DIAGNOSIS AND TREATMENT OF PEDIATRIC BIPOLAR DISORDER IN A COMMERCIALLY INSURED POPULATION

Stacie B. Dusetzina

A dissertation submitted to the faculty of the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Pharmaceutical Sciences in the Division of Pharmaceutical Outcomes and Policy, UNC Eshelman School of Pharmacy

Chapel Hill
2010

Approved by:

Richard A. Hansen, PhD

Betsy L. Sleath, PhD

Joel F. Farley, PhD

Morris Weinberger, PhD

Bradley N. Gaynes, MD, MPH

ABSTRACT

STACIE B. DUSETZINA: Diagnosis and Treatment of Pediatric Bipolar Disorder in a Commercially Insured Population
(Under the direction of Richard A. Hansen, PhD)

Recent reports indicate that bipolar disorder diagnosis is increasing in U.S. children. Increased diagnoses are concerning as diagnostic criteria are unclear and most medications prescribed to treat bipolar disorder have not been tested or approved for children. No studies have been conducted to assess the use of clinical treatment guidelines in children with bipolar disorder. This is troubling as current prescribing guidelines should dictate treatment in this population. The objectives of this dissertation are to examine the medication use patterns for privately insured children with bipolar spectrum disorders, and to assess the consistency of prescribing patterns with treatment guidelines.

MarketScan Commercial Claims and Encounters data (2005-2007) were used to identify children with diagnoses of bipolar disorder. Patient demographic and treatment characteristics were summarized for the cohort. Additionally, two measures were constructed to assess the quality of care received among children with bipolar I disorder. These measures, receipt of (1) appropriate first-line treatment, and (2) adequate duration of initial medication treatment, were used to determine whether a patient received guideline-recommended care. Generalized linear models were used to determine factors associated with receiving guideline-recommended care.

We found an average annual prevalence of any bipolar spectrum disorder was 0.25% among privately insured children. Most children received pharmacotherapy, and treatments were similar across all bipolar subtypes. Anticonvulsants, atypical antipsychotics, antidepressants, and stimulants were prescribed commonly. Approximately 40% of the population received polypharmacy.

Among children with bipolar I disorder, 84% received potentially inappropriate first line treatment. A majority of these children received either no medication or antidepressant medications without mood stabilizers. Several factors were associated with the receipt of recommended first line treatment, including bipolar episode type, having comorbid major depressive disorder diagnoses, and receiving care from a psychiatrist. Regarding early treatment regimen changes, 41% of children had initial treatment trials shorter than 6 weeks. However, none of the factors tested were consistently related to early regimen changes.

These results highlight the high prevalence of bipolar diagnoses and deficiencies in the diagnosis and treatment of bipolar spectrum disorders among children by identifying trends in prescribing and gaps in the quality of care received by children.

ACKNOWLEDGEMENTS

There are so many people to thank for helping me to reach this goal. Thank you to my mom and dad for the great educational foundation and the work ethic that got me to this point. To my sister, Audra, and one of my truest friends, Neepa, for talking so often with me about research questions and computer programming issues. Thank you to Ashley who is and who will always be my "student mentor." Your advice and enthusiasm for research has made me a better student and mentor. A heartfelt thank you to my classmates and colleagues at the UNC Eshelman School of Pharmacy for your support and for making graduate school a lot more fun!

Thanks to Rick Hansen, my advisor for all of your support and for allowing me to work to my full potential. I have appreciated so much that you have treated me like a colleague, not merely as a student. Also, thank you to Brad, Joel and Betsy for the support and direction, as your input has helped me to develop a great project. To Morris, your mentorship has been invaluable. Thank you so much for the time that you invested and all of the advice. I'm so grateful to have had you for my Sheps mentor, a committee member, and a friend. Finally, thank you to my husband and best friend, Bret. Your encouragement has meant the world to me. Thank you for believing in me, even when I did not. I would not be here without your love and support and, for that, I will be forever grateful.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AACAP	American Academy of Child and Adolescent Psychiatry
ADHD	Attention Deficit Hyperactivity Disorder
AHFS	American Hospital Formulary Service
APA	American Psychological Association
Bipolar NOS	Bipolar disorder, not otherwise specified / unspecified type
BPD	Bipolar Disorder
CABF	Child and Adolescent Bipolar Foundation
CBCL	Child Behavior Checklist
CD	Conduct Disorder
CMRS	Child Mania Rating Scale
CPT	Current Procedural Terminology
DALY'S	Disability Adjusted Life Years
DSM-III	Diagnostic and Statistics Manual for Mental Illness, Third Edition
DSM-IV-TR	Diagnostic and Statistics Manual for Mental Illness, Fourth Edition, Text Revision
ECT	Electroconvulsive Therapy
EPS	Extrapyramidal Symptoms
FDA	U.S. Food and Drug Administration
HCPCS	Healthcare Common Procedure Coding System

HMO	Health Maintenance Organization
ICD-9	International Disease Classification, Ninth Edition
IOM	Institute of Medicine
MAOIs	Monoamine Oxidase Inhibitors
MSA	Metropolitan Statistical Area
NAMCS	National Ambulatory Medical Care Survey
NCS-R	National Comorbidity Survey Replication
NIMH	National Institutes of Mental Health
ODD	Oppositional Defiant Disorder
PGBI-SF10	Parent General Behavior Inventory
P-MDQ	Parent Mood Disorder Questionnaire
POS	Non-Capitated Point of Service
PPO	Preferred Provider Organization
SNRI	Selective Norepinephrine Reuptake Inhibitors
SSRI	Selective Serotonin Reuptake Inhibitors
TCAs	Tricyclic Antidepressants
WHO	World Health Organization

CHAPTER ONE: INTRODUCTION

1.1 Overview

Over the past decade the diagnosis of bipolar disorder has increased in U.S. children at an alarming rate. Some studies indicate that there has been a 40-fold increase in this diagnosis among children under the age of 19 during the period 1992 – 2002.[1] Pediatric bipolar disorder is associated with significant risk for suicidality, psychiatric hospitalizations and externalizing disorders. [2-8] Additionally, children with bipolar disorder frequently have difficulty in both academic and social settings[4] and are often plagued by comorbid psychiatric conditions such as attention deficit hyperactivity disorder, oppositional defiant disorder, conduct disorder, anxiety disorders and substance use disorders. [3, 9-12]

Unfortunately, the evidence base that clinicians have available to inform treatment decisions has not been developed in a manner to support this drastic increase in prescribing among children.[13] For example, pharmacologic agents are commonly used for the treatment of pediatric bipolar disorder;[1, 14-16] however, most of the medications that are commonly prescribed to treat bipolar disorder in this age group have not been tested or approved for use in the pediatric population.[10, 17, 18]

In addition to the lack of formal regulatory approval for the use of these products in children, there are concerns regarding the use of inappropriate first-line therapies. For example, current guidelines recommend the treatment of bipolar I to be a single mood stabilizer or atypical antipsychotic agent;[17, 19] however, it is unknown the extent to which treatment varies from this recommendation. Findings from studies of drug class use among patients with bipolar disorder suggest that monotherapy is rare and that use of treatments such as antidepressants and stimulants is common.[1]

Similarly, regarding the adherence to recommendations, time on treatment prior to switching medication has not been studied in the pediatric population. While medication switching is common in the treatment and management of bipolar disorder, experts recommend that an adequate treatment period be maintained prior to making treatment regimen changes. Therefore, it is important to consider the factors that are associated with early medication switching (prior to a recommended 4-6 week drug treatment trial) in this population since this has important implications for clinical practice.[17, 19-21]

1.2 Specific Aims

Assessing the epidemiology of bipolar disorder, along with medication use and treatment patterns in a pediatric population is a necessary step for understanding how treatment patterns differ from current consensus guidelines, and can guide future interventions. These issues will be addressed by the following research questions:

Aim 1: To describe the treatment patterns and the demographic characteristics of a cohort of children who are diagnosed with bipolar disorder. Descriptive information regarding the medication classes and class combinations that are used to treat pediatric

bipolar disorder will be summarized. This information will be reported as frequencies of use for commonly prescribed medication classes and combinations of medication classes. In addition to medication summaries, characteristics of children with bipolar disorder will also be summarized for the selected cohort. These characteristics will include age at the time of diagnosis, sex, and number and type of co-morbidities.

Additionally, changes in diagnosis, treatment and co-morbid conditions will be assessed for the entire cohort and separately by age categories. There is currently a lack of information regarding the differences in treatment strategies and diagnosis of children who are under the age of 10 years.[22] This age group is particularly important because current recommendations are to conduct medication trials of only 10 to 17 year old children.[20] It is important to identify if younger children are receiving similar diagnoses and treatments as older children.[23] This information can then be used to inform medication trial designs that currently suggest excluding this group from analysis. Changes in the prevalence and type of diagnosis (separately and combined) will be analyzed using the one-year diagnostic prevalence for each year during the study period (2005, 2006 and 2007). The use of drug classes, drug class combinations and the presence of co-morbid diagnosis will be analyzed similarly over the study period.

Aim 2: Determine the factors associated with receiving a single mood stabilizer or atypical antipsychotic as first line treatment, compared to receiving any other bipolar treatment. Guidelines that have been developed regarding the treatment of pediatric bipolar disorder emphasize the importance of starting a child on a single mood stabilizer or atypical antipsychotic as first-line treatment of bipolar I disorder.[17, 19] It is further suggested

that children who receive medication for pre-morbid or co-morbid mental health disorders be taken off of those medications for a stabilization period.[17] Little is known about the extent to which these recommendations are followed in clinical practice.

To address this aim, pharmacologic treatment patterns within the dataset will be used to identify children with newly-diagnosed bipolar I disorder who received a guideline-recommended first-line treatment (versus those that received any other treatment or treatment combination). This information will then be used to assess differences in the characteristics of children who receive guideline concordant treatment versus those that receive non-concordant treatment. Generalized linear models will be used to assess the relationship between selected patient and provider characteristics and the probability of receiving guideline recommended first-line treatments.

Aim 3: Determine the factors associated with early treatment regimen changes, compared with no early regimen changes. In addition to recommendations regarding the use of appropriate first-line therapies, guidelines also recommend that medications be monitored for a minimum of 6-8 weeks in order to determine treatment effectiveness.[21] This is considered to be an adequate period of clinical exposure to a medication.[20] While switching medications is common and often appropriate for second-line treatment (because of side effects or a lack of efficacy), it is not recommended for first line treatments.[24] Because of this, early switching can be viewed as a proxy for guideline deviation (although switching is permitted if a patient cannot tolerate the medication). It is unclear to what extent early medication switching occurs in children with bipolar disorder and if there are factors that would predict early medication switching.

To address this aim, time from first medication fill will be used to identify children with newly-diagnosed bipolar I disorder who had adequate medication treatment trials versus those that switched early. This information will then be used to assess differences in the characteristics of children who receive adequate or inadequate medication treatment trials. Generalized linear models will be used to assess the relationship between selected patient and provider characteristics and the probability of having an early medication switch.

1.3 Importance of Proposed Research Plan

Child and adolescent psychiatric disorders have been called one of the "final frontiers" of epidemiology and experts have noted that an important task of epidemiology during the next decade is to monitor the trends in treatment rates, prevalence, and the burden of child and adolescent mental illness.[25] Currently there is a lack of information concerning national trends in the diagnosis of bipolar disorder and treatments that are received.[1] Few epidemiological studies have been conducted in the area of bipolar disorder in children and adolescents. Most of the evidence has been derived from patient samples. While these samples provide insight into the disorder, their limited size make it difficult to detect diagnostic and treatment patterns that may exist in the population.[26] On the other hand, epidemiologic samples are able to detect conditions on the bipolar spectrum that are underrepresented in clinical samples (such as bipolar II and bipolar NOS). Epidemiological studies are needed to provide accurate estimates of the prevalence and clinical characteristics of bipolar disorder in youth.[26]

The proposed project will add to the literature in several important ways. First, this study will provide necessary epidemiologic information on the potential risk factors for

bipolar disorder in the selected cohort. Trends in diagnosis and treatment for bipolar disorder were increasing at an alarming pace from 1994 to 2003[1] and there was no evidence of the trend leveling off in this previous analysis. This indicates that updated information regarding the current level of diagnosing, along with characteristics of the children who are diagnosed with bipolar disorder would add to our current knowledge regarding the etiology of pediatric bipolar disorder.

No studies as of yet have assessed the extent to which pediatric bipolar guidelines are followed. Other research in this area has been confined to the assessment of adult bipolar disorder and these studies have found variation in the use of practice guidelines and potentially deleterious effects on patient health outcomes.[27] Additionally, limited information exists regarding the safety and efficacy of available pharmacologic treatments for use in the pediatric population. In these instances, guidelines from expert panels should be used to dictate treatment.[28] The reliance on these published guidelines as the primary source for diagnostic and treatment information for pediatric patients who are suspected to have bipolar disorder confers the importance of assessing the extent to which guidelines are followed in this population. Finally, identifying modifiable factors that are associated with nonadherence to guidelines will provide targets for quality improvement efforts in the population.

CHAPTER TWO: BACKGROUND AND SIGNIFICANCE

2.1 Epidemiology and Disease Burden

2.1.1 Prevalence

Bipolar disorder, once considered rare in children, has now become one of the most common diagnoses among child and adolescent inpatients. Recent studies have indicated a sharp increase in the number of diagnoses of bipolar disorder in both inpatient and outpatient settings. [1, 29-32] Prior to 1998, few studies of bipolar prevalence existed[26, 33] but the data that were available suggested that the prevalence of bipolar disorder in youth was increasing faster than would typically be expected.[34]

There is significant variation in the reported prevalence estimates due to a lack of consensus of bipolar definitions and differences in reporting (for example, reporting any spectrum disorder versus reporting a single disorder on the spectrum). To date, most of the data used to describe the prevalence of pediatric bipolar disorder has been extrapolated from studies of the adult bipolar population. These estimates have ranged from less than 1% to nearly 9%, depending on how prevalence was defined.[13, 26, 35-44]

As of 2005, no data existed on the prevalence of pre-adolescent bipolar disorder.[45] However, community surveys and histories of adults with bipolar disorder indicate that

childhood and adolescent bipolar disorder is more common than previously considered.[26, 46, 47] For example, one community study showed a lifetime prevalence of any bipolar spectrum disorder was about 1% in youths aged 14-18. Most of the children in this sample, however, had bipolar-II or cyclothymia and another 5.7% had sub-syndromal bipolar symptoms instead of bipolar I disorder (see section 2.2.1 for a detailed description of bipolar spectrum disorders).[26] Additionally, data from retrospective studies indicate that as many as 60% of adults report early-onset bipolar disorder (prior to age 20) and 10-20% report childhood onset (prior to age 10).[46, 48-50]

Since few studies possess adequate samples of the population to estimate prevalence,[51] several retrospective studies have been conducted to try to estimate the prevalence of bipolar disorder among children. In such studies, prevalence is assessed using administrative claims data or national inpatient and outpatient surveys. While these estimates vary, they all point to an increase in the diagnostic prevalence of the disorder in the pediatric population. Perhaps the best examples of these noted increases are provided by studies conducted recently by Blader, Harpaz-Rotem and Moreno.[1, 29, 52-54]

In 2007, Blader and Carlson used a national hospital discharge database to detect trends in diagnoses of children and adolescents who were admitted to inpatient psychiatric care from 1996 to 2004. In 1996, bipolar disorder was one of the least frequent diagnoses recorded among child inpatients, but by 2004 it had become the most common diagnosis among this group. Similarly, among adolescents, there were twice as many discharges with a major depressive disorder as with bipolar disorder in 1996, but nearly the same number of discharges between the two groups by 2004.[29] As a proportion of total psychiatrically related

discharges, children diagnosed with bipolar disorder constituted 10% in 1996 and 34% by 2004.[29]

In 2004 and 2005, Harpaz-Rotem and colleagues used children's mental health insurance claims data to assess the proportion of youth with a diagnosis of bipolar disorder who received inpatient or outpatient mental heath services. They compared use in 1995 to use in 2000 and found that the proportion of youth that received outpatient treatment for bipolar disorder increased by 67%[54] and the proportion who received inpatient treatment increased by 74%.[53] Additionally, over the study period, the proportion of hospitalized children who were treated for bipolar disorder doubled, with increases in bipolar diagnoses among both adolescents and school-aged children.[53]

In 2007, Moreno and colleagues used the National Ambulatory Medical Care Survey (NAMCS) to detect trends in the diagnosis of bipolar disorder and the treatments received. They compared the annual number of office-based visits that included a diagnosis of bipolar disorder in 1994-1995 to those recorded in 2002-2003. They found that the annual number of office-based visits in the US that included a diagnosis of bipolar disorder increased in youth from 25 per 100,000 in 1994-1995 to 1,003 per 100,000 in 2002-2003. This represented a 40-fold increase in bipolar-related office visits for youth over the study period.[1]

While the true prevalence of pediatric bipolar disorder remains unknown, researchers now believe that bipolar disorder is more common in children than had previously been acknowledged.[55] In fact, the incidence of bipolar disorder in children is approaching that in adults.[56] It is important to note that increases in diagnosis of bipolar disorder may stem from several causes. They could be a reflection of a true increase in prevalence, a rectification of

previous under-recognition, changes in the definition or conceptualization of the disorder, or inappropriate application of the diagnosis to children who have other illnesses.[57]

2.1.2 Differences by Gender and Race

Consistent with studies of the adult bipolar population, there are few differences in bipolar incidence by gender, indicating that the prevalence, age of onset, phenomenology and course of bipolar disorder in adolescents is similar for males and females.[58] [26] Other studies in youth show similar results with rates of bipolar spectrum disorders or bipolar subtypes remaining constant in males and females.[59, 60] Similarly, studies of symptoms, symptom expression, and of treatment type have shown no variation by gender.[59, 61] There are, however, several key areas where gender differences emerge in pediatric bipolar disorder. In particular, early-onset cases (prior to age 13) are more frequently male,[19] and gender differences are found in the presentation of co-morbid conditions, the age at first treatment and in rates of symptomatic recovery.[59, 62]

Regarding racial and ethnic differences, there are no reports of differential incidence of Bipolar I Disorder based on race or ethnicity in the adult bipolar literature.[58] In the pediatric bipolar literature, however, studies of hospital discharge data have shown changes in bipolar diagnoses by both race and gender. For example, prior to 2001, white girls had few occurrences of bipolar diagnoses but since that time, rates have reached that of white boys.[29] Similarly, in more recent years (2003 - 2004), discharges for black boys and girls exceeded the rate among whites.[29, 62]

2.1.3 Disease Burden

Bipolar disorder is a devastating disease that results in substantial impairments across psychosocial domains. For patients with bipolar disorder there are high risks for the following events: suicide, psychosis, familial aggregation and a protracted illness course in which the cycles of the disorder appear to be more chronic than episodic.[14, 26, 63-69] According to the World Health Organization (WHO), bipolar disorder is ranked sixth among all medical disorders in years of lost life due to death or disability.[70] Additionally, bipolar disorder has been consistently rated among the top causes of disability adjusted life years (DALYs) for 15-44 year olds in developed countries.[71]

One of the most disabling features of bipolar disorder is its chronicity, as evidenced by the similarities between the 12 month and lifetime rates of bipolar disorder in both adults and in children.[72] Individuals with bipolar disorder generally experience a chronic, recurrent course of illness that increases their risk of lifelong disability and greatly impacts their lives and the lives of their families.[51, 73]

Children with bipolar disorder have significantly higher rates of morbidity and mortality than children without the disorder,[67, 74, 75] including psychosocial morbidity, impaired academic performance, impaired social and familial support, increased levels of substance abuse, weight problems, legal difficulties, and hospitalizations.[2-8] For example, one author reported that youth in her sample had poor social skills, reported having no friends and being teased by other children.[76] Even among asymptomatic adolescents with bipolar disorder there were significant interpersonal deficits as compared to healthy adolescents.[77]

Researchers have also shown that onset of bipolar disorder prior to age 18 is associated with suicidal ideation and suicide attempts.[78, 79] In fact, adolescents with bipolar disorder have a higher suicide risk than adolescents with any other psychiatric disorder, [34, 80-82] and more than 25% of pre-pubertal children or adolescents with bipolar disorder develop a suicide plan.[34] In the largest community-based study of bipolar disorder, researchers found that adolescents with bipolar disorder had a much higher percent of suicide attempts (44.4%) than adolescents who were not mentally ill (1.2%), and even compared to those with major depressive disorder (22.2%).[26] Given the chronic course of the disease, it is important to note that research has shown that between 25 and 50% of adults with bipolar disorder attempt suicide at least once in their lifetime and between 8 and 19% of them will die from suicide.[83]

The economic impact of bipolar disorder is extremely high, particularly when accounting for the opportunity costs of living with a mental illness.[84] In fact, a 2003 study found that bipolar disorder was the most expensive behavioral health care diagnosis for both patients and their insurance plans.[85] Since over 90% of patients with bipolar disorder experience recurrence and many experience progressive deterioration in functioning,[86] it is important to consider the impact of this disease from a societal perspective. This cost was estimated to be as high as $45 billion per year in the US in 1991.[87] In a 2003 study, the average lifetime cost per patient with bipolar disorder was estimated to range from $11,720 for persons with a single manic episode to $624,785 for persons with chronic episodes.[88] Regarding costs of treatment incurred by patients, one study estimated average charges and reimbursements per patient-year to be $12,797 and $6,581, respectively. Of these costs, 33% was directly attributable to bipolar disorder, and 67% was attributed to comorbidities.[89]

Given the very high rate of co-morbid conditions in children with bipolar disorder, this estimate is likely to be low.

2.2 Description of Pediatric Bipolar Disorder

2.2.1 DSM-IV-TR Definition

There are four disorders that make up the bipolar spectrum, as defined by the Diagnostic and Statistics Manual for Mental Illness. These are Bipolar I Disorder, Bipolar II Disorder, Cyclothymic Disorder and Bipolar, Not Otherwise Specified (Bipolar-NOS). Differentiation among the disorders on the spectrum is based on the severity and duration of manic and depressive episodes. Definitions of episode symptoms based on the DSM-IV-TR definitions are presented in Table 2.1. It is important to note that Cyclothymic Disorder is considered to be a milder form of bipolar illness and is clinically very different from the other three spectrum disorders.

Individuals with bipolar disorder generally meet criteria for major depressive episodes and/or manic episodes. Major depressive episodes are defined by having five or more depressive symptoms, along with one of the cardinal symptoms (either depressed mood or loss of interest or pleasure). These symptoms must be present during the same 2-week period and represent a change from previous functioning. For manic episodes, individuals must experience a distinct period of abnormally and persistently elevated, irritable or expansive mood, lasting at least 1 week (unless hospitalized, in which case duration can be any length). They must experience at least three manic symptoms during the mood

disturbance (four or more if the mood is only irritable) and these symptoms must be present to a significant degree.[58]

Table 2.1 - Manic and Depressive Episode Symptom Definitions (APA, 2000)

Depressive Symptoms	Manic Symptoms
• Depressed mood most of the day, nearly every day, as indicated by either subjective report or observation made by others. In children and adolescents, can be irritable mood. • Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day. • Significant weight loss when not dieting or weight gain (> 5% change of body weight in a month), or decrease or increase in appetite nearly every day. In children, failure to make expected weight gains. • Insomnia or hypersomnia nearly every day. • Psychomotor agitation or retardation nearly every day. • Fatigue or loss of energy nearly every day. • Feelings of worthlessness or excessive or inappropriate guilt nearly every day. • Diminished ability to think or concentrate, or indecisiveness, nearly every day • Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide	• Inflated self-esteem or grandiosity. • Decreased need for sleep (e.g., feels rested after only 3 hours of sleep). • More talkative than usual or pressure to keep talking. • Flight of ideas or subjective experience that thoughts are racing. • Distractibility. • Increase in goal-directed activity or psychomotor agitation. • Excessive involvement in pleasurable activities that have a high potential for painful consequences.

Hypomanic episodes may be diagnosed in individuals who experience persistently elevated, expansive or irritable moods that last at least 4 days and that represent marked changes from the patient's usual non-depressed mood. Those with hypomanic episodes experience three or more of the manic symptoms to a significant degree (or four or more symptoms if presenting with irritability alone).

In order to be diagnosed with a major depressive or manic episode, symptoms cannot meet criteria for mixed episodes. Mixed episodes are those in which criteria (with the exception of duration) for both major depressive episodes and manic episodes are met for

most days during a 1-week period. In addition to meeting the symptom and duration criteria defined above, for major depressive, manic and mixed episodes, symptoms must cause clinically significant distress or impairment in functioning and they must not be due to substance abuse or other general medical conditions.[58] Table 2.2 provides a summary of each of the bipolar spectrum disorders and conditions that must be met for diagnosis.

Table 2.2 - Bipolar Spectrum Disorders (APA, 2000)

Spectrum Disorder	Criteria for Diagnosis
Bipolar I Disorder	One or more Manic or Mixed Episodes, usually accompanied by a Major Depressive Episode.
Bipolar II Disorder	One or more Major Depressive Episodes accompanied by at least one Hypomanic Episode.
Cyclothymic Disorder	Two years of numerous hypomanic and depressive periods which do not meet full criteria for either Manic episodes or Major Depressive Episodes.
Bipolar Not Otherwise Specified	Bipolar features that do not meet criteria for a defined bipolar disorder (either due to inadequate duration or contradictory information).

2.2.2 Differences in Pediatric Bipolar Disorder from Classical Presentation

Uncomplicated classical mania is very uncommon in prepubertal children.[90] As compared to this classic presentation seen in most adults, there are several features agreed upon as being unique to pediatric bipolar disorder. These are (1) chronic course and long episode duration; (2) predominance of mixed episodes or rapid cycling; (3) irritability as a prominent feature and (4) high rates of co-morbidities.[6, 13, 34, 63, 66, 68, 91-93].

While adults generally experience periods of normal mood between discrete episodes of illness, children often experience chronic presentations of illness with no distinct periods of recovery.[94-96] This form of symptom presentation is reported in about 20% of adults, most of whom have treatment-resistant bipolar disorder.[83, 97] Early-onset bipolar disorder appears

to increase the severity and lead to worse long-term outcomes than later-onset bipolar disorder as evidenced by its chronicity, resistance to mood stabilizers and high rate of psychotic symptoms.[13, 86, 91, 95, 96, 98-102] Current literature shows that pediatric bipolar disorder follows a course where 70 to 100% of children will recover from their index episode but up to 80% will relapse, despite ongoing treatment for the disorder.[62] Additionally, some studies suggest that in these children, syndromal or subsyndromal symptoms are present for up to 70% of follow-up time.[68, 103, 104] During an 8-year follow up study of children with bipolar I disorder, the mean number of manic or mixed episodes was two, with significantly shorter second and third episodes.[103] In this study, subjects under 18 years of age were ill with mood episodes 65.5% of the time, while those over 18 were ill for about 49% of the time. [103]

Rapid cycling is also common in pediatric bipolar disorder. This term is used differently in adult and pediatric bipolar literature. In adults, rapid cycling represents four or more discrete episodes of illness within a year (with periods of normal mood between episodes).[61] In children, rapid cycling often represents daily or weekly mood changes. In studies of rapid cycling in pediatric bipolar patients, daily cycling was the most common form of cycling, with no patients experiencing the traditional rapid cycling seen in adults.[61, 105, 106]

2.2.3 Diagnosing Bipolar Disorder

The National Institutes of Mental Health (NIMH) has recommended using the adult criteria for bipolar disorder to diagnose children, however this is complicated because the symptom presentations differs between children and adults.[9] There are no clinical markers that can be used to assess bipolar disorder in children, therefore assessment of mental illness

in child and adolescent psychiatry often consists of structured interviews, questionnaires and screening instruments.[25] Many of the scales that are used to diagnose bipolar disorder in children are adapted from those originally designed for adults. This is problematic because (1) the presentation of the disorder may be different at younger ages; (2) symptoms that are measured may be inappropriate at younger developmental stages.[20]

Among the diagnostic instruments available, the Child Behavior Checklist (CBCL), the Parent Mood Disorder Questionnaire (P-MDQ), the Child Mania Rating Scale (CMRS), and the Parent General Behavior Inventory (PGBI-SF10) are most frequently used. [57] Currently there is no agreement among experts regarding the best instrument for diagnosing bipolar disorder in youth, making the physicians' clinical assessment key in the diagnostic process.

To further complicate matters, researchers in the field also disagree regarding the symptom presentation for pediatric bipolar disorder. Major disagreements in the field focus on the key symptoms for diagnosing bipolar disorder in children. In particular, the symptom of elated mood (euphoria / grandiosity) is the primary source of disagreement among clinicians and researchers. Many feel that this symptom must be observed in order to fully meet criteria for bipolar disorder,[76, 107] while others suggest that extreme irritability is the marker for such a disorder.[98, 108, 109] Current research of familial aggregation patterns and clinical correlates support the use of elated mood as a cardinal symptom of pediatric bipolar disorder,[104] but it is unknown to what extent this criterion is used in practice.

Differentiating among the bipolar spectrum disorders in children also poses unique problems. For example, researchers have found that initial presentations of bipolar I disorder

in children are generally depressive symptoms or full depressive episodes.[110] Further, children with bipolar II often receive diagnoses of major depressive disorder,[111] since they generally seek medical care during major depressive episodes. It is only through detailed accounting of a patient's history that clinicians are able to accurately distinguish between these disorders.[17] A large number of children also fail to meet the required DSM-IV duration criteria for hypomania or mania and are subsequently diagnosed as bipolar disorder not otherwise specified (NOS).[69]

Due to the atypical presentation of pediatric bipolar disorder, the diagnosis is often missed, leading to delays in appropriate treatment.[91] In fact, one study revealed that the delay from initial onset of bipolar symptoms to first treatment was, on average, 16.8 years for childhood onset and 11.5 years for adolescent onset.[91] Overlapping symptoms make differentiating bipolar disorder from other mental health conditions difficult, specifically with attention-deficit hyperactivity disorder (ADHD), conduct disorder (CD) and anxiety disorders.[34, 105, 112, 113] Several medical disorders also mimic symptoms of mania, including temporal lobe epilepsy, multiple sclerosis, hyperthyroidism, closed or open head injury and systemic lupus erythematosus.[17] In addition to this, several drug classes often increase mood cycling including tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), corticosteroids, serotonin and norepinephrine reuptake inhibitors (SNRIs), aminophylline and antibiotics such as clarithromycin, amoxicillin and erythromycin.[114] Developmental issues can also complicate the diagnosis as children often face difficulties in verbalizing their emotions. [115] These complexities provide compelling evidence for involving well-trained experts in mental health in the initial diagnosis and treatment of childhood bipolar disorder.[20]

2.2.4 Co-morbid and Pre-morbid Conditions

Children with bipolar disorder often meet DSM-IV criteria for other mental health disorders such as oppositional defiant disorder, conduct disorder, anxiety, and depression. [9, 10, 116, 117] Pediatric bipolar disorder is rarely seen without other serious co-morbid psychopathology. [90] In one study, 97.9% of children had one or more comorbid conditions and 20.4% had four or more comorbid conditions.[118] This makes differentiating between a person with bipolar disorder and one with an exacerbation of another disorder very difficult.

Understanding the extent to which co-morbid conditions exist for children with bipolar disorder is important in determining next steps for treatment development. For example, Frank (2002) found that alternative treatment plans were needed for adults with co-occurring bipolar disorder and panic disorder (as compared to those with bipolar alone).[119] Understanding the prevalence of co-occurring disorders is important for improving treatments in this area.[120]

There are varying estimates for the rates of specific comorbidities in children with pediatric bipolar disorder. Rates tend to differ by age, assessment method, sample (clinical versus community), and by the diagnostic classification system that is used (DSM-III versus DSM-IV).[120] Due to these variations, there is little to no consensus among researchers regarding the rates of diagnostic comorbidity.[120] Because of this and the symptom overlap between pediatric bipolar disorder and other mental illnesses, it is important to determine if symptoms of potential co-morbid conditions are present during episode-free phases (when the patient is not manic, hypomanic or depressed). [57]

Among pediatric bipolar samples, the most commonly comorbid condition is attention deficit hyperactivity disorder (ADHD). This condition often pre-dates the occurrence of pediatric bipolar disorder[100, 118, 121] and occurs most frequently in younger aged children.[7] Studies that have looked at age differences in the co-occurrence of these disorders have found higher rates of ADHD comorbidity among younger children than adolescents. [100] Estimates of the co-occurrence of these disorders are approximately 90% in prepubertal children and between 30 and 40% in adolecents.[7, 13, 114, 122, 123] Emerging evidence suggests that children with co-occurring BPD and ADHD have distinct illness from those with either bipolar disorder or ADHD alone. It is also possible that ADHD symptoms represent early illness manifestation for children who will go on to be diagnosed with bipolar disorder. [124]

Other commonly found comorbid or premorbid conditions are depression, [72, 106, 123] anxiety disorders, [3, 26, 123, 125, 126] oppositional defiant disorder, [123, 127] conduct disorder[66, 106, 123, 128] and pervasive developmental disorders.[6, 129] Estimates of the co-occurrence of these disorders with pediatric bipolar disorder differ by age and developmental stage. In general, adolescents appear to be more likely to have substance abuse, panic disorders and conduct disorders and children are more likely to have ADHD. Anxiety disorders, on the other hand, tend to be equally likely among young children and adolescents.[120]

2.2.5 Pharmacologic Treatments for Pediatric Bipolar Disorder

No currently available treatment is able to manage all phases of bipolar illness and to protect against recurrence of manic, mixed, manic-depressive, major depressive or other mild depressive states.[130, 131] The only drugs approved by the US Food and Drug Administration for use in treating acute mania in youth are lithium (for children aged 12 and older), and

risperidone, or aripiprazole (for children aged 10 and older, respectively). [10] Additionally, as of June of 2009, an FDA advisory panel recommended the inclusion of three additional drugs for use in children with bipolar disorder. These were Quetiapine, or Olanzapine (for children aged 13 - 17, respectively), and Ziprasidone (for children aged 10 - 17).[132] Evidence is emerging regarding the use of pharmacologic treatments for pediatric bipolar disorder, but a majority of the trials focus on the treatment of mania alone.[10] Additionally, the evidence-base for decision making relies heavily on efficacy and safety data from trials conducted in adult patients.[10] As we have learned from the failure of tricyclic antidepressants in pediatric depression, it is important to realize that we cannot assume that drugs that are effective at treating adults are similarly effective in treating children.[133, 134] Table 2.3 summarizes medications that are commonly used for treating bipolar disorder (both the generic name and Brand names as applicable).

Table 2.3 - Medications Used to Treat Bipolar Disorder

Medication Category	Generic Name (Brand Names)
Mood Stabilizers	
Lithium	lithium (Eskalith, Lithobid)
Anticonvulsants	divalproex sodium (Depakote, Depakote ER, Depakote Sprinkles); carbamazepine (Carbatrol, Equetro, Tegretol, Tegretol XR); lamotrigine (Lamictal); topiramate (Topamax); gabapentin (Neurontin); oxcarbazepine (Trileptal); levetiracetam (Kreppa, Kreppa XR); tiagabine (Gabitril)
Second Generation Antipsychotics	clozapine (Clozaril, FazaClo ODT); risperidone (Risperidal, Risperidal Consta, Risperidal M-Tab); olanzapine (Zyprexa, Zyprexa Zydis); quetiapine (Seroquel, Seroquel XR); ziprasidone (Geodon); aripiprazole (Abilify, Abilify Discmelt) paliperidone (Invega)
First Generation Antipsychotics	haloperidol (Haldol Decanoate, Haldol Lactate); loxapine (Loxitane); thiothixene (Navane); pimozide (Orap); fluphenazine (Prolixin); trifluoperazine (Stelazine); chlorpromazine (Thorazine); perphenazine (Trilafon)
Antidepressants	
Tricyclics	amitriptyline (Elavil); clomipramine (Anafranil); doxepin; imipramine (Tofranil, Tofranil-PM); trimipramine (Surmontil); desipramine (Norpramin); nortriptyline (Pamelor); protriptyline (Vivactil)
Tetracyclics	amoxapine; maprotiline
Selective Serotonin Reuptake Inhibitors (SSRIs)	fluoxetine (Prozac, Prozac Weekly, Sarafem); sertraline (Zoloft); citalopram (Celexa); escitalopram (Lexapro); fluvoxamine (Luvox, Luvox CR); paroxetine (Paxil, Paxil CR, Pexeva);
Other Antidepressants	venlafaxine (Effexor, Effexor XR, Venlafaxine ER Tablets); trazodone; nefazodone; mirtazapine (Remeron, Remeron SolTabs); duloxetine (Cymbalta); Bupropion HCl (Budeprion SR, Budeprion XL, Buproban, Wellbutrin, Wellbutrin SR, Wellbutrin XL, Zyban)
Monoamine oxidase inhibitors (MAOIs)	isocarboxazid (Marplan); phenelzine (Nardil); tranylcypromine (Parnate)
Stimulants	methylphenidate (Concerta, Metadate CD, Metadate ER, Methylin, Methylin ER, Ritalin, Ritalin LA, Ritalin SR); methylphenidate transdermal (Daytrana); dextroamphetamines (Dexedrine, ProCentra); amphetamine salt comb (Adderall, Adderall XR); dexmethylphenidate (Focalin, Focalin XR); lisdexamphetamine (Vyvanse)

2.2.5.1 Treatments for Bipolar Mania

Psychotropic medication use for treatment of bipolar disorder in children has increased dramatically in recent years. Several drug classes are commonly used to treat bipolar disorder. These are mood stabilizers, including both lithium and anticonvulsants, and antipsychotics (both typical and atypical). Standard therapy in adults generally includes lithium, divalproex and atypical antipsychotics.[17] Each of these classes, and the evidence for their use, are described below.

Lithium and Anticonvulsants

Of the treatment options available, lithium is the oldest and most researched medication. Lithium has been studied in adults and adolescents and has been found to be effective at treating acute mania[135] and in improving global functioning scores.[136] However, many studies of lithium (and most of the other mood stabilizers) have not controlled for adjunctive psychotropic medication use, making true estimates of a monotherapy's effectiveness difficult to determine. Additionally, there are several safety concerns regarding the use of Lithium. Lithium has been associated with weight gain and acne, [137, 138] which may be considered unacceptable side effects for children in their adolescent years. Lithium-induced hypothyroidism is also common, with some studies estimating an occurrence in 24% of children and adolescents taking lithium and divalproex.[139] Major safety concerns regarding long term use of lithium generally include lithium toxicity and decreased renal functioning.[140, 141]

In addition to lithium, other commonly used mood stabilizers are divalproex and carbamazepine. One study of these three agents suggested that all three drugs had similar response rates; however, response was achieved in less than half of the patients on any of these individual drugs.[142] Of those that did not respond to monotherapy in this study, 80% responded to combination mood stabilizer therapy during a 6-month continuation phase of the trial.[143] Others have also found significant improvement from baseline in outcome measures (depression, mania and global rating scales) for adolescents who are prescribed combination therapy of lithium and divalproex.[144] Accumulated evidence currently suggests that lithium and divalproex are equally efficacious in the acute and maintenance treatment of pediatric bipolar disorder.[145]

Evidence for divalproex and carbamazepine are mostly limited to open-label trials, case reports and retrospective chart reviews.[15, 146-150] In these studies, the rates of response have ranged from 60 to 100%.[10] However, similar to trials of lithium, it is unclear to what extent combination therapy may have led to these large response rates as adjunctive treatments were taken by as many as 43% of patients in these studies.[10]

Randomized trial evidence of these agents has proven less promising in this population. For example, a recent double-blind, placebo-controlled trial of divalproex ER showed no benefit over placebo for the treatment of youth with bipolar I manic or mixed episodes.[151] Additionally, a randomized trial of lithium, divalproex and placebo resulted in response rates of 41%, 56% and 30%, respectively.[142] Although responses were higher for lithium and divalproex than for placebo, the very high rate of response in the placebo group is cause for concern. These findings highlight the need for conducting placebo-controlled

trials in this population to determine the true benefit of mood stabilizing agents in the pediatric bipolar population.

Aside from divalproex and carbamazepine, the remaining antiepileptic agents have limited efficacy and safety data available. Two open studies of topiramate suggest that it may be a useful adjunctive treatment in bipolar youth.[152, 153] Unfortunately, there is no evidence of topiramate's usefulness as a monotherapy as a large controlled trial of topiramate monotherapy was discontinued early due to the drug's failure in adult trials.[154] Supportive evidence for oxcarbazepine is limited to case reports;[155, 156] however, one double-blind, placebo-controlled trial of this drug showed no difference in mania rating scale scores as compared to placebo.[157] Similarly, gabapentin has shown promise in two case reports,[158, 159] but has failed in adult placebo-controlled trials.[160, 161]

In addition to concerns regarding the lack of placebo-controlled trial data for these medications, medication safety has not been extensively studied for these drugs within the pediatric bipolar population. Commonly reported adverse effects of divalproex generally include gastrointestinal upsets, neurological symptoms (headache and dizziness).[141] However, several less common effects such as hepatotoxicity, teratogenicity, polycystic ovary syndrome, carcinogenesis and pancreatitis have been reported.[141, 162]

Regarding the use of Carbamazepine, there are several serious side effects that must be considered. The most common serious side effects of this drug include hematological, dermatological and hepatic manifestations. There is a black box warning regarding agranulocytosis and aplastic anemia.[141] Other side effects include nausea, psychosis, mania, worsening of seizures, development of seizures, ataxia, behavioral toxicity, diplopia,

sleepiness, and vertigo.[163] Fortunately, it appears that Carbamazepine does not alter metabolism or cause obesity, but due to its mechanism of action it interacts with many other medications so its use should be carefully considered.[164, 165]

Atypical Antipsychotics

Use of atypical antipsychotic agents for the treatment of pediatric bipolar disorder is increasing, as is the evidence for their use in this population. Two of these drugs, risperidone and aripiprazole are currently approved by the FDA for the treatment of mania in bipolar youth (10 years and older).[10] Approval for risperidone was based on a multicenter, randomized, double-blind, placebo-controlled trial. In this trial, the risperidone group had significantly more responders than the placebo group after 3 weeks of treatment.[166] Others have shown benefits of augmenting mood stabilizer therapy (lithium or divalproex) with risperidone.[167, 168]

For aripiprazole, efficacy was established in a 4-week double-blind, placebo-controlled trial conducted in 2007. In this trial, aripiprazole was found to be more efficacious than placebo for treating bipolar mania in youth aged 10 to 17 years.[169] Several other studies (one open label study and two retrospective chart reviews) also found that aripiprazole was effective and well tolerated in children and adolescents with bipolar mania.[170-172] Other medications in this class for which some evidence of efficacy as either monotherapies or adjunctive treatments has been accumulated are quetiapine,[173-175] olanzapine, [176, 177] ziprasidone, [178, 179] and clozapine.[180]

Regarding safety concerns for atypical antipsychotics, the most common side effects are hyperprolactinaemia, weight gain, sedation and extrapyramidal symptoms.[141] There is

also some concern that these drugs may lead to diabetes and hyperglycemia in some patients, but this has not been rigorously studied.[141] In particular, Olanzapine has been associated with the highest risk of weight gain (as compared to other antipsychotic medications),[181, 182] as well as a risks of hyperglycemia, hyperlipidemia, glucose dysregulation or diabetes mellitus.[182] Risperidone also is associated with weight gain due to increased appetite, and when used in combination with valproic acid, it may increase the risk for diabetes.[183] Risperidone has also been associated with extrapyramidal symptoms (e.g., dystonias, parkinsonism, tardive dyskinesias, tremors), although most of these were reversible with anticholinergic therapy or discontinuation of drug.[141]

Quetiapine has been associated with a greater frequency and severity of sedation, and the development of tachycardia (without QT prolongation), however, weight gain is not as prevalent with Quetiapine as with risperidone or olanzapine.[184, 185] Ziprasidone, the least studied of the atypical antipsychotics at this time, appears to be well tolerated (with the exception of sedation). Rare side effects are EPS and hyperprolactinemia.[184]

Clozapine is the antipsychotic that is considered for use in cases where multiple other treatments have failed. This is primarily because it requires intensive monitoring due to the risk of agranulocytosis. The major benefit of this medication is that it is not associated with extrapyramidal symptoms and tardive dyskinesia.[141] As with other antipsychotics, weight gain and sedation are common. Cardiovascular effects may also be of concern as one study indicated that 47 of 78 patients experienced tachycardia and another 20 of 70 patients experienced orthostatic hypotension.[186, 187] Less common, but serious, reported events are neutropenia, granulocytopenia, seizure risk, hyperlipidemmia and hyperglycemia.[188-190]

2.2.5.2 Treatments for Bipolar Depression

Treatments for bipolar depression are less commonly studied than for bipolar mania, although suicide risk is highest in those presenting with bipolar depression.[10] A delicate balance must be maintained in treating bipolar depression as to not induce bipolar mania. Available evidence for bipolar depressed children is almost exclusively based on evidence in the adult bipolar population. These studies have shown support for use of lithium, divalproex, lamotrigine, quetiapine, olanzapine and a combination of olanzapine and fluoxetine in adults with bipolar depression.[10] Of these treatments, only lithium and lamotrigine have been assessed in the pediatric population.

A single open-label study assessed the efficacy of lithium in treating adolescents with bipolar depression. In this study, lithium appeared to be well tolerated and efficacious for the treatment of acute depressive episodes.[191] Based on current evidence, lamotrigine appears to be effective for treatment-refractory bipolar disorder in adult patients, and recent studies in the pediatric population are promising.[192-195] However, lamotrigine has also received a black box warning for use in those under the age of 16 due to increased incidence of Steven-Johnson's rash.[28]

2.2.5.3 Maintenance Treatment for Pediatric Bipolar Disorder

Treatment of bipolar disorder generally focuses on the control of episodes (either manic or depressive). Very few studies exist regarding the use of maintenance treatments after episode-related symptoms are controlled. Recurrence is a common problem in pediatric bipolar disorder, particularly after discontinuation of maintenance treatments.[10] Maintenance

studies of lithium in adolescents have also provided mixed evidence. In one study, adolescents who responded to lithium treatment were randomly assigned to either lithium or placebo during a 2-week, double-blind follow-up maintenance period.[196] In this study, there was no difference between placebo and lithium. Additionally, symptom exacerbation was a problem for both groups and over half of the lithium-treated group relapsed during the discontinuation phase.[196] A second study of lithium and divalproex was conducted to test whether efficacy differed between these two agents for maintenance therapy. In this study, patients were randomized to receive either lithium or divalproex as maintenance treatment after being stabilized on a combination regimen of both medications.[197] Results indicated that both drugs were equally effective as maintenance treatments for bipolar youth who had syndromal remission when using the combination treatment.[197]

2.2.6 Guideline Recommendations for Treatment

Currently, there are two main sources for expert-based treatment recommendations for pediatric bipolar disorder. These are reports from the Child and Adolescent Bipolar Foundation (CABF) guidelines (March, 2005),[17] and the American Academy of Child and Adolescent Psychiatry (AACAP) practice parameters (January, 2007).[19] These guidelines focus on the treatment of bipolar mania (bipolar I) as the lack of evidence for treatment of bipolar depression (bipolar II) and bipolar NOS do not support the creation of guidelines for these spectrum disorders at this time. [17] While the published parameters are not intended to dictate standard of care or include all of the proper methods of care, they are suggested strategies for patient management.

2.2.6.1 Child and Adolescent Bipolar Foundation Guidelines

Child and Adolescent Bipolar Foundation (CABF) guidelines target the treatment of bipolar I, manic or mixed episodes for children ages 6 to 17 years. There are separate treatment guidelines based on the presence or absence of psychosis at initial presentation.

Initial Treatment of Pediatric Bipolar I Disorder without Psychosis

In brief, the recommended first line treatment for pediatric bipolar disorder without psychosis is monotherapy with a traditional mood stabilizer (lithium, divalproex, carbamazepine) or monotherapy with an atypical antipsychotic agent for which ample evidence exists (olanzapine, quetiapine, risperidone). Although the panel fell short of reaching agreement on which agent would be preferred from those recommended, a majority of the panel recommended lithium or divalproex due to the available studies of these agents.

When children did not respond to initial monotherapy, it was suggested to switch to an alternative monotherapy up to three times before initiating combination therapies. In cases of partial response to monotherapy, combination therapies were recommended as next steps. After three trials of monotherapy with no response, combination therapies were recommended. After two trials of monotherapy and one trial of combination therapy (with partial or no response), combinations of two mood stabilizers and one atypical antipsychotic agent were recommended.

If none of the monotherapies or combinations above were successful, alternate monotherapies such as oxcarbazepine, aripiprazole or ziprasidone were recommended (given the limited evidence of their effectiveness). In cases where no response was obtained for any

of the medication trials, final stages of treatment were clozapine and ECT (for adolescents only).

Initial Treatment of Pediatric Bipolar I Disorder with Psychosis

For patients with bipolar disorder with psychosis, initial treatment should be a combination of a traditional mood stabilizer (lithium, divalproex or carbamazepine) and an atypical antipsychotic agent. Similar to the guidelines for those who do not have psychosis, up to three medication trials of these combinations should be tested in cases with no response. If partial response is obtained during any of these stages, or if a patient has failed three stages, two mood stabilizers and one atypical agent should be used. If a patient does not respond to any of these trials, a combination of a mood stabilizer and oxcarbazepine, ziprasidone or aripiprazole is recommended. As before, final treatment stage recommendations are clozapine and ECT (for adolescents only).

2.2.6.2 American Academy of Child and Adolescent Psychiatry Practice Parameters

There is significant overlap between the recommendations made by the expert panels for the Child and Adolescent Bipolar Foundation (CABF) and the American Academy of Child and Adolescent Psychiatry (AACAP). However, the AACAP practice parameter was published two years after the CABF guideline and additional evidence was available for some antipsychotic agents at that time.

Regarding pharmacotherapy, recommendations were that first-line treatments consist only of agents that have been approved for use in adults with bipolar disorder (or approved in children if evidence became available). In this case, lithium, aripiprazole, divalproex, olanzapine, risperidone, quetiapine, and ziprasidone were noted as agents approved for the

treatment of acute mania in adults. The key changes from the previous recommendations were the addition of aripiprazole and ziprasidone as recommended first-line atypical antipsychotic agents.

2.2.6.3 Summary of Current Recommendations

Figure 2.1 provides an updated summary of the treatment recommendations for pediatric bipolar I disorder (mixed or manic episodes, without psychosis). This figure incorporates the recommendations made by both the CABF and the AACAP regarding appropriate pharmacologic treatment strategies. In order to assess response, both consensus panels recommended that each medication trial last a minimum of 4 to 6 weeks at an adequate dose (lithium may need up to 8 weeks) prior to switching or augmenting therapies.[17] Overall, the literature suggests that the acute phase treatment for bipolar I disorder is considered to be during the first 8 weeks of treatment.[143] Again, recommendations are for children ages 6 - 17 years. No recommendations are currently available for children under the age of 6 years.

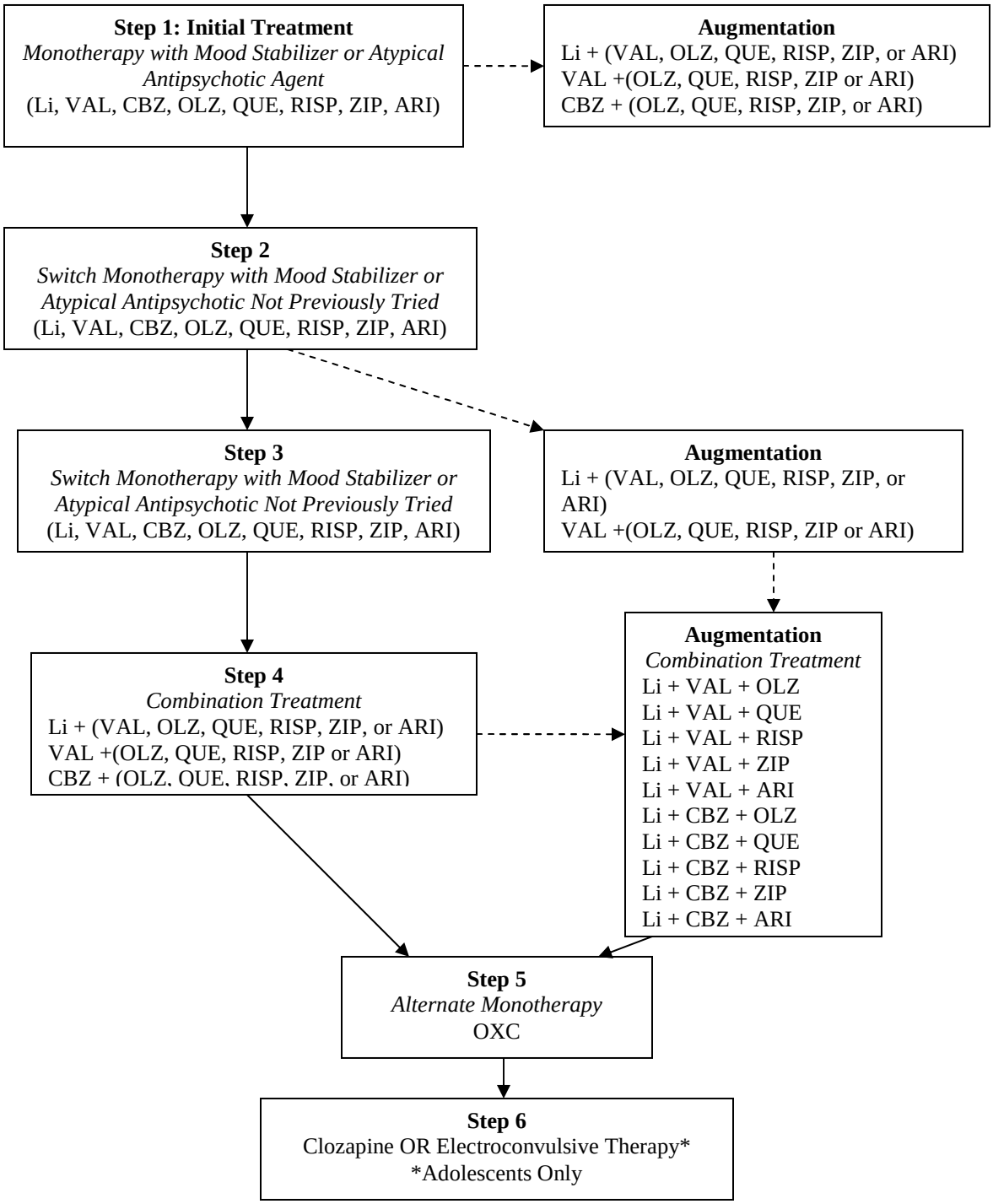
The CABF guidelines discussed treatment of comorbid disorders at length. They indicated that prior to treating comorbid disorders, symptoms of bipolar disorder should first be stabilized and the need for treatment should be reviewed after that time. If it is determined that the comorbid condition exists in episode-free periods (i.e., once the bipolar symptoms have been adequately treated), treatments for co-morbid disorders should be added sequentially to identify the benefits and side effects of each agent. This recommendation is of great importance as comorbid conditions are highly prevalent and they often worsen the prognosis of pediatric bipolar disorder.

