0.035	0.055	0.640	0.523
Alcohol and substance abuse	0.547	0.181	3.029	0.003
Bipolar disorder	0.228	0.194	1.173	0.242
Major depression	0.056	0.170	0.331	0.741
Other mental comorbidities	-0.013	0.150	-0.088	0.930
Pre-index healthcare utilization and cost				
Pre-index mental-health related cost	0.045	0.017	2.611	0.010
Pre-index mental-health related ER visits	0.171	0.178	0.959	0.338
Pre-index mental-health related hospitalizations	0.017	0.150	0.112	0.911
Pre-index mental-health related physician visits	-0.009	0.040	-0.224	0.823
Year of index prescription (ref: 1999)				
• 2000	-0.244	0.173	-1.411	0.159
• 2001	-0.436	0.197	-2.216	0.027

Table 21b: Ordinary Least Squares (OLS) regression model for the impact of index antipsychotic on mental healthcare cost among schizophrenia patients (second stage sample selection models): Risperidone vs. quetiapine (contd.)

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Pre-index period psychiatric medication use (days of supply)				
Mood stabilizers	0.011	0.000	2.204	0.028
Antipsychotics	0.001	0.002	0.297	0.767
Antidepressants	0.031	0.000	2.804	0.005
Benzodiazepines	-0.090	0.149	-0.605	0.546
Index prescription (ref: quetiapine)				
Risperidone	0.084	0.448	0.187	0.852
Inverse Mills Ratio	-0.031	0.280	-0.112	0.911

Model fit statistics:

Adjusted R-square = 18.19, **F** = 4.24, **p** = 0.00

Table 21c: Ordinary Least Squares (OLS) regression model for the impact of index antipsychotic on mental healthcare cost among schizophrenia patients (second stage sample selection models): Typicals vs. quetiapine

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Demographic characteristics				
Age (in years)	-0.004	0.007	-0.644	0.520
Males (ref: females)	0.002	0.001	2.461	0.014
Whites (ref: non-whites)	0.199	0.205	0.974	0.331
Metro (ref: non-metro)	-0.299	0.176	-1.695	0.091
Prescribing physician type				
Psychiatric prescriber	0.000	0.000	1.451	0.148
Schizophrenia subtype (ref: only schizophrenia)				
Schizoaffective disorder	0.019	0.208	0.093	0.926
Both schizoaffective disorder and schizophrenia	-0.955	0.228	-4.182	0.000
Pre-index co-morbidities				
Charlson Comorbidity Index	0.033	0.052	0.642	0.521
Alcohol and substance abuse	0.547	0.168	3.264	0.001
Bipolar disorder	-0.004	0.232	-0.017	0.986
Major depression	0.205	0.194	1.054	0.293
Other mental comorbidities	0.142	0.168	0.848	0.397
Pre-index healthcare utilization and cost				
Pre-index mental-health related cost	0.012	0.022	0.561	0.575
Pre-index mental-health related ER visits	0.027	0.221	0.122	0.903
Pre-index mental-health related hospitalizations	0.434	0.174	2.495	0.013
Pre-index mental-health related physician visits	-0.017	0.051	-0.332	0.740
Year of index prescription (ref: 1999)				
• 2000	-0.016	0.218	-0.074	0.941
• 2001	-0.129	0.282	-0.459	0.646

Table 21c: Ordinary Least Squares (OLS) regression model for the impact of index antipsychotic on mental healthcare cost among schizophrenia patients (second stage sample selection models): Typicals vs. quetiapine (contd.)

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Pre-index period psychiatric medication use (days of supply)				
Mood stabilizers	0.045	0.001	1.789	0.074
Antipsychotics	0.002	0.002	1.125	0.261
Antidepressants	0.021	0.000	2.866	0.004
Benzodiazepines	0.127	0.169	0.754	0.452
Index prescription (ref: quetiapine)				
Typical	0.001	0.001	1.450	0.148
Inverse Mills Ratio	0.394	0.354	1.114	0.266

Model fit statistics:

Adjusted R-square = 20.0%, **F** = 5.71, **p** = 0.00

Results for the OLS regression models for the impact of index antipsychotics on total and mental healthcare costs are presented in the tables 20a-20c for total and tables 21a-21c for mental healthcare costs, respectively. The results showed that there were no significant differences in total and mental healthcare-related costs between quetiapine and other index antipsychotics. The model was further tested for appropriate specifications. It was possible that multicollinarity resulting due to inclusion of IMR in the model may be inflating the standard errors. Therefore, a semi-log OLS model was developed without including the IMR and the output was compared with the outputs of regression models that included IMR. As the direction and significance of variables in all these outputs were similar, it was concluded that there were no significant differences in the total and mental healthcare costs between these cohorts.

Bipolar disorder

Results for univariate analysis comparing differences in total and mental costs for bipolar disorder patients are reported in table 22. Total post-index costs for quetiapine ($13,227 ± $18,862) were significantly lesser compared to risperidone ($17,539 ± $17,570) and typical antipsychotics ($17,570 ± $23,842). Total post-index mental health-related costs for quetiapine ($8,064 ± $7,368) were significantly lesser than for olanzapine ($10,203 ± $17,203).

The results of the first-stage multinomial logistic regression model are presented in table 23. Results of multivariate analysis show that there were no significant differences in total healthcare costs of the quetiapine cohort as compared to other index atypical antipsychotic cohorts. However, typical antipsychotics had 28.4% greater total

cost and 8.7% greater mental health-related costs than quetiapine. Results for the OLS regression models for the impact of index antipsychotics on total and mental healthcare costs are presented in tables 24a-24c for total and table 25a-25c for mental health-related costs, respectively.

Results for research objective 9

For schizophrenia and bipolar disorder patients, to compare the impact of quetiapine with risperidone, olanzapine, and typical antipsychotics on components of mental healthcare costs (costs associated with mental health-related inpatient, emergency room, outpatient and pharmacy services)

Schizophrenia

Univariate analysis for mental health-related inpatient, outpatient, ER, and pharmacy costs are reported in table18. The results indicated that the post-index inpatient costs were significantly higher for typical antipsychotics ($5,418 ± $15,787) compared to quetiapine ($4,865± $11,285). The post-index outpatient costs were also significantly higher for risperidone ($4,247 ± $10,209) and olanzapine ($4,136 ± $16,349) as compared to quetiapine ($2,071 ± $3,479). The post-index ER costs were significantly lower for risperidone ($152 ± $415) as compared to quetiapine ($231 ± $531). Compared to quetiapine ($2470 ± 1789), the post-index prescription costs were significantly higher for olanzapine ($3,072 ± 2,285) and significantly lower for typical antipsychotics ($1,421 ± $1,898).

Table 22: Healthcare costs comparison among bipolar disorder patients: (Quetiapine versus other antipsychotics)

	Olanzapine N = 283	*Risperidone N = 201*	*Quetiapine N = 106*	*Typical N = 205*
		Total Healthcare Costs		
Total Mean (±std)				
Pre-index	$10,382 (±$16,609)	$13,037[Q] (±$28,248)	$9,993 (±$11,103)	$9,533 (±$11,582)
Post-index	$15,866 (±$23,164)	$17,539[Q] (±$28,672)	$13,227[ORT] (±$18,862)	$17,570[Q] (±$23,842)
		Mental health-related Costs		
Total mental health-related Mean (±std)				
Pre-index	$6,286 (±$8,918)	$7,604[Q] (±$20,688)	$6,377[RT] (±$9,136)	$4,223[Q] (±$6,911)
Post-index	$10,203[Q] (±$17,724)	$9,475 (±$14,202)	$8,064[O] (±$11,615)	$7,368 (±$11,239)
Inpatient Mean (±std)				
Pre-index	$3,785 (±$7,219)	$4,107 (±$19,069)	$3,873 (±$7,161)	$2,274 (±$5,416)
Post-index	$3,753 (±$8,956)	$3,633 (±$9,592)	$4,054 (±$10,345)	$3,968 (±$9,305)
Outpatient Mean (±std)				
Pre-index	$2,017 (±$4,295)	$3,045 (±$7,731)	$2,042 (±$4,753)	$1,436 (±$3,096)
Post-index	$3,580 (±$14,553)	$3,610 (±$8,678)	$2,945 (±$4,456)	$2,124 (±$4,443)
ER Mean (±std)				
Pre-index	$127 (±$435)	$97 (±$339)	$89[T] (±$214)	$43[Q] (±$199)
Post-index	$218 (±$1,223)	$129[Q] (±$352)	$200[R] (±$486)	$157 (±$402)

Table 22: Healthcare costs comparison among bipolar disorder patients: (Quetiapine versus other antipsychotics) (contd.)

	Olanzapine ***N = 283***	***Risperidone*** ***N = 201***	***Quetiapine*** ***N = 106***	***Typical*** ***N = 205***
Prescription Mean (±std)				
Pre-index	$356 (±$578)	$354 (±$594)	$372 (±$503)	$469 (±$759)
Post-index	$2,650 (±$1,970)	$2,102 (±$1,761)	$2,084[T] (±$1,578)	$1,118[Q] (±$1,410)

[O] Significant difference between quetiapine and olanzapine cohorts at p<0.05
[R] Significant difference between quetiapine and risperidone cohorts at p<0.05
[T] Significant difference between quetiapine and typicals cohorts at p<0.05

Table 23: Multinomial logistic regression model determining predictors of index antipsychotic use among bipolar disorder patients (first-stage sample selection model)

	Olanzapine vs. Quetiapine		*Risperidone vs. Quetiapine*		*Typicals vs. Quetiapine*	
	Coefficient	***t-ratio***	***Coefficient***	***t-ratio***	***Coefficient***	***t-ratio***
Demographic characteristics						
Age (in years)	-0.001	-0.074	0.001	0.101	0.029	2.329
Age category	-0.687	-1.688	-0.979	-2.355	-1.352	-3.211
Males (ref: females)	0.070	0.419	0.002	1.002	0.001	0.431
Whites (ref: non-whites)	0.435	0.964	0.051	0.113	-0.167	-0.360
Metro (ref: non-metro)	0.304	0.774	-0.236	-0.594	0.148	0.351
Prescribing physician type						
Psychiatric prescriber	-0.012	-3.223*	-0.011	-3.408*	-0.011	-3.372*
Bipolar disorder subtype (ref: only bipolar disorder)						
Bipolar Disorder II	-0.976	-2.331*	-0.851	-2.032*	-1.457	-3.212*
Bipolar Disorder Mixed	-1.150	-2.788*	-2.132	-5.038*	-1.426	-3.265*
Pre-index co-morbidities						
Diabetes	0.509	1.082	0.706	1.455	0.974	1.993*
Hyperlipidemia	-0.316	-0.639	-0.193	-0.373	0.318	0.621
Hypertension	-0.266	-0.792	0.181	0.510	0.102	0.276
Alcohol and substance abuse	-0.435	-1.454	-0.870	-2.634*	-0.198	-0.596
Bipolar disorder	0.112	0.307	-0.207	-0.527	-0.050	-0.119
Major depression	0.241	0.742	-0.110	-0.313	-0.186	-0.485
Anxiety disorder	0.026	0.073	-0.203	-0.532	-0.149	-0.369
Personality disorder	-0.042	-0.104	-0.081	-0.190	-0.300	-0.656
Non-specified psychosis	0.661	0.810	0.840	0.985	0.477	0.531
Other affective psychosis	-0.356	-0.436	0.313	0.379	-28.865	0.000

Table 23: Multinomial logistic regression model determining predictors of index antipsychotic use among bipolar disorder patients (first-stage sample selection model) (contd.)

	Olanzapine vs. Quetiapine		***Risperidone vs. Quetiapine***		***Typicals vs. Quetiapine***	
	Coefficient	***t-ratio***	***Coefficient***	***t-ratio***	***Coefficient***	***t-ratio***
Attention deficit disorders	-0.43 8	-0.554	1.196	1.624	0.727	0.862
Mild to moderate depression	0.091	0.236	0.311	0.765	-0.382	-0.814
Pre-index healthcare utilization and cost						
Number of pre-index mental-health related ER visits	0.000	0.936	0.000	0.327	0.000	-0.631
Number of pre-index mental-health related hospitalizations	0.003	0.023	-0.069	-0.543	-0.254	-1.593
Number of psychotherapy visits	0.002	0.070	-0.037	-1.015	0.012	0.408
Number of medication management visits	-0.087	-2.383*	-0.058	-1.464	-0.158	-3.350*
Year of index prescription (ref: 1999)						
• 2000	-0.119	-0.363	0.220	0.633	-0.396	-1.109
• 2001	-0.292	-0.844	-0.120	-0.320	-1.256	-3.032*
Pre-index period psychiatric medication use (days of supply)						
Mood stabilizers	0.001	0.652	0.000	-0.129	-0.002	-1.948
Anticholinergics	-0.006	-1.291	-0.020	-1.560	-0.007	-0.971
Anxiolytics/hypnotics/ sedatives	0.897	0.052	0.000	-0.058	0.001	0.354
Antipsychotics	-0.004	-0.707	0.011	2.005*	0.012	2.119*
Antidepressants	0.001	0.866	0.000	0.197	-0.316	-0.035
Benzodiazepines	-0.012	-2.178*	-0.002	-1.816	-0.001	-1.341
Antiparkinsons	-0.002	-0.587	-0.006	-1.406	-0.001	-0.389

*significant at p<0.05 level

Model fit statistics:

Pseudo R-square = 12.94%, **-2 Log Likelihood** = 957.41; χ^2 = 284.75; p= 0.00

Table 24a: Ordinary Least Squares (OLS) regression model for the impact of index antipsychotic on total healthcare cost among bipolar disorder patients (second stage sample selection models): Olanzapine vs. quetiapine

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Demographic characteristics				
Age (in years)	0.006	0.004	1.432	0.153
Agecat	0.063	0.144	0.438	0.662
Males (ref: females)	0.502	0.001	0.049	0.961
Whites (ref: non-whites)	0.199	0.176	1.129	0.260
Metro (ref: non-metro)	-0.028	0.127	-0.217	0.828
Prescribing physician type				
Psychiatric prescriber	0.012	0.000	1.972	0.049
Bipolar disorder subtype (ref: bipolar disorder I)				
Bipolar disorder II disorder	-0.163	0.141	-1.154	0.249
Mixed	-0.189	0.174	-1.085	0.279
Pre-index co-morbidities				
Charlson Comorbidity Index	0.135	0.049	2.758	0.006
Alcohol and substance abuse	0.226	0.115	1.959	0.051
Bipolar disorder	0.100	0.147	0.681	0.496
Major depression	0.011	0.117	0.096	0.923
Other mental comorbidities	0.049	0.109	0.454	0.650
Pre-index healthcare utilization and cost				
Pre-index total health related cost	0.229	0.042	5.422	0.000
Pre-index total health related ER visits	-0.254	0.138	-1.842	0.066
Pre-index total health related hospitalizations	-0.097	0.120	-0.806	0.421
Pre-index total health related physician visits	0.008	0.006	1.266	0.206
Year of index prescription (ref: 1999)				
• 2000	-0.006	0.124	-0.044	0.965
• 2001	-0.235	0.146	-1.611	0.108

Table 24a: Ordinary Least Squares (OLS) regression model for the impact of index antipsychotic on total healthcare cost among bipolar disorder patients (second stage sample selection models): Olanzapine vs. quetiapine (contd.)

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Pre-index period psychiatric medication use (days of supply)				
Mood stabilizers	0.041	0.000	2.317	0.021
Antipsychotics	0.003	0.002	1.581	0.115
Antidepressants	0.000	0.000	0.654	0.513
Benzodiazepines	0.050	0.114	0.437	0.663
Index prescription (ref: quetiapine)				
Olanzapine	0.261	0.495	0.527	0.059
Inverse Mills Ratio	-0.058	0.295	-0.197	0.844

Model fit statistics:

Adjusted R-square = 22.22% , F = 5.77 , p = 0.000

Table 24b: Ordinary Least Squares (OLS) regression model for the impact of index antipsychotic on total healthcare cost among bipolar disorder patients (second stage sample selection models): Risperidone vs. quetiapine

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Demographic characteristics				
Age (in years)	0.012	0.005	2.382	0.018
agecat	0.115	0.173	0.661	0.509
Males (ref: females)	0.000	0.001	0.368	0.714
Whites (ref: non-whites)	0.481	0.206	2.34	0.020
Metro (ref: non-metro)	-0.266	0.160	-1.657	0.099
Prescribing physician type				
Psychiatric prescriber	0.506	0.000	0.293	0.770
Bipolar disorder subtype (ref: Bipolar disorder I)				
Bipolar disorder II	-0.001	0.174	-0.005	0.996
Mixed	-0.509	0.234	-2.174	0.031
Pre-index co-morbidities				
Charlson Comorbidity Index	0.178	0.055	3.266	0.001
Alcohol and substance abuse	0.235	0.184	1.277	0.203
Bipolar disorder	0.194	0.193	1.006	0.315
Major depression	0.019	0.165	0.114	0.909
Other mental comorbidities	-0.019	0.141	-0.135	0.892
Pre-index healthcare utilization and cost				
Pre-index total health related cost	0.089	0.022	4.007	0.000
Pre-index total health related ER visits	0.230	0.182	1.265	0.207
Pre-index total health related hospitalizations	-0.134	0.141	-0.95	0.343
Pre-index total health related physician visits	0.010	0.010	0.993	0.322
Year of index prescription (ref: 1999)				
• 2000	-0.119	0.168	-0.711	0.478
• 2001	-0.522	0.193	-2.698	0.007

Table 24b: Ordinary Least Squares (OLS) regression model for the impact of index antipsychotic on total healthcare cost among bipolar disorder patients (second stage sample selection models): Risperidone vs. quetiapine (contd.)

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Pre-index period psychiatric medication use (days of supply)				
Mood stabilizers	0.031	0.000	2.877	0.004
Antipsychotics	-0.001	0.001	-0.368	0.713
Antidepressants	0.507	0.387	1.309	0.192
Benzodiazepines	0.032	0.141	0.226	0.822
Index prescription (ref: quetiapine)				
Risperidone	-0.329	0.439	-0.751	0.454
Inverse Mills Ratio	0.314	0.268	1.171	0.243

Model fit statistics:

Adjusted R-square = 27.58% , F = 5.66 , p = 0.000

Table 24c: Ordinary Least Squares (OLS) regression model for the impact of index antipsychotic on total healthcare cost among bipolar disorder patients (second stage sample selection models): Typicals vs. quetiapine

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Demographic characteristics				
Age (in years)	0.002	0.006	0.348	0.728
agecat	0.278	0.179	1.553	0.122
Males (ref: females)	0.000	0.001	0.324	0.746
Whites (ref: non-whites)	0.431	0.211	2.04	0.042
Metro (ref: non-metro)	-0.280	0.193	-1.451	0.148
Prescribing physician type				
Psychiatric prescriber	0.000	0.000	1.384	0.168
Bipolar disorder subtype (ref: Bipolar disorder I)				
Bipolar disorder II	0.389	0.221	1.758	0.080
Mixed	0.020	0.213	0.095	0.924
Pre-index co-morbidities				
Charlson Comorbidity Index	0.212	0.049	4.306	0.000
Alcohol and substance abuse	0.215	0.175	1.23	0.220
Bipolar disorder	-0.272	0.236	-1.153	0.250
Major depression	0.176	0.197	0.896	0.371
Other mental comorbidities	0.360	0.162	2.23	0.027
Pre-index healthcare utilization and cost				
Pre-index total health related cost	0.244	0.066	3.727	0.000
Pre-index total health related ER visits	0.304	0.221	1.378	0.169
Pre-index total health related hospitalizations	0.185	0.191	0.97	0.333
Pre-index total health related physician visits	0.004	0.011	0.353	0.725
Year of index prescription (ref: 1999)				
• 2000	-0.053	0.201	-0.262	0.794
• 2001	-0.382	0.258	-1.479	0.140

Table 24c: Ordinary Least Squares (OLS) regression model for the impact of index antipsychotic on total healthcare cost among bipolar disorder patients (second stage sample selection models): Typicals vs. quetiapine (contd.)

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Pre-index period psychiatric medication use (days of supply)				
Mood stabilizers	0.001	0.001	1.015	0.311
Antipsychotics	-0.001	0.002	-0.548	0.584
Antidepressants	0.001	0.000	1.032	0.303
Benzodiazepines	0.045	0.157	0.285	0.776
Index prescription (ref: quetiapine)				
Typical	0.250	0.417	2.30	0.028
Inverse Mills Ratio	0.083	0.260	0.319	0.750

Model Statistics:

Adjusted R-square = 31.72%, **F** = 6.76, **p** = 0.000

Table 25a: Ordinary Least Squares (OLS) regression model for the impact of index antipsychotic on mental healthcare cost among bipolar disorder patients (second stage sample selection models): Olanzapine vs. quetiapine

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Demographic characteristics				
Age (in years)	0.004	0.005	0.829	0.407
Agecat	0.104	0.157	0.665	0.506
Males (ref: females)	0.002	0.001	1.581	0.115
Whites (ref: non-whites)	0.293	0.192	1.525	0.128
Metro (ref: non-metro)	-0.122	0.139	-0.878	0.380
Prescribing physician type				
Psychiatric prescriber	0.000	0.000	1.831	0.068
Bipolar disorder subtype (ref: Bipolar disorder I)				
Bipolar disorder II	-0.219	0.154	-1.420	0.156
Mixed	-0.444	0.189	-2.346	0.020
Pre-index co-morbidities				
Charlson Comorbidity Index	0.117	0.051	2.285	0.023
Alcohol and substance abuse	0.363	0.126	2.890	0.004
Schizophrenia	0.006	0.160	0.036	0.971
Major depression	0.067	0.128	0.519	0.604
Other mental comorbidities	0.114	0.119	0.956	0.340
Pre-index healthcare utilization and cost				
Pre-index mental-health related cost	0.074	0.017	4.366	0.000
Pre-index mental-health related ER visits	-0.302	0.146	-2.064	0.040
Pre-index mental-health related hospitalizations	0.158	0.122	1.296	0.196
Pre-index mental-health related physician visits	0.001	0.031	0.024	0.981
Year of index prescription (ref: 1999)				
• 2000	0.019	0.136	0.139	0.890
• 2001	-0.143	0.157	-0.907	0.365

Table 25a: Ordinary Least Squares (OLS) regression model for the impact of index antipsychotic on mental healthcare cost among bipolar disorder patients (second stage sample selection models): Olanzapine vs. quetiapine (contd.)

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Pre-index period psychiatric medication use (days of supply)				
Mood stabilizers	0.001	0.000	1.676	0.095
Antipsychotics	0.004	0.002	1.737	0.083
Antidepressants	0.000	0.000	0.890	0.374
Benzodiazepines	0.020	0.124	0.160	0.873
Index prescription (ref: quetiapine)				
Olanzapine	0.203	0.539	0.377	0.070
Inverse Mills Ratio	-0.024	0.322	-0.074	0.941

Model fit statistics:

Adjusted R-square = 20.33%, F = 5.27, p = 0.00

Table 25b: Ordinary Least Squares (OLS) regression model for the impact of index antipsychotic on mental healthcare cost among bipolar disorder patients (second stage sample selection models): Risperidone vs. quetiapine

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Demographic characteristics				
Age (in years)	0.011	0.006	1.900	0.058
agecat	0.026	0.194	0.135	0.893
Males (ref: females)	0.001	0.001	1.007	0.315
Whites (ref: non-whites)	0.409	0.233	1.758	0.080
Metro (ref: non-metro)	-0.195	0.180	-1.080	0.281
Prescribing physician type				
Psychiatric prescriber	0.535	0.000	0.276	0.783
Bipolar disorder subtype (ref: Bipolar disorder I)				
Bipolar disorder II	-0.227	0.196	-1.155	0.249
Mixed	-0.849	0.264	-3.212	0.002
Pre-index co-morbidities				
Charlson Comorbidity Index	0.069	0.059	1.183	0.238
Alcohol and substance abuse	0.482	0.208	2.324	0.021
Schizophrenia	0.180	0.219	0.820	0.413
Major depression	0.088	0.186	0.471	0.638
Other mental comorbidities	0.046	0.161	0.285	0.776
Pre-index healthcare utilization and cost				
Pre-index mental-health related cost	0.038	0.018	2.057	0.041
Pre-index mental-health related ER visits	0.193	0.195	0.990	0.323
Pre-index mental-health related hospitalizations	-0.131	0.163	-0.799	0.425
Pre-index mental-health related physician visits	0.009	0.048	0.194	0.846
Year of index prescription (ref: 1999)				
• 2000	-0.179	0.187	-0.953	0.341
• 2001	-0.438	0.216	-2.025	0.044

Table 25b: Ordinary Least Squares (OLS) regression model for the impact of index antipsychotic on mental healthcare cost among bipolar disorder patients (second stage sample selection models): Risperidone vs. quetiapine (contd.)

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Pre-index period psychiatric medication use (days of supply)				
Mood stabilizers	0.081	0.000	1.864	0.063
Antipsychotics	0.001	0.002	0.315	0.753
Antidepressants	0.051	0.000	2.759	0.006
Benzodiazepines	-0.234	0.159	-1.472	0.142
Index prescription (ref: quetiapine)				
Risperidone	-0.647	0.502	-1.288	0.199
Inverse Mills Ratio	0.405	0.307	1.322	0.187

Model fit statistics:

Adjusted R-square = 19.56% , F = 3.98 , p = 0.000

Table 25c: Ordinary Least Squares (OLS) regression model for the impact of index antipsychotic on mental healthcare cost among bipolar disorder patients (second stage sample selection models): Typicals vs. quetiapine

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Demographic characteristics				
Age (in years)	-0.011	0.008	-1.366	0.173
agecat	0.114	0.227	0.499	0.618
Males (ref: females)	0.002	0.001	2.403	0.017
Whites (ref: non-whites)	0.342	0.269	1.273	0.204
Metro (ref: non-metro)	-0.239	0.245	-0.974	0.331
Prescribing physician type				
Psychiatric prescriber	0.000	0.000	1.738	0.083
Bipolar Disorder subtype (ref: Bipolar disorder I)				
Bipolar disorder II	0.155	0.282	0.550	0.583
Mixed	-0.919	0.276	-3.332	0.001
Pre-index co-morbidities				
Charlson Comorbidity Index	0.072	0.057	1.275	0.203
Alcohol and substance abuse	0.587	0.221	2.649	0.009
Schizophrenia	-0.117	0.301	-0.388	0.699
Major depression	0.437	0.251	1.742	0.083
Other mental comorbidities	0.196	0.205	0.954	0.341
Pre-index healthcare utilization and cost				
Pre-index mental-health related cost	-0.018	0.024	-0.735	0.463
Pre-index mental-health related ER visits	-0.027	0.269	-0.099	0.921
Pre-index mental-health related hospitalizations	0.592	0.218	2.719	0.007
Pre-index mental-health related physician visits	0.024	0.062	0.387	0.699
Year of index prescription (ref: 1999)			**(contd.)**	
• 2000	-0.014	0.252	-0.054	0.957
• 2001	-0.213	0.319	-0.668	0.505

Table 25c: Ordinary Least Squares (OLS) regression model for the impact of index antipsychotic on mental healthcare cost among bipolar disorder patients (second stage sample selection models): Typicals vs. quetiapine

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Pre-index period psychiatric medication use (days of supply)				
Mood stabilizers	0.001	0.001	0.856	0.393
Antipsychotics	0.001	0.002	0.412	0.681
Antidepressants	0.062	0.001	3.348	0.001
Benzodiazepines	0.039	0.198	0.195	0.845
Index prescription (ref: quetiapine)				
Typical	0.083	0.535	2.568	0.008
Inverse Mills Ratio	0.357	0.332	1.076	0.283

Model fit statistics:

Adjusted R-square = 22.41%, **F** = 4.58, **p** = 0.000

Multivariate analysis results for mental health-related inpatient costs

The results of the two-part model used to estimate the impact of antipsychotic on mental health-related inpatient costs are presented in the tables 26a and 26b. The first-part logistic regression model comparing the risk of incurring any inpatient cost to no inpatient costs showed no significant difference between quetiapine and other antipsychotics. The second-part semi-log OLS regression which was carried out only on those patients who had incurred any mental health-related inpatient costs showed that patients initiated on typical antipsychotics incurred 3.7% higher costs than patients initiated on quetiapine.

