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DISSERTATION

SAFETY AND EFFECTIVENESS OF ANTIDEPRESSANTS IN MEDICAID-ENROLLED PEDIATRIC BIPOLAR DEPRESSION

by

DEBAJYOTI BHOWMIK

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Safety and Effectiveness of Antidepressants in Medicaid-Enrolled Pediatric Bipolar Depression

BY

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SPECIFIC AIMS

Pediatric bipolar disorder (I and II) patients suffer from recurrent episodes of depression and mania or hypomania (American Psychiatric Association, 1994), or mixed episodes with rapid cycling (Findling et al., 2001; Geller et al., 2002). Worldwide prevalence of bipolar disorder was 5% (Tondo et al., 2003), and in the USA was 2.6% in adults and 0-3% in adolescents (Bipolar Disorder). Early-onset bipolar disorder in childhood was associated with a higher number of lifetime episodes of manic and depressive phases, more comorbidities such as anxiety and substance abuse, rapid cycling between different phases, and higher incidence of suicide attempts compared to adulthood onset of bipolar disorder (Potter et al., 2009; Leverich et al., 2007; Perlis et al., 2004). Lifetime prevalence of the depressive phase among bipolar disorder patients is 3-fold higher than the mania phase (Post et al., 2003). Untreated bipolar depression among all the phases of bipolar disorder, particularly in children and adolescents, is associated with a high risk of suicidality (Tondo et al., 1998), substance abuse, functional disability, and poor academic and social performance among children and adolescents (Baldessarini et al., 2008; Angst et al., 2002; Frye et al., 2006; Thase, 2006; Dutta et al., 2007; Huxley and Baldessarini, 2007; Tondo and Baldessarini, 2007). Despite a higher prevalence of the depressive phase and associated risk of morbidity and mortality among bipolar disorder patients, research on the bipolar depressive phase is limited (Bhangoo et al., 2003).

Although medication regimens includingmood stabilizers, antidepressants, and antipsychotics for treating bipolar depression in adults is well established (Lin et al., 2006), similar treatment guidelines for bipolar depression in younger populations are unavailable. Efficacy of different classes of medications in treating pediatric bipolar depression has been examined in several randomized trials or observational studies and documented (Kowatch et al.,

2005), but psychiatric practice for children and adolescents in this regard is mostly extrapolated from adult guideline, expert consensus, or clinicians' experience. Accordingly, mood stabilizers and second-generation antipsychotics (SGA) are considered to be the 1st line therapy for pediatric bipolar depression, while antidepressants selective serotonin reuptake inhibitors (SSRI) and bupropion are recommended only as adjunct therapy when 1st line treatment is ineffective (Kowatch et al., 2005). However, the utilization pattern of medications in treating bipolar depression in pediatric population is mostly unexplored. Subsequently, real-world safety and effectiveness of psychotropic medications in pediatric bipolar depression is also limited.

Controversy prevails over the safety of using antidepressants in bipolar depression patients due to the concerns about possible manic or hypomanic switching, rapid cycling, and long-term mood destabilization. Although a potential risk of mood destabilization with the use of antidepressants has been suggested historically, critical evaluation of those clinical trials suggested presence of bias and a lack of control groups to accurately address the issue. Quantitative real-world data on comparative safety of antidepressants, antipsychotics, and mood stabilizers, in terms of risk of short-term manic switch among pediatric bipolar depression patients, is limited as well.

Effectiveness of psychotropic pharmacotherapy in bipolar disorder is examined for outcomes such as response, remission, recovery, and relapse of the depressive phase. Such outcomes are measured using mania and depression rating scales, such as Young's mania rating scale, Montgomery-Asberg depression rating scale, etc. Unavailability of such severity scales in administrative data hinders direct assessment of comparative effectiveness of psychotropic medications in real-world patients. Overall, numerical data on comparative effectiveness of antidepressants, antipsychotics, and mood stabilizers in pediatric bipolar depression is limited.

Considering the prevalence of bipolar depression among children and adolescents and the associated risk of morbidity and mortality, and paucity of knowledge regarding drug utilization pattern, and comparative safety and effectiveness of antidepressant pharmacotherapy in this patient population, the specific aims of this study will be-

Aim I: To assess adherence to psycho-pharmacotherapeutic regimens during 6 months after the initial bipolar depression diagnosis among Medicaid-enrolled children and adolescents, in terms of-

(1) Continuation of antidepressant monotherapy, antipsychotic monotherapy, mood stabilizer monotherapy, antidepressant polytherapy (with antipsychotic or mood stabilizer), antipsychotic-mood stabilizer polytherapy, and 3-class polytherapy regimens during 6 months after initial bipolar depression diagnosis,

(2) Augmentation pattern with a new class of medications among antidepressant, antipsychotic, and mood stabilizer monotherapy; and antidepressant, and antipsychotic-mood stabilizer polytherapy regimens during the 6 months of follow up after initial bipolar depression diagnosis,

(3) Switch from initial treatment regimen including antidepressant, antipsychotic, and mood stabilizer monotherapy; and antidepressant, antipsychotic-mood stabilizer, and 3-class polytherapy to regimens inclusive of other therapeutic classes, during the 6 months of follow up after initial bipolar depression diagnosis,

(4) All medication class discontinuation patterns in antidepressant, antipsychotic, and mood stabilizer monotherapy; and antidepressant, antipsychotic-mood stabilizer, and 3-class polytherapy regimens, during 6 the months of follow up after initial bipolar depression diagnosis.