Both consensus panels stressed the importance of using comprehensive treatment approaches that combine psychopharmacology and adjunctive psychosocial therapies. The authors assert that medications tend to help with core symptoms, but they do not address the associated functional and developmental impairments and the need for skills building and support.

2.2.6.4 Treatment Algorithm Synthesis

Figure 2.1 presents a summary of the current treatment recommendations for children ages 6 - 17 who are diagnosed with bipolar I disorder without psychosis. Recommended first step treatment is use of a single traditional mood stabilizer (lithium, divalproex, or carbamazepine) or a single atypical antipsychotic agent (olanzapine, quetiapine, risperidone, ziprasidone, or aripiprazole). Patients move through the different treatment steps based on a sequence of decisions regarding a patients' response (either none, partial, or full). If a patient has no response at each of the steps, they would continue to move through the treatment algorithm following the solid lines until they end at Step 6 (clozapine or electroconvulsive therapy). If, however, a patient experiences partial response at any of the steps, they would move through the treatment algorithm following the dashed lines from their previous step for treatment augmentation. As an example, if a patient experiences partial response of symptoms in Step 1, the next course of action would be for the initial monotherapy to be augmented with a second medication. Finally, if a patient fully responds within a step, their treatment is not changed further (essentially, they stay within that step).

Figure 2.1 - Summary of Current MedicationGuideline Recommendations for the Treatment of Bipolar I Disorder without Psychosis in children ages 6 to 17



FOOTNOTE: Dashed lines represent recommendations when a partial response is achieved.
SOURCE: Adapted from CABF and AACAPGuidelines.[17, 19]
Li = lithium; VAL = valproate; CBZ = carbamazepine; OLZ = olanzapine; RISP = risperidone; QUE = quetiapine; OXC = oxcarbazepine; ARI = aripiprazole ZIP = ziprazodone.

2.2.7 Actual Prescribing Practices and Management

While current guidelines emphasize the importance of avoiding polypharmacy, and no controlled-trial data support combining medication classes in youth with non-psychotic bipolar disorder,[1] in practice it appears that a majority of children receive treatment with several psychotropic medications simultaneously.[143] Even more notable, some of the combinations that are being prescribed are explicitly noted as being guideline discordant treatment combinations. For example, use of antidepressants (particularly SSRIs) and stimulants in this population are highly controversial,[18, 76, 115, 198-204] but they are often prescribed with or without mood stabilizers. This practice is unacceptable based on current practice standards for adults, let alone children.[52]

Studies of prescribing behavior have revealed high levels of combination therapy use in youth and adults with bipolar disorder. Although pharmacoepidemiologic studies are limited in this area, those that have been conducted have provided some interesting information regarding medication prescribing in children with bipolar disorder. One study of the National Ambulatory Medical Care Survey (NAMCS) was particularly useful for outlining the practice patterns for outpatient treatment of pediatric bipolar disorder.[1] In this study, Moreno and colleagues noted that for youth with a diagnosis of bipolar disorder: 90% of office visits resulted in a prescription of one or more psychotropic medications; mood stabilizers were prescribed in approximately 2/3 of the visits; antidepressants were prescribed without mood stabilizers for 34% of the sample; stimulants were prescribed without mood stabilizers for 36% of the sample; antipsychotics were prescribed in over 47% of the sample; combination

treatment occurred in approximately 63% of the sample; and psychotherapy occurred in approximately 42% of the sample.

Two other studies that utilized the National Ambulatory Medical Care Survey (NAMCS) found similar medication use patterns for children with bipolar disorder. First, a study by Aparasu and colleagues, outpatient visits for which 11 typical and 6 atypical antipsychotic agents were prescribed were selected and characteristics of children and adolescents that received these drugs from 2003-2004 were described.[205] They found that 40% of the visits in which these medications were prescribed were for children with bipolar disorder diagnoses, and that specialists prescribed 82% of these drugs. They also noted that children who were 10-14 and 15-19 were significantly more likely to get an antipsychotic than those under the age of 10 years. [205]

A separate study looked at the treatment of bipolar disorder and how treatment has changed from 1992-1995 as compared to 1996-1999. While this study focused mainly on the treatment of adults, they did not exclude those under the age of 18. What they found was that nearly a third of patients with a bipolar diagnosis did not receive any mood stabilizer and over 45% of the visits resulted in a prescription for an antidepressant (generally SSRIs).[206] Over the study period, the use of lithium decreased by 40%, while the use of valproate increased by 250% and the use of anticonvulsants nearly doubled. The use of antidepressants, particularly without a mood stabilizer is concerning because of potential for drug-induced mania in this population. However, one antidepressant was shown to have lower manicogenic properties but this particular drug, bupropion, only represented 8% of the antidepressant prescriptions in this group.[206]

Bhangoo and colleagues also explored the use of a variety of psychotropic medications among children and adolescents with bipolar disorder using a sample of 111 patients who were receiving treatment for bipolar disorder through a psychiatrist.[207] They found that a variety of agents were used in practice, including mood stabilizers, antipsychotics, stimulants, SSRIs and tricyclic antidepressants, and that polypharmacy was common. In fact, the mean number of current psychotropic agents among the sample was 3.4 agents. Approximately 18% of the children were taking five or more medications and only 30% were taking 2 or fewer medications. Children had, on average, over 6 past medication trials; over 20% had 10 or more medication trials and 25% had 3 or fewer trials.[207] In the sample, 98% had received a trial of a mood stabilizer (79% received valproate, 51% lithium, 29% gabapentin). However, 15% of the sample received treatment with gabapentin, topiramate or lamotrigine without having received a trial of lithium.[207] These drugs currently have the weakest evidence for use in children, indicating that their use should only be considered after a lithium trial has failed. A trial of lithium, depakote, and/or possibly carbamazepine would be indicated prior to use of a newer anticonvulsant.[207] Additionally, 77% of the children received an antipsychotic medication (58% received risperidone, 35% olanzapine, 26% quetiapine, 12% a neuroleptic, 4% ziprasidone and 1% clozapine).[207]

Use of medications has also been studied using the National Comorbidity Survey Replication (NCS-R).[41] Although this study focused on adult populations, the use of a nationally representative survey and the 9,282 patients made it particularly useful for studying patterns of medication use for patients with bipolar disorder. In this study, medication use was classified as "appropriate" or "inappropriate." Medications were

"appropriate" if they were mood stabilizers, anticonvulsants or antipsychotics; and "inappropriate" if they were antidepressants or other psychotropic medications used without an antimanic agent. At the 12 month treatment mark, appropriate medication use was higher among patients receiving psychiatric care (45%) versus those receiving general medical care (9%). Inappropriate treatment was received by 73.1% of patients treated by a general medical professional and by 43.4% of those treated by a psychiatrist.[41]

2.3 Quality of Care in Pediatric Bipolar Disorder

2.3.1 Quality of Care in the U.S. Pediatric Population

In 1999, the Institute of Medicine published a report on the quality of health care services in the U.S. and since that time, much attention has been given to assessment and improvement of health care quality.[208] The Institute of Medicine defines quality of care as "the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge."[209] Unfortunately this effort has been focused primarily on the quality of health care services for the adult or elderly populations and studies related to quality of health care services for pediatric populations are limited.[210]

In October of 2007, a landmark paper by Mangione-Smith and colleagues in the New England Journal of Medicine, provided evidence of the disparities between recommended and received care for children in the United States.[210] This study found that pediatric outpatients received only 46.5% of indicated care overall (with deficits in acute, chronic and preventative care) and that these deficiencies were similar in magnitude to those reported for

adults.[210] Because of these deficiencies, it is important that our focus on quality improvement is not limited only to adults and the elderly, but children as well. Children's health and health care deserve particular attention because (1) childhood is a developmentally unique stage of life, (2) the child health care system is distinctive, (3) child health is connected with adult health, and (4) children are more likely than adults to be socially and economically disadvantaged.[110, 211, 212]

2.3.2 Quality of Mental Health Care in the U.S.

In 2005, the Institute of Medicine (IOM) published a report that focused on improving the quality of health care for patients with mental illness.[208] Since this time, efforts have been made to quantify the extent to which patients with mental illness receive appropriate care. As was the case with quality of care efforts for other disease areas, the focus has been heavily shifted towards the adult population. Even prior to the report by the IOM, changes were seen in the use of mental health services in the US. For example, national trends in the treatment of mental health disorders revealed that annual visits to mental health specialists between 1992 and 2000 increased by 50%.[213] Additionally, the number of people receiving treatment for depression tripled between 1987 and 1997[214] and the number of people who were treated by a specialist for a serious mental illness increased by 20% between 1997 and 2001.[215] As of 2000, the proportion of discharges who were diagnosed with bipolar disorder rose dramatically, from 2.9% to 15.1% from 1990 to 2000.[31] This increase in diagnosis has been seen in both children and adults with bipolar disorder;[1] however, management of the disease has changed significantly over this time as well. For example, in a study by Case and colleagues, the length of hospital stays for children and

adolescents with bipolar disorder were dramatically reduced from 1990 to 2000 with a reduction in length of stay of 72%.[31]

Increases in use of mental health services do not necessarily equate to receipt of appropriate care, improvement in the quality of mental health care, or even adequate levels of disease detection and treatment in the population. For example, over a decade ago, the epidemiologic catchment area study indicated that in a given year nearly 40% of individuals with bipolar disorder were not receiving treatment.[216] Similarly, in a notable study by Kessler and colleagues, they estimated that treatment for emotional disorders increased from 12.2% between 1990 and 1992 to 20.1% between 2001 and 2003.[39] Although there was a significant increase in the treatment of disorders during this timeframe (with more than 150% increase in the rate of treatment), only 40.5% of respondents who had a serious mental illness between 2001 and 2003 received treatment for their illness. Further, they found that many patients who received treatment in this sector did not complete clinical assessments or receive treatment with appropriate ongoing monitoring.[39]

Other studies have indicated that, similar to adults, many children who need mental health services are not receiving them.[217-220] One estimate suggested that approximately 1 in 10 children have a major mental illness or functional impairment and that only about 1/5th of the children who were impaired received treatment for their illnesses.[25, 221] More recent estimates suggest that as many as 20% of children have a diagnosable mental health disorder.[222-225]

2.3.3 Quality of Care for Bipolar Disorder

There are several key areas of concern regarding quality of health care for patients with bipolar disorder. For example, diagnosis of bipolar disorder, (including misdiagnosis, overdiagnosis, and delays in diagnosing) [46, 47, 107, 123, 226, 227] shortages of available health care professionals who are trained to identify and treat bipolar disorder,[228, 229] inappropriate use of medications (including use of unapproved medications, overuse or underuse of medications, and polypharmacy),[19, 227] and lack of adherence to guidelines for treatment and management of the disease.[230]

2.3.4 Evaluating Quality of Care for Bipolar Disorder Using Published Guidelines

It has been well documented that physicians do not always adhere to published evidence-based guidelines for the treatment of chronic conditions.[231] The reasons for this vary by condition and by physician type but often include lack of awareness or familiarity, disagreement, discomfort, low outcome expectancy or low self efficacy and practice inertia related to guidelines.[231] Guideline non-adherence has previously been reported as a factor that influences patient health outcomes in the area of mental health. For example, guidelines for the treatment of major depression have been available since 1993 yet there are numerous studies that reveal that inadequate dosing schedules or treatment periods are still routinely used by medical care providers.[232] Similar studies have been conducted in the areas of ADHD[233] and bipolar disorder[234-236] and these reveal that physician adherence to guidelines is inconsistent in these areas as well.

For example, Alisa Busch and colleagues published a report that detailed changes in the quality of care for commercially insured adults with bipolar disorder from 1991-1999.[237]

When comparing results from 1994 to 1999, they found that there were some improvements in the quality of care based on appropriate use of antimanic agents (increase from 64% to 77%), and a reduction in use of antidepressants in the absence of antimanic agents (decrease from 23% to 14%). However, they also found that psychotherapy use declined during the period (from 89% to 69%).[237] Similarly, when looking at quality of care for adults with bipolar disorder who receive Medicaid, only one-third of enrollees were noted to have received guideline-recommended treatments and nearly one-fifth of patients received guideline-discouraged treatments. In this case, the quality measures were receipt of recommended care (an antimanic agent plus psychotherapy) or receipt of discouraged care (antidepressants without an antimanic agent).[235]

In 2001, Lim and colleagues conducted a study to assess the prescribing patterns for patients who were diagnosed with Bipolar I disorder to determine how well these patterns fit with guideline recommendations.[236] They discovered that only one in three patients with psychotic features was discharged on medications recommended as preferred treatments. Additionally, they found that for patients with bipolar disorder and no psychosis, this dropped to only one in six receiving recommended treatments.[236] This study indicated that there was variation in prescribing patterns and that few patients actually received guideline recommended treatment, however, there was no information regarding how these differences impacted the patient's health outcomes.

There have been several studies, however, that have tied guideline adherence back to patient outcomes in the area of bipolar disorder. The Texas Medication Algorithm Projects, for example, utilized prescribing algorithms for severe mental illness (including bipolar

disorder) and assessed the extent to which adherence to these algorithms impacted patient health and economic outcomes.[27] Additionally, a recent study of inpatients with acute mania was conducted to determine how well current prescribing patterns reflected the published clinical guidelines and the overall impact of short-term clinical outcomes. The researchers found generally good concordance with treatment guidelines and a statistically significant relationship between early medication initiation and reduced time to hospital discharge.[230] Although these study samples were restricted to adults with bipolar disorder, they provide evidence that treatment patterns are useful tools for assessing the quality of care and patient outcomes in bipolar disorder.

As described above, specific efforts aimed at evaluating the quality of care for patients with bipolar disorder have been made. However, these have been limited to adults and have used older data sources (with most recent quality assessments limited to data from 2000 and earlier). Up-to-date evidence is specifically needed for the use of guideline-recommended care for children with bipolar disorder.

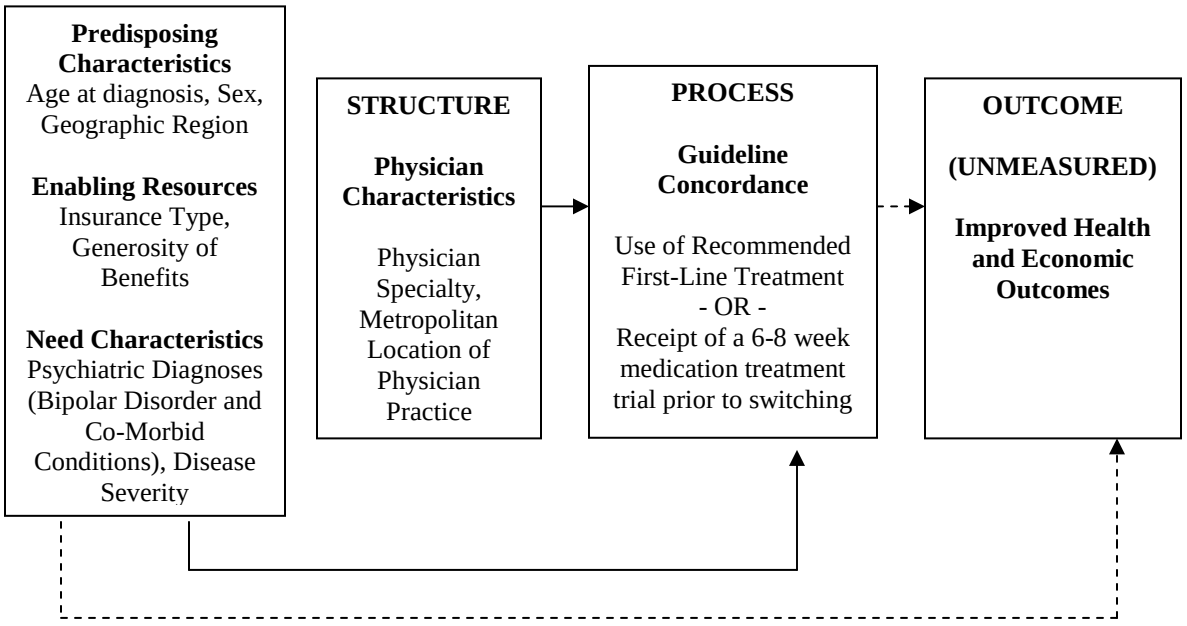
2.4 Framework for Guideline Assessment

2.4.1 Conceptual Framework

In order to assess the relationship between patient and provider characteristics and the receipt of guideline recommended treatment, a conceptual framework is needed. Figure 2.2 represents the proposed conceptual framework for this study. This model is based on two theoretical frameworks - Donabedian's framework of structure, process and outcome, [238](Figure 2.3) and Andersen's Behavioral Model of Health Care (Figure 2.4).[239] First, the

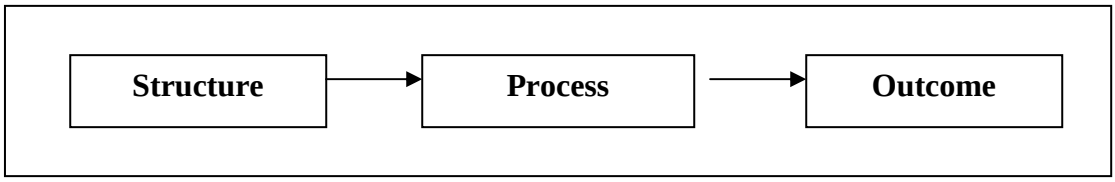
framework proposed by Donabedian consisted of these three elements: structure, process and outcomes. The underlying assumption for this particular model is that good structure increases the likelihood of good process and that, in turn, increases the likelihood of a good outcome.[238] Next, Andersen's model suggests that people's use of health services is a function of their predisposition to use services, factors that enable the use of services and the need for those services.[239] In order to detail the influence of patient characteristics, the Andersen framework will be combined with the structure-process-outcome framework by Donabedian. The factors contributed by each of these frameworks are detailed below.

Figure 2.2 - Conceptual Framework for the Association between Guideline Concordant Treatment and Patient and Physician Characteristics



2.4.1.1 Structure, Process and Outcome Variables

Figure 2.3 - Donabedian's Structure, Process and Outcomes Model



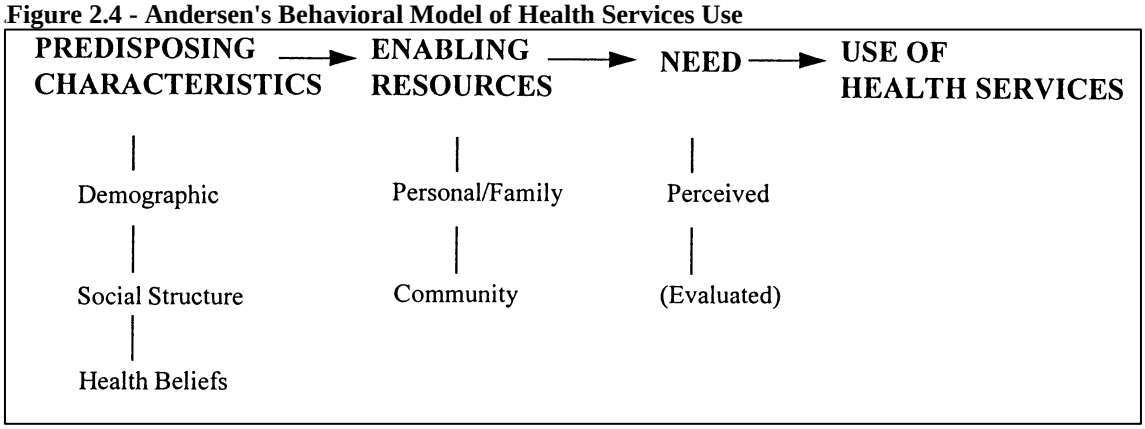
Structure is defined as the attributes of the settings in which care occurs. These characteristics were described by Donabedian as including the number, mix, and qualifications of the staff, the organization and governance of the staff, and features such as the physical space.[240] When measuring quality of health care, however, structural elements can be adapted to include characteristics of physicians and their practice settings.[241] The attributes in the proposed model that encompass structure include two such provider characteristics. Specifically, physician specialty type (primary care or specialist) and metropolitan statistical area (MSA) of the practice are considered. These two characteristics were selected to identify if there are differences in guideline adherence based on the physician type or if there is notable variation in guideline adherence by metropolitan service area status.

Process is defined as what is done in giving and receiving care, or more specifically, whether or not guidelines were followed. This will be assessed by comparing the treatment that was received (as evidenced in the patient's medical and pharmacy claims files) and how well these treatment patterns conform to the recommended course of treatments per the published guidelines.

Outcome is defined as the effects of care on the health status of patients and populations. This component will not be assessed in the proposed research plan. As discussed previously, evidence suggests that health and economic outcomes would improve if guideline-based treatment were used.[27] The focus of the current research plan is on establishing the patient and provider factors that are associated with receipt of guideline non-concordant care.

2.4.1.2 Predisposing, Enabling and Need Variables

Figure 2.4 - Andersen's Behavioral Model of Health Services Use



Predisposing characteristics are considered biological and social imperatives that suggest the likelihood of needing health services.[242] In this case, factors such as the child's age at diagnosis, their sex and their geographic region are considered predisposing characteristics.

Enabling resources are factors that promote or inhibit service use. In this case, patient insurance type (fee for service or health maintenance organization) will be used as an enabling factor, as will the generosity of the patients' outpatient prescription drug benefits. Although all patients in the data source are privately insured, there may be differences in the

use of health services by plan structure (fee for service or health maintenance organization, for example or by the generosity of the insurance plan's prescription drug benefit).[243]

Need factors represent the perceived and evaluated need for health services. Although perceived need will not be measured, evaluated need will be considered to be a diagnosis of bipolar disorder. Additionally, need variables will include the presence of other co-morbid conditions and disease severity indicators.

2.4.1.3 Rationale for Proposed Conceptual Framework

The proposed conceptual framework will allow us to evaluate the influence of both physician-level and patient-level characteristics on the use of guideline-recommended treatment. This is important as process measures have recently become the focus of quality measurement efforts. These measures can provide actionable information regarding the extent to which clinical practice varies from guideline recommendations.[244] If process measures identify substantial nonadherence to recommendations, physician-level and patient-level factors can be explored to identify targets for process-related improvements. Establishing these associations is key to improving the quality of health care services delivered to children with bipolar disorder.

CHAPTER THREE: METHODS

3.1 Data Source and Aims

Data for this project originated from the MarketScan Commercial Claims and Encounters database. This data source contains de-identified information on clinical utilization and expenditures for inpatient, outpatient and pharmacy services. The data represented approximately 100 payers within the United States. From the first quarter of 2005 through the last quarter of 2007 the average annual population of enrolled children was 6,048,159. These data were used to answer the following aims.

Aim 1: To describe the treatment patterns and the demographic characteristics of a cohort of children who are diagnosed with bipolar disorder.

Aim 2: To determine the factors associated with receiving a single mood stabilizer or atypical antipsychotic as first line treatment, compared with receiving any other bipolar treatment.

Aim 3: To determine the factors associated with early treatment regimen changes, compared with no early regimen changes.

Each of the aims described above are further detailed and explicit methods for their analysis are provided in section 3.6.

3.2 Study Sample

In order to address the multiple aims of this research project, four samples were constructed. These samples were constructed using inclusion and exclusion criteria based on studies previously conducted in the pediatric bipolar literature, as well as expert-consensus recommendations regarding the design of clinical trials for pediatric bipolar disorder. Details of the study sample inclusion and exclusion criteria are provided below.

The overall study sample included patients in the MarketScan Commercial Claims and Encounters database from January 1, 2005 through December 31, 2007. Patients were included if they were under the age of 18 years at the time of their first recorded bipolar diagnosis and had either one inpatient or two or more outpatient insurance claims with unique service dates for a bipolar spectrum disorder (ICD-9 codes noted in Table 3.1). DSM-IV codes were mapped to the respective ICD-9 codes to provide conservative estimates of the diagnostic prevalence of the spectrum disorders. This mapping was consistent with previous literature in this area.[235, 245, 246]

Overlapping claims for both inpatient and outpatient services on the same date were counted as inpatient claims. Additionally, because several medical disorders mimic symptoms of mania, children with any of the following medical disorders were excluded: temporal lobe epilepsy (ICD-9 code 345.4), multiple sclerosis (ICD-9 code 340), hyperthyroidism (ICD-9 code 242.9), closed or open head injury (ICD-9 codes 800.x - 801.x and 850.x - 854.x) and systemic lupus erythematosus (ICD-9 code 710.0) or if they were

pregnant (ICD-9 code V22 - V24 and V27 - V29).[3, 247] Patients meeting the criteria noted above were included in the initial study sample. Further inclusion and exclusion criteria were added to refine the initial study sample for each aim. These modifications are listed below by aim with corresponding sample flow diagrams provided in Chapter 4.

Table 3.1 - International Disease Classification, Ninth Edition (ICD-9) and Diagnostic and Statistics Manual for Mental Illness, Text Revision (DSM-IV-TR)

ICD-9 Code	ICD-9 Description	DSM-IV-TR Code	DSM-IV Description
296.0x	Manic disorder, single episode	296	Bipolar disorders
296.1x	Manic disorder, recurrent episode	296	Bipolar disorders
296.4x	Bipolar affective disorder, manic	296.4x	Bipolar I disorder, most recent episode hypomanic
296.5x	Bipolar affective disorder, depressed	296.5x	Bipolar I disorder, most recent episode depressed
296.6x	Bipolar affective disorder, mixed	296.6x	Bipolar I disorder, most recent episode mixed
296.7x	Bipolar affective disorder, unspecified	296.7x	Bipolar I disorder, most recent episode unspecified
296.80	Manic-depressive psychosis, unspecified	296.80	Bipolar disorder NOS
296.89	Other	296.89	Bipolar II disorder
301.13	Cyclothymic Disorder	301.13	Cyclothymic Disorder

Aim 1 was analyzed in two ways (labeled hereafter as aim 1a and aim 1b to differentiate the study designs). Aim 1a utilized a repeated cross-sectional study design to identify the diagnostic prevalence of bipolar spectrum disorders, along with the treatments and demographic characteristics of children with bipolar disorder. This analytic strategy allowed us to determine the prevalence of diagnosed bipolar disorder by using annual cross-sections. Aim 1b: Restricted the patient population to newly diagnosed patients by including only those patients who had no previous diagnosis or treatment for a bipolar spectrum disorder (an antipsychotic, anticonvulsant or lithium). Using this strategy, patients were

followed forward in time to determine if there were changes in their diagnoses or treatments. Using this sample, patient characteristics and physician characteristics were summarized by the child's index bipolar diagnosis subtype.

3.2.1 Aim1a: Repeated cross-sectional design, prevalence study

For aim 1a patients were classified by the bipolar diagnosis code received at their last bipolar-related visit. Because the original study sample required only that patients be under the age of 18 years at the time of their first recorded diagnosis, there may have been patients in the aim 1a sample who were over the age of 17 years by their last bipolar-related visit. Therefore, the age under 18 age limit was re-applied to the aim 1a sample. This sample was used for the prevalence and demographic analyses related to aim 1a.

3.2.2 Aim1a: Repeated cross-sectional design, medication use study

Further criteria were applied to accurately identify the prescription drug eligible sample. In order to identify medication us in the 30 days following the patient's most recent diagnosis, the index diagnosis was modified from the initial sample and above by only considering diagnoses that took place prior to December 1st in each study year. Again, the age less than 18 restriction was applied to this study sample. Only patients who had drug data reported by their insurance provider to MarketScan were included. These patients were identified within the MarketScan claims data as having medication drug information available (yes/no). This restriction only required that drug records be available, not that patients had a prescription drug claim. Patients were also required to be enrolled in their

insurance plan at the time of their diagnosis and up to 30 days after their diagnosis in order to correctly classify their use or non-use of medications.

3.2.3 Aim1b: Incident Diagnosis Study Design

Next, additional exclusionary criteria were applied to address Aim 1b. In order to identify patients who were newly diagnosed and to accurately identify their treatments received over time, the initial sample was reduced by restricting the sample to patients whose first diagnosis occurred between July 1, 2005 and December 31, 2006. Patients also were required to have had continuous enrollment over the 18 month study period, and no previous evidence of a bipolar diagnosis or treatment (antipsychotic, anticonvulsant or lithium) for 6 months prior to their index diagnosis. The index diagnosis was the first recorded diagnosis date among patients who met these criteria.[248] Similar inclusion criteria have been used previously when analyzing prescription claims data for patients with bipolar disorder.[235, 248]

Patients were excluded from this cohort if they had a diagnosis of schizophrenia (ICD-9 code 295.x),[20, 235, 249, 250] a pervasive developmental disorder (i.e., autism or autism spectrum disorder, ICD-9 code 299.x),[20, 250] mental retardation (ICD-9 codes 317 - 319), or a substance abuse disorder (ICD-9 codes 303 - 304)[20] in the 6 months prior to their bipolar diagnosis. These criteria are consistent with requirements for clinical trials and with other studies in the area of pediatric bipolar disorder.[20] Patients who were identified as substance users (ICD-9 code 305) were not excluded from the current study.

In addition to these criteria, patients whose insurance plans did not provide information on medication use were excluded so that we could differentiate between non-use

of medications and non-reporting of medications. Characteristics of children in the aim 1b sample were reported for only those children who had medication information available.

3.2.4 Aims 2 and 3 Study Sample

Finally, in order to address Aims 2 and 3 of the research plan, the sample was further reduced by excluding patients who had a bipolar spectrum disorder other than bipolar I disorder (i.e., excluded those with bipolar unspecified, bipolar II and cyclothymic disorder), and children under the age of 6 years at the time of their diagnosis. These exclusions were made because the treatment guidelines were specifically designed for patients with bipolar I disorder and for children ages 6 - 17 years.[17] Patients with bipolar I disorder, depressed subtype were included in the analysis but indicator variables were used to identify this subtype since the guidelines were designed specifically for manic or mixed subtypes of the disorder.

Because medication use during hospitalization could not be detected in insurance claims data, children with hospitalizations 60 days prior to or 45 days post initial bipolar diagnosis were excluded. After these exclusions were made, the index treatment date was identified as the date at which the first dispensing of bipolar medications was made post initial diagnosis.

3.3 Sample Size

Sample size calculations were based on the most narrowly defined cohort of patients with Bipolar I disorder (the subset of patients needed for aims 2 and 3). Using a conservative estimate of the published prevalence of Bipolar I disorder, we assumed that 0.05% of the

children in our sample would have this diagnosis. In 2002, there were 944,502 children in the MarketScan database.[251] We assumed that half of 1% of these would have a bipolar diagnosis, so we expected 4,722 children to be eligible for our cohort prior to applying inclusion and exclusion criteria. Using Cohen's criteria for assessing power, with an alpha level of 0.05 for a two-sided test of significance, and a minimum power of 80%, we should have been able to detect small differences in means or proportions.[252]

3.4 Study Design

A retrospective cohort was constructed using MarketScan Commercial Claims and Encounters database from January 1, 2005 to December 31, 2007. Inclusion and exclusion criteria were defined previously and are provided in Figures 4.1 - 4.5. To address Aim 1, two samples were created. The first sample (aim 1a) was used to assess the diagnostic prevalence of bipolar spectrum disorders and treatments for the disorders by using a repeated cross-sectional study design. In this design, information regarding the demographic and treatment characteristics of children who were diagnosed with any bipolar spectrum disorder were assessed using frequency information for each variable of interest (e.g., age, gender, co-morbid conditions, treatment received). Cross-sections were extracted from January 1st to December 31st) for each year (2005 - 2007).

The second sample for aim 1 (aim 1b) included only those patients who were newly diagnosed with a bipolar spectrum disorder. This was achieved by requiring that patients have a 6 month "clean" period (no evidence of bipolar diagnosis or treatment) prior to their initial diagnosis, followed by a 12 month period of continuous enrollment. Constructing the sample in this way allowed us to follow patients forward in time to determine if there were

changes in their diagnoses or treatments. This sample was also utilized in aims 2 and 3 after applying additional inclusion and exclusion criteria; however, the focus of aims 2 and 3 were on the date that medication was received and not the date of the diagnosis. For these aims, guideline concordant care was assessed by identifying care received among those who were new bipolar treatment initiators. Patients who did not initiate treatment within 90 days of diagnosis were categorized as guideline discordant. Descriptive information on patient and provider characteristics by type of care (guideline concordant versus non-concordant) was assessed for this sample.

3.5 Measures

Variables for the analysis and coding specifications are noted in tables 3.2 - 3.3 and described below.

Table 3.2 - Variable Descriptions and Coding Strategies for Patient and Physician Characteristics

Patient Characteristics	Variable Coding	Variable Definition
Predisposing Characteristics		
Age at Diagnosis	Continuous, Years	Age in years at time of service.
Sex	1 = Male, 2 = Female	Patient sex from enrollment file.
Geographic Region	Northeast, North central, West, South	Geographic region of employee residence.
Enabling Resources		
Insurance Type	Comprehensive, HMO, POS, PPO, Other, and Unknown	Insurance type reported at the time of service.
Generosity of Benefits	None/Poor, Fair, Good	Ratio of patient out of pocket payments to total payments for prescription drugs.
Cost of Medical Care	Continuous, Dollars	Annual cost for Inpatient, Outpatient and Pharmacy services per patient.
Need Characteristics		
Diagnostic Category		
Bipolar I	0 = Absent, 1 = Present	Diagnosis code: 296.0x, 296.1x, 296.4x, 296.5x, 296.6x
Bipolar II	0 = Absent, 1 = Present	Diagnosis code: 296.89
Bipolar NOS	0 = Absent, 1 = Present	Diagnosis code: 296.7x, 296.8x (except 296.89)
Cyclothymic Disorder	0 = Absent, 1 = Present	Diagnosis code: 301.13
Co-Morbid Diagnosis		
Attention Deficit Hyperactivity Disorder	0 = Absent, 1 = Present	Diagnosis code: 314.00, 314.01
Conduct Disorder	0 = Absent, 1 = Present	Diagnosis code: 312.x
Oppositional Defiant Disorder	0 = Absent, 1 = Present	Diagnosis code: 313.81
Separation Anxiety Disorder	0 = Absent, 1 = Present	Diagnosis code: 309.21
Post Traumatic Stress Disorder	0 = Absent, 1 = Present	Diagnosis code: 309.81
Obsessive Compulsive Disorder	0 = Absent, 1 = Present	Diagnosis code: 300.3
Generalized Anxiety Disorder	0 = Absent, 1 = Present	Diagnosis code: 300.02
Social Phobia	0 = Absent, 1 = Present	Diagnosis code: 300.23
Major Depressive Disorder	0 = Absent, 1 = Present	Diagnosis code: 296.2x, 296.3x
Dysthymic Disorder	0 = Absent, 1 = Present	Diagnosis code: 300.4
Tourette's or Tic Disorders	0 = Absent, 1 = Present	Diagnosis code: 307.23, 307.2x,
Disease Severity		
Number of Diagnoses	Continuous, Number of Diagnoses	Count of total unique diagnoses in the year (mental health and other)
Any Inpatient Mental Health Days	0 = No Days , 1 = Any Days	Any inpatient mental health days (Diagnosis codes: 290.00 - 319.99)
Physician Characteristics		
Structural Characteristics		
Provider Specialty	0 = Unclassified, 1 = Other Medical Specialist, 2 = Other Mental Health, 3 = Primary Care, 4 = Psychiatry	Psychiatry, Primary Care, Other Mental Health Provider, Other Medical Specialist, and Unclassified
Metropolitan Statistical Area	0 = Non-MSA, 1 = MSA	Metropolitan Statistical Area of the primary beneficiary.

Table 3.3 - Variable Descriptions and Coding Strategies for Treatment Characteristics

Treatment Characteristics	Variable Type	Variable Range
Medications Prescribed		
Mood Stabilizers	Categorical	1 = Present, 0 = Absent
Lithium	Categorical	1 = Present, 0 = Absent
Anticonvulsants	Categorical	1 = Present, 0 = Absent
Antipsychotic	Categorical	1 = Present, 0 = Absent
Antidepressant	Categorical	1 = Present, 0 = Absent
Stimulant	Categorical	1 = Present, 0 = Absent
Polypharmacy		
2+ Mood Stabilizers	Categorical	1 = Present, 0 = Absent
2+ Antipsychotics	Categorical	1 = Present, 0 = Absent
Mood Stabilizer + Antipsychotic	Categorical	1 = Present, 0 = Absent
Mood Stabilizer + Antidepressant	Categorical	1 = Present, 0 = Absent
Mood Stabilizer + Psychostimulant	Categorical	1 = Present, 0 = Absent
Antipsychotic + Antidepressant	Categorical	1 = Present, 0 = Absent
Antipsychotic + Psychostimulant	Categorical	1 = Present, 0 = Absent
Psychotherapy		
Any Use	Categorical	1 = Present, 0 = Absent
Frequency of Use	Continuous	Number of Visits per Year
Other Treatment		
Use Pharmacotherapy	Categorical	1 = Yes, 0 = No
Use Electroconvulsive Therapy	Categorical	1 = Yes, 0 = No

3.5.1 Patient Characteristics

3.5.1.1 Predisposing Characteristics

Specific predisposing characteristics of interest were age, sex, and geographic region. These variables are available within the MarketScan dataset and were coded as follows: Age at Onset was calculated as the age at the time of initial bipolar diagnosis (for aims 1b, 2 and 3), age at the last bipolar-related visit for the study year for aim 1a demographic analyses,

and age at the last bipolar-related visit prior to December 1st in the study year for the aim 1a medication related analyses. Sex was coded as "male" or "female." Geographic Region was based on the "Region" variable in the MarketScan database. This variable is coded as Northeast, North Central, West and South and is based on the Geographic Region of employee residence. Northeast was used as the reference category.

3.5.1.2 Enabling Resources

Enabling resources were assessed based on available information within the MarketScan dataset. Included variables were insurance type and generosity of insurance benefits. These variables were coded as follows: Insurance type was based on the "Plan Indicator" variable in the MarketScan database. This variable was coded as follows: Comprehensive, Health Maintenance Organization (HMO), Non-Capitated Point-of-Service (POS), Preferred Provider Organization (PPO), Other (Basic/Major Medical, Exclusive Provider Organization, Capitated or Partially-Capitated Point-of-Service and Consumer-Driven Health Plans), and Unknown.

The generosity of benefits was assessed using a ratio described previously by Artz and colleagues.[243] This variable is based on a sum of patients' coinsurance, copayments and deductible payments for prescription drugs divided by the total net prescription drug payments (from all payment sources, minus discounts). This ratio was categorized into four levels: None (ratio > 0.99), Poor (ratio > 0.80 and ≤ 0.99), Fair (ratio > 0.20 and ≤ 0.80), and Good (ratio ≥ 0 and ≤ 0.20). Only a small number of patients were categorized as either "None" or "Poor," therefore these two categories were combined into one category (None / Poor). Finally, cost of medical care was summarized for inpatient, outpatient and pharmacy

claims for each patient. These cost estimates were used in aim 1b to identify the mean annual expenditures for patients with newly diagnosed bipolar disorder.

3.5.1.3 Need Characteristics

Need characteristics included both the type of bipolar spectrum disorder (Bipolar I, Bipolar II, Bipolar-NOS or Cyclothymic Disorder), as well as co-morbid conditions and disease severity. These variables were coded as follows: Bipolar Spectrum Disorder Type was coded as Bipolar I, Bipolar II, Bipolar Unspecified (NOS), and Cyclothymic Disorder. These were based on diagnostic claims information and ICD-9 codes in the MarketScan database and provided in table 3.2. Indicators for diagnosis are "Present" or "Absent" for each person in the database. It was anticipated that individuals would have more than one diagnosis over time as bipolar diagnosis is unstable in children. For analysis for aim 1a (prevalence study), the diagnosis was recorded as the current bipolar diagnosis as of December 31st of each year. For analysis for aim 1b (newly diagnosed sample), the diagnosis was recorded as the first diagnosis of bipolar disorder following a 6-month clean period.

Comorbid mental health diagnoses were of primary interest and were summarized for the following conditions: attention deficit hyperactivity disorder, other disruptive disorders (conduct disorder and oppositional defiant disorder), anxiety disorders (separation anxiety disorder, post traumatic stress disorder, obsessive-compulsive disorder, generalized anxiety disorder, social phobia, panic disorder), depressive disorders (major depressive disorder, dysthymic disorder), and tic disorders (Tourette's, chronic motor or vocal tic disorder, transient tic disorder). All comorbid conditions were identified using the appropriate ICD-9 codes to identify patterns of comorbidities within the children in the cohort (see table 3.2 for

specific codes). Conditions were identified as present or absent and also categorized within diagnostic classes. Additionally, the presence or absence of Schizophrenia, Pervasive Developmental Disorders, Substance Abuse Disorders and Mental Retardation were summarized for Aim 1a of the proposal. In addition to summarizing the presence of any comorbid mental health condition, summaries for aim 1b also include identification of conditions that occurred prior to the index diagnosis (pre-morbid) and those that occurred post index diagnosis (post-morbid).

Disease severity measures were also used. Although ICD-9 severity indicators were available within the dataset, these indicators have long been considered to be unreliable. Therefore, several variables that have been shown to be associated with severity were included and ICD-9 severity indicators were not used. Previous studies have operationalized illness severity in a number of ways. For example, the number of comorbid Axis I disorders,[253] the presence of psychosis,[2] age at disease onset,[254] and previous hospitalizations[255] have all been suggested as indicators of illness severity. One insurance claims analysis used three indicators for illness severity: number of different diagnoses (all diagnoses, not just mental health) in the year, if the child had a dual diagnosis (mental illness and substance abuse) and if the child had any inpatient mental health days during the year (identified using ICD-9 codes from 290.00 - 319.99).[32] This study utilized two of the measures identified in the study conducted by Martin and Leslie - the number of different diagnoses and the presence of any inpatient mental health days. The measure associated with dual diagnosis was not used as patients with substance abuse diagnoses were excluded from

the cohort. Finally, aims 2 and 3 utilized an indicator variable for the presence or absence of psychosis. This variable was based on the fifth digit of the ICD-9 code, where available.

3.5.1.4 Treatment Characteristics

Medications were identified by coding individual drugs as present or absent and then grouping them by drug categories. Coding in the MarketScan dataset follows that of the American Hospital Formulary Service (AHFS) Pharmacologic-Therapeutic Classification system.(AHFS, 2008) Medication use was grouped into four major categories: mood stabilizers (lithium and anticonvulsants - codes 28.28 and 28.12.92), antipsychotics (code 28.16.08), antidepressants (code 28.16.04), and stimulants (code 28.20.04).

These categories were further subdivided as follows: Mood stabilizers included lithium, divalproex and other anticonvulsants (carbamazepine, lamotrigine, topiramate, gabapentin, oxcarbazepine, levetiracetam, and tiagabine). Consistent with other studies, lithium use was summarized separately from other mood stabilizers, unless otherwise indicated.[1, 76, 206] Antipsychotics included clozapine, other second generation agents (risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole), and other first generation agents. First generation antipsychotics use was summarized separately from second generation antipsychotics, unless otherwise indicated. Antidepressants included tricyclics and tetracyclics, selective serotonin reuptake inhibitors (fluoxetine, sertraline, citalopram, escitalopram, fluvoxamine, and paroxetine), other antidepressants (venlafaxine, trazodone, nefazodone, mirtazapine, duloxetine, and bupropion) and monoamine oxidase inhibitors. Stimulants included methylphenidate, methylphenidate transdermal, dextroamphetamines, amphetamine salt combinations, dexmethylphenidate, and lisdexamphetamine.

Medication use patterns were structured to not only identify drug class use, but use of drug class combinations (polypharmacy). This was categorized as use of concurrent drugs (two or more mood stabilizers or two or more antipsychotics) as well as combinations of drug classes (such as mood stabilizers and antipsychotics; mood stabilizers and antidepressants, etc.). Specifically, polypharmacy was captured by looking at concurrent use of multiple medications and medication classes.

Finally, use of psychotherapy or counseling was captured (as any use and then by number of visits per year), as was use of electroconvulsive therapy (ECT) and non-use of medications. These services were identified in the MarketScan database using Current Procedural Terminology, 4th Edition (CPT-4) codes, ICD-9 codes or Healthcare Common Procedure Coding System (HCPCS) codes. Electroconvulsive therapy was identified using the following procedure codes: 90870, 90871 or 9427. Psychotherapy was defined by the presence of any of the following procedure codes: 90804 - 90819, 90821 - 90824, 90826 - 90829, 90841 - 90844, 90846 - 90849, 90853, 90855, 90857, 90862, 90875, or 90876 in any procedure code field (inpatient, outpatient or facility). For those who had any psychotherapy use, the total number of visits was calculated to determine the frequency of use.

Use of either psychotherapy or ECT was calculated among patients who had mental health / substance abuse coverage indicators in the MarketScan database. This allowed for accurate capture of use, or non-use, as patients without this indicator may have received services from a carve-out vendor that were not captured in the MarketScan claims.

3.5.2 Structural Measures

3.5.2.1 Physician Characteristics

Physician characteristics were also assessed based on available information within the MarketScan dataset. Variables that were included in this analysis were provider specialty type and Metropolitan Statistical Area classification of the physician's practice.[40, 205, 248] These variables were coded as follows: Provider Specialty was defined using provider indicators in the MarketScan database. Providers were classified into one of five categories: Psychiatry, Primary Care, Other Mental Health Provider, Other Medical Specialist, and Unclassified. Specialty was identified for aim 1a as the provider at the last bipolar-related visit. For aim 1b, the provider was categorized using the first bipolar related claim for newly diagnosed patients. Aims 2 and 3 used the provider who was seen at the visit that was closest to the prescription fill date (on or before the fill date). Additionally, provider type was classified so that in cases where multiple providers were seen on the same date, the most specific provider would be selected (ordered from most to least specific as: Psychiatry, Primary Care, Other Mental Health Provider, Other Medical Specialist, and Unclassified). Metropolitan Statistical Area was categorized as MSA or Non-MSA based on the MarketScan variables. This variable was based on the MSA of the primary beneficiaries' zip code.

3.5.3 Process Measures

3.5.3.1 Use of Recommended First-Line Treatment

The process measure evaluated by aim 2 of this proposal evaluated whether or not patients received the appropriate first-line treatment upon diagnosis with bipolar I disorder.

Appropriate treatment is specified by the expert-consensus treatment guidelines produced in 2005 and 2007.[17, 19] These guidelines indicate that initial treatment for patients with Bipolar I disorder without psychosis be a mood stabilizer or antipsychotic monotherapy. Therefore, individuals were classified as receiving appropriate first-line treatment if they received any one of the following drugs: Lithium, divalproex, carbamazepine, olanzapine, quetiapine, risperidone, ziprasidone or aripiprazole. Any other drug or combination of drugs would be specifically contraindicated by the guidelines, and therefore were classified as inappropriate first-line treatment. Additionally, children who did not receive a medication for bipolar disorder within 90 days of their initial bipolar diagnosis were considered to have received guideline discordant treatment as guidelines recommend pharmacotherapy as a "minimal standard" (i.e., expected to apply at least 95% of the time) for children with bipolar I disorder.[19]

3.5.3.2 Receipt of a 6-8 week medication treatment trial prior to treatment regimen changes.

The process measure evaluated by aim 3 of this proposal used the number of weeks that initial medication trials lasted prior to switching or augmenting treatment to identify early medication regimen changes. Studies suggest that medication trials last a minimum of six to eight weeks at adequate doses prior to making drug regimen changes. This allows for sufficient time to assess medication response.[17, 20] It is unclear to what extent this recommendation is followed in clinical practice. It is also clear that polypharmacy and multiple drug regimen changes are common in this field (which may be appropriate), but it is

important that drug trials be sufficiently long to assess effectiveness prior to making these changes.

Individuals were then classified as receiving early medication regimen changes if they had initial medication trials that were shorter than the guideline recommended time (conservatively, six weeks was used as the recommended time).[20] Only initial medication therapy was analyzed using this criteria, as evidence from the Treatment of Early Age Mania study indicated that, in the context of second medication trials, there is no longer consensus that eight weeks is a sufficient medication trial.[24]

3.6 Data Analysis by Aim

3.6.1 Aim 1: Describe the treatment patterns and the demographic characteristics of children who are diagnosed with bipolar disorder.

Information regarding diagnostic and treatment patterns among children with bipolar disorder were summarized in this aim. To achieve this, two study designs were used - a prevalence design (aim 1a) and an incident diagnosis design (aim 1b).

For Aim 1a, repeated cross-sections of data were used to identify the diagnostic prevalence of bipolar spectrum disorders and treatments for the disorders among a cohort of children under the age of 18 years. A retrospective cohort was constructed using MarketScan Commercial Claims and Encounters database from January 1, 2005 to December 31, 2007. Information regarding the demographic and treatment characteristics of children who were diagnosed with any bipolar spectrum disorder was assessed using frequency information for

each variable of interest (e.g., age, gender, co-morbid conditions, treatment received). Cross-sections were extracted from January 1st to December 31st for each year (2005 - 2007).

The annual diagnostic prevalence of bipolar spectrum disorders used the total number of children with a specific bipolar diagnosis over each one-year study period (January 1 - December 31) divided by the total number of children in the dataset at the mid-point of the study period. Although this method did not allow us to account for the impact of non-continuous enrollment, it has been used previously in claims based annual-prevalence studies.[256] A patients' bipolar type (Bipolar I, II, Unspecified, or Cyclothymia) was classified according to the bipolar diagnosis code received at their last bipolar-related visit during the study year. In addition to the diagnostic prevalence, patient characteristics (e.g., age, gender, co-morbid conditions and disease severity), and physician specialty information were summarized by study year for this sample.

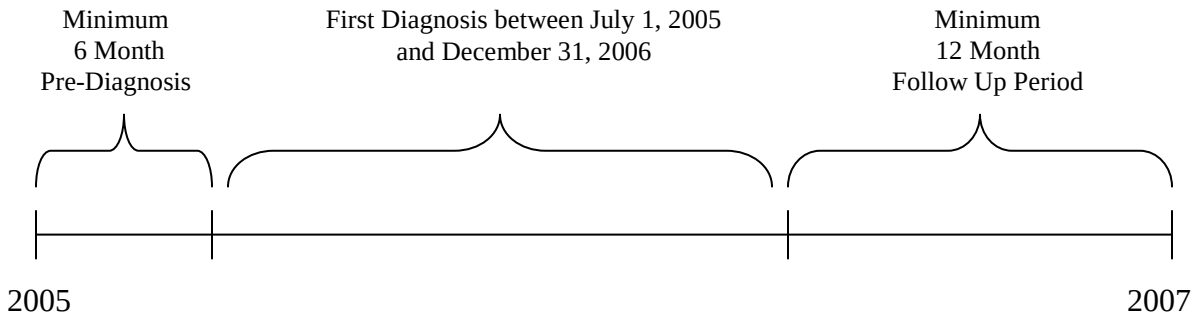
Descriptive information regarding the medication classes and class combinations that were used to treat pediatric bipolar disorder were also summarized by year for the medication use sample. For this analysis, patients' bipolar type was classified according to the bipolar diagnosis code received at the last bipolar-related visit prior to December 1st in each calendar year. This was done to ensure that, for all included patients, their medication use could be observed for 30 days after their last diagnosis. Summaries included drug-level and class-level use, as well as a count variable that indicated the number of drugs taken by each child during the 30-days after their last diagnosis.

In addition to the summaries proposed above, changes in diagnosis, treatment and co-morbid conditions were also assessed by age categories for aim 1a. There is currently a lack

of information regarding the differences in treatment strategies and diagnosis of children who are under the age of 10 years.[22] This age group is particularly important because current recommendations are to conduct medication trials of only 10 to 17 year old children.[20] Therefore, age categories were constructed to assess diagnosis, treatment and comorbidities for children under the age of 10 and those ages 10-17 separately. Each summary described above was replicated separately for those ages less than 10 years and those ages 10-17 years inclusive.

For Aim 1b, a sample of newly-diagnosed patients was constructed. This was achieved by requiring that patients have a 6 month "clean" period (no evidence of bipolar diagnosis or treatment) prior to their initial (first identified) diagnosis, followed by a 12 month period of continuous enrollment. Using this sample, patients were followed forward in time to determine if there were changes in their diagnoses or treatments (Figure 3.1). To be included in the aim 1b cohort, patients must have had their first diagnosis of bipolar disorder between July 1, 2005 and December 31, 2006. Patient characteristics were captured within the 6 month pre-diagnosis period and medication use was summarized within the 12 month follow-up period for each patient.

Figure 3.1 Timeline for Assessments



Patient characteristics (age at diagnosis, gender, geographic region, insurance type, generosity of benefits, co-morbid conditions and disease severity), and physician characteristics (specialty, metropolitan location), were summarized by the child's index bipolar diagnosis subtype. In addition to these descriptive summaries, changes in patients' bipolar diagnoses were tracked over the one year follow-up period. This allowed us to identify the extent to which initial bipolar diagnoses were stable in this population. Finally, we were able to summarize comorbid mental health conditions as occurring prior to initial diagnosis (pre-morbid) or occurring post initial diagnosis (post-morbid).

Drug classes were summarized in several ways using this study design. Because we were able to identify new users, initially prescribed therapies were summarized at the drug class level and by specific drug within each class for each disorder subtype. Initially prescribed therapies were defined in two ways: (1) medications used within 30 days of diagnosis, and (2) medications used within 90 days of diagnosis. Polypharmacy was assessed by identifying the number of drugs used over the selected timeframe. Specific drug use was captured as the number of prescriptions for each specific agent within a class over the selected timeframes. For this analysis, fills were standardized to a 30 day supply to allow for comparisons of use across agents.

Drug class use within the year following index diagnosis was also summarized. This is presented as the number of agents used in the first year from index diagnosis (count of medications) as well as the frequency of use for each drug class. Use of psychotherapy and electroconvulsive therapy was also assessed for each bipolar subtype by identifying any use, and the frequency of use among users. Finally, payments made for treatment were

summarized for both patients alone, and patients and insurers combined. These summaries included estimates of the median and mean payments for medical care among all patients and then separately among users of services.

3.6.2 Aim 2: Determine the factors associated with receiving a single mood stabilizer or atypical antipsychotic as first line treatment.

The sample for this proposed analysis consisted of children ages 6 - 17 years who were newly diagnosed with Bipolar I disorder. The sample from aim 1b was used as a starting point, but restricted to only children ages 6 - 17 as the published guidelines were not intended for children under the age of 6 years. Additionally, those with an initial diagnosis other than Bipolar I disorder (bipolar unspecified, bipolar II or Cyclothymic disorder) were excluded. Although guidelines are specifically targeted towards children with bipolar I disorder, manic or mixed subtype,[17] the sample included children with bipolar I disorder, depressed episode. An indicator variable was created to identify children with this particular form of bipolar I disorder. Finally, because medication use during hospitalization could not be detected in insurance claims data, children with hospitalizations 60 days prior to or 45 days post index diagnosis were also excluded.