Multivariate analysis results for mental health-related ER costs

The results of two part model estimating the impact of index antipsychotic therapy on mental health-related ER costs are presented in table 27a and 27b. The first part logistic regression analysis revealed that there were no significant differences in the likelihood of incurring any ER cost between quetiapine and other cohorts. The subsequent semi-log OLS analysis carried out using only the patients who have incurred ER costs also showed no significant differences in mental health-related ER costs between quetiapine and other antipsychotics.

Multivariate analysis results for mental health-related pharmacy costs

The results show that patients initiated on olanzapine incur 27.88% higher mental healthcare-related pharmacy cost than patients initiated on quetiapine. Patients initiated on typical antipsychotics incur 53.92% lesser mental healthcare-related pharmacy cost than patients initiated on quetiapine. Results for the OLS regression models for the

impact of index antipsychotics on mental-health related pharmacy healthcare costs are presented in table 28.

Multivariate analysis results for mental health-related outpatient costs

The results of semi-log regression analysis show that the patients initiated on typical antipsychotics incur 3.0% higher outpatient costs than patients initiated on quetiapine. Results for the OLS regression models for the impact of index antipsychotics on mental-health related outpatient healthcare costs are presented in table 29.

Bipolar Disorder

Univariate analysis for mental health-related inpatient, outpatient, ER, and pharmacy costs are reported in table 23. There were no significant differences in mental-health related inpatient and outpatient costs between quetiapine and other antipsychotics. The post-index ER costs were significantly lower for risperidone ($129 $\pm$ $352) compared to quetiapine ($200 $\pm$ $486). The post-index prescription costs were significantly lower for typicals ($1,118 $\pm$ $1,118) compared to quetiapine ($2,084 $\pm$ 1,578).

Multivariate analysis results for mental health-related inpatient costs

The results of the two-part model used to estimate the impact of antipsychotic on mental health-related inpatient costs are presented in tables 30a and 30b. Results of the two part model show that there were no significant differences in the mental health-related inpatient costs between quetiapine and other antipsychotics.

Multivariate analysis results for mental health-related ER costs

The results of two part model estimating the impact of index antipsychotic therapy on mental health-related ER costs are presented in tables 31a and 31b. The first

part logistic regression analysis and the subsequent semi-log OLS analysis revealed that there were no significant differences in the mental health-related ER cost between quetiapine and other cohorts.

Multivariate analysis results for mental health-related pharmacy costs

Patients initiated on typical antipsychotics incur 52.76% lesser mental healthcare-related pharmacy cost than patients initiated on quetiapine. Patients initiated on olanzapine incur 12.41% greater mental healthcare-related pharmacy cost than patients initiated on quetiapine. Results for the OLS regression models for the impact of index antipsychotics on mental-health related pharmacy healthcare costs are presented in table 32.

Multivariate analysis results for mental health-related outpatient costs

The results of semi-log regression analysis show that the patients initiated patients initiated on typical antipsychotics incur 7.78% higher outpatient costs than patients initiated on quetiapine. Results for the OLS regression models for the impact of index antipsychotics on mental-health related outpatient healthcare costs are presented in table 33.

TWO-PART MODEL-PART 1

Table 26a: Logistic regression model for the impact of index antipsychotic on having a mental health-related hospitalization episode among schizophrenia patients

	Beta	*SE*	*Sig. (p)*	*Odds ratio*	*95% CI for odds ratio*	
					Lower limit	*Upper limit*
Demographic characteristics						
Age (in years)	-0.008	0.007	0.266	0.992	0.978	1.006
Males (ref: females)	-0.005	0.008	0.495	0.995	0.980	1.010
Whites (ref: non-whites)	-0.562	0.286	0.049	0.570	0.326	0.998
Metro (ref: non-metro)	0.361	0.195	0.065	1.435	0.979	2.105
Prescribing physician type						
Psychiatric prescriber	0.000	0.000	0.730	1.000	1.000	1.000
Schizophrenia subtype (ref: only schizophrenia)						
Schizoaffective disorder	0.366	0.207	0.077	1.441	0.962	2.160
Both schizoaffective disorder and schizophrenia	0.758	0.219	0.001	2.135	1.391	3.276
Pre-index co-morbidities						
Alcohol and substance abuse	-0.888	0.181	<.0001	0.411	0.289	0.586
Bipolar disorder	-0.362	0.244	0.138	0.697	0.432	1.123
Major depression	-0.229	0.206	0.268	0.796	0.531	1.192
Mild to Moderate depression	-0.246	0.236	0.297	0.782	0.492	1.242
Other mental comorbidities	-0.083	0.187	0.656	0.920	0.638	1.327
diabetes	-0.385	0.267	0.150	0.680	0.403	1.149
hyperlipedemia	0.298	0.328	0.364	1.347	0.709	2.559
hypertension	0.245	0.226	0.279	1.278	0.820	1.990
Charlson Comorbidity Index	-0.197	0.063	0.002	0.821	0.726	0.930

Table 26a: Logistic regression model for the impact of index antipsychotic on having a mental health-related hospitalization episode among schizophrenia patients(contd.)

	Beta	*SE*	*Sig. (p)*	*Odds ratio*	*95% CI for odds ratio*	
					Lower limit	*Upper limit*
Pre-index period psychiatric medication use (days of supply)						
Mood stabilizers	0.000	0.001	0.722	1.000	0.999	1.001
Antipsychotics	-0.002	0.002	0.387	0.998	0.995	1.002
Antidepressants	-0.001	0.001	0.049	0.999	0.998	1.000
Benzodiazepines	-0.001	0.001	0.345	0.999	0.998	1.001
Pre-index healthcare utilization and cost						
Number of psychotherapy visits	-0.005	0.017	0.777	0.995	0.962	1.029
Number of medication management visits	0.076	0.030	0.011	1.079	1.018	1.143
Any pre-index mental-health related ER visits	-0.329	0.288	0.252	0.719	0.410	1.264
Pre-index mental-health related physician visits	0.039	0.055	0.484	1.039	0.933	1.158
Any pre-index mental-health related hospitalizations	-0.752	0.169	<.0001	0.471	0.339	0.656
Year of index prescription (ref: 1999)						
• 2000	-0.127	0.216	0.555	0.880	0.577	1.343
• 2001	0.260	0.261	0.318	1.297	0.778	2.161
Index prescription (ref: quetiapine)						
Risperidone	0.356	0.276	0.197	1.428	0.831	2.453
Olanzapine	0.103	0.241	0.670	1.108	0.691	1.776
Typicals	0.202	0.260	0.436	1.224	0.736	2.037

Model Statistics:
-2 Log Likehood = 1207.17 , **chi-square** = 161.00 , $p < 0.0001$

TWO-PART MODEL-PART 2

Table 26b: Ordinary Least Squares (OLS) regression model for the impact of index antipsychotic on mental healthcare-related hospitalization cost among schizophrenia patients

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Demographic characteristics				
Age (in years)	0.003	0.005	0.670	0.506
Males (ref: females)	0.000	0.107	0.000	0.997
Whites (ref: non-whites)	0.315	0.199	1.590	0.114
Metro (ref: non-metro)	0.114	0.131	0.870	0.384
Prescribing physician type				
Psychiatric prescriber	0.000	0.000	-0.380	0.705
Schizophrenia subtype (ref: only schizophrenia)				
Schizoaffective disorder	-0.084	0.129	-0.650	0.515
Both schizoaffective disorder and schizophrenia	-0.122	0.206	-0.590	0.554
Pre-index co-morbidities				
Alcohol and substance abuse	0.301	0.107	2.800	0.006
Bipolar disorder	-0.001	0.145	-0.010	0.992
Major depression	0.153	0.126	1.210	0.226
Mild to Moderate depression	0.262	0.138	1.900	0.059
Other mental comorbidities	0.147	0.118	1.250	0.214
diabetes	0.036	0.161	0.230	0.821
hyperlipedemia	-0.116	0.206	-0.560	0.576
hypertension	0.177	0.141	1.250	0.212
Charlson Comorbidity Index	0.024	0.041	0.590	0.553
Pre-index period psychiatric medication use`(days of supply)				
Mood stabilizers	0.000	0.000	-1.290	0.199
Antipsychotics	0.001	0.001	0.880	0.378
Antidepressants	0.000	0.000	0.090	0.929
Benzodiazepines	0.000	0.000	-1.060	0.289

Table 26b: Ordinary Least Squares (OLS) regression model for the impact of index antipsychotic on mental healthcare-related hospitalization cost among schizophrenia patients (contd.)

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Pre-index healthcare utilization and cost				
Number of psychotherapy visits	-0.006	0.009	-0.660	0.510
Number of medication management visits	-0.011	0.020	-0.540	0.593
Number of pre-index mental-health related ER visits	-0.025	0.073	-0.340	0.731
Pre-index mental-health related physician visits	-0.060	0.033	-1.830	0.068
Number of pre-index mental-health related hospitalizations	0.015	0.006	2.590	0.010
Pre-index mental health-related cost	0.256	0.134	1.910	0.058
Year of index prescription (ref: 1999)				
• 2000	-0.187	0.166	-1.120	0.263
• 2001	-0.111	0.175	-0.640	0.526
Index prescription (ref: quetiapine)				
Risperidone	-0.269	0.154	-1.750	0.081
Olanzapine	-0.174	0.164	-1.060	0.290
Typicals	0.036	0.015	0.670	0.026

Model fit statistics:

Adjusted R-square = 20.07% , F = 2.14, p < 0.0001

TWO-PART MODEL-PART 1

Table 27a: Logistic regression model for the impact of index antipsychotic on having a mental health-related ER episode among schizophrenia patients

	Beta	*SE*	*Sig. (p)*	*Odds ratio*	*95% CI for odds ratio*	
					Lower limit	*Upper limit*
Demographic characteristics						
Age (in years)	-0.003	0.007	0.655	0.997	0.983	1.011
Males (ref: females)	0.000	0.001	0.675	1.000	0.997	1.002
Whites (ref: non-whites)	-0.909	0.293	0.002	0.403	0.227	0.716
Metro (ref: non-metro)	0.487	0.198	0.014	1.628	1.105	2.398
Prescribing physician type						
Psychiatric prescriber	0.000	0.000	0.034	1.000	0.999	1.000
Schizophrenia subtype (ref: only schizophrenia)						
Schizoaffective disorder	0.900	0.216	<.0001	2.460	1.611	3.755
Both schizoaffective disorder and schizophrenia	0.772	0.212	0.000	2.163	1.427	3.280
Pre-index co-morbidities						
Alcohol and substance abuse	-1.242	0.181	<.0001	0.289	0.203	0.412
Bipolar disorder	-0.229	0.241	0.340	0.795	0.496	1.274
Major depression	-0.170	0.207	0.413	0.844	0.562	1.267
Mild to Moderate depression	-0.384	0.236	0.104	0.681	0.429	1.083
Other mental comorbidities	-0.395	0.183	0.031	0.674	0.470	0.965
diabetes	-0.504	0.266	0.058	0.604	0.359	1.017

Table 27a: Logistic regression model for the impact of index antipsychotic on having a mental health-related ER episode among schizophrenia patients (contd.)

	Beta	*SE*	*Sig. (p)*	*Odds ratio*	*95% CI for odds ratio*	
					Lower limit	*Upper limit*
hyperlipedemia	0.155	0.315	0.624	1.167	0.629	2.165
hypertension	-0.132	0.219	0.547	0.876	0.571	1.346
Charlson Comorbidity Index	-0.062	0.064	0.331	0.940	0.829	1.065
Pre-index period psychiatric medication use (days of supply)						
Mood stabilizers	-0.001	0.001	0.053	0.999	0.998	1.000
Antipsychotics	0.000	0.002	0.799	1.000	0.997	1.004
Antidepressants	0.000	0.001	0.537	1.000	0.999	1.001
Benzodiazepines	-0.001	0.001	0.362	0.999	0.998	1.001
Pre-index healthcare utilization and cost						
Number of psychotherapy visits	-0.015	0.016	0.367	0.985	0.955	1.017
Number of medication management visits	0.032	0.028	0.246	1.033	0.978	1.090
Any pre-index mental-health related ER visits	-0.717	0.286	0.012	0.488	0.279	0.854
Pre-index mental-health related physician visits	-0.020	0.054	0.710	0.980	0.882	1.089
Any pre-index mental-health related hospitalizations	-0.308	0.171	0.072	0.735	0.525	1.028
Year of index prescription (ref: 1999)						
• 2000	0.395	0.219	0.071	1.484	0.967	2.278
• 2001	0.349	0.254	0.169	1.418	0.862	2.331

Table 27a: Logistic regression model for the impact of index antipsychotic on having a mental health-related ER episode among schizophrenia patients (contd.)

	Beta	*SE*	*Sig. (p)*	*Odds ratio*	*95% CI for odds ratio*	
					Lower limit	*Upper limit*
Index prescription (ref: quetiapine)						
Risperidone	0.211	0.271	0.437	1.234	0.726	2.100
Olanzapine	0.118	0.240	0.623	1.125	0.703	1.800
Typicals	-0.100	0.258	0.698	0.905	0.546	1.499

Model fit statistics:

-2 Log Likehood = 1057.6 , chi-square = 178.25 , $p < 0.0001$

TWO-PART MODEL-PART 2

Table 27b: Ordinary Least Squares (OLS) regression model for the impact of index antipsychotic on mental healthcare-related ER cost among schizophrenia patients

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Demographic characteristics				
Age (in years)	-0.006	0.007	-0.750	0.456
Males (ref: females)	0.000	0.001	-0.200	0.844
Whites (ref: non-whites)	-0.076	0.306	-0.250	0.803
Metro (ref: non-metro)	0.158	0.188	0.840	0.402
Prescribing physician type				
Psychiatric prescriber	0.000	0.000	-0.520	0.606
Schizophrenia subtype (ref: only schizophrenia)				
Schizoaffective disorder	-0.063	0.205	-0.310	0.759
Both schizoaffective disorder and schizophrenia	-0.256	0.199	-1.290	0.199
Pre-index co-morbidities				
Alcohol and substance abuse	0.281	0.157	1.790	0.074
Bipolar disorder	0.096	0.207	0.460	0.645
Major depression	0.368	0.191	1.930	0.055
Mild to Moderate depression	0.244	0.206	1.190	0.236
Other mental comorbidities	0.035	0.172	0.200	0.840
Diabetes	0.435	0.245	1.780	0.077
Hyperlipedemia	-0.177	0.302	-0.590	0.558
Hypertension	0.106	0.205	0.520	0.606
Charlson Comorbidity Index	0.155	0.074	2.100	0.037
Pre-index period psychiatric medication use (days of supply)				
Mood stabilizers	0.000	0.001	0.380	0.706
Antipsychotics	-0.003	0.002	-1.450	0.147
Antidepressants	0.000	0.001	0.850	0.395
Benzodiazepines	-0.001	0.001	-1.800	0.073
Number of psychotherapy visits	-0.031	0.012	-2.730	0.007

Table 27b: Ordinary Least Squares (OLS) regression model for the impact of index antipsychotic on mental healthcare-related ER cost among schizophrenia patients (contd.)

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Pre-index healthcare utilization and cost				
Number of medication management visits	-0.010	0.028	-0.350	0.723
Number of pre-index mental-health related ER visits	-0.030	0.109	-0.280	0.782
Pre-index mental-health related physician visits	-0.019	0.044	-0.440	0.663
Number of pre-index mental-health related hospitalizations	0.150	0.250	0.460	0.651
Pre-index mental health-related cost	0.006	0.012	0.460	0.644
Year of index prescription (ref: 1999)				
• 2000	0.234	0.202	1.160	0.248
• 2001	0.071	0.233	0.310	0.760
Index prescription (ref: quetiapine)				
Risperidone	-0.535	0.259	-2.060	0.060
Olanzapine	-0.390	0.227	-1.720	0.086
Typicals	-0.375	0.239	-1.570	0.118

Model fit statistics:

Adjusted R-square = 7.26% , F = 1.8, $p < 0.0001$

Table 28: Ordinary Least Squares (OLS) regression model for the impact of index antipsychotic on mental healthcare-related pharmacy cost among schizophrenia patients

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Demographic characteristics				
Age (in years)	0.001	0.003	0.46	0.643
Males (ref: females)	0.000	0.000	0.47	0.639
Whites (ref: non-whites)	-0.007	0.115	-0.06	0.948
Metro (ref: non-metro)	-0.042	0.088	-0.48	0.630
Prescribing physician type				
Psychiatric prescriber	0.000	0.000	5.26	<.0001
Schizophrenia subtype (ref: only schizophrenia)				
Schizoaffective disorder	0.006	0.093	0.07	0.946
Both schizoaffective disorder and schizophrenia	-0.222	0.097	-2.29	0.022
Pre-index co-morbidities				
Alcohol and substance abuse	-0.139	0.086	-1.61	0.107
Bipolar disorder	0.005	0.113	0.04	0.966
Major depression	0.056	0.095	0.58	0.560
Mild to Moderate depression	0.010	0.112	0.09	0.927
Other mental comorbidities	0.027	0.083	0.33	0.742
Diabetes	0.098	0.127	0.77	0.444
Hyperlipedemia	0.010	0.141	0.07	0.945
Hypertension	-0.040	0.102	-0.4	0.692
Charlson Comorbidity Index	-0.066	0.030	-2.19	0.029
Pre-index period psychiatric medication use (days of supply)				
Mood stabilizers	0.091	0.000	5.45	<.0001
Antipsychotics	0.001	0.001	1.36	0.174
Antidepressants	0.072	0.000	5.14	<.0001
Benzodiazepines	0.034	0.000	2.82	0.005

Table 28: Ordinary Least Squares (OLS) regression model for the impact of index antipsychotic on mental healthcare-related pharmacy cost among schizophrenia patients

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Pre-index healthcare utilization and cost				
Number of psychotherapy visits	0.001	0.008	0.13	0.894
Number of medication management visits	-0.010	0.012	-0.88	0.380
Number of pre-index mental-health related ER visits	-0.038	0.073	-0.53	0.599
Pre-index mental-health related physician visits	-0.00073	0.025	-0.03	0.976
Number of pre-index mental-health related hospitalizations	0.043	0.036	1.18	0.237
Pre-index psychiatric drug cost	0.003	0.005	0.54	0.586
Year of index prescription (ref: 1999)				
• 2000	-0.043	0.095	-0.45	0.654
• 2001	0.022	0.110	0.2	0.845
Index prescription (ref: quetiapine)				
Risperidone	0.032	0.121	0.26	0.794
Olanzapine	0.246	0.108	2.28	0.023
Typicals	-0.775	0.116	-6.65	<.0001

Model fit statistics:

Adjusted R-square = 27.78% , F = 12.00, $p < 0.0001$

Table 29: Ordinary Least Squares (OLS) regression model for the impact of index antipsychotic on mental healthcare-related outpatient cost among schizophrenia patients

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Demographic characteristics				
Age (in years)	0.009	0.013	0.67	0.504
Males (ref: females)	0.004	0.002	2.06	0.040
Whites (ref: non-whites)	0.203	0.486	2.48	0.013
Metro (ref: non-metro)	-0.637	0.369	-1.73	0.085
Prescribing physician type				
Psychiatric prescriber	0.001	0.000	2.76	0.006
Schizophrenia subtype (ref: only schizophrenia)				
Schizoaffective disorder	0.567	0.391	1.45	0.147
Both schizoaffective disorder and schizophrenia	-0.649	0.425	-6.23	<.0001
Pre-index co-morbidities				
Alcohol and substance abuse	0.991	0.366	2.71	0.007
Bipolar disorder	0.626	0.476	1.31	0.189
Major depression	-0.083	0.400	-0.21	0.836
Mild to Moderate depression	0.626	0.473	1.32	0.186
Other mental comorbidities	-1.166	0.351	-3.32	0.001
diabetes	0.182	0.536	0.34	0.734
hyperlipedemia	-0.277	0.593	-0.47	0.641
hypertension	-0.210	0.428	-0.49	0.624
Charlson Comorbidity Index	-0.193	0.127	-1.52	0.129
Pre-index period psychiatric medication use (days of supply)				
Mood stabilizers	-0.001	0.001	-0.85	0.396
Antipsychotics	-0.002	0.004	-0.64	0.520
Antidepressants	0.000	0.001	-0.24	0.811
Benzodiazepines	-1.318	0.490	2.69	0.007

Table 29: Ordinary Least Squares (OLS) regression model for the impact of index antipsychotic on mental healthcare-related outpatient cost among schizophrenia patients (contd.)

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Pre-index healthcare utilization and cost				
Number of psychotherapy visits	0.000	0.033	0.01	0.990
Number of medication management visits	0.082	0.051	1.6	0.110
Number of pre-index mental-health related ER visits	-0.207	0.306	-0.68	0.499
Pre-index mental-health related physician visits	-0.064	0.106	-0.6	0.547
Number of pre-index mental-health related hospitalizations	0.320	0.153	2.09	0.037
Pre-index outpatient drug cost	0.365	0.025	14.51	<.0001
Year of index prescription (ref: 1999)				
• 2000	-0.047	0.401	-0.12	0.907
• 2001	-0.365	0.465	-0.79	0.432
Index prescription (ref: quetiapine)				
Risperidone	-0.540	0.508	-1.06	0.288
Olanzapine	-0.412	0.455	-0.91	0.365
Typicals	0.03	0.001	2.3	0.022

Model fit statistics:

Adjusted R-square = 35.91% , $F = 19.03$, $p < 0.0001$

TWO-PART MODEL-PART 1

Table 30a: Logistic regression model for the impact of index antipsychotic on having a mental health-related hospitalization episode

	Beta	*SE*	*Sig. (p)*	*Odds ratio*	*95% CI for odds ratio*	
					Lower	*Upper*
Demographic characteristics						
Age (in years)	-0.012	0.008	0.121	0.988	0.972	1.003
18 years or above (ref: less than 18 years)	-0.277	0.241	0.250	0.758	0.473	1.215
Males (ref: females)	-0.005	0.008	0.533	0.995	0.979	1.011
Whites (ref: non-whites)	-0.763	0.350	0.029	0.466	0.235	0.927
Metro (ref: non-metro)	0.421	0.230	0.068	1.523	0.970	2.391
Prescribing physician type						
Psychiatric prescriber	0.000	0.000	0.506	1.000	0.999	1.000
Bipolar disorder subtype (ref: Bipolar disorder I)						
Bipolar disorder II	0.448	0.241	0.064	1.565	0.975	2.511
Mixed	0.835	0.243	0.001	2.305	1.432	3.712
Pre-index co-morbidities						
Alcohol and substance abuse	-0.889	0.206	<.0001	0.411	0.275	0.615
Schizophrenia	-0.228	0.275	0.407	0.796	0.464	1.364
Major depression	-0.153	0.232	0.509	0.858	0.545	1.351
Mild to Moderate depression	-0.069	0.268	0.797	0.933	0.552	1.578
Other mental comorbidities	-0.192	0.207	0.354	0.825	0.550	1.238
Diabetes	-0.363	0.297	0.221	0.696	0.389	1.244
Hyperlipedemia	0.228	0.359	0.525	1.256	0.622	2.536
Hypertension	0.219	0.246	0.375	1.245	0.768	2.017

Table 30a: Logistic regression model for the impact of index antipsychotic on having a mental health-related hospitalization episode (contd.)

	Beta	*SE*	*Sig. (p)*	*Odds ratio*	*95% CI for odds ratio*	
					Lower	*Upper*
Charlson Comorbidity Index	-0.189	0.066	0.004	0.828	0.727	0.942
Pre-index period psychiatric medication use (days of supply)						
Mood stabilizers	0.000	0.001	0.731	1.000	0.998	1.001
Antipsychotics	-0.002	0.002	0.302	0.998	0.994	1.002
Antidepressants	-0.001	0.001	0.083	0.999	0.998	1.000
Benzodiazepines	-0.001	0.001	0.459	0.999	0.998	1.001
Pre-index healthcare utilization and cost						
Number of psychotherapy visits	-0.001	0.024	0.977	0.999	0.953	1.048
Number of medication management visits	0.100	0.036	0.006	1.105	1.029	1.186
Any pre-index mental-health related ER visits	-0.190	0.321	0.553	0.827	0.441	1.550
Pre-index mental-health related physician visits	0.028	0.063	0.653	1.029	0.910	1.163
Any pre-index mental-health related hospitalizations	-0.749	0.190	<.0001	0.473	0.326	0.686
Year of index prescription (ref: 1999)						
• 2000	-0.198	0.233	0.396	0.821	0.520	1.296
• 2001	0.233	0.287	0.417	1.263	0.719	2.216
Index prescription (ref: quetiapine)						
Risperidone	0.268	0.316	0.397	1.307	0.704	2.426
Olanzapine	0.082	0.286	0.774	1.086	0.620	1.903
Typicals	0.078	0.315	0.806	1.081	0.583	2.003

Model fit statistics:
-2 Log Likehood = 845.24, chi-square = 136.88, p = 0.00

TWO-PART MODEL-PART 2

Table 30b: Ordinary Least Squares (OLS) regression model for the impact of index antipsychotic on mental healthcare-related hospitalization cost among bipolar disorder patients

	Beta	***S.E***	***t-statistic***	***Significance (p)***
Demographic characteristics				
Age (in years)	0.005	0.005	0.930	0.354
18 years or above (ref: less than 18 years)	0.100	0.163	0.610	0.541
Males (ref: females)	-0.030	0.119	-0.250	0.801
Whites (ref: non-whites)	0.484	0.245	1.970	0.050
Metro (ref: non-metro)	0.082	0.158	0.520	0.606
Prescribing physician type				
Psychiatric prescriber	0.000	0.000	-0.730	0.465
Bipolar disorder subtype (ref: Bipolar disorder I)				
Bipolar disorder II	-0.056	0.151	-0.370	0.711
Mixed	-0.181	0.206	-0.880	0.382
Pre-index co-morbidities				
Alcohol and substance abuse	0.318	0.123	2.590	0.010
Bipolar disorder	0.031	0.166	0.180	0.854
Major depression	0.171	0.143	1.200	0.232
Mild to Moderate depression	0.039	0.160	0.250	0.806
Other mental comorbidities	0.125	0.130	0.970	0.335
diabetes	-0.043	0.170	-0.250	0.800
hyperlipedemia	-0.190	0.219	-0.870	0.387
hypertension	0.179	0.152	1.180	0.241
Charlson Comorbidity Index	0.044	0.042	1.050	0.295
Pre-index period psychiatric medication use (days of supply)				
Mood stabilizers	-0.021	0.000	-1.670	0.096
Antipsychotics	0.000	0.001	0.380	0.702
Antidepressants	0.000	0.000	-0.320	0.750
Benzodiazepines	0.000	0.000	-0.630	0.528

Table 30b: Ordinary Least Squares (OLS) regression model for the impact of index antipsychotic on mental healthcare-related hospitalization cost among bipolar disorder patients

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Pre-index healthcare utilization and cost				
Number of psychotherapy visits	0.013	0.014	0.920	0.357
Number of medication management visits	-0.020	0.026	-0.770	0.445
Number of pre-index mental-health related ER visits	-0.008	0.078	-0.100	0.919
Pre-index mental-health related physician visits	-0.048	0.037	-1.300	0.195
Number of pre-index mental-health related hospitalizations	0.094	0.206	0.460	0.647
Pre-index mental health-related cost	0.020	0.007	2.960	0.004
Year of index prescription (ref: 1999)				
• 2000	0.300	0.143	2.110	0.036
• 2001	-0.186	0.184	-1.010	0.314
Index prescription (ref: quetiapine)				
Risperidone	-0.201	0.200	-1.010	0.315
Olanzapine	-0.414	0.184	-2.250	0.225
Typicals	-0.343	0.201	-1.710	0.089

Model fit statistics:

Adjusted R-square = 12.26% , **F** = 2.01, **p** = 0.000

TWO-PART MODEL-PART 1

Table 31a: Logistic regression model for the impact of index antipsychotic on having a mental health-related ER episode among bipolar disorder patients

	Beta	*SE*	*Sig. (p)*	*Odds ratio*	*95% CI for odds ratio*	
					Lower Limit	*Upper Limit*
Demographic characteristics						
Age (in years)	-0.003	0.008	0.709	0.997	0.982	1.013
18 years or above (ref: less than 18 years)	-0.526	0.242	0.030	0.591	0.368	0.950
Males (ref: females)	0.000	0.001	0.919	1.000	0.997	1.002
Whites (ref: non-whites)	-0.866	0.342	0.011	0.421	0.215	0.823
Metro (ref: non-metro)	0.487	0.230	0.035	1.627	1.036	2.554
Prescribing physician type						
Psychiatric prescriber	0.000	0.000	0.164	1.000	0.999	1.000
Bipolar disorder subtype (ref: bipolar disorder I)						
Bipolar disorder I	0.827	0.247	0.001	2.287	1.408	3.713
Mixed	0.846	0.237	0.000	2.330	1.465	3.706
Pre-index co-morbidities						
Alcohol and substance abuse	-1.093	0.204	<.0001	0.335	0.225	0.500
Schizophrenia	-0.332	0.266	0.211	0.717	0.426	1.207
Major depression	-0.181	0.228	0.429	0.835	0.534	1.306
Mild to Moderate depression	-0.217	0.262	0.408	0.805	0.481	1.346
Other mental comorbidities	-0.420	0.203	0.038	0.657	0.442	0.977
diabetes	-0.513	0.293	0.080	0.598	0.337	1.063
hyperlipedemia	0.100	0.345	0.771	1.106	0.562	2.175
hypertension	-0.144	0.237	0.542	0.866	0.544	1.376

Table 31a: Logistic regression model for the impact of index antipsychotic on having a mental health-related ER episode among bipolar disorder patients (contd.)