Aim II: To examine the risk of manic switch with the use of antidepressant in Medicaid-enrolled pediatric bipolar depression patients –

(1) To assess comparative safety of antidepressant monotherapy against antipsychotic monotherapy, in terms of risk of manic switch in pediatric bipolar depression population,

(2) To assess comparative safety of antidepressant monotherapy against mood stabilizer monotherapy, in terms of risk of manic switch in pediatric bipolar depression population,

(3) To assess comparative safety of antidepressant polytherapy against antipsychotic-mood stabilizer polytherapy, in terms of risk of manic switch in pediatric bipolar depression population.

Aim III: To evaluate the effectiveness of antidepressant pharmacotherapy among Medicaid enrolled children and adolescents with bipolar depression -

(1) To assess risk of treatment augmentation in pediatric bipolar depression patients, comparing

(i) Antidepressant monotherapy vs. antipsychotic monotherapy,

(ii) Antidepressant monotherapy vs. mood stabilizer monotherapy,

(iii) Antidepressant polytherapy vs. antipsychotic-mood stabilizer polytherapy.

(2) To assess risk of mental-health related hospitalization in pediatric bipolar depression patients, comparing

(i) Antidepressant monotherapy vs. antipsychotic monotherapy,

(ii) Antidepressant monotherapy vs. mood stabilizer monotherapy,

(iii) Antidepressant polytehrapy vs. antipsychotic-mood stabilizer polytherapy

BACKGROUND, SIGNIFICANCE AND RATIONALE

Background

(1) Bipolar Disorder: Clinical States and Subtypes

Bipolar disorder (BD), which is also known as manic-depressive disorder, bipolar affective disorder, or manic depression, is a kind of mood disorder characterized by presence of episodes of highly elevated energy level (mania phase) and episodes of depression. The psychiatric condition where both the phases occur at the same time is known as a mixed phase. Generally, mania and depressive phases are divided by episodes of stable mood condition (euthymia); however, in some individuals these two alternating states may occur very rapidly, which is known as rapid cycling. The markedly distinguished clinical states of bipolar disorder are bipolar I disorder (characterized by at least one mania or mixed phase, with or without episodes of depressive phase), and bipolar II disorder characterized by episodes of at least one hypomania (milder mania) and one major depressive phase (depressive phases are more frequent and intense than mania phases in this state). Bipolar disorder in the pediatric population manifests itself in forms of "narrow" and "broad" phenotypes as concluded in the National Institute of Mental Health Research Roundtable on pre-pubertal bipolar disorder (2001) (Pavuluri et al., 2005). Among children and adolescents, the "narrow" phenotype is characterized by recurrent episodes of major depression, mania or hypomania as defined by BD I and BD II descriptions in DSM-IV (American Psychiatric Association, 1994). Rapid cycling is also a common manifestation of bipolar disorder in this age group (Findling et al., 2001; Geller et al., 2002). Among the pediatric population, "broad" phenotypes are more prevalent and marked by severe irritability, "affective storms", mood lability, severe temper outbursts, depressive symptoms, anxiety, hyperactivity,

poor concentration, and impulsivity (Biederman et al., 1996). Some of the unique features that distinguish pediatric bipolar disorder are chronicity with long episodes, predominance of mixed episodes and rapid cycling, prevalent attention deficit hyperactivity disorder (ADHD) comorbidity, anxiety disorders, etc. (Birmaher et al., 2002; Findling et al., 2001; Geller et al., 1998; McClellan et al., 1999; Wozniak et al., 1995).

A community-based study to identify bipolar disorder among adolescents in high school showed a lifetime prevalence of 1% in youths of age 14-18 years (Lewinsohn et al., 1995) by using the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS scale) (Orvaschel and Puig-Antich, 1987). A 6-month study on a national sample of 13-18 year old Dutch adolescents identified a prevalence of 1.9% for mania and of 3.6% for major depression (Verhulst et al., 1997). Another study suggested a 3-fold higher prevalence of major depression as compared to mania among BD patients (Post et al., 2003).