Pharmacologic treatment patterns within the dataset were used to identify children who received a guideline-recommended first-line treatment (versus those that received any other treatment or treatment combination). Appropriate treatment was defined as a mood stabilizer or atypical antipsychotic monotherapy. Therefore, individuals were classified as receiving appropriate first-line treatment if they received any one of the following drugs: Lithium, divalproex, carbamazepine, olanzapine, quetiapine, risperidone, ziprasidone or

aripiprazole. Any other drug or combination of drugs were specifically not recommended by the guidelines, and therefore were classified as inappropriate first-line treatment. This variable was dichotomized as receipt of guideline appropriate first line therapy or not. Patients who did not fill a medication within 90 days of their first diagnosis were classified as receiving guideline discordant care, as guidelines recommend pharmacotherapy as a "minimal standard" (i.e., expected to apply at least 95% of the time) for children with bipolar I disorder.[19]

The proposed generalized linear model will include each of the predictors noted below, along with control variables for geographic region, patient insurance type and year of diagnosis. Details of the rationale for inclusion of these variables and initially proposed hypotheses for the relationships are provided below.

HYPOTHESIS: Compared with patients with bipolar I disorder who are prescribed guideline recommended first line treatment, those who do not receive the recommended treatments are more likely to:

Predisposing Characteristics

- have a younger age of diagnosis (H_{02a})
- be male (H_{02b})

Enabling Resources

- have more generous insurance benefits (H_{02c})

Need Characteristics

- have co-morbid mental health conditions (H_{02d})

- have higher levels of disease severity (H_{02e})
- have an initial diagnosis of bipolar I depressed episode (H_{02f})
- have treatment plans that exclude psychotherapy or counseling (H_{02g})

Physician Characteristics

- have received their diagnosis from a primary care provider (H_{02h})
- reside in a non-Metropolitan Statistical Area (H_{02i})

Initially Proposed Model for Aim 2

Risk of Recommended Drug Use = $\alpha + \beta_1$ (Age) + β_2 (Sex) + β_3 (Insurance Generosity) + β_4 (ADHD)+ β_5 (Depressive Disorders) + β_6 (Tic Disorders) + β_7 (Anxiety Disorders) + β_8 (Other Disruptive Disorders) + β_9 (Disease Severity, Number of Diagnoses) + β_{10} (Disease Severity, Any Inpatient Days) + β_{11} (Disease Severity, Psychosis) + β_{12} (Bipolar I Depressed Episode) + β_{13} (Psychotherapy or Counseling) + β_{14} (Primary Care) + β_{15} (Metropolitan Statistical Area Classification) + β_{16} (Region) + β_{17} (Insurance Type) + β_{18} (Year Diagnosed)

Previous research suggests that children who were over the age of 10 were significantly more likely to get an antipsychotic than those under the age of 10 years.[205] This suggests that older age may be associated with a higher likelihood of receiving mood stabilizers as first line therapy. Additionally, young age is often associated with the presence of comorbid attention deficit hyperactivity disorder.[63] This comorbid condition may lead to treatment combinations, (such as mood stabilizers and stimulants) or reluctance to discontinue current ADHD treatment upon diagnosis with bipolar disorder. Similarly, male

sex is associated with ADHD diagnosis,[59] higher rates of comorbidity,[61] and early onset bipolar disorder.[61] Therefore, it is likely that male sex would be associated with receiving guideline discordant treatment.

Regarding enabling factors, generosity of insurance benefits are associated with increased prescription drug use, even when controlling for drug use and insurance selection factors.[243] It is possible that generosity of benefits may lead to receiving more than one medication (initial combination therapy) as patient out of pocket spending would be reduced.

Regarding need characteristics, comorbid conditions are likely to complicate the treatment of bipolar disorder and to lead to a lower likelihood of receiving a monotherapy that is recommended by guidelines. Guidelines support the discontinuation of treatments for comorbid mental health disorders until a patient is stabilized on the treatment for bipolar disorder.[17] It is unclear, however, if this recommendation is adhered to in clinical practice. Comorbid conditions were modeled individually and then combined as appropriate to improve the efficiency of the statistical model. For example, conduct disorder and oppositional defiant disorder have been identified as having significant overlap for the pediatric bipolar population. These disorders have been previously combined into a single "disruptive behavior disorder" category without influencing the outcome.[257] Others have suggested that the combination of ADHD and conduct disorder may represent one disorder and thus their collinearity was assessed.[12] Finally, some have suggested that comorbid conditions may synergistically influence the primary disorder.[3, 11] Therefore, interaction terms were added to test if effect measure modification is present for combinations of comorbid conditions.

Disease severity is also hypothesized to be associated with receipt of guideline discordant treatment. This measure utilizes information regarding the number of total diagnoses that a child has received, the presence of any inpatient days, and psychosis. Treating children who have severe disease may lead to more complex treatment strategies that are not specifically recommended by guidelines. Guideline recommendations that are being evaluated for this aim are specifically related to patients with bipolar I disorder, manic or mixed subtypes without psychosis.[17] Given this, psychosis should be a predictor for guideline discordant treatment in this sample, as should initial diagnosis of bipolar I, depressive subtype. Additionally, use of psychotherapy or counseling is likely to be associated with receiving guideline recommended therapy as combined therapy (counseling and medication) are recommended by guidelines.

Overall, the literature supports that specialists would be more likely to have adequate training to diagnose and treat bipolar disorder in children, and they would likely be more familiar with expert-consensus guidelines from the field as compared with primary care physicians.[20] Because of this, referral to a mental health specialist is strongly recommended for the diagnosis and management of this disorder.[21] This suggests that specialists may be more informed regarding the appropriate treatment for children with bipolar disorder, and therefore more likely to adhere to guideline recommendations. Additionally, metropolitan statistical area classifications of the physician's practice or of the patient have previously been associated with guideline use (where urban location was associated with the receipt of guideline recommended treatment) in several studies of the treatment of depression.[258, 259]

Three control variables (insurance type, geographic region, and year of diagnosis) will be used in the proposed analysis. Hypotheses regarding the association between guideline use and insurance plan type, as well as geographic region will not be tested. Instead, these will be used as control variables in the primary analysis and later explored to identify if any relationships exist. Private insurance has previously been associated with a lower likelihood of receiving antipsychotic medications, as compared to public insurance;[205] however it is unclear if these relationships exist when comparing insurance plan types within private insurance. Additionally, geographic variation in practice guideline adoption and attitudes towards service use should be controlled for in this population.[205] Finally, year of diagnosis will be included in the model to account for time-dependent changes in guideline adoption or drug approval changes over the study period.

3.6.2.1 Aim 2: Statistical Analysis, Variable Selection and Modeling

Each of the variables in the initially proposed model was reviewed to determine the extent of missing data for covariates of interest. When including all of the variables from the proposed model above, 73% of patients had no missing values and 25% had only 1 missing value. Upon further inspection, it was determined that a majority of the missing values were due to the Metropolitan Statistical Area variable. There were 176 missing values for this variable. In addition to high levels of missing values, there was little variation in the response to this variable. In fact, over 98% of patients were categorized as "MSA" (compared with Non-MSA). This extreme lack of variation is likely due to the sampling strategy within the MarketScan dataset. Because MarketScan data is comprised of insurance information from large employers, nearly all patients are in MSA regions. Because of these two reasons, MSA

Status was excluded from the analysis. This resulted in complete information for 95% of patients (no missing values).

In order to assess the extent to which missing values were related to the outcome, generalized linear models were used to compare the number of missing values among patients with and without guideline recommended care. The model indicated that missing data was not related to the outcome ($p = 0.15$) for the relationship between missing values and the type of care received. Based on this assessment, the remaining missing values were considered to be missing at random.

Next, each variable in the initially proposed model was assessed to determine the appropriate coding. Categorical and continuous variables were modeled in several ways to determine which cut-points represented the true relationship between the exposure and outcome. Age was assed as a three-level categorical variable (ages 6 - 11, 12 - 14, and 15-17). These categories were selected due to the low sample sizes for children under the age of 11. Additionally, age was modeled as a continuous variable (ages 6 - 17) which assumes that the risk of the outcome increases or decreases incrementally by each one year change. After modeling the relationship using both coding schemes, it was determined that the dose-response relationship was relatively flat (slight negative slope) and that there were no differences between the categorical and continuous age variable for the relationship with the outcome. This led us to use the continuous coding for age in years as it was the more statistically efficient variable.

Next, insurance generosity was reviewed to determine the most appropriate coding. This variable is based on a sum of patients' coinsurance, copayments and deductible

payments for prescription drugs divided by the total net prescription drug payments (from all payment sources, minus discounts). This ratio was originally categorized into three levels: None/Poor (ratio > 0.80), Fair (ratio > 0.20 and ≤ 0.80), and Good (ratio ≥ 0 and ≤ 0.20). Due to the low number of patients who had none / poor insurance generosity (n = 26), this category was set to missing for the analysis as re-categorizing these patients as "fair insurance generosity" may have introduced more bias than removing them from the analysis. However, there was a significant problem with this variable that had to be addressed. As a limitation of the data, we are unable to calculate benefit generosity measures for patients who had no medication use during the study period (we calculate this from filled prescriptions, not specific information about their benefit designs). This resulted in 81 patients who had "unknown" benefit generosity, all of which would have been categorized as "guideline discordant" (as they never received medications). Including this measure for analyses that included patients with no medications would have provided biased estimates. Therefore, it was determined that the resulting variable should be classified as 0 = fair, 1 = good, and used only in the analysis restricted to medication users.

The distribution of each comorbid condition was considered next. Sample sizes were small for a majority of the comorbidities measured. Therefore, comorbidities were grouped as disruptive disorders (attention deficit hyperactivity disorder, conduct disorder, and oppositional defiant disorder), anxiety disorders (separation anxiety, post-traumatic stress disorder, obsessive compulsive disorder, generalized anxiety disorder, Social phobia, and panic disorder), and depressive disorders (major depressive disorder, and dysthymic disorder). First, disruptive disorders were assessed. There appeared to be no relationship

between the occurrence of disruptive disorders and receipt of recommended care ($p = 0.89$). To ensure that combining the three disorders into one category did not influence the result, ADHD, conduct disorder and oppositional defiant disorder were tested separately. While none of the relationships were statistically significant, the risk estimates differed in that ADHD was negatively associated with receipt of recommended care and conduct / oppositional defiant disorder were positively associated with receipt of recommended care. This suggests that these variables should not be combined. Therefore, this information was included in the final model as ADHD (yes/no) and Other Disruptive Disorder (Yes / No).

Similarly, tests of the influence of anxiety disorders revealed a non-significant impact on the outcome ($p = 0.80$). Because only 6.2% of the total sample had pre-existing anxiety disorders, this category was excluded from the final model.

Occurrences of depressive disorders appeared to be related to the outcome with both major depressive disorder and dysthymic disorder increasing the risk of receiving non-recommended care. Therefore, this variable was included in the model as depressive disorders (yes/no) with dysthymic disorder and major depressive disorder combined.

Disease severity measures were also assessed. These measures included the number of diagnoses received on or prior to the date of bipolar diagnosis, the occurrence of mental health hospitalizations prior to diagnosis, and psychosis. Number of diagnoses was based on unique diagnoses received during the 6-month pre-diagnosis period. After modeling this variable in multiple ways, it was determined that the relationship between the number of diagnoses and the outcome had no discernable pattern. Instead, the relationship indicated that the risk varied widely based on the number of diagnoses (plotting this risk estimate resulted

in a zig-zag shaped line). Given the random distribution of risk and the non-significant relationship between this variable and the outcome (no matter how the variable was coded), the decision was made to include this predictor as a continuous variable.

Next, the number of prior inpatient hospitalizations was analyzed. First, only hospitalizations prior to initial diagnosis were considered. In this case, very few patients had prior mental health hospitalizations. This was likely due to the exclusion of those with hospitalizations surrounding their diagnosis date. As a sensitivity analysis, this definition was expanded to include hospitalizations any time during the study period. This resulted in a higher number of patients within the category. Although the relationship between inpatient hospitalizations and the receipt of guideline appropriate care was non-significant, there was a trend that indicated that patients with inpatient hospitalizations were more likely to receive guideline recommended care. Because of the small sample size when including only information for prior hospitalizations, the inpatient mental health visit indicator was constructed using any inpatient visit over the study period. While treatment decisions would have been made without knowledge of future hospitalizations, these events may be relevant as children who are hospitalized later may have a more severe presentation of their illness.

Presence of psychotherapy or counseling was assessed by considering the occurrence of prior psychotherapy or counseling, or that which was received within 30 days of the date of treatment initiation. This was defined by searching for counseling or psychotherapy CPT codes in the 90 days prior to and 30 days following initial bipolar diagnosis among patients who had mental health / substance abuse coverage information. Of the 730 patients, 606 had coverage information available. Patients without mental health / substance abuse coverage

were categorized as "unknown" as their use of counseling or psychotherapy could not be determined. This variable was coded using three disjoint indicators for the receipt of psychotherapy: Psychotherapy Received (yes/no), Psychotherapy Not Received (yes/no), and Psychotherapy Unknown (yes/no). Physician variables were originally defined in five categories: Psychiatry, Primary Care, Other Mental Health (non-Physician), Other Medical Specialist, and Unclassified. However, the provider type variable in the MarketScan dataset is considered to be somewhat unreliable as coding standards differ by each data contributor (MarketScan User Guide). Given this, and the small number of patients in each of the Other Medical Specialists and Unclassified provider categories, the final provider variable was coded as: Psychiatry, Primary Care, Other Mental Health (non-Physician), and Other/Unclassified. Psychiatry was used as the reference category for the statistical models.

In addition to these variables, several categorical variables were also added to the model based on their relevance noted in the literature: the presence of psychosis, sex, and current bipolar I episode type. While the initial model only included an indicator for bipolar I depressive episode type, it was determined that each episode type should be considered. Therefore, episode types were coded as: Mania, Depressive, Mixed, or Generic (non-specific coding of disorder). Generic type was used as the reference category. The revised model consisted of the following:

Revised General Model for Aim 2

Risk of Recommended Drug Use = $\alpha + \beta_1$ (Age) + β_2 (Sex) + β_3 (Insurance Generosity) + β_4 (ADHD)+ β_5 (Other Disruptive Behavioral Disorder) + β_6 (Depressive Disorders) + β_7

(Disease Severity, Number of Diagnoses) + β_8 (Disease Severity, Any Inpatient Days) + β_9 (Disease Severity, Psychosis) + β_{10} (Bipolar I Episode Type) + β_{11} (Psychotherapy or Counseling) + β_{12} (Provider Type) + β_{13} (Region) + β_{14} (Insurance Type) + β_{15} (Year Diagnosed)

Unadjusted estimates of the risk of receipt of guideline recommended care were first generated using PROC GENMOD in SAS 9.1. Categorical variables were assessed using a log link and a binomial distribution within the GENMOD procedure. Continuous variables were assessed using an identity link and a binomial distribution. Within the GENMOD procedure, the link describes the functional relation between the dependent variable and the linear combination of covariates, while the distribution is related to the distribution of the dependent variable. Using an identity link provides estimates of the linear risk, while using a log link provides estimates of the log risk.

Each variable was tested separately to determine the bivariate relationship between each predictor and the outcome, without controlling for other variables. After these relationships were evaluated, the proposed control variables, insurance type and region, were evaluated to determine if they should be added to the model. Neither variable was related to the outcome of guideline recommended care in the bivariate assessment. Additionally, they were not identified as being necessary components to the model based on a review of the literature in the area of quality of care in bipolar disorder. It was therefore determined that they did not add to the explanatory capability of the model, but only decreased the model efficiency. Because of these reasons, these two variables were excluded from the final model.

Finally, a series of interaction terms were added to the model to determine if there was variation based on clinically plausible relationships. For example, age and sex variables were used in interactions with comorbid mental health disorders, type of bipolar episode, and inpatient mental health hospitalizations to determine if there was variation in the influence of these predictors based on a patients' age, sex or both. Such examinations would be able to detect differential use of guidelines for young versus old children with ADHD comorbidity, or males or females with ADHD, for example. After examining interaction terms for the model, it was determined that there was no effect measure modification (interactions were not significant), and thus they added no additional explanatory power to the statistical model. The final model was specified as noted below and hypotheses were restated based on the revised model:

Final Model for Aim 2

Risk of Recommended Drug Use = $\alpha + \beta_1$ (Age) + β_2 (Sex) + β_3 (Insurance Generosity) + β_4 (ADHD)+ β_5 (Other Disruptive Behavioral Disorder) + β_6 (Depressive Disorders) + β_7 (Disease Severity, Number of Diagnoses) + β_8 (Disease Severity, Any Inpatient Days) + β_9 (Disease Severity, Psychosis) + β_{10} (Bipolar I Depressed Episode) + β_{11} (Psychotherapy or Counseling) + β_{12} (Provider Type) + β_{13} (Year Diagnosed)

HYPOTHESIS: Compared with patients with bipolar I disorder who are prescribed guideline recommended first line treatment, those who do not receive the recommended treatments are more likely to:

Predisposing Characteristics

- have a younger age of diagnosis (H_{02a})
- be male (H_{02b})

Enabling Resources

- have more generous insurance benefits (H_{02c}) (only considered for medication users analysis)

Need Characteristics

- have co-morbid mental health conditions (H_{02d})
- have higher levels of disease severity (H_{02e})
- have an initial diagnosis of bipolar I depressed episode (H_{02f})
- have treatment plans that exclude psychotherapy or counseling (H_{02g})

Physician Characteristics

- have received their diagnosis from a provider other than a psychiatrist (H_{02h})

Once the final model was established, a log binomial model was used to determine the effect of each predictor on the likelihood of receiving guideline recommended care, while controlling for the effect of each of the other variables in the model. The log binomial model was selected because it allows for direct estimation of adjusted risk ratios (which are preferred to using odds ratios when outcomes are not rare).[260,261] This model is implemented in PROC GENMOD by using a log link and a binomial distribution to assess the relationship between the predictors and the outcome.

This process was used for three separate definitions of the outcome: (1) explicit definition of guideline recommended care and non-recommended - only medications specifically recommended by guidelines, appropriate pharmacotherapy received; (2) expanded definition of guideline recommended care and non-recommended - any anticonvulsant or antipsychotic monotherapy considered appropriate; (3) guideline recommended and non-recommended, among only patients who received medication - explicit definition for recommended care, exclusion of patients who did not use medications (comparison of appropriate and inappropriate care among medications users).

3.6.3 Aim 3: Determine the factors associated with early treatment regimen changes.

The sample for this proposed analysis will consist of the same sub-cohort as used in aim 2 (described in section 3.6.2). This process measure will use the time from first medication fill (in weeks) to identify children with newly-diagnosed bipolar I disorder who had adequate medication treatment trials versus those that switched or augmented treatment early. Individuals will then be classified as receiving early medication regimen changes if they have initial medication trials that are shorter than the guideline recommended time (between 4 and 8 weeks, depending on the agent used).[17] To reflect recommendations for clinical trial design in the area of pediatric bipolar disorder, the primary analysis will use a six week timeframe to identify early switching. [20] Additionally, a sensitivity analysis will be conducted using the shorter timeframe recommended by guidelines (4 weeks) to determine what degree of switching occurs in the first month.

This aim will utilize two strategies to account for the influence of medication discontinuation. First, analyses will be conducted among only patients who have evidence of

ongoing therapy. In other words, patients who discontinue early (within the first 6 weeks) will be excluded from this analysis. Patients must have at least two claims or a 60 day supply of medications during their first 6 weeks of treatment to be included in this initial analysis. Patients who have early switching or augmenting of treatment will be considered to have received guideline discordant treatment. Those who do not experience early switching or augmenting then are considered to have received guideline concordant treatment. A second analysis will be conducted in which patients who discontinue therapy within the first 6 weeks will be considered to have received guideline discordant treatment. Characteristics of patients in this group (early treatment discontinuers) will be compared to patients who did not discontinue therapy (treatment continuers) and these characteristics will be summarized.

In order to account for medication switches that are made due to problems with tolerability of the medication, switches made during the first three weeks could be considered to be potentially appropriate medication changes.[20, 24] The primary analysis categorized all switches made within the first 6 weeks to be inappropriate switches. Again, only initial medication therapy will be analyzed using this criteria, as evidence from the Treatment of Early Age Mania study indicated that, in the context of second medication trials, there is no longer consensus that eight weeks is a sufficient medication trial.[24] Sensitivity analyses were planned to determine the impact of drug switching over the first three weeks to determine the impact of outcome misclassification on statistically important risk ratio estimates. However, adjusted risk ratio estimates resulted in non-significant effects for all variables, negating the need for this sensitivity analysis.

Patient level and physician level factors that predict guideline recommended treatment trials were then explored. Characteristics of children who receive guideline concordant treatment versus those that receive non-concordant treatment were assessed using a log binomial regression model. Specific variables of interest and their hypothesized relationships are stated below.

HYPOTHESIS: Compared with patients with bipolar I disorder who receive a guideline recommended period of exposure ($\geq$ 6 weeks) before switching drug classes or augmenting treatment, those who do not receive the guideline recommended period of exposure are more likely to:

Predisposing Characteristics

- have a younger age of diagnosis (H_{03a})
- be male (H_{03b})

Enabling Resources

- have less generous insurance benefits (H_{03c})

Need Characteristics

- have co-morbid mental health conditions (H_{03d})
- have higher levels of disease severity (H_{03e})
- have an initial diagnosis of bipolar I depressed episode (H_{02f})
- have treatment plans that exclude psychotherapy or counseling (H_{02g})

Physician Characteristics

- have received their diagnosis from a primary care provider (H_{03h})

- reside in a Metropolitan Statistical Area (H_{03i})

Treatment Characteristics

- be initially prescribed an antidepressant (H_{03j})
- use combination treatments(H_{03k})

The proposed generalized linear model will include each of the predictors noted above, along with control variables for geographic region, patient insurance type, and year of diagnosis.

Initially Proposed Model for Aim 3:

Risk of Early Treatment Regimen Changes $= \alpha + \beta_1$ (Age) + β_2 (Sex) + β_3 (Insurance Generosity) + β_4 (ADHD)+ β_5 (Depressive Disorders) + β_6 (Tic Disorders) + β_7 (Anxiety Disorders) + β_8 (Other Disruptive Disorders) + β_9 (Disease Severity, Number of Diagnoses) + β_{10} (Disease Severity, Any Inpatient Days) + β_{11} (Disease Severity, Psychosis) + β_{12} (Bipolar I Depressed Episode) + β_{13} (Psychotherapy or Counseling) + β_{14} (Primary Care) + β_{15} (Provider Metropolitan Statistical Area Classification) + β_{16} (Antidepressant Use) + β_{17} (Use of Combination Treatments) + β_{18} (Region) + β_{19} (Insurance Type) + β_{20} (Year Diagnosed)

In addition to these specific hypotheses that will be tested, the relationship between drug class prescribed and early regimen changes will be explored, as will the relationship between receiving recommended first line therapy and early treatment regimen changes. These analyses will be exploratory in nature and will focus on hypothesis generation, rather than hypothesis testing.

As mentioned previously, treatment guidelines are not tailored for younger children, thus their treatment may be managed differently than for older children. This may lead to more short-term medication trial periods in younger children since evidence in this group is lacking. Additionally, male sex may also contribute to switching treatments early due to the higher rates of comorbidities and earlier age at onset. Insurance generosity may also be related to switching. For example, if patients are unable to afford their prescription due to benefits that are less generous, they may request a different medication that has better coverage, or a generic of a covered brand.

Comorbid conditions are also likely to complicate the treatment of bipolar disorder and to lead to a lower likelihood of receiving a treatment exposure period that is recommended by guidelines, as treatments for comorbid mental health disorders may be re-introduced prior to the recommended 6-week stabilization period.[17] The presence of psychosis is also associated with worse illness severity and thus is believed to increase the likelihood of early medication changes. Therefore, illness severity is likely to be positively associated with early medication switching. Additionally, initial diagnosis of bipolar I depressive subtype is likely to lead to less stable treatments as this may be an indicator of diagnostic uncertainty since guidelines do not address this particular manifestation of bipolar spectrum disorder. Use of psychotherapy or counseling is also hypothesized to be associated with receipt of adequate initial medication trials as it may be an indicator of increased adherence to published guidelines.

Similar to aim 2, specialists are thought to be more likely to have adequate training to diagnose and treat bipolar disorder in children, and they would likely be more familiar with

expert-consensus guidelines from the field as compared with primary care physicians.[20] Also, as mentioned previously, metropolitan statistical area classifications of the physician's practice or of the patient have previously been associated with guideline use.[258, 259] However, it is also possible that patients in non-MSA regions may have fewer visits to their physicians. This may contribute to non-MSA areas being related to lower switching rates.

Finally, two specific treatment characteristics will be considered in this analysis. These are the use of antidepressants and the use of multiple drug classes from initial treatment. Antidepressant use is believed to lead to drug-induced mania so patients who are prescribed these agents will likely experience medication changes earlier than those who do not receive them. Additionally, the use of multiple drug classes may influence drug regimen changes as there would likely be more potential for drug interactions or side effects.

Three additional factors (insurance type, geographic region, and year of diagnosis) will be used as control variables in the proposed analysis. Hypotheses regarding the association between guideline use and insurance plan type, as well as geographic region will not be tested. Instead, these will be explored to identify if any relationships exist.

3.6.3.1 Aim 3: Statistical Analysis, Variable Selection and Modeling

Similar to aim 2, each of the variables in the initially proposed model was reviewed to determine the extent of missing data for covariates of interest. When including all of the variables from the proposed model above, 96.3% of patients had no missing values after the exclusion of the variable for Metropolitan Statistical Area. After assessing the extent to which missing values were related to the outcome, it was determined that missing data was not related to the outcome ($p = 0.15$) for the relationship between missing values and the type

of care received. Based on this assessment, the remaining missing values were considered to be missing at random.

Variables were tested to determine the appropriate coding for the risk relationship with the outcome of receiving an early medication change. Age was assessed in several ways to determine the true relationship with early medication changes. After modeling the relationship using one year age categories, it was determined that there was an increased risk of early medication changes in the youngest aged children (6-7 year olds) but this estimate was unstable because of the very small number of children within this group (n = 18). It also appeared that the risk went down between the ages of 8 and 11 and increased after that time. After assessing several coding schemes, it was determined that the coding that best reflected the true relationship between age and the outcome was a three-level classification of age (ages 6-9, 10-13, 14-17).

As with aim 2, patients with none/poor insurance generosity were recoded as missing for the analysis, with the resulting variable classified as 0 = fair, 1 = good. The cutoffs were fair (ratio > 0.20 and ≤ 0.80), and good (ratio ≥ 0 and ≤ 0.20), representing the proportion of the total drug costs that were paid by the patient.

Similar to aim 2, comorbidities were grouped as ADHD, other disruptive disorders (conduct disorder, and oppositional defiant disorder), anxiety disorders (separation anxiety, post-traumatic stress disorder, obsessive compulsive disorder, generalized anxiety disorder, Social phobia, and panic disorder), and depressive disorders (major depressive disorder, and dysthymic disorder). There appeared to be no relationship between the occurrence of anxiety disorders and the receipt of recommended care (p = 0.65). Because of the lack of relationship

with the outcome and the small sample sizes for these comorbidities (only 8% had pre-existing anxiety disorders), this category was excluded from the final model. Consistent with Aim 2, both Attention Deficit Hyperactivity Disorder and other disruptive behavioral disorders were included in the final model.

Depressive disorders were common (nearly 26% of patients had a depressive disorder on or before the date of bipolar diagnosis) and appeared to be associated with an increased risk of receiving non-recommended care. This variable was included in the model as depressive disorders (yes/no) with dysthymic disorder and major depressive disorder combined.

Disease severity measures were also assessed. These measures included the number of diagnoses received on or prior to the date of bipolar diagnosis, the occurrence of mental health hospitalizations prior to diagnosis, and psychosis. Number of diagnoses was based on unique diagnoses received during the 6-month pre-diagnosis period. After modeling this variable in multiple ways, it was determined that the relationship between the number of diagnoses and the outcome was flat, no matter how it was modeled (the risk of early medication changes did not vary based on the number of diagnoses). The decision was made to include this variable as a continuous predictor in the final model.

Similar to aim 2, the number inpatient hospitalizations included hospitalizations any time during the study period. Because of the small sample size when including only information for prior hospitalizations, the inpatient mental health visit indicator was constructed using any inpatient visit over the study period. As with aim 2, treatment decisions would have been made without knowledge of future hospitalizations, but these

events may be relevant as children who are hospitalized later may have a more severe presentation of their illness or more difficult treatment courses.

Presence of psychotherapy or counseling was assessed by considering the occurrence of prior psychotherapy or counseling, or that which was received within 30 days of the date of treatment initiation. This was defined by searching for counseling or psychotherapy CPT codes in the 90 days prior to and 30 days following initial bipolar diagnosis among patients who had mental health / substance abuse coverage information. Of the 375 patients included in the primary analysis, 322 had coverage information available. Patients without mental health / substance abuse coverage were categorized as "unknown" as their use of counseling or psychotherapy could not be determined. This variable was coded using three disjoint indicators for the receipt of psychotherapy: Psychotherapy Received (yes/no), Psychotherapy Not Received (yes/no), and Psychotherapy Unknown (yes/no).

Physician variables were originally defined in five categories: Psychiatry, Primary Care, Other Mental Health (non-Physician), Other Medical Specialist, and Unclassified. However, the provider type variable in the MarketScan dataset is considered to be somewhat unreliable as coding standards differ by each data contributor (MarketScan User Guide). Given this, and the small number of patients in each of the Other Medical Specialists and Unclassified provider categories, the final provider variable was coded as: Psychiatry, Primary Care, Other Mental Health (non-Physician), and Other/Unclassified. Psychiatry was used as the reference category for the statistical models.

There were two variables that were unique to the aim 3 analysis (not used in aim 2). These were (1) an initial treatment regimen that included an antidepressant (yes/no), and

initial treatment plans that included combination therapy (yes/no). These variables were included in the final model, and an interaction term was tested to determine if there was risk ratio modification when a patient received both an antidepressant at treatment initiation, and combination therapy.

In addition to these variables, several categorical variables were also added to the model based on their relevance noted in the literature: the presence of psychosis, sex, and current bipolar I episode type. While the initial model only included an indicator for bipolar I depressive episode type, it was determined that each episode type should be considered. Therefore, episode types were coded as: Mania, Depressive, Mixed, or Generic (non-specific coding of disorder). Generic type was used as the reference category. The revised model consisted of the following:

Revised Model for Aim 3:

Risk of Early Treatment Regimen Changes $= \alpha + \beta_1$ (Age - Young, Middle, Old) + β_2 (Sex) + β_3 (Insurance Generosity) + β_4 (ADHD) + β_5 (Other Disruptive Disorders) + β_6 (Depressive Disorders) + β_7 (Disease Severity, Number of Diagnoses) + β_8 (Disease Severity, Any Inpatient Days) + β_9 (Disease Severity, Psychosis) + β_{10} (Bipolar I Episode Type) + β_{11} (Psychotherapy or Counseling) + β_{12} (Provider Type) + β_{13} (Antidepressant Use) + β_{14} (Use of Combination Treatments) + β_{15} (Region) + β_{16} (Insurance Type) + β_{17} (Year Diagnosed)

Unadjusted estimates of the risk of receipt of guideline recommended care were first generated using PROC GENMOD in SAS 9.1. As with aim 2, categorical variables were assessed using a log link and a binomial distribution within the GENMOD procedure.

Continuous variables were assessed using an identity link and a binomial distribution. Each variable was tested separately to determine the bivariate relationship between the each predictor and the outcome, without controlling for other variables.

After these relationships were evaluated, the proposed control variables, insurance type and region, were evaluated to determine if they should be added to the model. Neither variable was related to the outcome of guideline recommended care in the bivariate assessment. Additionally, they were not identified as being necessary components to the model based on a review of the literature in the area of quality of care in bipolar disorder. It was therefore determined that they did not add to the explanatory capability of the model, but only decreased the model efficiency. Because of these reasons, these two variables were excluded from the final model.

Finally, a series of interaction terms were added to the model to determine if there was variation based on clinically plausible relationships. For example, age and sex variables were used in interactions with comorbid mental health disorders, type of bipolar episode, and inpatient mental health hospitalizations to determine if there was variation in the influence of these predictors based on a patients' age, sex or both. After examining interaction terms for the model, only one interaction term was statistically significant - this was the interaction between patient sex and bipolar subtype (specifically, girls with bipolar I manic type). After further inspection, it was determined that this interaction would not be included due to the small number of children within this category (n = 16). Finally, the interaction term between the use of antidepressants at treatment initiation and the use of combination therapies at

initiation was tested. This resulted in a statistically non-significant interaction term ($p = 0.46$) and was therefore not included in the final model.

After each variable was assessed, a final model was tested using the coding strategy identified above. Coding as noted above resulted in a model that did not meet the Hessian Convergence criteria. Therefore, variables were further scrutinized to determine which were unnecessary for the final model or those that could be recoded to allow for model convergence. First, year was removed from the model ($p = 0.65$ in bivariate assessment), as was the total number of diagnoses ($p = 0.34$). Age was included in the final model, but was included as a continuous variable since the model indicated that the three-level categorical variable was problematic. Finally, physician type was re-classified as "mental health professional" (Psychiatrist or other mental health professional) or "non-mental health professional" in order to allow for model convergence. The final model was specified as noted below and hypotheses were restated based on the revised model:

Final Model for Aim 3

Risk of Early Treatment Regimen Changes $= \alpha + \beta_1$ (Age) $+ \beta_2$ (Sex) $+ \beta_3$ (Insurance Generosity) $+ \beta_4$ (ADHD) $+ \beta_5$ (Other Disruptive Disorders) $+ \beta_6$ (Depressive Disorders) $+ \beta_7$ (Disease Severity, Number of Diagnoses) $+ \beta_8$ (Disease Severity, Any Inpatient Days) $+ \beta_9$ (Disease Severity, Psychosis) $+ \beta_{10}$ (Bipolar I Episode Type) $+ \beta_{11}$ (Psychotherapy or Counseling) $+ \beta_{12}$ (Provider Type) $+ \beta_{13}$ (Antidepressant Use) $+ \beta_{14}$ (Use of Combination Treatments)

HYPOTHESIS: Compared with patients with bipolar I disorder who receive a guideline recommended period of exposure ($\geq$ 6 weeks) before switching drug classes or augmenting treatment, those who do not receive the guideline recommended period of exposure are more likely to:

Predisposing Characteristics

- have a younger age of diagnosis (H_{03a})
- be male (H_{03b})

Enabling Resources

- have less generous insurance benefits (H_{03c})

Need Characteristics

- have co-morbid mental health conditions (H_{03d})
- have higher levels of disease severity (H_{03e})
- have an initial diagnosis of bipolar I depressed episode (H_{02f})
- have treatment plans that exclude psychotherapy or counseling (H_{02g})

Physician Characteristics

- have received their diagnosis from a non-mental health provider (H_{03h})

Treatment Characteristics

- be initially prescribed an antidepressant (H_{03j})
- use combination treatments(H_{03k})

Once the final model was established, a log binomial model was used to determine the effect of each predictor on the likelihood of receiving guideline recommended care, while

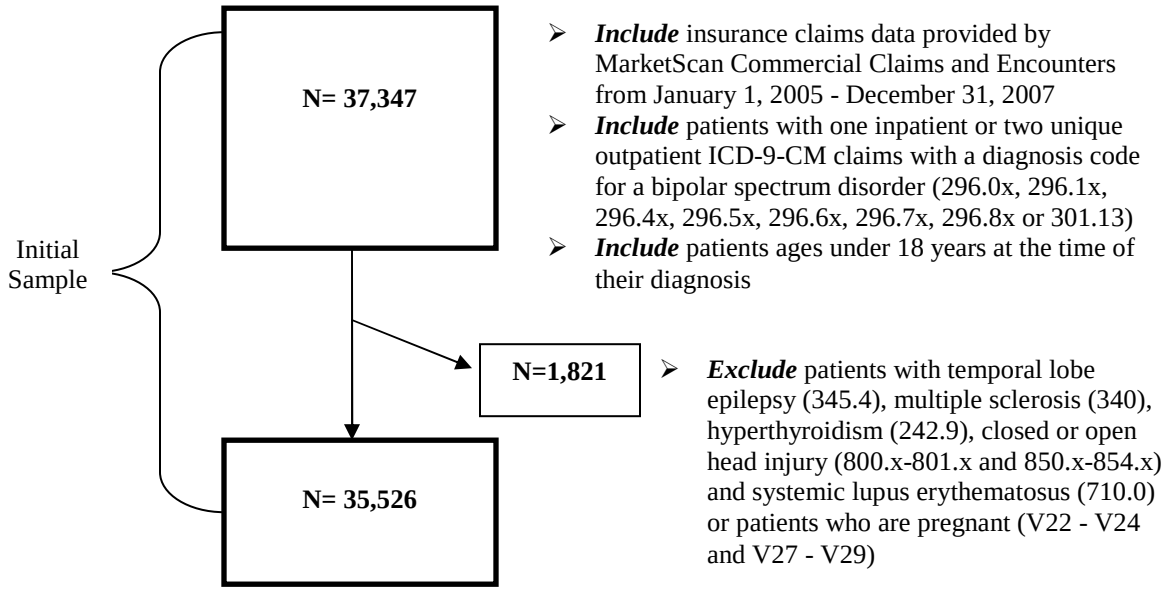
controlling for the effect of each of the other variables in the model. Again, the log binomial model was selected because it allows for direct estimation of adjusted risk ratios (which are preferred to using odds ratios when outcomes are not rare).[260,261] This model is implemented in PROC GENMOD by using a log link and a binomial distribution to assess the relationship between the predictors and the outcome.

This process was used for three separately defined populations: (1) those with changes in the first 6 weeks, among patients with continuous therapy; (2) those with changes in the first 6 weeks, with early discontinuers considered to have received non-recommended care; (3) those with changes in the first 4 weeks, among patients with continuous therapy.

CHAPTER FOUR: RESULTS

Using the MarketScan database from January 1, 2005 to December 31, 2007, there were 35,526 patients who were eligible for inclusion in the initial study sample. Patients were included if they had one inpatient or two unique outpatient claims for a bipolar spectrum disorder, and if they were under 18 years of age at the time of their first diagnosis. Patients with conditions that mimic mania or that complicated the treatment of bipolar disorder were excluded (details regarding specific exclusionary conditions are provided in Figure 4.1 and in Chapter 3).

Figure 4.1 - Inclusion and Exclusion Criteria - Initial Study Sample

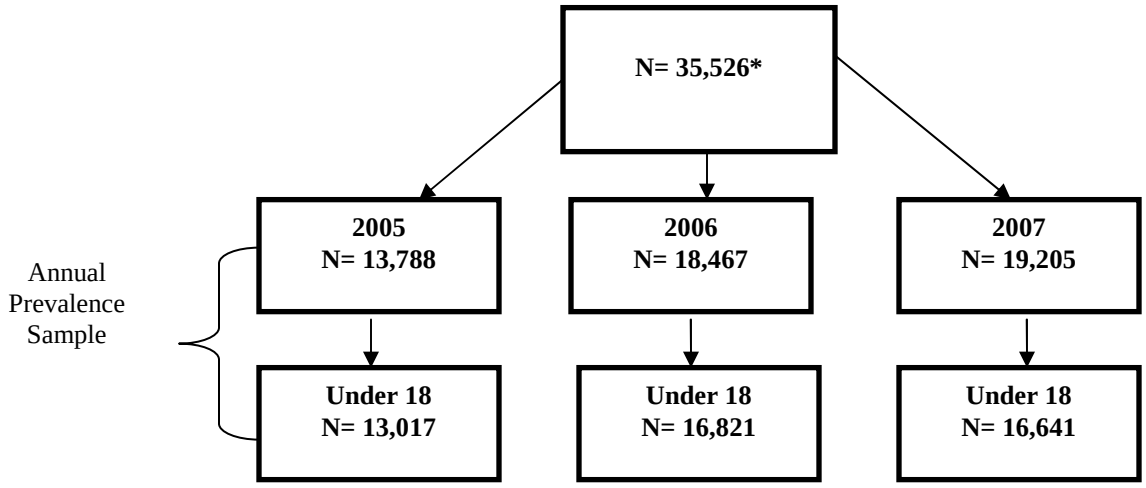


4.1 Aim 1a Results

4.1.1 Aim 1a: Repeated Cross Sectional Design, Prevalence Study

The initial study sample was used as the basis for the repeated cross-sectional prevalence study. For aim 1a patients were classified by the bipolar diagnosis code received at their last bipolar-related visit. Because the original study sample required only that patients be under the age of 18 years at the time of their first recorded diagnosis, there may have been patients in the aim 1a sample who were over the age of 17 years by their last bipolar-related visit. Therefore, the age under 18 age limit was re-applied to the aim 1a sample. This sample was used for the prevalence and demographic analyses related to aim 1a (Figure 4.2).

Figure 4.2 - Inclusion and Exclusion Criteria: Aim 1a Prevalence Study



* Sample sizes across years do not equal the total sample size as patients may contribute to more than one calendar year in the prevalence study.

It is important to note that the study design used in aim 1a allowed patients from the initial sample to be included in multiple years. For example, if a patient had insurance claims

for 2005, 2006, and 2007, they would be counted in each sample. This design then results in three non-independent samples. Therefore, all comparisons for the cross-sectional study design will be made across bipolar subtypes, within each year. Formal comparisons (statistical tests) will not be used to compare across years as this approach would be invalid. Instead, trends over time will be described, but interpreted cautiously.

The annual diagnostic prevalence of any bipolar spectrum disorder was 0.24% in 2005 and increased to 0.26% by 2006. The prevalence remained unchanged from 2006 to 2007. In 2007, there were 16,641 children with at least two outpatient or one inpatient visit for a bipolar spectrum disorder out of the 6.3 million children enrolled in the MarketScan database (Table 4.1). Of patients with a bipolar spectrum disorder, a majority had bipolar disorder unspecified type in each year (49.0%, 2005; 49.9%, 2006; 51.9%, 2007), followed by bipolar I disorder (37.1%, 2005; 36.8%, 2006; 35.3%, 2007), and bipolar II disorder (11%, 2005; 11.4%, 2006; 10.6%, 2007). Cyclothymic disorder was rare in the sample, representing 2.8% or less of the bipolar spectrum disorders in each study year.

Table 4.1 - Annual Treated Prevalence of Bipolar Spectrum Disorders by Year

	2005	2006	2007
	N = 5,462,802	N = 6,372,448	N = 6,309,227
	n (%)	n (%)	n (%)
Prevalence of Any Bipolar Spectrum Disorder	13,017 (0.24)	16,821 (0.26)	16,641 (0.26)
Disorder Subtype at Most Recent Visit			
Bipolar I	4,834 (37.1)	6,194 (36.8)	5,870 (35.3)
Bipolar II	1,446 (11.1)	1,909 (11.4)	1,769 (10.6)
Bipolar Unspecified	6,379 (49.0)	8,388 (49.9)	8,644 (51.9)
Cyclothymic Disorder	358 (2.8)	330 (2.0)	358 (2.2)

N = Total number of children from January 1 - December 31 of each year who are under the age of 18 as of December 31.
n = Total number of children with the specified diagnosis during the period January 1 - December 31 of each year who had at least 1 inpatient or 2 outpatient claims for a bipolar spectrum disorder.
SOURCE: Repeated Cross Sectional Analysis Using Aim 1a Prevalence Study Sample

Patient characteristics and provider characteristics were measured for each study year and are summarized by the patients' bipolar subtype at their last visit (Tables 4.2 - 4.4). Year-to-year changes were small and are noted where statistically important. When comparing within years, patients with bipolar unspecified type were slightly younger, with proportionally more children in younger age groups (both ages 0-6 and ages 7-12) than patients with other bipolar subtypes. Patients with bipolar II disorder were slightly older than those with other disorder subtypes, across all study years. Bipolar I and bipolar unspecified were more common among males, while bipolar II and Cyclothymic disorder were slightly more likely to occur among females (with the exception of 2006, where boys and girls were equally likely to receive a diagnosis of Cyclothymic disorder).

Inpatient mental health days were more common among patients with bipolar I or bipolar unspecified type (approximately 28% experiencing inpatient mental health stays in each group, in each year). Total number of unique diagnoses during the year were highest among patients with bipolar I or bipolar unspecified, in each year, as were the number of comorbid mental health conditions.

Patients with bipolar unspecified type were less likely than patients with other subtypes to have seen a psychiatrist or other mental health professional, and more likely to have seen a primary care physician at their last bipolar-related visit. Patients with bipolar unspecified type were also more likely to be categorized as having received care by an "unclassified" provider. This classification was used when only facility information was available (the actual provider information was not provided). For example, if the provider type was "Acute Care Hospital" or another type of facility, it was impossible to distinguish

the training of the provider who treated the child. Psychiatrists were the predominant provider across all bipolar spectrum disorders and years.

Table 4.2 - Patient and Physician Characteristics by Bipolar Subtype: Aim 1a - Study Year 2005

	Bipolar I	Bipolar II	Bipolar NOS	Cyclothymia*
	N = 4,834	N = 1,446	N = 6,379	N = 358
Patient Characteristics				
Age - Mean (SD)	13.8 (3.0)	14.1 (2.9)	13.4 (3.2)	13.8 (2.8)
0 - 6 Years	125 (2.6)	27 (1.9)	220 (3.5)	7 (2.0)
7 - 12 Years	1,193 (24.7)	318 (22.0)	1,916 (30.0)	88 (24.6)
13 - 17 Years	3,516 (72.7)	1,101 (76.1)	4,243 (66.5)	263 (73.5)
Sex - N (%) Female	2,182 (45.1)	742 (51.3)	2,672 (41.9)	189 (52.8)
Comorbid Mental Health Conditions	1.3 (1.3)	1.2 (1.2)	1.3 (1.3)	1.2 (1.2)
Total Number of Unique Diagnoses in Year	9.8 (7.0)	9.5 (6.8)	9.9 (7.0)	8.7 (5.9)
Any Inpatient Mental Health Visits	1,383 (28.6)	344 (23.8)	1,778 (27.9)	61 (17.0)
Physician Characteristics				
Psychiatrist	1,989 (41.1)	581 (40.2)	2,134 (33.5)	143 (39.9)
Other Mental Health Professional	960 (19.9)	335 (23.2)	799 (12.5)	85 (23.7)
Primary Care Physician / M.D.	655 (13.5)	152 (10.5)	1,199 (18.8)	36 (10.1)
Other Medical Specialist	123 (2.5)	37 (2.6)	217 (3.4)	7 (2.0)
Unclassified	779 (16.1)	246 (17.0)	1,635 (25.6)	57 (15.9)
Missing	328 (6.8)	95 (6.6)	395 (6.2)	30 (8.4)
MSA Status	3,620 (97.4)	1,131 (98.4)	4,331 (95.8)	274 (98.6)

SOURCE: Repeated Cross Sectional Analysis Using Aim 1a Prevalence Study Sample
* Cyclothymia is considered to be the mildest disorder on the bipolar spectrum.

Table 4.3 - Patient and Physician Characteristics by Bipolar Subtype: Aim 1a - Study Year 2006

	Bipolar I	Bipolar II	Bipolar NOS	Cyclothymia*
	N = 6,194	N = 1,909	N = 8,388	N = 330
Patient Characteristics				
Age - Mean (SD)	13.8 (3.0)	14.4 (2.7)	13.4 (3.2)	13.8 (2.9)
0 - 6 Years	148 (2.4)	25 (1.3)	306 (3.7)	8 (2.4)
7 - 12 Years	1,536 (24.8)	378 (19.8)	2,480 (29.6)	86 (26.1)
13 - 17 Years	4,510 (72.8)	1,506 (78.9)	5,602 (66.8)	236 (71.5)
Sex - N (%) Female	2,766 (44.7)	1,004 (52.6)	3,456 (41.2)	173 (52.4)
Comorbid Mental Health Conditions	1.3 (1.3)	1.2 (1.2)	1.4 (1.3)	1.1 (1.2)
Total Number of Unique Diagnoses in Year	10.0 (7.4)	9.8 (7.2)	10.1 (7.1)	8.8 (6.3)
Any Inpatient Mental Health Visits	1,808 (29.2)	420 (22.0)	2,379 (28.4)	50 (15.2)
Physician Characteristics				
Psychiatrist	2,531 (40.9)	737 (38.6)	2,771 (33.0)	143 (43.3)
Other Mental Health Professional	1,051 (17.0)	444 (23.3)	976 (11.6)	70 (21.2)
Primary Care Physician / M.D.	1,104 (17.8)	264 (13.8)	1,748 (20.8)	47 (14.2)
Other Medical Specialist	100 (1.6)	26 (1.4)	269 (3.2)	6 (1.8)
Unclassified	895 (14.4)	281 (14.7)	1,663 (19.8)	40 (12.1)
Missing	513 (8.3)	157 (8.2)	961 (11.5)	24 (7.3)
MSA Status	4,606 (97.1)	1,513 (98.1)	5,821 (94.6)	270 (98.5)

SOURCE: Repeated Cross Sectional Analysis Using Aim 1a Prevalence Study Sample
* Cyclothymia is considered to be the mildest disorder on the bipolar spectrum.

Table 4.4 - Patient and Physician Characteristics by Bipolar Subtype: Aim 1a - Study Year 2007

	Bipolar I	Bipolar II	Bipolar NOS	Cyclothymia*
	N = 5,870	N = 1,769	N = 8,644	N = 358
Patient Characteristics				
Age - Mean (SD)	13.9 (2.9)	14.3 (2.8)	13.6 (3.1)	13.9 (3.0)
0 - 6 Years	135 (2.3)	32 (1.8)	242 (2.8)	8 (2.2)
7 - 12 Years	1,404 (23.9)	338 (19.1)	2,451 (28.4)	86 (24.0)
13 - 17 Years	4,331 (73.8)	1,399 (79.1)	5,951 (68.9)	265 (73.7)
Sex - N (%) Female	2,649 (45.1)	918 (51.9)	3,711 (42.9)	173 (48.3)
Comorbid Mental Health Conditions	1.4 (1.3)	1.2 (1.3)	1.5 (1.4)	1.3 (1.3)
Total Number of Unique Diagnoses in Year	10.6 (7.8)	10.4 (7.8)	11.0 (8.1)	9.7 (6.7)
Any Inpatient Mental Health Visits	1,692 (28.8)	375 (21.2)	2,554 (29.6)	82 (22.9)
Physician Characteristics				
Psychiatrist	2,416 (41.2)	646 (36.6)	2,791 (32.3)	150 (41.9)
Other Mental Health Professional	1,052 (17.9)	423 (23.9)	1,015 (11.7)	75 (20.9)
Primary Care Physician / M.D.	1,053 (17.9)	271 (15.3)	1,952 (22.6)	44 (12.3)
Other Medical Specialist	106 (1.8)	28 (1.6)	251 (2.9)	4 (1.1)
Unclassified	741 (12.6)	259 (14.6)	1,591 (18.4)	38 (10.6)
Missing	502 (8.6)	142 (8.0)	1,044 (12.1)	47 (13.1)
MSA Status	4,468 (97.4)	1,385 (98.4)	5,842 (94.3)	279 (98.6)

SOURCE: Repeated Cross Sectional Analysis Using Aim 1a Prevalence Study Sample
* Cyclothymia is considered to be the mildest disorder on the bipolar spectrum.

Comorbid mental health conditions were common across all bipolar spectrum disorders and all years (Tables 4.5 - 4.7). Approximately 30% of children with each bipolar subtype also had co-morbid diagnoses of attention deficit hyperactivity disorder (ADHD) during the year. Children with bipolar unspecified type were more likely to have comorbid ADHD as compared with children with bipolar I disorder. Over the three years, co-morbidity with ADHD appeared to increase in children with bipolar unspecified (33.5% comorbidity in 2005; 37.3% in 2006; 39.3% in 2007). Conduct disorder and Oppositional Defiant disorder were also present in approximately 8 - 14% of children, depending on bipolar subtype and year. Conduct disorder was most common among children with bipolar unspecified and least common among children with bipolar II diagnoses.

Anxiety disorders were uncommon, as were tic disorders, schizophrenia and pervasive developmental disorders. Depressive disorders, however, were common and occurred in at least 20% of patients, regardless of bipolar subtype or year. Major depressive disorder was present in approximately 25% of patients with bipolar I diagnoses in each study year. Major depressive disorder comorbidity was least common among patients with bipolar unspecified, although comorbidity was still high (19.7% - 21.1%, depending on the year studied).

Table 4.5 - Comorbid Mental Health Conditions by Bipolar Subtype: Aim 1a - Study Year 2005

	Bipolar I	Bipolar II	Bipolar NOS	Cyclothymia*
	N = 4,834	N = 1,446	N = 6,379	N = 358
Mental Health Diagnosis				
Disruptive Behavior Disorders				
Attention Deficit Hyperactivity Disorder	1,411 (29.2)	436 (30.2)	2,137 (33.5)	100 (27.9)
Conduct Disorder	506 (10.5)	121 (8.4)	796 (12.5)	35 (9.8)
Oppositional Defiant Disorder	442 (9.1)	129 (8.9)	750 (11.8)	28 (7.8)
Anxiety Disorders				
Separation Anxiety Disorder	21 (0.43)	2 (0.14)	30 (0.47)	0 (0.0)
Post-Traumatic Stress Disorder	163 (3.4)	46 (3.2)	257 (4.0)	15 (4.2)
Obsessive Compulsive Disorder	109 (2.3)	44 (3.0)	149 (2.3)	11 (3.1)
Generalized Anxiety Disorder	156 (3.2)	48 (3.3)	177 (2.8)	15 (4.2)
Social Phobia	19 (0.39)	7 (0.48)	16 (0.25)	2 (0.56)
Panic Disorder	44 (0.91)	18 (1.2)	52 (0.82)	3 (0.84)
Depressive Disorders				
Major Depressive Disorder	1,289 (26.7)	364 (25.2)	1,343 (21.1)	81 (22.6)
Dysthymic Disorder	258 (5.3)	95 (6.6)	312 (4.9)	28 (7.8)
Tic Disorders				
Tourette's Syndrome or Other Tic Disorder	26 (0.54)	11 (0.76)	65 (1.0)	1 (0.28)
Other Mental Health Disorders				
Schizophrenia	139 (2.9)	23 (1.6)	137 (2.2)	3 (0.84)
Autism or Other Pervasive Developmental Disorder	175 (3.6)	39 (2.7)	264 (4.1)	5 (1.4)
Mental Retardation	21 (0.43)	5 (0.35)	43 (0.67)	2 (0.56)
Other Mood Disorders	716 (14.8)	186 (12.9)	1,133 (17.8)	39 (10.9)
Substance Abuse / Use				
Alcohol Dependence	57 (1.2)	14 (0.97)	68 (1.1)	9 (2.5)
Drug Dependence	177 (3.7)	50 (3.5)	240 (3.8)	14 (3.9)
Drug or Alcohol Use	399 (8.3)	119 (8.2)	523 (8.2)	25 (7.0)

SOURCE: Repeated Cross Sectional Analysis Using Aim 1a Prevalence Study Sample
* Cyclothymia is considered to be the mildest disorder on the bipolar spectrum.