	Beta	*SE*	*Sig. (p)*	*Odds ratio*	*95% CI for odds ratio*	
					Lower Limit	*Upper Limit*
Charlson Comorbidity Index	-0.047	0.067	0.481	0.954	0.836	1.088
Pre-index period psychiatric medication use (days of supply)						
Mood stabilizers	-0.001	0.001	0.130	0.999	0.998	1.000
Antipsychotics	0.002	0.002	0.502	1.002	0.997	1.006
Antidepressants	0.000	0.001	0.377	1.000	0.998	1.001
Benzodiazepines	-0.001	0.001	0.353	0.999	0.998	1.001
Pre-index healthcare utilization and cost						
Number of psychotherapy visits	-0.010	0.021	0.644	0.990	0.950	1.032
Number of medication management visits	0.033	0.032	0.300	1.034	0.971	1.100
Any pre-index mental-health related ER visits	-0.758	0.314	0.016	0.469	0.253	0.868
Pre-index mental-health related physician visits	-0.057	0.060	0.346	0.945	0.840	1.063
Any pre-index mental-health related hospitalizations	-0.403	0.190	0.034	0.668	0.460	0.971
Year of index prescription (ref: 1999)						
• 2000	0.214	0.234	0.360	1.239	0.783	1.959
• 2001	0.297	0.277	0.284	1.346	0.782	2.317
Index prescription (ref: quetiapine)						
Risperidone	0.161	0.308	0.601	1.175	0.642	2.150
Olanzapine	0.044	0.281	0.876	1.045	0.602	1.813
Typicals	-0.215	0.310	0.489	0.807	0.439	1.482

Model fit statistics:

-2 Log Likehood = 866.29 , chi-square = 142.48 , $p < 0.0001$

TWO-PART MODEL-PART 2

Table 31b: Ordinary Least Squares (OLS) regression model for the impact of index antipsychotic on mental healthcare-related ER cost among bipolar disorder patients

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Demographic characteristics				
Age (in years)	0.001	0.008	0.180	0.858
18 years or above (ref: less than 18 years)	0.197	0.243	0.810	0.419
Males (ref: females)	0.000	0.001	0.170	0.863
Whites (ref: non-whites)	-0.129	0.346	-0.370	0.709
Metro (ref: non-metro)	-0.038	0.222	-0.170	0.864
Prescribing physician type				
Psychiatric prescriber	0.000	0.000	-0.730	0.465
Bipolar disorder subtype (ref: Bipolar disorder I)				
Bipolar disorder I	-0.056	0.231	-0.240	0.807
Mixed	-0.488	0.216	-2.260	0.025
Pre-index co-morbidities				
Alcohol and substance abuse	0.382	0.175	2.180	0.030
Schizophrenia	0.115	0.232	0.500	0.619
Major depression	0.402	0.206	1.950	0.052
Mild to Moderate depression	0.307	0.231	1.330	0.186
Other mental comorbidities	-0.118	0.193	-0.610	0.539
diabetes	0.466	0.258	1.810	0.072
hyperlipedemia	-0.370	0.320	-1.160	0.249
hypertension	0.041	0.217	0.190	0.849
Charlson Comorbidity Index	0.158	0.080	1.970	0.050
Pre-index period psychiatric medication use (days of supply)				
Mood stabilizers	0.051	0.001	1.170	0.244
Antipsychotics	-0.004	0.002	-1.560	0.121
Antidepressants	0.004	0.001	0.340	0.732
Benzodiazepines	-0.045	0.001	-1.550	0.123

Table 31b: Ordinary Least Squares (OLS) regression model for the impact of index antipsychotic on mental healthcare-related ER cost among bipolar disorder patients (contd.)

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Pre-index healthcare utilization and cost				
Number of psychotherapy visits	-0.029	0.016	-1.850	0.065
Number of medication management visits	-0.007	0.032	-0.210	0.831
Number of pre-index mental-health related ER visits	-0.040	0.114	-0.350	0.726
Pre-index mental-health related physician visits	-0.021	0.049	-0.440	0.663
Number of pre-index mental-health related hospitalizations	0.028	0.063	0.650	0.910
Pre-index mental health-related cost	0.000	0.013	0.030	0.978
Year of index prescription (ref: 1999)				
• 2000	0.229	0.211	1.080	0.280
• 2001	0.005	0.257	0.020	0.984
Index prescription (ref: quetiapine)				
Risperidone	-0.681	0.293	-2.320	0.071
Olanzapine	-0.494	0.264	-1.870	0.063
Typicals	-0.436	0.287	-1.520	0.130

Model fit statistics:

Adjusted R-square = 19.95% , F = 2.47, $p < 0.000$

Table 32: Ordinary Least Squares (OLS) regression model for the impact of index antipsychotic on mental healthcare-related pharmacy cost among bipolar disorder patients

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Demographic characteristics				
Age (in years)	0.001	0.003	0.37	0.714
18 years or above (ref: less than 18 years)	0.034	0.101	0.34	0.735
Males (ref: females)	0.000	0.001	0.66	0.507
Whites (ref: non-whites)	0.026	0.134	0.19	0.848
Metro (ref: non-metro)	-0.005	0.102	-0.05	0.961
Prescribing physician type				
Psychiatric prescriber	0.000	0.000	4.66	<.0001
Bipolar disorder subtype (ref: bipolar disorder I)				
Bipolar disorder I	0.039	0.108	0.36	0.717
Mixed	-0.249	0.107	-2.32	0.021
Pre-index co-morbidities				
Alcohol and substance abuse	-0.198	0.099	-2	0.045
Schizophrenia	-0.069	0.127	-0.54	0.590
Major depression	0.079	0.106	0.74	0.458
Mild to Moderate depression	-0.022	0.125	-0.17	0.863
Other mental comorbidities	0.084	0.092	0.92	0.360
Diabetes	0.124	0.142	0.88	0.381
Hyperlipedemia	0.025	0.158	0.16	0.876
Hypertension	-0.092	0.112	-0.82	0.411
Charlson Comorbidity Index	-0.044	0.032	-1.4	0.161
Pre-index period psychiatric medication use (days of supply)				
Mood stabilizers	0.041	0.000	4.73	<.0001
Antipsychotics	0.001	0.001	0.61	0.539
Antidepressants	0.045	0.000	5.3	<.0001
Benzodiazepines	0.032	0.000	2.34	0.020

Table 32: Ordinary Least Squares (OLS) regression model for the impact of index antipsychotic on mental healthcare-related pharmacy cost among bipolar disorder patients (contd.)

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Pre-index healthcare utilization and cost				
Number of psychotherapy visits	0.016	0.010	1.61	0.108
Number of medication management visits	-0.026	0.013	-1.93	0.054
Number of pre-index mental-health related ER visits	-0.068	0.078	-0.87	0.383
Pre-index mental-health related physician visits	0.014	0.028	0.48	0.632
Number of pre-index mental-health related hospitalizations	0.022	0.039	0.56	0.575
Pre-index mental health-related pharmacy cost	0.305	-0.060	0.9546	0.028
Year of index prescription (ref: 1999)				
• 2000	-0.044	0.103	-0.43	0.670
• 2001	0.016	0.121	0.13	0.898
Index prescription (ref: quetiapine)				
Risperidone	-0.002	0.137	-0.02	0.986
Olanzapine	0.117	0.126	2.22	0.035
Typicals	-0.859	0.139	-6.17	<.0001

Model fit statistics:

Adjusted R-square = 25.70% , **F =** 9.91, **p <** 0.0001

Table 33: Ordinary Least Squares (OLS) regression model for the impact of index antipsychotic on mental healthcare-related outpatient cost

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Demographic characteristics				
Age (in years)	0.003	0.015	0.17	0.865
18 years or above (ref: less than 18 years)	-0.194	0.431	-0.45	0.653
Males (ref: females)	0.005	0.002	2.08	0.038
Whites (ref: non-whites)	1.653	0.574	2.88	0.004
Metro (ref: non-metro)	-0.896	0.438	-2.05	0.041
Prescribing physician type				
Psychiatric prescriber	0.001	0.000	2.29	0.022
Bipolar disorder subtype (ref: bipolar disorder I)				
Bipolar disorder II	0.524	0.462	1.13	0.258
Mixed	-0.929	0.481	-2.89	<.0001
Pre-index co-morbidities				
Alcohol and substance abuse	1.048	0.425	2.46	0.014
Schizophrenia	0.747	0.543	1.37	0.170
Major depression	0.101	0.452	0.22	0.823
Mild to Moderate depression	0.785	0.535	1.47	0.143
Other mental comorbidities	-1.456	0.394	-3.7	0.000
diabetes	-0.068	0.607	-0.11	0.911
hyperlipedemia	-0.441	0.678	-0.65	0.516
hypertension	-0.335	0.478	-0.7	0.483
Charlson Comorbidity Index	-0.153	0.135	-1.13	0.257
Pre-index period psychiatric medication use (days of supply)				
Mood stabilizers	-0.001	0.001	-0.84	0.399
Antipsychotics	-0.006	0.004	-1.29	0.197
Antidepressants	0.000	0.001	-0.26	0.794
Benzodiazepines	0.003	0.001	2.51	0.012

Table 33: Ordinary Least Squares (OLS) regression model for the impact of index antipsychotic on mental healthcare-related outpatient cost (contd.)

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Pre-index healthcare utilization and cost				
Number of psychotherapy visits	-0.017	0.042	-0.41	0.683
Number of medication management visits	0.053	0.059	0.9	0.368
Number of pre-index mental-health related ER visits	-0.307	0.332	-0.92	0.356
Pre-index mental-health related physician visits	0.015	0.121	0.12	0.903
Number of pre-index mental-health related hospitalizations	0.374	0.168	2.23	0.026
Pre-index mental health-related outpatient cost	0.371	0.027	13.63	<.0001
Year of index prescription (ref: 1999)				
• 2000	-0.323	0.442	-0.73	0.466
• 2001	-0.623	0.518	-1.2	0.230
Index prescription (ref: quetiapine)				
Risperidone	-0.806	0.584	-1.38	0.168
Olanzapine	-0.629	0.537	-1.17	0.241
Typicals	0.075	0.597	2.95	0.003

Model fit statistics:

Adjusted R-square = 38.22% , **F** = 16.93, **p** < 0.0001

Results for research objective 10

For schizophrenia and bipolar patients, to compare the impact of quetiapine with risperidone, olanzapine, and typical antipsychotics on mental health-related healthcare hospitalizations.

Schizophrenia

Results of univariate analysis of mental-health inpatient utilization are presented in table 34. Though there were significantly greater proportion of patients with pre-index mental health-related hospitalizations and number of inpatient visits in the quetiapine cohort as compared to the typical antipsychotic cohort, there were no significant differences in the proportion of patients having post-index hospitalization and the post-index length of stay between quetiapine and other atypical antipsychotics. Though the length of stay among pre-index hospitalized patients in olanzapine cohort was significantly longer compared to quetiapine cohort, there were no significant differences in the length of stay between quetiapine and other atypical antipsychotic cohorts. However, length of stay in the post-index period was significantly shorter for quetiapine (9.9 $\pm$ 12.6) as compared to typical antipsychotics (13.4 $\pm$ 11.0).

Multivariate analysis for the number of hospitalization visits

As number of hospitalization is count data, poisson or negative binomial model was used to compare the impact of index antipsychotic on number of mental health-related hospitalizations. Poisson regression assumes that the conditional mean of the outcome is equal to conditional variance. Poisson regression model carried out for estimating the number of hospitalizations was found to be overdispersed ie. the variance was greater than the conditional mean. This was due to high proportion of patients with

zero count. Therefore, a negative binomial model was used for estimation of number of hospitalization as it relaxes the assumption that the conditional mean should be equal to the variance. The model statistics and the results are presented in table 35. The results show that there is no significant impact of receiving quetiapine as index antipsychotic compared to other index antipsychotics on number of mental health-related hospitalizations.

Time to the first-mental health-related hospitalization

Univariate Kaplan Meier analysis revealed that time to the first mental health-related hospitalization was not significantly different among the index cohorts as indicated by log rank statistics of 1.43 ($p = 0.696$). The Kaplan Meier survival curves are presented in figure 4.

A multivariate Cox proportional model that controlled for confounders did not show any significant impact of using quetiapine as index antipsychotic on time to first mental health-related hospitalization (table 36).

Bipolar Disorder

Results of univariate analysis of mental-health inpatient utilization in bipolar disorder patients are presented in table 37. There were no significant differences between quetiapine and other antipsychotics in terms of post-index proportion of patients with mental health-related inpatient visits, number of inpatient visits and length of stay.

The results of the negative binomial model show that there is no significant impact of receiving quetiapine as index antipsychotic compared to other index antipsychotics on number of mental health-related hospitalizations (table 38).

Table 34: Mental health-related hospitalization comparison (Quetiapine versus other antipsychotics) among schizophrenia patients

	Olanzapine N = 346	*Risperidone N = 201*	*Quetiapine N = 149*	*Typical N = 303*
Patients hospitalized				
N (%)				
Pre-index	126 (36.4%)	66 (32.8%)	58[T] (38.9%)	79[Q] (26.1%)
Post-index	107 (30.9%)	52 (25.9%)	46 (30.9%)	87 (28.7%)
Number of Inpatient Visits				
Mean (±std)				
Pre-index	0.6 (±1.1)	0.5 (±1.2)	0.5[T] (±0.8)	0.4[Q] (±0.7)
Post-index	0.6 (±1.2)	0.5 (±1.1)	0.5 (±1.1)	0.6 (±1.2)
Length of Stay				
Mean (±std)				
Pre-index	13.4 [Q] (±17.6)	13.6 (±40.9)	8.9[O] (±7.8)	12.0 (±11.8)
Post-index	12.2 (±13.6)	10.2 (±9.4)	9.9 [T] (±12.6)	13.4 [Q] (±11.0)

[O] Significant difference between quetiapine and olanzapine cohorts at $p<0.05$
[R] Significant difference between quetiapine and risperidone cohorts at $p<0.05$
[T] Significant difference between quetiapine and typicals cohorts at $p<0.05$

Table 35: Negative binomial model for the impact of index antipsychotic therapy of number of mental health-related hospitalization among schizophrenia patients

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Demographic characteristics				
Age (in years)	0.004	0.006	0.590	0.442
Males (ref: females)	0.005	0.007	0.540	0.464
Whites (ref: non-whites)	0.610	0.234	6.780	0.009
Metro (ref: non-metro)	-0.131	0.153	0.740	0.390
Prescribing physician type				
Psychiatric prescriber	0.000	0.000	0.160	0.691
Schizophrenia subtype (ref: only schizophrenia)				
Schizoaffective disorder	-0.501	0.164	9.370	0.002
Both schizoaffective disorder and schizophrenia	-0.695	0.176	15.640	<.0001
Pre-index co-morbidities				
Alcohol and substance abuse	0.859	0.134	41.120	<.0001
Bipolar disorder	0.227	0.185	1.500	0.220
Major depression	0.147	0.162	0.820	0.366
Mild to Moderate depression	0.390	0.176	4.900	0.027
Other mental comorbidities	0.173	0.146	1.400	0.236
diabetes	0.435	0.201	4.700	0.030
hyperlipedemia	-0.229	0.251	0.830	0.362
hypertension	-0.062	0.175	0.120	0.724
Charlson Comorbidity Index	0.169	0.051	11.160	0.001
Pre-index period psychiatric medication use (days of supply)				
Mood stabilizers	0.000	0.001	0.300	0.585
Antipsychotics	0.001	0.002	0.280	0.597
Antidepressants	0.001	0.000	1.810	0.178
Benzodiazepines	0.001	0.001	0.880	0.348

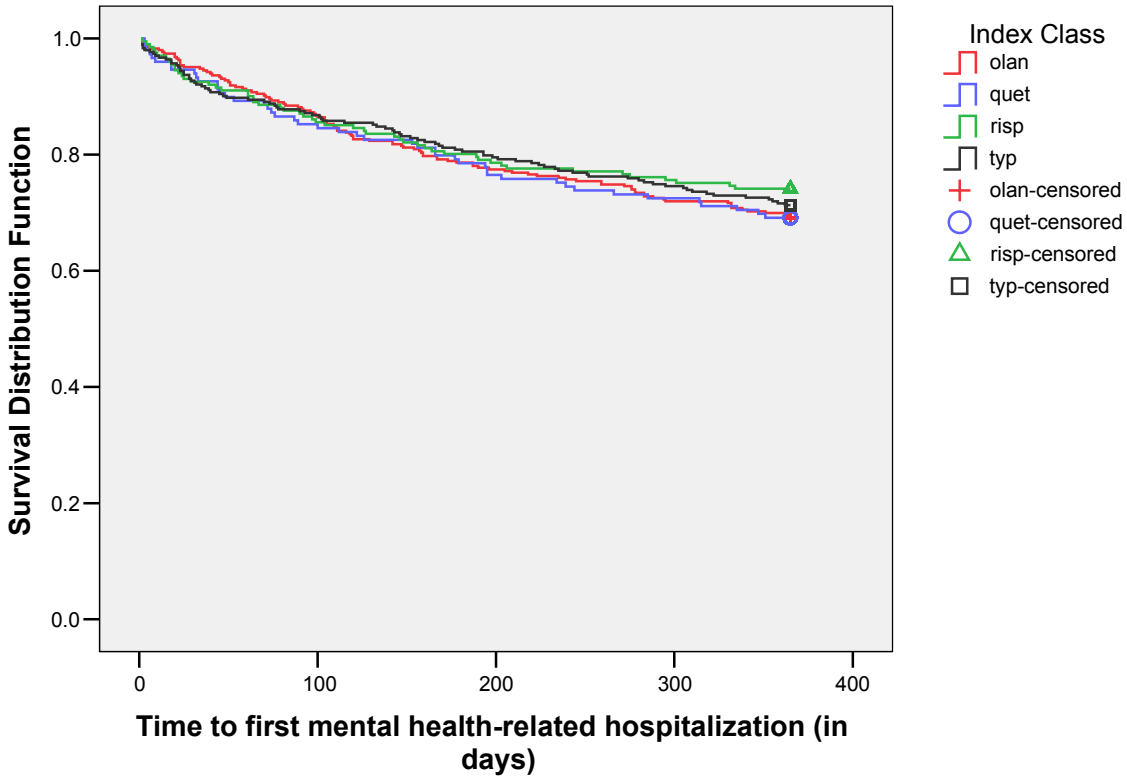
Table 35: Negative binomial model for the impact of index antipsychotic therapy of number of mental health-related hospitalization among schizophrenia patients (contd.)

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Pre-index healthcare utilization and cost				
Number of psychotherapy visits	-0.002	0.013	0.030	0.866
Number of medication management visits	-0.066	0.024	7.390	0.007
Number of pre-index mental-health related ER visits	-0.096	0.117	0.670	0.413
Pre-index mental-health related physician visits	-0.049	0.043	1.270	0.261
Number of pre-index mental-health related hospitalizations	0.291	0.059	24.010	<.0001
Year of index prescription (ref: 1999)				
• 2000	0.203	0.166	1.490	0.222
• 2001	-0.170	0.205	0.690	0.406
Index prescription (ref: quetiapine)				
Risperidone	-0.276	0.219	1.590	0.208
Olanzapine	-0.307	0.194	2.510	0.113
Typicals	-0.167	0.203	0.670	0.412

Model fit statistics:

-2 Log Likehood = 1008.08, $\chi^2 = 220.39$, p = 0.0001
Dispersion estimate = 1.36, p = 0.00

Figure 4: Kaplan Meier Survival Curves for time to first mental health-related hospitalization among schizophrenia patients



Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	1.439	3	.696

Test of equality of survival distributions for the different levels of index class

Table 36: Cox Proportional hazard model for the impact of index antipsychotic therapy on time to the first mental health-related hospitalization among schizophrenia patients (contd.)

	Beta	*SE*	*Sig. (p)*	*Hazards Ratio*	*95% CI for hazards ratio*	
					Lower limit	*Upper limit*
Demographic characteristics						
Age (in years)	0.003	0.007	0.727	1.003	0.988	1.017
Males (ref: females)	-0.461	0.161	0.004	0.631	0.461	0.864
Whites (ref: non-whites)	0.488	0.305	0.110	1.628	0.896	2.959
Metro (ref: non-metro)	-0.279	0.186	0.134	0.757	0.526	1.089
Prescribing physician type						
Psychiatric prescriber	-0.105	0.186	0.574	0.901	0.625	1.298
Schizophrenia subtype (ref: only schizophrenia)						
Schizoaffective disorder	-0.392	0.195	0.045	0.675	0.461	0.990
Both schizoaffective disorder and schizophrenia	-0.699	0.209	0.001	0.497	0.330	0.748
Pre-index co-morbidities						
Alcohol and substance abuse	0.658	0.163	<.0001	1.931	1.403	2.657
Bipolar disorder	0.357	0.218	0.101	1.429	0.933	2.190
Major depression	0.170	0.191	0.373	1.185	0.815	1.724
Mild to Moderate depression	0.241	0.195	0.216	1.273	0.869	1.866
Other mental comorbidities	0.076	0.188	0.688	1.078	0.746	1.559
diabetes	0.303	0.233	0.192	1.354	0.859	2.136
hyperlipedemia	-0.490	0.317	0.123	0.613	0.329	1.141
hypertension	-0.235	0.208	0.259	0.791	0.526	1.189

Table 36: Cox Proportional hazard model for the impact of index antipsychotic therapy on time to the first mental health-related hospitalization among schizophrenia patients (contd.)

	Beta	*SE*	*Sig. (p)*	*Hazards Ratio*	*95% CI for hazards ratio*	
					Lower limit	*Upper limit*
Charlson Comorbidity Index	0.168	0.051	0.001	1.183	1.071	1.306
Pre-index period psychiatric medication use (days of supply)						
Mood stabilizers	0.000	0.001	0.959	1.000	0.999	1.001
Antipsychotics	-0.002	0.003	0.448	0.998	0.992	1.003
Antidepressants	0.000	0.000	0.672	1.000	0.999	1.001
Benzodiazepines	0.000	0.001	0.673	1.000	0.999	1.001
Pre-index healthcare utilization and cost						
Number of psychotherapy visits	0.004	0.012	0.738	1.004	0.981	1.027
Number of medication management visits	-0.072	0.029	0.014	0.931	0.879	0.986
Any pre-index mental-health related ER visits	-0.011	0.091	0.904	0.989	0.828	1.181
Pre-index mental-health related physician visits	0.022	0.042	0.588	1.023	0.943	1.109
Any pre-index mental-health related hospitalizations	0.154	0.059	0.008	1.167	1.040	1.309
Year of index prescription (ref: 1999)						
• 2000	0.131	0.186	0.480	1.140	0.792	1.641
• 2001	-0.110	0.229	0.631	0.896	0.571	1.404
Index prescription (ref: quetiapine)						
Risperidone	-0.273	0.251	0.277	0.761	0.465	1.245
Olanzapine	-0.160	0.205	0.436	0.852	0.570	1.274
Typicals	-0.250	0.235	0.288	0.779	0.491	1.235

Model fit statistics:
-2 Log Likelihood = 2349.62, χ^2 = 100.91, $p < 0.0001$

Table 37: Mental health-related hospitalization comparison (Quetiapine versus other antipsychotics) among bipolar disorder patients

	Olanzapine N = 283	*Risperidone N = 231*	*Quetiapine N = 106*	*Typical N = 205*
Patients hospitalized N (%)				
Pre-index	102 (36.0%)	72 (31.1%)	39[T] (36.8%)	51[Q] (24.8%)
Post-index	84 (29.7%)	60 (26.0%)	30 (28.3%)	59 (28.9%)
Number of Inpatient Visits Mean (std)				
Pre-index	0.7 (±1.1)	0.5 (±0.9)	0.5 (±1.2)	0.3 (±0.7)
Post-index	0.5 (±1.1)	0.6 (±1.1)	0.4 (±1.1)	0.5 (±1.0)
Length of Stay Mean (±std)				
Pre-index	11.8 (±18.6)	11.2 (±16.2)	8.6 (±6.2)	10.9 (±12.8)
Post-index	10.0 (±13.3)	9.2 (±10.1)	8.2 (±12.0)	10.4 (±10.2)

[O] Significant difference between quetiapine and olanzapine cohorts at $p<0.05$
[R] Significant difference between quetiapine and risperidone cohorts at $p<0.05$
[T] Significant difference between quetiapine and typicals cohorts at $p<0.05$

Table 38: Negative binomial model for the impact of index antipsychotic therapy of number of mental health-related hospitalization among bipolar disorder patients

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Demographic characteristics				
Age (in years)	0.009	0.006	2.190	0.139
18 years or above (ref: less than 18 years)	0.292	0.194	2.280	0.131
Males (ref: females)	0.005	0.008	0.460	0.499
Whites (ref: non-whites)	0.772	0.287	7.240	0.007
Metro (ref: non-metro)	-0.119	0.177	0.460	0.500
Prescribing physician type				
Psychiatric prescriber	0.000	0.000	0.080	0.775
Bipolar disorder subtype (ref: bipolar disorder I)				
Bipolar disorder II	-0.477	0.188	6.450	0.011
Mixed	-0.732	0.191	14.620	0.000
Pre-index co-morbidities				
Alcohol and substance abuse	0.898	0.150	35.910	<.0001
Bipolar disorder	0.212	0.207	1.050	0.305
Major depression	0.108	0.181	0.350	0.552
Mild to Moderate depression	0.221	0.200	1.230	0.268
Other mental comorbidities	0.189	0.162	1.360	0.243
diabetes	0.357	0.215	2.760	0.097
hyperlipedemia	-0.209	0.267	0.620	0.433
hypertension	0.008	0.187	0.000	0.966
Charlson Comorbidity Index	0.171	0.051	11.120	0.001
Pre-index period psychiatric medication use (days of supply)				
Mood stabilizers	0.000	0.001	0.170	0.679
Antipsychotics	0.001	0.002	0.150	0.698
Antidepressants	0.000	0.001	0.530	0.465
Benzodiazepines	0.001	0.001	1.450	0.228

Table 38: Negative binomial model for the impact of index antipsychotic therapy of number of mental health-related hospitalization among bipolar disorder patients (contd.)

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Pre-index healthcare utilization and cost				
Number of psychotherapy visits	0.009	0.016	0.310	0.579
Number of medication management visits	-0.084	0.029	8.360	0.004
Number of pre-index mental-health related ER visits	-0.084	0.123	0.470	0.493
Pre-index mental-health related physician visits	-0.026	0.047	0.300	0.585
Number of pre-index mental-health related hospitalizations	0.263	0.063	17.690	<.0001
Year of index prescription (ref: 1999)				
• 2000	0.306	0.176	3.010	0.083
• 2001	-0.186	0.226	0.680	0.410
Index prescription (ref: quetiapine)				
Risperidone	-0.158	0.242	0.430	0.514
Olanzapine	-0.371	0.228	2.650	0.104
Typicals	-0.158	0.242	0.430	0.514

Model fit statistics:

-2 Log Likehood = 880.56, χ^2 = 323.98 , $p < 0.0001$
Dispersion estimate = 1.05, p = 0.00

The univariate Kaplan Meier analysis revealed that time to the first mental health-related hospitalization was not significantly different between the index cohorts as indicated by log rank statistics of 0.577 (p = 0.902). The Kaplan Meier survival curves are presented in figure 5.

A multivariate Cox proportional model that controlled for confounders did not show any significant impact of using quetiapine as index antipsychotic on time to first mental health-related hospitalization (table 39).

Results for research objective 11

For schizophrenia patients, to compare the impact of quetiapine with risperidone, olanzapine, and typical antipsychotics on mental healthcare-related emergency room visits.

Schizophrenia

Results of univariate analysis of mental-health-related ER utilization are presented in table 40. Univariate analysis revealed that there were significantly greater proportion of patients with pre-index mental health related ER visits and significantly greater number of pre-index mental health related ER visits in the quetiapine cohort as compared to typical cohort. However, there were no significant differences in the post-index comparisons.

Multivariate analysis of number of mental health-related ER visit

If the proportion of zeroes is disproportionately large, negative binomial regression has to be replaced by zero inflated models. Zero inflated poisson models allows for proportion of zero values to be higher than poisson or negative binomial regression. As there were many patients with no mental health-related ER visit, zero

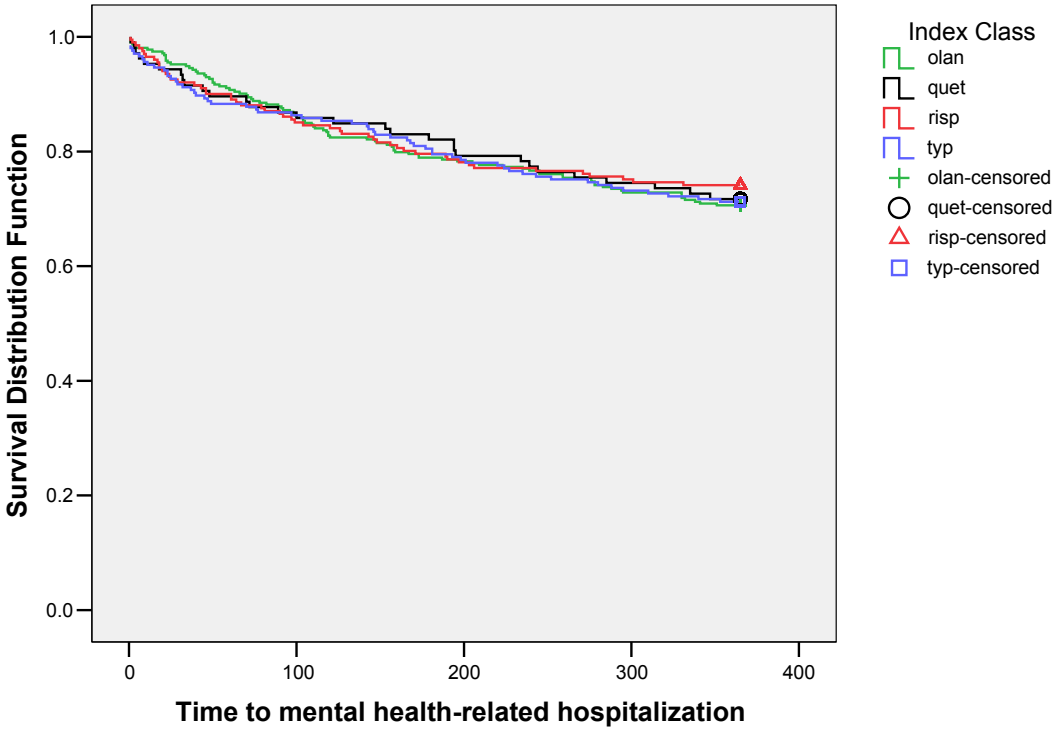
inflated model was used for multivariate comparisons. The model statistics and results are presented in the table 41. Vuong statistic is significant and positive supporting the use of zero inflated model. Patients initiated on quetiapine did not have any significant difference in mental health related ER visits compared to patients initiated on other index antipsychotics.

Bipolar Disorder

Results of univariate analysis of mental-health-related ER utilization are presented in table 42. Univariate analysis reveals that there were significantly a greater proportion of patients with pre-index mental health related ER visits in the quetiapine cohort (11.3%) as compared to the typical cohort (1.9%). Also, there was a significantly greater proportion of patients with pre-index mental health related ER visits in the risperidone cohort (15.1%) compared to quetiapine cohort (11.3%). However, there were no significant differences in the post-index comparisons.

The multivariate zero inflated model also did not show any significant differences in the mental health related ER visits among patients initiated on Quetiapine as compared to patients initiated on other index antipsychotics (Table 43).

Figure 5: Kaplan Meier Survival Curves for time to first mental health-related hospitalization among bipolar disorder patients



Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	.577	3	.902

Test of equality of survival distributions for the different levels of index class.

Table 39: Cox Proportional hazard model for the impact of index antipsychotic therapy on time to the first mental health-related hospitalization among bipolar disorder patients

	Beta	*SE*	*Sig. (p)*	*Hazards Ratio*	*95% CI for hazards ratio*	
					Lower limit	*Upper limit*
Demographic characteristics						
Age (in years)	0.008	0.008	0.363	1.008	0.991	1.024
18 years or above (ref: less than 18 years)	0.039	0.234	0.866	1.040	0.658	1.646
Males (ref: females)	-0.490	0.179	0.006	0.613	0.431	0.871
Whites (ref: non-whites)	0.722	0.374	0.054	2.058	0.988	4.287
Metro (ref: non-metro)	-0.284	0.218	0.192	0.753	0.492	1.153
Prescribing physician type						
Psychiatric prescriber	-0.239	0.209	0.253	0.787	0.523	1.186
Bipolar disorder subtype (ref: Bipolar disorder I)						
Bipolar disorder II	-0.487	0.231	0.035	0.614	0.390	0.967
Mixed	-0.926	0.238	0.000	0.396	0.248	0.632
Pre-index co-morbidities						
Alcohol and substance abuse	0.760	0.189	<.0001	2.139	1.475	3.101
Bipolar disorder	0.194	0.250	0.438	1.214	0.743	1.984
Major depression	0.174	0.213	0.414	1.191	0.784	1.809
Mild to Moderate depression	0.053	0.226	0.814	1.054	0.677	1.641
Other mental comorbidities	0.246	0.209	0.240	1.279	0.849	1.927
Diabetes	0.371	0.253	0.143	1.449	0.882	2.380
Hyperlipedemia	-0.288	0.336	0.392	0.750	0.388	1.449
Hypertension	-0.304	0.227	0.180	0.738	0.473	1.151

Table 39: Cox Proportional hazard model for the impact of index antipsychotic therapy on time to the first mental health-related hospitalization among bipolar disorder patients (contd.)

	Beta	*SE*	*Sig. (p)*	*Hazards Ratio*	*95% CI for hazards ratio*	
					Lower limit	*Upper limit*
Charlson Comorbidity Index	0.168	0.054	0.002	1.182	1.064	1.314
Pre-index period psychiatric medication use (days of supply)						
Mood stabilizers	0.000	0.001	0.691	1.000	0.999	1.002
Antipsychotics	-0.002	0.003	0.555	0.998	0.992	1.004
Antidepressants	0.000	0.001	0.468	1.000	0.999	1.001
Benzodiazepines	0.000	0.001	0.805	1.000	0.999	1.001
Pre-index healthcare utilization and cost						
Number of psychotherapy visits	0.020	0.022	0.364	1.020	0.977	1.064
Number of medication management visits	-0.104	0.036	0.004	0.901	0.840	0.967
Any pre-index mental-health related ER visits	-0.051	0.111	0.647	0.950	0.764	1.182
Pre-index mental-health related physician visits	0.069	0.049	0.158	1.071	0.974	1.179
Any pre-index mental-health related hospitalizations	0.132	0.067	0.049	1.142	1.001	1.303
Year of index prescription (ref: 1999)						
• 2000	0.119	0.211	0.571	1.127	0.746	1.702
• 2001	-0.130	0.262	0.618	0.878	0.526	1.465
Index prescription (ref: quetiapine)						
Risperidone	-0.312	0.289	0.279	0.732	0.416	1.288
Olanzapine	-0.227	0.248	0.361	0.797	0.490	1.297

Table 39: Cox Proportional hazard model for the impact of index antipsychotic therapy on time to the first mental health-related hospitalization among bipolar disorder patients (contd.)

	Beta	*SE*	*Sig. (p)*	*Hazards Ratio*	*95% CI for hazards ratio*	
					Lower limit	*Upper limit*
Typicals	-0.179	0.293	0.541	0.836	0.471	1.484

Model fit statistics:

-2 Log Likelihood = 1822.14, χ^2 = 94.26, $p < 0.0001$

Table 40: Mental health-related ER visits comparison (Quetiapine versus other antipsychotics) among schizophrenia patients

	Olanzapine *N = 346*	*Risperidone* *N = 201*	*Quetiapine* *N = 149*	*Typical* *N = 303*
Patients with Mental-Health Related ER visits N (%)				
Pre-index	36 (10.4%)	24 (11.9%)	14[T] (9.4%)	10[Q] (3.3%)
Post-index	61 (17.6%)	31 (15.4%)	27 (18.1%)	47 (15.5%)
Number of Mental -Health Related ER Mean (±std)				
Pre-index	0.14 (±0.49)	0.21 (±0.81)	0.12[T] (±0.41)	0.04[Q] (±0.27)
Post-index	0.39 (±1.63)	0.23 (±0.67)	0.32 (±0.84)	0.26 (±0.82)

[O] Significant difference between quetiapine and olanzapine cohorts at $p<0.05$
[R] Significant difference between quetiapine and risperidone cohorts at $p<0.05$
[T] Significant difference between quetiapine and typicals cohorts at $p<0.05$

Table 41: Zero-inflated poisson regression model for the impact of index antipsychotic therapy of number of mental health-related ER visit among schizophrenia patients

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Demographic characteristics				
Age (in years)	0.010	0.006	1.755	0.079
Males (ref: females)	0.125	0.125	1.005	0.315
Whites (ref: non-whites)	0.989	0.299	3.304	0.001
Metro (ref: non-metro)	0.107	0.138	0.775	0.438
Prescribing physician type				
Psychiatric prescriber	0.001	0.000	4.673	0.000
Schizophrenia subtype (ref: only schizophrenia)				
Schizoaffective disorder	-0.690	0.164	-4.210	0.000
Both schizoaffective disorder and schizophrenia	-0.745	0.171	-4.344	0.000
Pre-index co-morbidities				
Alcohol and substance abuse	0.668	0.127	5.265	0.000
Bipolar disorder	0.151	0.166	0.909	0.363
Major depression	0.455	0.141	3.232	0.001
Mild to Moderate depression	0.338	0.149	2.260	0.024
Other mental comorbidities	0.363	0.139	2.604	0.009
diabetes	-0.153	0.218	-0.699	0.485
hyperlipedemia	-0.315	0.282	-1.119	0.263
hypertension	-0.144	0.169	-0.852	0.394
Charlson Comorbidity Index	0.036	0.050	0.720	0.472
Pre-index period psychiatric medication use (days of supply)				
Mood stabilizers	-0.001	0.001	-1.862	0.063
Antipsychotics	-0.014	0.004	-3.410	0.001
Antidepressants	0.000	0.000	-0.660	0.509
Benzodiazepines	0.000	0.001	0.613	0.540

Table 41: Zero-inflated poisson regression model for the impact of index antipsychotic therapy of number of mental health-related ER visit among schizophrenia patients (contd.)

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Pre-index healthcare utilization and cost				
Number of psychotherapy visits	-0.013	0.012	-1.126	0.260
Number of medication management visits	-0.021	0.022	-0.950	0.342
Number of pre-index mental-health related ER visits	0.366	0.064	5.680	0.000
Pre-index mental-health related physician visits	0.013	0.008	1.574	0.116
Number of pre-index mental-health related hospitalizations	-0.138	0.065	-2.136	0.033
Year of index prescription (ref: 1999)				
• 2000	-0.006	0.154	-0.041	0.967
• 2001	-0.276	0.189	-1.459	0.145
Index prescription (ref: quetiapine)				
Risperidone	-0.500	0.225	-2.218	0.087
Olanzapine	0.039	0.176	0.224	0.823
Typicals	-0.103	0.196	-0.524	0.600

Model fit statistics:

Log Likelihood = -702.84, χ^2 = 331.27, p = 0.0001
Vuong statistic = 1.76, p = 0.00

Table 42: Mental health-related ER visits comparison (Quetiapine versus other antipsychotics) among bipolar disorder patients

	Olanzapine *N = 283*	*Risperidone* *N = 231*	*Quetiapine* *N = 106*	*Typical* *N = 205*
Patients with Mental-Health Related ER visits N (%)				
Pre-index	32 (11.3%)	35 [Q] (15.1%)	12[T] (11.3%)	4[Q] (1.9%)
Post-index	53 (18.7%)	45 (19.5%)	19 (17.9%)	34 (16.5%)
Number of Mental -Health Related ER Mean (±std)				
Pre-index	0.12 (±0.51)	0.11 (±0.72)	0.14 (±0.52)	0.14 (±0.10)
Post-index	0.32 (±1.62)	0.22 (±0.63)	0.34 (±0.97)	0.21 (±0.73)

[O] Significant difference between quetiapine and olanzapine cohorts at $p<0.05$
[R] Significant difference between quetiapine and risperidone cohorts at $p<0.05$
[T] Significant difference between quetiapine and typicals cohorts at $p<0.05$

Table 43: Zero-inflated poisson regression model for the impact of index antipsychotic therapy of number of mental health-related ER visit among bipolar disorder patients (contd.)

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Demographic characteristics				
Age (in years)	0.019	0.006	2.920	0.004
Males (ref: females)	0.298	0.196	1.525	0.127
Whites (ref: non-whites)	0.169	0.138	1.218	0.223
Metro (ref: non-metro)	1.029	0.333	3.089	0.002
Prescribing physician type				
Psychiatric prescriber	0.006	0.158	0.036	0.972
Bipolar disorder subtype (ref: bipolar disorder I)				
Bipolar disorder II	0.001	0.000	4.808	0.000
Mixed	-0.756	0.187	-4.035	0.000
Pre-index co-morbidities				
Alcohol and substance abuse	-0.962	0.188	-5.117	0.000
Bipolar disorder	0.596	0.145	4.112	0.000
Major depression	0.208	0.182	1.146	0.252
Mild to Moderate depression	0.560	0.153	3.646	0.000
Other mental comorbidities	0.158	0.173	0.912	0.362
diabetes	0.565	0.156	3.625	0.000
hyperlipedemia	-0.189	0.231	-0.817	0.414
hypertension	-0.104	0.293	-0.356	0.722
Charlson Comorbidity Index	-0.177	0.180	-0.984	0.325
Pre-index period psychiatric medication use (days of supply)				
Mood stabilizers	0.019	0.055	0.342	0.733
Antipsychotics	-0.001	0.001	-1.997	0.046
Antidepressants	-0.012	0.004	-2.835	0.005
Benzodiazepines	-0.001	0.000	-1.242	0.214
Pre-index healthcare utilization and cost				
Number of psychotherapy visits	0.001	0.001	0.886	0.376

Table 43: Zero-inflated poisson regression model for the impact of index antipsychotic therapy of number of mental health-related ER visit among bipolar disorder patients (contd.)

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Number of medication management visits	0.000	0.014	0.022	0.982
Number of pre-index mental-health related ER visits	-0.034	0.025	-1.348	0.178
Pre-index mental-health related physician visits	0.332	0.072	4.625	0.000
Number of pre-index mental-health related hospitalizations	0.017	0.008	2.037	0.042
Year of index prescription (ref: 1999)				
• 2000	-0.138	0.072	-1.922	0.055
• 2001	-0.063	0.171	-0.371	0.711
Index prescription (ref: quetiapine)				
Risperidone	-0.193	0.205	-0.940	0.347
Olanzapine	-0.273	0.208	-1.313	0.189
Typicals	0.627	0.244	2.566	0.110

Model fit statistics:

Log Likelihood = -570.92, χ^2 = 283.47, p = 0.0001
Vuong statistic = 1.59, p = 0.00

Results for research objective 12

For schizophrenia and bipolar disorder patients, to compare the impact of quetiapine with risperidone, olanzapine, and typical antipsychotics on mental healthcare-related physician visits.

Schizophrenia

Results of univariate analysis of mental-health-related outpatient utilization are presented in table 44. Patients in quetiapine cohort had a greater number of pre-index mental health-related physician office visits, psychotherapy sessions, and medication management visits than patients in other cohorts. Univariate analysis revealed the average number of post-index mental health-related physician office visits and medication management visits were significantly greater for quetiapine patients compared to other antipsychotics. The average number of psychotherapy sessions was significantly greater among risperidone patients (1.25 + 7.83) as compared to quetiapine patients (0.77 + 2.68).

Multivariate analysis to assess the impact of index antipsychotic was performed only for the mental health-related physician office visits. Results of negative binomial model revealed that mental health related physician office visit was not significantly different among patients initiated on quetiapine and other index antipsychotics (Table 45).

Table 44: Physician office-visits, psychotherapy, and medication management psychotherapy sessions comparison (Quetiapine versus other antipsychotics) among schizophrenia patients

	Olanzapine N = 346	*Risperidone N = 201*	*Quetiapine N = 149*	*Typical N = 303*
Number of Mental Health-Related physician office visits Mean (±std)				
Pre-index	0.57 (±1.70)	0.33 [Q] (±1.14)	0.67 [T] (±2.02)	0.14 [Q] (±0.84)
Post-index	0.86 [Q] (±2.22)	0.45 [Q] (±1.17)	1.06 [TR] (±2.48)	0.42 [Q] (±1.27)
Number of Psychotherapy Sessions Mean (±std)				
Pre-index	0.76 (±6.31)	0.28 [Q] (±1.85)	0.70 [T] (±3.98)	0.26 [Q] (±3.24)
Post-index	1.25 [Q] (±7.83)	0.63 (±2.53)	0.77 [T] (±2.68)	0.38 [Q] (±2.92)
Number of Medication Management Sessions Mean (±std)				
Pre-index	1.56 [Q] (±2.79)	1.66 [Q] (±2.88)	2.44 [OTR] (±4.15)	1.27 [Q] (±2.61)
Post-index	3.49 [Q] (±4.12)	3.09 [Q] (±4.12)	4.29 [OTR] (±4.25)	0.38 [Q] (±2.92)

[O] Significant difference between quetiapine and olanzapine cohorts at $p<0.05$
[R] Significant difference between quetiapine and risperidone cohorts at $p<0.05$
[T] Significant difference between quetiapine and typicals cohorts at $p<0.05$

Table 45: Negative binomial model for the impact of index antipsychotic therapy of number of mental health-related physician visit among schizophrenia patients

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Demographic characteristics				
Age (in years)	-0.005	0.008	0.310	0.577
Males (ref: females)	0.000	0.001	0.110	0.736
Whites (ref: non-whites)	0.365	0.342	1.140	0.286
Metro (ref: non-metro)	0.283	0.233	1.470	0.225
Prescribing physician type				
Psychiatric prescriber	0.000	0.000	2.120	0.146
Schizophrenia subtype (ref: only schizophrenia)				
Schizoaffective disorder	-0.226	0.262	0.750	0.388
Both schizoaffective disorder and schizophrenia	-0.082	0.271	0.090	0.763
Pre-index co-morbidities				
Alcohol and substance abuse	0.155	0.226	0.470	0.491
Bipolar disorder	0.376	0.289	1.690	0.194
Major depression	0.675	0.240	7.900	0.005
Mild to Moderate depression	-0.100	0.287	0.120	0.729
Other mental comorbidities	-0.007	0.215	0.000	0.974
diabetes	0.303	0.334	0.820	0.364
hyperlipedemia	-0.407	0.390	1.090	0.296
hypertension	0.308	0.263	1.370	0.242
Charlson Comorbidity Index	-0.166	0.102	2.660	0.103
Pre-index period psychiatric medication use (days of supply)				
Mood stabilizers	0.000	0.001	0.350	0.554
Antipsychotics	-0.001	0.003	0.040	0.849
Antidepressants	0.001	0.001	1.980	0.160
Benzodiazepines	0.001	0.001	0.650	0.419
Pre-index healthcare utilization and cost				
Number of psychotherapy visits	-0.002	0.026	0.000	0.944

Table 45: Negative binomial model for the impact of index antipsychotic therapy of number of mental health-related physician visit among schizophrenia patients (contd.)

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Number of medication management visits	-0.104	0.034	9.330	0.002
Number of pre-index mental-health related ER visits	0.135	0.185	0.530	0.467
Pre-index mental-health related physician visits	0.325	0.073	20.150	<.0001
Number of pre-index mental-health related hospitalizations	0.022	0.098	0.050	0.824
Year of index prescription (ref: 1999)				
• 2000	0.365	0.256	2.030	0.154
• 2001	0.230	0.306	0.570	0.451
Index prescription (ref: quetiapine)				
Risperidone	-0.147	0.282	0.270	0.602
Olanzapine	0.364	0.243	2.250	0.134
Typicals	0.554	0.305	3.290	0.070

Model fit statistics:

-2 Log Likelihood = 1074.08, χ^2 = 179.09, p = 0.0001
Dispersion estimate = 1.11, p = 0.00

Bipolar Disorder

Results of univariate analysis of mental-health-related outpatient utilization are presented in table 46. The average number of post-index mental health-related physician office visits were significantly greater for quetiapine patients (0.92 + 2.21) as compared to risperidone (0.41 + 1.05) and typical antipsychotic (0.48 + 1.43) patients. The average pre- and post-index numbers of psychotherapy sessions were significantly higher for quetiapine patients compared to typical antipsychotic cohort. The average numbers of medication management sessions were significantly higher for patients on quetiapine compared to patients on other antipsychotics.

Results of negative binomial model revealed that mental health related physician office visit was not significantly different among patients initiated on quetiapine and other index antipsychotics (Table 47).

Results for research objective 13

For schizophrenia patients, to compare the impact of quetiapine with risperidone, olanzapine, and typical antipsychotics on psychiatric medication utilization.

Schizophrenia

Results of univariate analysis of mental-health-related pharmacy utilization are presented in table 48. Results of Mantel Hansel tests show that significantly greater proportions of patients in quetiapine cohort (39.6%) were using mood stabilizers as compared to the olanzapine cohort (27.5%), risperidone cohort (24.9%) and typicals cohort (16.8%) in the pre-index period. However, post-index comparisons showed significant differences only among quetiapine (55.0%) and typical antipsychotic (32.3%) cohort.

Table 46: Physician office-visits, psychotherapy, and medication management psychotherapy sessions comparison (Quetiapine versus other antipsychotics) among bipolar disorder patients

	Olanzapine N = 283	*Risperidone N = 231*	*Quetiapine N = 106*	*Typical N = 205*
Number of Mental Health-Related physician office visits Mean (±std)				
Pre-index	0.55 (±1.63)	0.30 (±1.03)	0.60[T] (±1.90)	0.20[Q] (±1.00)
Post-index	0.89 (±2.29)	0.41 [Q] (±1.05)	0.92[RT] (±2.21)	0.48 [Q] (±1.43)
Number of Psychotherapy Sessions Mean (±std)				
Pre-index	0.57 (±4.98)	0.25 (±1.66)	0.70 [T] (±4.00)	0.28 [Q] (±3.84)
Post-index	1.08 (±6.47)	0.57 (±2.28)	0.91 [T] (±3.01)	0.14 [Q] (±1.50)
Number of Medication Management Sessions Mean (±std)				
Pre-index	1.57 (±2.86)	1.50 (±2.59)	2.63 [T] (±4.14)	0.99 [Q] (±2.47)
Post-index	3.57 [Q] (±4.23)	2.78 [Q] (±3.76)	4.72 [ORT] (±4.20)	2.31 [Q] (±3.95)

[O] Significant difference between quetiapine and olanzapine cohorts at p<0.05
[R] Significant difference between quetiapine and risperidone cohorts at p<0.05
[T] Significant difference between quetiapine and typicals cohorts at p<0.05

Table 47: Negative binomial model for the impact of index antipsychotic therapy of number of mental health-related physician visit among bipolar disorder patients

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Demographic characteristics				
Age (in years)	-0.006	0.009	-0.500	0.479
18 years or above (ref: less than 18 years)	-0.404	0.251	-2.590	0.107
Males (ref: females)	0.000	0.001	0.000	0.969
Whites (ref: non-whites)	0.434	0.388	1.250	0.264
Metro (ref: non-metro)	0.195	0.262	0.550	0.457
Prescribing physician type				
Psychiatric prescriber	0.000	0.000	1.770	0.183
Bipolar disorder subtype (ref: Bipolar disorder I)				
Bipolar disorder II	0.279	0.291	0.920	0.339
Mixed	-0.083	0.296	-0.080	0.780
Pre-index co-morbidities				
Alcohol and substance abuse	0.195	0.253	0.590	0.441
Bipolar disorder	0.274	0.320	0.730	0.392
Major depression	0.711	0.262	7.370	0.007
Mild to Moderate depression	-0.181	0.316	-0.330	0.568
Other mental comorbidities	0.116	0.232	0.250	0.618
diabetes	0.269	0.366	0.540	0.463
hyperlipedemia	-0.269	0.410	-0.430	0.511
hypertension	0.324	0.284	1.300	0.254
Charlson Comorbidity Index	-0.174	0.105	-2.740	0.098
Pre-index period psychiatric medication use (days of supply)				
Mood stabilizers	0.000	0.001	0.150	0.695
Antipsychotics	-0.003	0.003	-1.240	0.265
Antidepressants	0.001	0.001	0.580	0.448

Table 47: Negative binomial model for the impact of index antipsychotic therapy of number of mental health-related physician visit among bipolar disorder patients (contd.)

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Benzodiazepines	0.001	0.001	0.620	0.432
Pre-index healthcare utilization and cost				
Number of psychotherapy visits	0.000	0.030	0.000	0.990
Number of medication management visits	-0.096	0.037	-6.660	0.010
Number of pre-index mental-health related ER visits	0.109	0.200	0.300	0.585
Pre-index mental-health related physician visits	0.330	0.075	19.530	<.0001
Number of pre-index mental-health related hospitalizations	0.046	0.100	0.210	0.643
Year of index prescription (ref: 1999)				
• 2000	0.331	0.273	1.470	0.225
• 2001	0.224	0.329	0.460	0.496
Index prescription (ref: quetiapine)				
Risperidone	0.564	0.357	2.490	0.115
Olanzapine	0.226	0.270	0.700	0.402
Typicals	-0.067	0.290	-0.050	0.818

Model fit statistics:

-2 Log Likelihood = 1059.08, χ^2 = 129.05, p = 0.0001
Dispersion estimate = 1.01, p = 0.00

Table 48: Psychiatric medication use comparison (Quetiapine versus other antipsychotics) among schizophrenia patients

	Olanzapine N = 346	*Risperidone N = 201*	*Quetiapine N = 149*	*Typical N = 303*
Mood Stabilizers N (%)				
Pre-index	95 [Q] (27.5%)	50 [Q] (24.9%)	59 [ORT] (39.6%)	51 [Q] (16.8%)
Post-index	172 (49.7%)	98 (48.8%)	82 [T] (55.0%)	98 [Q] (32.3%)
Antidepressants N (%)				
Pre-index	159 [Q] (45.9%)	83 [Q] (41.3%)	92 [ORT] (61.7%)	93 [Q] (30.7%)
Post-index	265 (76.6%)	140 (69.6%)	113 [T] (75.8%)	164 [Q] (54.1%)
Anxiolytics/Hypnotics/Sedatives N (%)				
Pre-index	52 (15.0%)	22 (10.9%)	23 [T] (15.4%)	20 [Q] (6.6%)
Post-index	67 (19.3%)	32 (15.9%)	29 (19.5%)	46 (15.2%)
Antiparkinsons N (%)				
Pre-index	10 (2.9%)	3 (1.5%)	5 (3.3%)	17 (5.6%)
Post-index	25 (7.2%)	13 (6.5%)	12 [T] (8.0%)	66 [Q] (21.8%)

[O] Significant difference between quetiapine and olanzapine cohorts at $p<0.05$
[R] Significant difference between quetiapine and risperidone cohorts at $p<0.05$
[T] Significant difference between quetiapine and typicals cohorts at $p<0.05$

Table 48: Psychiatric medication use comparison (Quetiapine versus other antipsychotics) among schizophrenia patients (contd.)