Table 4.6 - Comorbid Mental Health Conditions by Bipolar Subtype: Aim 1a - Study Year 2006

	Bipolar I	Bipolar II	Bipolar NOS	Cyclothymia*
	N = 6,194	N = 1,909	N = 8,388	N = 330
Mental Health Diagnosis				
Disruptive Behavior Disorders				
Attention Deficit Hyperactivity Disorder	1,935 (31.2)	567 (29.7)	3,127 (37.3)	100 (30.3)
Conduct Disorder	653 (10.5)	142 (7.4)	1,075 (12.8)	25 (7.6)
Oppositional Defiant Disorder	678 (10.9)	165 (8.6)	1,070 (12.8)	37 (11.2)
Anxiety Disorders				
Separation Anxiety Disorder	22 (0.36)	7 (0.37)	47 (0.56)	2 (0.61)
Post-Traumatic Stress Disorder	232 (3.8)	53 (2.8)	316 (3.8)	11 (3.3)
Obsessive Compulsive Disorder	152 (2.5)	53 (2.8)	216 (2.6)	9 (2.7)
Generalized Anxiety Disorder	221 (3.6)	86 (4.5)	296 (3.5)	14 (4.2)
Social Phobia	35 (0.57)	12 (0.63)	34 (0.41)	3 (0.91)
Panic Disorder	68 (1.1)	28 (1.5)	87 (1.0)	5 (1.5)
Depressive Disorders				
Major Depressive Disorder	1,563 (25.2)	470 (24.6)	1,649 (19.7)	65 (19.7)
Dysthymic Disorder	295 (4.8)	111 (5.8)	332 (4.0)	19 (5.8)
Tic Disorders				
Tourette's Syndrome or Other Tic Disorder	54 (0.87)	6 (0.31)	79 (0.93)	3 (0.91)
Other Mental Health Disorders				
Schizophrenia	177 (2.9)	23 (1.2)	163 (1.9)	1 (0.30)
Autism or Other Pervasive Developmental Disorder	227 (3.7)	57 (3.0)	365 (4.4)	6 (1.8)
Mental Retardation	28 (0.45)	8 (0.42)	53 (0.63)	0 (0.0)
Other Mood Disorders	961 (15.5)	312 (16.3)	1,665 (19.9)	38 (11.5)
Substance Abuse / Use				
Alcohol Dependence	59 (0.95)	17 (0.89)	88 (1.1)	3 (0.91)
Drug Dependence	224 (3.6)	59 (3.1)	307 (3.7)	8 (2.4)
Drug or Alcohol Use	528 (8.5)	132 (6.9)	706 (8.4)	16 (4.9)

SOURCE: Repeated Cross Sectional Analysis Using Aim 1a Prevalence Study Sample
* Cyclothymia is considered to be the mildest disorder on the bipolar spectrum.

Table 4.7 - Comorbid Mental Health Conditions by Bipolar Subtype: Aim 1a - Study Year 2007

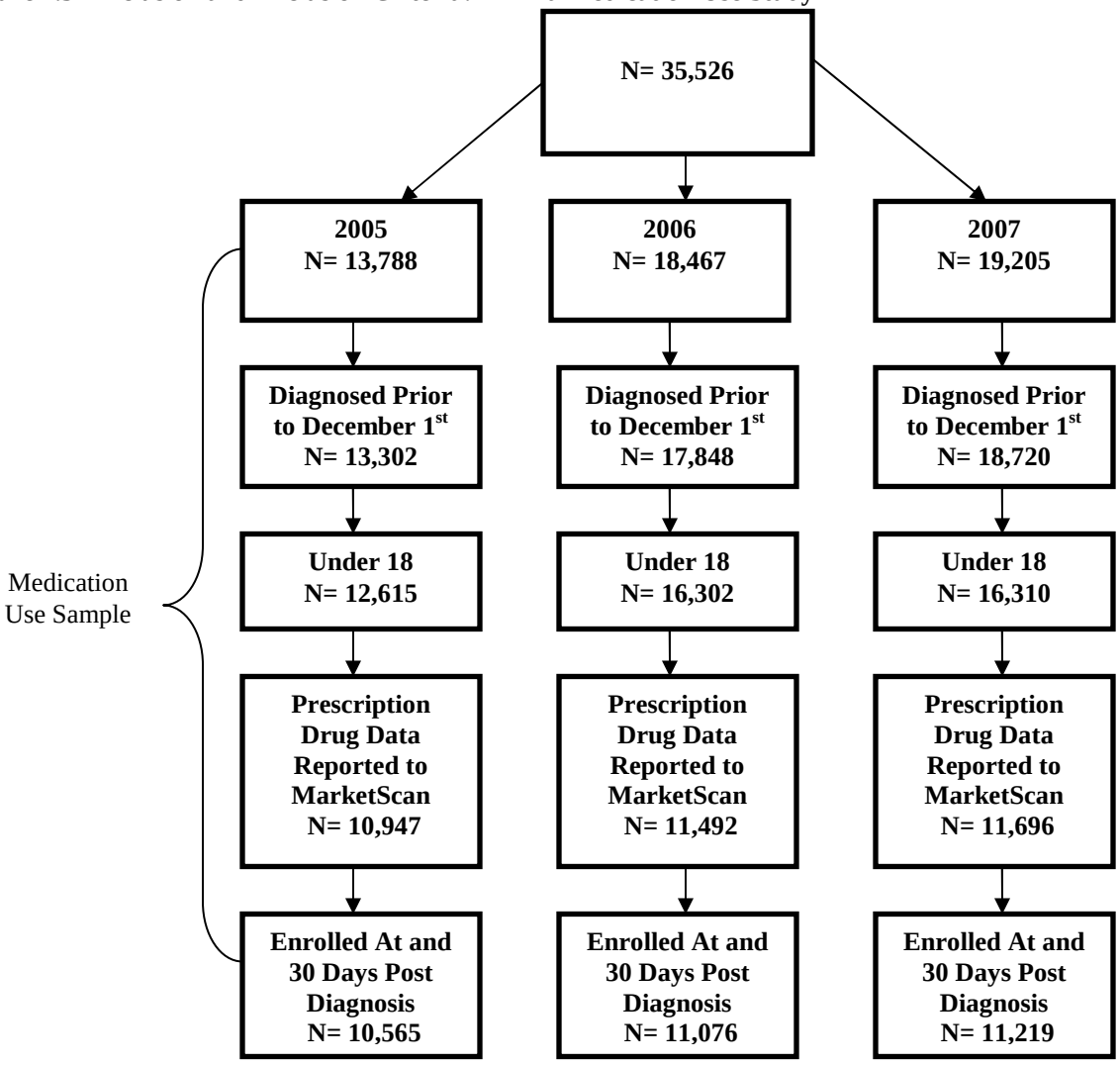
	Bipolar I	Bipolar II	Bipolar NOS	Cyclothymia*
	N = 5,870	N = 1,769	N = 8,644	N = 358
Mental Health Diagnosis				
Disruptive Behavior Disorders				
Attention Deficit Hyperactivity Disorder	1,978 (33.7)	527 (29.8)	3,394 (39.3)	104 (29.1)
Conduct Disorder	647 (11.0)	141 (8.0)	1,114 (12.9)	31 (8.7)
Oppositional Defiant Disorder	641 (10.9)	178 (10.1)	1,198 (13.9)	48 (13.4)
Anxiety Disorders				
Separation Anxiety Disorder	15 (0.26)	4 (0.23)	29 (0.34)	2 (0.56)
Post-Traumatic Stress Disorder	214 (3.7)	75 (4.2)	397 (4.6)	15 (4.2)
Obsessive Compulsive Disorder	156 (2.7)	59 (3.3)	246 (2.9)	17 (4.8)
Generalized Anxiety Disorder	249 (4.2)	83 (4.7)	354 (4.1)	22 (6.2)
Social Phobia	30 (0.51)	15 (0.85)	45 (0.52)	4 (1.1)
Panic Disorder	73 (1.2)	20 (1.1)	114 (1.3)	3 (0.84)
Depressive Disorders				
Major Depressive Disorder	1,438 (24.5)	384 (21.7)	1,711 (19.8)	71 (19.8)
Dysthymic Disorder	263 (4.5)	86 (4.9)	380 (4.4)	20 (5.6)
Tic Disorders				
Tourette's Syndrome or Other Tic Disorder	56 (0.95)	18 (1.0)	103 (1.2)	6 (1.7)
Other Mental Health Disorders				
Schizophrenia	147 (2.5)	26 (1.5)	192 (2.2)	1 (0.28)
Autism or Other Pervasive Developmental Disorder	256 (4.4)	57 (3.2)	486 (5.6)	9 (2.5)
Mental Retardation	34 (0.58)	9 (0.51)	55 (0.64)	0 (0.0)
Other Mood Disorders	1,036 (17.7)	284 (16.1)	1,881 (21.8)	59 (16.5)
Substance Abuse / Use				
Alcohol Dependence	57 (0.97)	21 (1.2)	109 (1.3)	4 (1.1)
Drug Dependence	217 (3.7)	62 (3.5)	362 (4.2)	9 (2.5)
Drug or Alcohol Use	516 (8.8)	143 (8.1)	893 (10.3)	25 (7.0)

SOURCE: Repeated Cross Sectional Analysis Using Aim 1a Prevalence Study Sample
* Cyclothymia is considered to be the mildest disorder on the bipolar spectrum.

4.1.2 Aim1a: Repeated cross-sectional design, medication use study

The prevalence study samples for each year were used as the starting point for the medication use study for aim 1a, with additional criteria applied to accurately identify the prescription drug eligible sample (Figure 4.3). In order to identify medication us in the 30 days following the patient's most recent diagnosis, the index diagnosis was modified by only considering diagnoses that took place prior to December 1st in each study year. Again, the age less than 18 restriction was applied to this study sample. Additionally, only patients who had drug data reported by their insurance provider to MarketScan were included. This did not require that patients have medication use, but ensured that if they did use medications they would be recorded in the dataset. Patients were also required to be enrolled in their insurance plan at the time of their diagnosis and up to 30 days after their diagnosis in order to correctly classify their use or non-use of medications. As with the prevalence study sample, patients in the overall sample could contribute to multiple years. Again, this does not allow for comparisons across years, rather comparisons within years and across subtypes will be made. Year-to-year changes are assessed by describing trends, but not via statistical testing.

Figure 4.3 - Inclusion and Exclusion Criteria: Aim 1a Medication Use Study



When comparing patients who were included in the medication use cohort to those in the overall cohort, there were few differences in patient characteristics over the study period. Patients in the medication use population (Table 4.8) were slightly more likely to have an inpatient mental health visit during the year (OR: 1.05, 95% CI: 1.01, 1.09) and slightly less likely to have comorbid mental health conditions (OR: 0.97, 95% CI: 0.96, 0.99) than those in the prevalence study sample, although differences were small.

Table 4.8 - Patient and Physician Characteristics by Bipolar Subtype, Study Years 2005 - 2007: Aim 1a Medication Use Population

	Bipolar I	Bipolar II	Bipolar NOS	Cyclothymia*
		Study Year 2005		
Patient Characteristics	N = 3,983	N = 1,193	N = 5,106	N = 283
Age - Mean (SD)	13.8 (3.0)	14.1 (2.9)	13.3 (3.2)	13.8 (2.8)
Sex - N (%) Female	1,792 (45.0)	596 (50.0)	2,113 (41.4)	154 (54.4)
Comorbid Mental Health Conditions	1.3 (1.3)	1.2 (1.2)	1.3 (1.3)	1.2 (1.2)
Number of Unique Diagnoses in Year	9.8 (7.0)	9.4 (6.5)	9.8 (6.8)	8.6 (5.9)
Any Inpatient Mental Health Visits	1,151 (28.9)	285 (23.9)	1,431 (28.0)	51 (18.0)
Physician Specialty				
Psychiatrist	1,681 (42.2)	494 (41.4)	1,782 (34.9)	121 (42.8)
Other Mental Health Professional	799 (20.1)	268 (22.5)	683 (13.4)	69 (24.4)
Primary Care Physician / M.D.	538 (13.5)	132 (11.1)	918 (18.0)	28 (9.9)
Other Medical Specialist	104 (2.6)	27 (2.3)	171 (3.3)	4 (1.4)
Unclassified	654 (16.4)	210 (17.6)	1,305 (25.6)	44 (15.5)
Missing	207 (5.2)	62 (5.2)	247 (4.8)	17 (6.0)
		Study Year 2006		
Patient Characteristics	N = 4,132	N = 1,339	N = 5,362	N = 243
Age - Mean (SD)	13.9 (2.9)	14.3 (2.8)	13.4 (3.2)	13.9 (2.9)
Sex - N (%) Female	1,845 (44.7)	672 (50.2)	2,237 (41.7)	133 (54.7)
Comorbid Mental Health Conditions	1.2 (1.3)	1.1 (1.1)	1.3 (1.3)	1.1 (1.1)
Number of Unique Diagnoses in Year	9.6 (6.6)	9.4 (6.7)	9.7 (6.6)	8.6 (5.8)
Any Inpatient Mental Health Visits	1,198 (29.0)	273 (20.4)	1,485 (27.7)	40 (16.5)
Physician Specialty				
Psychiatrist	1,876 (45.4)	606 (45.3)	2,046 (38.2)	120 (49.4)
Other Mental Health	818 (19.8)	331 (24.7)	730 (13.6)	57 (23.5)
Primary Care / M.D.	589 (14.3)	133 (9.9)	1,002 (18.7)	28 (11.5)
Other Medical Specialist	70 (1.7)	11 (0.80)	151 (2.8)	3 (1.2)
Unclassified	676 (16.4)	216 (16.1)	1,268 (23.6)	31 (12.8)
Missing	103 (2.5)	42 (3.1)	165 (3.1)	4 (1.6)
		Study Year 2007		
Patient Characteristics	N = 4,035	N = 1,261	N = 5,665	N = 258
Age - Mean (SD)	13.9 (2.9)	14.4 (2.8)	13.6 (3.1)	13.8 (2.9)
Sex - N (%) Female	1,847 (45.8)	673 (53.4)	2,460 (43.4)	119 (46.1)
Comorbid Mental Health Conditions	1.3 (1.3)	1.2 (1.2)	1.4 (1.4)	1.2 (1.3)
Number of Unique Diagnoses in Year	10.3 (7.5)	9.9 (7.1)	10.4 (7.4)	9.6 (6.5)
Any Inpatient Mental Health	1,163 (28.8)	265 (21.0)	1,608 (28.4)	63 (24.4)
Physician Specialty				
Psychiatrist	1,859 (46.1)	531 (42.1)	2,133 (37.7)	119 (46.1)
Other Mental Health	813 (20.1)	346 (27.4)	786 (13.9)	62 (24.0)
Primary Care / M.D.	612 (15.2)	130 (10.3)	1,182 (20.9)	32 (12.4)
Other Medical Specialist	66 (1.6)	17 (1.3)	137 (2.4)	1 (0.40)
Unclassified	589 (14.6)	211 (16.7)	1,266 (22.3)	35 (13.6)
Missing	96 (2.4)	26 (2.1)	161 (2.8)	9 (3.5)

SOURCE: Repeated Cross Sectional Analysis Using Aim 1a Medication Use Study Sample
* Cyclothymia is considered to be the mildest disorder on the bipolar spectrum.

Information regarding drug class use within the 30 days following a patients' last bipolar diagnosis is provided in Table 4.9. In each year, approximately 35% of patients did not use any psychotropic medications in the 30 day period following their last diagnosis. Twenty-five percent used one psychotropic medication, 23% used two medications and nearly 16% used 3 or more medications. Antipsychotic monotherapy increased over each study year by approximately 2% (from 11.2% in 2005 to 14.1% in 2007). Mood stabilizer (either lithium or anticonvulsants) and antipsychotic combination therapy was common, with over 12% of patients in each year using combinations of these two classes. Additionally, these classes were paired with antidepressants in over 6% of patients and with stimulants for nearly 5% of patients.

When looking at the number of prescriptions filled (Table 4.10), atypical antipsychotic medications were the most commonly filled drug class, followed by anticonvulsants, antidepressants, stimulants, lithium, and typical antipsychotics. Among the anticonvulsant medications filled, divalproex was the most frequently used, representing over 35% of the anticonvulsant medications filled in each year. Lamotrigine use increased over the study period (from 21.8% in 2005 to 33.2% in 2007), while oxcarbazepine use decreased (from 25.2% in 2005 to 17.2% in 2007). Three agents dominated use in the atypical antipsychotic class - aripiprazole, risperidone and quetiapine. Each agent represented over 25% of the antipsychotic medications filled in each year.

Antidepressants represented over 20% of the prescribed psychotropic medications in each study year. Tricyclics, tetracyclics, and MAOIs were rarely used. Selective serotonin reuptake inhibitors (SSRIs) were the most heavily prescribed type of antidepressants

(representing nearly 60% of total antidepressant use in each year). Of the SSRIs, escitalopram, fluoxetine and sertraline were the most commonly filled medications, with fluoxetine and sertraline each contributing over 27% of SSRI use in each year. Among the category of other antidepressants, bupropion was prescribed nearly twice as often as any other agent in the category.

Table 4.9 - Annual Drug Class Use Among Medication Users within 30 Days of Most Recent Bipolar Diagnosis: Aim 1a, 2005 - 2007

	Year of Diagnosis		
	2005	**2006**	**2007**
	N = 10,565	N = 11,076	N = 11,219
Total Number of Psychotropic Medications Used in 30 Days Following the Last Diagnosis			
None	3,751 (35.5)	3,852 (34.8)	4,154 (37.0)
1	2,633 (24.9)	2,870 (25.9)	2,905 (25.9)
2	2,443 (23.1)	2,589 (23.4)	2,473 (22.0)
3	1,252 (11.9)	1,313 (11.9)	1,267 (11.3)
4 +	486 (4.6)	452 (4.1)	420 (3.7)
Medication Use Among Users	N = 6,814	N = 7,224	N = 7,056
Single Class Use			
Lithium	178 (2.6)	163 (2.3)	149 (2.1)
> 1 Lithium Fill - n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Anticonvulsants	802 (11.8)	775 (10.7)	777 (11.0)
> 1 Anticonvulsant Fill - n (%)	36 (4.5)	40 (5.2)	38 (4.9)
Antipsychotics	760 (11.2)	914 (12.7)	997 (14.1)
> 1 Antipsychotic Fill - n (%)	42 (5.5)	61 (6.7)	58 (5.8)
Antidepressants	601 (8.8)	642 (8.9)	598 (8.5)
> 1 Antidepressant Fill - n (%)	62 (10.3)	48 (7.5)	66 (11.0)
Stimulants	438 (6.4)	535 (7.4)	550 (7.8)
> 1 Stimulant Fill - n (%)	6 (1.4)	10 (1.9)	4 (7.3)
Combination Therapy			
Two Classes			
Lithium + Anticonvulsant	56 (0.80)	52 (0.70)	39 (0.60)
Mood Stabilizer and Antipsychotic	855 (12.5)	871 (12.1)	880 (12.5)
Mood Stabilizer and Antidepressant	577 (8.5)	552 (7.6)	468 (6.6)
Mood Stabilizer and Stimulant	362 (5.3)	385 (5.3)	327 (4.6)
Antipsychotic and Antidepressant	444 (6.5)	478 (6.6)	494 (7.0)
Antipsychotic and Stimulant	299 (4.4)	388 (5.4)	410 (5.8)
Antidepressant and Stimulant	157 (2.3)	140 (1.9)	153 (2.2)
Three or More Classes			
Mood Stabilizer, Antipsychotic and Antidepressant	446 (6.5)	441 (6.1)	429 (6.1)
Mood Stabilizer, Antipsychotic and Stimulant	352 (5.2)	391 (5.4)	332 (4.7)
Mood Stabilizer, Antidepressant and Stimulant	155 (2.3)	162 (2.2)	148 (2.1)
Antipsychotic, Antidepressant and Stimulant	152 (2.2)	177 (2.5)	173 (2.5)
Mood Stabilizer, Antipsychotic, Antidepressant and Stimulant	180 (2.6)	158 (2.2)	141 (2.0)

SOURCE: Repeated Cross Sectional Analysis Using Aim 1a Medication Use Study Sample
Atypical and typical antipsychotic agents were combined as typicals represented only 1.2% of this category.
Mood stabilizers include lithium or any anticonvulsant agent. Lithium represented 24% of the mood stabilizers.
Calculations for more than one class level fill exclude multiple fills of the same agent on the same service date.

Table 4.10 - Psychotropic Drug Use by Drug Prescribed 30 Days After Most Recent Bipolar Diagnosis: Aim 1a, 2005 - 2007

	Year of Diagnosis		
	2005	2006	2007
Total Medications Filled*	**N = 15,660**	**N = 16,272**	**N = 15,524**
Lithium	*1,145 (7.3)*	*1,026 (6.3)*	*928(6.0)*
Anticonvulsants	*4,130 (26.4)*	*4,188 (25.7)*	*3,926 (25.3)*
Carbamazepine	158 (3.8)	149 (3.6)	170 (4.3)
Divalproex	1,638 (39.7)	1,574 (37.6)	1,404 (35.8)
Gabapentin	68 (1.6)	67 (1.6)	70 (1.8)
Lamotrigine	900 (21.8)	1,171 (28.0)	1,304 (33.2)
Levetiracetam	12 (0.29)	15 (0.36)	16 (0.41)
Oxcarbazepine	1,039 (25.2)	885 (21.1)	677 (17.2)
Tiagabine	23 (0.56)	13 (0.31)	7 (0.18)
Topiramate	294 (7.1)	315 (7.5)	279 (7.1)
Atypical Antipsychotics	*4,273 (27.3)*	*4,709(28.9)*	*4,677 (30.1)*
Aripiprazole	1,209 (28.3)	1,530 (32.5)	1,499 (32.1)
Clozapine	2 (0.05)	10 (0.21)	10 (0.21)
Olanzapine	281 (6.6)	254 (5.4)	211 (4.5)
Paliperidone	0 (0.0)	0 (0.0)	92 (2.0)
Quetiapine	1,114 (26.1)	1,271 (27.0)	1,303 (27.9)
Risperidone	1,322 (30.9)	1,245 (26.4)	1,188 (25.4)
Ziprasidone	343 (8.0)	398 (8.4)	376 (8.0)
Typical Antipsychotics	*47 (0.30)*	*47(0.29)*	*37 (0.24)*
Antidepressants	*3,576 (22.8)*	*3,536 (21.7)*	*3,309 (21.3)*
Tricyclics	N = 79	N = 111	N = 82
Tetracyclics	N = 0	N = 0	N = 0
Selective Serotonin Reuptake Inhibitors	N = 2,133	N = 2,107	N = 1,998
Citalopram	187 (8.8)	195 (9.2)	205 (10.3)
Escitalopram	527 (24.7)	487 (23.1)	440 (22.0)
Fluoxetine	597 (28.0)	580 (27.5)	562 (28.1)
Fluvoxamine	49 (2.3)	44 (2.1)	59 (3.0)
Paroxetine	151 (7.1)	142 (6.7)	112 (5.6)
Sertraline	622 (29.2)	658 (31.2)	618 (30.9)
Monoamine Oxidase Inhibitors	N = 1	N = 0	N = 0
Other Antidepressants	N = 1,364	N = 1,318	N = 1,229
Bupropion	712 (52.2)	667 (50.6)	530 (43.1)
Duloxetine	57 (4.2)	104 (7.9)	112 (9.1)
Mirtazapine	87 (6.4)	110 (8.3)	89 (7.2)
Nefazodone	4 (0.29)	1 (0.08)	0 (0.0)
Trazodone	289 (21.2)	302 (22.9)	319 (26.0)
Venlafaxine	215 (15.8)	133 (10.1)	180 (14.6)
Stimulants	*2,536 (16.2)*	*2,766 (17.0)*	*2,657 (17.1)*

N = Total number of prescriptions obtained. Patients may have more than one prescription therefore the total N is not equal to the study sample size.
*Prescription fills are standardized to a 30-day supply.
SOURCE: Repeated Cross Sectional Analysis Using Aim 1a Medication Use Study Sample.

Table 4.11 provides information on medication class use by bipolar subtype and year. Lithium use and antidepressant use decreased over the study period for each bipolar subtype. Use of this agent varied by study year and bipolar subtype. For example, in 2005, patients with bipolar unspecified type were more likely to receive lithium than patients with bipolar I disorder (RR: 1.22, 95%CI: 1.07, 1.39). However, this relationship was not evident in subsequent years. Use of anticonvulsants, similarly, differed slightly by year and bipolar subtype, but differences were minor (indicating similar risks of use, regardless of bipolar subtype or over time).

When comparing antipsychotic use over time and by disorder, patients with bipolar II disorder or Cyclothymic disorder were less likely to receive second generation antipsychotics, as compared with patients with bipolar I disorder, over the study period. Patients with bipolar unspecified type were slightly more likely to use second generation antipsychotics (as compared with patients with bipolar I disorder) for the study years 2006 and 2007, but the differences were small. Use of typical antipsychotic agents (first generation antipsychotics) was rare among all bipolar subtypes and years.

Across the three study years, antidepressant use was lower among patients with bipolar unspecified type (as compared with patients with bipolar I disorder). Finally, stimulant use appeared to be stable across bipolar subtype and year, with the exception of an increase in stimulant use among patients with bipolar unspecified type in 2006 (RR: 1.11, 95% CI: 1.03, 1.20).

Table 4.11 - Medication Class Use by Bipolar Subtype - Drug Prescribed 30 Days After Most Recent Bipolar Diagnosis: Aim 1a, 2005 - 2007

	Bipolar Subtype		
	Bipolar I		
	2005	2006	2007
Medication Class Use	N = 3,983	N = 4,132	N = 4,035
Lithium	327 (8.2)	314 (7.6)	299 (7.4)
Anticonvulsants	1,208 (30.3)	1,282 (31.0)	1,164 (28.8)
Atypical Antipsychotics	1,324 (33.2)	1,422 (34.4)	1,348 (33.4)
Typical Antipsychotics	16 (0.40)	15 (0.40)	19 (0.50)
Antidepressants	1,078 (27.1)	1,109 (26.8)	1,009 (25.0)
Stimulants	795 (20.0)	836 (20.2)	790 (19.6)
	Bipolar II		
	2005	2006	2007
Medication Class Use	N = 1,193	N = 1,339	N = 1,261
Lithium	93 (7.8)	87 (6.5)	72 (5.7)
Anticonvulsants	400 (33.5)	397 (29.6)	341 (27.0)
Atypical Antipsychotics	334 (28.0)	359 (26.8)	359 (28.5)
Typical Antipsychotics	4 (0.30)	4 (0.30)	4 (0.30)
Antidepressants	319 (26.7)	328 (24.5)	283 (22.4)
Stimulants	248 (20.8)	245 (18.3)	248 (19.7)
	Bipolar Unspecified		
	2005	2006	2007
Medication Class Use	N = 5,106	N = 5,362	N = 5,665
Lithium	510 (10.0)	458 (8.5)	406 (7.2)
Anticonvulsants	1,584 (31.0)	1,567 (29.2)	1,531 (27.0)
Atypical Antipsychotics	1,760 (34.5)	1,953 (36.4)	2,056 (36.3)
Typical Antipsychotics	24 (0.50)	24 (0.40)	24 (0.40)
Antidepressants	1,250 (24.5)	1,252 (23.3)	1,256 (22.2)
Stimulants	1,005 (19.7)	1,208 (22.5)	1,155 (20.4)
	Cyclothymic Disorder*		
	2005	2006	2007
Medication Class Use	N = 283	N = 243	N = 258
Lithium	22 (7.8)	18 (7.4)	15 (5.8)
Anticonvulsants	82 (29.0)	67 (27.6)	84 (32.6)
Atypical Antipsychotics	48 (17.0)	59 (24.3)	63 (24.4)
Typical Antipsychotics	0 (0.0)	0 (0.0)	0 (0.0)
Antidepressants	65 (23.0)	61 (25.1)	56 (21.7)
Stimulants	47 (16.6)	47 (19.3)	41 (15.9)

SOURCE: Repeated Cross Sectional Analysis Using Aim 1a Medication Use Study Sample
* Cyclothymia is considered to be the mildest disorder on the bipolar spectrum.

Patient treatments received, including use of counseling or electroconvulsive therapy, are summarized by bipolar subtype and year in Table 4.12. There was little difference in the use of pharmacotherapy by year or bipolar subtype. Patients with bipolar II disorder were slightly more likely to receive pharmacotherapy in 2005 and slightly less likely to receive pharmacotherapy in 2006, as compared with patients with bipolar I disorder. These differences were very small, with confidence intervals very close to 1.0. Overall, a majority of patients received pharmacotherapy (over 63% of patients with bipolar I disorder, 60% of patients with bipolar II, 63% with bipolar unspecified, and 57% with Cyclothymic disorder) in each year.

A majority of patients received psychotherapy or counseling visits, across all bipolar subtypes, over the study period. Patients with bipolar II disorder were slightly more likely than patients with bipolar I disorder to receive counseling or psychotherapy over the study period. Over each year, patients with bipolar unspecified type were less likely to receive counseling or psychotherapy than patients with bipolar I disorder. In addition, patients with bipolar unspecified who received counseling had fewer visits as compared with patients with bipolar I who received counseling.

Table 4.12 - Summary of Treatments Received by Bipolar Subtype: Aim 1a, 2005 - 2007

	Bipolar Subtype		
	Bipolar I		
	2005	2006	2007
Pharmacotherapy*	N = 3,983	N = 4,132	N = 4,035
Yes	2,538 (63.7)	2,701 (65.4)	2,553 (63.3)
No	1,445 (36.3)	1,431 (34.6)	1,482 (36.7)
Psychotherapy	N = 3,000	N = 3,226	N = 2,960
Any Use - n (%)	2,722 (90.7)	2,901 (89.9)	2,680 (90.5)
Num. Visits - Median (IQR)	12.1 (13)	8 (13)	8 (13)
Electroconvulsive Therapy*			
Any Use - n (%)	1 (0.03)	0 (0.0)	1 (0.03)
	Bipolar II		
Pharmacotherapy*	N = 1,193	N = 1,339	N = 1,261
Yes	801 (67.1)	821 (61.3)	759 (60.2)
No	392 (32.9)	518 (38.7)	502 (39.8)
Psychotherapy	N = 911	N = 1,065	N = 966
Any Use - n (%)	858 (94.2)	991 (93.1)	900 (93.2)
Num. Visits - Median (IQR)	9 (12)	9 (13)	8 (12)
Electroconvulsive Therapy*			
Any Use - n (%)	1 (0.11)	0 (0.0)	2 (0.21)
	Bipolar Unspecified		
Pharmacotherapy*	N = 5,106	N = 5,362	N = 5,665
Yes	3,313 (64.9)	3,549 (66.2)	3,593 (63.4)
No	1,793 (35.1)	1,813 (33.8)	2,072 (36.6)
Psychotherapy	N = 3,708	N = 4,103	N = 4,066
Any Use - n (%)	3,200 (86.3)	3,515 (85.7)	3,406 (83.8)
Num. Visits - Median (IQR)	8 (12)	8 (12)	8 (12)
Electroconvulsive Therapy*			
Any Use - n (%)	0 (0.0)	1 (0.02)	1 (0.02)
	Cyclothymic Disorder**		
Pharmacotherapy*	N = 283	N = 243	N = 258
Yes	162 (57.2)	153 (63.0)	160 (62.0)
No	121 (42.8)	90 (37.0)	98 (38.0)
Psychotherapy	N = 214	N = 189	N = 192
Any Use - n (%)	200 (93.5)	180 (95.2)	180 (93.8)
Num. Visits - Median (IQR)	6 (9)	7 (10)	7.5 (10)
Electroconvulsive Therapy*			
Any Use - n (%)	0 (0.0)	0 (0.0)	0 (0.0)

* Sample size for Pharmacotherapy cohort = Medication Use Cohort. Sample size for psychotherapy and ECT use is based on patients who had mental health / substance abuse coverage available.
* *Cyclothymia is considered to be the mildest disorder on the bipolar spectrum.

4.1.3 Aim 1a: Repeated cross-sectional design, age related comparisons of demographic and treatment characteristics

Patient demographic and treatment characteristics were next assessed for children by age group. Comparisons were made between patients who were under the age of 10 years at the time of their diagnosis (Ages 0 - 9) and those who were 10 years and older (Ages 10 - 17). Because year-to-year changes in patient demographic characteristics were uncommon, only patient characteristics for 2007 are presented (Table 4.13). For children with each bipolar subtype, the proportion of females who received the diagnosis was higher among older children as compared with younger children. The risk ratios for female gender by age group were 1.56 (95%CI: 1.38, 1.77, for bipolar I), 2.14 (95% CI: 1.61, 2.85, for bipolar II), 1.61 (95% CI: 1.45, 1.77, for bipolar unspecified), and 1.80 (95% CI: 1.08, 3.00, for Cyclothymic disorder). Younger children were similar to older children in the number of comorbid mental health conditions identified within each bipolar subtype. However, for patients with bipolar I, bipolar II or bipolar unspecified, older children were more likely to have a higher number of total diagnoses in the year [RD: 2.44, 95%CI: 1.79, 3.08, for bipolar I disorder; RD: 1.85, 95% CI: 0.52, 3.18, bipolar II disorder; RD: 2.04, 95%CI: 1.53, 2.55, bipolar unspecified]. Additionally, older children with bipolar I, bipolar II or bipolar unspecified were more likely to have inpatient mental health visits during the year [RR: 1.76, 95%CI: 1.47, 2.10 for bipolar I disorder; 2.89, 95%CI: 1.63, 5.13 for bipolar II disorder; and 1.52, 95%CI: 1.32, 1.74 for bipolar disorder unspecified type]. Finally, when comparing within bipolar subtype, there were no differences in the types of providers seen by children in younger versus older age groups.

Table 4.13 - Patient and Physician Characteristics by Bipolar Subtype and Age Group: Aim 1a Prevalence Sample - Study Year 2007

	Bipolar I		Bipolar II		Bipolar NOS		Cyclothymia*	
	Age 0 - 9	Age 10 - 17	Age 0 - 9	Age 10 - 17	Age 0 - 9	Age 10 - 17	Age 0 - 9	Age 10 - 17
	N = 617	N = 5,253	N = 142	N = 1,627	N = 1,119	N = 7,525	N = 39	N = 319
Patient Characteristics								
Age - Mean (SD)	7.6 (1.5)	14.6 (2.1)	7.5 (1.7)	14.9 (1.9)	7.6 (1.4)	14.5 (2.1)	7.5 (1.4)	14.7 (2.1)
Sex - N (%) Female	185 (30.0)	2,464 (46.9)	36 (25.3)	882 (54.2)	314 (28.1)	3,397 (45.1)	11 (28.2)	162 (50.8)
Comorbid Mental Health Conditions	1.3 (1.2)	1.4 (1.4)	1.2 (1.1)	1.2 (1.3)	1.5 (1.3)	1.5 (1.4)	1.5 (1.0)	1.2 (1.3)
Number of Unique Diagnoses	8.4 (5.7)	10.8 (7.9)	8.7 (6.1)	10.6 (7.9)	9.2 (6.4)	11.2 (8.3)	9.2 (5.2)	9.8 (6.9)
Any Inpatient Mental Health Visits	106 (17.2)	1,586 (30.2)	11 (7.7)	364 (22.4)	216 (19.3)	2,338 (31.1)	8 (20.5)	74 (23.2)
Physician Specialty								
Psychiatrist	269 (43.6)	2,147 (40.9)	53 (37.3)	593 (36.4)	370 (33.1)	2,421 (32.2)	17 (43.6)	133 (41.7)
Other Mental Health	104 (16.9)	948 (18.0)	31 (21.8)	392 (24.1)	137 (12.2)	878 (11.7)	4 (10.3)	71 (22.3)
Primary Care / M.D.	93 (15.1)	960 (18.3)	16 (11.3)	255 (15.7)	259 (23.1)	1,693 (22.5)	5 (12.8)	39 (12.2)
Other Medical Specialist	8 (1.3)	98 (1.9)	5 (3.5)	23 (1.4)	34 (3.0)	217 (2.9)	0 (0.0)	4 (1.3)
Unclassified	84 (13.6)	657 (12.5)	23 (16.2)	236 (14.5)	192 (17.2)	1,399 (18.6)	6 (15.4)	32 (10.0)
Missing	59 (9.6)	443 (8.4)	14 (9.9)	128 (7.9)	127 (11.3)	917 (12.2)	7 (17.9)	40 (12.5)

SOURCE: Repeated Cross Sectional Analysis Using Aim 1a Prevalence Study Sample

* Cyclothymia is considered to be the mildest disorder on the bipolar spectrum.

When comparing comorbid mental health conditions by age group (Tables 4.14 - 4.16), older patients were much less likely to have comorbid Attention Deficit Hyperactivity Disorder (ADHD) than younger patients among those with bipolar I, bipolar II or bipolar unspecified disorders. In 2007, the risk ratio for having comorbid ADHD was 0.61 (95%CI: 0.59, 0.66, for bipolar I), 0.56 (95%CI: 0.47, 0.67, for bipolar II), and 0.62 (95%CI: 0.60, 0.67, for bipolar unspecified). However, older patients with bipolar I, bipolar II or bipolar unspecified disorders were much more likely to have a comorbid diagnosis of major depressive disorder. The risk ratio of having comorbid diagnoses of major depressive disorder were 2.70 (95% CI: 2.11, 3.44, for bipolar I), 4.10 (95%CI: 2.08, 8.09, for bipolar II), and 2.71 (95%CI: 2.21, 3.32, for bipolar unspecified).

There were no differences by age group for the occurrence of oppositional defiant disorders among children with bipolar I disorder and bipolar II disorders; however, older children with bipolar unspecified type were less likely to be diagnosed with oppositional defiant disorder as compared with younger children (2007 RR: 0.73, 95%CI: 0.64, 0.84). Children with Cyclothymic disorder were equally likely to be diagnosed with oppositional defiant disorder, regardless of age, in 2005 and 2006. However, in 2007, it appeared that younger children were more likely to be diagnosed with this disorder than older children (2007 RR: 0.41, 95%CI: 0.23, 0.74). Similarly, conduct disorder appeared to be most common in younger children with bipolar unspecified type. In this group, in 2007, the risk ratio for conduct disorder comorbidity was 0.77 (95% CI: 0.67, 0.90).

Table4.14 - Comorbid Mental Health Conditions by Bipolar Subtype and Age Group: Aim 1a - Study Year 2005

	Bipolar I		Bipolar II		Bipolar NOS		Cyclothymia	
	Age 0 - 9	Age 10 - 17	Age 0 - 9	Age 10 - 17	Age 0 - 9	Age 10 - 17	Age 0 - 9	Age 10 - 17
Mental Health Diagnosis	N = 544	N = 4,290	N = 139	N = 1,307	N = 916	N = 5,463	N = 32	N = 326
Disruptive Behavior Disorders								
Attention Deficit Hyperactivity Disorder	246 (45.2)	1,165 (27.2)	64 (46.0)	372 (28.5)	456 (49.8)	1,681 (30.8)	10 (31.3)	90 (27.6)
Conduct Disorder	64 (11.8)	442 (10.3)	14 (10.1)	107 (8.2)	138 (15.1)	658 (12.0)	6 (18.8)	29 (8.9)
Oppositional Defiant Disorder	52 (9.6)	390 (9.1)	11 (7.9)	118 (9.0)	134 (14.6)	616 (11.3)	1 (3.1)	27 (8.3)
Anxiety Disorders								
Separation Anxiety Disorder	5 (0.92)	16 (0.37)	0 (0.0)	2 (0.15)	12 (1.3)	18 (0.33)	0 (0.0)	0 (0.0)
Post-Traumatic Stress Disorder	17 (3.1)	146 (3.4)	6 (4.3)	40 (3.1)	29 (3.2)	228 (4.2)	2 (6.3)	13 (4.0)
Obsessive Compulsive Disorder	19 (3.5)	90 (2.1)	4 (2.9)	40 (3.1)	24 (2.6)	125 (2.3)	1 (3.1)	10 (3.1)
Generalized Anxiety Disorder	26 (4.8)	130 (3.0)	3 (2.2)	45 (3.4)	25 (2.7)	152 (2.8)	2 (6.3)	13 (4.0)
Social Phobia	3 (0.55)	16 (0.37)	0 (0.0)	7 (0.54)	2 (0.22)	14 (0.26)	0 (0.0)	2 (0.61)
Panic Disorder	1 (0.18)	43 (1.0)	0 (0.0)	18 (1.4)	3 (0.33)	49 (0.90)	0 (0.0)	3 (0.92)
Depressive Disorders								
Major Depressive Disorder	45 (8.3)	1,244 (29.0)	11 (7.9)	353 (27.0)	83 (9.1)	1,260 (23.1)	0 (0.0)	81 (24.9)
Dysthymic Disorder	10 (1.8)	248 (5.8)	5 (3.6)	90 (6.9)	21 (2.3)	291 (5.3)	2 (6.3)	26 (8.0)
Tic Disorders								
Tourette's Syndrome or Other Tic Disorder	6 (1.1)	20 (0.47)	2 (1.4)	9 (0.69)	13 (1.4)	52 (0.95)	0 (0.0)	1 (0.31)
Other Mental Health Disorders								
Schizophrenia	5 (0.92)	134 (3.1)	1 (0.72)	22 (1.7)	7 (0.76)	130 (2.4)	0 (0.0)	3 (0.92)
Autism or Other Pervasive Developmental Disorders	43 (7.9)	132 (3.1)	12 (8.6)	27 (2.1)	67 (7.3)	197 (3.6)	0 (0.0)	6 (1.5)
Mental Retardation	1 (0.18)	18 (0.42)	0 (0.0)	5 (0.38)	7 (0.76)	36 (0.66)	0 (0.0)	2 (0.61)
Other Mood Disorders	94 (17.3)	622 (14.5)	20 (14.4)	166 (12.7)	139 (15.2)	994 (18.2)	2 (6.3)	37 (11.4)
Substance Abuse / Use								
Alcohol Dependence	1 (0.18)	56 (1.3)	0 (0.0)	14 (1.1)	1 (0.11)	67 (1.2)	0 (0.0)	9 (2.8)
Drug Dependence	0 (0.0)	177 (4.1)	0 (0.0)	50 (3.8)	2 (0.22)	238 (4.4)	0 (0.0)	14 (4.3)
Drug or Alcohol Use	3 (0.55)	396 (9.2)	0 (0.0)	119 (9.1)	1 (0.11)	522 (9.6)	0 (0.0)	25 (7.7)

SOURCE: Repeated Cross Sectional Analysis Using Aim 1a Prevalence Study Sample

* Cyclothymia is considered to be the mildest disorder on the bipolar spectrum.

Table4.15 - Comorbid Mental Health Conditions by Bipolar Subtype and Age Group: Aim 1a - Study Year 2006

	Bipolar I		Bipolar II		Bipolar NOS		Cyclothymia*	
	Age 0 - 9	Age 10 - 17	Age 0 - 9	Age 10 - 17	Age 0 - 9	Age 10 - 17	Age 0 - 9	Age 10 - 17
Mental Health Diagnosis	N = 687	N = 5,507	N = 151	N = 1,758	N = 1,201	N = 7,187	N = 31	N = 299
Disruptive Behavior Disorders								
Attention Deficit Hyperactivity Disorder	358 (52.1)	1,577 (28.6)	79 (52.3)	488 (27.8)	643 (53.5)	2,484 (34.6)	12 (38.7)	88 (29.4)
Conduct Disorder	97 (14.1)	556 (10.1)	18 (11.9)	124 (7.1)	214 (17.8)	861 (12.0)	7 (22.6)	18 (6.0)
Oppositional Defiant Disorder	86 (12.5)	592 (10.8)	19 (12.6)	146 (8.3)	194 (16.2)	876 (12.2)	5 (16.1)	32 (10.7)
Anxiety Disorders								
Separation Anxiety Disorder	4 (0.58)	18 (0.33)	2 (1.3)	5 (0.28)	18 (1.5)	29 (0.40)	0 (0.0)	2 (0.67)
Post-Traumatic Stress Disorder	20 (2.9)	212 (3.9)	4 (2.7)	49 (2.8)	41 (3.4)	275 (3.8)	2 (6.5)	9 (3.0)
Obsessive Compulsive Disorder	20 (2.9)	132 (2.4)	7 (4.6)	46 (2.6)	40 (3.3)	176 (2.5)	1 (3.2)	8 (2.7)
Generalized Anxiety Disorder	21 (3.1)	200 (3.6)	8 (5.3)	78 (4.4)	50 (4.2)	246 (3.4)	1 (3.2)	13 (4.4)
Social Phobia	1 (0.15)	34 (0.62)	0 (0.0)	12 (0.68)	1 (0.08)	33 (0.46)	0 (0.0)	3 (1.0)
Panic Disorder	1 (0.15)	67 (1.2)	2 (1.3)	26 (1.5)	5 (0.42)	82 (1.1)	0 (0.0)	5 (1.7)
Depressive Disorders								
Major Depressive Disorder	57 (8.3)	1,506 (27.4)	13 (8.6)	457 (26.0)	87 (7.2)	1,562 (21.7)	1 (3.2)	64 (21.4)
Dysthymic Disorder	15 (2.2)	280 (5.1)	1 (0.66)	110 (6.3)	18 (1.5)	314 (4.4)	0 (0.0)	19 (6.4)
Tic Disorders								
Tourette's Syndrome or Other Tic Disorder	8 (1.2)	46 (0.84)	3 (2.0)	3 (0.17)	18 (1.5)	60 (0.83)	2 (6.5)	1 (0.33)
Other Mental Health Disorders								
Schizophrenia	10 (1.5)	167 (3.0)	0 (0.0)	23 (1.3)	10 (0.83)	153 (2.1)	0 (0.0)	1 (0.33)
Autism or Other Pervasive Developmental Disorders	39 (5.7)	188 (3.4)	14 (9.3)	43 (2.5)	97 (8.1)	268 (3.7)	1 (3.2)	5 (1.7)
Mental Retardation	2 (0.29)	26 (0.47)	2 (1.3)	6 (0.34)	9 (0.75)	44 (0.61)	0 (0.0)	0 (0.0)
Other Mood Disorders	104 (15.1)	857 (15.6)	28 (18.5)	284 (16.2)	270 (22.5)	1,395 (19.4)	3 (9.7)	35 (11.7)
Substance Abuse / Use								
Alcohol Dependence	0 (0.0)	59 (1.1)	0 (0.0)	17 (0.97)	0 (0.0)	88 (1.2)	0 (0.0)	3 (1.0)
Drug Dependence	1 (0.15)	223 (4.1)	0 (0.0)	59 (3.4)	0 (0.0)	307 (4.3)	0 (0.0)	8 (2.7)
Drug or Alcohol Use	3 (0.44)	525 (9.5)	0 (0.0)	132 (7.5)	2 (0.17)	704 (9.8)	0 (0.0)	16 (5.4)

SOURCE: Repeated Cross Sectional Analysis Using Aim 1a Prevalence Study Sample

* Cyclothymia is considered to be the mildest disorder on the bipolar spectrum.

Table 4.16 - Comorbid Mental Health Conditions by Bipolar Subtype and Age Group: Aim 1a - Study Year 2007

	Bipolar I		Bipolar II		Bipolar NOS		Cyclothymia*	
	Age 0 - 9	Age 10 - 17	Age 0 - 9	Age 10 - 17	Age 0 - 9	Age 10 - 17	Age 0 - 9	Age 10 - 17
Mental Health Diagnosis	N = 617	N = 5,253	N = 142	N = 1,627	N = 1,119	N = 7,525	N = 39	N = 319
Disruptive Behavior Disorders								
Attention Deficit Hyperactivity Disorder	320 (51.9)	1,658 (31.6)	71 (50.0)	456 (28.0)	646 (57.7)	2,748 (36.5)	22 (56.4)	82 (25.7)
Conduct Disorder	89 (14.4)	558 (10.6)	13 (9.1)	128 (7.9)	179 (16.0)	935 (12.4)	6 (15.4)	25 (7.8)
Oppositional Defiant Disorder	72 (11.7)	569 (10.8)	15 (10.6)	163 (10.0)	202 (18.1)	996 (13.2)	11 (28.2)	37 (11.6)
Anxiety Disorders								
Separation Anxiety Disorder	8 (1.3)	7 (0.13)	1 (0.70)	3 (0.18)	13 (1.2)	16 (0.21)	1 (2.6)	1 (0.31)
Post-Traumatic Stress Disorder	24 (3.9)	190 (3.6)	6 (4.2)	69 (4.2)	46 (4.1)	351 (4.7)	2 (5.1)	13 (4.1)
Obsessive Compulsive Disorder	16 (2.6)	140 (2.7)	6 (4.2)	53 (3.3)	30 (2.7)	216 (2.9)	0 (0.0)	17 (5.3)
Generalized Anxiety Disorder	26 (4.2)	223 (4.3)	9 (6.3)	74 (4.6)	50 (4.5)	304 (4.0)	2 (5.1)	20 (6.3)
Social Phobia	0 (0.0)	30 (0.57)	1 (0.70)	14 (0.86)	5 (0.45)	40 (0.53)	0 (0.0)	4 (1.3)
Panic Disorder	2 (0.32)	71 (1.4)	1 (0.70)	19 (1.2)	6 (0.54)	108 (1.4)	0 (0.0)	3 (0.94)
Depressive Disorders								
Major Depressive Disorder	60 (9.7)	1,378 (26.2)	8 (5.6)	376 (23.1)	89 (8.0)	1,622 (21.6)	3 (7.7)	68 (21.3)
Dysthymic Disorder	5 (0.81)	258 (4.9)	4 (2.8)	82 (5.0)	21 (1.9)	359 (4.8)	2 (5.1)	18 (5.6)
Tic Disorders								
Tourette's Syndrome or Other Tic Disorder	4 (0.65)	52 (0.99)	5 (3.5)	13 (0.80)	15 (1.3)	88 (1.2)	1 (2.6)	5 (1.6)
Other Mental Health Disorders								
Schizophrenia	3 (0.49)	144 (2.7)	2 (1.4)	24 (1.5)	9 (0.80)	183 (2.4)	0 (0.0)	1 (0.31)
Autism or Other Pervasive Developmental Disorders	46 (7.5)	210 (4.0)	10 (7.0)	47 (2.9)	121 (10.8)	365 (4.9)	3 (7.7)	6 (1.9)
Mental Retardation	1 (0.16)	33 (0.63)	1 (0.70)	8 (0.49)	5 (0.45)	50 (0.66)	0 (0.0)	0 (0.0)
Other Mood Disorders	101 (16.4)	935 (17.8)	22 (15.5)	262 (16.1)	252 (22.5)	1,629 (21.7)	6 (15.4)	53 (16.6)
Substance Abuse / Use								
Alcohol Dependence	0 (0.0)	57 (1.1)	0 (0.0)	21 (1.3)	1 (0.09)	108 (1.4)	0 (0.0)	4 (1.3)
Drug Dependence	0 (0.0)	217 (4.1)	0 (0.0)	62 (3.8)	1 (0.09)	361 (4.8)	0 (0.0)	9 (2.8)
Drug or Alcohol Use	3 (0.49)	513 (9.8)	0 (0.0)	143 (8.8)	1 (0.09)	892 (11.9)	0 (0.0)	25 (7.8)

SOURCE: Repeated Cross Sectional Analysis Using Aim 1a Prevalence Study Sample

* Cyclothymia is considered to be the mildest disorder on the bipolar spectrum.

As with patient characteristics in the prevalence study sample, the characteristics for patients in the medication use sample did not vary significantly over the study period. Therefore, only estimates from 2007 are provided (Table 4.17). Results between the overall patient characteristics and those for patients included in the medication use study were similar. As with the overall sample, there were smaller proportions of females in the younger age groups, for each diagnostic subtype. Additionally, there were lower inpatient mental health visits for younger age groups for all subtypes, with the exception of Cyclothymic disorder. Young children with bipolar I or bipolar unspecified diagnoses had fewer diagnoses during the year, RD: 2.43 (95%CI: 1.67, 3.18) for bipolar I, RD: 2.12 (95%CI: 1.54, 2.69) for bipolar unspecified. Finally, there were no differences in the type of provider seen by younger children and older children within each bipolar subtype.

Table 4.17 - Patient and Physician Characteristics by Bipolar Subtype and Age Group: Aim 1a Medication Use Population - Study Year 2007

	Bipolar I		Bipolar II		Bipolar NOS		Cyclothymia*	
	Age 0 - 9	Age 10 - 17	Age 0 - 9	Age 10 - 17	Age 0 - 9	Age 10 - 17	Age 0 - 9	Age 10 - 17
	N = 420	N = 3,615	N = 101	N = 1,160	N = 731	N = 4,934	N = 28	N = 230
Patient Characteristics								
Age - Mean (SD)	7.6 (1.5)	14.6 (2.1)	7.4 (1.6)	15.0 (1.9)	7.6 (1.4)	14.5 (2.1)	7.8 (1.1)	14.5 (2.2)
Sex - N (%) Female	124 (29.5)	1,723 (47.7)	25 (24.7)	648 (55.9)	205 (28.0)	2,255 (45.7)	7 (25.0)	112 (48.7)
Comorbid Mental Health Conditions	1.2 (1.2)	1.3 (1.3)	1.2 (1.1)	1.1 (1.2)	1.4 (1.2)	1.4 (1.4)	1.5 (1.1)	1.2 (1.3)
Number of Unique Diagnoses	8.1 (5.3)	10.5 (7.7)	8.4 (6.3)	10.1 (7.1)	8.6 (5.7)	10.7 (7.6)	8.9 (5.6)	9.7 (6.6)
Any Inpatient Mental Health Visits	67 (15.9)	1,096 (30.3)	10 (9.9)	255 (22.0)	126 (17.2)	1,482 (30.0)	7 (25.0)	56 (24.3)
Physician Specialty								
Psychiatrist	202 (48.1)	1,657 (45.8)	38 (37.6)	493 (42.5)	281 (38.4)	1,852 (37.5)	13 (46.4)	106 (46.1)
Other Mental Health	84 (20.0)	729 (20.2)	30 (29.7)	316 (27.2)	105 (14.4)	681 (13.8)	4 (14.3)	58 (25.2)
Primary Care / M.D.	61 (14.5)	551 (15.2)	6 (5.9)	124 (10.7)	150 (20.5)	1,032 (20.9)	3 (10.7)	29 (12.6)
Other Medical Specialist	3 (0.70)	63 (1.7)	4 (4.0)	13 (1.1)	23 (3.1)	114 (2.3)	0 (0.0)	1 (0.40)
Unclassified	63 (15.0)	526 (14.6)	22 (21.8)	189 (16.3)	146 (20.0)	1,120 (22.7)	6 (21.4)	29 (12.6)
Missing	7 (1.7)	89 (2.5)	1 (1.0)	25 (2.2)	26 (3.6)	135 (2.7)	2 (7.1)	7 (3.0)

SOURCE: Repeated Cross Sectional Analysis Using Aim 1a Medication Use Study Sample

* Cyclothymia is considered to be the mildest disorder on the bipolar spectrum.