	Olanzapine N = 346	*Risperidone N = 201*	*Quetiapine N = 149*	*Typical N = 303*
Anticholinergics N (%)				
Pre-index	5 (1.4%)	2 (1.0%)	6 (4.0%)	1 (0.3%)
Post-index	8 (2.3%)	6 (2.9%)	2 (1.3%)	4 (1.3%)
Clozapine N (%)				
Pre-index	1 (0.3%)	0 (0.0)	1 (0.7%)	1 (0.3%)
Post-index	5 (1.4%)	0 (0.0)	0 (0.0)	5 (1.6%)
Benzodiazepine N (%)				
Pre-index	104 (30.0%)	59 [Q] (29.3%)	70 [RT] (46.9%)	65 [Q] (21.4%)
Post-index	145 [Q] (41.9%)	82 [Q] (40.8%)	79 [ORT] (53.0%)	123 [Q] (40.6%)

[O] Significant difference between quetiapine and olanzapine cohorts at $p<0.05$
[R] Significant difference between quetiapine and risperidone cohorts at $p<0.05$
[T] Significant difference between quetiapine and typicals cohorts at $p<0.05$

Though significantly greater proportions of patients in the quetiapine cohort (61.7%) were using antidepressants compared to the olanzapine cohort (45.9%), risperidone cohort (41.3%) and typicals cohort (30.7%) in the pre-index period, proportions of patients on antidepressants were almost similar among the atypical cohort in the post-index index. The quetiapine cohort did have greater proportions of patients (75.8%) on antidepressants in the post-index period than typical antipsychotics (54.1%).

Though there was no significant difference in proportions of patients on antiparkinsons drugs in the pre-index period between quetiapine and other antipsychotics, there were significantly greater proportion of patients on antiparkinson drugs among typical antipsychotic cohort (21.8%) compared to quetiapine cohort (8.0%) in the post-index period.

Proportions of patients with benzodiazepine use were greater in quetiapine cohort as compared to other antipsychotics in both pre-index and post-index periods. There were no significant differences in the proportion of patients using anxiolytics/ hypnotics/ sedatives in the pre-index and post-index periods. As the sample size of patients using clozapine was very small, statistical tests could not be carried out.

Bipolar Disorder

Results of univariate analysis of mental-health-related pharmacy utilization are presented in table 49. Results of Mantel Hansel tests show that there was no significant difference in the proportion of patients on mood stabilizers in the pre-index and post-index period between quetiapine and other antipsychotics. There were significantly a greater proportion of patients on antidepressants in the quetiapine cohort as compared to the other antipsychotics in the pre-index period. There were significantly a greater

proportion of patients on antidepressants in the quetiapine cohort (81.1%) than in typical antipsychotic cohort (51.7%) in the post-index period. There were significantly greater proportions of patients on anxiolytics/ hypnotics/ sedatives in the quetiapine cohort during the pre-index period as compared to the other cohorsts. However, the proportions of patients on anxiolytics/ hypnotics/ sedatives were greater in the risperidone cohort (24.7%) than quetiapine cohort (20.7%) in the post-index period. The proportions of patients on anxiolytics/ hypnotics/ sedatives were greater in the quetiapine cohort than in the typical antipsychotic cohort (18.0%).

There were significantly greater proportions of patients on antiparkinsons drugs in the typical antipsychotic cohort (19.0%) than in the quetiapine cohort (5.6%). There were a significantly greater proportion of patients (48.1%) on benzodiazepines in the quetiapine cohort as compared to the other antipsychotics in the pre-index period. The post-index comparisons show significantly greater proportions of patients on benzodiazepines in the quetiapine cohort (48.1%) compared to olanzapine (43.1%) and typical antipsychotic cohorts (44.3%).

Table 49: Psychiatric medication use comparison (Quetiapine versus other antipsychotics) among bipolar disorder patients

	Olanzapine N = 283	*Risperidone N = 231*	*Quetiapine N = 106*	*Typical N = 205*
Mood Stabilizers N (%)				
Pre-index	146 (51.6%)	101 (43.7%)	56 (52.8%)	102 (49.7%)
Post-index	153 (54.1%)	98 (42.4%)	55 (51.8%)	112 (54.6%)
Antidepressants N (%)				
Pre-index	146 [Q] (51.6%)	89 [Q] (38.5%)	68 [ORT] (64.1%)	70 [Q] (34.1%)
Post-index	241 (85.2%)	180 (77.9%)	86 [T] (81.1%)	106 [Q] (51.7%)
Anxiolytics/Hypnotics/Sedatives N (%)				
Pre-index	47 [Q] (16.6%)	34 [Q] (14.7%)	20 [ORT] (18.8%)	19 [Q] (9.2%)
Post-index	62 (21.9%)	57 [Q] (24.7%)	22 [RT] (20.7%)	37 [Q] (18.0%)
Antiparkinsons N (%)				
Pre-index	10 (3.5%)	10 (4.3%)	4 (3.7%)	7 (3.4%)
Post-index	24 (8.4%)	19 (8.2%)	6 [T] (5.6%)	39 [Q] (19.0%)

Table 49: Psychiatric medication use comparison (Quetiapine versus other antipsychotics) among bipolar disorder patients (contd.)

	Olanzapine N = 283	*Risperidone N = 201*	*Quetiapine N = 106*	*Typical N = 205*
Anticholinergics N (%)				
Pre-index	7 (2.4%)	5 (2.4%)	4 (3.7%)	2 (0.9%)
Post-index	8 (2.8%)	4 (1.7%)	2 (1.8%)	8 (3.9%)
Clozapine N (%)				
Pre-index	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Post-index	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.9%)
Benzodiazepine N (%)				
Pre-index	94 [Q] (33.2%)	92 [Q] (39.8%)	51 [ORT] (48.1%)	53 [Q] (25.8%)
Post-index	135 (47.7%)	115 (49.8%)	57 [T] (53.7%)	91 [Q] (44.3%)

[O] Significant difference between quetiapine and olanzapine cohorts at $p<0.05$
[R] Significant difference between quetiapine and risperidone cohorts at $p<0.05$
[T] Significant difference between quetiapine and typicals cohorts at $p<0.05$

Results for research objective 14

For schizophrenia and bipolar disorder patients, to compare the impact of quetiapine with risperidone, olanzapine, and typical antipsychotics on patient's adherence to the index medications in the post-index period.

Schizophrenia

Results of univariate analysis presented in table 50 show that there was a significant difference in the average medication possession ratio between quetiapine (0.78 ± 0.25) and typical antipsychotic cohort (0.55 ± 0.32). Results of the multivariate analysis presented in table showed that patients initiated on typical antipsychotics were about 22% less adherent than patients initiated on quetiapine (Table 51).

Bipolar Disorder

Results of univariate analysis presented in table 52 show that there was a significant difference in the average medication possession ratio between quetiapine (0.71 ± 0.25) and typical antipsychotic cohort (0.46 ± 0.34). Results of the multivariate analysis presented in table showed that patients initiated on typical antipsychotics were about 24.4% less adherent than patients initiated on quetiapine (Table 53).

Table 50: Univariate comparison of medication possession ratio (mpr) among schizophrenia patients

	Olanzapine N = 346	*Risperidone N = 201*	*Quetiapine N = 149*	*Typical N = 303*
Medication Possession Ratio (MPR)				
Mean (±std)	0.77 (±0.26)	0.75 (±0.27)	0.78 [T] (±0.25)	0.55 [Q] (±0.32)

[O] Significant difference between quetiapine and olanzapine cohorts at $p<0.05$
[R] Significant difference between quetiapine and risperidone cohorts at $p<0.05$
[T] Significant difference between quetiapine and typicals cohorts at $p<0.05$

Table 51: Ordinary Least Squares (OLS) regression model for adherence to the index antipsychotic therapy among schizophrenia patients

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Demographic characteristics				
Age (in years)	0.001	0.001	1.250	0.212
Males (ref: females)	0.000	0.000	-0.300	0.762
Whites (ref: non-whites)	0.001	0.030	0.030	0.978
Metro (ref: non-metro)	-0.043	0.023	-1.870	0.062
Prescribing physician type				
Psychiatric prescriber	0.000	0.000	0.230	0.818
Schizophrenia subtype (ref: only schizophrenia)				
Schizoaffective disorder	-0.042	0.024	-1.730	0.084
Both schizoaffective disorder and schizophrenia	-0.046	0.025	-1.810	0.070
Pre-index co-morbidities				
Alcohol and substance abuse	-0.036	0.023	-1.580	0.114
Bipolar disorder	-0.008	0.030	-0.270	0.784
Major depression	0.057	0.025	2.260	0.024
Mild to Moderate depression	-0.002	0.030	-0.080	0.938
Other mental comorbidities	0.002	0.022	0.090	0.931
diabetes	-0.021	0.033	-0.620	0.537
hyperlipedemia	0.064	0.037	1.720	0.085
hypertension	-0.070	0.027	-2.620	0.009
Charlson Comorbidity Index	-0.009	0.008	-1.160	0.246
Pre-index period psychiatric medication use (days of supply)				
Mood stabilizers	0.000	0.000	2.060	0.039
Antipsychotics	0.000	0.000	0.800	0.424
Antidepressants	0.000	0.000	1.780	0.075
Benzodiazepines	0.000	0.000	0.270	0.790

Table 51: Ordinary Least Squares (OLS) regression model for adherence to the index antipsychotic therapy among schizophrenia patients (contd.)

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Pre-index healthcare utilization and cost				
Number of psychotherapy visits	0.001	0.002	0.270	0.788
Number of medication management visits	-0.011	0.003	-3.560	0.000
Number of pre-index mental-health related ER visits	-0.022	0.019	-1.130	0.261
Pre-index mental-health related physician visits	-0.005	0.007	-0.690	0.492
Number of pre-index mental-health related hospitalizations	0.027	0.010	2.870	0.004
Year of index prescription (ref: 1999)				
• 2000	0.020	0.025	0.810	0.419
• 2001	0.043	0.029	1.490	0.138
Index prescription (ref: quetiapine)				
Risperidone	-0.026	0.032	-0.800	0.421
Olanzapine	-0.011	0.028	-0.370	0.711
Typicals	-0.220	0.031	-7.190	<.0001

Model fit statistics:

Adjusted R-square =12.2%, **F** = 5.57, **p** < 0.0001

Table 52: Univariate comparison of medication possession ratio (mpr) among bipolar disorder patients

	Olanzapine *N = 313*	*Risperidone* *N = 231*	*Quetiapine* *N = 106*	*Typical* *N = 205*
Medication Possession Ratio (MPR)				
Mean (±std)	0.68 (±0.27)	0.68 (±0.27)	0.71 [Q] (±0.25)	0.46 [T] (±0.34)

[O] Significant difference between quetiapine and olanzapine cohorts at $p<0.05$
[R] Significant difference between quetiapine and risperidone cohorts at $p<0.05$
[T] Significant difference between quetiapine and typicals cohorts at $p<0.05$

Table 53: Ordinary Least Squares (OLS) regression model for adherence to the index antipsychotic therapy among bipolar disorder patients

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Demographic characteristics				
Age (in years)	0.001	0.001	1.420	0.157
18 years or above (ref: less than 18 years)	0.038	0.026	1.460	0.145
Males (ref: females)	0.000	0.000	-1.090	0.277
Whites (ref: non-whites)	0.012	0.035	0.340	0.731
Metro (ref: non-metro)	-0.055	0.027	-2.060	0.040
Prescribing physician type				
Psychiatric prescriber	0.000	0.000	-0.340	0.735
Bipolar Disorder subtype (ref: Bipolar disorder I)				
Bipolar disorder II	-0.043	0.028	-1.520	0.130
Mixed	-0.040	0.028	-1.440	0.150
Pre-index co-morbidities				
Alcohol and substance abuse	-0.055	0.026	-2.160	0.031
Bipolar disorder	0.001	0.033	0.040	0.967
Major depression	0.042	0.027	1.510	0.131
Mild to Moderate depression	0.009	0.033	0.290	0.774
Other mental comorbidities	0.011	0.024	0.470	0.635
diabetes	-0.026	0.037	-0.700	0.485
hyperlipedemia	0.085	0.041	2.060	0.040
hypertension	-0.073	0.029	-2.510	0.012
Charlson Comorbidity Index	-0.013	0.008	-1.580	0.114
Pre-index period psychiatric medication use (days of supply)				
Mood stabilizers	0.000	0.000	2.300	0.022
Antipsychotics	0.000	0.000	0.620	0.534
Antidepressants	0.000	0.000	2.310	0.021

Table 53: Ordinary Least Squares (OLS) regression model for adherence to the index antipsychotic therapy among bipolar disorder patients (contd.)

	Beta	*S.E*	*t-statistic*	*Significance (p)*
Benzodiazepines	0.000	0.000	-0.100	0.924
Pre-index healthcare utilization and cost				
Number of psychotherapy visits	0.001	0.003	0.240	0.814
Number of medication management visits	-0.013	0.003	-3.800	0.000
Number of pre-index mental-health related ER visits	-0.019	0.020	-0.940	0.347
Pre-index mental-health related physician visits	-0.007	0.007	-0.890	0.372
Number of pre-index mental-health related hospitalizations	0.023	0.010	2.250	0.025
Year of index prescription (ref: 1999)				
• 2000	0.021	0.027	0.790	0.430
• 2001	0.052	0.031	1.650	0.099
Index prescription (ref: quetiapine)				
Risperidone	-0.038	0.035	-1.060	0.290
Olanzapine	-0.030	0.033	-0.920	0.359
Typicals	-0.244	0.036	-6.760	<.0001

Model fit statistics:

Adjusted R-square = 15.13%, **F** = 5.47, **p** < 0.0001

Results for research objective 15

For schizophrenia and bipolar disorder patients, to compare the impact of quetiapine with risperidone, olanzapine, and typical antipsychotics on subsequent index antipsychotic therapy modification

Schizophrenia

Table 54 presents information on modification of index antipsychotic therapy. The average time to modification of therapy for the quetiapine cohort was 228.5 days as compared to 208.2 days for the olanzapine cohort, 201.8 days for the risperidone cohort and 192.8 days for the typical antipsychotic cohort. About 36.91% of patients in the quetiapine cohort, 50.58% in the olanzapine cohort, 47.76% in the risperidone cohort and 74.26% in the typical antipsychotic cohort modified the index antipsychotic therapy within the 12-month follow-up period.

Figure 6 presents the Kaplan Meier survival curves for time to modification of therapy for all four study cohorts. The survival curves were significantly different as indicated by log rank statistics of 43.86 ($p < 0.00$). Cox proportional hazard model presented in table 55 revealed that patients initiated on risperidone were 1.5 times more likely and patients initiated on typical antipsychotics were about 2.5 times more likely to modify therapy i.e discontinue or switch or augment with another antipsychotic (polytherapy) as compared to patients initiated on quetiapine ($p <.0001$).

Bipolar Disorder

Table 56 presents information on modification of index antipsychotic therapy. The average time to modification of therapy for the quetiapine cohort was 219.7 days compared to 200.9 days for the olanzapine cohort, 194.8 days for the risperidone cohort

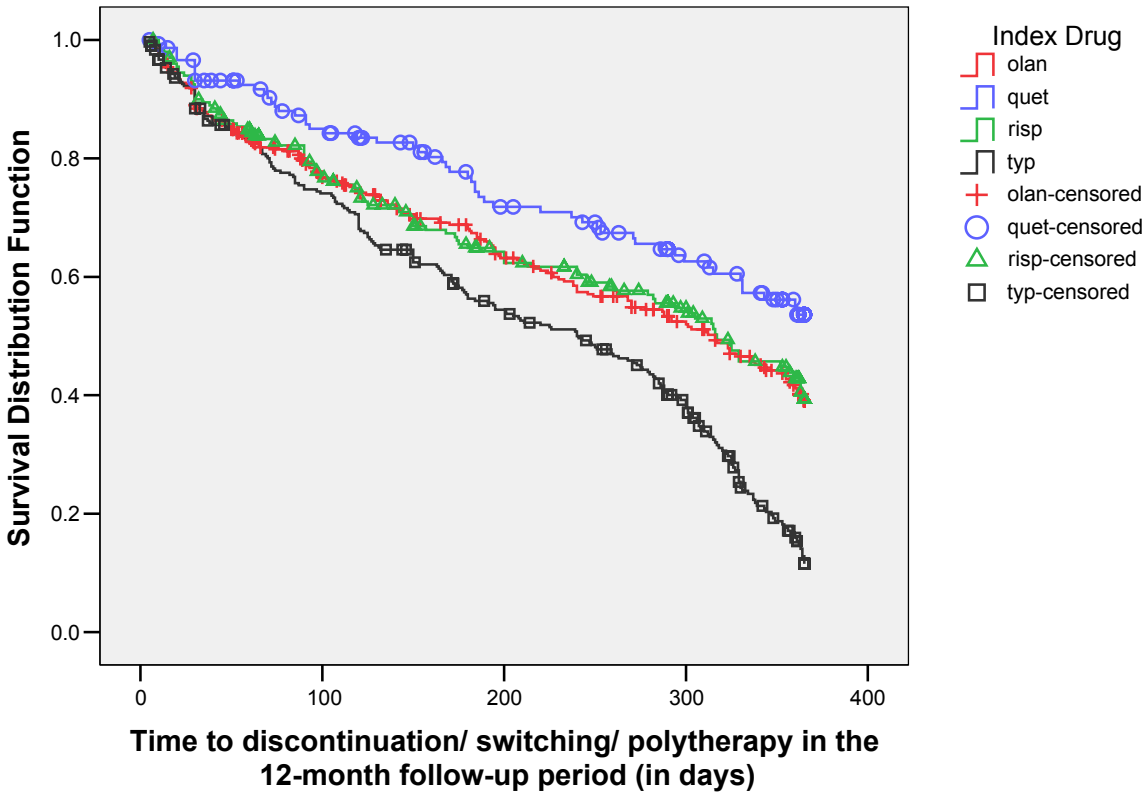
and 179.2 days for the typical antipsychotic cohort. About 38.7% of patients in the quetiapine cohort, 55.5% in the olanzapine cohort, 39.8% in the risperidone cohort and 64.4% in the typical antipsychotic cohort modified the index antipsychotic therapy within the 12-month follow-up period.

The Kaplan Meier survival curves presented in figure 7 revealed that hazards were different for the typical antipsychotic cohort within 250 days of initiating patients on index antipsychotics and after 250 days of initiation on index antipsychotics. Therefore, an extended Cox proportional hazards model was used to estimate impact of index antipsychotic use on time to modification of therapy. There was no significant difference in the hazard of discontinuation or switch or polytherapy between quetiapine and other antipsychotics in the initial 250 days of therapy. However, patients initiated on typical antipsychotics were about 6.3 times more likely to modify therapy i.e discontinue or switch or augment with another antipsychotic (polytherapy) compared to patients initiated on quetiapine in later 250 days of antipsychotic therapy ($p < .0001$). The extended Cox proportional hazard model has been presented in table 57.

Table 54: Therapy modification among schizophrenia patients

	Olanzapine *N = 346*	*Risperidone* *N = 201*	*Quetiapine* *N = 149*	*Typical* *N = 303*
Time to index therapy modification in days Mean (±std)				
	208.15 (±130.52)	201.83 (±128.15)	228.53 (±128.59)	192.81 (±124.54)
Patients having therapy modification N (%)				
	175 (50.58%)	96 (47.76%)	55 (36.91%)	225 (74.26%)

Figure 6: Kaplan-Meier Survival Curves for the time to modification of index antipsychotic prescription in schizophrenia patients



Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	43.867	3	.000

Test of equality of survival distributions for the different levels of index class.

Table 55: Cox Proportional hazard model for the impact of index antipsychotic therapy on time to discontinuation/ switch or polytherapy among schizophrenia patients

	Beta	*S.E*	*Significance (p)*	*Hazard Ratio*	*95% CI for Hazard Ratio*	
					Lower limit	*Upper Limit*
Demographic characteristics						
Age (in years)	-0.010	0.005	0.065	0.990	0.980	1.001
Males (ref: females)	-0.101	0.117	0.389	0.904	0.719	1.137
Whites (ref: non-whites)	-0.062	0.196	0.751	0.940	0.639	1.381
Metro (ref: non-metro)	0.043	0.136	0.749	1.044	0.800	1.363
Prescribing physician type						
Psychiatric prescriber	0.117	0.140	0.403	1.124	0.855	1.478
Schizoaffective disorder	0.091	0.144	0.524	1.096	0.827	1.452
Both schizoaffective disorder and schizophrenia	-0.107	0.155	0.490	0.899	0.663	1.217
Pre-index co-morbidities						
Alcohol and substance abuse	0.201	0.133	0.131	1.223	0.942	1.587
Bipolar disorder	0.082	0.180	0.648	1.086	0.763	1.544
Major depression	0.062	0.151	0.678	1.064	0.793	1.430
Mild to Moderate depression	0.030	0.164	0.853	1.031	0.748	1.421
Other mental comorbidities	0.045	0.135	0.740	1.046	0.803	1.363
Diabetes	-0.141	0.194	0.468	0.869	0.595	1.270
Hyperlipedemia	0.077	0.220	0.728	1.080	0.701	1.663
Hypertension	0.193	0.156	0.214	1.213	0.894	1.646

Table 55: Cox Proportional hazard model for the impact of index antipsychotic therapy on time to discontinuation/ switch or polytherapy among schizophrenia patients (contd.)

	Beta	*S.E*	*Significance (p)*	*Hazard Ratio*	*95% CI for Hazard Ratio*	
					Lower limit	*Upper Limit*
Charlson Comorbidity Index	0.091	0.047	0.052	1.095	0.999	1.201
Pre-index period psychiatric medication use (days of supply)						
Mood stabilizers	0.000	0.000	0.407	1.000	0.999	1.001
Antipsychotics	-0.002	0.002	0.353	0.998	0.995	1.002
Antidepressants	0.000	0.000	0.166	1.000	1.000	1.001
Benzodiazepines	0.000	0.001	0.546	1.000	0.999	1.001
Pre-index healthcare utilization and cost						
Number of psychotherapy visits	0.000	0.013	0.990	1.000	0.976	1.025
Number of medication management visits	-0.030	0.020	0.124	0.970	0.933	1.008
Number of pre-index mental-health related ER visits	-0.020	0.097	0.835	0.980	0.811	1.184
Pre-index mental-health related physician visits	0.012	0.036	0.734	1.012	0.944	1.086
Number of pre-index mental-health related hospitalizations	-0.019	0.056	0.727	0.981	0.879	1.094
Year of index prescription (ref: 1999)						
• 2000	0.269	0.140	0.055	1.309	0.994	1.723
• 2001	0.189	0.170	0.265	1.208	0.867	1.684
Index prescription (ref: quetiapine)						
Risperidone	0.411	0.204	0.045	1.508	1.010	2.251

Table 55: Cox Proportional hazard model for the impact of index antipsychotic therapy on time to discontinuation/ switch or polytherapy among schizophrenia patients (contd.)

	Beta	*S.E*	*Significance (p)*	*Hazard Ratio*	*95% CI for Hazard Ratio*	
					Lower limit	*Upper Limit*
Olanzapine	0.248	0.182	0.173	1.281	0.897	1.830
Typicals	0.913	0.189	<.0001	2.491	1.721	3.605

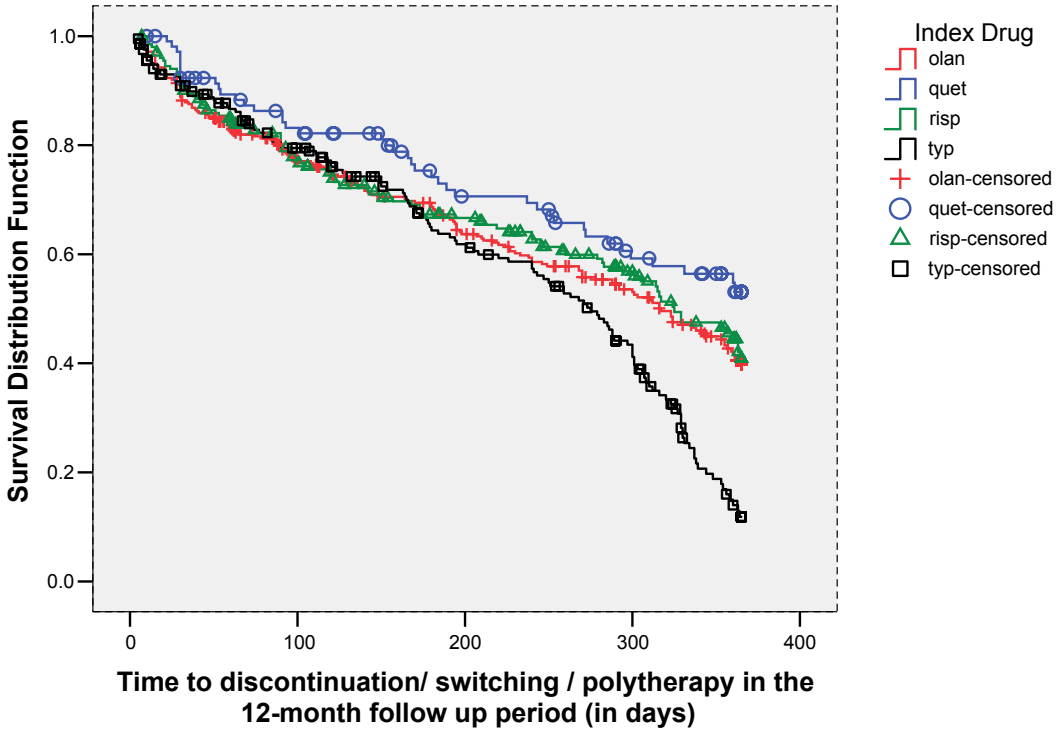
Model fit statistics:

-2 Log Likelihood = 3911.63, chi-square = 56.10, $p < 0.002$

Table 56: Therapy modification among bipolar disorder patients

	Olanzapine *N = 283*	*Risperidone* *N = 231*	*Quetiapine* *N = 106*	*Typical* *N = 205*
Time to index therapy modification in days Mean (±std)				
	200.9 (±130.4)	194.8 (±127.8)	219.8 (±128.9)	179.2 (±123.0)
Patients having therapy modification N (%)				
	157 (55.47%)	92 (39.82%)	41 (38.67%)	132 (64.39%)

Figure 7: Kaplan-Meier Survival Curves for time to modification of index antipsychotic prescription in bipolar disorder patients



Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	27.155	3	.000

Test of equality of survival distributions for the different levels of index class.