When looking at drug class use by age group (Table 4.18), there are few differences in the number of psychotropic medication taken in the 30 days following the child's most recent diagnosis. In 2006, there were slightly fewer young children who received no medications as compared with older children. In 2005 and 2006 there were no differences in the proportions of young and older children who were taking anticonvulsant monotherapy. However, by 2007, it appears that older children were more likely to receive anticonvulsant monotherapy as compared with younger children (RR: 1.41, 95% CI: 1.11, 1.80).

Antipsychotic use was more common among younger children over each study year, with nearly 20% of younger aged children receiving monotherapy antipsychotic treatment in each year. When looking at 2007, the risk ratio for use of antipsychotics for older children as compared with younger children was 0.64 (95%CI: 0.55, 0.74). Antidepressant monotherapy was more common among older children, as was the use of any combination regimen that included antidepressants. Among combination regimens, mood stabilizers and antipsychotic combinations were used in approximately 14% of younger aged children and 12% of older aged children.

Prescription drug fills by specific drug also show some differences in use by age group for agents within drug classes (Table 4.19). Among anticonvulsants, young children were more likely than older children to receive divalproex and oxcarbazepine, and less likely to receive lamotrigine. For second generation antipsychotics, young children were more likely to receive risperidone and less likely to receive quetiapine. Regarding antidepressant use, young children were less likely to receive escitalopram (among SSRIs) and venlafaxine

(among other antidepressants) and more likely to receive sertraline (SSRI) and trazodone (other antidepressant), as compared with older children.

Table 4.18 - Annual Drug Class Use among Medication Users within 30 Days of Most Recent Bipolar Diagnosis by Age Group: Aim 1a, 2005 - 2007

	Year of Diagnosis					
	2005		2006		2007	
	Age 0 - 9	Age 10 - 17	Age 0 - 9	Age 10 - 17	Age 0 - 9	Age 10 -17
	N = 1,320	N = 9,245	N = 1,327	N = 9,749	N = 1,280	N = 9,939
Total Number of Psychotropic Medications Used in 30 Days Following the Last Diagnosis						
None	414 (31.4)	3,337 (36.1)	384 (28.9)	3,468 (35.6)	460 (35.9)	3,694 (37.2)
1	382 (28.9)	2,251 (24.3)	395 (29.8)	2,475 (25.4)	351 (27.4)	2,554 (25.7)
2	325 (24.6)	2,118 (22.9)	351 (26.5)	2,238 (23.0)	310 (24.2)	2,163 (21.8)
3	151 (11.4)	1,101 (11.9)	145 (10.9)	1,168 (12.0)	115 (9.0)	1,152 (11.6)
4 +	48 (3.6)	438 (4.7)	52 (3.9)	400 (4.1)	44 (3.4)	376 (3.8)
Medication Use Among Users	N = 906	N = 5,908	N = 943	N = 6,281	N = 820	N = 6,245
Single Class Use						
Lithium	16 (1.8)	162 (2.7)	13 (1.4)	150 (2.4)	10 (1.2)	139 (2.2)
> 1 Lithium Fill - n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Anticonvulsants	106 (11.7)	696 (11.8)	90 (9.5)	685 (10.9)	66 (8.0)	711 (11.4)
> 1 Anticonvulsant Fill - n (%)	7 (6.6)	29 (4.2)	3 (3.3)	37 (5.4)	6 (9.1)	32 (4.5)
Antipsychotics	173 (19.1)	587 (9.9)	176 (18.7)	738 (11.7)	170 (20.7)	827 (13.2)
> Antipsychotic Fill - n (%)	10 (5.8)	32 (5.5)	14 (8.0)	47 (6.4)	10 (5.9)	48 (5.8)
Antidepressants	32 (3.5)	569 (9.6)	45 (4.8)	597 (9.5)	26 (3.2)	572 (9.2)
> 1 Antidepressant Fill - n (%)	1 (3.1)	61 (10.7)	2 (4.4)	46 (7.7)	1 (3.8)	65 (11.4)
Stimulants	75 (8.3)	363 (6.1)	92 (9.8)	443 (7.1)	96 (11.7)	454 (7.3)
> 1 Stimulant Fill - n (%)	2 (2.7)	4 (1.1)	2 (2.2)	8 (1.8)	0 (0.0)	4 (0.88)

Continued

Table 4.18 - Annual Drug Class Use among Medication Users within 30 Days of Most Recent Bipolar Diagnosis by Age Group: Aim 1a, 2005 - 2007 (Continued)

	Year of Diagnosis					
	2005		2006		2007	
	Age 0 - 9	Age 10 - 17	Age 0 - 9	Age 10 - 17	Age 0 - 9	Age 10 -17
Medication Use Among Users	N = 906	N = 5,908	N = 943	N = 6,281	N = 820	N = 6,245
Combination Therapy						
Two Classes						
Lithium + Anticonvulsant	4 (0.40)	52 (0.90)	3 (0.30)	49 (0.80)	2 (0.20)	37 (0.60)
Mood Stabilizer and Antipsychotic	134 (14.8)	721 (12.2)	135 (14.3)	736 (11.7)	104 (12.7)	776 (12.4)
Mood Stabilizer and Antidepressant	22 (2.4)	555 (9.4)	15 (1.6)	537 (8.5)	13 (1.6)	455 (7.3)
Mood Stabilizer and Stimulant	68 (7.5)	294 (5.0)	56 (5.9)	329 (5.2)	44 (5.4)	283 (4.5)
Antipsychotic and Antidepressant	39 (4.3)	405 (6.9)	36 (3.8)	442 (7.0)	39 (4.8)	455 (7.3)
Antipsychotic and Stimulant	80 (8.8)	219 (3.7)	117 (12.4)	271 (4.3)	118 (14.4)	292 (4.7)
Antidepressant and Stimulant	8 (0.90)	149 (2.5)	12 (1.3)	128 (2.0)	12 (1.5)	141 (2.3)
Three or More Classes						
Mood Stabilizer, Antipsychotic and Antidepressant	37 (4.1)	409 (6.9)	40 (4.2)	401 (6.4)	21 (2.6)	408 (6.5)
Mood Stabilizer, Antipsychotic and Stimulant	71 (7.8)	281 (4.8)	63 (6.7)	328 (5.2)	58 (7.1)	274 (4.4)
Mood Stabilizer, Antidepressant and Stimulant	8 (0.90)	147 (2.5)	10 (1.1)	152 (2.4)	12 (1.5)	136 (2.2)
Antipsychotic, Antidepressant and Stimulant	17 (1.9)	135 (2.3)	21 (2.2)	156 (2.5)	17 (2.1)	156 (2.5)
Mood Stabilizer, Antipsychotic, Antidepressant and Stimulant	16 (1.8)	164 (2.8)	19 (2.0)	139 (2.2)	12 (1.5)	129 (2.1)

SOURCE: Repeated Cross Sectional Analysis Using Aim 1a Medication Use Study Sample
Calculations for more than one class level fill exclude multiple fills of the same agent on the same service date.

Table 4.19 - Psychotropic Drug Use by Drug Prescribed 30 Days after Most Recent Diagnosis, by Age Group: Aim 1a, 2005 - 2007

	Year of Diagnosis					
	2005		2006		2007	
	Age 0 - 9	Age 10 - 17	Age 0 - 9	Age 10 - 17	Age 0 - 9	Age 10 - 17
Total Fills	**N = 1,910**	**N = 13,794**	**N = 1,980**	**N = 14,293**	**N = 1,637**	**N = 13,884**
Lithium	*110 (5.8)*	*1,036 (7.5)*	*101 (5.1)*	*924 (6.5)*	*72 (4.4)*	*856 (6.2)*
Anticonvulsants	*506 (26.5)*	*3,624 (26.3)*	*462 (23.3)*	*3,726 (26.1)*	*352 (21.5)*	*3,574 (25.7)*
Carbamazepine	19 (3.8)	139 (3.8)	14 (3.0)	135 (3.6)	22 (6.3)	149 (4.2)
Divalproex	248 (49.0)	1,390 (38.4)	229 (49.6)	1,345 (36.1)	161 (45.7)	1,242 (34.8)
Gabapentin	4 (0.79)	64 (1.8)	4 (0.87)	63 (1.7)	6 (1.7)	64 (1.8)
Lamotrigine	68 (13.4)	832 (23.0)	74 (16.0)	1,097 (29.4)	49 (13.9)	1,254 (35.1)
Levetiracetam	1 (0.20)	11 (0.30)	4 (0.87)	11 (0.29)	4 (1.1)	12 (0.34)
Oxcarbazepine	148 (29.2)	890 (24.6)	114 (24.7)	771 (20.7)	93 (26.4)	584 (16.3)
Tiagabine	3 (0.59)	20 (0.55)	1 (0.22)	12 (0.32)	2 (0.57)	5 (0.14)
Topiramate	15 (3.0)	279 (7.7)	23 (5.0)	292 (7.8)	15 (4.3)	264 (7.4)
Atypical Antipsychotics	*667 (34.9)*	*3,605 (26.1)*	*730 (36.9)*	*3,980 (27.8)*	*649 (39.6)*	*4,028 (29.0)*
Aripiprazole	179 (26.8)	1,030 (28.6)	195 (26.7)	1,335 (33.5)	217 (33.4)	1,282 (31.8)
Clozapine	0 (0.0)	2 (0.06)	1 (0.14)	9 (0.23)	0 (0.0)	10 (0.25)
Olanzapine	34 (5.1)	248 (6.9)	35 (4.8)	219 (5.5)	32 (4.9)	179 (4.4)
Paliperidone	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	9 (1.4)	83 (2.1)
Quetiapine	127 (19.0)	987 (27.4)	151 (20.7)	1,121 (28.2)	124 (19.1)	1,180 (29.3)
Risperidone	294 (44.1)	1,028 (28.5)	303 (41.5)	942 (23.7)	236 (36.4)	951 (23.6)
Ziprasidone	33 (4.9)	310 (8.6)	45 (6.2)	353 (8.9)	31 (4.8)	344 (8.5)
Typical Antipsychotics	*3 (0.16)*	*39.5 (0.29)*	*6 (0.30)*	*41 (0.29)*	*6 (0.37)*	*32 (0.23)*

Continued

Table 4.19 - Psychotropic Drug Use by Drug Prescribed 30 Days after Most Recent Diagnosis, by Age Group: Aim 1a, 2005 - 2007 (Continued)

	Year of Diagnosis					
	2005		2006		2007	
	Age 0 - 9	Age 10 - 17	Age 0 - 9	Age 10 - 17	Age 0 - 9	Age 10 - 17
Total Fills	**N = 1,910**	**N = 13,794**	**N = 1,980**	**N = 14,293**	**N = 1,637**	**N = 13,884**
Antidepressants	*233 (12.2)*	*3,344 (24.2)*	*246 (12.4)*	*3,290 (23.0)*	*143 (8.7)*	*3,152 (22.7)*
Tricyclics	18	61	13	98	13	68
Tetracyclics	0	0	0	0	0	0
Selective Serotonin Reuptake Inhibitors	144	1,989	153	1,954	91	1,906
Citalopram	7 (4.9)	180 (9.0)	15 (9.8)	180 (9.2)	8 (8.8)	197 (10.3)
Escitalopram	24 (16.7)	503 (25.3)	21 (13.7)	466 (23.8)	17 (18.7)	423 (22.2)
Fluoxetine	40 (27.8)	556 (28.0)	41 (26.8)	539 (27.6)	21 (23.1)	541 (28.4)
Fluvoxamine	6 (4.2)	43 (2.2)	2 (1.3)	42 (2.1)	4 (4.4)	56 (2.9)
Paroxetine	9 (6.3)	142 (7.1)	13 (8.5)	129 (6.6)	5 (5.5)	108 (5.7)
Sertraline	58 (40.3)	564 (28.4)	60 (39.2)	598 (30.6)	36 (39.6)	581 (30.5)
MAOIs	0	1	0	0	0	0
Other Antidepressants	71	1,293	80	1,238	38	1,178
Bupropion	38 (53.5)	675 (52.2)	33 (41.3)	634 (51.2)	18 (47.4)	512 (43.5)
Duloxetine	0 (0.0)	57 (4.4)	6 (7.5)	98 (7.9)	3 (7.9)	109 (9.2)
Mirtazapine	7 (9.9)	80 (6.2)	21 (26.3)	89 (7.2)	13 (34.2)	76 (6.4)
Nefazodone	0 (0.0)	4 (0.31)	0 (0.0)	1 (0.08)	0 (0.0)	0 (0.0)
Trazodone	20 (28.2)	269 (20.8)	19 (23.8)	283 (22.9)	13 (34.2)	306 (26.0)
Venlafaxine	6 (8.4)	209 (16.2)	1 (1.3)	132 (10.7)	4 (10.5)	176 (14.9)
Stimulants	*391 (20.5)*	*2,145 (15.6)*	*435 (22.0)*	*2,332 (16.3)*	*415 (25.4)*	*2,242 (16.1)*

N = Total prescriptions obtained. Patients may have more than one prescription therefore the total N is not equal to the study sample size. Prescription fills are standardized to a 30-day supply.
SOURCE: Repeated Cross Sectional Analysis Using Aim 1a Medication Use Study Sample

Table 4.20 provides information on medication class use by patient age group separately for each bipolar subtype and year. For patients with bipolar I disorder, use of lithium does not differ over the study period by age group, nor does the use of anticonvulsant medications. Use of antipsychotics among children with bipolar I disorder is lower among older children in each study year (2005 RR: 0.70, 95%CI: 0.63, 0.79; 2006 RR: 0.76, 95%CI: 0.68, 0.85; 2007 RR: 0.86, 95%CI: 0.76, 0.98). However, it appears that use of second generation antipsychotics has decreased somewhat in the younger age groups and has increased in the older age groups over the study period. Use of antidepressant agents was higher among older children with bipolar I disorder as compared with younger children, across each study year (2005 RR: 1.78, 95%CI: 1.43, 2.20; 2006 RR: 1.78, 95%CI: 1.42, 2.22; 2007 RR: 2.10, 95%CI: 1.62, 2.71). Finally, use of stimulants was lower in the older aged children, as compared with younger children, throughout the study period (2005 RR: 0.63, 95%CI: 0.54, 0.74; 2006 RR: 0.62, 95%CI: 0.53, 0.72; 2007 RR: 0.62, 95%CI: 0.53, 0.73).

Among children with bipolar II disorder, treatment patterns were similar to those seen for patients with bipolar I disorder with a few exceptions. Children in both age groups were equally likely to receive lithium or anticonvulsants (except for study year 2007, when younger children were less likely to receive anticonvulsants). Younger children with bipolar II disorder were more likely to receive atypical antipsychotic medications, as compared with older children. Children with bipolar II disorder in both age groups were equally likely to receive stimulants in 2006 and 2007, but younger children were more likely to receive stimulants in this group in 2005.

For children with bipolar disorder, unspecified type, it appeared that there was a trend for older aged children receiving lithium more often than younger aged children, but use in this category was low. Use of the other drug classes (anticonvulsants, antipsychotics, antidepressants, and stimulants) mirrored that of children with bipolar I disorder (no differences in anticonvulsant use by age group; lower atypical antipsychotic use among older children; higher antidepressant use among older children; lower stimulant use among older children).

Finally, among patients with Cyclothymic disorder, there were few detectable differences in treatment characteristics by age group. This is likely due to the small number of children who were under the age of 10 years in this category. It appeared that second generation antipsychotic use was higher in younger aged children and that antidepressant use was lower in younger aged children.

When comparing overall treatment use by age group and bipolar subtype (Table 4.21), in 2005 and 2006, younger patients with bipolar I or bipolar unspecified disorders were more likely to receive pharmacotherapy, as compared with older children. However, by 2007, treatment rates for both age groups were similar. There were no significant difference by age group for the use of psychotherapy or counseling or the number of visits received across any of the years studied across any of the bipolar subtypes.

Table 4.20 - Medication Class Use by Bipolar Subtype - Drug Prescribed 30 Days Following Most Recent Bipolar Diagnosis - By Age Group: Aim 1a, 2005 - 2007

	Bipolar Subtype					
	Bipolar I					
	2005		**2006**		**2007**	
	Age 0 - 9	Age 10 - 17	Age 0 - 9	Age 10 - 17	Age 0 - 9	Age 10 - 17
Medication Class Use	N = 455	N = 3,528	N = 436	N = 3,696	N = 420	N = 3,615
Lithium	36 (7.9)	291 (8.2)	31 (7.1)	283 (7.7)	21 (5.0)	278 (7.7)
Anticonvulsants	143 (31.4)	1065 (30.2)	128 (29.4)	1,154 (31.2)	104 (24.8)	1,060 (29.3)
Atypical Antipsychotics	205 (45.1)	1,119 (31.7)	191 (43.8)	1,231 (33.3)	160 (38.1)	1,188 (32.9)
Typical Antipsychotics	2 (0.40)	14 (0.40)	0 (0.0)	15 (0.40)	1 (0.20)	18 (0.50)
Antidepressants	73 (16.0)	1,005 (28.5)	69 (15.8)	1,040 (28.1)	53 (12.6)	956 (26.4)
Stimulants	135 (29.7)	660 (18.7)	134 (30.7)	702 (19.0)	125 (29.8)	665 (18.4)
	Bipolar II					
	2005		**2006**		**2007**	
	Age 0 - 9	Age 10 - 17	Age 0 - 9	Age 10 - 17	Age 0 - 9	Age 10 - 17
Medication Class Use	N = 112	N = 1,081	N = 114	N = 1,225	N = 101	N = 1,160
Lithium	7 (6.3)	86 (8.0)	9 (7.9)	78 (6.4)	5 (5.0)	67(5.8)
Anticonvulsants	37 (33.0)	363 (33.6)	31 (27.2)	366 (29.9)	18 (17.8)	323 (27.8)
Atypical Antipsychotics	46 (41.1)	288 (26.6)	45 (39.5)	314 (25.6)	42 (41.6)	317 (27.3)
Typical Antipsychotics	0 (0.0)	4 (0.40)	0 (0.0)	4 (0.30)	0 (0.0)	4 (0.30)
Antidepressants	16 (14.3)	303 (28.0)	20 (17.5)	308 (25.1)	11 (10.9)	272 (23.4)
Stimulants	33 (29.5)	215 (19.9)	27 (23.7)	218 (17.8)	22 (21.8)	226 (19.5)

Continued

Table 4.20 - Medication Class Use by Bipolar Subtype - Drug Prescribed 30 Days Following Most Recent Bipolar Diagnosis - By Age Group: Aim 1a, 2005 - 2007 (Continued)

	Bipolar Unspecified					
	2005		2006		2007	
	Age 0 - 9	Age 10 - 17	Age 0 - 9	Age 10 - 17	Age 0 - 9	Age 10 - 17
Medication Class Use	N = 727	N = 4,379	N = 755	N = 4,607	N = 731	N = 4,934
Lithium	56 (7.7)	454 (10.4)	54 (7.2)	404 (8.8)	40 (5.5)	366 (7.4)
Anticonvulsants	226 (31.1)	1,358 (31.0)	206 (27.3)	1,361 (29.5)	167 (22.8)	1,364 (27.6)
Atypical Antipsychotics	300 (41.3)	1,459 (33.3)	363 (48.1)	1,590 (34.5)	322 (44.0)	1,734 (35.1)
Typical Antipsychotics	5 (0.70)	19 (0.40)	5 (0.70)	19 (0.40)	5 (0.70)	19 (0.40)
Antidepressants	87 (12.0)	1,163 (26.6)	106 (14.0)	1,146 (24.9)	83 (11.4)	1,173 (23.8)
Stimulants	170 (23.4)	835 (19.1)	223 (29.5)	985 (21.4)	215 (29.4)	940 (19.1)
	Cyclothymic Disorder*					
	2005		2006		2007	
	Age 0 - 9	Age 10 - 17	Age 0 - 9	Age 10 - 17	Age 0 - 9	Age 10 - 17
Medication Class Use	N = 26	N = 257	N = 22	N = 221	N = 28	N = 230
Lithium	1 (3.8)	21 (8.2)	1 (4.5)	17 (7.7)	1 (3.6)	14 (6.1)
Anticonvulsants	5 (19.2)	77 (30.0)	8 (36.4)	59 (26.7)	8 (28.6)	76 (33.0)
Atypical Antipsychotics	12 (45.2)	36 (14.0)	7 (31.8)	52 (23.5)	11 (39.3)	52 (22.6)
Typical Antipsychotics	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Antidepressants	3 (11.5)	62 (24.1)	3 (13.6)	58 (26.2)	5 (17.9)	51 (22.2)
Stimulants	5 (19.2)	42 (16.3)	6 (27.3)	41 (18.6)	7 (25.0)	34 (14.8)

SOURCE: Repeated Cross Sectional Analysis Using Aim 1a Medication Use Study Sample

* Cyclothymia is considered to be the mildest disorder on the bipolar spectrum.

Table 4.21 Summary of Treatment Received by Bipolar Subtype and Age Group: Aim 1a, 2005 - 2007

	Bipolar Subtype					
	Bipolar I					
	2005		2006		2007	
	Age 0 - 9	Age 10 - 17	Age 0 - 9	Age 10 - 17	Age 0 - 9	Age 10 - 17
Pharmacotherapy*	N = 455	N = 3,528	N = 436	N = 3,696	N = 420	N = 3,615
Yes	312 (68.6)	2,226 (63.1)	308 (70.6)	2,393 (64.8)	267 (63.6)	2,286 (63.2)
No	143 (31.4)	1,302 (36.9)	128 (29.4)	1,303 (35.3)	153 (36.4)	1,329 (36.8)
Psychotherapy	N = 338	N = 2,662	N = 327	N = 2,899	N = 300	N = 2,660
Any Use - n (%)	313 (92.6)	2,409 (90.5)	395 (90.2)	2,606 (89.9)	269 (89.7)	2,411 (90.6)
Visits - Median (IQR)	10.9 (10.0)	9.0 (13.0)	8.0 (11.0)	8.0 (13.0)	7.0 (11.0)	8.0 (13.0)
ECT*						
Any Use - n (%)	0 (0.0)	1 (0.04)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.04)
	Bipolar II					
	Age 0 - 9	Age 10 - 17	Age 0 - 9	Age 10 - 17	Age 0 - 9	Age 10 - 17
Pharmacotherapy*	N = 112	N = 1,081	N = 114	N = 1,225	N = 101	N = 1,160
Yes	78 (69.6)	723 (66.9)	77 (67.5)	744 (60.7)	61 (60.4)	698 (60.2)
No	34 (30.4)	358 (33.1)	37 (32.5)	481 (39.3)	40 (39.6)	462 (39.8)
Psychotherapy	N = 79	N = 832	N = 86	N = 979	N = 79	N = 887
Any Use - n (%)	76 (96.2)	782 (94.0)	82 (95.3)	909 (92.9)	78 (98.7)	826 (93.1)
Visits - Median (IQR)	9.5 (13.0)	9.0 (12.0)	10.5 (10.0)	9.0 (13.0)	7.5 (10.0)	8.0 (12.0)
ECT*						
Any Use - n (%)	0 (0.0)	1 (0.12)	0 (0.0)	0 (0.0)	1 (1.3)	1 (0.11)

Continued

Table 4.21 Summary of Treatment Received by Bipolar Subtype and Age Group: Aim 1a, 2005 - 2007 (Continued)

	Bipolar Unspecified					
	Age 0 - 9	Age 10 - 17	Age 0 - 9	Age 10 - 17	Age 0 - 9	Age 10 - 17
Pharmacotherapy*	N = 727	N = 4,379	N = 755	N = 4,607	N = 731	N = 4,934
Yes	498 (68.5)	2,815 (64.3)	543 (71.9)	3,006 (65.3)	472 (64.6)	3,121 (63.3)
No	229 (31.5)	1,564 (35.7)	212 (28.1)	1,601 (34.8)	259 (35.4)	1,813 (36.8)
Psychotherapy	N = 530	N = 3,178	N = 563	N = 3,540	N = 506	N = 3,560
Any Use - n (%)	463 (87.4)	2,732 (86.1)	493 (87.6)	3,022 (85.4)	421 (83.2)	2,985 (83.8)
Visits - Median (IQR)	8.0 (11.0)	8.0 (12.0)	8.0 (10.0)	8.0 (12.0)	8.0 (11.0)	8.0 (12.0)
ECT*						
Any Use - n (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.03)	0 (0.0)	1 (0.03)
	Cyclothymic Disorder*					
	Age 0 - 9	Age 10 - 17	Age 0 - 9	Age 10 - 17	Age 0 - 9	Age 10 - 17
Pharmacotherapy*	N = 26	N = 257	N = 22	N = 221	N = 28	N = 230
Yes	18 (69.2)	144 (56.0)	15 (68.2)	138 (62.4)	20 (71.4)	140 (60.9)
No	8 (30.8)	113 (44.0)	7 (31.8)	83 (37.6)	8 (28.6)	90 (39.1)
Psychotherapy	N = 21	N = 193	N = 19	N = 170	N = 20	N = 172
Any Use - n (%)	19 (90.5)	181 (93.8)	17 (89.5)	163 (95.9)	19 (95.0)	161 (93.6)
Visits - Median (IQR)	6.0 (10.0)	6.0 (9.0)	4.0 (8.0)	8.0 (11.0)	9.0 (8.0)	7.0 (12.0)
ECT*						
Any Use - n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

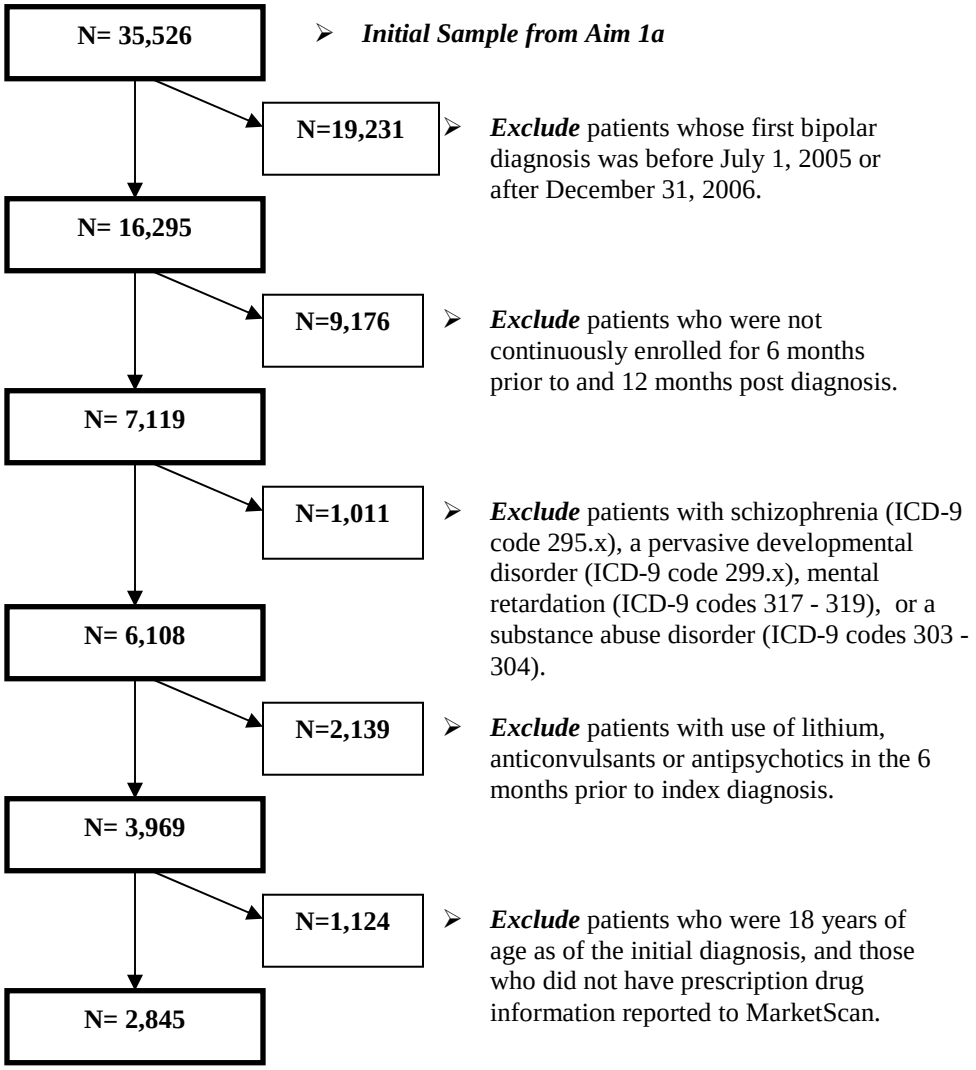
SOURCE: Repeated Cross Sectional Analysis Using Aim 1a Medication Use Study Sample
ECT = Electroconvulsive Therapy.
* Cyclothymia is considered to be the mildest disorder on the bipolar spectrum.

4.2 Aim 1b: Incident Diagnosis Design

Next, additional exclusionary criteria were applied to address Aim 1b. In order to identify patients who were newly diagnosed and to accurately identify their treatments received over time, the initial sample was reduced by restricting the sample to patients whose first diagnosis occurred between July 1, 2005 and December 31, 2006. Patients also were required to have had continuous enrollment over the period spanning 6 months prior to their index diagnosis and 12 months following their index diagnosis, and no previous evidence of a bipolar diagnosis or treatment (antipsychotic, anticonvulsant or lithium) for 6 months prior to their index diagnosis. The index diagnosis was the first recorded diagnosis date among patients who met these criteria.

Patients who had a diagnosis of schizophrenia, a pervasive developmental disorder, mental retardation, or a substance abuse disorder and those whose insurance plans did not provide information on medication use were excluded. Details of these exclusions are provided in Figure 4.4 and in Chapter 3.

Figure 4.4 - Inclusion and Exclusion Criteria: Aim 1b



Characteristics of children who were newly diagnosed with a bipolar spectrum disorder from July 1, 2005 through December 31, 2006 are provided in Table 4.22. When comparing patient characteristics by bipolar subtype (with patients with bipolar I disorder as the reference group), patients with bipolar unspecified were younger on average (RD: -0.40, 95%CI: -0.65, -0.15) with proportionately more children in the middle age group (RR: 1.23, 95%CI: 1.05, 1.44, ages 7 - 12) and fewer in the oldest age group (RR: 0.92, 95%CI: 0.88,

0.97, ages 13 - 17). Children with bipolar II disorder were more likely to be older than those with bipolar I disorder (RD: 0.54, 95%CI: 0.18, 0.89), with proportionately more children in the oldest age group (RR: 1.08, 95%CI: 1.02, 1.14). Children with bipolar II disorder and Cyclothymic disorder were more likely to be female, as compared with children with bipolar I disorder (RR: 1.13, 95% CI: 1.02, 1.25, for bipolar II and RR: 1.26, 95%CI: 1.08, 1.47, for Cyclothymic disorder).

Across all bipolar subtypes, there were no differences in the number of comorbid mental health conditions or the total number of diagnoses received over the 18 month study period. Children with Cyclothymic disorder were slightly less likely to have inpatient mental health days, as compared with children with bipolar I disorder (RR: 0.71, 95%CI: 0.49, 1.03), although this difference was not statistically significant.

There were several differences noted when comparing bipolar subtype distributions by region and insurance status. It is important to note, however, that the MarketScan data are not sampled in a way that provides reliable information on regional variation of disease. Additionally, insurance type may be correlated with region so interpretations of differences in insurance or regional variation by bipolar subtype should be made in light of these data limitations.

While regional distributions within each bipolar subtype largely reflected the sampling strategy of MarketScan (where the south is more heavily represented than other regions), there were some differences in region by bipolar subtype. For example, in the south, bipolar II disorder was diagnosed proportionately less often than bipolar I disorder (RR: 0.75, 95%CI: 0.64, 0.88). In the west, there were proportionately higher diagnoses of bipolar NOS

(RR: 1.22, 95%CI: 1.03, 1.45), bipolar II (RR: 1.56, 95%CI: 1.26, 1.93), and Cyclothymic disorder (RR: 1.59, 95%CI: 1.11, 2.26) as compared with bipolar I disorder.

When comparing insurance types, patients with bipolar unspecified type were slightly more likely to have an insurance type categorized as "other" (as compared with patients with bipolar I disorder), although few patients were included in this category overall. Regarding benefit generosity patients with bipolar unspecified were less likely than those with bipolar I disorder to have fair benefits or no benefits (RR: 0.90, 95%CI: 0.82, 0.98, for fair and RR: 0.59, 95%CI: 0.37, 0.94 for none), and more likely to have good generosity of benefits (RR: 1.13, 95%CI: 1.02, 1.25). Similarly, compared with patients with bipolar I disorder, patients with bipolar II disorder were less likely to have no benefits (RR: 0.39, 95%CI: 0.17, 0.91), and more likely to have good benefits (RR: 1.19, 95%CI: 1.04, 1.36)

Patients with bipolar unspecified type were more likely to receive their diagnosis from a primary care provider (RR: 1.29, 95%CI: 1.10, 1.52) or an unclassified provider (RR: 1.23, 95%CI: 1.06, 1.44), and were less likely to receive their diagnosis from mental health provider (non-psychiatry) (RR: 0.59, 95%CI: 0.49, 0.71) as compared with those with bipolar I disorder. Patients with bipolar II and Cyclothymic disorder were more likely than patients with bipolar I to receive their diagnosis from a psychiatrist (RR: 1.19, 95%CI: 1.04, 1.36, for bipolar II and RR: 1.30, 95%CI: 1.04, 1.62 for Cyclothymic disorder). Additionally, patients with bipolar II disorder were less likely to receive their diagnosis from a primary care provider (RR: 0.60, 95%CI: 0.44, 0.82).

Table 4.22 - Patient and Physician Characteristics by Bipolar Subtype: Aim 1b

	Bipolar I	Bipolar II	Bipolar NOS	Cyclothymia*
	N = 1,036	N = 398	N = 1,314	N = 97
Patient Characteristics				
Age - Mean (SD)	13.9 (2.9)	14.5 (2.5)	13.5 (3.3)	14.1 (2.8)
0 - 6 Years	38 (3.7)	6 (1.5)	66 (5.0)	3 (3.1)
7 - 12 Years	200 (19.3)	61 (15.3)	312 (23.7)	17 (17.5)
13 - 17 Years	798 (77.0)	331 (83.2)	936 (71.2)	77 (79.4)
Sex - N (%) Female	541 (52.2)	234 (58.8)	664 (50.5)	64 (66.0)
Geographic Region				
Northeast	108 (10.4)	37 (9.3)	123 (9.4)	6 (6.2)
North Central	288 (27.8)	119 (29.9)	384 (29.2)	27 (27.8)
South	453 (43.7)	131 (32.9)	526 (40.0)	37 (38.1)
West	175 (16.9)	105 (26.4)	271 (20.6)	26 (26.8)
Unknown	12 (1.2)	6 (1.5)	10 (0.76)	1 (1.0)
Insurance Type				
Comprehensive	70 (6.8)	35 (8.8)	111 (8.4)	10 (10.3)
HMO	225 (21.7)	94 (23.6)	269 (20.5)	21 (21.7)
POS	126 (12.2)	49 (12.3)	171 (13.0)	9 (9.3)
PPO	558 (53.9)	200 (50.3)	664 (50.5)	53 (54.6)
Other	30 (2.9)	12 (3.0)	65 (5.0)	4 (4.1)
Unknown	27 (2.6)	8 (2.0)	34 (2.6)	0 (0.0)
Generosity of Prescription Drug Benefits				
None / Poor	40 (4.3)	6 (1.7)	30 (2.6)	4 (4.4)
Fair	498 (54.1)	178 (49.6)	566 (49.4)	50 (54.4)
Good	383 (41.6)	175 (48.8)	549 (48.0)	38 (41.3)
Disease Severity				
Comorbid Mental Health Conditions	1.4 (1.2)	1.3 (1.1)	1.5 (1.2)	1.3 (1.3)
Number of Unique Diagnoses in Year	12.8 (8.4)	12.0 (7.7)	12.9 (8.0)	12.1 (8.0)
Any Inpatient Mental Health Visits	345 (33.3)	117 (29.4)	472 (35.9)	23 (23.7)
Physician Specialty				
Psychiatrist	379 (37.6)	173 (44.9)	443 (34.8)	46 (50.0)
Other Mental Health	206 (20.4)	83 (21.6)	154 (12.1)	19 (20.7)
Primary Care / M.D.	186 (18.4)	43 (11.2)	305 (23.9)	11 (12.0)
Other Medical Specialist	25 (2.5)	8 (2.1)	41 (3.2)	0 (0.0)
Unclassified	212 (21.0)	78 (20.3)	332 (26.0)	16 (17.4)
MSA Status	750 (97.7)	337 (98.0)	919 (94.9)	79 (100.0)

SOURCE: Aim1b Incident Diagnosis Design Sample

* Cyclothymia is considered to be the mildest disorder on the bipolar spectrum.

When considering the impact of comorbid mental health conditions (Table 4.23), there was no difference in the occurrence of ADHD, either occurring prior to bipolar diagnosis or occurring post bipolar diagnosis, across any bipolar spectrum disorder. ADHD

diagnoses occurred (either before or after bipolar diagnosis) in over 30% of children with bipolar I, or bipolar unspecified disorders, and in approximately 25% of children with bipolar II or Cyclothymic disorders. Conduct disorder was less likely to be diagnosed in children with bipolar II disorder (RR: 0.67, 95%CI: 0.46, 1.00), and was more likely to be diagnosed in children with bipolar NOS (RR: 1.39, 95%CI: 1.12, 1.73) , as compared with those with bipolar I disorder.

Anxiety disorders were rare and there were no differences in the occurrence of these disorders by bipolar subtype (with bipolar I as the reference group), with the exception of co-morbid panic disorder among patients with bipolar unspecified. However, there were only a small number of patients in this category so the confidence interval for this estimate was somewhat imprecise (RR: 3.64, 95%CI: 1.16, 11.41).

Patients with bipolar unspecified type were less likely to have a diagnosis of major depressive disorder in either the pre or post diagnosis periods as compared with those with bipolar I disorder (RR: 0.84, 95%CI: 0.75, 0.94). Dysthymic disorder was less common than major depressive disorder, and was more likely to be diagnosed in children with bipolar II disorder prior to their index bipolar diagnosis (RR: 1.63, 95%CI: 1.02, 2.61). Children with bipolar unspecified type were more likely than children with bipolar I disorder to receive a mental health diagnosis for an "other mood disorder" (RR: 1.26, 95%CI: 1.06, 1.49).

Substance use (alcohol or drug use, excluding abuse) was less common prior to diagnosis, among all bipolar subtypes. Overall, the use of drugs or alcohol did not differ by bipolar subtype. However, between 7 and 8% of children were identified as substance users in the period following their initial bipolar diagnosis.

Table 4.23 - Occurrence of Comorbid Mental Health Conditions by Timing of Diagnosis: Aim 1b

	Bipolar I		Bipolar II		Bipolar NOS		Cyclothymia*	
	N = 1,036		N = 398		N = 1,314		N = 97	
Mental Health Diagnosis	Pre-Dx	Post-Dx	Pre-Dx	Post-Dx	Pre-Dx	Post-Dx	Pre-Dx	Post-Dx
Disruptive Behavior Disorders								
Attention Deficit Hyperactivity Disorder	186 (18.0)	133 (12.8)	79 (19.8)	30 (7.5)	270 (20.5)	170 (12.9)	15 (15.5)	9 (9.3)
Conduct Disorder	48 (4.6)	64 (6.2)	9 (2.3)	20 (5.0)	74 (5.6)	124 (9.4)	3 (3.1)	7 (7.2)
Oppositional Defiant Disorder	47 (4.5)	72 (6.9)	18 (4.5)	15 (3.8)	70 (5.3)	106 (8.1)	7 (7.2)	2 (2.1)
Anxiety Disorders								
Separation Anxiety Disorder	2 (0.20)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.20)	2 (0.20)	0 (0.0)	1 (1.0)
Post-Traumatic Stress Disorder	15 (1.4)	19 (1.8)	5 (1.3)	4 (1.0)	27 (2.1)	35 (2.7)	1 (1.0)	1 (1.0)
Obsessive Compulsive Disorder	10 (1.0)	6 (0.60)	3 (0.80)	5 (1.3)	19 (1.4)	17 (1.3)	2 (2.1)	1 (1.0)
Generalized Anxiety Disorder	19 (1.8)	39 (3.8)	12 (3.0)	6 (1.5)	34 (2.6)	29 (2.2)	2 (2.1)	5 (5.2)
Social Phobia	5 (0.50)	4 (0.40)	1 (0.30)	3 (0.80)	2 (0.20)	2 (0.20)	0 (0.0)	2 (2.1)
Panic Disorder	5 (0.50)	5 (0.50)	3 (0.80)	6 (1.5)	6 (0.50)	12 (0.90)	0 (0.0)	2 (2.1)
Depressive Disorders								
Major Depressive Disorder	193 (18.6)	183 (17.7)	81 (20.4)	72 (18.1)	198 (15.1)	203 (15.4)	13 (13.4)	13 (13.4)
Dysthymic Disorder	43 (4.2)	38 (3.7)	27 (6.8)	11 (2.8)	65 (4.9)	35 (2.7)	7 (7.2)	7 (7.2)
Other Mental Health Disorders								
Other Mood Disorders	54 (5.2)	124 (12.0)	31 (7.8)	41 (10.3)	102 (7.8)	182 (13.9)	6 (6.2)	7 (7.2)
Tic Disorders								
Tourette's Syndrome or Other Tic Disorders	3 (0.30)	4 (0.40)	0 (0.0)	2 (0.50)	3 (0.20)	6 (0.50)	0 (0.0)	0 (0.0)
Substance Use								
Drug or Alcohol Use	24 (2.3)	84 (8.1)	6 (1.5)	27 (6.8)	25 (1.9)	100 (7.6)	2 (2.1)	7 (7.2)

SOURCE: Aim1b Incident Diagnosis Design Sample

* Cyclothymia is considered to be the mildest disorder on the bipolar spectrum.

Newly diagnosed patients were evaluated over the course of one year to determine how stable their bipolar diagnoses were over time. Table 4.24 details the extent to which the patient's initial bipolar spectrum diagnosis matched their final bipolar spectrum diagnosis (after one year of follow up). Approximately 80% of patients in each bipolar subtype had the same diagnosis at the beginning and end of the study period. Approximately 13% of patients who were initially diagnosed with bipolar I disorder or bipolar II disorder had a bipolar unspecified disorder diagnosis at their last visit. Approximately 8% of patients with a Cyclothymic disorder diagnosis at the initial visit had a bipolar II diagnosis at their last visit. Approximately 14% of patients with a bipolar unspecified type at the first visit had bipolar I diagnoses at the last visit.

Table 4.24 - Diagnostic Stability of Bipolar Spectrum Disorders Over One Year from Initial Diagnosis: Aim 1b

	Last Bipolar Subtype			
Initial Bipolar Subtype				
	Bipolar I	Bipolar II	Bipolar NOS	Cyclothymia*
Bipolar I	861 (83.1)	34 (3.3)	140 (13.5)	1 (0.10)
Bipolar II	34 (8.5)	310 (77.9)	53 (13.3)	1 (0.30)
Bipolar NOS	179 (13.6)	44 (3.3)	1,085 (82.6)	6 (0.50)
Cyclothymia	7 (7.2)	8 (8.2)	7 (7.2)	75 (77.3)

SOURCE: Aim1b Incident Diagnosis Design Sample
* Cyclothymia is considered to be the mildest disorder on the bipolar spectrum.

Overall, a majority of patients had no changes in their bipolar diagnostic subtype over the course of one year after their initial diagnosis (Table 4.25). Changes were most likely for patients who received diagnoses of bipolar II disorder, with approximately 34% of these patients having a diagnosis change in the year. Patients with initial diagnoses of bipolar II

disorder had the most diagnostic switching over the year (with a range of 0 switches to 36 switches). Having 4 or more diagnostic changes was also most common for patients with bipolar II disorders (occurring in 11% of patients).

Table 4.25 - Number of Bipolar Diagnostic Changes Over One Year from Initial Diagnosis: Aim 1b

	Initial Bipolar Subtype			
	Bipolar I	Bipolar II	Bipolar NOS	Cyclothymia*
	N = 1,036	N = 398	N = 1,314	N = 97
Number of Diagnostic Changes				
No Changes	761 (73.5)	264 (66.3)	962 (73.2)	70 (72.2)
1 Change	117 (11.3)	48 (12.1)	136 (10.4)	16 (16.5)
2 Changes	62 (6.0)	24 (6.0)	77 (5.9)	7 (7.2)
3 Changes	28 (2.7)	17 (4.3)	30 (2.3)	1 (1.0)
4+ Changes	68 (6.6)	45 (11.3)	109 (8.3)	3 (3.1)
Range	0 - 22	0 - 36	0 - 24	0 - 21

SOURCE: Aim1b Incident Diagnosis Design Sample
* Cyclothymia is considered to be the mildest disorder on the bipolar spectrum.

When comparing drug class use by bipolar subtype, there was no difference in the number of drugs received at 30 days, 90 days or one year following diagnosis (Tables 4.26 - 4.28) for any bipolar subtype. Children with bipolar II disorder were somewhat more likely than children with bipolar I to receive at least one drug at each of the time points (RR: 1.07, 95%CI: 1.01, 1.13, at one year). Use of specific drug classes was also evaluated to see if there were any bipolar-related treatment differences at the different time points.

Drug use in the 30 days after a child's first bipolar diagnosis was similar among all bipolar subtypes, and ranged from 56.1% (bipolar NOS) to 62.6% (bipolar II) (Table 4.26). Of those that received medication in the first 30 days following initial diagnosis, there was no statistically significant difference in the use of lithium, or stimulants. Use of lithium was rare

across all bipolar subtypes, particularly for those with bipolar II disorder. Antidepressant use was lower among patients with bipolar unspecified type (RR: 0.87, 95%CI: 0.77, 0.98) and patients with bipolar II (RR: 0.79, 95%CI: 0.66, 0.94) as compared with patients with bipolar I. Anticonvulsant use was somewhat higher among patients with bipolar II disorder as compared with patients with bipolar I disorder (RR: 1.20, 95% CI: 1.02, 1.42). Finally, antipsychotic agents were less likely to be used by patients with bipolar II disorder (RR: 0.69, 95%CI: 0.55, 0.86), and those with Cyclothymic disorder (RR: 0.50, 95%CI: 0.30, 0.84) as compared with those with bipolar I disorder during the 30 day period.

Table 4.26 - Drug Class Use 30 Days Following Initial Diagnosis by Bipolar Subtype: Aim 1b

	Bipolar I	**Bipolar II**	**Bipolar NOS**	**Cyclothymia***
	N = 1,036	N = 398	N = 1,314	N = 97
Total Number of Psychotropic Medications Used in 30 Days Following Initial Diagnosis				
None	449 (43.3)	149 (37.4)	577 (43.9)	38 (39.2)
1	312 (30.1)	153 (38.4)	398 (30.3)	38 (39.2)
2	189 (18.2)	74 (18.6)	250 (19.0)	17 (17.5)
3	72 (6.9)	21 (5.3)	73 (5.6)	4 (4.1)
4 +	14 (1.3)	1 (0.25)	16 (1.2)	0 (0.0)
Medication Class Use Among Users**	N = 587	N = 249	N = 737	N = 59
Lithium	39 (6.6)	10 (4.0)	44 (6.0)	5 (8.5)
Anticonvulsants	227 (38.7)	116 (46.6)	313 (42.5)	26 (44.1)
Antipsychotics	238 (40.5)	69 (27.7)	317 (43.0)	12 (20.3)
Antidepressants	284 (48.4)	95 (38.2)	310 (42.1)	26 (44.1)
Stimulants	119 (20.3)	56 (22.5)	142 (19.3)	11 (18.6)

SOURCE: Aim1b Incident Diagnosis Design Sample
* Cyclothymia is considered to be the mildest disorder on the bipolar spectrum.
** Drug class use does not sum to the total medication users sample size as users could be included in multiple categories.

When comparing medication class use over the first 90 days following initial diagnosis, a larger proportion of patients were receiving treatment (ranging from approximately 70 to 75% within each bipolar subtype) (Table 4.27). As with the 30 day time

point, there were no differences in the use of lithium or stimulants by bipolar subtype. However, patients with bipolar II disorder and those with Cyclothymic disorder were less likely to receive antipsychotic medications as compared with those with bipolar I disorder (RR: 0.75, 95%CI: 0.62, 0.90 for bipolar II and RR: 0.65, 95%CI: 0.44, 0.95 for Cyclothymic disorder). Patients with bipolar II disorder were also more likely to receive anticonvulsants (RR: 1.31, 95%CI: 1.15, 1.50) and less likely to receive antidepressants (RR: 0.85, 95%CI: 0.74, 0.97) than those with bipolar I disorder.

Table 4.27 - Drug Class Use 90 Days Following Initial Diagnosis by Bipolar Subtype: Aim 1b

	Bipolar I	**Bipolar II**	**Bipolar NOS**	**Cyclothymia***
	N = 1,036	N = 398	N = 1,314	N = 97
Total Number of Psychotropic Medications Used in 90 Days Following Initial Diagnosis				
None	314 (30.3)	94 (23.6)	403 (30.7)	24 (24.7)
1	290 (28.0)	137 (34.4)	380 (28.9)	36 (37.1)
2	267 (25.8)	97 (24.4)	317 (24.1)	25 (25.8)
3	112 (10.8)	54 (13.6)	152 (11.6)	9 (9.3)
4 +	53 (5.1)	16 (4.0)	62 (4.7)	3 (3.1)
Medication Class Use Among Users**	N = 722	N = 304	N = 911	N = 73
Lithium	52 (7.2)	17 (5.6)	60 (6.6)	6 (8.2)
Anticonvulsants	307 (42.5)	170 (55.9)	432 (47.4)	38 (52.0)
Antipsychotics	307 (42.5)	96 (31.6)	422 (46.3)	20 (27.4)
Antidepressants	393 (54.4)	140 (46.0)	435 (47.8)	36 (49.3)
Stimulants	192 (26.6)	78 (25.7)	233 (25.6)	14 (19.2)

SOURCE: Aim1b Incident Diagnosis Design Sample.
* Cyclothymia is considered to be the mildest disorder on the bipolar spectrum.
** Drug class category use does not sum to the total medication users sample size as users could be included in multiple categories.

Finally, when looking at drug class use over one year following diagnosis, a majority of patients received at least one psychotropic prescription over the year (Table 4.28). Over the course of the year, there was no difference in the proportion of children who received

lithium, stimulants, or antidepressants by bipolar subtype. However, anticonvulsant use was higher in patients with bipolar II disorder (RR: 1.26, 95%CI: 1.13, 1.41) and those with Cyclothymic disorder (RR: 1.25, 95%CI: 1.03, 1.51) when compared with those with bipolar I disorder. Antipsychotic use also differed by bipolar subtype with patients with bipolar II and patients with Cyclothymic disorder being less likely to receive antipsychotics (RR: 0.86, 0.74, 0.90, for bipolar II, and RR: 0.70, 95% CI: 0. 52, 0.96, for Cyclothymic disorder) as compared with children with bipolar I disorder.

Table 4.28 - Drug Class Use One Year Following Initial Diagnosis by Bipolar Subtype: Aim 1b

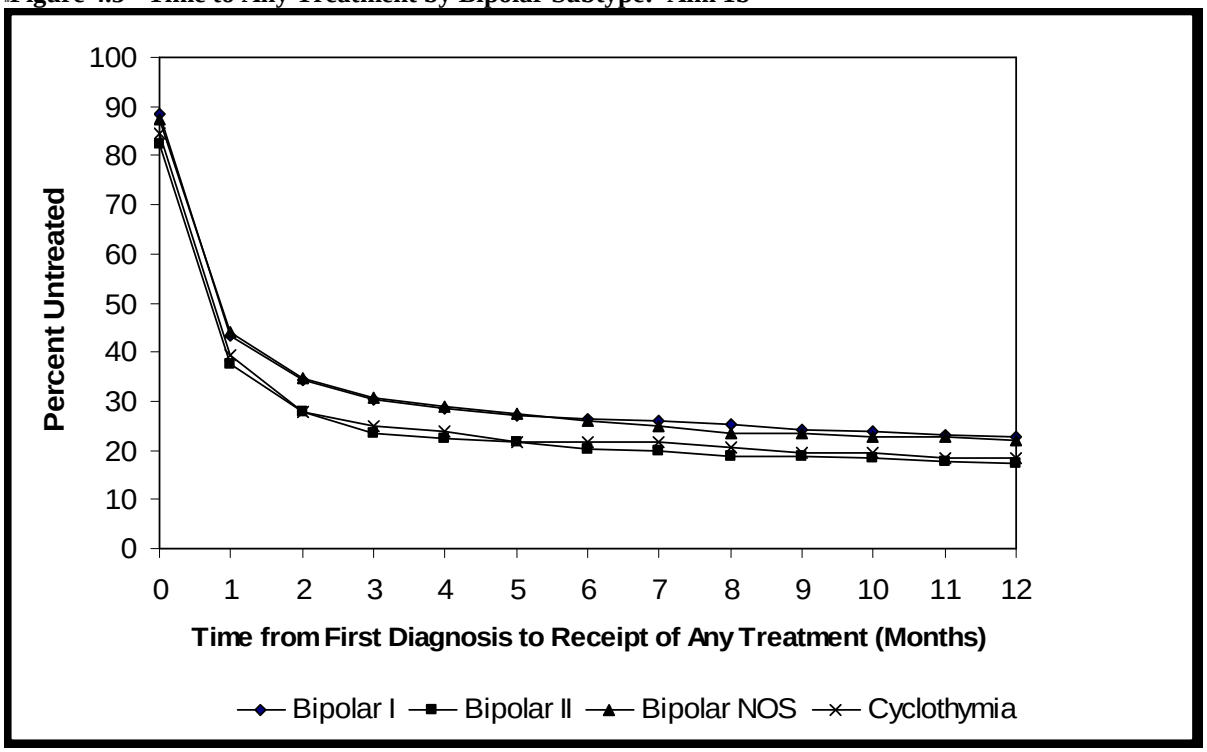
	Bipolar I	Bipolar II	Bipolar NOS	Cyclothymia*
	N = 1,036	N = 398	N = 1,314	N = 97
Total Number of Psychotropic Medications Used During the Year				
None	234 (22.6)	69 (17.3)	289 (22.0)	18 (18.6)
1	221 (21.3)	94 (23.6)	290 (22.1)	23 (23.7)
2	228 (22.0)	99 (24.9)	303 (23.1)	25 (25.8)
3	177 (17.1)	67 (16.8)	203 (15.4)	15 (15.5)
4 +	176 (17.0)	69 (17.3)	229 (17.4)	16 (16.5)
Medication Class Use Among Users**	N = 802	N = 329	N = 1,025	N = 79
Lithium	78 (9.7)	23 (7.0)	89 (8.7)	8 (10.1)
Anticonvulsants	391 (48.7)	202 (61.4)	534 (52.1)	48 (60.8)
Antipsychotics	407 (50.7)	142 (43.2)	555 (54.1)	28 (35.4)
Antidepressants	494 (61.6)	183 (55.6)	587 (57.3)	47 (59.5)
Stimulants	262 (32.9)	107 (32.5)	360 (35.1)	20 (25.3)

SOURCE: Aim1b Incident Diagnosis Design Sample
* Cyclothymia is considered to be the mildest disorder on the bipolar spectrum.
** Drug class category use does not sum to the total medication users sample size as users could be included in multiple categories.

Figure 4.5 shows the time in months until patients received any psychotropic treatment by each bipolar spectrum disorder. Rates of treatment were similar, regardless of bipolar subtype recorded at the patients' initial visit. For example, at 6 months, 73.6% of patients with bipolar I disorder, 79.6% of those with bipolar II disorder, 74.0% of those with

bipolar unspecified, and 78.3% of those with Cyclothymic disorder had received treatment. At one year, treatment rates were 77.4% for bipolar I disorder, 82.7% for bipolar II disorder, 77.9% for bipolar unspecified, and 81.4% for Cyclothymic disorder.

Figure 4.5 - Time to Any Treatment by Bipolar Subtype: Aim 1b



* Treatments included use of lithium, anticonvulsants, antipsychotics, antidepressants or stimulants.
* Cyclothymia is considered to be the mildest disorder on the bipolar spectrum.

Prescription drug use by specific agent at each time point (30 days, 90 days and 1 year after diagnosis) is provided in Table 4.29. Antidepressant medications were the most commonly filled psychotropic medications within 30 days of diagnosis, followed by anticonvulsants, and atypical antipsychotics. Of the anticonvulsants, divalproex was the most commonly filled medication after 30 days and after 90 days from diagnosis. After one year, lamotrigine surpassed divalproex in the number of fills. Another commonly prescribed agent

within the anticonvulsant class was oxcarbazepine, although use of this agent appeared to decline slightly over the three time points.

Table 4.29 - Medication Use by Drug Prescribed: Aim 1b

	30 Days After Diagnosis	90 Days After Diagnosis	One Year After Diagnosis
Total Medications Filled	**N = 3,173**	**N = 8,262**	**N = 27,698**
Mood Stabilizers			
Lithium	126 (4.0)	312 (3.8)	1,020 (3.7)
Anticonvulsants	851 (26.8)	2,199 (26.6)	6,936 (25.0)
Carbamazepine	21 (2.5)	48 (2.2)	140 (2.0)
Divalproex	376 (44.2)	880 (40.0)	2,298 (33.1)
Gabapentin	5 (0.59)	19 (0.86)	86 (1.2)
Lamotrigine	208 (24.4)	708 (32.2)	2,730 (39.4)
Levetiracetam	0 (0.0)	2 (0.09)	9 (0.13)
Oxcarbazepine	201 (23.6)	447 (20.3)	1,343 (19.4)
Tiagabine	2 (0.23)	4 (0.18)	13 (0.19)
Topiramate	37 (4.3)	91 (4.1)	317 (4.6)
Atypical Antipsychotics	816 (25.7)	1,970 (23.8)	6,510 (23.5)
Aripiprazole	229 (28.1)	583 (29.6)	2,121 (32.6)
Clozapine	0 (0.0)	0 (0.0)	9 (0.14)
Olanzapine	58 (7.1)	117 (5.9)	273 (4.2)
Paliperidone	0 (0.0)	0 (0.0)	9 (0.14)
Quetiapine	238 (29.2)	582 (29.5)	1,807 (27.8)
Risperidone	227 (27.8)	533 (27.1)	1,763 (27.1)
Ziprasidone	64 (7.8)	155 (7.9)	528 (8.1)
Typical Antipsychotics	3 (0.09)	7 (0.85)	9 (0.03)
Antidepressants	973 (30.7)	2,523 (30.5)	8,418 (30.4)
Tricyclics	N = 28	N = 75	N = 246
Tetracyclics	N = 0	N = 0	N = 0
Selective Serotonin Reuptake Inhibitors	N = 626	N = 1,646	N = 5,387
Citalopram	64 (10.2)	154 (9.4)	475 (8.8)
Escitalopram	147 (23.5)	392 (23.8)	1,316 (24.4)
Fluoxetine	196 (31.3)	497 (30.2)	1,569 (29.1)
Fluvoxamine	3 (0.48)	12 (0.73)	70 (1.3)
Paroxetine	26 (4.1)	84 (5.1)	287 (5.3)
Sertraline	190 (30.3)	507 (30.8)	1,670 (31.0)
Monoamine Oxidase Inhibitors	N = 0	N = 0	N = 0
Other Antidepressants	N = 319	N = 801	N = 2,785
Bupropion	129 (40.4)	364 (45.4)	1,332 (47.8)
Duloxetine	8 (2.5)	44 (5.5)	233 (8.4)
Mirtazapine	28 (8.8)	62 (7.7)	216 (7.8)
Nefazodone	0 (0.0)	0 (0.0)	0 (0.0)
Trazodone	104 (32.6)	207 (25.8)	547 (19.6)
Venlafaxine	50 (15.7)	124 (15.5)	457 (16.4)
Stimulants	404 (12.7)	1,258 (15.2)	4,814 (17.4)

N = Total prescriptions obtained. Patients may have more than one prescription therefore the total N is not equal to the study sample size. Prescription fills are standardized to a 30-day supply.
SOURCE: Aim1b Incident Diagnosis Design Sample

Among atypical antipsychotic agents, aripiprazole, quetiapine, and risperidone were the most heavily prescribed agents over each time point. Clozapine, often considered to be the agent of last resort, was not used in any of the newly diagnosed patients in the first 30 or 90 days, but there were 9 fills for clozapine during the one year period. Finally, of antidepressant use, SSRIs were the most frequently filled antidepressants, followed by agents in the "other antidepressants" class. Among the SSRIs, escitalopram, fluoxetine, and sertraline were the most commonly filled agents. Bupropion was the most commonly filled drug of the other antidepressant over each time point.

Table 4.30 - Annual Payments for Medical Care by Bipolar Subtype: Aim 1b

	Bipolar I	Bipolar II	Bipolar NOS	Cyclothymia*
Total Medical Payments	N = 1,036	N = 398	N = 1,314	N = 97
Patient Payment				
Median (IQR), $	852 (1,721)	695 (1,185)	793 (1,236)	882 (1,183)
Mean (SD)	1,341 (1,274)	1,085 (1,151)	1,232 (1,592)	1,481 (3,097)
Patient & Insurer Payment				
Median (IQR), $	4,958 (8,346)	4,775 (7,186)	5,235 (8,316)	4,416 (4,738)
Mean (SD)	8,930 (13,140)	8,202 (14,270)	9,446 (15,011)	7,333 (9,808)
Inpatient Payments				
Patient Payment				
Median (IQR), $	0 (42)	0 (0)	0 (104)	0 (0)
Mean (SD)	348 (1,126)	221 (671)	292 (956)	535 (2,909)
Patient & Insurer Payment				
Median (IQR), $	0 (3,670)	0 (2,080)	0 (3,988)	0 (0)
Mean (SD)	3,424 (8,784)	3,046 (11,634)	3,861 (12,239)	1,842 (5,219)
Outpatient Payments				
Patient Payment				
Median (IQR), $	401 (682)	339 (576)	385 (665)	426 (683)
Mean (SD)	668 (931)	537 (574)	619 (916)	590 (573)
Patient & Insurer Payment				
Median (IQR), $	2,133 (3,219)	2,023 (3,256)	2,121 (3,068)	2,136 (2,477)
Mean (SD)	3,768 (6,868)	3,213 (3,547)	3,697 (5,187)	3,538,021 (5,555)
Medication Payments				
Patient Payment				
Median (IQR), $	213 (422)	198 (391)	182 (410)	238 (466)
Mean (SD)	325 (352)	328 (373)	320 (390)	356 (394)
Patient & Insurer Payment				
Median (IQR), $	1,057 (2,310)	1,162 (2,362)	1,015 (2,310)	1,232 (2,431)
Mean (SD)	1,739 (2,203)	1,943 (2,151)	1,888 (3,254)	1,953 (2,415)

SOURCE: Aim1b Incident Diagnosis Design Sample
All dollars are inflation adjusted to 2007 dollars using the Medical Consumer Price Index.
* Cyclothymia is considered to be the mildest disorder on the bipolar spectrum.

Payments made for medical care over one year following the patient's index diagnosis are summarized in Tables 4.30 and 4.31. Patient payments represent the total that the patient paid in copayments, coinsurance, and deductible payments. Patient and Insurer Payments represent the total payments made for services after applying pricing guidelines (fee schedules and discounts) but before applying deductibles, copayments, and coinsurance. Therefore, both the patient cost and the cost to the insurer are combined in this second cost

measure. When considering average payments for all patients, the mean patient medical payments ranged from $1,085 to $1,481 over the one year period following diagnosis. The mean total medical payments, when considering payments made by both patients and the insurance providers combined, ranged from $7,333 to $9,446.

When considering payments made by service users only, inpatient payments were highest for patients with Cyclothymic disorder (mean payment was $2,470). However, for all patient and insurer payments combined, inpatient services appeared to be slightly higher among patients with bipolar II disorder ($11,225).

Table 4.31 - Annual Payments for Medical Care by Service Type among Users, by Bipolar Subtype: Aim 1b

	Bipolar I	Bipolar II	Bipolar NOS	Cyclothymia*
Inpatient Payments	N = 331	N = 108	N = 458	N = 21
Patient Payment				
Median (IQR), $	520 (1,354)	477 (6,252)	433 (965)	758 (1,101)
Mean (SD)	1,088 (1,780)	807 (1,092)	839 (1,471)	2,470 (5,967)
Patient & Insurer Payment				
Median (IQR), $	6,505 (8,501)	5,652 (6,481)	6,277 (7,454)	5,117 (6,203)
Mean (SD)	10,715 (12,792)	11,225 (20,238)	11,078 (18,715)	8,509 (8,436)
Outpatient Payments	N = 1,026	N = 393	N = 1,307	N = 97
Patient Payment				
Median (IQR), $	406 (683)	344 (574)	387 (674)	426 (683)
Mean (SD)	674 (933)	543 (575)	622 (917)	590 (573)
Patient & Insurer Payment				
Median (IQR), $	2,163 (3,249)	2,076 (3,234)	2,140 (3,063)	2,136 (2,477)
Mean (SD)	3,804 (6,891)	3,253 (3,551)	3,717 (5,194)	3,538 (5,555)
Medication Payments	N = 923	N = 360	N = 1,148	N = 92
Patient Payment				
Median (IQR), $	260 (428)	231 (389)	235 (411)	262 (515)
Mean (SD)	365 (352)	362 (376)	367 (397)	376 (395)
Patient & Insurer Payment				
Median (IQR), $	1,316 (2,303)	1,346 (2,334)	1,278 (2,459)	1,349 (2,416)
Mean (SD)	1,952 (2,243)	2,148 (2,163)	2,161 (3,395)	2,059 (2,436)

SOURCE: Aim1b Incident Diagnosis Design Sample
All dollars are inflation adjusted to 2007 dollars using the Medical Consumer Price Index.
Sample sizes represent the number of people who received the type of medical care described.
* Cyclothymia is considered to be the mildest disorder on the bipolar spectrum.

4.3 Aim 2: Receipt of Appropriate First Line Therapy

In order to address Aims 2 and 3 of the research plan, the aim 1b study sample was restricted to patients who were initially diagnosed with bipolar I disorder, those with no evidence of hospitalizations 60 days prior to or 45 days post diagnosis, and children under the age of 6 years at the time of their diagnosis. Rationale regarding the use of these inclusion and exclusion criteria is provided in Chapter 3. After all exclusions, there were 730 patients remaining for aim 2 and aim 3 analyses.

Figure 4.6 - Inclusion and Exclusion Criteria: Aims 2 and 3

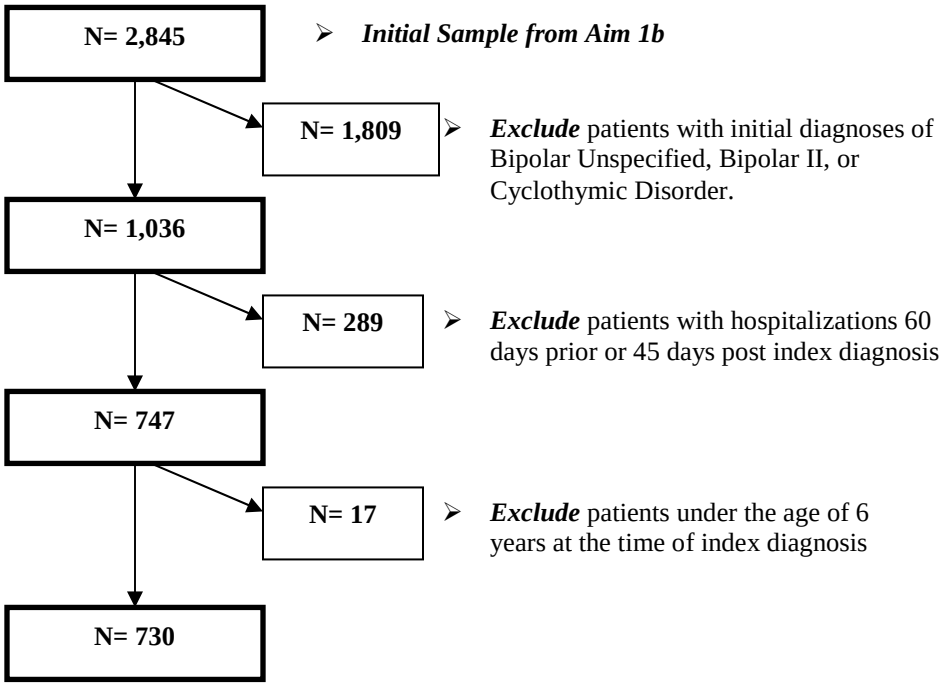


Table 4.32 provides basic frequency information for patient and provider characteristics by the type of care received, and overall. Based on the unadjusted frequencies, it appears that patients who received guideline recommended care were more likely to be in a

younger age group (31.7% vs. 23.9%) and were less likely to be female (46.7% versus 52.5%). They were more likely to be diagnosed with bipolar I mixed episode type (53.3% vs. 40.2%), and less likely to be diagnosed with a generic bipolar type (8.3% versus 20.0%). They were also less likely to have a diagnosis for a depressive disorder (major depressive disorder or dysthymic disorder, 13.3% versus 22.3%) at or prior to their bipolar diagnosis. Patients who received guideline recommended care also appeared to have been more likely to have received care by a psychiatrist (61.7% versus 40.3%), and less likely to receive care by a non-psychiatric mental health provider (8.3% versus 25.2%). Finally, patients who received guideline recommended care appeared to be slightly more likely to have treatment plans that included psychotherapy (71.7% versus 64.4%).

Table 4.33 provides information about the treatments received among those with and without recommended care. Among those who received recommended care, 55.8% received antipsychotics, 32.5% received anticonvulsants, and 11.7% received lithium. There were 66 children (10.8%) that received non-recommended anticonvulsants. These medications were used as monotherapy but were not recommended by the guidelines because of a lack of evidence for their use in children. Sensitivity analysis of an expanded guideline definition included these children as receiving appropriate care, but the primary analysis did not.

Among patients who did not receive the recommended treatments, a majority received no psychotropic medications (40.2%) and 25.2% received antidepressant monotherapy. Approximately 14% of children received combination therapy at treatment initiation.

Table 4.32- Patient and Physician Characteristics by Type of Care Received and Overall: Aim 2

	All Patients	Guideline Concordant	Guideline Discordant
	N = 730	N = 120	N = 610
Patient Characteristics			
Age - Mean (SD)	13.9 (2.9)	13.5 (3.4)	13.9 (2.8)
6 - 12 Years	184 (25.2)	38 (31.7)	146 (23.9)
13 - 17 Years	546 (74.8)	82 (68.3)	464 (76.1)
Sex - N (%) Female	376 (51.5)	56 (46.7)	320 (52.5)
Bipolar I Episode Type			
Bipolar I Mania	103 (14.1)	18 (15.0)	85 (13.9)
Bipolar I Depression	186 (25.5)	28 (23.3)	158 (25.9)
Bipolar I Mixed Episode	309 (42.3)	64 (53.3)	245 (40.2)
Generic Bipolar I	132 (18.1)	10 (8.3)	122 (20.0)
Comorbid Mental Health Diagnoses at Visit			
Attention Deficit Hyperactivity Disorder	144 (19.7)	22 (18.3)	122 (20.0)
Other Disruptive Behavioral Disorders	61 (8.4)	13 (10.8)	48 (7.9)
Anxiety Disorders	45 (6.2)	8 (6.7)	37 (6.1)
Depressive Disorders	152 (20.8)	16 (13.3)	136 (22.3)
Disease Severity			
Prior Comorbid Mental Health Conditions - Mean (SD)	0.67 (0.79)	0.60 (0.71)	0.68 (0.81)
Unique Diagnoses Prior to Bipolar Visit - Mean (SD)	4.5 (3.1)	4.5 (3.2)	4.5 (3.1)
Inpatient Mental Health Visits in Year	64 (8.8)	13 (10.8)	51 (8.4)
Psychosis Present at Visit	58 (7.9)	13 (10.8)	45 (7.4)
Physician Specialty			
Psychiatrist	320 (43.8)	74 (61.7)	246 (40.3)
Primary Care / M.D.	133 (18.2)	21 (17.5)	112 (18.4)
Other Mental Health	164 (22.5)	10 (8.3)	154 (25.2)
Other / Unclassified	105 (14.4)	15 (12.5)	90 (14.7)
Treatment Plan Included Psychotherapy*			
Yes	479 (65.6)	86 (71.7)	393 (64.4)
No	125 (17.1)	14 (11.7)	111 (18.2)
Unknown	126 (17.3)	20 (16.7)	106 (17.4)

SOURCE: Aim 2 Study Sample

* Only patients who had mental health / substance abuse coverage information provide to MarketScan were included for this variable. Those without coverage were categorized as unknown.

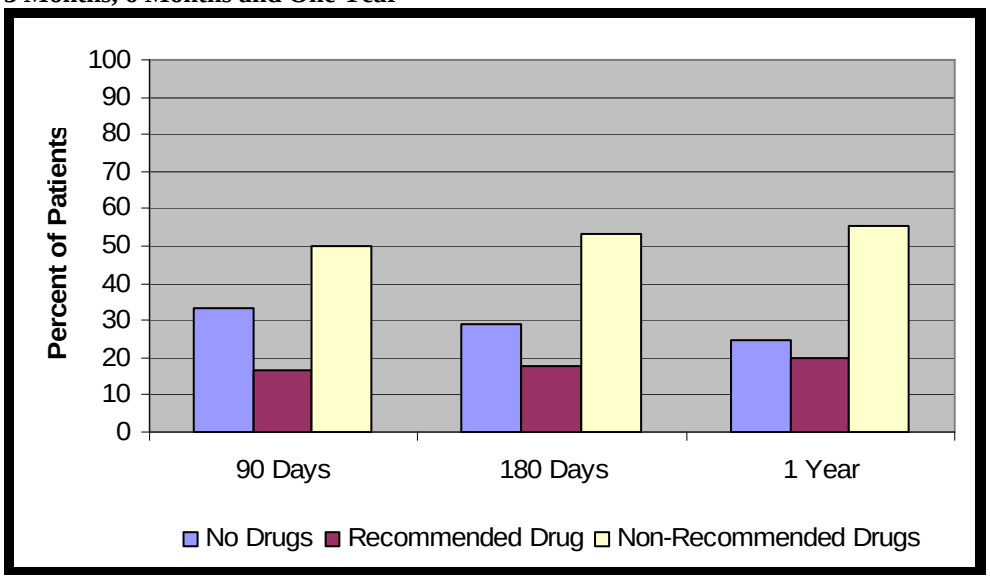
Table 4.33 Drug Class Use by guideline Concordance Status

Medication Class Use - Guideline Concordant Care	N = 120
Lithium	14 (11.7)
Anticonvulsants	39 (32.5)
Antipsychotics	67 (55.8)
Medication Class Use - Guideline Discordant Care	N = 610
No Medications in 90 Days	245 (40.2)
Single Class Use	
Non-Recommended Anticonvulsant	66 (10.8)
Non-Recommended Antipsychotic	0 (0.0)
Antidepressant	154 (25.2)
Stimulant	62 (10.2)
Combination Therapy	
Lithium + Anticonvulsant	1 (0.16)
Mood Stabilizer and Antipsychotic	16 (2.6)
Mood Stabilizer and Antidepressant	20 (3.3)
Mood Stabilizer and Stimulant	1 (0.16)
Antipsychotic and Antidepressant	19 (3.1)
Antipsychotic and Stimulant	7 (1.1)
Antidepressant and Stimulant	10 (1.6)
Three or More Classes	
Mood Stabilizer, Antipsychotic and Antidepressant	5 (0.82)
Mood Stabilizer, Antipsychotic and Stimulant	2 (0.33)
Mood Stabilizer, Antidepressant and Stimulant	2 (0.33)

SOURCE: Aim 2 Study Sample
Mood stabilizer category includes both lithium and anticonvulsants.

To assess the extent to which appropriate treatment was received over time, the assessment period was expanded to look at treatments over three timeframes: 90 days, 180 days, and 1 year. This was done to determine to what extent delays in treatment were influencing our classification of appropriate or inappropriate care. Figure 4.7 presents the type of care received over the three time points using the primary guideline concordance definition (only patients who received the medications listed as acceptable were considered guideline concordant). Figure 4.8 uses an expanded version of the guideline (including any monotherapy lithium, antipsychotic or anticonvulsant as acceptable).

Figure 4.7- Treatments Received After Initial Diagnosis of Bipolar I Disorder: 3 Months, 6 Months and One Year

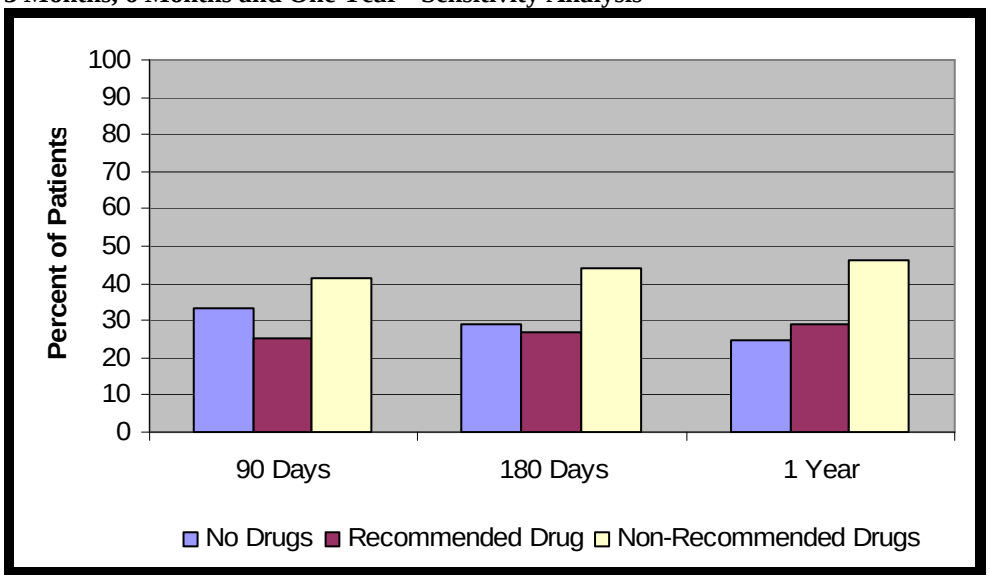


SOURCE: Aim 2 Study Sample
Recommended drugs include only those identified as acceptable in the 2005 or 2007 guidelines (Lithium, divalproex, carbamazepine, olanzapine, quetiapine, risperidone, ziprasidone or aripiprazole).

When considering the more restrictive definition of guideline concordant care, and the 90 day timeframe, only 16% of children received the recommended care (Figure 4.7). By expanding the timeframe to 180 days, and 1 year, we saw only a slight increase in the proportion of children who received recommended care (19.7% at one year). By one year, approximately 25% of children had no medication, and over 55% received non-recommended treatments.

Even when considering the less restrictive definitions for guideline concordant care (where all monotherapy lithium, antipsychotic or anticonvulsant treatments were acceptable), a majority receive non-recommended treatments (46% at one year), with only 29.3% receiving approved therapies in the same timeframe (Figure 4.8).

Figure 4.8 - Treatments Received After Initial Diagnosis of Bipolar I Disorder: 3 Months, 6 Months and One Year - Sensitivity Analysis



SOURCE: Aim 2 Study Sample
Recommended drugs include Lithium, any anticonvulsant monotherapy or any atypical antipsychotic monotherapy.

Unadjusted estimates of the risk of receiving guideline recommended care are provided in Table 4.34. Three definitions of guideline recommended care were considered: (1) explicit definition of guideline recommended care and non-recommended - only medications specifically recommended by guidelines, appropriate pharmacotherapy received; (2) expanded definition of guideline recommended care and non-recommended - any anticonvulsant or antipsychotic monotherapy considered appropriate; (3) guideline recommended and non-recommended, among only patients who received medication - explicit definition for recommended care, exclusion of patients who did not use medications (comparison of appropriate and inappropriate care among medications users). Corresponding risk ratios (crude and adjusted) are provided in Tables 4.35 - 4.37.

Table 4.34 - Risk of Receipt of Guideline Recommended Care by Guideline Definition: Aim 2, Unadjusted Estimates of Risk

	Proportion Receiving Recommended Care		
	Guideline Recommended Care	Expanded Guideline Definition	Medication Users Only
	N = 120 Concordant N = 610 Discordant	N = 184 Concordant N = 546 Discordant	N = 120 Concordant N = 367 Discordant
Categorical Variables			
Sex			
Female	0.149	0.261	0.220
Male	0.181	0.243	0.276
Insurance Generosity*			
Good	--	--	0.288
Fair	--	--	0.224
Bipolar I Episode Type			
Bipolar I Mania	0.175	0.282	0.273
Bipolar I Depression	0.150	0.242	0.228
Bipolar I Mixed Episode	0.207	0.317	0.296
Generic Bipolar I	0.076	0.091	0.122
Comorbid Mental Health Diagnoses at Visit			
Attention Deficit Hyperactivity Disorder	0.153	0.201	0.206
Other Disruptive Behavioral Disorders	0.213	0.295	0.317
Depressive Disorders	0.105	0.178	0.134
Disease Severity			
Inpatient Mental Health Visits in Year	0. 203	0.312	0.271
Psychosis Present at Visit	0.224	0.362	0.289
Physician Specialty			
Primary Care / M.D.	0.158	0.233	0.244
Other Mental Health	0.061	0.116	0.120
Other / Unclassified	0.143	0.200	0.197
Psychiatrist	0.231	0.353	0.306

Continued

Table 4.34 - Risk of Receipt of Guideline Recommended Care by Guideline Definition: Aim 2, Unadjusted Estimates of Risk (Continued)

	Proportion Receiving Recommended Care		
	Guideline Recommended Care	Expanded Guideline Definition	Medication Users Only
	N = 120 Concordant N = 610 Discordant	N = 184 Concordant N = 546 Discordant	N = 120 Concordant N = 367 Discordant
Categorical Variables			
Treatment Plan Included Psychotherapy			
Yes	0.179	0.273	0.251
Continuous Variables	Estimate (β)	Estimate (β)	Estimate (β)
Age	-0.0057	0.0023	-0.0113
Unique Diagnoses Prior to Bipolar Visit	0.0004	-0.0010	-0.0004

SOURCE: Aim 2 Study Sample
Unadjusted proportions (risks) were generated using SAS PROC GENMOD with a binomial distribution.
A log link was used for categorical variables and an identity link was used for continuous variables.
*Insurance generosity is only considered in the medication use analysis.

Primary Outcome Model Results - Aim 2

Crude and adjusted risk ratio estimates for the primary outcome model are provided in Table 4.35. This model defines guideline recommended care as the receipt of only those medications specifically recommended by guidelines. Patients with no medications or those with non-recommended medications were classified as receiving inappropriate therapy in this analysis.

When considering the unadjusted results, five variables were statistically significantly related to the receipt of guideline recommended care (Table 4.35). These were having a episode type coded as bipolar I mania, bipolar I depression, or bipolar I mixed (as compared with having a generic code for bipolar disorder; having a depressive disorder on or before the initial bipolar diagnosis, and receiving a diagnosis from a non-psychiatric mental health provider. In the adjusted model, each of these variables were significant at the $p < 0.10$ level, and three were significant at a $p < 0.05$ level. These were bipolar I mixed episode type (RR: 2.21, 95%CI: 1.15, 4.20), having a depressive disorder on or before the initial bipolar diagnosis (RR: 0.60, 95%CI: 0.36, 0.98), and receiving a diagnosis from a non-psychiatric mental health provider (RR: 0.28, 95%CI: 0.15, 0.53).

Sensitivity Analysis Results - Part 1, Aim 2

Crude and adjusted risk ratio estimates for the first sensitivity analysis of aim 2 are presented in Table 4.36. This model defines guideline recommended care as the receipt of any monotherapy mood stabilizer or antipsychotic medication. Patients with no medications or those with non-recommended medications were classified as receiving inappropriate therapy in this analysis.

When considering the unadjusted results (Table 4.36), eight variables were statistically significantly related to the receipt of guideline recommended care once the definition for guideline recommended care was expanded. In the unadjusted model, the bipolar episode type (manic, depressive, or mixed), and the presence of psychosis at the time of diagnosis was associated with a higher likelihood of receiving recommended treatment. Depressive disorders on or before the index bipolar diagnosis reduced the likelihood that a patient would receive recommended treatment, as did receiving a diagnosis from any non-psychiatric provider.

The adjusted results remained somewhat consistent with the crude analysis results; however, after adjustment, psychosis was no longer a statistically significant predictor of receiving guideline recommended treatment, and the presence of inpatient mental health days became a statistically significant predictor (RR: 1.58, 95% CI: 1.11, 2.24). In the adjusted model, as in the crude, each of the bipolar episode types were associated with receiving recommended first line therapy (as compared with receiving a generic bipolar diagnosis type). The corresponding risk ratios were 2.83 (95%CI: 1.52, 5.26) for bipolar I mania, 2.28 (95%CI: 1.26, 4.12) for bipolar I depression, and 2.85 (95%CI: 1.62, 5.03) for bipolar I mixed episode type. Having a co-morbid diagnosis for attention deficit hyperactivity disorder or a depressive disorder decreased a patient's likelihood of receiving recommended treatment (RR: 0.65, 95% CI: 0.46, 0.92, and RR: 0.61, 95%CI: 0.42, 0.87, respectively). Finally, two provider types were associated with a lower likelihood of receiving recommended first line treatment. These were non-psychiatric mental health

professionals (RR: 0.35, 95%CI: 0.22, 0.54), and Other / Unclassified professionals (RR: 0.59, 95%CI: 0.40, 0.89).

Sensitivity Analysis Results - Part 2, Aim 2

The final model for aim 2 utilized the same definition for guideline recommended first line treatment as the primary outcome measure. However, patients were categorized as receiving guideline non-recommended treatment only if they received a non-recommended drug. In this case, patients who received no medications were excluded from the analysis. Crude and adjusted risk ratio estimates for this model are provided in Table 4.37.

In the unadjusted model, there were four predictors that were related to receipt of recommended first line therapy. These were having a diagnosis for bipolar I mania, or bipolar I mixed episode type, having a depressive disorder at the time of bipolar diagnosis, and receiving the diagnosis from a non-psychiatric mental health provider. In the adjusted model, each of these factors was identified as being statistically significantly related to the outcome, with the exception of bipolar I manic episode type ($p = 0.07$).

Summary of Aim 2 Results

A-priori hypotheses regarding the receipt of appropriate care were that patients who received guideline discordant care were more likely to:

- have a younger age of diagnosis (H_{02a})
- be male (H_{02b})
- have more generous insurance benefits (H_{02c})
- have co-morbid mental health conditions (H_{02d})
- have higher levels of disease severity (H_{02e})

- have an initial diagnosis of bipolar I depressed episode (H_{02f})
- have treatment plans that exclude psychotherapy or counseling (H_{02g})
- have received their diagnosis from a provider other than a psychiatrist (H_{02h})

Across all three guideline concordance definitions, there were several variables that were consistently related (either positively or negatively associated) to the receipt of guideline recommended care (Tables 4.35 - 4.37). These were having a diagnosis code for bipolar I mixed type episode, having a depressive disorder diagnosis (major depressive disorder or dysthymic disorder) on or prior to bipolar diagnosis, and receiving care by a non-psychiatric mental health professional.

Patient age was not related to the receipt of guideline recommended care in any of the models (crude or adjusted) for any definition of the outcome. Sex was also unrelated in the crude and adjusted analyses. Similarly, the generosity of a patient's insurance benefits did not appear to be related to the receipt of guideline appropriate care, although it is important to note that this variable was only considered for the Medication Users sensitivity analysis (Table 4.37).

The influence of comorbid mental health conditions was more complex than originally anticipated. Previous studies have suggested that ADHD and other disruptive disorders could be combined into a single category. However, we found that these disorders differed in their relationships to the outcome. We found that ADHD was related to a lower likelihood of receiving recommended care (marginally significant in the adjusted model for the original definition, and statistically significant in the other models at a $p < 0.10$). Surprisingly, the other disruptive disorders (oppositional defiant disorder and conduct

disorder, combined) were associated with a higher likelihood of receiving recommended care for all comparisons (although this finding was not statistically significant).

Of the mental health comorbidities, the presence of depressive disorders on or before bipolar diagnosis was related to a lower likelihood of receiving recommended care. This relationship was consistent across all models. Using the primary outcome definition of guideline recommended care (Table 4.35), the adjusted estimate for the effect of depressive disorder comorbidities was RR: 0.60 (95%CI: 0.36, 0.98). This indicated that patients with existing or comorbid diagnoses of major depressive disorder or dysthymic disorder were 40% less likely to receive recommended care as those without these comorbidities.

When considering the role of disease severity, three indicators were used: number of unique diagnoses prior to the bipolar diagnosis, any inpatient mental health visits during the study period, and psychosis at initial presentation. The first of these indicators, number of unique diagnoses, was not significantly related to the receipt of recommended care in any model tested. When considering the role of inpatient mental health visits, it appeared that patients who had inpatient mental health visits were more likely to receive recommended care when considering the primary outcome definition (Table 4.35, RR: 1.53, 95%CI: 0.95, 2.47) and the expanded definition (Table 4.36, RR: 1.58, 95%CI: 1.11, 2.24); although some estimates were not statistically significant. Similarly, the presence of psychosis also appeared to increase the likelihood of receiving guideline recommended care (Table 4.35, RR: 1.18, 95%CI: 0.71, 1.96; primary outcome definition, adjusted model) but this result was not statistically significant in any model. It is important to note that there were only a small

number of patients who had inpatient visits or the presence of psychosis, likely one reason for the variability in the estimates.

The role of the initial episode type indicated that patients with coding for specific bipolar I episode types were more likely to receive recommended care than those with a generic bipolar diagnosis (ICD-9 codes 296.0x or 296.1x). The risk ratio for receiving recommended care for the primary outcome definition (Table 4.35, adjusted estimates) was 1.97 (95%CI: 0.94, 4.13) for patients with bipolar I manic type episode, 1.80 (95%CI: 0.91, 3.56) for patients with bipolar I depressed type episode, and 2.21 (95%CI: 1.16, 4.20) for patients with mixed type episodes.

Use of psychotherapy in a patients' treatment plan also appeared to be positively related to the use of guideline recommended care. The risk ratio for receiving recommended care for the primary outcome definition was 1.44 (95%CI: 1.00, 2.09), and that for the expanded outcome definition was 1.31 (95%CI: 1.00, 1.72). However, use of psychotherapy was not statistically related to the receipt of guideline recommended care when restricting to patients with medication use only (Table 4.37).

Finally, when comparing the type of provider that initiated treatment, it appeared that receiving guideline recommended care was much more likely if a patient received treatment from a psychiatrist. Using psychiatry as the reference group, the risk ratio for receiving recommended care was lower among all other specialties as compared with psychiatry, although most estimates were not statistically significant. Perhaps most notably, the probability of receiving recommended care was lowest among non-psychiatric mental health professionals. This was true across all comparisons, even those that considered only

medication users (non-users were excluded). The risk ratio for receiving recommended care was 0.28 (95% CI: 0.15, 0.53, primary guideline definition, adjusted estimate) for other mental health providers, as compared with psychiatrists. This indicates that patients who received care from a non-psychiatric mental health provider were 72% less likely to receive guideline recommended care as those who received their treatment from a psychiatrist. When looking among medication users only, patients who see a non-psychiatric mental health provider were 53% less likely to receive recommended care (Adjusted RR: 0.47, 95%CI: 0.25, 0.86).

Table 4.35- Risk Ratio for Receipt of Guideline Recommended Care: Aim 2 Primary Guideline Definition

	Crude Risk Ratio	95% CI	Crude p-value	Adjusted Risk Ratio	95% CI	Adjusted p-value
Categorical Variables						
Sex						
Female	0.82	(0.59, 1.14)	0.247	0.96	(0.69, 1.33)	0.794
Male	1.00	REF		1.00	REF	
Bipolar I Episode Type						
Bipolar I Mania	2.31	(1.11, 4.78)	0.025	1.97	(0.94, 4.13)	0.072
Bipolar I Depression	1.99	(1.00, 3.95)	0.050	1.80	(0.91, 3.56)	0.093
Bipolar I Mixed	2.73	(1.45, 5.16)	0.002	2.21	(1.16, 4.20)	0.015
Generic Bipolar I	1.00	REF		1.00	REF	
Comorbid Mental Health Diagnoses at Visit						
Attention Deficit Hyperactivity Disorder	0.91	(0.60, 1.40)	0.677	0.72	(0.47, 1.11)	0.135
Other Disruptive Behavioral Disorders	1. 33	(0.79, 2.22)	0.272	1.20	(0.73, 1.97)	0.476
Depressive Disorders	0. 58	(0.36, 0.96)	0.033	0.60	(0.36, 0.98)	0.043
Disease Severity						
Inpatient Mental Health Visits in Year	1.26	(0.75, 2.12)	0.372	1.53	(0.95, 2.47)	0.079
Psychosis Present at Visit	1.41	(0.85, 2.34)	0.188	1.18	(0.71, 1.96)	0.527
Physician Specialty						
Primary Care / M.D.	0.68	(0.44, 1.06)	0.089	0.86	(0.55, 1.36)	0.526
Other Mental Health	0.26	(0.14, 0.50)	< 0.001	0.28	(0.15, 0.53)	< 0.001
Other / Unclassified	0.62	(0.37, 1.03)	0.064	0.67	(0.40, 1.12)	0.127
Psychiatrist	1.00	REF		1.00	REF	

Continued

Table 4.35- Risk Ratio for Receipt of Guideline Recommended Care: Aim 2 Primary Guideline Definition (Continued)

	Crude Risk Ratio	95% CI	Crude p-value	Adjusted Risk Ratio	95% CI	Adjusted p-value
Categorical Variables						
Treatment Plan Included Psychotherapy						
Yes	1.32	(0.92, 1.91)	0.132	1.44	(1.00, 2.09)	0.050
Continuous Variables	Estimate (β)	95% CI	Crude p-value	Adjusted Estimate (β)	95% CI	Adjusted p-value
Age	-0.0057	(-0.01, 0.00)	0.210	-0.040	(-0.09, 0.01)	0.132
Diagnoses Prior to Bipolar Visit	0.0004	(-0.01, 0.01)	0.919	0.0123	(-0.04, 0.06)	0.639

SOURCE: Aim 2 Study Sample
Reference category for dichotomous variables is 0, condition not present.
Crude risk ratios were generated using SAS PROC GENMOD with a binomial distribution.
A log link was used for categorical variables and an identity link was used for continuous variables.
Adjusted risk ratios were calculated using a log binomial model, controlling for each variable listed above.

Table 4.36- Risk Ratio for Receipt of Guideline Recommended Care: Aim 2 Expanded Guideline Definition

	Crude Risk Ratio	95% CI	Crude p-value	Adjusted Risk Ratio	95% CI	Adjusted p-value
Categorical Variables						
Sex						
Female	1.07	(0.83, 1.38)	0.583	1.20	(0.94, 1.54)	0.150
Male	1.00	REF		1.00	REF	
Bipolar I Episode Type						
Bipolar I Mania	3.10	(1.66, 5.77)	<0.001	2.83	(1.52, 5.26)	0.001
Bipolar I Depression	2.66	(1.47, 4.83)	0.001	2.28	(1.26, 4.12)	0.006
Bipolar I Mixed	3.49	(1.98, 6.13)	<0.001	2.85	(1.62, 5.03)	< 0.001
Generic Bipolar I	1.00	REF		1.00	REF	
Comorbid Mental Health Diagnoses at Visit						
Attention Deficit Hyperactivity Disorder	0. 76	(0.53, 1.08)	0.129	0.65	(0.46, 0.92)	0.015
Other Disruptive Behavioral Disorders	1.19	(0.78, 1.79)	0.407	1.11	(0.76, 1.61)	0.586
Depressive Disorders	0.65	(0.45, 0.94)	0.023	0.61	(0.42, 0.87)	0.006
Disease Severity						
Inpatient Mental Health Visits in Year	1.27	(0.86, 1.87)	0.227	1.58	(1.11, 2.24)	0.010
Psychosis Present at Visit	1.49	(1.03, 2.15)	0.032	1.30	(0.91, 1.86)	0.149
Physician Specialty						
Primary Care / M.D.	0.66	(0.47, 0.93)	0.017	0.84	(0.60, 1.18)	0.308
Other Mental Health	0.33	(0.21, 0.51)	< 0.001	0. 35	(0.22, 0.54)	< 0.001
Other / Unclassified	0.57	(0.38, 0.85)	0.007	0.59	(0.40, 0.89)	0.011
Psychiatrist	1.00	REF		1.00	REF	

Continued

Table 4.36- Risk Ratio for Receipt of Guideline Recommended Care: Aim 2 Expanded Guideline Definition (Continued)

	Crude Risk Ratio	95% CI	Crude p-value	Adjusted Risk Ratio	95% CI	Adjusted p-value
Categorical Variables						
Treatment Plan Included Psychotherapy						
Yes	1.29	(0.98, 1.71)	0.070	1.31	(1.00, 1.72)	0.052
Continuous Variables	Estimate (β)	95% CI	Crude p-value	Adjusted Estimate (β)	95% CI	Adjusted p-value
Age	0.0023	(-0.01, 0.01)	0.665	0.001	(-0.04, 0.04)	0.942
Diagnoses Prior to Bipolar Visit	-0.0010	(-0.01, 0.01)	0.836	0.005	(-0.04, 0.05)	0.829

SOURCE: Aim 2 Study Sample
Reference category for dichotomous variables is 0, condition not present.
Crude risk ratios were generated using SAS PROC GENMOD with a binomial distribution.
A log link was used for categorical variables and an identity link was used for continuous variables.
Adjusted risk ratios were calculated using a log binomial model, controlling for each variable listed above.

Table 4.37- Risk Ratio for Receipt of Guideline Recommended Care: Aim 2, Medication Users Only

	Crude Risk Ratio	95% CI	Crude p-value	Adjusted Risk Ratio	95% CI	Adjusted p-value
Categorical Variables						
Sex						
Female	0. 80	(0.58, 1.09)	0.151	0.94	(0.68, 1.30)	0.726
Male	1.00	REF		1.00	REF	
Insurance Generosity						
Good	1.29	(0.94, 1.76)	0.111	1.11	(0.81, 1.53)	0.521
Fair	1.00	REF		1.00	REF	
Bipolar I Episode Type						
Bipolar I Mania	2.34	(1.11, 4.51)	0.025	1.95	(0.95, 3.98)	0.067
Bipolar I Depression	1.87	(0.96, 3.63)	0.066	1.88	(0.97, 3.64)	0.063
Bipolar I Mixed	2.43	(1.31, 4.50)	0.005	2.16	(1.15, 4.04)	0.017
Generic Bipolar I	1.00	REF		1.00	REF	
Comorbid Mental Health Diagnoses at Visit						
Attention Deficit Hyperactivity Disorder	0.80	(0.53, 1.21)	0.278	0.68	(0.45, 1.03)	0.068
Other Disruptive Behavioral Disorders	1.32	(0.82, 2.13)	0.253	1.21	(0.74, 1.97)	0.442
Depressive Disorders	0.48	(0.29, 0.77)	0.003	0.50	(0.30, 0.84)	0.008
Disease Severity						
Inpatient Mental Health Visits in Year	1.11	(0.68, 1.82)	0.675	1.38	(0.87, 2.20)	0.174
Psychosis Present at Visit	1.19	(0.73, 1.94)	0.477	1.06	(0.65, 1.74)	0.812
Physician Specialty						
Primary Care / M.D.	0.80	(0.53, 1.21)	0.291	0.97	(0.62, 1.51)	0.879
Other Mental Health	0.39	(0.21, 0.73)	0.003	0.47	(0.25, 0.86)	0.015
Other / Unclassified	0.64	(0.39, 1.05)	0.081	0.71	(0.43, 1.15)	0.166
Psychiatrist	1.00	REF		1.00	REF	

Continued

Table 4.37- Risk Ratio for Receipt of Guideline Recommended Care: Aim 2, Medication Users Only (Continued)

	Crude Risk Ratio	95% CI	Crude p-value	Adjusted Risk Ratio	95% CI	Adjusted p-value
Categorical Variables						
Treatment Plan Included Psychotherapy						
Yes	1.06	(0.75, 1.50)	0.734	1.10	(0.70, 1.72)	0.685
Continuous Variables	Estimate (β)	95% CI	Crude p-value	Adjusted Estimate (β)	95% CI	Adjusted p-value
Age	-0.0113	(-0.02, 0.00)	0.091	-0.043	(-0.09, 0.00)	0.064
Diagnoses Prior to Bipolar Visit	-0.0004	(-0.01, 0.01)	0.946	0.018	(-0.03, 0.06)	0.454

SOURCE: Aim 2 Study Sample
Reference category for dichotomous variables is 0, condition not present.
Crude risk ratios were generated using SAS PROC GENMOD with a binomial distribution.
A log link was used for categorical variables and an identity link was used for continuous variables.
Adjusted risk ratios were calculated using a log binomial model, controlling for each variable listed above.

4.4 Aim 3: Receipt of Early Treatment Changes

In order to address Aim 3 of the research plan, patients who did not receive any medications within 90 days of their initial bipolar diagnosis were excluded from the initial sample for Aims 2 and 3. After excluding patients who did not have medication use, there were 487 patients available for the analyses.

Three samples were used for Aim 3 analysis. The primary analysis used a 6-week timeframe to assess medication therapy changes. Additionally, this definition required that patients only be included if they had continuous medication therapy over the 6 week timeframe (more than one medication fill and/or more than 42 days of medication supply, N = 375). A secondary analysis was conducted in which patients who discontinued therapy early were considered to have received non-recommended care (early treatment regimen changes, N = 486). Finally, the primary analysis was revised to consider early medication changes over the first four weeks of therapy (rather than 6 weeks), as guidelines recommend medication therapy to last between 4 and 6 weeks (N = 470).

Patients who continued therapy were similar to those who discontinued therapy, with the exception of one predictor. Those who discontinued early were less likely to have antidepressants as part of their initial treatment regimen as compared with those who continued therapy (Crude RR: 0.63, 95%CI: 0.44, 0.90).

Table 4.38 provides basic frequency information for patient and provider characteristics by the type of care received and overall for patients included in the primary analysis for Aim 3. Based on the unadjusted frequencies, it appeared that patients who discontinued early were less likely to have a generic bipolar diagnosis. They were also more

likely to have comorbid Attention Deficit Hyperactivity Disorder or Other Disruptive Behavioral disorders and less likely to have a depressive disorder at the time of their bipolar diagnosis. Overall, it appeared that disease severity measures did not differ between those who received the recommended time on treatment and those that did not, with the exception of the presence of psychosis. Patients who received early treatment regimen changes were more likely to have psychosis than those who did not. Finally, it appeared that having psychotherapy as part of the treatment plan was related to having early regimen changes.

Table 4.38- Patient and Physician Characteristics by Type of Care Received and Overall: Aim 3

	All Patients	Guideline Concordant	Guideline Discordant
	N = 375	N = 222	N = 153
Patient Characteristics			
Age - Mean (SD)	13.9 (2.9)	13.8 (2.9)	13.9 (3.0)
6 - 11 Years	39 (10.4)	21 (9.5)	18 (11.8)
12-14 Years	88 (23.5)	58 (26.1)	30 (19.6)
15-17 Years	248 (66.1)	143 (64.4)	105 (68.6)
Sex - N (%) Female	200 (53.3)	122 (54.9)	78 (51.0)
Bipolar I Episode Type			
Bipolar I Mania	46 (12.3)	26 (11.7)	20 (13.1)
Bipolar I Depression	99 (26.4)	56 (25.2)	43 (28.1)
Bipolar I Mixed Episode	171 (45.6)	99 (44.6)	72 (47.1)
Generic Bipolar I	59 (15.7)	41 (18.5)	18 (11.8)
Comorbid Mental Health Diagnoses at Visit			
Attention Deficit Hyperactivity Disorder	89 (23.7)	44 (19.8)	45 (29.4)
Other Disruptive Behavioral Disorders	27 (7.2)	11 (4.9)	16 (10.5)
Anxiety Disorders	31 (8.3)	21 (9.5)	10 (6.5)
Depressive Disorders	98 (26.1)	62 (27.9)	36 (23.5)
Disease Severity			
Prior Comorbid Mental Health Conditions - Mean (SD)	0.79 (0.83)	0.75 (0.80)	0.86 (0.87)
Unique Diagnoses Prior to Bipolar Visit - Mean (SD)	4.5 (2.8)	4.6 (2.9)	4.3 (2.6)
Inpatient Mental Health Visits in Year	35 (9.3)	20 (9.0)	15 (9.8)
Psychosis Present at Visit	32 (8.5)	14 (6.3)	18 (11.8)
Physician Specialty			
Psychiatrist	187 (49.9)	112 (50.4)	75 (49.0)
Primary Care Physician / M.D.	56 (14.9)	36 (16.2)	20 (13.1)
Other Mental Health Professional	68 (18.1)	38 (17.1)	30 (19.6)
Other / Unclassified	64 (17.1)	36 (16.2)	28 (18.3)
Treatment Plan Included Psychotherapy			
Yes	269 (71.7)	154 (69.4)	115 (75.2)
No	53 (14.1)	34 (15.3)	19 (12.4)
Unknown*	48 (12.8)	31 (14.0)	17 (11.1)

SOURCE: Aim 3 Study Sample, primary outcome definition.

Table 4.39- Medication Regimen at Treatment Initiation by Type of Care Received and Overall: Aim 3

	All Patients	Guideline Concordant	Guideline Discordant
	N = 375	N = 222	N = 153
Initially Prescribed Therapy			
Lithium in Initial Regimen	**18 (4.8)**	**9 (4.0)**	**9 (5.9)**
Monotherapy Only	10 (55.5)	4 (44.4)	6 (66.7)
Anticonvulsant in Initial Regimen	**114 (30.4)**	**60 (27.0)**	**54 (35.3)**
Monotherapy Only	64 (56.1)	35 (58.3)	29 (53.7)
Antipsychotic in Initial Regimen	**103 (27.5)**	**58 (26.1)**	**45 (29.4)**
Monotherapy Only	46 (44.7)	29 (50.0)	17 (37.8)
Antidepressant in Initial Regimen	**177 (47.2)**	**108 (48.6)**	**69 (45.1)**
Monotherapy Only	104 (58.8)	67 (62.0)	37 (53.6)
Stimulant in Initial Regimen	**73 (19.5)**	**44 (19.8)**	**29 (18.9)**
Monotherapy Only	42 (57.5)	27 (61.4)	15 (51.7)

* Among patients who had continuous therapy over the first 6 weeks, primary outcome definition.

Table 4.39 provides a summary of initially prescribed treatment regimens for patients in the primary analysis. Overall, the most commonly prescribed class of psychotropic medications were antidepressants. Approximately 47% of all patients received an antidepressant in their initial therapy, and nearly 60% of those patients received monotherapy antidepressant treatment. Patients who had early regimen changes appeared to be more likely to have initial therapies that included anticonvulsants or antipsychotics, as compared with those who did not have early regimen changes. The patients who had early regimen changes were also less likely to have initially prescribed antidepressants.

Table 4.40 provides information on the risk of receiving an early treatment regimen change by the population studied. Risk of changes were highest when using the 6 week timeframe and when classifying those who did not have continuous therapy as receiving non-recommended care. The risk estimates were lowest when using the 4 week discontinuation definition as a majority of patients had medication coverage during that time and regimen changes in this timeframe were less common.

Table 4.40 - Risk of Receipt of Early Treatment Regimen Changes by Population Selected: Aim 3, Unadjusted Estimates of Risk

	Proportion Receiving Early Regimen Changes		
	Changes in 6 Weeks, Continuous Users	Changes in 6 Weeks, All Users	Changes in 4 Weeks, Continuous Users
	N = 222 Concordant N = 153 Discordant	N = 221 Concordant N = 265 Discordant	N = 378 Concordant N = 92 Discordant
Categorical Variables			
Age			
6-11 Years	0. 461	0.571	0. 255
12-14 Years	0.341	0.468	0.165
15-17 Years	0.423	0.567	0.197
Sex			
Female	0.390	0.520	0.183
Male	0.429	0.573	0.210
Insurance Generosity			
Good	0.447	0.554	0.233
Fair	0.387	0.537	0.178
Bipolar I Episode Type			
Bipolar I Mania	0.435	0.606	0.254
Bipolar I Depression	0.434	0.541	0.231
Bipolar I Mixed	0.421	0.546	0.192
Generic Bipolar I	0.305	0.500	0.103
Comorbid Mental Health Diagnoses at Visit			
Attention Deficit Hyperactivity Disorder	0.506	0.589	0.272
Other Disruptive Behavioral Disorders	0.593	0.732	0.263
Depressive Disorders	0.367	0.483	0.179
Disease Severity			
Inpatient Mental Health Visits in Year	0.429	0.583	0.217
Psychosis Present at Visit	0.562	0.689	0.238

Continued

Table 4.40 - Risk of Receipt of Early Treatment Regimen Changes by Population Selected: Aim 3, Unadjusted Estimates of Risk (Continued)

	Proportion Receiving Early Regimen Changes		
	Changes in 6 Weeks, Continuous Users	Changes in 6 Weeks, All Users	Changes in 4 Weeks, Continuous Users
	N = 222 Concordant N = 153 Discordant	N = 221 Concordant N = 265 Discordant	N = 378 Concordant N = 92 Discordant
Non-Mental Health Professional	0. 400	0.553	0.192
Mental Health Professional	0.412	0.541	0.197
Treatment Plan Included Psychotherapy			
Yes	0.427	0.554	0.210
Initial Treatment Characteristics			
Antidepressant at Initial Treatment	0.390	0.498	0.181
Combination Therapy at Initial Treatment	0.453	0.453	0.221
Continuous Variables	Estimate (β)	Estimate (β)	Estimate (β)
Unique Diagnoses Prior to Bipolar Visit	-0.0192	0.0073	-0.0126

Unadjusted proportions (risks) were generated using SAS PROC GENMOD with a binomial distribution.
A log link was used for categorical variables and an identity link was used for continuous variables.