Table 57: Extended Cox Proportional hazard model for the impact of index antipsychotic therapy on time to discontinuation/ switch or polytherapy among bipolar disorder patients

	Beta	*S.E*	*Significance (p)*	*Hazard Ratio*	*95% CI for Hazard Ratio*	
					Lower limit	*Upper Limit*
Demographic characteristics						
Age (in years)	-0.009	0.006	0.122	0.991	0.979	1.000
18 years or above (ref: less than 18 years)	-0.258	0.161	0.109	0.773	0.563	1.059
Males (ref: females)	-0.172	0.131	0.187	0.842	0.651	1.087
Whites (ref: non-whites)	0.215	0.236	0.362	1.240	0.780	1.970
Metro (ref: non-metro)	0.005	0.159	0.973	1.005	0.737	1.372
Prescribing physician type						
Psychiatric prescriber	0.131	0.161	0.415	1.140	0.832	1.562
Bipolar Disorder subtype (ref: Bipolar disorder I)						
Bipolar disorder I	0.090	0.168	0.590	1.094	0.788	1.520
Mixed	-0.126	0.175	0.471	0.882	0.626	1.242
Pre-index co-morbidities						
Alcohol and substance abuse	0.338	0.155	0.029	1.402	1.035	1.901
Bipolar disorder	0.126	0.206	0.540	1.134	0.758	1.699
Major depression	0.259	0.168	0.124	1.295	0.932	1.800
Mild to Moderate depression	0.045	0.189	0.813	1.046	0.723	1.513
Other mental comorbidities	-0.045	0.156	0.774	0.956	0.705	1.298
Diabetes	0.062	0.216	0.775	1.064	0.697	1.623
Hyperlipedemia	-0.078	0.251	0.755	0.925	0.565	1.512
Hypertension	0.254	0.168	0.132	1.289	0.927	1.792

Table 57: Extended Cox Proportional hazard model for the impact of index antipsychotic therapy on time to discontinuation/ switch or polytherapy among bipolar disorder patients (contd.)

	Beta	*S.E*	*Significance (p)*	*Hazard Ratio*	*95% CI for Hazard Ratio*	
					Lower limit	*Upper Limit*
Charlson Comorbidity Index	-0.041	0.055	0.462	0.960	0.861	1.070
Pre-index period psychiatric medication use (days of supply)						
Mood stabilizers	-0.001	0.001	0.068	0.999	0.998	1.000
Antipsychotics	0.001	0.002	0.479	1.001	0.998	1.005
Antidepressants	0.000	0.000	0.389	1.000	1.000	1.001
Benzodiazepines	-0.001	0.001	0.388	0.999	0.998	1.001
Pre-index healthcare utilization and cost						
Number of psychotherapy visits	-0.008	0.014	0.585	0.992	0.964	1.021
Number of medication management visits	-0.018	0.022	0.408	0.982	0.942	1.025
Number of pre-index mental-health related ER visits	-0.093	0.103	0.369	0.911	0.745	1.116
Pre-index mental-health related physician visits	0.013	0.041	0.751	1.013	0.935	1.098
Number of pre-index mental-health related hospitalizations	-0.010	0.060	0.873	0.990	0.881	1.114
Year of index prescription (ref: 1999)						
• 2000	0.204	0.157	0.193	1.226	0.902	1.666
• 2001	0.268	0.189	0.156	1.307	0.903	1.893
Index prescription (ref: quetiapine)						
Risperidone	0.347	0.231	0.133	1.415	0.900	2.223

Table 57: Extended Cox Proportional hazard model for the impact of index antipsychotic therapy on time to discontinuation/ switch or polytherapy among bipolar disorder patients (contd.)

	Beta	*S.E*	*Significance (p)*	*Hazard Ratio*	*95% CI for Hazard Ratio*	
					Lower limit	*Upper Limit*
Olanzapine	0.232	0.210	0.270	1.261	0.835	1.903
Typicals *(less than 250 days)*	0.238	0.274	0.386	1.268	0.741	2.171
Typicals *(equal or more than 250 days)*	1.847	0.255	<.0001	6.338	3.844	10.452

Model fit statistics:

-2 Log Likehood = 3072.98, χ^2 = 101.17, $p < 0.0001$

PHASE 2 - Discussion

The aim of phase II is to compare quetiapine with risperidone, olanzapine, and typical antipsychotics on multiple healthcare outcomes such as healthcare costs, inpatient, outpatient, ER and pharmacy utilization, adherence and treatment modification. Intent-to-treat methodology was used for the economic comparisons. Intent to treat methodology includes the costs of patient dropouts due to adverse effects or treatment failure into economic evaluations. Without the intent-to-treat perspective, it will be difficult to include the cost impact of the additional expenses incurred by the patients who do not respond to treatment or fail treatment while comparing different treatment options. Policy makers find studies with intent-to-treat methodology and studies reporting costs of all patients instead only those patients who repond to initial treatment more useful while making healthcare decisions (Croghan, Johnstone, Buesching, & Kessler, 1999).

Total and mental healthcare costs for schizophrenia and bipolar disorder patients

The study demonstrated that there were no difference in the total and mental health-related costs between schizophrenia patients initiated on quetiapine and other antipsychotics. These findings were reported after controlling for various confounders such as patient demographics, co-morbidities, pre-index medication use, healthcare utilization and costs. To our knowledge, this is the first study reporting total and mental healthcare cost comparisons of quetiapine with other antipsychotics for schizophrenia patients.

Till date, pharmacoeconomic evaluations of antipsychotics have compared the impact of risperidone, olanzapine and typical antipsychotics on healthcare costs and

utilizations. Most of these studies have also not found any significant difference in total and mental healthcare costs between the different antipsychotic treatments. The lack of difference is mainly due to variable effect of the antipsychotic use on healthcare component costs such as inpatient costs, outpatient costs, and pharmacy costs. Usually the high pharmacy costs associated with atypical antipsychotics were offset by lesser inpatient and outpatient costs. For example, Edgell and colleagues reported that olanzapine had higher pharmacy costs and lower inpatient costs compared to risperidone resulting in no significant difference in total healthcare costs (Edgell et al., 2000). Gibson and colleagues also report no significant difference in total healthcare costs between olanzapine, risperidone and typical antipsychotics (Gibson et al., 2004). However, after excluding the cost of index prescription, they found that the total costs associated with olanzapine were significantly lower than risperidone. Few other studies have reported varying results. A study by Zhao and colleagues comparing risperidone and olanzapine use among uncontrolled schizophrenia population from a employer-based insurance population reported lower total costs for olanzapine than risperidone (Zhao, 2004). On the other hand, a study by Rascati and colleagues comparing olanzapine and risperidone in a Texas Medicaid population reported lower costs for risperidone as compared to olanzapine (Rascati et al., 2003).

The PRIZE (the Partial Responders International schizophrenia Evaluation) study conducted in a UK population as compared quetiapine treatment to haloperidol in terms of clinical endpoints (Emsley, Raniwalla, Bailey, & Jones, 2000). A markov model based on this study results estimated similar total costs with quetiapine (£38,106) compared to haloperidol (£38,350) (Tilden et al., 2002). This study reported that higher

acquisition costs of quetiapine were offset by higher inpatient and outpatient costs of haloperidol. In present study, the impact of the index antipsychotic on each component of healthcare costs were evaluated to examine cost offsets among these healthcare components.

Total healthcare costs evaluation for bipolar disorder patients found no significant differences between quetiapine and other index antipsychotics. However, evaluation of mental healthcare costs for bipolar disorder patients revealed that patients initiated on quetiapine incur lower mental healthcare costs compared to patients initiated on typical antipsychotics. There were no significant differences in mental healthcare costs between quetiapine and other atypical antipsychotics.

There is only one other study that compared the impact of antipsychotics on healthcare costs and utilization in bipolar disorder patients. This study reported that patients on quetiapine incurred $76 lesser mental-health related charges per patient per month compared to olanzapine. There was no significant difference in costs between risperidone and quetiapine (Gianfrancesco et al., 2005). This study did not include comparison with typical antipsychotics. The difference in results between our study and the study by Gianfrancesco may be due to differences in patient population and study methodology. The study by Gianfrancesso was conducted in a private health plan population using treatment episode methodology. Comparisons between the antipsychotics in the study by Gianfrancesso were based on costs incurred between the initiation of therapy and discontinuation with the therapy. Therefore, it did not consider costs associated with treatment discontinuation or adverse effects in the analysis. With the use of treatment episode methodology, it is possible that a person who has not

stabilized on earlier antipsychotic therapy may get initiated on another antipsychotic in the next episode and incur higher costs. Therefore, treatment episodes with newer antipsychotics may have higher costs due to inclusion of more severe patients.

Mental health-related inpatient utilization and cost

Our study found no significant difference in inpatient costs between quetiapine and other atypical antipsychotics. However, mental health-related inpatient costs among patients initiated on typical antipsychotics were higher than those of patients initiated on quetiapine. The Markov model by Tilden and colleagues had also estimated lower inpatient costs with quetiapine (£22,798) as compared to haloperidol (£24,716) (Tilden et al., 2002). Two other studies comparing costs between the atypical antipsychotics (olanzapine and risperidone) have also reported similar inpatient costs between the atypical antipsychotics.(Byerly et al., 2003; Jerrell, 2002).

Analysis of inpatient utilization revealed that there were no significant differences in the proportion of schizophrenia patient who were hospitalized and number of inpatient visits between quetiapine and typical antipsychotic cohorts. A study by Jerrell and colleagues also reported no significant difference in time to hospitalization and number of hospitalizations in patients initiated on risperidone, olanzapine and typical antipsychotics (Jerrell, 2002).

Our study did not find any significant difference in mental health-related inpatient utilization and costs between quetiapine and other antipsychotics in bipolar disorder patients. These results are consistent with the findings of the study by Gianfrancesso reporting no significant differences in inpatient costs (Gianfrancesco et al., 2005). It is likely that among bipolar disorder patients antipsychotics are being used as an adjunct to

other medications like mood stabilizers and antidepressants to manage patients. Therefore, there may not be a significant impact of antipsychotic on inpatient utilization by itself.

Mental health-related ER and outpatient utilization and cost

Our study categorized the outpatient costs into ER and outpatient costs. We found that there was no significant difference between quetiapine and other antipsychotics in terms of ER costs and ER utilization for both schizophrenia and bipolar disorder patients. Study of outpatient utilization is complex for mental health patients as outpatient utilization can be psychotherapy, psychotherapy tests, routine physician visits or emergency room visits. Utilization of outpatient services can also depend upon access to mental health clinics or hospitals which may be lacking in many places especially rural areas. Many patients lacking access to appropriate healthcare service may use ER for routine care services (Lehman & Steinwachs, 1998).

Studies that categorize healthcare utilization usually separate them into inpatient and outpatient services. ER utilization and costs are usually aggregated with those of other outpatient services (Byerly et al., 2003; Jerrell, 2002). This may be due to lower utilization rates for ER services compared to other services.

In our study, comparison of mental health-related physician visits, psychotherapy and medication management visits revealed there were significant differences between quetiapine and other antipsychotics among both schizophrenia and bipolar disorder patients. Multivariate analysis was conducted for the outpatient costs and physician visits. Though there were no significant differences between the cohorts in terms of number of mental health-related physician visits, the outpatient costs were slightly higher

for patients initiated on typical antipsychotics as compared to patients initiated on quetiapine. The utilization of psychotherapy sessions and medication management visits are probably reflected in the analysis of outpatient costs.

There were no significant differences in outpatient costs between quetiapine and other atypical antipsychotics in schizophrenia and bipolar disorder patients. However, the outpatient costs of typical antipsychotic were slightly higher than quetiapine. Markov modeling by Tinden and colleagues estimated higher outpatient costs for typicals (£9,698) as compared to quetiapine (£9,036) in the schizophrenia population. This may be due to better treatment response and lesser side-effects associated with quetiapine (Tilden et al., 2002). Comparison of outpatient costs among schizophrenia patients by Jerrell and colleagues also found no difference between the atypical antipsychotics - risperidone and olanzapine (Jerrell, 2002). However, interpreting the impact of antipsychotic on outpatient costs can be complicated. Schizophrenia and bipolar disorder patients require regular care not only in the acute phases of disease but also in the maintenance phase. Many patients with schizophrenia and bipolar disorder are also treated for substance abuse in outpatient settings. Therefore, utilization of non-emergency services may also be an indicator of appropriate treatment and patient management that may improve patient outcomes in future (American Psychiatric Association, 1997; Lehman et al., 2004a; Lehman et al., 2004c).

Mental health-related pharmacy utilization and cost

Our study found that the pharmacy costs for patients initiated on olanzapine were significantly higher than quetiapine in both the schizophrenia and bipolar disorder populations. This may be result of higher acquisition costs of olanzapine, greater use of

concomitant medications in the olanzapine cohort, or better adherence or persistence with olanzapine therapy. Further analysis of number of days of therapy with the index antipsychotic revealed no significant difference between days of therapy with olanzapine and quetiapine in the post-index period. Therefore, a higher pharmacy cost in the olanzapine cohort compared to quetiapine is not due to better adherence or persistence with olanzapine therapy. Uses of concomitant medications were similar for psychiatric drugs between olanzapine and quetiapine cohort. Even after controlling for use of concomitant medications as well as other confounding factors such as patient demographics and co-morbidities, the difference in pharmacy costs between quetiapine and olanzapine was still significant suggesting a very high acquisition cost for olanzapine. As expected, the pharmacy costs of quetiapine were significantly higher than typical antipsychotics mainly due to higher acquisition costs for quetiapine.

Though the drug acquisition cost for each healthcare system may differ, the Average Wholesale Price (AWP) per month is higher for olanzapine (approx: $599) compared to risperidone (approx: $385), quetiapine (approx: $351) and typical antipsychotics (approx: $40) according to the Red Book. This is reflected in the results of all studies comparing pharmacy costs of antipsychotics. Most studies have compared inpatient pharmacy costs between antipsychotics. Kasper and colleagues reported significantly higher average total inpatient drug costs for olanzapine ($297.5) as compared to risperidone ($159.9) based on retrospective chart reviews of hospitalized schizophrenia patients (Kasper et al., 2001). Analysis of daily drug costs from an inpatient data by Kelly and colleagues found patients initiated on risperidone incurred lower drug costs ($6.42) compared to schizophrenia patients initiated on olanzapine

($12.29) (Kelly et al., 2001). Analysis of VA data revealed that there are no significant differences in inpatient and outpatient costs among schizophrenia patients initiated on risperidone or olanzapine, and therefore it is more economic to prescribe risperidone due to its lower drug acquisition costs (Byerly et al., 2003). Similarly, Gibson and colleagues report that after subtracting the cost of index antipsychotic from total costs, post-index cost of olanzapine treated schizophrenia patient cohort was lower than risperidone treated schizophrenia cohort. None of these analyses have included quetiapine in their cost comparisons.

The only study reporting cost comparisons among schizophrenia patients for quetiapine examined total pharmacy costs in an acute care inpatient medical setting. Based on retrospective chart reviews of patients initiated on olanzapine, risperidone or quetiapine, the study reported that the average daily pharmacy cost was $4.35 less for risperidone and $1.41 less for quetiapine as compared to olanzapine (Mladsi et al., 2004). This study has certain limitations. The results of this study apply only to those patients who respond to the treatment as the study sample included only those patients who were discharged within 30 days of hospitalizations. In addition, the study did not control for use of concomitant medications during the inpatient stay. However, the results of all the studies suggest that patients initiated on olanzapine do incur higher pharmacy costs.

The only study reporting pharmacy costs for bipolar disorder patients on antipsychotics was the study by Gianfrancesso using the treatment episode mythology. Despite the difference in methodology from our study, this study reports results similar to ours that the per-patient per-month pharmacy costs of olanzapine group was 49% more than that of quetiapine group (Gianfrancesco et al., 2005).

Our study found that use of concomitant medications was highly prevalent among schizophrenia and bipolar disorder patients in both pre-index as well as post-index period. Few studies have reporting detailed utilization of concomitant medication use in these patient populations. A study by Al-Zakhwani and colleagues reported greater use of mood stabilizers among patient on atypical antipsychotic (44.5%) as compared to patient on typical antipsychotics (31.88%). The use of antidepressants was also more prevalent among atypical users (81.0%) compared to typical users (51.8%) (Al Zakwani et al., 2003). Menzin and colleagues reported lower likelihood of receiving anxiolytics (OR=0.44) and anticholinergics (OR=0.15) among patients on atypical antipsychotics compared to patients on typical antipsychotics (Menzin et al., 2003). Greater use of anticholinergic drugs for typical antipsychotics is indicative of need for treatment of extra pyramidal symptoms among patients initiated on typical antipsychotics.

Pre-index and post-index prevalence of mood stabilizer use was similar among all study antipsychotic drugs for bipolar disorder patients initiated on antipsychotics. Pre and post index prevalence of benzodiazepine use was very high among bipolar disorder patients initiated on quetiapine. However, there was a very slight change in the proportion of patients on benzodiazepine in the post-index period from the pre-index period. Proportions of patients on anxiolytics/hypnotics/sedatives and antidepressants were very high across all study cohorts. However, proportion of patients on antiparkinson and anticholinergics were not very high across study antipsychotic cohorts among bipolar disorder patients as compared to schizophrenia patients. The study by Gainfrancesso did not find any significant differences in concomitant medication use between risperidone, olanzapine and quetiapine in bipolar disorder patients.

Index antipsychotic adherence and therapy modification

Though there was no significant difference in adherence measured in terms of medication possession ratio between quetiapine and atypical antipsychotics, there were significant differences in adherence between quetiapine and typical antipsychotics for both schizophrenia and bipolar disorder. Published studies have shown lower adherence for typical antipsychotics due to side-effects such as extrapyramidal symptoms and tardive dyskinesia (Crismon ML et al., 1997; APA, 1997; Carpenter, Jr. et al., 1994). A study by Al-Zakhwani and colleagues compared persistence with index therapy and medication possession ratio between typicals and atypical antipsychotics in a patient population with psychosis (Al Zakwani et al., 2003). They reported that average days of supply of atypical antipsychotic in a year were 136 days compared to 80 days with typical antipsychotics. The medication possession ratio reported for atypical antipsychotics was 0.53 compared to 0.24 for typical antipsychotics. Though the lower adherence for typical antipsychotics as compared to atypical antipsychotics is consistent with our study results, the ratio of adherence in their study population was considerably lower than that found in our study (about 0.7 for atypicals and 0.5 for typicals). This may be because their study sample was not restricted to schizophrenia or bipolar disorder population. It is possible that patients in their study may be receiving antipsychotics for short term duration for disease conditions that are not indicated for antipsychotic use.

Another study by Menzin and colleagues conducted in the California Medicaid schizophrenia population compared persistence with therapy, switching and discontinuation between atypical and typical antipsychotics (Menzin et al., 2003). They found that patients initiated on atypical antipsychotics (61%) had greater days of index

medication supply in 1-year post-index period compared to typicals (58%). They also reported higher rates of discontinuation among patients initiated on typicals (58%) as compared to patients initiated on atypicals (33%). Though their analysis did not include quetiapine, their results with respect to comparison of atypical with typical are consistent with our study. Dolder and colleagues compared adherence between atypical antipsychotics (including risperidone, olanzapine, or quetiapine) to typical antipsychotics in a California VA population with psychosis. They reported poorer adherence rates with typical antipsychotics (50.1%) compared to atypical antipsychotics (54.9%) (Dolder et al., 2002).

To our knowledge, there are no studies comparing quetiapine with other atypical antipsychotics and typical antipsychotics in terms of persistence with therapy, adherence, or therapy modifications such as interrupted, switching and polytherapy. In addition to comparisons of quetiapine with other antipsychotics in terms of persistence with therapy and adherence, this study conducted a detailed analysis examining time to modification of index antipsychotic. Modification of index antipsychotic can take place due to discontinuation of index antipsychotic use, switching to another antipsychotic or augmenting with another antipsychotic (later polytherapy). This study found that the patients initiated on typical antipsychotic had higher the risk of therapy modification as compared to patients initiated on quetiapine among schizophrenia patients. Among bipolar disorder patients, the risk of therapy modification with typical antipsychotics increased 6-fold in the latter part of post-index period. Though specific reasons for therapy modifications such as physicians' judgment or patient preference cannot be ascertained from a retrospective database analysis, therapy modification can have

implications on costs and utilization (Centorrino et al., 2004; McCombs et al., 2000; Loosbrock et al., 2003).

CHAPTER FIVE

CONCLUSIONS

This chapter presents conclusions drawn from the study, lists limitations and implications of the study and provides recommendations for future research.

Phase 1

The primary goal of the phase I was to describe and evaluate antipsychotic utilization patterns among schizophrenia and bipolar disorder patients.

Conclusions from research objective 1

To determine the annual prevalence rate of schizophrenia and bipolar disorder in West Virginia Medicaid from 1998 to 2002

This was an exploratory question examining the overall prevalence rate of schizophrenia and bipolar disorder among WV Medicaid enrollees from 1998 and 2002. The annual prevalence rates of schizophrenia in the WV Medicaid population from 1998 to 2002 ranged from 0.9% to 1.5%. These rates were similar to the national estimate of 1.1% prevalence. The annual prevalence rate for bipolar disorder in the WV Medicaid population from 1998 to 2002 ranged from 0.6% to 1.7%. These rates were lower than the national estimate of 1.3 to 1.6% for the year 1998 but similar to the national estimates between the years 1999 and 2000. The annual prevalence rate of bipolar disorder among population between 20 and 64 years of age between the year 2000 and 2002 ranged from 3.2% to 3.5% which is similar to the national estimate of 3.7% among adult US population.

Conclusions from research objective 2

To determine the medical conditions for which antipsychotics are being prescribed in the West Virginia Medicaid population as well as describe patterns of distribution of certain demographic factors such as age, gender, and ethnicity in patients using antipsychotics.

This was an exploratory analysis to determine the mental health conditions as well as describe patterns of distribution of certain demographic factors such as age, gender, and ethnicity in patients who were initiated on antipsychotics in the West Virginia Medicaid population. We conclude that there were patients who were initiated on antipsychotics for conditions that are not yet FDA indicated for antipsychotic use such as non-schizophrenic psychosis, attention deficit disorder, major depression, mild to moderate depression, and anxiety. As WV Medicaid population consists of large percentage of Caucasian women, the variation in distribution according to gender and race among patients initiated on antipsychotics followed the general demographic characteristics of WV Medicaid beneficiaries. Therefore, it cannot be concluded from our study that the initiation of antipsychotics varies by gender or race.

Conclusions from research objective 3

For schizophrenia and bipolar disorder patients, determine different types of utilization pattern of antipsychotics.

The null hypotheses for this research question was there are no differences in the utilization patterns of antipsychotics among patients. This hypothesis was investigated among schizophrenia and bipolar disorder patients. For both schizophrenia and bipolar disorder patients, there were significant number of patients using antipsychotic polytherapy, switching from index antipsychotic, having interrupted/ non-adherent

therapy with index antipsychotic and having continuous/ adherent therapy with index antipsychotic. Lower proportion of less than 18 years old bipolar disorder patients received continuous/ adherent index antipsychotic therapy compared to bipolar disorder patients who are 18 years or older. As these utilization patterns were defined on the basis of refill claims, they only indicate that the patient has refilled the medication. They do not indicate whether the patient has taken the medication. However, these definitions based on refill claims can be accepted to capture the utilization patterns of antipsychotics as 1) several studies have validated the positive correlation between refill claims and patient diaries and drug blood serum levels and 2) As Medicaid offers complete prescription drug coverage, Medicaid patients may not refill prescriptions outside the system. Therefore, we reject our null hypothesis and conclude from this study that significantly different antipsychotic utilization patterns exist among schizophrenia and bipolar disorder patients.

Conclusions from research objective 4

For schizophrenia and bipolar disorder patients, determine the gaps between the refills of antipsychotics.

The null hypotheses for this research question was there are no gaps in the antipsychotic therapy among schizophrenia and bipolar disorder patients. Large proportion of schizophrenia and bipolar disorder patients had gaps of greater than 15 days between the refills of antipsychotics. Among bipolar disorder patients, there were differences in duration of gaps and proportions of patients with large gaps between patients who are 18 years or older and patients who are less than 18 years. As Medicaid offers comprehensive coverage for prescriptions, patients in Medicaid are not very likely

to fill their prescriptions outside the system. Therefore, we can reject our hypothesis and conclude that there are gaps in the antipsychotic therapy among schizophrenia and bipolar disorder patients

Conclusions from research objective 5

For schizophrenia and bipolar disorder patients, determine predictors of different utilization patterns of antipsychotics

The null hypothesis for this research question was there is no association between utilization patterns of antipsychotics and patient demographics, prescribing physician type, mental health diagnosis, other medical diagnosis, type of antipsychotic, year of index antipsychotic, pre-index concomitant medication use, pre-index alcohol and substance abuse and pre-index healthcare utilization among schizophrenia and bipolar disorder patients. Based on our results the null hypothesis was rejected. We concluded that factors such as schizophrenia subtypes, alcohol and substance abuse, major depression, prior use of mood stabilizers and antidepressants in the pre-index period and use of typical antipsychotic as index antipsychotic were significant predictors of different patterns of utilization of antipsychotics among schizophrenia patients. We also concluded that among bipolar disorder patients, factors such as less than 18 years of age, psychiatric prescriber, alcohol and substance abuse, major depression, anxiety, prior use of mood stabilizers, and use of typical antipsychotic as index antipsychotic were significant predictors of different patterns of utilization of antipsychotics.

Conclusions from research objective 6

For schizophrenia and bipolar disorder patients, determine the relationship between utilization pattern of antipsychotics and total health-related healthcare costs.

The null hypothesis was there is no association between utilization patterns of antipsychotics and total health healthcare utilization and costs for schizophrenia and bipolar disorder patients. This null hypothesis was rejected based on our results. We concluded that compared to continuous/adherent antipsychotic therapy with index antipsychotic, patterns of antipsychotic utilization such as polytherapy, and interrupted/ non-adherent therapy were significantly associated with higher total healthcare costs for schizophrenia patients. We also concluded that switching from index antipsychotic was not significantly associated with total healthcare costs compared to continuous/adherent antipsychotic therapy with index antipsychotic for schizophrenia patients. Among bipolar disorder patients, it was concluded that patterns of antipsychotic utilization such as polytherapy, switching from index antipsychotic and interrupted/ non-adherent therapy were significantly associated with higher total healthcare costs compared to continuous/adherent antipsychotic therapy with index antipsychotic.

Conclusions from research objective 7

For schizophrenia and bipolar disorder patients, determine the relationship between utilization pattern of antipsychotics and mental health care utilization and costs.

The null hypothesis was there is no association between utilization patterns of antipsychotics and mental health healthcare utilization and costs for schizophrenia and bipolar disorder patients. Based on the results, we concluded that the patterns of antipsychotic utilization such as polytherapy, and interrupted/ non-adherent therapy were significantly associated with higher mental healthcare costs as compared to continuous/adherent antipsychotic therapy with index antipsychotic, for both schizophrenia and bipolar disorder patients. We also concluded that switching from

index antipsychotic was not significantly associated with mental healthcare costs compared to continuous/adherent antipsychotic therapy with index antipsychotic among both schizophrenia and bipolar disorder patients.

Phase 2

The aim of phase II is to compare quetiapine with risperidone, olanzapine, and typical antipsychotics on multiple healthcare outcomes such as healthcare costs, inpatient, outpatient, ER and pharmacy utilization, adherence and treatment modification.

Conclusions from research objective 8

For schizophrenia and bipolar disorder patients, to compare the impact of quetiapine with risperidone, olanzapine, and typical antipsychotics on total and mental healthcare costs

The null hypothesis was that there is no difference in the impact of quetiapine compared with risperidone, olanzapine, and typical antipsychotics on total and mental healthcare costs for schizophrenia and bipolar disorder patients. After controlling for various confounding such as patient demographics, prescribing physician type, mental health diagnosis, other medical diagnosis, type of antipsychotic, year of index antipsychotic, pre-index concomitant medication use, pre-index alcohol and substance abuse and pre-index healthcare utilization, there were no significant differences in total and mental healthcare costs among patients initiated on quetiapine compared to patients initiated on risperidone, olanzapine, or typical antipsychotics for schizophrenia patients (ref: table). Therefore, the null hypothesis was accepted as true for schizophrenia patients. However, there were significant differences in total and mental healthcare costs among patients initiated on quetiapine compared to patients initiated on typical

antipsychotics for bipolar disorder patients. Therefore, the null hypothesis was rejected and it was concluded that bipolar disorder patients initiated on typical antipsychotics incur higher mental and total healthcare costs.