Primary Outcome Model Results - Aim 3

Crude and adjusted risk ratio estimates for the primary outcome model are provided in Table 4.41. This model defines guideline recommended care as having no medication switching or augmenting within the first 6 weeks following initial bipolar I treatment. Patients who did not have continuous medication use over the 6 week period were excluded from this analysis.

When considering the unadjusted results, three variables were statistically significantly related to the receipt of guideline recommended care (Table 4.41). These were having comorbid attention deficit hyperactivity disorder (RR: 1.34, 95%CI: 1.04, 1.72), having other disruptive behavioral disorders (RR: 1.50, 95%CI: 1.07, 2.11), and having psychosis at the initial bipolar visit (RR: 1.43, 95%CI: 1.02, 1.99). After adjustment, however, only one factor remained statistically significantly related to the outcome at the p = 0.05 level (comorbid ADHD).

Sensitivity Analysis Results - Part 1, Aim 3

Crude and adjusted risk ratio estimates for the first sensitivity analysis of aim 3 are presented in Table 4.42. Similar to the primary outcome model, this model defines guideline recommended care as having no medication switching or augmenting within the first 6 weeks following initial bipolar I treatment. However, patients who did not have continuous medication use over the 6 week period were included in this model as having received guideline discordant care.

When considering the unadjusted results (Table 4.42), only other behavioral disorders and psychosis were related to the likelihood of having early treatment regimen changes

(RR: 1.39, 95%CI: 1.13, 1.70, and RR: 1.30, 95%CI: 1.05, 1.61, respectively). In the adjusted model, only the presence of comorbid disruptive behavior disorders remained statistically significantly related to the outcome (RR: 1.30, 95%CI: 1.04, 1.63).

Sensitivity Analysis Results - Part 2, Aim 3

The final model for aim 3 utilized the same definition for guideline recommended first line treatment as the primary outcome measure, however treatment changes were evaluated within the first 4 weeks (rather than 6 weeks) for this analysis.

In the unadjusted model, there were three predictors that were related to receipt of recommended first line therapy. These were having a diagnosis for bipolar I mania, or bipolar I depressive episode type, and having a comorbid diagnosis for ADHD. In the adjusted model, two of these factors was identified as being statistically significantly related to the outcome (at $p = 0.05$). These were having an initial episode type coded as bipolar I mania (RR: 2.50, 95%CI: 1.12, 5.59), and having an initial episode type coded as bipolar I depression (RR: 2.37, 95%CI: 1.12, 5.02).

Summary of Aim 3 Results

A-priori hypotheses regarding the receipt of appropriate care were that patients who received guideline discordant care were more likely to:

- have a younger age of diagnosis (H_{03a})
- be male (H_{03b})
- have less generous insurance benefits (H_{03c})
- have co-morbid mental health conditions (H_{03d})
- have higher levels of disease severity (H_{03e})

- have an initial diagnosis of bipolar I depressed episode (H_{02f})
- have treatment plans that exclude psychotherapy or counseling (H_{02g})
- have received their diagnosis from a non-mental health provider (H_{03h})
- be initially prescribed an antidepressant (H_{03j})
- use combination treatments(H_{03j})

Across all models (6 week, continuous users only; 6 week, all users; 4 week, continuous users) patient age and sex were unrelated to the risk of early treatment regimen changes. This was true for both the crude estimates and the adjusted estimates (Tables 4.41 - 4.43). Similarly insurance generosity, the type of provider, or having treatment plans that included psychotherapy, having an antidepressant in the initial medication regimen, or using combination therapy from initiation were not related to an increased risk of receiving early treatment changes.

Regarding disease severity, having psychosis appeared to increase the risk of receiving early regimen changes in two of the crude models, but this result was inconsistent and not seen in the adjusted model. Initial bipolar subtype appeared to be unrelated to the receipt of early regimen changes, with the exception of the model that utilized a 4 week assessment period (Table 4.43). In this model, bipolar I depressive episode type and bipolar I manic episode type appeared to increase the risk of early treatment changes.

Table 4.41- Risk Ratio for Receipt of Early Treatment Regimen Changes within the First 6 Weeks of Treatment - Medication Continuers Only: Aim 3

	Crude Risk Ratio	95% CI	Crude p-value	Adjusted Risk Ratio	95% CI	Adjusted p-value
Categorical Variables						
Sex						
Female	0.91	(0.71, 1.16)	0.448	0.94	(0.73, 1.22)	0.660
Male	1.00	REF		1.00	REF	
Insurance Generosity						
Good	1.15	(0.90, 1.47)	0.251	1.11	(0.86, 1.42)	0.426
Fair	1.00	REF		1.00	REF	
Bipolar I Episode Type						
Bipolar I Mania	1.42	(0.86, 2.37)	0.171	1.23	(0.71, 2.14)	0.460
Bipolar I Depression	1.42	(0.91, 2.22)	0.120	1.40	(0.89, 2.22)	0.146
Bipolar I Mixed Episode	1.38	(0.90, 2.11)	0.136	1.30	(0.84, 2.02)	0.235
Generic Bipolar I	1.00	REF		1.00	REF	
Comorbid Mental Health Diagnoses at Visit						
Attention Deficit Hyperactivity Disorder	1.34	(1.04, 1.72)	0.024	1.33	(1.01, 1.74)	0.040
Other Disruptive Behavioral Disorders	1.50	(1.07, 2.11)	0.018	1.45	(0.98, 2.14)	0.062
Depressive Disorders	0. 87	(0.65, 1.17)	0.352	0.95	(0.69, 1.31)	0.755
Disease Severity						
Inpatient Mental Health Visits in Year	1.06	(0.70, 1.58)	0.797	1.12	(0.74, 1.70)	0.581
Psychosis	1.43	(1.02, 1.99)	0.035	1.23	(0.85, 1.78)	0.273

Continued

Table 4.41- Risk Ratio for Receipt of Early Treatment Regimen Changes within the First 6 Weeks of Treatment - Medication Continuers Only: Aim 3 (Continued)

	Crude Risk Ratio	95% CI	Crude p-value	Adjusted Risk Ratio	95% CI	Adjusted p-value
Categorical Variables						
Physician Specialty						
Non-Mental Health Professional	0.97	(0.75, 1.26)	0.829	1.06	(0.80, 1.40)	0.680
Mental Health Professional	1.00	REF		1.00	REF	
Treatment Plan Included Psychotherapy						
Yes	1.19	(0.89, 1.59)	0.234	1.12	(0.83, 1.51)	0.440
Initial Treatment Characteristics						
Antidepressant at Initial Treatment	0.92	(0.72, 1.17)	0.500	0.99	(0.74, 1.32)	0.930
Combination Therapy at Initial Treatment	1.15	(0.88, 1.50)	0.829	1.02	(0.76, 1.38)	0.869
Continuous Variables	Estimate (β)	95% CI	Adjusted p-value	Adjusted Estimate (β)	95% CI	Adjusted p-value
Age	0.013	(-0.01, 0.02)	0.985	-0.0121	(-0.05, 0.02)	0.514

Crude risk ratios were generated using SAS PROC GENMOD with a binomial distribution.
A log link was used for categorical variables and an identity link was used for continuous variables.
Adjusted risk ratios were calculated using a log binomial model, controlling for each variable listed above.

Table 4.42- Risk Ratio for Receipt of Early Treatment Regimen Changes within the First 6 Weeks of Treatment - Full Study Population: Discontinuers Classified as Early Regimen Changes: Aim 3

	Crude Risk Ratio	95% CI	Crude p-value	Adjusted Risk Ratio	95% CI	Adjusted p-value
Categorical Variables						
Sex						
Female	0.91	(0.77, 1.07)	0.236	0.95	(0.82, 1.09)	0.455
Male	1.00	REF		1.00	REF	
Insurance Generosity						
Good	1.03	(0.87, 1.22)	0.716	1.01	(0.86, 1.17)	0.942
Fair	1.00	REF		1.00	REF	
Bipolar I Episode Type						
Bipolar I Mania	1.21	(0.91, 1.62)	0.195	1.09	(0.81, 1.46)	0.566
Bipolar I Depression	1.08	(0.82, 1.42)	0.569	1.07	(0.83, 1.39)	0.578
Bipolar I Mixed	1.09	(0.85, 1.40)	0.484	1.03	(0.82, 1.31)	0.778
Generic Bipolar I	1.00	REF		1.00	REF	
Comorbid Mental Health Diagnoses at Visit						
Attention Deficit Hyperactivity Disorder	1.10	(0.92, 1.33)	0.289	1.10	(0.92, 1.30)	0.300
Other Disruptive Behavioral Disorders	1.39	(1.13, 1.70)	0.002	1.30	(1.04, 1.63)	0.021
Depressive Disorders	0.85	(0.69, 1.05)	0.137	0.91	(0.75, 1.11)	0.356
Disease Severity						
Inpatient Mental Health Visits in Year	1.08	(0.84, 1.39)	0.562	1.07	(0.84, 1.37)	0.587
Psychosis	1.30	(1.05, 1.61)	0.017	1.17	(0.94, 1.45)	0.151

Continued

Table 4.42- Risk Ratio for Receipt of Early Treatment Regimen Changes within the First 6 Weeks of Treatment - Full Study Population: Discontinuers Classified as Early Regimen Changes: Aim 3 (Continued)

	Crude Risk Ratio	95% CI	Crude p-value	Adjusted Risk Ratio	95% CI	Adjusted p-value
Categorical Variables						
Physician Specialty						
Non-Mental Health Professional	1.02	(0.86, 1.21)	0.814	1.03	(0.88, 1.22)	0.689
Mental Health Professional	1.00	REF		1.00	REF	
Treatment Plan Included Psychotherapy						
Yes	1.06	(0.88, 1.27)	0.558	1.03	(0.87, 1.22)	0.719
Initial Treatment Characteristics						
Antidepressant at Initial Treatment	0.85	(0.72, 1.01)	0.067	0.95	(0.80, 1.14)	0.605
Combination Therapy at Initial Treatment	0.80	(0.63, 1.01)	0.061	0.84	(0.68, 1.03)	0.096
Continuous Variables	Estimate (β)	95% CI	Adjusted p-value	Adjusted Estimate (β)	95% CI	Adjusted p-value
Age	0.0073	(-0.01, 0.02)	0.356	0.024	(-0.00, 0.05)	0.101

Crude risk ratios were generated using SAS PROC GENMOD with a binomial distribution.
A log link was used for categorical variables and an identity link was used for continuous variables.
Adjusted risk ratios were calculated using a log binomial model, controlling for each variable listed above.

Table 4.43- Risk Ratio for Receipt of Early Treatment Regimen Changes within the First 4 Weeks of Treatment - Medication Continuers Only: Aim 3

	Crude Risk Ratio	95% CI	Crude p-value	Adjusted Risk Ratio	95% CI	Adjusted p-value
Categorical Variables						
Sex						
Female	0.87	(0.60, 1.26)	0.267	0.97	(0.66, 1.42)	0.876
Male	1.00	REF		1.00	REF	
Insurance Generosity						
Good	1.31	(0.91, 1.88)	0.152	1.20	(0.82, 1.76)	0.341
Fair	1.00	REF		1.00	REF	
Bipolar I Episode Type						
Bipolar I Mania	2.47	(1.13, 5.41)	0.023	2.50	(1.12, 5.59)	0.025
Bipolar I Depression	2.26	(1.08, 4.69)	0.029	2.37	(1.12, 5.02)	0.024
Bipolar I Mixed Episode	1.87	(0.92, 3.82)	0.084	1.98	(0.95, 4.11)	0.067
Generic Bipolar I	1.00	REF		1.00	REF	
Comorbid Mental Health Diagnoses at Visit						
Attention Deficit Hyperactivity Disorder	1.56	(1.06, 2.29)	0.024	1.49	(0.99, 2.24)	0.058
Other Disruptive Behavioral Disorders	1.39	(0.79, 2.44)	0.258	1.25	(0.69, 2.26)	0.460
Depressive Disorders	0.89	(0.57, 1.38)	0.612	1.02	(0.64, 1.61)	0.944
Disease Severity						
Inpatient Mental Health Visits in Year	1.12	(0.63, 2.01)	0.693	1.33	(0.74, 2.39)	0.341
Psychosis	1.24	(0.70, 2.21)	0.459	1.11	(0.62, 1.98)	0.732

Continued

Table 4.43- Risk Ratio for Receipt of Early Treatment Regimen Changes within the First 4 Weeks of Treatment - Medication Continuers Only: Aim 3 (Continued)

	Crude Risk Ratio	95% CI	Crude p-value	Adjusted Risk Ratio	95% CI	Adjusted p-value
Categorical Variables						
Physician Specialty						
Non-Mental Health Professional	0.97	(0.66, 1.44)	0.895	1.17	(0.79, 1.74)	0.438
Mental Health Professional	1.00	REF		1.00	REF	
Treatment Plan Included Psychotherapy						
Yes	1.31	(0.85, 2.02)	0.226	1.26	(0.81, 1.97)	0.301
Initial Treatment Characteristics						
Antidepressant at Initial Treatment	0.87	(0.60, 1.26)	0.258	1.00	(0.66, 1.51)	0.992
Combination Therapy at Initial Treatment	1.17	(0.76, 1.80)	0.482	1.06	(0.66, 1.70)	0.798
Continuous Variables	Estimate (β)	95% CI	Adjusted p-value	Adjusted Estimate (β)	95% CI	Adjusted p-value
Age	-0.0058	(-0.02, 0.01)	0.380	-0.0032	(-0.07, 0.07)	0.922

Crude risk ratios were generated using SAS PROC GENMOD with a binomial distribution.
A log link was used for categorical variables and an identity link was used for continuous variables.
Adjusted risk ratios were calculated using a log binomial model, controlling for each variable listed above.

The role of drug class initially prescribed on the receipt of early treatment regimen changes was considered next. None of the drug classes prescribed was statistically significantly related to the likelihood of receiving early treatment regimen changes (lithium, stimulants, antidepressants, antipsychotics, or anticonvulsants. However, there was a marginally significant effect for anticonvulsants (RR: 1.25, 95%CI: 0.97, 1.65) indicating that patients with anticonvulsants in the initial treatment regimen were more likely to receive early regimen changes.. Finally, when considering the impact of a patient receiving initial treatments recommended by guidelines, it appeared that those patients were more likely to have early regimen changes (RR: 1.28, 95%CI: 0.86, 1.48) as compared with patients who did not receive initially recommended treatments (although the result was not statistically significant, $p = 0.39$).

CHAPTER FIVE: DISCUSSION

5.1 Aim 1a - Prevalence Study

Estimates of the annual diagnostic prevalence of bipolar spectrum disorders were lower than anticipated based on the literature to date, with annual prevalence rates of 0.24% to 0.26% over the three study years. This may be due to the population studied, privately insured children versus clinic population or children on public insurance, and due to the way that bipolar disorders were counted in the population. Even within community samples, prevalence estimates have ranged from 0.10% in the Great Smoky Mountain Study [40] to 6.6% in the National Comorbidity Survey Replication-Adolescent study.[262] Most of these differences are attributed to the populations studied and the timeframes selected for assessment.

In this study, patients were only included as having bipolar spectrum disorders if they had two outpatient or one inpatient claim for the disorder. Patients who had only one outpatient claim were not included as it is unclear in that case if the physician was using the bipolar diagnostic code to "rule-out" bipolar disorder, or if the patient was a true case. If patients in this category were included, the initial sample would have increased from 35,526 to 46,317 (approximately 30% more patients). While the method selected may have led to an underestimate of the disorder, it was the most conservative way to identify cases without

risking overestimating the true prevalence. Methodologists with expertise in claims-based analyses have determined that such methods of patient selection improve the specificity, which can lead to unbiased risk estimates.[263] Moreover, this method has been employed commonly in other claims-based studies of bipolar disorder, which allows for better comparisons across studies.[235, 237, 245, 246]

In addition to finding a lower than anticipated diagnostic prevalence, the rate of bipolar diagnosis did not increase as dramatically as has been previously noted in the literature. For example, Moreno's widely cited study showed a 40-fold increase in visits for bipolar disorder from 1994-1995 to 2002-2003.[1] This study found an 8% increase in bipolar diagnoses from 2005 to 2006 and no increase from 2006 to 2007. It is possible that increased media and academic attention to bipolar disorder in children over the past five years has led to more sensitivity in diagnosing the disorder.[264] This would lead to lower diagnosis rates (slower rate of growth) over time. Also, we do not have estimates of the prevalence of bipolar spectrum disorders in children who were in the MarketScan database in years prior to 2005. It is possible that the current estimates of the prevalence are higher than estimates would have been in the mid 1990s (as found by Moreno and colleagues) and that the rate of increase had leveled off as of 2006.

Another reason that our results may have differed from others was likely due to the study design. The study design that was used for this evaluation is not ideal for evaluating longitudinal trends. The cross-sectional design employed included all children within each year who met our inclusion criteria, thus samples were not independent from year to year, nor were there repeated measures on all subjects. Because the purpose of this project was to

identify aggregate patterns in use and not longitudinal trends specifically, the design selected met our initial study goals but did not allow for true longitudinal comparisons.

When considering the prevalence of each bipolar subtype, bipolar unspecified type was the most common diagnosis in our sample. Most studies conducted using patients with bipolar disorder have focused on only one subtype (bipolar I). One notable study that provided information on multiple disorders on the bipolar spectrum showed bipolar I to be the most prevalent bipolar subtype.[250] However, epidemiologic surveys have shown higher rates of sub-threshold bipolar disorders, than bipolar I or bipolar II disorders.[41] The higher rate in bipolar unspecified disorder in our sample (than in clinic samples) may be due to several potential factors.

First, there may be less accurate assessment of the disorder in privately insured patients. This could be due to intentional vagueness in coding of diagnosis (such as clinicians not wanting to label children with a serious mental illness like bipolar I disorder), or that most clinicians are unable to determine the appropriate bipolar subtype. For example, non-identification of the appropriate bipolar subtype could occur if diagnostic assessment tools are not used, or if the history of the child's bipolar symptoms are inadequately collected or reported. We also identified a larger proportion of children with Bipolar NOS were diagnosed by primary care physicians or by an unclassified physician type (as compared with children with any other bipolar subtype).

The unclassified physician type was made up of primarily acute care center affiliations. This finding suggests that diagnoses made in primary care providers or in acute care settings are associated with receiving less specific bipolar diagnosis coding. However,

the causal relationship is unclear. For example, patients who do not meet the symptom criteria for bipolar I or bipolar II disorder could be more likely to visit an acute care center or a primary care physician for their care. Conversely, these providers could be hesitant to diagnose children with a more specific disorder due to having less expertise in the area of severe childhood mental illness than a mental health professional.

Alternatively, our results related to the elevated diagnosis of bipolar unspecified type could be due to the privately insured population more closely resembling patients from community-based samples than clinic samples. In such cases, milder forms of the disorder would be seen more commonly in our sample than reported in children who were referred to specialty psychiatric clinics (the source population for most of the evidence to date).

When looking at patient characteristics by bipolar subtype, our results were similar to those reported in the Course and Outcome for Bipolar Youth (COBY) study.[250] For example, children with bipolar unspecified type where slightly younger, and patients with bipolar II were slightly older than those with bipolar I disorder. Our gender distribution also was similar across disorders, with the exception of bipolar II disorder (our sample showed nearly equal percentages of males and females had bipolar II disorder, while the COBY study showed higher percentages [60%] of females with bipolar II).

Similar to other studies, attention deficit hyperactivity disorder was the most common comorbid condition in our overall sample. Comorbid major depressive disorder, oppositional defiant disorders, conduct disorder, and anxiety disorders were also somewhat common. It is important to note, for this particular evaluation, the occurrence of comorbid mental health disorders capture the recording of diagnoses during the year in which the patient had a

bipolar diagnosis. The COBY study and other clinic samples generally assess lifetime history of comorbid mental health conditions. While estimates provided in the COBY study are higher than those seen here, this is expected due to the nature of the data collected. A recently published study that used MarketScan claims from April 2004 to March 2005 to study bipolar disorder in children provides nearly identical estimates of the prevalence of comorbid mental health conditions (although the definition of the initial cohort was less reliable as they included patients with one or more diagnoses for bipolar spectrum disorders).[265]

The comorbidity of major depressive disorder diagnosis (which occurred in approximately 25% of children) is of serious concern, as it is clinically inaccurate to diagnose a patient as having both a bipolar spectrum disorder, and a major depressive disorder. As mentioned above, comorbid mental health diagnoses were collected as any diagnosis that occurred during the year that the bipolar diagnosis occurred. It is unclear from the prevalence study how many patients were diagnosed with major depressive disorder prior to their bipolar diagnosis (potential misdiagnosis of major depressive disorder, later clarified), or how many patients received a new diagnosis of major depressive disorder following the bipolar diagnosis (potential misdiagnosis of bipolar disorder, later clarified).

5.2 Aim 1a - Medication Use Study

When considering prevalent medication use, there appeared to be little variation in the likelihood of receiving pharmacotherapy when comparing patients by coded bipolar subtype. Additionally, medication use was similar across all bipolar subtypes when considering class-level use. Use of anticonvulsants, lithium, and antidepressants differed only

slightly over time or by bipolar subtype. This finding was surprising, as the primary spectrum disorders (bipolar I, bipolar II, and bipolar NOS) differ widely in symptom presentation.

Perhaps most concerning was the similarity in treatment characteristics for children with diagnoses of Cyclothymic disorder (considered to be the mildest disorder on the bipolar spectrum) to those with bipolar I mania. It is possible that the similarities in treatment across spectrum disorders may be due to the lack of evidence-based recommendations for effective treatments in this area. Even recent guidelines emphasize that evidence does not exist for treatment recommendations outside of those made for bipolar I disorder. Treatments for each of the other spectrum disorders remain largely untested, particularly in children. It is possible that clinicians are merely treating each spectrum disorder similarly, since there are few alternatives for additional guidance on treatment selections.

While lithium has traditionally had the most evidence for use in children, it was rarely used in this population. In fact, of each of the drug classes studied (with the exception of typical antipsychotics), lithium was used the least frequently. One potential reason for this is that there are potential safety concerns regarding lithium overdose or severe adverse drug reactions. While these concerns are important, lithium has also been shown to reduce the risk of suicide as compared with divalproex.[249] This is a critically important consideration considering the high risk of suicide attempts and completed suicide among patients who have bipolar disorders.

Another reason for the lower-than-expected use of lithium may be that it is no longer actively marketed, as opposed to many of the anticonvulsant and atypical antipsychotic

agents which are heavily marketed to physicians. For example, one study indicated that divalproex generated at least 10 times more sales revenue than lithium, resulting in far more industry-sponsored education regarding divalproex.[249] It is also possible that clinicians would adopt prescribing practices that heavily favored some of the newer medications, as initial monotherapy response rates for patients taking lithium have been low (less than 40%).[142] This could lead clinicians to rely on newer agents, even if those agents have less safety or effectiveness data available.

Anticonvulsant medications were used commonly, with divalproex being the most heavily prescribed among all anticonvulsants. During the study period, divalproex and carbamazepine had the most evidence for use in this population and these agents were the only anticonvulsants supported by the prescribing guidelines as of 2005.[17] However, this study found a very low rate of prescribing of carbamazepine (approximately 4% of anticonvulsants prescribed), and a very high rate of prescribing for lamotrigine (approximately 32% of anticonvulsants prescribed). Although lamotrigine had some initial evidence for use in maintenance treatment for bipolar disorder, there was little to no evidence for its use in children during this timeframe. It is possible that initial evidence regarding its effectiveness for bipolar depression may have led to the high levels of use during the study period. Lamotrigine is often used for seizure disorders in children, which may increase a clinician's comfort with prescribing this agent in the face of less evidence. Similarly, the broad use of this agent could also be related to the favorable side-effect profile seen for this anticonvulsant agent, as compared with similar agents in the drug class. For example, weight gain is a common side effect of most of the mood stabilizing agents, but is not a prominent

side effect of lamotrigine. Given the concerns of clinicians and parents in the long term impact of weight gain on the child's physical and mental health, avoiding this side effect may be sufficient motivation for prescribing this product.

As anticipated, two of the most commonly prescribed atypical antipsychotics were risperidone and aripiprazole, both of which were approved for use in children (ages 10 to 17) as of 2007. Quetiapine was also heavily prescribed during the timeframe, although it was not recommended specifically by the guidelines at that time. Quetiapine prescribing was somewhat concerning due to the increased risk of tachycardia with this agent. However, it may have been popular due to a lower risk of weight gain.

Antidepressant use was common, with or without mood stabilizers. SSRIs were the most commonly used subclass of antidepressants, representing approximately 60% of the antidepressants used. This finding is particularly concerning as (1) there is concern in the literature regarding possible manic switching due to antidepressant treatment,[203] and (2) SSRIs have been associated with increased suicide risk in children with depressive disorders, although it is unclear at this time if the risk for suicide completion is elevated.[266] Nevertheless, due to the already elevated risk of suicide in children with bipolar disorder, prescribing medications that are known to increase the risk of suicide is risky. The practice of prescribing antidepressants for children with bipolar disorder is unacceptable based on current practice standards for adults, let alone children.[52]

Similar to other reports,[1, 267] polypharmacy was common in our study population, with nearly 40% of the population receiving at least 2 medications in a 30 day period following their diagnosis. However, in this evaluation, a large portion of children received no

medications (35%). This is consistent with one previous study that used MarketScan data in a similar population,[265] but is somewhat lower than estimates from the study by Moreno and colleagues (where 90% of office visits resulted in a prescription of one or more psychotropic medications). In a separate study of 111 children and adolescents with bipolar disorder, researchers found the mean number of current psychotropic agents among the sample was 3.4 agents. Approximately 18% of the children were taking five or more medications and only 30% were taking 2 or fewer medications.[207] The use of multiple drugs was somewhat lower in our study, but this is likely due to the previous study population being treated in psychiatric clinics (i.e., they may have more severe, or closely managed illness).

Finally, when considering the use of psychotherapy or counseling, use in the prevalence study population was higher than anticipated based on a review of the literature. For example, Moreno's study found that psychotherapy occurred in approximately 42% of the sample [1]. Rates of psychotherapy use were nearly 90% among all bipolar subtypes and each year. Part of this may be due to the inclusion of only a subset of patients in this evaluation. Specifically, patients whose mental health / substance abuse data were not available were excluded as it would be impossible to determine if they did or did not receive services. This may have biased our results towards overestimating counseling or psychotherapy among the population.

5.3 Aim 1a - Age Related Treatment Differences

Age related differences in demographic and treatment characteristics of children with bipolar disorder have important implications for clinical trials testing and treatment. When comparing young children (ages 0-9) to older children (ages 10-17) several interesting

findings emerge. Literature in this area has previously identified early-onset cases (prior to age 13) are more frequently male, [19] and gender differences are found in the presentation of co-morbid conditions, the age at first treatment, and in rates of symptomatic recovery. [59, 62] As expected, younger girls were much less likely to receive diagnoses of bipolar spectrum disorders, as compared with younger boys. This could be due to symptom presentation, where boys are more likely to display aggressive features which would make parents more likely to seek treatment earlier. Also consistent with what is known regarding comorbidity with bipolar disorder, younger children were more likely to have comorbid Attention Deficit Hyperactivity Disorder and less likely to have depressive disorders.

Reasons for the sex differences in childhood-onset bipolar diagnoses and adolescent-onset bipolar diagnoses are largely unknown. There are several plausible explanations that could be leading to the differences found in this study. For example, young boys with bipolar disorder diagnoses are more likely to be diagnosed with attention deficit hyperactivity disorder (ADHD), as compared with young girls.[61] Additionally, some studies have identified possible links between treatment emergent mania and stimulant use in children who are subsequently diagnosed with bipolar disorder.[226] It is also possible that young boys are more often referred for treatment for ADHD, as compared with young girls, and subsequently they are determined to have bipolar disorder. If this were true, it would suggest that young boys are more likely to be seen by a health care provider, and thus are more likely to receive an earlier diagnosis or treatment for bipolar disorder. Surprisingly, there were no differences in the number of medications used by younger and older children. When looking at the 30 days following a child's most recent diagnosis, approximately 30% of children in each age

group had 2 or more psychotropic medications. Treatment characteristics, however, showed some surprising differences in class-level medication use. The probability of receiving any medication was similar among both age groups, but young children were much more likely to receive antipsychotic medications over each study year, as compared with older children. These findings may be related to a general increase in the use of antipsychotics among very young children. Several recent studies have shown significant increases in the use of antipsychotic agents among very young children (ages 2 through 5 years), both in public[268] and private[269] insurance plans. This finding is particularly troublesome as there is little evidence of the effectiveness and safety of antipsychotics in children younger than 10 years of age.[269]

Other important, but anticipated, class level differences in medication use were that young patients were more likely to receive stimulants and older patients were more likely to receive antidepressants. These treatments coincide with the elevated rates of ADHD in young children and major depressive disorder in older children.

5.4 Aim 1b - Incident Bipolar Diagnoses

In addition to prevalent drug use information, an incident diagnosis study design was employed to assess new diagnoses and treatments for bipolar disorder. Using this study design allowed us to capture information in a way that provides a better understanding of the chronology of the disease and treatment.[263]

When considering the characteristics of newly diagnosed patients to those observed in the prevalence study, most characteristics were similar across the samples. However, there was one notable difference. This was related to the distribution of females within the bipolar

subtypes. When considering the newly diagnosed patients, girls made up a higher proportion of each of the bipolar spectrum disorders. This is in contrast to the prevalence study, where boys were either slightly more likely or equally likely to be diagnosed with bipolar I, bipolar unspecified, or bipolar II disorder. Most of the increase that is seen for girls, however, can be explained by the exclusion of children with previous use of lithium, anticonvulsants, or antipsychotics. In fact, 58% of the 2,139 children excluded for previous medication use were male. This provides further evidence that bipolar diagnosis in girls and boys is stable after puberty.[62,19]

As mentioned above, a major advantage of using this design was that information on comorbid mental health conditions could be captured as those existing prior to the bipolar diagnosis, versus those that were diagnosed after the bipolar diagnosis. There were several interesting patterns that emerged when evaluating comorbidities in this manner. First, a majority of patients with ADHD comorbidity received their diagnosis prior to their initial bipolar diagnosis. However, the occurrence of new ADHD diagnoses after bipolar diagnosis was fairly high, with between 7 and 13% of patients receiving an ADHD diagnosis in the year after bipolar diagnosis. The occurrence of conduct disorder and oppositional defiant disorder also seemed to occur more commonly after a diagnosis of bipolar disorder had been established.

There were high rates of Major Depressive Disorder diagnosed prior to bipolar diagnoses. This is not completely surprising, as children often present with depressive symptoms, thus misdiagnosis with Major Depressive Disorder is a major concern. However, between 11 and 17% of children received a diagnosis of Major Depressive Disorder after

their initial bipolar diagnosis. This was not anticipated as major depressive episodes are considered to be symptoms of bipolar disorder, thus an additional diagnosis of comorbid Major Depressive Disorder is not clinically meaningful. It is unclear to what extent these patients are receiving clarifying diagnoses (bipolar diagnosis was inaccurate and the clinician is clarifying the diagnosis as major depression).

It is important to note, that this evaluation assessed pre-diagnosis conditions as those that were present within the 6 month pre-period, and post-diagnosis conditions as those occurring in the year following diagnosis. The differences in the timeframe may have led to a higher proportion with post-diagnosis conditions (since they had twice the follow up time for diagnoses to be present). Because the focus of this evaluation is on describing the timing of patients' diagnoses of comorbidities, and not on directly comparing differences in the rate of comorbid diagnoses before and after bipolar diagnosis, we felt that it was more appropriate to use all of the available information than to create similar assessment times.

Next, we tested the extent to which patients' bipolar diagnostic classification changed over the one year study period. This was done because there has been concern about diagnostic switching within children with bipolar disorder. We found that a majority of patients had the same bipolar diagnostic subtype at both their first and last visits during the study year. Approximately 20% of children in each category switched diagnostic subtypes. Switching diagnoses was most common among patients with bipolar II disorder (with only 66% with no diagnostic switches over one year). It is possible that this lower rate of diagnostic stability is related more to the billing codes, rather than to true diagnostic confusion among bipolar subtypes. Bipolar II is defined by the DSM-IV by the diagnostic

code "296.89." However, the corresponding ICD-9 description for code "296.89" is "other" bipolar disorder. It is possible that this incongruence between the diagnostic manual and the major coding classification leads to less stability for assessing this bipolar subtype in billing claims data.

Theoretically, diagnostic switching would have implications for treatment; however, this study found no major differences in the types of treatment received by bipolar subtype diagnosed. Results for medication use in the 30 or 90 days following initial bipolar diagnosis indicated that there was no difference in medication class use by bipolar subtype, with the exception of antipsychotics (used less frequently in those with bipolar II or Cyclothymic disorder). This indicates that the coded diagnosis may have little to do with the actual treatment received. This is not surprising, however, as clinicians have little guidance for treating patients with bipolar disorders other than bipolar I.

5.5 Quality of Care in Children with Bipolar Disorder

While guidance does not exist for the treatment of most of the bipolar spectrum disorders, experts consensus guidelines exist for the treatment of children with bipolar I disorder. When considering patients with new diagnoses of bipolar I, we found that a majority of patients did not receive recommended first line therapy. Our primary analysis found only 16% of patients received appropriate first-line therapy within 90 days of their first bipolar diagnosis. Even after one year, less than 20% of these children received recommended pharmacotherapy. Considering the least restrictive definition for appropriate care, there were still over 70% of patients receiving inappropriate initial treatment for bipolar I disorder after one year. Surprisingly, the most commonly used medication class among all

children was antidepressants. These agents were used as first line treatment, without other mood stabilizing agents, in 25% of children. Additionally, approximately 40% of patients received no medication after initial diagnosis with bipolar I disorder.

When considering the factors that were associated with the receipt of recommended care, the type of episode at treatment initiation appeared to be strongly related to the receipt of recommended care. For example, patients with bipolar I depressive episodes and mixed episode types were more likely to receive recommended first line therapy, as compared with patients with generic bipolar episode types. It is possible that patients who receive generic bipolar diagnoses (ICD-9 codes 296.0x or 296.1x) have less clear illness presentation, limiting the clinician's confidence in the diagnosis and treatment strategy. When more defined episode types are selected (such as bipolar I mixed episode type) it may be an indicator of more clinical certainty in the diagnosis.

Additionally, having certain comorbid mental health conditions was related to receipt of guideline recommended care. In particular, patients with comorbid Major Depressive Disorder were less likely to receive guideline recommended care. The high level of antidepressant use at treatment initiation may be related to continued treatment of Major Depressive Disorder after diagnosis of bipolar disorder. It is important to note, however, that guidelines specifically address the importance of discontinuing ongoing therapies upon diagnosis of bipolar I disorder. This is because patients often receive multiple diagnoses (and often multiple treatments) prior to establishing the bipolar I diagnosis. Once bipolar disorder is recognized and treatment has been initiated, comorbidities should be re-assessed to determine if they exist once a patients' bipolar disorder is stabilized.

Receiving recommended treatment was also consistently related to receiving care from a psychiatrist. This could be due to psychiatrists' being more aware of guideline recommendations, their having better methods to assess bipolar disorder, or perhaps due to differences in patient characteristics that could not be measured in this evaluation. Children who were seen by non-psychiatric mental health professionals were the least likely to receive recommended treatment (as compared with psychiatrists). This is likely due to the guidelines recommending pharmacotherapy as initial treatment (and many non-psychiatric mental health professionals do not have prescribing privileges).

Early treatment regimen changes were also common among children with newly diagnosed bipolar I disorder. Over 40% of children experienced treatment regimen changes within the first 6 weeks of initiating treatment. When considering the factors associated with early treatment regimen changes, few of the variables that were included in the final adjusted model were related to treatment changes, and results were inconsistent across models. However, there did appear to be a consistent relationship between the receipt of a bipolar I depressive or manic episode type and the occurrence of early regimen changes. The findings here were not completely surprising, as regimen changes could likely be more closely related to a patient's tolerance for the medication, and their complete clinical picture, rather than indicators that are present at the time of medication initiation. Many un-measureable factors could be involved in this relationship, such as parent demand for medications, adverse reactions to medications, or partial improvement in symptoms. None of these factors could be identified with the current database, but they may be more relevant for such an analysis.

Notably, there was a marginally significant effect for the type of medication at initiation and the length of time on the medication. Patients with anticonvulsants at treatment initiation were more likely to have regimen changes, as were those who received recommended first-line therapy (from aim 2). These findings may indicate that treatment changes are more likely for patients who receive close disease management (or conversely, the more severely ill the patient, the more likely they are to receive medication changes).

The findings related to the use of published guidelines are not altogether surprising. Studies of physician' adherence to published guidelines routinely find that there are often large gaps in what is recommended in guidelines and what occurs in clinical practice. The reasons for this vary by condition and by physician type but often include lack of awareness or familiarity, disagreement, discomfort, low outcome expectancy or low self efficacy and practice inertia related to guidelines.[231] Non-use of guidelines is common, but unacceptable, as guidelines signal increasing consensus in the medical literature, and they promote awareness of this consensus.[237] In disorders that are as complex as pediatric bipolar disorder, reliance on expert consensus guidelines (based on current evidence) should be considered best practice.

For the purposes of this study, we utilized a conceptual framework based on the Andersen model and Donabedian's structure process and outcome model (Chapter 2, Figure 2.2). Based on this framework, we expected both patient characteristics and physician characteristics would be associated with receipt of guideline recommended care. We also assumed that receipt of guideline recommended care would be associated with improved health and economic outcomes for patients. While the latter assumption was not evaluated in

this study, there have been several studies that have tied guideline adherence back to patient outcomes in the area of bipolar disorder. The Texas Medication Algorithm Projects, for example, utilized prescribing algorithms for severe mental illness (including bipolar disorder) and assessed the extent to which adherence to these algorithms impacted patient health and economic outcomes.[27] Additionally, a recent study of inpatients with acute mania was conducted to determine how well current prescribing patterns reflected the published clinical guidelines and the overall impact of short-term clinical outcomes. The researchers found generally good concordance with treatment guidelines and a statistically significant relationship between early medication initiation and reduced time to hospital discharge.[230] Although these study samples were restricted to adults with bipolar disorder, they provide some evidence that treatment patterns are useful tools for assessing the quality of care and patient outcomes in bipolar disorder. They also provide initial evidence that guideline recommended prescribing is associated with improved health outcomes.

Interestingly, we found that none of the patient's predisposing characteristics (age, sex, or geographic region) were associated with either of the guideline-related measures of quality of care. This was also the case for patient enabling resources (insurance type, or generosity of benefits). However, enabling resources may still provide relevant information regarding the access to health care. This study utilized a sample of privately insured children, and specific plan information (such as details of the drug benefits) was unavailable. It is likely that no differences were found due to a floor effect (where everyone had some level of coverage). Patients who are uninsured, those with public insurance, or those with highly restrictive or expensive benefit structures may differ from the patients observed in this study.

Several need characteristics, as well as physician type (structural variable) appeared to be influential in the relationship with guideline recommended care. For example, having depressive disorders was associated with receiving non-recommended first-line therapy. Having a more specific diagnostic classification was associated with receiving recommended first line therapy, as was having a diagnosis provided by a psychiatrist.

Most of the other disease severity indicators were not statistically significantly related to the likelihood of receiving recommended first line treatment, or to the likelihood of having early treatment regimen changes. This finding was likely due to difficulties in accurately identifying disease severity in the claims database, and may not represent the true relationship between diseases severity / patient need and the likelihood of receiving recommended care. Perhaps more detailed information about the patient's true clinical picture would lend itself to be a better predictor of the type of care received.

5.6 Limitations

There are several limitations to the proposed project. First, this project utilized Marketscan Commercial Claims data, which limits the generalizability of the results to the privately insured U.S. population. This study does not represent children who are covered by public insurance (such as Medicaid or SCHIP), and there may be important differences in the prevalence of bipolar disorder and the treatments received in these other populations. The benefits of using this source were the large size (millions of covered lives available) which resulted in a reasonably large sample size for the desired cohort.

Next, the process-related outcome variables were based on guidelines for treatment that were published in 2005 and 2007, respectively. Clinicians might have used other

evidence for treatment decisions during that time, and the 2005-2007 recommendations may no longer reflect current practice. However, the quality indicators that were selected for inclusion were both considered to be "minimal standards of care" per the guidelines. According to the guidelines, recommendations within this category are based on rigorous empirical evidence and/or overwhelming clinical consensus and the minimal standards are expected to apply over 95% of the time (or in nearly all cases).[19] In addition to this, we are not able to determine the extent to which these guidelines were promoted for use in practice or how quickly they were adopted by clinicians.

Another important factor is related to the use of secondary databases. Secondary datasets, such as prescription drug claims and encounters data, rely on diagnosis codes, rather than structured evaluations, to identify patients. Researchers then infer, based on the presence of diagnostic codes, that a patient has the disease of interest if the codes are recorded. This method of identification may lead to misclassification bias, where patients who received a diagnosis may not actually have the disease in question. For example, clinicians may hesitate to diagnose a child with a major mental illness (perhaps due to concerns regarding labeling children with major disorders, or due to stigma regarding the condition). Conversely, diagnoses could be used to "rule-out" conditions and may not actually reflect true disease presence. This misclassification bias can be minimized to some degree by including only those who had evidence of more than one bipolar diagnosis (two unique service dates).[263]

Additionally, because data are collected for non-research purposes (i.e., billing), it is possible that clinicians could "up-code" diagnoses to ensure that payment is received. For example, clinicians may "up-code" severe behavioral disturbances to major mood disorder

that represent more pernicious illness.[29] This would bias our results by including patients who had less severe behavioral diagnoses as cases of bipolar disorder. Similarly, they may code for diagnoses for which they are more certain that payment would be received, or for which reimbursements are higher. This would cause us to underestimate the true prevalence of the disorder.

While we do not know the extent to which "rule-outs" and "up-coding" impact our sample, a previous validation effort in the area of bipolar disorder provides some evidence that the impact is likely small. This validation study compared diagnoses in an administrative database (Group Health Cooperative of Puget Sound, a staff model HMO) with medical records and found a false positive rate of less than 10% for (1) patients with any inpatient diagnoses of bipolar disorder, (2) patients with any outpatient diagnoses of bipolar disorder who were seen by a mental health professional, and (3) patients with any diagnoses of bipolar disorder and accompanying mood stabilizers from a non-mental health provider.[270] Our definition for inclusion of patients was somewhat less restrictive regarding the type of provider who was seen, but required at least two diagnostic codes (on unique service dates) for patients who were seen in an outpatient setting.

Additionally, we were unable to detect medication use outside of the insurance claims data or prior treatment for bipolar disorder (in advance of the 6 month wash-out period). This is particularly important when evaluating physician adherence to guidelines for initial therapy. It also was possible for patients to obtain medications outside of their insurance but the high costs associated with commonly used medications for bipolar disorder (particularly

newer antipsychotic agents) would have made it more likely that a patient would make these purchases through their insurer.

Similarly, patients may receive medication samples from their physician, which would cause us to underestimate medication use in the population. A recent study of the 2004 Medical Expenditure Panel Survey (MEPS) indicated that samples are used in approximately 4.9% of all children, and approximately 10% of children who received prescription medications.[271] In this study, several of the agents of interest were identified as being used as samples, including amphetamine / dextroamphetamines (Adderall), escitalopram (Lexapro), paroxetine (Paxil), and methylphenidate (Ritalin). Among these agents, Adderall was among the top 15 most sampled products.[271] Medication non-use is also undetectable in insurance claims data. If a provider wrote a prescription that was not filled by the patient, this would not be detected within the database. Only filled prescriptions are recorded.

Another limitation of claims based analysis is the relationship between the provider type and the medication prescribed. In these data, as with most prescription claims data sources, providers are associated with services, and not specifically with medication dispensing. This requires that temporal associations be created to identify the most likely provider. For example, analyses of initial regimen prescribed considered the provider type to be the provider seen at the closest date to the date of medication dispensing. It is possible that a patient may have seen multiple providers, or could have been delayed in obtaining their prescription medication. This leads to less certainty regarding the relationships established between the type of the provider and the appropriateness of therapy.

Finally, this project does not address the extent to which treatment, diagnosis or the available guidelines are appropriate for use in the pediatric population. Nor does it address the adequacy of detecting bipolar disorder in children. Due to the nature of our data (secondary analysis) and the lack of clinical focus of this project, we assessed only the extent to which guidelines were followed and the variables that were associated with receiving guideline recommended care or not.

5.7 Summary and Future Research

This project adds to current epidemiologic information on the potential risk factors for bipolar disorder, including current estimates of the diagnostic prevalence of bipolar spectrum disorders in a cohort of privately insured children. Most of the previous studies in this area have been limited to clinic samples (generally from specialty clinics or psychiatry practices). These studies are generally restricted to the most severely ill patients (those who would seek specialized care), and their limited size make it difficult to detect diagnostic and treatment patterns that may exist in the population.[26] Because of the size of the study population utilized, we were able to identify aggregate treatment patterns for some of the less common bipolar spectrum disorders (such as bipolar II disorder and Cyclothynic disorder).

Perhaps more importantly, this study provided some insight into the current pharmacologic treatment of bipolar spectrum disorders in privately insured patients. No studies to date have identified differences in treatments received by children with bipolar subtypes other than bipolar I disorder. Focus of research efforts and guideline development have almost exclusively targeted bipolar I disorder, as this is perceived to be the most severe of the bipolar spectrum disorders. Treatment of each of the other subtypes has been largely

ignored in the literature. It is interesting to note that we found treatment rates were similarly high across each bipolar subtype (the proportion of children receiving psychotropic medications was similar), and the medication classes used varied only slightly.

We found significant areas of concern regarding the medication prescribing practices for children with bipolar spectrum disorders. For example, we identified significant differences in the rates of use of atypical antipsychotic agents among young children (under the age of 10 years) as compared with older children. We also found similarly high rates of treatment, including combination therapy, in young children (as compared with older children). This age group is particularly important because current recommendations are to conduct medication trials of only 10 to 17 year old children.[20] Routine exclusion of young children from clinical trials testing should be carefully considered, particularly for testing of atypical antipsychotic agents. While this is certainly a complex issue (inclusion of young children in clinical trials), excluding them from trials forces physicians to make treatment decisions without good evidence. Given concerns about the impact of psychotropic medications on childhood developmental processes, studying medication use in a rigorous manner (a controlled trial) versus collecting case reports of complications seems to be a more prudent response.

Next, we were able to identify the extent to which initial first line therapies matched those that were suggested by recent expert consensus guidelines. We found that very few children received treatments that were recommended by the guidelines. Instead, we found that a majority of children received either no treatment, or antidepressant monotherapy. These findings are of significant concern as patients with bipolar I disorder should receive

pharmacotherapy (per the guideline, pharmacotherapy is indicated in over 95% of cases), and antidepressant use is still considered to be questionable in this population. Similarly, we were able to assess the extent to which medication changes occurred early for patients with newly treated bipolar I disorder. Again, a large proportion of children received early treatment regimen changes (shorter medication trials than recommended by guidelines).

Both of these assessments were structured to identify factors that were associated with non-adherence to guidelines. The rationale for this was to try to identify targets for quality improvement efforts in the pediatric bipolar population. Unfortunately, the evaluation related to early regimen changes added little information about the factors that drive these medication changes. However, the analysis of initial first line therapy provided some useful information for quality improvement.

First, we found a significant disconnect between the actual medication prescribing in the population and what the guidelines recommend. This finding could be due to several potential causes. First, physicians may be either unfamiliar with the guidelines, or they may disagree with the guidelines on the appropriate management of patients with this disorder. In such cases physicians may use their clinical judgment or previous experience to guide their prescribing behavior, rather than the expert consensus guidelines. Understanding the extent to which physicians are aware of and agree with the guidelines would be important for determining the appropriate strategy for improving their adoption among clinicians.

Second, there may be some detection problems within the data source used that would impact our findings. For example, there could also be problems with misclassification bias, as patients could be inaccurately diagnosed as having bipolar I disorder (coding error,

upcoding for higher reimbursments, or misdiagnosis). However, we tried to improve the specificity of our detection of bipolar diagnoses by requiring that patients have at least one inpatient or two outpatient diagnoses. While this may impact our results to some extent, the overwhelming majority of children received inappropriate treatment. This would suggest that a majority of the patients in this study would have to be misclassified to change our conclusions substantially.

Third, there may be other factors that promote the use of non-recommended drugs, or the non-use of drugs, such as pharmaceutical company drug promotion, patient or parent demand for particular medications, or patient or parent hesitation in using prescribed medications. Regarding parent hesitation in using prescribed medications, parents may not want to give their children powerful psychotropic medications due to concerns regarding side effects, potential impact on childhood development, or stigma related to having or treating a severe mental illness. Alternatively, parents may demand medications that they believe would help their child to function better. For example, if a child had severe depressive episodes in the course of their bipolar disorder, a parent may request that an antidepressant be given to the child to help with the depressive phase of the bipolar illness. These behaviors could influence both the prescribing clinician's decisions regarding initially prescribed therapies (which medications, if any, to choose), and their use of an adequate treatment trial.

Based on this research, it appears that the quality of medication prescribing and use in children with bipolar disorder is poor. It is critical to determine why there is a disconnect between the expert-consensus recommendations and medication prescribing patterns in the community. There are several things that should be done to identify the extent to which the

currently available guidelines are suitable for the pediatric bipolar population. Perhaps the single most important first step to improving the quality of care received would be to determine the extent to which antidepressant monotherapy at treatment initiation is causing harm (or benefit) in the pediatric bipolar population. This was the single most used drug category and is specifically noted in the guidelines as not recommended for children with bipolar disorder. If experts believe that this is a truly inappropriate treatment for these patients, emphasis should be placed on changing this common prescribing behavior.

Next, if pharmacotherapy is the primary treatment mechanism (as is noted in the guideline), the mental health community should further emphasize the importance of referral of these patients to a provider trained in the area of mental health (psychiatrist) so that appropriate pharmacotherapy can be selected. Although it is currently unclear to what extent guideline discordant treatment impacts a patient's health outcomes, it is important to ensure that all children are receiving what is currently believed to be the most appropriate treatment course.

In addition to the above recommendations, it will be critical for future studies in this area to (1) determine the extent to which use of medication treatment guidelines is related to patient health outcomes; (2) confirm that medication use patterns identified within this evaluation are consistent across other samples; (3) better measure factors associated with disease severity to understand their true relationship with how care is delivered; and (4) identify gaps in clinician training that could be addressed to improve the adoption of guidelines for mental health treatment.

Regarding the first goal, to identify the extent to which use (or non-use) of guidelines impacts patient health outcomes, claims based analyses may be a starting point for this type of evaluation. This study provided evidence that guidelines for medication management in children with bipolar disorder are not followed in most cases, and we identified potential factors that are related to receiving recommended care. However, we need to establish how receipt of recommended care is related to improvements in the patient's outcomes. If guideline concordance is found to be related to improvements in patient outcomes, then it will be critical that interventions be developed, or training programs be implemented to improve clinician awareness and/or adoption of these guidelines. Establishing this link will help to quantify the need for quality improvement in this area by providing evidence for the importance of using guidelines in this vulnerable population.

To address the second goal (confirming that medication use patterns are consistent across other samples), claims based analyses could be used as a starting point. It is important to understand if these prescribing patterns are consistent across other privately insured populations, but also to understand if our findings could be generalized to publicly insured children. To establish this, we would need to evaluate medication use patterns within other privately insured plans (e.g., Blue Cross and Blue Shield, State Employees Health Plan), and for children in public insurance programs (i.e., Medicaid).

The next goal - to better measure factors associated with disease severity and to understand the true relationship of disease severity and receipt of appropriate care - is somewhat more complex. Given the difficulty in diagnosing and treating bipolar disorder in children, and the controversy within the field of child psychiatry regarding the existence of

true bipolar disorder in children, a claims-based analysis is unlikely to provide enough details regarding the patients' true clinical picture to allow for a thorough investigation of outcomes. This is because claims data are collected for billing purposes, so many variables related to a patient's true diagnostic or treatment picture are either unmeasured or are crude estimators. It is important to identify the extent to which the patient's true disease severity is associated with the use of treatment guidelines, as this may help to clarify why guidelines are so infrequently used (or what group of patients does not receive recommended treatment).

One potential way to address this would be for future studies to utilize detailed medical records to determine if there are differences in treatment strategies for patients with different clinical presentations of bipolar I disorder. Utilizing patient medical records would also potentially allow for an investigation of how adherence to medication treatment guidelines leads to improvements in patient health outcomes. This level of clinical detail would be necessary for thorough outcomes evaluations, as "improvement" in outcomes would need to consider changes in manic or depressive symptoms, and not just crude measures such as hospitalizations.

Finally, improving the connection between guideline development and clinical practice will be necessary for improving the quality of care received by children with bipolar disorder. Guidelines should be developed and disseminated in a way that actively encourages physician adoption (by eliciting physician feedback, or by identifying trends in practice that need to be reversed). Prior to developing new or revised guidelines, experts should seek to identify the barriers that physicians face when prescribing medication to children with bipolar disorder. This may help to create guidelines that are more useful for practicing

clinicians, or to address concerns that would prohibit a clinician from adopting the guideline recommendations. Finally, incorporating guideline recommended treatment algorithms into electronic order-entry systems may be one way to improve physicians' knowledge about guidelines, or their awareness of current recommendations. As the area of electronic health records develops over the coming years, integration of guideline recommendation-based prompts may be one way to help to decrease the gap between expert recommendations and clinical practice.

WORKS CITED

1. Moreno C, Laje G, Blanco C, Jiang H, Schmidt AB, Olfson M. National trends in the outpatient diagnosis and treatment of bipolar disorder in youth. *Arch Gen Psychiatry.* 2007;64(9):1032-1039.

2. Goldstein TR, Birmaher B, Axelson D, et al. Psychosocial functioning among bipolar youth. *J Affect Disord.* 2008;18:18.

3. Dickstein DP, Rich BA, Binstock AB, et al. Comorbid anxiety in phenotypes of pediatric bipolar disorder. *J Child Adolesc Psychopharmacol.* 2005;15(4):534-548.

4. Wilens TE, Biederman J, Forkner P, et al. Patterns of comorbidity and dysfunction in clinically referred preschool and school-age children with bipolar disorder. *J Child Adolesc Psychopharmacol.* 2003;13(4):495-505.

5. Jolin EM, Weller EB, Weller RA. The public health aspects of bipolar disorder in children and adolescents. *Curr Psychiatry Rep.* 2007;9(2):106-113.

6. Pavuluri MN, Birmaher B, Naylor MW. Pediatric bipolar disorder: a review of the past 10 years. *J Am Acad Child Adolesc Psychiatry.* 2005;44(9):846-871.