Conclusions from research objective 9

For schizophrenia and bipolar disorder patients, to compare the impact of quetiapine with risperidone, olanzapine, and typical antipsychotics on components of mental healthcare costs (costs associated with mental health-related inpatient, emergency room, outpatient and pharmacy services)

The null hypothesis was that there is no difference in the impact of quetiapine compared with risperidone, olanzapine, and typical antipsychotics on components of mental healthcare costs (costs associated with mental health-related inpatient, emergency room, outpatient and pharmacy services) for schizophrenia and bipolar disorder patients. The null hypothesis was rejected for this research objective. Based on the results, we concluded that schizophrenia patients initiated on typical antipsychotics incurred slightly higher inpatient and outpatient costs but lower pharmacy costs compared to patients initiated on quetiapine. We also concluded that schizophrenia patients initiated on olanzapine incurred higher pharmacy costs compared to patients initiated on quetiapine. We also conclude that bipolar disorder patients initiated on typical antipsychotics incur slightly higher outpatient costs and lower pharmacy costs than patients who are initiated on quetiapine. Bipolar disorder patients initiated on olanzapine incur higher pharmacy costs than patients initiated on quetiapine.

Conclusions from research objective 10

For schizophrenia and bipolar patients, to compare the impact of quetiapine with risperidone, olanzapine, and typical antipsychotics on mental health-related healthcare hospitalizations.

The null hypothesis was that there is no difference in the impact of quetiapine compared with risperidone, olanzapine, and typical antipsychotics on mental health-related healthcare hospitalizations for schizophrenia and bipolar disorder patients. Based on the results, we conclude that there were no significant difference in the number of mental health-related hospitalizations, proportion of patients hospitalized and time to first hospitalization among patients initiated on quetiapine and patients initiated on risperidone, olanzapine, or typical antipsychotics for both bipolar disorder and schizophrenia. However, the length of stay in hospital among schizophrenia patients initiated on typical antipsychotics was longer compared to patients initiated on quetiapine. Relevant information on hospitalization such as patient condition at the time of hospitalization and hospital discharge information were not controlled for in the analysis as they are not available in the administrative database. Therefore, we cannot conclude that there were no differences in inpatient utilization between the quetiapine and other antipsychotic cohorts. The null hypothesis was inconclusive for this objective.

Conclusions from research objective 11

For schizophrenia patients and bipolar disorder patients, to compare the impact of quetiapine with risperidone, olanzapine, and typical antipsychotics on mental healthcare-related emergency room visits.

The null hypothesis was that there is no difference in the impact of quetiapine compared with risperidone, olanzapine, and typical antipsychotics on mental healthcare-related emergency room visits for schizophrenia and bipolar disorder patients. The null hypothesis was accepted and we concluded that there were no significant differences in the number of mental health-related ER visits and proportion of patients having ER visit among patients initiated on quetiapine and patients initiated on risperidone, olanzapine, or typical antipsychotics for both bipolar disorder and schizophrenia.

Conclusions from research objective 12

For schizophrenia and bipolar disorder patients, to compare the impact of quetiapine with risperidone, olanzapine, and typical antipsychotics on mental healthcare-related outpatient visits.

The null hypothesis was that there is no difference in the impact of quetiapine compared with risperidone, olanzapine, and typical antipsychotics on mental health-related outpatient visits for schizophrenia and bipolar disorder patients. Based on univariate analyis, outpatient visits such as psychotherapy, physician office visits and medication management visits were significantly greater among patients initiated on quetiapine compared to patients initiated on risperidone, olanzapine, and typical antipsychotics for schizophrenia and bipolar disorder patients. However, after controlling for various confounding such as patient demographics, prescribing physician type, mental health diagnosis, other medical diagnosis, type of antipsychotic, year of index antipsychotic, pre-index concomitant medication use, pre-index alcohol and substance abuse and pre-index healthcare utilization, we conclude that there was no significant

difference in physician office visits among patients initiated on quetiapine and patients initiated on risperidone, olanzapine, or typical antipsychotics.

Conclusions from research objective 13

For schizophrenia and bipolar disorder patients, to compare the impact of quetiapine with risperidone, olanzapine, and typical antipsychotics on psychiatric medication utilization.

The null hypothesis was that there is no difference in the impact of quetiapine compared with risperidone, olanzapine, and typical antipsychotics on psychiatric medication utilization for schizophrenia and bipolar disorder patients. This null hypothesis was rejected as we found significant differences in the proportion of patients using different psychiatric drugs among patients initiated on quetiapine and patients initiated on risperidone, olanzapine, and typical antipsychotics. Among schizophrenia and bipolar disorder patients, lesser proportion of patients initiated on quetiapine used antiparkinsons drugs compared to patients initiated on typical antipsychotics. Also, larger proportion of patients initiated on quetiapine used benzodiazepine and antidepressants compared to patients initiated on typicals. Among bipolar disorder patients, greater proportion of patients initiated on risperidone used anxiolytics/ hypnotics/ sedatives compared to patients initiated on quetiapine. However, greater proportion of patients initiated on quetiapine used anxiolytics/ hypnotics/ sedatives compared to patients initiated on typicals antipsychotics.

Conclusions from research objective 14

For schizophrenia and bipolar disorder patients, to compare the impact of quetiapine with risperidone, olanzapine, and typical antipsychotics on patient's adherence to the index medications in the post-index period.

The null hypothesis was that there is no difference in the impact of quetiapine compared with risperidone, olanzapine, and typical antipsychotics on patient's adherence to index medication for schizophrenia and bipolar disorder patients. Based on the results, we reject null hypothesis and conclude that the patients initiated on quetiapine showed similar adherence to index antipsychotics compared to patients initiated on olanzapine and risperidone but better adherence to index antipsychotics compared to patients initiated on typical antipsychotics for both schizophrenia and bipolar disorder patients.

Conclusions from research objective 15

For schizophrenia and bipolar disorder patients, to compare the impact of quetiapine with risperidone, olanzapine, and typical antipsychotics on subsequent index antipsychotic therapy modification

The null hypothesis was that there is no difference in the impact of quetiapine compared with risperidone, olanzapine, and typical antipsychotics on subsequent modification of index antipsychotic therapy by discontinuing, switching or augmenting by additional antipsychotics for schizophrenia and bipolar disorder patients. The null hypothesis was rejected and we concluded that there is significant difference in the impact of quetiapine as compared to risperidone, olanzapine and typical antipsychotics on subsequent modification of index antipsychotics. Patients initiated on typical antipsychotics and risperidone had higher hazard to modify the index antipsychotic

therapy compared to patients initiated on quetiapine among schizophrenia patients. There are no significant differences in the hazard of index antipsychotic therapy modification among patients initiated on quetiapine compared to patients initiated on risperidone or olanzapine among bipolar patients. Bipolar patients initiated on typical antipsychotics had higher hazard to modify index antipsychotic therapy compared to patients initiated on quetiapine therapy.

Limitations

Pattern of antipsychotic use were identified based on events such as polytherapy, switching or discontinuation from index antipsychotic that occurred first after initiation of patient on index antipsychotic. However, it is possible that patients may show multiple patterns of antipsychotic utilization in course of treatment. A patient who has switched to another antipsychotic may have later discontinued antipsychotic treatment all together or switched back to index antipsychotic. As various combinations of such patterns may exist among patients, it is difficult to define, categorize and evaluate them. In addition, factors such as duration of polytherapy will also impact the costs associated with it. However, as we found significant increase in costs associated with at least one event of polytherapy, it is likely that the cost will increase further with longer duration of polytherapy. Though our study describes the pattern of antipsychotic use, it is not possible to explore all the reasons for such patterns of utilization from the information available in administrative claims data. Various factors such as physician's clinical judgment and past experience, marketing influence of pharmaceutical companies, and patient preferences can also impact these patterns.

We have used refill records of antipsychotics to measure adherence with the therapy. This indicates that claim for that drug was paid to the provider and not that the medication was taken correctly by the patient. Information such as dates of service, amounts dispensed, and days of supply were used to calculate adherence. This is not a direct but a proxy measure of adherence. However, studies have shown significant correlations between adherence measured from refill information and other methods such as self-report, pill count, medication diary, and serum drug levels(Choo et al., 1999; Deyo, Inui, & Sullivan, 1981). In addition, claims records are useful in calculating gaps in therapy. As Medicaid offers comprehensive coverage for prescriptions, patients in Medicaid are not very likely to fill their prescriptions outside the system. Therefore, long gaps between the refills found among the patients in our study demonstrates significant non-adherence to antipsychotic therapy in our population.

As schizophrenia and bipolar disorder are chronic illnesses, studying long term impact of drug use is important for making policy decisions. Our study follow-up period was restricted to one-year due to loss of continuously eligible patients and a change in WV Medicaid prior authorization policy for antipsychotics in the year 2003. The latter would have biased our study results. If the impact on hospitalization and ER cost is due to non-adherence or therapy discontinuation, the impact is likely to significantly increase in longer follow-ups.

The use of intent-to-treat methodology attributes all costs incurred in the follow-up period to the index drug. It may be argued that it is inappropriate to assign costs incurred by the patient while on another drug to the index drug. However, intent-to-treat methodology allows us to account for costs associated with patients who do not respond

to treatment or fail treatment while comparing different treatment options. This approach is more useful to healthcare policy makers while making formulary decisions (Croghan et al., 1999).

Patients initiated on any of the typical antipsychotics during the index period were pooled together to form single cohort of typical antipsychotics. All healthcare utilization and costs incurred by these patients were aggregated and attributed to the typical antipsychotic cohort, irrespective of the type of typical antipsychotic.

Generalizability of the study is limited to populations that are similar to WV Medicaid. Factors such age, sex, race, socioeconomic status, geography, co-pays, formularies, and provider access should be taken into account before generalizing the results to a different population. Practice patterns and costs may also vary by time and introduction of new drugs.

The study is vulnerable to the limitations of using administrative claims data for research purpose (Motheral et al., 1997). Inaccurate identification of cases can seriously affect the validity of study. However, care was taken in our study to identify patients with schizophrenia and bipolar disorder based on validated algorithms for identifying this population from an administrative database (Lurie P et al., 1992; Simon et al., 1999). It is also possible that differences in costs and utilization may be due to unobserved patient differences such as disease severity. However, a study by Sernyak has validated the use of sociodemographic variables, prior utilization and cost variables obtained from administrative data as risk adjusters to predict future utilization and costs (Sernyak et al., 2003). We have statistically controlled for various confounding factors including patient

demographics, prescribing physician type, mental health diagnosis, other medical diagnosis, type of antipsychotic, year of index antipsychotic, pre-index concomitant medication use, pre-index alcohol and substance abuse and pre-index healthcare utilization.

Research Implications

Implications for payers

Considering the rising prescription drug expenditures and adverse effects of inappropriate therapy, it is important to take steps to improve prescribing and use of prescription drugs. This is particularly imperative in the case of use of expensive antipsychotics in schizophrenia and bipolar disorder population. This patient population is known to be non-adherent to medications and suffer from alcohol and substance use disorder that further aggravates the problem. Our study found very high level of non-adherence to antipsychotic medication. The healthcare costs of non-adherent patients were higher compared to adherent patients. If payers are paying for expensive drugs, they need to be used appropriately to maximize the benefits gained from them. Our study results should encourage payers to develop policies to improve medication adherence in schizophrenia and bipolar disorder patients. Prescribing behaviors such as polytherapy and off-label use of antipsychotics should be investigated.

Implications for providers

The study findings should make the physicians aware of the extent of non-adherence to antipsychotic therapy among schizophrenia and bipolar disorder patients. The issue of non-adherence should be given attention during patient evaluation and making pharmacotherapy choice. Our study results also show significant off-label use of

antipsychotics for mental health conditions. Patients using antipsychotics for off-label indications should be monitored closely by physicians and pharmacists for adverse effects.

Direction for Future Research

Studies with longer follow-up period are needed to capture the impact of antipsychotic non-adherence and treatment modification on healthcare costs and utilization. Future economic evaluations should include new atypical drugs such as Ziprasidone (Pfizer 2001) and Aripiprazole (Bristol Myers Squibb 2002) that could not be evaluated during the study period of this research. As schizophrenia and bipolar disorder are associated with loss of productivity, disability and caregiver burden, the impact of pharmacotherapy on productivity and societal costs should be evaluated. Studies assessing impact of antipsychotic pharmacotherapy of quality-of-life are also needed.

Our study findings reveal that a large proportion of schizophrenia and bipolar disorder patients on antipsychotics were concomitantly utilizing various psychiatric drugs such as mood stabilizers and antidepressants. Clinical trials investigating efficacy and safety of such drug combinations are necessary to assist in developing treatment guidelines for disease conditions. Future studies can also examine the role of antipsychotic monotherapy versus antipsychotic combination therapy with mood stabilizer among bipolar disorder patients. Though we found prevalence of off-label antipsychotic use among various disease conditions such as major depression, attention-deficit disorder, autism, and others, clinical evidence supporting such use is lacking.

Randomized clinical trials are needed to evaluate if antipsychotics offer any therapeutic advantage among patients with these disease conditions.

Reasons for switching antipsychotic and using antipsychotic polytherapy can be explored using a physician survey. Survey of physicians can also provide more information regarding outcomes associated with antipsychotic polypharmacy and off-label antipsychotic use. There is a need for developing and evaluating behavioral interventions that can improve medication adherence among schizophrenia and bipolar disorder patients.

REFERENCES

Treatment of schizophrenia 1999. The expert consensus guideline series (1999). *J.Clin.Psychiatry, 60 Suppl 11,* 3-80.

Al Zakwani, I. S., Barron, J. J., Bullano, M. F., Arcona, S., Drury, C. J., & Cockerham, T. R. (2003). Analysis of healthcare utilization patterns and adherence in patients receiving typical and atypical antipsychotic medications. *Curr.Med.Res.Opin., 19,* 619-626.

Amadio, P. B., Cross, L. B., & Amadio, P., Jr. (1997). New drugs for schizophrenia: an update for family physicians. *Am.Fam.Physician, 56,* 1149-1160.

American Psychiatric Association (1997). Practice guidelines for the treatment of patients with schizophrenia. *Am J Psychiatry, 154 (Suppl 4)*.

APA (1994). *Diagnostic and Statistical Manual of Mental Disorders*. (4th ed ed.) Washington DC: American Psychiatric Association.

APA (1997). Practice guideline for the treatment of patients with schizophrenia. American Psychiatric Association. *Am.J.Psychiatry, 154,* 1-63.

Ascher-Svanum, H., Zhu, B., Faries, D., & Ernst, F. R. (2004). A comparison of olanzapine and risperidone on the risk of psychiatric hospitalization in the naturalistic treatment of patients with schizophrenia. *Ann Gen.Hosp.Psychiatry, 3,* 11.

Barbee, J. G., Conrad, E. J., & Jamhour, N. J. (2004). The effectiveness of olanzapine, risperidone, quetiapine, and ziprasidone as augmentation agents in treatment-resistant major depressive disorder. *J.Clin.Psychiatry, 65,* 975-981.

Bebbington, P. & Ramana, R. (1995). The epidemiology of bipolar affective disorder. *Soc.Psychiatry Psychiatr.Epidemiol., 30,* 279-292.

Bogan, A. M., Shellhorn, E., Brown, E. S., McDanald, C., & Suppes, T. (2000). Switching outpatients between atypical antipsychotics. *Prog.Neuropsychopharmacol.Biol.Psychiatry, 24,* 351-355.

Bottlender, R., Rudolf, D., Strauss, A., & Moller, H. J. (2001). Mood-stabilisers reduce the risk of developing antidepressant-induced maniform states in acute treatment of bipolar I depressed patients. *J.Affect.Disord., 63,* 79-83.

Bowden, C. L. (2000). Efficacy of lithium in mania and maintenance therapy of bipolar disorder. *J.Clin.Psychiatry, 61 Suppl 9,* 35-40.

Brenner, H. D., Dencker, S. J., Goldstein, M. J., Hubbard, J. W., Keegan, D. L., Kruger, G. et al. (1990). Defining treatment refractoriness in schizophrenia. *Schizophr.Bull., 16,* 551-561.

Bright, R. A., Avorn, J., & Everitt, D. E. (1989). Medicaid data as a resource for epidemiologic studies: strengths and limitations. *J.Clin.Epidemiol., 42,* 937-945.

Burns, T., Chabannes, J. P., & Demyttenaere, K. (2002). Switching antipsychotic medications: general recommendations and switching to amisulpride. *Curr.Med Res.Opin., 18,* 201-208.

Byerly, M. J., Weber, M., Brooks, D., Casey, S. B., Elliot, S., & Hawkins, J. (2003). Cost evaluation of risperidone compared with olanzapine. *Psychiatr.Serv., 54,* 742-744.

Carpenter, W. T., Jr. & Buchanan, R. W. (1994). Schizophrenia. *N.Engl.J.Med, 330,* 681-690.

Centorrino, F., Goren, J. L., Hennen, J., Salvatore, P., Kelleher, J. P., & Baldessarini, R. J. (2004). Multiple versus single antipsychotic agents for hospitalized psychiatric patients: case-control study of risks versus benefits. *Am.J.Psychiatry, 161,* 700-706.

Choo, P. W., Rand, C. S., Inui, T. S., Lee, M. L., Cain, E., Cordeiro-Breault, M. et al. (1999). Validation of patient reports, automated pharmacy records, and pill counts with electronic monitoring of adherence to antihypertensive therapy. *Med Care, 37,* 846-857.

Clark, R. E., Bartels, S. J., Mellman, T. A., & Peacock, W. J. (2002). Recent trends in antipsychotic combination therapy of schizophrenia and schizoaffective disorder: implications for state mental health policy. *Schizophr.Bull., 28,* 75-84.

Clark, R. E., Teague, G. B., Ricketts, S. K., Bush, P. W., Xie, H., McGuire, T. G. et al. (1998). Cost-effectiveness of assertive community treatment versus standard case management for persons with co-occurring severe mental illness and substance use disorders. *Health Serv.Res., 33,* 1285-1308.

Cooper, W. O., Hickson, G. B., Fuchs, C., Arbogast, P. G., & Ray, W. A. (2004). New Users of Antipsychotic Medications Among Children Enrolled in TennCare. *Arch.Pediatr.Adolesc.Med, 158,* 753-759.

Craig, T. J., Grossman, S., Mojtabai, R., Gibson, P. J., Lavelle, J., Carlson, G. A. et al. (2004). Medication use patterns and 2-year outcome in first-admission bipolar disorder with psychotic features. *Bipolar.Disord., 6,* 406-415.

Crismon ML & Dorson PG. (1997). Schizophrenia. In DiPiro JT, Talbert RL, & Yee GC (Eds.), *Pharmacotherapy: A Pathophysiologic Approach* (3rd ed., pp. 1367-1394). Stamford, Conn: Appleton & Lange.

Croghan, T. W., Johnstone, B. M., Buesching, D. P., & Kessler, R. C. (1999). Information needs for medication coverage decisions in a state Medicaid program. *Med.Care, 37,* AS24-AS31.

Crown, W. H., Obenchain, R. L., Englehart, L., Lair, T., Buesching, D. P., & Croghan, T. (1998). The application of sample selection models to outcomes research: the case of evaluating the effects of antidepressant therapy on resource utilization. *Stat.Med., 17,* 1943-1958.

Crown, W. H., Treglia, M., Meneades, L., & White, A. (2001). Long-term costs of treatment for depression: impact of drug selection and guideline adherence. *Value.Health, 4,* 295-307.

Csernansky, J. G. & Schuchart, E. K. (2002). Relapse and rehospitalisation rates in patients with schizophrenia: effects of second generation antipsychotics. *CNS.Drugs, 16,* 473-484.

Deyo, R. A., Cherkin, D. C., & Ciol, M. A. (1992). Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J.Clin.Epidemiol., 45,* 613-619.

Deyo, R. A., Inui, T. S., & Sullivan, B. (1981). Noncompliance with arthritis drugs: magnitude, correlates, and clinical implications. *J Rheumatol., 8,* 931-936.

Dolder, C. R., Lacro, J. P., Dunn, L. B., & Jeste, D. V. (2002). Antipsychotic medication adherence: is there a difference between typical and atypical agents? *Am.J.Psychiatry, 159,* 103-108.

Eaddy, M., Grogg, A., & Locklear, J. (2005). Assessment of compliance with antipsychotic treatment and resource utilization in a medicaid population. *Clin.Ther., 27,* 263-272.

Edgell, E. T., Andersen, S. W., Johnstone, B. M., Dulisse, B., Revicki, D., & Breier, A. (2000). Olanzapine versus risperidone. A prospective comparison of clinical and economic outcomes in schizophrenia. *Pharmacoeconomics., 18,* 567-579.

Emsley, R. A., Raniwalla, J., Bailey, P. J., & Jones, A. M. (2000). A comparison of the effects of quetiapine ('seroquel') and haloperidol in schizophrenic patients with a history of and a demonstrated, partial response to conventional antipsychotic treatment. PRIZE Study Group. *Int.Clin.Psychopharmacol., 15,* 121-131.

Foster, R. H. & Goa, K. L. (1998). Risperidone. A pharmacoeconomic review of its use in schizophrenia. *Pharmacoeconomics., 14,* 97-133.

Fountoulakis, K. N., Vieta, E., Sanchez-Moreno, J., Kaprinis, S. G., Goikolea, J. M., & Kaprinis, G. S. (2005). Treatment guidelines for bipolar disorder: A critical review. *J.Affect.Disord., 86,* 1-10.

Freudenreich, O. & Goff, D. C. (2002). Antipsychotic combination therapy in schizophrenia. A review of efficacy and risks of current combinations. *Acta Psychiatr.Scand., 106,* 323-330.

Frye, M. A., Ketter, T. A., Altshuler, L. L., Denicoff, K., Dunn, R. T., Kimbrell, T. A. et al. (1998). Clozapine in bipolar disorder: treatment implications for other atypical antipsychotics. *J.Affect.Disord., 48,* 91-104.

Fuller, M. A., Shermock, K. M., Secic, M., Laich, J. S., & Durkin, M. B. (2002). Service use and costs among VA patients with schizophrenia taking risperidone or olanzapine. *Psychiatr.Serv., 53,* 855-860.

Ganguly, R., Kotzan, J. A., Miller, L. S., Kennedy, K., & Martin, B. C. (2004). Prevalence, trends, and factors associated with antipsychotic polypharmacy among Medicaid-eligible schizophrenia patients, 1998-2000. *J.Clin.Psychiatry, 65,* 1377-1388.

Gianfrancesco, F., Durkin, M. B., Mahmoud, R., & Wang, R. H. (2002). Use of healthcare services by patients treated with risperidone versus conventional antipsychotic agents. *Pharmacoeconomics., 20,* 413-427.

Gianfrancesco, F., Pesa, J., & Wang, R. H. (2005). Comparison of mental health resources used by patients with bipolar disorder treated with risperidone, olanzapine, or quetiapine. *J.Manag.Care Pharm., 11,* 220-230.

Gibson, P. J., Damler, R., Jackson, E. A., Wilder, T., & Ramsey, J. L. (2004). The impact of olanzapine, risperidone, or haloperidol on the cost of schizophrenia care in a medicaid population. *Value.Health, 7,* 22-35.

Gilmer, T. P., Dolder, C. R., Lacro, J. P., Folsom, D. P., Lindamer, L., Garcia, P. et al. (2004). Adherence to treatment with antipsychotic medication and health care costs among Medicaid beneficiaries with schizophrenia. *Am.J.Psychiatry, 161,* 692-699.

Goldberg, J. F., Harrow, M., & Grossman, L. S. (1995). Course and outcome in bipolar affective disorder: a longitudinal follow-up study. *Am.J.Psychiatry, 152,* 379-384.

Goldner, E. M., Jones, W., & Waraich, P. (2003). Using Administrative Data to Analyze the Prevalence and Distribution of Schizophrenic Disorders. *Psychiatric Services, 54,* 1017-1021.

Greene, W. H. (2000). *Econometric analysis* . (4th ed.) Upper Saddle River, NJ: Prentice Hall.

Hamner, M. B., Arvanitis, L. A., Miller, B. G., Link, C. G., & Hong, W. W. (1996). Plasma prolactin in schizophrenia subjects treated with Seroquel (ICI 204,636). *Psychopharmacol.Bull., 32,* 107-110.

Harrow, M., Goldberg, J. F., Grossman, L. S., & Meltzer, H. Y. (1990). Outcome in manic disorders. A naturalistic follow-up study. *Arch.Gen.Psychiatry, 47,* 665-671.

Haywood, T. W., Kravitz, H. M., Grossman, L. S., Cavanaugh, J. L., Jr., Davis, J. M., & Lewis, D. A. (1995). Predicting the "revolving door" phenomenon among patients

with schizophrenic, schizoaffective, and affective disorders. *Am.J.Psychiatry, 152,* 856-861.

Heckman, J. J. (1979). Sample selection bias as a specification error. *Econometrica, 47 ,* 153-161.

Hilty, D. M., Brady, K. T., & Hales, R. E. (1999). A review of bipolar disorder among adults. *Psychiatr.Serv., 50,* 201-213.

Hirschfeld RMA, Calabrese JR, & Weissman M (2005). Lifetime prevalence of bipolar I and II disorders in the United States. Abstract presented at: The 155th Annual Meeting of the American Psychiatric Association; May 18-23, 2002; Philadelphia, PA. In.

Hogan, M. F. (1998). The public sector and mental health parity: time for inclusion. *J.Ment.Health Policy Econ., 1,* 189-198.

Hogan, M. F. (1999). Public-sector mental health care: new challenges. *Health Aff.(Millwood.), 18,* 106-111.

Hopkins, H. S. & Gelenberg, A. J. (1994). Treatment of bipolar disorder: how far have we come? *Psychopharmacol.Bull., 30,* 27-38.

Hudson, T. J., Owen, R. R., Thrush, C. R., Han, X., Pyne, J. M., Thapa, P. et al. (2004). A pilot study of barriers to medication adherence in schizophrenia. *J.Clin.Psychiatry, 65,* 211-216.

Hunt, G. E., Bergen, J., & Bashir, M. (2002). Medication compliance and comorbid substance abuse in schizophrenia: impact on community survival 4 years after a relapse. *Schizophr.Res., 54,* 253-264.

Jenkins, R. (1997). Reducing the burden of mental illness. *Lancet, 349,* 1340.

Jerrell, J. M. (2002). Cost-effectiveness of risperidone, olanzapine, and conventional antipsychotic medications. *Schizophr.Bull., 28,* 589-605.

Kamali, M., Kelly, L., Gervin, M., Browne, S., Larkin, C., & O'Callaghan, E. (2001). Psychopharmacology: insight and comorbid substance misuse and medication compliance among patients with schizophrenia. *Psychiatr.Serv., 52,* 161-3, 166.

Kaplan, M. (2000). Atypical antipsychotics for treatment of mixed depression and anxiety. *J.Clin.Psychiatry, 61,* 388-389.

Kashner, T. M., Rader, L. E., Rodell, D. E., Beck, C. M., Rodell, L. R., & Muller, K. (1991). Family characteristics, substance abuse, and hospitalization patterns of patients with schizophrenia. *Hosp.Community Psychiatry, 42,* 195-196.

Kasper, S., Jones, M., & Duchesne, I. (2001). Risperidone olanzapine drug outcomes studies in schizophrenia (RODOS): health economic results of an international naturalistic study. *Int.Clin.Psychopharmacol., 16,* 189-196.

Keck, P. E., Jr., McElroy, S. L., Strakowski, S. M., Bourne, M. L., & West, S. A. (1997). Compliance with maintenance treatment in bipolar disorder. *Psychopharmacol.Bull., 33,* 87-91.

Kelly, D. L., Nelson, M. W., Love, R. C., Yu, Y., & Conley, R. R. (2001). Comparison of discharge rates and drug costs for patients with schizophrenia treated with risperidone or olanzapine. *Psychiatr.Serv., 52,* 676-678.

Kessler, R. C., McGonagle, K. A., Zhao, S., Nelson, C. B., Hughes, M., Eshleman, S. et al. (1994). Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. *Arch.Gen.Psychiatry, 51,* 8-19.

Knapp, M. (1997). Costs of schizophrenia. *Br.J.Psychiatry, 171,* 509-518.

Knapp, M., King, D., Pugner, K., & Lapuerta, P. (2004). Non-adherence to antipsychotic medication regimens: associations with resource use and costs. *Br.J.Psychiatry, 184,* 509-516.

Kogut, S. J., Yam, F., & Dufresne, R. (2005). Prescribing of antipsychotic medication in a medicaid population: use of polytherapy and off-label dosages. *J.Manag.Care Pharm., 11,* 17-24.

Koro, C. E., Fedder, D. O., L'Italien, G. J., Weiss, S. S., Magder, L. S., Kreyenbuhl, J. et al. (2002). Assessment of independent effect of olanzapine and risperidone on risk of diabetes among patients with schizophrenia: population based nested case-control study. *BMJ, 325,* 243.

Lacro, J. P., Dunn, L. B., Dolder, C. R., Leckband, S. G., & Jeste, D. V. (2002). Prevalence of and risk factors for medication nonadherence in patients with schizophrenia: a comprehensive review of recent literature. *J.Clin.Psychiatry, 63,* 892-909.

Lehman, A. F., Kreyenbuhl, J., Buchanan, R. W., Dickerson, F. B., Dixon, L. B., Goldberg, R. et al. (2004a). The Schizophrenia Patient Outcomes Research Team (PORT): updated treatment recommendations 2003. *Schizophr.Bull., 30,* 193-217.

Lehman, A. F., Lieberman, J. A., Dixon, L. B., McGlashan, T. H., Miller, A. L., Perkins, D. O. et al. (2004c). Practice guideline for the treatment of patients with schizophrenia, second edition. *Am.J.Psychiatry, 161,* 1-56.

Lehman, A. F., Lieberman, J. A., Dixon, L. B., McGlashan, T. H., Miller, A. L., Perkins, D. O. et al. (2004b). Practice guideline for the treatment of patients with schizophrenia, second edition. *Am.J.Psychiatry, 161,* 1-56.

Lehman, A. F. & Steinwachs, D. M. (1998). Patterns of usual care for schizophrenia: initial results from the Schizophrenia Patient Outcomes Research Team (PORT) Client Survey. *Schizophr.Bull., 24,* 11-20.

Leslie, D. L. & Rosenheck, R. A. (2001). Use of pharmacy data to assess quality of pharmacotherapy for schizophrenia in a national health care system: individual and facility predictors. *Med.Care, 39,* 923-933.

Levine, J., Chengappa, K. N., Brar, J. S., Gershon, S., & Kupfer, D. J. (2001). Illness characteristics and their association with prescription patterns for bipolar I disorder. *Bipolar.Disord., 3,* 41-49.

Lewinsohn, P. M., Klein, D. N., & Seeley, J. R. (1995). Bipolar disorders in a community sample of older adolescents: prevalence, phenomenology, comorbidity, and course. *J.Am.Acad.Child Adolesc.Psychiatry, 34,* 454-463.

Licht, R. W., Gouliaev, G., Vestergaard, P., Dybbro, J., Lund, H., & Merinder, L. (1994). Treatment of manic episodes in Scandinavia: the use of neuroleptic drugs in a clinical routine setting. *J.Affect.Disord., 32,* 179-185.

Lindenmayer, J. P., Czobor, P., Volavka, J., Citrome, L., Sheitman, B., McEvoy, J. P. et al. (2003). Changes in glucose and cholesterol levels in patients with schizophrenia treated with typical or atypical antipsychotics. *Am.J.Psychiatry, 160,* 290-296.

Liperoti, R., Mor, V., Lapane, K. L., Pedone, C., Gambassi, G., & Bernabei, R. (2003). The use of atypical antipsychotics in nursing homes. *J.Clin.Psychiatry, 64,* 1106-1112.

Lish, J. D., Dime-Meenan, S., Whybrow, P. C., Price, R. A., & Hirschfeld, R. M. (1994). The National Depressive and Manic-depressive Association (DMDA) survey of bipolar members. *J.Affect.Disord., 31,* 281-294.

Loosbrock, D. L., Zhao, Z., Johnstone, B. M., & Morris, L. S. (2003). Antipsychotic medication use patterns and associated costs of care for individuals with schizophrenia. *J.Ment.Health Policy Econ., 6,* 67-75.

Lurie P, Popkin M, Dysken M, & Finch M. (1992). Accuracy of Diagnosis of Schizophrenia in Medicaid Claims. *Hospital and Community Psychiatry, 43,* 69-71.

Maarbjerg, K., Aagaard, J., & Vestergaard, P. (1988). Adherence to lithium prophylaxis: I. Clinical predictors and patient's reasons for nonadherence. *Pharmacopsychiatry, 21,* 121-125.

Mark, T. L. & Coffey, R. M. (2003). What drove private health insurance spending on mental health and substance abuse care, 1992-1999? *Health Aff.(Millwood.), 22,* 165-172.

Mauskopf, J. A., David, K., Grainger, D. L., & Gibson, P. J. (1999). Annual health outcomes and treatment costs for schizophrenia populations. *J.Clin.Psychiatry, 60 Suppl 19,* 14-19.

McCollam, P. L., Lage, M. J., & Bala, M. (2001). A comparison of total hospital costs for percutaneous coronary intervention patients receiving abciximab versus tirofiban. *Catheter.Cardiovasc.Interv., 54,* 152-157.

McCombs, J. S., Nichol, M. B., Johnstone, B. M., Stimmel, G. L., Shi, J., & Smith, R. (2000). Antipsychotic drug use patterns and the cost of treating schizophrenia. *Psychiatr.Serv., 51,* 525-527.

McCombs, J. S., Nichol, M. B., Stimmel, G. L., Shi, J., & Smith, R. R. (1999a). Use patterns for antipsychotic medications in medicaid patients with schizophrenia. *J.Clin.Psychiatry, 60 Suppl 19,* 5-11.

McCombs, J. S., Nichol, M. B., Stimmel, G. L., Shi, J., & Smith, R. R. (1999b). Use patterns for antipsychotic medications in medicaid patients with schizophrenia. *J.Clin.Psychiatry, 60 Suppl 19,* 5-11.

McCue, R. E., Waheed, R., & Urcuyo, L. (2003). Polypharmacy in patients with schizophrenia. *J.Clin.Psychiatry, 64,* 984-989.

McElroy, S. L., Keck, P. E., Jr., & Strakowski, S. M. (1996). Mania, psychosis, and antipsychotics. *J.Clin.Psychiatry, 57 Suppl 3,* 14-26.

Menzin, J., Boulanger, L., Friedman, M., Mackell, J., & Lloyd, J. R. (2003). Treatment adherence associated with conventional and atypical antipsychotics in a large state Medicaid program. *Psychiatr.Serv., 54,* 719-723.

Miller, A. L. (2004). PORT treatment recommendations. *Schizophr.Bull., 30,* 601-604.

Miller, A. L., Chiles, J. A., Chiles, J. K., Crismon, M. L., Rush, A. J., & Shon, S. P. (1999). The Texas Medication Algorithm Project (TMAP) schizophrenia algorithms. *J.Clin.Psychiatry, 60,* 649-657.

Mladsi, D. M., Grogg, A. L., Irish, W. D., Lopez, R. B., Degen, K., Swann, A. et al. (2004). Pharmacy cost evaluation of risperidone, olanzapine, and quetiapine for the treatment of schizophrenia in acute care inpatient settings. *Curr.Med.Res.Opin., 20,* 1883-1893.

Mojtabai, R., Lavelle, J., Gibson, P. J., Sohler, N. L., Craig, T. J., Carlson, G. A. et al. (2002). Gaps in use of antipsychotics after discharge by first-admission patients with schizophrenia, 1989 to 1996. *Psychiatr.Serv., 53,* 337-339.

Moller, H. J. & Nasrallah, H. A. (2003). Treatment of bipolar disorder. *J.Clin.Psychiatry, 64 Suppl 6,* 9-17.

Mortimer, A., Williams, P., & Meddis, D. (2003). Impact of side-effects of atypical antipsychotics on non-compliance, relapse and cost. *J.Int.Med Res., 31,* 188-196.

Motheral, B. R. & Fairman, K. A. (1997). The use of claims databases for outcomes research: rationale, challenges, and strategies. *Clin.Ther., 19,* 346-366.

Namjoshi, M. A., Rajamannar, G., Jacobs, T., Sanger, T. M., Risser, R., Tohen, M. F. et al. (2002). Economic, clinical, and quality-of-life outcomes associated with olanzapine treatment in mania. Results from a randomized controlled trial. *J.Affect.Disord., 69,* 109-118.

Narrow, W. E., Regier, D. A., Rae, D. S., Manderscheid, R. W., & Locke, B. Z. (1993). Use of services by persons with mental and addictive disorders. Findings from the National Institute of Mental Health Epidemiologic Catchment Area Program. *Arch.Gen.Psychiatry, 50,* 95-107.

Nightengale, B. S., Garrett, L., Waugh, S., Lawrence, B. J., & Andrus, J. (1998). Economic outcomes associated with the use of risperidone in a naturalistic group practice setting. *Am.J.Manag.Care, 4,* 360-366.

O'Connell, R. A., Mayo, J. A., Flatow, L., Cuthbertson, B., & O'Brien, B. E. (1991). Outcome of bipolar disorder on long-term treatment with lithium. *Br.J.Psychiatry, 159,* 123-129.

Ostroff, R. B. & Nelson, J. C. (1999). Risperidone augmentation of selective serotonin reuptake inhibitors in major depression. *J.Clin.Psychiatry, 60,* 256-259.

Perlis, R. H. (2005). The role of pharmacologic treatment guidelines for bipolar disorder. *J.Clin.Psychiatry, 66 Suppl 3:37-47.,* 37-47.

Perry, A., Tarrier, N., Morriss, R., McCarthy, E., & Limb, K. (1999). Randomised controlled trial of efficacy of teaching patients with bipolar disorder to identify early symptoms of relapse and obtain treatment. *BMJ, 318,* 149-153.

Pigott, T. A., Carson, W. H., Saha, A. R., Torbeyns, A. F., Stock, E. G., & Ingenito, G. G. (2003). Aripiprazole for the prevention of relapse in stabilized patients with chronic schizophrenia: a placebo-controlled 26-week study. *J.Clin.Psychiatry, 64,* 1048-1056.

Procyshyn, R. M., Kennedy, N. B., Tse, G., & Thompson, B. (2001). Antipsychotic polypharmacy: a survey of discharge prescriptions from a tertiary care psychiatric institution. *Can.J.Psychiatry, 46,* 334-339.

Procyshyn, R. M. & Thompson, B. (2004). Patterns of antipsychotic utilization in a tertiary care psychiatric institution. *Pharmacopsychiatry, 37,* 12-17.

Procyshyn, R. M. & Zerjav, S. (1998). Drug utilization patterns and outcomes associated with in-hospital treatment with risperidone or olanzapine. *Clin.Ther., 20,* 1203-1217.

Rascati, K. L., Johnsrud, M. T., Crismon, M. L., Lage, M. J., & Barber, B. L. (2003). Olanzapine versus risperidone in the treatment of schizophrenia : a comparison of costs among Texas Medicaid recipients. *Pharmacoeconomics., 21,* 683-697.

Regier, D. A., Narrow, W. E., Rae, D. S., Manderscheid, R. W., Locke, B. Z., & Goodwin, F. K. (1993). The de facto US mental and addictive disorders service system. Epidemiologic catchment area prospective 1-year prevalence rates of disorders and services. *Arch.Gen.Psychiatry, 50,* 85-94.

Revicki, D. A. (1997). Methods of pharmacoeconomic evaluation of psychopharmacologic therapies for patients with schizophrenia. *J.Psychiatry Neurosci., 22,* 256-266.

Revicki, D. A., Paramore, L. C., Sommerville, K. W., Swann, A. C., & Zajecka, J. M. (2003). Divalproex sodium versus olanzapine in the treatment of acute mania in bipolar disorder: health-related quality of life and medical cost outcomes. *J.Clin.Psychiatry, 64,* 288-294.

Rural Urban Continuum codes (2003). Available at:(http://www.ers.usda.gov/Data/RuralUrbanContinuumCodes/) Accessed on 01/20/2005 [On-line].

Russo, P., Smith, M. W., Dirani, R., Namjoshi, M., & Tohen, M. (2002). Pharmacotherapy patterns in the treatment of bipolar disorder. *Bipolar.Disord., 4,* 366-377.

Sachs, G. S., Printz, D. J., Kahn, D. A., Carpenter, D., & Docherty, J. P. (2000). The Expert Consensus Guideline Series: Medication Treatment of Bipolar Disorder 2000. *Postgrad.Med, Spec No,* 1-104.

Salloum, I. M. & Thase, M. E. (2000). Impact of substance abuse on the course and treatment of bipolar disorder. *Bipolar.Disord., 2,* 269-280.

Sanger, T. M., Tohen, M., Vieta, E., Dunner, D. L., Bowden, C. L., Calabrese, J. R. et al. (2003). Olanzapine in the acute treatment of bipolar I disorder with a history of rapid cycling. *J.Affect.Disord., 73,* 155-161.

Schou, M. (1997). The combat of non-compliance during prophylactic lithium treatment. *Acta Psychiatr.Scand., 95,* 361-363.

Schumacher, J. E., Makela, E. H., & Griffin, H. R. (2003). Multiple antipsychotic medication prescribing patterns. *Ann Pharmacother., 37,* 951-955.

Schumann, C., Lenz, G., Berghofer, A., & Muller-Oerlinghausen, B. (1999). Non-adherence with long-term prophylaxis: a 6-year naturalistic follow-up study of affectively ill patients. *Psychiatry Res., 89,* 247-257.

Schwartz, A. H., Perlman, B. B., Paris, M., Schmidt, K., & Thornton, J. C. (1980). Psychiatric diagnoses as reported to Medicaid and as recorded in patient charts. *Am.J.Public Health, 70,* 406-408.

Scott, J. (1993). Homelessness and mental illness. *Br.J.Psychiatry, 162,* 314-324.

Scott, J. & Pope, M. (2002). Self-reported adherence to treatment with mood stabilizers, plasma levels, and psychiatric hospitalization. *Am.J.Psychiatry, 159,* 1927-1929.

Sernyak, M. J. & Rosenheck, R. (2003). Risk adjustment in studies using administrative data. *Schizophr.Bull., 29,* 267-271.

Sernyak, M. J. & Rosenheck, R. (2004). Clinicians' reasons for antipsychotic coprescribing. *J.Clin.Psychiatry, 65,* 1597-1600.

Shattell, M. & Keltner, N. L. (2004). The case for atypical antipsychotics in bipolar disorder. *Perspect.Psychiatr.Care, 40,* 34-38.

Shelton, R. C. (2003). The combination of olanzapine and fluoxetine in mood disorders. *Expert.Opin.Pharmacother., 4,* 1175-1183.

Shepherd, G. & Hill, R. G. (1996). Manic depression: do people receive adequate support? *Nurs.Times, 92,* 42-44.

Simon, G. E. & Unutzer, J. (1999). Health care utilization and costs among patients treated for bipolar disorder in an insured population. *Psychiatr.Serv., 50,* 1303-1308.

Solomon, D. A., Keitner, G. I., Miller, I. W., Shea, M. T., & Keller, M. B. (1995). Course of illness and maintenance treatments for patients with bipolar disorder. *J.Clin.Psychiatry, 56,* 5-13.

Strakowski, S. M., Del Bello, M. P., Adler, C. M., & Keck, P. E., Jr. (2003). Atypical antipsychotics in the treatment of bipolar disorder. *Expert.Opin.Pharmacother., 4,* 751-760.

Strakowski, S. M. & DelBello, M. P. (2000). The co-occurrence of bipolar and substance use disorders. *Clin.Psychol.Rev., 20,* 191-206.

Strakowski, S. M., Sax, K. W., McElroy, S. L., Keck, P. E., Jr., Hawkins, J. M., & West, S. A. (1998). Course of psychiatric and substance abuse syndromes co-occurring with bipolar disorder after a first psychiatric hospitalization. *J.Clin.Psychiatry, 59,* 465-471.

Strom, B. (2005). *Pharmacoepidemiology*. (Third ed.) New York: Wiley and Sons.

Suppes, T., Baldessarini, R. J., Faedda, G. L., & Tohen, M. (1991). Risk of recurrence following discontinuation of lithium treatment in bipolar disorder. *Arch.Gen.Psychiatry, 48,* 1082-1088.

Suppes, T., Rush, A. J., Dennehy, E. B., Crismon, M. L., Kashner, T. M., Toprac, M. G. et al. (2003). Texas Medication Algorithm Project, phase 3 (TMAP-3): clinical results for patients with a history of mania. *J.Clin.Psychiatry, 64,* 370-382.

Tapp, A., Wood, A. E., Secrest, L., Erdmann, J., Cubberley, L., & Kilzieh, N. (2003). Combination antipsychotic therapy in clinical practice. *Psychiatr.Serv., 54,* 55-59.

Tempier, R. P. & Pawliuk, N. H. (2003). Conventional, atypical, and combination antipsychotic prescriptions: a 2-year comparison. *J.Clin.Psychiatry, 64,* 673-679.

Tilden, D., Aristides, M., Meddis, D., & Burns, T. (2002). An economic assessment of quetiapine and haloperidol in patients with schizophrenia only partially responsive to conventional antipsychotics. *Clin.Ther., 24,* 1648-1667.

Tohen, M. & Zarate, C. A., Jr. (1998). Antipsychotic agents and bipolar disorder. *J.Clin.Psychiatry, 59 Suppl 1,* 38-48.

Tohen, M., Zhang, F., Taylor, C. C., Burns, P., Zarate, C., Sanger, T. et al. (2001). A meta-analysis of the use of typical antipsychotic agents in bipolar disorder. *J.Affect.Disord., 65,* 85-93.

Tse, S. S. & Walsh, A. E. (2001). How does work work for people with bipolar affective disorder? *Occup.Ther.Int., 8,* 210-225.

Van Putten, T. (1974). Why do schizophrenic patients refuse to take their drugs? *Arch.Gen.Psychiatry, 31,* 67-72.

Voris, J. C. & Glazer, W. M. (1999). Use of risperidone and olanzapine in outpatient clinics at six Veterans Affairs hospitals. *Psychiatr.Serv., 50,* 163-4, 168.

Waddington, J. L., Youssef, H. A., & Kinsella, A. (1998). Mortality in schizophrenia. Antipsychotic polypharmacy and absence of adjunctive anticholinergics over the course of a 10-year prospective study. *Br.J.Psychiatry, 173,* 325-329.

Weiden, P., Aquila, R., & Standard, J. (1996). Atypical antipsychotic drugs and long-term outcome in schizophrenia. *J.Clin.Psychiatry, 57 Suppl 11,* 53-60.

Weiden, P. J., Kozma, C., Grogg, A., & Locklear, J. (2004). Partial compliance and risk of rehospitalization among California Medicaid patients with schizophrenia. *Psychiatr.Serv., 55,* 886-891.

Weiden, P. J. & Olfson, M. (1995). Cost of relapse in schizophrenia. *Schizophr.Bull., 21,* 419-429.

Weissman, M. M., Bland, R. C., Canino, G. J., Faravelli, C., Greenwald, S., Hwu, H. G. et al. (1996). Cross-national epidemiology of major depression and bipolar disorder. *JAMA, 276,* 293-299.

Weissman, M. M., Leaf, P. J., Tischler, G. L., Blazer, D. G., Karno, M., Bruce, M. L. et al. (1988). Affective disorders in five United States communities. *Psychol.Med, 18,* 141-153.

Williams, C. L., Johnstone, B. M., Kesterson, J. G., Javor, K. A., & Schmetzer, A. D. (1999). Evaluation of antipsychotic and concomitant medication use patterns in patients with schizophrenia. *Med.Care, 37,* AS81-AS86.

Wyatt, R. J. & Henter, I. (1995). An economic evaluation of manic-depressive illness--1991. *Soc.Psychiatry Psychiatr.Epidemiol., 30,* 213-219.

Zhao, Z. (2002). A retrospective economic evaluation of olanzapine versus risperidone in the treatment of schizophrenia. *Manag.Care Interface, 15,* 75-81.

Zhao, Z. (2004). Economic outcomes associated with olanzapine versus risperidone in the treatment of uncontrolled schizophrenia. *Curr.Med.Res.Opin., 20,* 1039-1048.

CURRICULUM VITAE

Mariam K. Hassan
E-mail: mhassan@hsc.wvu.edu

EDUCATION

August 1999-July 2005
Doctor of Philosophy (Ph.D.), Dept. of Pharmaceutical Systems & Policy, West Virginia University
Dissertation: *Evaluating Medication Utilization Patterns and Healthcare Outcomes in Patients receiving Antipsychotics*

June 1994-June 1998
Bachelor of Pharmacy (B. Pharm), University of Mumbai, India

RESEARCH AND PROFESSIONAL EXPERIENCE

December 2004-Present
Principal Investigator
Research Grant funded by AstraZeneca, for the project "Economic Evaluation of Antipsychotics." Total Funding: $54,000.00, Grant/ Contract #: 1002887R

October 2003-November 2003
Research Assistant
Assisted on a report reviewing various Pharmacy Benefit Management (PBM) strategies for the West Virginia Worker's Compensation Commission (WVWCC)

May 2003-August 2003
Summer Intern
Health Benchmarks, Inc

- Conducted a retrospective claims data analysis comparing utilization, cost and adherence between dual and single controller asthma medications using advanced regression models and survival analysis (***Study sponsored by GlaxoSmithKline***)
- Carried out a cost-benefit analysis of chiropractic insurance coverage in a managed care network using techniques such as sample selection models and two-part models (***Study sponsored by American Specialty Health***)
- Patient-reported outcomes analysis for REACH (Registry for the Enhancement of Asthma Control and Health)

Aug 2002-December 2004
Research Assistant
Examine utilization characteristics of narcotic analgesics in the WV Worker's Compensation system for a project funded by the WV Bureau of Employment Programs. Developed the study design and data analysis method to identify

overuse/inappropriate use of narcotic analgesics and evaluate their cost and utilization

Aug 2002-December 2003
Research Assistant
Survey of West Virginia Medicaid beneficiaries to assess the prevalence of tobacco use & need for smoking cessation programs for a study funded by West Virginia Bureau of Medical Services. Assisted in data analysis and preparing manuscripts

Aug 2001-December 2004
Research Assistant, School of Medicine, West Virginia University
Responsibilities include IRB application process, research design, literature review, data analysis, SAS programming, preparing reports, manuscripts and presentations as well as providing consultations for student practicum projects for the Masters in Public Health (MPH) program

Aug 2001-December 2004
Research Assistant
Development and management of prospective epidemiological database for studies on occupational and environmental hazards. The project was funded by Institute of Occupational and Environmental Health (IOEH) and Association of Occupational and Environmental Clinics (AOEC).
Responsibilities include IRB application process, developing physician survey, and patient data collection

Aug 1999-July 2001
Teaching Assistant, School of Pharmacy, West Virginia University
Responsibilities include lecturing, grading, management of course material, and facilitation of student projects

July 1998-July 1999
Research Apprentice, R & D Formulations, Elder Pharmaceutical Limited, Bombay, India
Responsibilities included pre-formulation and formulation studies of antispasmodic agent – Oxybutynin chloride (Nocturin®), dosage form design, supervision of "Product Development Trial Batches" of tablets and syrups, coordinated meetings between formulation development and marketing

PUBLICATIONS

Hassan M and Amonkar MM. "Aspirin Use for Primary and Secondary Prophylaxis of Cardiovascular Disease." *Current Therapeutic Research*.2001; 62:676-690.

Hassan M, Joshi A, Madhavan S, and Amonkar M. "Obesity and Health-Related Quality of Life: A Cross-sectional Analysis of US population." *International Journal of Obesity* 2003; 27(10):1227-32.

Scobbo RR, Vondohlen TW, **Hassan M** and Islam S. "Serum TSH Variability in Normal Individuals: Influence of Time of Sample Collection." *West Virginia Medical Journal*. 2004; 100 (July/August): 138-142.

Hassan M and Miller L. Compliance Therapy in Schizophrenia: Addressing Possible Reasons for No Significant Differences and the Need to Adjust for Antipsychotic Type. (Letter to Editor) *British Medical Journal* 2003; 327: 834-0. Available at: http://bmj.bmjjournals.com/cgi/eletters/327/7419/834#39684.

Hassan M, Kalsekar I, Madhavan S, Mody R and Amonkar M. Determinants of Readiness to Quit Smoking among Women of Child Bearing Age. (Under review) *Women's Health Issues.*

PRESENTATIONS

Hassan M, Kavookjian J, Madhavan S. **"**Study gaps in economic evaluations of pharmacotherapy in bipolar disorder." Poster presentation, Tenth Annual International Meeting of International Society for Pharmacoeconomic and Outcome Research (ISPOR), May 15-18, 2005, Washington DC.

Islam S, **Hassan M**, Doyle E. Becker J, Weikle P, Ducatman A. "Quantification of Suspected Addiction Treatment of Narcotic Analgesics using Prescription Sequence Analysis: Experience of a State-Based Worker's Compensation System." Poster presentation, International Society for Pharmacoeconomic and Outcome Research (ISPOR) 7th Annual European Congress, October 24-26, 2004, Hamburg, Germany.

Legoretta A, **Hassan M**. "Prevalence of Antidepressant Use in Children and Adolescents: Who Prescribes and What are the Diagnoses." Poster presentation, Annual Meeting of the American Pharmaceutical Association (APhA), March 26-30, 2004, Seattle, Washington.

Hassan M, Islam S, Doyle E, Ducatman A. "Utilization Characteristics of Narcotic Analgesics in WV Workers' Compensation Claimants." Poster Presentation, Eight Annual International Meeting of International Society for Pharmacoeconomic and Outcome Research (ISPOR), May 18-21, 2003, Arlington, Virginia.

Hassan M, Amonkar M. "Resource Utilization for Inpatient Asthma Care in Children and Adults: An analysis of HCUP data." Poster Presentation, Seventh Annual International Meeting of International Society for Pharmacoeconomic and Outcome Research (ISPOR), May 19-22, 2002, Arlington, Virginia.

Wierman T, Slain D, **Hassan M**, Miller K, Amonkar M. "A Benchmarking Survey Study on Lipid-Based Amphotericin B Usage at Various U.S Institutions." Poster Presentation, 36th Annual American Society of Health-System Pharmacists (ASHP) Midyear Clinical Meeting, December 2-6, 2001, New Orleans, Louisiana.

Hassan M, Kamal K, Mody R, Amonkar M. "Breast and Cervical Cancer Screening among Obese Women in the United States." Poster Presentation, 129th Annual Meeting of American Public Health Association (APHA), October 21-25, 2001, Atlanta, Georgia.

Hassan M, Joshi A, Madhavan S, Amonkar M. "Impact of Obesity on Health-Related Quality of Life: An Analysis of BRFSS Data." Poster presentation, Sixth Annual International Meeting of International Society for Pharmacoeconomic and Outcome Research (ISPOR), May 20-23, 2001, Arlington, Virginia.

Hassan M, Amonkar M. "Aspirin Use for Primary and Secondary Prevention of Cardiovascular Disease: An Analysis of BRFSS Data." Poster presentation, 148th Annual Meeting of the American Pharmaceutical Association (APhA), March 16-20, 2001, San Francisco, California.

RELEVANT COURSE WORK

Pharmacoeconomics, Econometrics, SAS, Quality of Life Assessment, Epidemiology, Data Management and Analyses, Decision Modeling, Survey Research, Qualitative Methods, Health Services Marketing, and Health Behavior Theories

COMPUTER SKILLS

Statistical and Econometric Software- SAS®, SPSS®, STATA®, Ethnograph®, LIMDEP®, Decision Analysis by TreeAge®

HONORS and PROFESSIONAL AFFILIATIONS

WVU Graduate Research Award
ISPOR Poster Finalist Award: Seventh Annual European Congress and Eight Annual International Meeting
Rho Chi National Pharmacy Honor Society
American Pharmaceutical Association (APhA) *(2000 – current)*
International Society for Pharmacoeconomics and Outcomes Research (ISPOR) *(2000 – current)*
Institute of Occupational and Environmental Health (IOEH) Research Process Council
Treasurer- WVU ISPOR Chapter
Judge- Podium Presentations (ISPOR 2002)