7. Geller B, Luby J. Child and adolescent bipolar disorder: a review of the past 10 years. *J Am Acad Child Adolesc Psychiatry.* 1997;36(9):1168-1176.

8. Akiskal HS, Downs J, Jordan P, Watson S, Daugherty D, Pruitt DB. Affective disorders in referred children and younger siblings of manic-depressives. Mode of onset and prospective course. *Arch Gen Psychiatry.* 1985;42(10):996-1003.

9. Carlson GA, Meyer SE. Phenomenology and diagnosis of bipolar disorder in children, adolescents, and adults: complexities and developmental issues. *Dev Psychopathol.* 2006;18(4):939-969.

10. Nandagopal JJ, DelBello MP, Kowatch R. Pharmacologic treatment of pediatric bipolar disorder. *Child Adolesc Psychiatr Clin N Am.* 2009;18(2):455-469.

11. Biederman J, Faraone S, Mick E, et al. Attention-deficit hyperactivity disorder and juvenile mania: an overlooked comorbidity? *J Am Acad Child Adolesc Psychiatry.* 1996;35(8):997-1008.

12. Biederman J, Newcorn J, Sprich S. Comorbidity of attention deficit hyperactivity disorder with conduct, depressive, anxiety, and other disorders. *Am J Psychiatry.* 1991;148(5):564-577.

13. Wozniak J, Biederman J, Kiely K, et al. Mania-like symptoms suggestive of childhood-onset bipolar disorder in clinically referred children. *J Am Acad Child Adolesc Psychiatry.* 1995;34(7):867-876.

14. Strober M, Schmidt-Lackner S, Freeman R, Bower S, Lampert C, DeAntonio M. Recovery and relapse in adolescents with bipolar affective illness: a five-year naturalistic, prospective follow-up. *J Am Acad Child Adolesc Psychiatry.* 1995;34(6):724-731.

15. Pavuluri MN, Henry DB, Carbray JA, Naylor MW, Janicak PG. Divalproex sodium for pediatric mixed mania: a 6-month prospective trial. *Bipolar Disord.* 2005;7(3):266-273.

16. Rizzo CJ, Esposito-Smythers C, Swenson L, et al. Factors associated with mental health service utilization among bipolar youth. *Bipolar Disord.* 2007;9(8):839-850.

17. Kowatch RA, Fristad M, Birmaher B, Wagner KD, Findling RL, Hellander M. Treatment guidelines for children and adolescents with bipolar disorder. *J Am Acad Child Adolesc Psychiatry.* 2005;44(3):213-235.

18. Pavuluri MN, Henry DB, Devineni B, Carbray JA, Naylor MW, Janicak PG. A pharmacotherapy algorithm for stabilization and maintenance of pediatric bipolar disorder. *J Am Acad Child Adolesc Psychiatry.* 2004;43(7):859-867.

19. McClellan J, Kowatch R, Findling RL. Practice parameter for the assessment and treatment of children and adolescents with bipolar disorder. *J Am Acad Child Adolesc Psychiatry.* 2007;46(1):107-125.

20. Carlson GA, Jensen PS, Findling RL, et al. Methodological issues and controversies in clinical trials with child and adolescent patients with bipolar disorder: report of a consensus conference. *J Child Adolesc Psychopharmacol.* 2003;13(1):13-27.

21. Cummings CM, Fristad MA. Pediatric bipolar disorder: recognition in primary care. *Curr Opin Pediatr.* 2008;20(5):560-565.

22. Carlson GA, Findling RL, Post RM, et al. AACAP 2006 Research Forum--Advancing research in early-onset bipolar disorder: barriers and suggestions. *J Child Adolesc Psychopharmacol.* 2009;19(1):3-12.

23. Cahill C, Hanstock T, Jairam R, Hazell P, Walter G, Malhi GS. Comparison of diagnostic guidelines for juvenile bipolar disorder. *Aust N Z J Psychiatry.* 2007;41(6):479-484.

24. Dawson R, Lavori PW, Luby JL, Ryan ND, Geller B. Adaptive strategies for treating childhood mania. *Biol Psychiatry.* 2007;61(6):758-764. Epub 2006 Dec 2012.

25. Costello EJ, Egger H, Angold A. 10-year research update review: the epidemiology of child and adolescent psychiatric disorders: I. Methods and public health burden. *J Am Acad Child Adolesc Psychiatry.* 2005;44(10):972-986.

26. Lewinsohn PM, Klein DN, Seeley JR. Bipolar disorders in a community sample of older adolescents: prevalence, phenomenology, comorbidity, and course. *J Am Acad Child Adolesc Psychiatry.* 1995;34(4):454-463.

27. Dennehy EB, Suppes T, Rush AJ, et al. Does provider adherence to a treatment guideline change clinical outcomes for patients with bipolar disorder? Results from the Texas Medication Algorithm Project. *Psychol Med.* 2005;35(12):1695-1706. Epub 2005 Sep 1629.

28. Hamrin V, Pachler M. Pediatric bipolar disorder: evidence-based psychopharmacological treatments. *J Child Adolesc Psychiatr Nurs.* 2007;20(1):40-58.

29. Blader JC, Carlson GA. Increased rates of bipolar disorder diagnoses among U.S. child, adolescent, and adult inpatients, 1996-2004. *Biol Psychiatry.* 2007;62(2):107-114. Epub 2007 Feb 2016.

30. Youngstrom E, Youngstrom JK, Starr M. Bipolar diagnoses in community mental health: Achenbach Child Behavior Checklist profiles and patterns of comorbidity. *Biol Psychiatry.* 2005;58(7):569-575. Epub 2005 Jun 2013.

31. Case BG, Olfson M, Marcus SC, Siegel C. Trends in the inpatient mental health treatment of children and adolescents in US community hospitals between 1990 and 2000. *Arch Gen Psychiatry.* 2007;64(1):89-96.

32. Martin A, Leslie D. Psychiatric inpatient, outpatient, and medication utilization and costs among privately insured youths, 1997-2000. *Am J Psychiatry.* 2003;160(4):757-764.

33. Carlson GA, Kashani JH. Manic symptoms in a non-referred adolescent population. *J Affect Disord.* 1988;15(3):219-226.

34. Geller B, Williams M, Zimerman B, Frazier J, Beringer L, Warner KL. Prepubertal and early adolescent bipolarity differentiate from ADHD by manic symptoms, grandiose delusions, ultra-rapid or ultradian cycling. *J Affect Disord.* 1998;51(2):81-91.

35. Katzow JJ, Hsu DJ, Nassir Ghaemi S. The bipolar spectrum: a clinical perspective. *Bipolar Disord.* 2003;5(6):436-442.

36. Judd LL, Akiskal HS. The prevalence and disability of bipolar spectrum disorders in the US population: re-analysis of the ECA database taking into account subthreshold cases. *J Affect Disord.* 2003;73(1-2):123-131.

37. Grant BF, Stinson FS, Hasin DS, et al. Prevalence, correlates, and comorbidity of bipolar I disorder and axis I and II disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *J Clin Psychiatry.* 2005;66(10):1205-1215.

38. Kessler RC, Rubinow DR, Holmes C, Abelson JM, Zhao S. The epidemiology of DSM-III-R bipolar I disorder in a general population survey. *Psychol Med.* 1997;27(5):1079-1089.

39. Kessler RC, Demler O, Frank RG, et al. Prevalence and treatment of mental disorders, 1990 to 2003. *N Engl J Med.* 2005;352(24):2515-2523.

40. Costello EJ, Angold A, Burns BJ, et al. The Great Smoky Mountains Study of Youth. Goals, design, methods, and the prevalence of DSM-III-R disorders. *Arch Gen Psychiatry.* 1996;53(12):1129-1136.

41. Merikangas KR, Akiskal HS, Angst J, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. *Arch Gen Psychiatry.* 2007;64(5):543-552.

42. Angst J. The emerging epidemiology of hypomania and bipolar II disorder. *J Affect Disord.* 1998;50(2-3):143-151.

43. Szadoczky E, Papp Z, Vitrai J, Rihmer Z, Furedi J. The prevalence of major depressive and bipolar disorders in Hungary. Results from a national epidemiologic survey. *J Affect Disord.* 1998;50(2-3):153-162.

44. Weissman MM, Bland RC, Canino GJ, et al. Cross-national epidemiology of major depression and bipolar disorder. *Jama.* 1996;276(4):293-299.

45. Danielyan A, Kowatch RA. Management options for bipolar disorder in children and adolescents. *Paediatr Drugs.* 2005;7(5):277-294.

46. Lish JD, Dime-Meenan S, Whybrow PC, Price RA, Hirschfeld RM. The National Depressive and Manic-depressive Association (DMDA) survey of bipolar members. *J Affect Disord.* 1994;31(4):281-294.

47. Hirschfeld RM, Calabrese JR, Weissman MM, et al. Screening for bipolar disorder in the community. *J Clin Psychiatry.* 2003;64(1):53-59.

48. Egeland JA, Hostetter AM, Pauls DL, Sussex JN. Prodromal symptoms before onset of manic-depressive disorder suggested by first hospital admission histories. *J Am Acad Child Adolesc Psychiatry.* 2000;39(10):1245-1252.

49. Joyce PR. Age of onset in bipolar affective disorder and misdiagnosis as schizophrenia. *Psychol Med.* 1984;14(1):145-149.

50. Loranger AW, Levine PM. Age at onset of bipolar affective illness. *Arch Gen Psychiatry.* 1978;35(11):1345-1348.

51. Costello EJ, Pine DS, Hammen C, et al. Development and natural history of mood disorders. *Biol Psychiatry.* 2002;52(6):529-542.

52. Blader JC. Increase in out-based physician diagnoses of bipolar disorder in youth in the USA. *Evid Based Ment Health.* 2008;11(2):60.

53. Harpaz-Rotem I, Leslie DL, Martin A, Rosenheck RA. Changes in child and adolescent inpatient psychiatric admission diagnoses between 1995 and 2000. *Soc Psychiatry Psychiatr Epidemiol.* 2005;40(8):642-647. Epub 2005 Aug 2018.

54. Harpaz-Rotem I, Rosenheck RA. Changes in outpatient psychiatric diagnosis in privately insured children and adolescents from 1995 to 2000. *Child Psychiatry Hum Dev.* 2004;34(4):329-340.

55. Carlson GA. Identifying prepubertal mania. *J Am Acad Child Adolesc Psychiatry.* 1995;34(6):750-753.

56. Apps J, Winkler J, Jandrisevits MD. Bipolar disorders: symptoms and treatment in children and adolescents. *Pediatr Nurs.* 2008;34(1):84-88.

57. Argelinda Baroni. Practitioner Review: The assessment of bipolar disorder in children and adolescents. *Journal of Child Psychology and Psychiatry.* 2008;9999(9999).

58. APA. *Diagnostic and statistical manual of mental disorders (4th ed., text revision).* Washington, DC: American Psychiatric Association; 2000.

59. Biederman J, Kwon A, Wozniak J, et al. Absence of gender differences in pediatric bipolar disorder: findings from a large sample of referred youth. *J Affect Disord.* 2004;83(2-3):207-214.

60. Duax JM, Youngstrom EA, Calabrese JR, Findling RL. Sex differences in pediatric bipolar disorder. *J Clin Psychiatry.* 2007;68(10):1565-1573.

61. Geller B, Zimerman B, Williams M, et al. Diagnostic characteristics of 93 cases of a prepubertal and early adolescent bipolar disorder phenotype by gender, puberty and comorbid attention deficit hyperactivity disorder. *J Child Adolesc Psychopharmacol.* 2000;10(3):157-164.

62. Birmaher B, Axelson D. Course and outcome of bipolar spectrum disorder in children and adolescents: a review of the existing literature. *Dev Psychopathol.* 2006;18(4):1023-1035.

63. Biederman J, Faraone SV, Wozniak J, Mick E, Kwon A, Aleardi M. Further evidence of unique developmental phenotypic correlates of pediatric bipolar disorder: findings from a large sample of clinically referred preadolescent children assessed over the last 7 years. *J Affect Disord.* 2004;82(Suppl 1):S45-58.

64. Weller RA, Weller EB, Tucker SG, Fristad MA. Mania in prepubertal children: has it been underdiagnosed? *J Affect Disord.* 1986;11(2):151-154.

65. Carlson GA, Bromet EJ, Driessens C, Mojtabai R, Schwartz JE. Age at onset, childhood psychopathology, and 2-year outcome in psychotic bipolar disorder. *Am J Psychiatry.* 2002;159(2):307-309.

66. Findling RL, Gracious BL, McNamara NK, et al. Rapid, continuous cycling and psychiatric co-morbidity in pediatric bipolar I disorder. *Bipolar Disord.* 2001;3(4):202-210.

67. Geller B, Bolhofner K, Craney JL, Williams M, DelBello MP, Gundersen K. Psychosocial functioning in a prepubertal and early adolescent bipolar disorder phenotype. *J Am Acad Child Adolesc Psychiatry.* 2000;39(12):1543-1548.

68. Geller B, Tillman R, Craney JL, Bolhofner K. Four-year prospective outcome and natural history of mania in children with a prepubertal and early adolescent bipolar disorder phenotype. *Arch Gen Psychiatry.* 2004;61(5):459-467.

69. Lewinsohn PM, Klein DN, Seeley JR. Bipolar disorder during adolescence and young adulthood in a community sample. *Bipolar Disord.* 2000;2(3 Pt 2):281-293.

70. WHO. *The global burden of disease: 2004 update, Part 3: Disease incidence, prevalence and disability.* Geneva, Switzerland: World Health Organization; 2008.

71. WHO. *The global burden of disease: 2004 update, Part 4: Burden of disease: DALYs.* Geneva, Switzerland: World Health Organization; 2008.

72. Geller B, Craney JL, Bolhofner K, DelBello MP, Williams M, Zimerman B. One-year recovery and relapse rates of children with a prepubertal and early adolescent bipolar disorder phenotype. *Am J Psychiatry.* 2001;158(2):303-305.

73. Birmaher B, Ryan ND, Williamson DE, et al. Childhood and adolescent depression: a review of the past 10 years. Part I. *J Am Acad Child Adolesc Psychiatry.* 1996;35(11):1427-1439.

74. Garfinkel BD, Froese A, Hood J. Suicide attempts in children and adolescents. *Am J Psychiatry.* 1982;139(10):1257-1261.

75. Brent DA. Correlates of the medical lethality of suicide attempts in children and adolescents. *J Am Acad Child Adolesc Psychiatry.* 1987;26(1):87-91.

76. Geller B, Craney JL, Bolhofner K, Nickelsburg MJ, Williams M, Zimerman B. Two-year prospective follow-up of children with a prepubertal and early adolescent bipolar disorder phenotype. *Am J Psychiatry.* 2002;159(6):927-933.

77. Goldstein TR, Miklowitz DJ, Mullen KL. Social skills knowledge and performance among adolescents with bipolar disorder. *Bipolar Disord.* 2006;8(4):350-361.

78. Carter TD, Mundo E, Parikh SV, Kennedy JL. Early age at onset as a risk factor for poor outcome of bipolar disorder. *J Psychiatr Res.* 2003;37(4):297-303.

79. Slama F, Bellivier F, Henry C, et al. Bipolar patients with suicidal behavior: toward the identification of a clinical subgroup. *J Clin Psychiatry.* 2004;65(8):1035-1039.

80. Tondo L, Baldessarini RJ. Reduced suicide risk during lithium maintenance treatment. *J Clin Psychiatry.* 2000;61(Suppl 9):97-104.

81. Sanchez LE, Le LT. Suicide in mood disorders. *Depress Anxiety.* 2001;14(3):177-182.

82. Baldessarini RJ, Jamison KR. Effects of medical interventions on suicidal behavior. Summary and conclusions. *J Clin Psychiatry.* 1999;60(Suppl 2):117-122.

83. Goodwin FK. From the Alcohol, Drug Abuse, and Mental Health Administration. *Jama.* 1990;264(19):2495.

84. Feinberg DT. The real cost of pediatric bipolar disorder. *J Child Adolesc Psychopharmacol.* 2003;13(4):431-433.

85. Peele PB, Xu Y, Kupfer DJ. Insurance expenditures on bipolar disorder: clinical and parity implications. *Am J Psychiatry.* 2003;160(7):1286-1290.

86. Perlis RH, Ostacher MJ, Patel JK, et al. Predictors of recurrence in bipolar disorder: primary outcomes from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). *Am J Psychiatry.* 2006;163(2):217-224.

87. Wyatt RJ, Henter I. An economic evaluation of manic-depressive illness--1991. *Soc Psychiatry Psychiatr Epidemiol.* 1995;30(5):213-219.

88. Begley CE, Annegers JF, Swann AC, et al. The lifetime cost of bipolar disorder in the US: an estimate for new cases in 1998. *Pharmacoeconomics.* 2001;19(5 Pt 1):483-495.

89. Guo JJ, Keck PE, Jr., Li H, Jang R, Kelton CM. Treatment costs and health care utilization for patients with bipolar disorder in a large managed care population. *Value Health.* 2008;11(3):416-423. Epub 2007 Dec 2017.

90. Carlson GA, Meyer SE. Bipolar disorder in youth. *Curr Psychiatry Rep.* 2000;2(2):90-94.

91. Leverich GS, Post RM, Keck PE, Jr., et al. The poor prognosis of childhood-onset bipolar disorder. *J Pediatr.* 2007;150(5):485-490.

92. Birmaher B, Kennah A, Brent D, Ehmann M, Bridge J, Axelson D. Is bipolar disorder specifically associated with panic disorder in youths? *J Clin Psychiatry.* 2002;63(5):414-419.

93. McClellan J, McCurry C. Early onset psychotic disorders: diagnostic stability and clinical characteristics. *Eur Child Adolesc Psychiatry.* 1999;8(Suppl 1):I13-19.

94. Feinstein SC, Wolpert EA. Juvenile manic-depressive illness. Clinical and therapeutic considerations. *J Am Acad Child Psychiatry.* 1973;12(1):123-136.

95. McGlashan TH. Adolescent versus adult onset of mania. *Am J Psychiatry.* 1988;145(2):221-223.

96. Carlson GA, Bromet EJ, Sievers S. Phenomenology and outcome of subjects with early- and adult-onset psychotic mania. *Am J Psychiatry.* 2000;157(2):213-219.

97. Judd LL, Akiskal HS, Schettler PJ, et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. *Arch Gen Psychiatry.* 2002;59(6):530-537.

98. Biederman J. Resolved: mania is mistaken for ADHD in prepubertal children. *J Am Acad Child Adolesc Psychiatry.* 1998;37(10):1091-1096; discussion 1096-1099.

99. Biederman J, Mick E, Faraone SV, Spencer T, Wilens TE, Wozniak J. Pediatric mania: a developmental subtype of bipolar disorder? *Biol Psychiatry.* 2000;48(6):458-466.

100. Faraone SV, Biederman J, Wozniak J, Mundy E, Mennin D, O'Donnell D. Is comorbidity with ADHD a marker for juvenile-onset mania? *J Am Acad Child Adolesc Psychiatry.* 1997;36(8):1046-1055.

101. Schurhoff F, Bellivier F, Jouvent R, et al. Early and late onset bipolar disorders: two different forms of manic-depressive illness? *J Affect Disord.* 2000;58(3):215-221.

102. Pavuluri MN, Herbener ES, Sweeney JA. Psychotic symptoms in pediatric bipolar disorder. *J Affect Disord.* 2004;80(1):19-28.

103. Geller B, Tillman R, Bolhofner K, Zimerman B. Child bipolar I disorder: prospective continuity with adult bipolar I disorder; characteristics of second and third episodes; predictors of 8-year outcome. *Arch Gen Psychiatry.* 2008;65(10):1125-1133.

104. Birmaher B, Axelson D, Strober M, et al. Clinical course of children and adolescents with bipolar spectrum disorders. *Arch Gen Psychiatry.* 2006;63(2):175-183.

105. Geller B, Zimerman B, Williams M, et al. DSM-IV mania symptoms in a prepubertal and early adolescent bipolar disorder phenotype compared to attention-deficit hyperactive and normal controls. *J Child Adolesc Psychopharmacol.* 2002;12(1):11-25.

106. Geller B, Sun K, Zimerman B, Luby J, Frazier J, Williams M. Complex and rapid-cycling in bipolar children and adolescents: a preliminary study. *J Affect Disord.* 1995;34(4):259-268.

107. Leibenluft E, Charney DS, Towbin KE, Bhangoo RK, Pine DS. Defining clinical phenotypes of juvenile mania. *Am J Psychiatry.* 2003;160(3):430-437.

108. Mick E, Spencer T, Wozniak J, Biederman J. Heterogeneity of irritability in attention-deficit/hyperactivity disorder subjects with and without mood disorders. *Biol Psychiatry.* 2005;58(7):576-582. Epub 2005 Aug 2008.

109. Wozniak J, Biederman J, Kwon A, et al. How cardinal are cardinal symptoms in pediatric bipolar disorder? An examination of clinical correlates. *Biol Psychiatry.* 2005;58(7):583-588. Epub 2005 Sep 2028.

110. Chang K. Adult bipolar disorder is continuous with pediatric bipolar disorder. *Can J Psychiatry.* 2007;52(7):418-425.

111. Bhargava Raman RP, Sheshadri SP, Janardhan Reddy YC, Girimaji SC, Srinath S, Raghunandan VN. Is bipolar II disorder misdiagnosed as major depressive disorder in children? *J Affect Disord.* 2007;98(3):263-266. Epub 2006 Sep 2001.

112. Kim EY, Miklowitz DJ. Childhood mania, attention deficit hyperactivity disorder and conduct disorder: a critical review of diagnostic dilemmas. *Bipolar Disord.* 2002;4(4):215-225.

113. Weckerly J. Pediatric bipolar mood disorder. *J Dev Behav Pediatr.* 2002;23(1):42-56.

114. Kowatch RA, Youngstrom EA, Danielyan A, Findling RL. Review and meta-analysis of the phenomenology and clinical characteristics of mania in children and adolescents. *Bipolar Disord.* 2005;7(6):483-496.

115. Birmaher B. Longitudinal course of pediatric bipolar disorder. *Am J Psychiatry.* 2007;164(4):537-539.

116. Angold A, Costello EJ. Depressive comorbidity in children and adolescents: empirical, theoretical, and methodological issues. *Am J Psychiatry.* 1993;150(12):1779-1791.

117. Caron C, Rutter M. Comorbidity in child psychopathology: concepts, issues and research strategies. *J Child Psychol Psychiatry.* 1991;32(7):1063-1080.

118. Tillman R, Geller B, Bolhofner K, Craney JL, Williams M, Zimerman B. Ages of onset and rates of syndromal and subsyndromal comorbid DSM-IV diagnoses in a prepubertal and early adolescent bipolar disorder phenotype. *J Am Acad Child Adolesc Psychiatry.* 2003;42(12):1486-1493.

119. Frank E, Cyranowski JM, Rucci P, et al. Clinical significance of lifetime panic spectrum symptoms in the treatment of patients with bipolar I disorder. *Arch Gen Psychiatry.* 2002;59(10):905-911.

120. Birmaher B, Axelson D, Strober M, et al. Comparison of manic and depressive symptoms between children and adolescents with bipolar spectrum disorders. *Bipolar Disord.* 2009;11(1):52-62.

121. West SA, Strakowski SM, Sax KW, Minnery KL, McElroy SL, Keck PE, Jr. The comorbidity of attention-deficit hyperactivity disorder in adolescent mania: potential diagnostic and treatment implications. *Psychopharmacol Bull.* 1995;31(2):347-351.

122. Kafantaris V, Coletti DJ, Dicker R, Padula G, Pollack S. Are childhood psychiatric histories of bipolar adolescents associated with family history, psychosis, and response to lithium treatment? *J Affect Disord.* 1998;51(2):153-164.

123. Faedda GL, Baldessarini RJ, Glovinsky IP, Austin NB. Pediatric bipolar disorder: phenomenology and course of illness. *Bipolar Disord.* 2004;6(4):305-313.

124. Singh MK, DelBello MP, Kowatch RA, Strakowski SM. Co-occurrence of bipolar and attention-deficit hyperactivity disorders in children. *Bipolar Disord.* 2006;8(6):710-720.

125. Perlis RH, Miyahara S, Marangell LB, et al. Long-term implications of early onset in bipolar disorder: data from the first 1000 participants in the systematic treatment enhancement program for bipolar disorder (STEP-BD). *Biol Psychiatry.* 2004;55(9):875-881.

126. Mick E, Biederman J, Faraone SV, Murray K, Wozniak J. Defining a developmental subtype of bipolar disorder in a sample of nonreferred adults by age at onset. *J Child Adolesc Psychopharmacol.* 2003;13(4):453-462.

127. Masi G, Perugi G, Millepiedi S, et al. Developmental differences according to age at onset in juvenile bipolar disorder. *J Child Adolesc Psychopharmacol.* 2006;16(6):679-685.

128. Kovacs M, Pollock M. Bipolar disorder and comorbid conduct disorder in childhood and adolescence. *J Am Acad Child Adolesc Psychiatry.* 1995;34(6):715-723.

129. Wozniak J, Biederman J, Faraone SV, et al. Mania in children with pervasive developmental disorder revisited. *J Am Acad Child Adolesc Psychiatry.* 1997;36(11):1552-1559; discussion 1559-1560.

130. Baldessarini RJ, Tondo L. Long-term lithium for bipolar disorder. *Am J Psychiatry.* 2001;158(10):1740.

131. Baldessarini RJ. Treatment research in bipolar disorder: issues and recommendations. *CNS Drugs.* 2002;16(11):721-729.

132. Kuehn BM. FDA Panel OKs 3 Antipsychotic Drugs for Pediatric Use, Cautions Against Overuse. *JAMA.* August 26, 2009 2009;302(8):833-834.

133. Leibenluft E. Pediatric bipolar disorder comes of age. *Arch Gen Psychiatry.* 2008;65(10):1122-1124.

134. Craney JL, Geller B. A prepubertal and early adolescent bipolar disorder-I phenotype: review of phenomenology and longitudinal course. *Bipolar Disord.* 2003;5(4):243-256.

135. Kafantaris V, Coletti DJ, Dicker R, Padula G, Kane JM. Lithium treatment of acute mania in adolescents: a large open trial. *J Am Acad Child Adolesc Psychiatry.* 2003;42(9):1038-1045.

136. Geller B, Cooper TB, Sun K, et al. Double-blind and placebo-controlled study of lithium for adolescent bipolar disorders with secondary substance dependency. *J Am Acad Child Adolesc Psychiatry.* 1998;37(2):171-178.

137. Livingstone C, Rampes H. Lithium: a review of its metabolic adverse effects. *J Psychopharmacol.* 2006;20(3):347-355. Epub 2005 Sep 2020.

138. Yeung CK, Chan HH. Cutaneous adverse effects of lithium: epidemiology and management. *Am J Clin Dermatol.* 2004;5(1):3-8.

139. Gracious BL, Findling RL, Seman C, Youngstrom EA, Demeter CA, Calabrese JR. Elevated thyrotropin in bipolar youths prescribed both lithium and divalproex sodium. *J Am Acad Child Adolesc Psychiatry.* 2004;43(2):215-220.

140. Gitlin M. Lithium and the kidney: an updated review. *Drug Saf.* 1999;20(3):231-243.

141. Heaton PC, Garlick CM, Tran D. Evaluating drug safety in children and adolescents with bipolar disorder. *Curr Drug Saf.* 2006;1(3):307-318.

142. Kowatch RA, Suppes T, Carmody TJ, et al. Effect size of lithium, divalproex sodium, and carbamazepine in children and adolescents with bipolar disorder. *J Am Acad Child Adolesc Psychiatry.* 2000;39(6):713-720.

143. Kowatch RA, Sethuraman G, Hume JH, Kromelis M, Weinberg WA. Combination pharmacotherapy in children and adolescents with bipolar disorder. *Biol Psychiatry.* 2003;53(11):978-984.

144. Findling RL, McNamara NK, Gracious BL, et al. Combination lithium and divalproex sodium in pediatric bipolarity. *J Am Acad Child Adolesc Psychiatry.* 2003;42(8):895-901.

145. Lopez-Larson M, Frazier JA. Empirical evidence for the use of lithium and anticonvulsants in children with psychiatric disorders. *Harv Rev Psychiatry.* 2006;14(6):285-304.

146. West SA, Keck PE, McElroy SL, et al. Open Trial of Valproate in the Treatment of Adolescent Mania. *Journal of Child and Adolescent Psychopharmacology.* Win 1994;4(4):263-267.

147. Papatheodorou G, Kutcher SP, Katic M, Szalai JP. The efficacy and safety of divalproex sodium in the treatment of acute mania in adolescents and young adults: an open clinical trial. *J Clin Psychopharmacol.* 1995;15(2):110-116.

148. Deltito JA, Levitan J, Damore J, Hajal F, Zambenedetti M. Naturalistic experience with the use of divalproex sodium on an in-patient unit for adolescent psychiatric patients. *Acta Psychiatr Scand.* 1998;97(3):236-240.

149. Wagner KD, Weller EB, Carlson GA, et al. An open-label trial of divalproex in children and adolescents with bipolar disorder. *J Am Acad Child Adolesc Psychiatry.* 2002;41(10):1224-1230.

150. Chang KD, Dienes K, Blasey C, Adleman N, Ketter T, Steiner H. Divalproex monotherapy in the treatment of bipolar offspring with mood and behavioral disorders and at least mild affective symptoms. *J Clin Psychiatry.* 2003;64(8):936-942.

151. Wagner KD, Redden L, Kowatch RA, et al. A Double-Blind, Randomized, Placebo-Controlled Trial of Divalproex Extended-Release in the Treatment of Bipolar Disorder in Children and Adolescents. *J Am Acad Child Adolesc Psychiatry.* 2009;24:24.

152. DelBello MP, Kowatch RA, Warner J, et al. Adjunctive topiramate treatment for pediatric bipolar disorder: a retrospective chart review. *J Child Adolesc Psychopharmacol.* 2002;12(4):323-330.

153. Yatham LN, Kusumakar V, Calabrese JR, Rao R, Scarrow G, Kroeker G. Third generation anticonvulsants in bipolar disorder: a review of efficacy and summary of clinical recommendations. *J Clin Psychiatry.* 2002;63(4):275-283.

154. Delbello MP, Findling RL, Kushner S, et al. A pilot controlled trial of topiramate for mania in children and adolescents with bipolar disorder. *J Am Acad Child Adolesc Psychiatry.* 2005;44(6):539-547.

155. Davanzo P, Nikore V, Yehya N, Stevenson L. Oxcarbazepine treatment of juvenile-onset bipolar disorder. *Journal of Child and Adolescent Psychopharmacology.* Fal 2004;14(3):344-345.

156. Teitelbaum M. Oxcarbazepine in bipolar disorder. *Journal of the American Academy of Child and Adolescent Psychiatry.* Sep 2001;40(9):993-994.

157. Wagner KD, Kowatch RA, Emslie GJ, et al. A double-blind, randomized, placebo-controlled trial of oxcarbazepine in the treatment of bipolar disorder in children and adolescents. *Am J Psychiatry.* 2006;163(7):1179-1186.

158. Hamrin V, Bailey K. Gabapentin and methylphenidate treatment of a preadolescent with attention deficit hyperactivity disorder and bipolar disorder. *J Child Adolesc Psychopharmacol.* 2001;11(3):301-309.

159. Soutullo CA, Casuto LS, Keck PE, Jr. Gabapentin in the treatment of adolescent mania: a case report. *J Child Adolesc Psychopharmacol.* 1998;8(1):81-85.

160. Frye MA, Ketter TA, Kimbrell TA, et al. A placebo-controlled study of lamotrigine and gabapentin monotherapy in refractory mood disorders. *J Clin Psychopharmacol.* 2000;20(6):607-614.

161. Pande AC, Crockatt JG, Janney CA, Werth JL, Tsaroucha G. Gabapentin in bipolar disorder: a placebo-controlled trial of adjunctive therapy. Gabapentin Bipolar Disorder Study Group. *Bipolar Disord.* 2000;2(3 Pt 2):249-255.

162. Kovacs G. *Polycystic Ovary Syndrome*. Cambridge: Cambridge University Press; 2000.

163. Sillanpaa M. Carbamazepine. Pharmacology and clinical uses. *Acta Neurol Scand Suppl.* 1981;88:1-202.

164. Wang PW, Ketter TA. Clinical use of carbamazepine for bipolar disorders. *Expert Opin Pharmacother.* 2005;6(16):2887-2902.

165. Novak PH, Ekins-Daukes S, Simpson CR, Milne RM, Helms P, McLay JS. Acute drug prescribing to children on chronic antiepilepsy therapy and the potential for adverse drug interactions in primary care. *Br J Clin Pharmacol.* 2005;59(6):712-717.

166. Pandina GJ, Bilder R, Harvey PD, Keefe RS, Aman MG, Gharabawi G. Risperidone and cognitive function in children with disruptive behavior disorders. *Biol Psychiatry.* 2007;62(3):226-234. Epub 2007 Jan 2008.

167. Pavuluri MN, Henry DB, Carbray JA, Sampson G, Naylor MW, Janicak PG. Open-label prospective trial of risperidone in combination with lithium or divalproex sodium in pediatric mania. *J Affect Disord.* 2004;82(Suppl 1):S103-111.

168. Pavuluri MN, Henry DB, Carbray JA, Sampson GA, Naylor MW, Janicak PG. A one-year open-label trial of risperidone augmentation in lithium nonresponder youth with preschool-onset bipolar disorder. *J Child Adolesc Psychopharmacol.* 2006;16(3):336-350.

169. Chang KD NM, Aurang C, Johnson B, Jin N, Marcus R, Forbes RA, Carson WH, Kahn A, Findling RL. Efficacy of aripiprazole in children (10-17 years old) with

mania. Paper presented at: 54th Annual Meeting of the American Academy of Child and Adolescent Psychiatry, 2007; Boston, MA.

170. Biederman J, McDonnell MA, Wozniak J, et al. Aripiprazole in the treatment of pediatric bipolar disorder: a systematic chart review. *CNS Spectr.* 2005;10(2):141-148.

171. Biederman J, Mick E, Spencer T, et al. An open-label trial of aripiprazole monotherapy in children and adolescents with bipolar disorder. *CNS Spectr.* 2007;12(9):683-689.

172. Barzman DH, DelBello MP, Kowatch RA, et al. The effectiveness and tolerability of aripiprazole for pediatric bipolar disorders: a retrospective chart review. *J Child Adolesc Psychopharmacol.* 2004;14(4):593-600.

173. DelBello MP, Kowatch RA, Adler CM, et al. A double-blind randomized pilot study comparing quetiapine and divalproex for adolescent mania. *J Am Acad Child Adolesc Psychiatry.* 2006;45(3):305-313.

174. Delbello MP, Schwiers ML, Rosenberg HL, Strakowski SM. A double-blind, randomized, placebo-controlled study of quetiapine as adjunctive treatment for adolescent mania. *J Am Acad Child Adolesc Psychiatry.* 2002;41(10):1216-1223.

175. Marchand WR, Wirth L, Simon C. Quetiapine adjunctive and monotherapy for pediatric bipolar disorder: a retrospective chart review. *J Child Adolesc Psychopharmacol.* 2004;14(3):405-411.

176. Frazier JA, Biederman J, Tohen M, et al. A prospective open-label treatment trial of olanzapine monotherapy in children and adolescents with bipolar disorder. *J Child Adolesc Psychopharmacol.* 2001;11(3):239-250.

177. Tohen M, Kryzhanovskaya L, Carlson G, et al. Olanzapine versus placebo in the treatment of adolescents with bipolar mania. *Am J Psychiatry.* 2007;164(10):1547-1556.

178. Barnett MS. Ziprasidone monotherapy in pediatric bipolar disorder. *J Child Adolesc Psychopharmacol.* 2004;14(3):471-477.

179. Biederman J, Mick E, Spencer T, Dougherty M, Aleardi M, Wozniak J. A prospective open-label treatment trial of ziprasidone monotherapy in children and adolescents with bipolar disorder. *Bipolar Disord.* 2007;9(8):888-894.

180. Masi G, Mucci M, Millepiedi S. Clozapine in adolescent inpatients with acute mania. *J Child Adolesc Psychopharmacol.* 2002;12(2):93-99.

181. Ratzoni G, Gothelf D, Brand-Gothelf A, et al. Weight gain associated with olanzapine and risperidone in adolescent patients: a comparative prospective study. *J Am Acad Child Adolesc Psychiatry.* 2002;41(3):337-343.

182. Bloch Y, Vardi O, Mendlovic S, Levkovitz Y, Gothelf D, Ratzoni G. Hyperglycemia from olanzapine treatment in adolescents. *J Child Adolesc Psychopharmacol.* 2003;13(1):97-102.

183. Saito E, Kafantaris V. Can diabetes mellitus be induced by medication? *J Child Adolesc Psychopharmacol.* 2002;12(3):231-236.

184. Toren P, Ratner S, Laor N, Weizman A. Benefit-risk assessment of atypical antipsychotics in the treatment of schizophrenia and comorbid disorders in children and adolescents. *Drug Saf.* 2004;27(14):1135-1156.

185. Stigler KA, Potenza MN, Posey DJ, McDougle CJ. Weight gain associated with atypical antipsychotic use in children and adolescents: prevalence, clinical relevance, and management. *Paediatr Drugs.* 2004;6(1):33-44.

186. Blanz B, Schmidt MH. Clozapine for schizophrenia. *J Am Acad Child Adolesc Psychiatry.* 1993;32(1):223-224.

187. Frazier JA, Gordon CT, McKenna K, Lenane MC, Jih D, Rapoport JL. An open trial of clozapine in 11 adolescents with childhood-onset schizophrenia. *J Am Acad Child Adolesc Psychiatry.* 1994;33(5):658-663.

188. Masi G. Pharmacotherapy of pervasive developmental disorders in children and adolescents. *CNS Drugs.* 2004;18(14):1031-1052.

189. Kumra S, Frazier JA, Jacobsen LK, et al. Childhood-onset schizophrenia. A double-blind clozapine-haloperidol comparison. *Arch Gen Psychiatry.* 1996;53(12):1090-1097.

190. Centorrino F, Price BH, Tuttle M, et al. EEG abnormalities during treatment with typical and atypical antipsychotics. *Am J Psychiatry.* 2002;159(1):109-115.

191. Patel NC, DelBello MP, Bryan HS, et al. Open-label lithium for the treatment of adolescents with bipolar depression. *J Am Acad Child Adolesc Psychiatry.* 2006;45(3):289-297.

192. Nierenberg AA, Ostacher MJ, Calabrese JR, et al. Treatment-resistant bipolar depression: a STEP-BD equipoise randomized effectiveness trial of antidepressant augmentation with lamotrigine, inositol, or risperidone. *Am J Psychiatry.* 2006;163(2):210-216.

193. Carandang CG, Maxwell DJ, Robbins DR, Oesterheld JR. Lamotrigine in adolescent mood disorders. *J Am Acad Child Adolesc Psychiatry.* 2003;42(7):750-751.

194. Chang K, Saxena K, Howe M. An open-label study of lamotrigine adjunct or monotherapy for the treatment of adolescents with bipolar depression. *J Am Acad Child Adolesc Psychiatry.* 2006;45(3):298-304.

195. Pavuluri MN, Henry DB, Moss M, Mohammed T, Carbray JA, Sweeney JA. Effectiveness of lamotrigine in maintaining symptom control in pediatric bipolar disorder. *J Child Adolesc Psychopharmacol.* 2009;19(1):75-82.

196. Kafantaris V, Coletti DJ, Dicker R, Padula G, Pleak RR, Alvir JM. Lithium treatment of acute mania in adolescents: a placebo-controlled discontinuation study. *J Am Acad Child Adolesc Psychiatry.* 2004;43(8):984-993.

197. Findling RL, McNamara NK, Youngstrom EA, et al. Double-blind 18-month trial of lithium versus divalproex maintenance treatment in pediatric bipolar disorder. *J Am Acad Child Adolesc Psychiatry.* 2005;44(5):409-417.

198. Baumer FM, Howe M, Gallelli K, Simeonova DI, Hallmayer J, Chang KD. A pilot study of antidepressant-induced mania in pediatric bipolar disorder: Characteristics, risk factors, and the serotonin transporter gene. *Biol Psychiatry.* 2006;60(9):1005-1012. Epub 2006 Aug 1030.

199. Biederman J, Mick E, Prince J, et al. Systematic chart review of the pharmacologic treatment of comorbid attention deficit hyperactivity disorder in youth with bipolar disorder. *J Child Adolesc Psychopharmacol.* 1999;9(4):247-256.

200. Carlson GA, Loney J, Salisbury H, Kramer JR, Arthur C. Stimulant treatment in young boys with symptoms suggesting childhood mania: a report from a longitudinal study. *J Child Adolesc Psychopharmacol.* 2000;10(3):175-184.

201. Scheffer RE, Kowatch RA, Carmody T, Rush AJ. Randomized, placebo-controlled trial of mixed amphetamine salts for symptoms of comorbid ADHD in pediatric bipolar disorder after mood stabilization with divalproex sodium. *Am J Psychiatry.* 2005;162(1):58-64.

202. DelBello MP, Soutullo CA, Hendricks W, Niemeier RT, McElroy SL, Strakowski SM. Prior stimulant treatment in adolescents with bipolar disorder: association with age at onset. *Bipolar Disord.* 2001;3(2):53-57.

203. Goldberg JF, Truman CJ. Antidepressant-induced mania: an overview of current controversies. *Bipolar Disord.* 2003;5(6):407-420.

204. Pagano ME, Demeter CA, Faber JE, Calabrese JR, Findling RL. Initiation of stimulant and antidepressant medication and clinical presentation in juvenile bipolar I disorder. *Bipolar Disord.* 2008;10(2):334-341.

205. Aparasu RR, Bhatara V. Patterns and determinants of antipsychotic prescribing in children and adolescents, 2003-2004. *Curr Med Res Opin.* 2007;23(1):49-56.

206. Blanco C, Laje G, Olfson M, Marcus SC, Pincus HA. Trends in the treatment of bipolar disorder by outpatient psychiatrists. *Am J Psychiatry.* 2002;159(6):1005-1010.

207. Bhangoo RK, Lowe CH, Myers FS, et al. Medication use in children and adolescents treated in the community for bipolar disorder. *J Child Adolesc Psychopharmacol.* 2003;13(4):515-522.

208. Committee on Quality of Health Care in America IoM, ed. *To Err Is Human: Building a Safer Health System*: The National Academies Press; 2000. Linda T. Kohn JMC, and Molla S. Donaldson, ed.

209. Lohr KN, Schroeder SA. A strategy for quality assurance in Medicare. *N Engl J Med.* 1990;322(10):707-712.

210. Mangione-Smith R, DeCristofaro AH, Setodji CM, et al. The quality of ambulatory care delivered to children in the United States. *N Engl J Med.* 2007;357(15):1515-1523.

211. Dougherty D, Meikle SF, Owens P, Kelley E, Moy E. Children's Health Care in the First National Healthcare Quality Report and National Healthcare Disparities Report. *Med Care.* 2005;43(3 Suppl):I58-63.

212. Forrest CB, Simpson L, Clancy C. Child health services research. Challenges and opportunities. *Jama.* 1997;277(22):1787-1793.

213. Manderscheid RW, Henderson MJ, Witkin MJ, Atay JE. The U.S. mental health system of the 1990s. The challenges of managed care. *Int J Law Psychiatry.* 2000;23(3-4):245-259.

214. Olfson M, Marcus SC, Druss B, Elinson L, Tanielian T, Pincus HA. National trends in the outpatient treatment of depression. *Jama.* 2002;287(2):203-209.

215. Mechanic D. Closing gaps in mental health care for persons with serious mental illness. *Health Serv Res.* 2001;36(6 Pt 1):1009-1017.

216. Regier DA, Farmer ME, Rae DS, et al. Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study. *Jama.* 1990;264(19):2511-2518.

217. Briggs-Gowan MJ, Horwitz SM, Schwab-Stone ME, Leventhal JM, Leaf PJ. Mental health in pediatric settings: distribution of disorders and factors related to service use. *J Am Acad Child Adolesc Psychiatry.* 2000;39(7):841-849.

218. Costello EJ, Costello AJ, Edelbrock C, et al. Psychiatric disorders in pediatric primary care. Prevalence and risk factors. *Arch Gen Psychiatry.* 1988;45(12):1107-1116.

219. Horwitz SM, Leaf PJ, Leventhal JM. Identification of psychosocial problems in pediatric primary care: do family attitudes make a difference? *Arch Pediatr Adolesc Med.* 1998;152(4):367-371.

220. Wu P, Hoven CW, Bird HR, et al. Depressive and disruptive disorders and mental health service utilization in children and adolescents. *J Am Acad Child Adolesc Psychiatry.* 1999;38(9):1081-1090; discussion 1090-1082.

221. Edelsohn GA, Braitman LE, Rabinovich H, Sheves P, Melendez A. Predictors of urgency in a pediatric psychiatric emergency service. *J Am Acad Child Adolesc Psychiatry.* 2003;42(10):1197-1202.

222. Briggs-Gowan MJ, Carter AS, Skuban EM, Horwitz SM. Prevalence of social-emotional and behavioral problems in a community sample of 1- and 2-year-old children. *J Am Acad Child Adolesc Psychiatry.* 2001;40(7):811-819.

223. Cassidy LJ, Jellinek MS. Approaches to recognition and management of childhood psychiatric disorders in pediatric primary care. *Pediatr Clin North Am.* 1998;45(5):1037-1052.

224. Kelleher KJ, McInerny TK, Gardner WP, Childs GE, Wasserman RC. Increasing identification of psychosocial problems: 1979-1996. *Pediatrics.* 2000;105(6):1313-1321.

225. Williams J, Klinepeter K, Palmes G, Pulley A, Foy JM. Diagnosis and treatment of behavioral health disorders in pediatric practice. *Pediatrics.* 2004;114(3):601-606.

226. Faedda GL, Baldessarini RJ, Glovinsky IP, Austin NB. Treatment-emergent mania in pediatric bipolar disorder: a retrospective case review. *J Affect Disord.* 2004;82(1):149-158.

227. Das AK, Olfson M, Gameroff MJ, et al. Screening for bipolar disorder in a primary care practice. *Jama.* 2005;293(8):956-963.

228. Costello EJ, Burns BJ, Angold A, Leaf PJ. Epidemiology and health care reform. *J Am Acad Child Adolesc Psychiatry.* 1994;33(7):1058-1059.

229. Thomas CR, Holzer CE, 3rd. National distribution of child and adolescent psychiatrists. *J Am Acad Child Adolesc Psychiatry.* 1999;38(1):9-15; discussion 15-16.

230. Streeruwitz A, Barnes TR, Fehler J, Ohlsen R, Curtis VA. Pharmacological management of acute mania: does current prescribing practice reflect treatment guidelines? *J Psychopharmacol.* 2007;21(2):206-209.

231. Cabana MD, Rand CS, Powe NR, et al. Why don't physicians follow clinical practice guidelines? A framework for improvement. *Jama.* 1999;282(15):1458-1465.

232. Trivedi MH, Claassen CA, Grannemann BD, et al. Assessing physicians' use of treatment algorithms: Project IMPACTS study design and rationale. *Contemp Clin Trials.* 2007;28(2):192-212. Epub 2006 Aug 2016.

233. Rushton JL, Fant KE, Clark SJ. Use of practice guidelines in the primary care of children with attention-deficit/hyperactivity disorder. *Pediatrics.* 2004;114(1):e23-28.

234. Perlis RH. Use of treatment guidelines in clinical decision making in bipolar disorder: a pilot survey of clinicians. *Curr Med Res Opin.* 2007;23(3):467-475.

235. Busch AB, Huskamp HA, Landrum MB. Quality of care in a Medicaid population with bipolar I disorder. *Psychiatr Serv.* 2007;58(6):848-854.

236. Lim PZ, Tunis SL, Edell WS, Jensik SE, Tohen M. Medication prescribing patterns for patients with bipolar I disorder in hospital settings: adherence to published practice guidelines. *Bipolar Disord.* 2001;3(4):165-173.

237. Busch AB, Ling D, Frank RG, Greenfield SF. Changes in the quality of care for bipolar I disorder during the 1990s. *Psychiatr Serv.* 2007;58(1):27-33.

238. Donabedian A. Evaluating the quality of medical care. 1966. *Milbank Q.* 2005;83(4):691-729.

239. Andersen RM. Revisiting the behavioral model and access to medical care: does it matter? *J Health Soc Behav.* 1995;36(1):1-10.

240. Donabedian A. The quality of medical care. *Science.* 1978;200(4344):856-864.

241. Brook RH, McGlynn EA, Cleary PD. Quality of health care. Part 2: measuring quality of care. *N Engl J Med.* 1996;335(13):966-970.

242. Hulka BS, Wheat JR. Patterns of utilization. The patient perspective. *Med Care.* 1985;23(5):438-460.

243. Artz MB, Hadsall RS, Schondelmeyer SW. Impact of generosity level of outpatient prescription drug coverage on prescription drug events and expenditure among older persons. *Am J Public Health.* 2002;92(8):1257-1263.

244. Golden WE, Hermann RC, Jewell M, Brewster C. Development of evidence-based performance measures for bipolar disorder: overview of methodology. *J Psychiatr Pract.* 2008;14(Suppl 2):18-30.

245. Baldessarini RJ, Leahy L, Arcona S, Gause D, Zhang W, Hennen J. Patterns of psychotropic drug prescription for U.S. patients with diagnoses of bipolar disorders. *Psychiatr Serv.* Jan 2007;58(1):85-91.

246. Baldessarini R, Henk H, Sklar A, Chang J, Leahy L. Psychotropic medications for patients with bipolar disorder in the United States: polytherapy and adherence. *Psychiatr Serv.* Oct 2008;59(10):1175-1183.

247. Maniscalco ER, Hamrin V. Assessment and diagnostic issues in pediatric bipolar disorder. *Arch Psychiatr Nurs.* 2008;22(6):344-355. Epub 2008 Oct 2014.

248. Ohsfeldt RL, Lage MJ, Rajagopalan K. Medication use, service utilization, and medical costs associated with new episodes of bipolar disorder: evidence from a retrospective claims database. *Prim Care Companion J Clin Psychiatry.* 2007;9(4):280-286.

249. Goodwin FK, Fireman B, Simon GE, Hunkeler EM, Lee J, Revicki D. Suicide risk in bipolar disorder during treatment with lithium and divalproex. *Jama.* 2003;290(11):1467-1473.

250. Axelson D, Birmaher B, Strober M, et al. Phenomenology of children and adolescents with bipolar spectrum disorders. *Arch Gen Psychiatry.* 2006;63(10):1139-1148.

251. Yoon EY, Dombkowski KJ, Rocchini A, Lin JJ, Davis MM. Off-label utilization of antihypertensive medications in children. *Ambul Pediatr.* 2007;7(4):299-303.

252. Cohen J. A Power Primer. *Psychological Bulletin.* Jul 1992;112(1):155-159.

253. McElroy SL, Altshuler LL, Suppes T, et al. Axis I psychiatric comorbidity and its relationship to historical illness variables in 288 patients with bipolar disorder. *Am J Psychiatry.* 2001;158(3):420-426.

254. Faraone SV, Glatt SJ, Tsuang MT. The genetics of pediatric-onset bipolar disorder. *Biol Psychiatry.* 2003;53(11):970-977.

255. Danielyan A, Pathak S, Kowatch RA, Arszman SP, Johns ES. Clinical characteristics of bipolar disorder in very young children. *J Affect Disord.* 2007;97(1-3):51-59. Epub 2006 Jul 2005.

256. Unutzer J, Simon G, Pabiniak C, Bond K, Katon W. The treated prevalence of bipolar disorder in a large staff-model HMO. *Psychiatr Serv.* 1998;49(8):1072-1078.

257. DelBello MP, Hanseman D, Adler CM, Fleck DE, Strakowski SM. Twelve-month outcome of adolescents with bipolar disorder following first hospitalization for a manic or mixed episode. *Am J Psychiatry.* 2007;164(4):582-590.

258. Fortney J, Rost K, Zhang M, Warren J. The impact of geographic accessibility on the intensity and quality of depression treatment. *Med Care.* 1999;37(9):884-893.

259. Duhoux A, Fournier L, Nguyen CT, Roberge P, Beveridge R. Guideline concordance of treatment for depressive disorders in Canada. *Soc Psychiatry Psychiatr Epidemiol.* 2009;44(5):385-392. Epub 2008 Oct 2022.

260. Spiegelman D, Hertzmark E. Easy SAS calculations for risk or prevalence ratios and differences. *Am J Epidemiol.* 2005;162(3):199-200. Epub 2005 Jun 2029.

261. Petersen MR, Deddens JA. Re: "Easy SAS calculations for risk or prevalence ratios and differences". *Am J Epidemiol.* 2006;163(12):1158-1159; author reply 1159-1161.

262. Kessler RC, Avenevoli S, Green J, et al. National comorbidity survey replication adolescent supplement (NCS-A): III. Concordance of DSM-IV/CIDI diagnoses with clinical reassessments. *J Am Acad Child Adolesc Psychiatry.* 2009;48(4):386-399.

263. Schneeweiss S, Avorn J. A review of uses of health care utilization databases for epidemiologic research on therapeutics. *Journal of Clinical Epidemiology.* 2005;58(4):323-337.

264. Danner S, Fristad MA, Arnold LE, et al. Early-onset bipolar spectrum disorders: diagnostic issues. *Clin Child Fam Psychol Rev.* 2009;12(3):271-293.

265. Olfson M, Crystal S, Gerhard T, Huang CS, Carlson GA. Mental health treatment received by youths in the year before and after a new diagnosis of bipolar disorder. *Psychiatr Serv.* 2009;60(8):1098-1106.

266. Hetrick S, Merry S, McKenzie J, Sindahl P, Proctor M. Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents. *Cochrane Database Syst Rev.* 2007(3):CD004851.

267. Kowatch RA, DelBello MP. The use of mood stabilizers and atypical antipsychotics in children and adolescents with bipolar disorders. *CNS Spectr.* 2003;8(4):273-280.

268. Zito JM, Safer DJ, Valluri S, Gardner JF, Korelitz JJ, Mattison DR. Psychotherapeutic medication prevalence in Medicaid-insured preschoolers. *J Child Adolesc Psychopharmacol.* 2007;17(2):195-203.

269. Olfson M, Crystal S, Huang C, Gerhard T. Trends in Antipsychotic Drug Use by Very Young, Privately Insured Children. *Journal of the American Academy of Child & Adolescent Psychiatry.*49(1):13-23.

270. Unutzer J, Simon G, Pabiniak C, Bond K, Katon W. The use of administrative data to assess quality of care for bipolar disorder in a large staff model HMO. *Gen Hosp Psychiatry.* 2000;22(1):1-10.

271. Cutrona SL, Woolhandler S, Lasser KE, et al. Free drug samples in the United States: characteristics of pediatric recipients and safety concerns. *Pediatrics.* 2008;122(4):736-742.