(2) Treatment of Bipolar Depression

Objectives of treating bipolar depression patients are (1) to improve the depressive symptoms, (2) to protect against future depressive relapse, and (3) to prevent switching to mania. General treatment recommendations for bipolar depression suggest use of mood stabilizers (lithium, valproate, lamotrigine, carbamazepine, oxcarbazepine, etc.) and an atypical antipsychotic such as olanzapine, and adjunct therapy of antidepressants (SSRI and bupropion) with mood stabilizers (Lin et al., 2006). No treatment guidelines for pediatric PD were available before 2003; even the treatment algorithm proposed by clinicians and Child and Adolescent Bipolar Foundation (CABF) in 2003 was not meant to be considered as the absolute standard care (Kowatch et al., 2005). The review article published by Kowatch et al. summarized the available information

gathered by the panel of clinicians and CABF from pediatric and/or adult population studies about psychotropic medications that have been observed to be effective in treating bipolar depression in randomized trials, retrospective studies, and case reports. Apart from mood stabilizers and antipsychotics, newer antidepressants such as SSRI and bupropion were also listed as effective adjunctive treatments for pediatric bipolar depression (Kowatch et al., 2005), especially for non-response to mood stabilizer therapy or to treat severe depressive episodes (American Psychiatric Association, 2002; Keck et al., 2004; Suppes et al., 2002). However, administration of antidepressant monotherapy in treating BD is contraindicated because of their hypothesized risk of precipitating or worsening mania (Biederman et al., 1996), or TEAS, and rapid cycling (Thase, 2006). Most of the SSRIs also carry a 'black-box' warning in terms of use in pediatric population for their association with suicidality. A double-blind, placebo-controlled study conducted by Sachs et al. indicated that adjunctive antidepressant therapy as compared to mood stabilizers did not add any beneficial impact in terms of durable recovery (8 consecutive weeks of euthymia), nor added any significant risk of TEAS during maximum 26 weeks of follow-up period (Sachs et al., 2007). In randomized clinical trials, effectiveness of pharmacotherapy in treating bipolar depression is measured using various depression severity rating scales, such as Hamilton Depression Rating Scale (HDRS) or Montgomery-Asberg Depression Rating Scale (MADRS). Unavailability of such rating scales in retrospective data hinders direct measurement of effectiveness of antidepressants and other pharmacotherapies in treating large numbers of real world bipolar depression patients. Some of the viable outcomes for studying the long-term comparative effectiveness and safety of antidepressants, mood stabilizers, and antipsychotics in bipolar depression treatment using retrospective data are – effectiveness: adherence to pharmacotherapy as a measure of extent of safety and tolerability of

pharmacotherapy, incidence of treatment escalation regimen augmentation) and hospitalization; and safety: risk of short-term manic switch. Limited data are available regarding the impact of pharmacotherapy on the aforementioned outcomes.

(3) Antidepressants and Risk of Treatment Emergent Affective Switch (TEAS)

Supporting evidence suggests that certain medications or non-pharmacological treatments for BD, with varying mechanisms of action, e.g. sleep deprivation, exogenous corticosteroids, dopamine agonism, etc. may induce TEAS. Several neurobiological factors are believed to trigger this condition, including abnormalities in catecholamine concentration, upregulation of neurotrophic and neuroplastic factors, circadian rhythms, etc. (Salvadore et al., 2010). Also, several clinical factors are suggested to exacerbate the risk of TEAS, such as gender, age, history of mania, history of TEAS, etc. (Salvadore et al., 2010). Although antidepressant-induced TEAS is not fully understood, use of TCAs is believed to carry a higher risk of TEAS compared to other classes of antidepressants. Use of antidepressants has been suggested to induce short-term acute manic switch and long-term risk of mood destabilization (Ghaemi et al., 2003). Published studies based on unipolar depression clinical data suggested a higher risk of TEAS with the SSRI fluoxetine among BD-II patients (RR= 12.4, 95% CI 2.1-73.1) versus unipolar depression patients (Amsterdam et al., 1998). According to general consensus, the prevalence of TEAS in the real-world setting is 40% with TCAs and 20% with newer antidepressants. Also, some evidence suggests that concomitant therapy with a mood stabilizer may reduce antidepressant-induced TEAS (Ghaemi et al. 2003). Thus, from clinical trials a causal linkage between antidepressant use and risk of TEAS can be established. However, quantitative data on

differential risk of TEAS with antidepressants and mood stabilizers, monotherapy and polytherapy, in real world pediatric bipolar depression population are limited.

(4) Effectiveness of Pharmacotherapy in Bipolar Depression Treatment

Primary aims of treatment of acute bipolar depression include relieving depressive symptoms and protecting against future recurrence of depressive symptoms. Some of the effectiveness measures used in clinical trials and observational studies are response, remission, recovery, relapse, recurrence, etc. (Tohen et al., 2009). All these outcomes in clinical trials are defined using symptom and severity rating scales such as Hamilton Rating Scale for Depression (HAMD) or Montgomery-Asberg Depression Rating Scale (MADRS) at different time points of the bipolar depressive phase. For example, response and remission are measured based on the presence or absence of depressive symptoms during the 4 months of the acute treatment phase, recovery and relapse outcomes are measured during the 2 months of the maintenance treatment phase, and recurrence is identified after the maintenance phase. Absence of such symptom severity scales in observational data hinders direct measurement of effectiveness of pharmacotherapy in post-marketing comparative effectiveness studies. Some of the effectiveness outcomes evaluated in clinical trials and observational studies that which suit the claims data structure are remission, relapse, hospitalization (which has been used as a marker of relapse of symptoms and discontinuation of treatment), tolerability (defined as discontinuation of treatment), and change in the level of psychiatric care (physician office visit or treatment). This study aimed to measure effectiveness of antidepressants in a Medicaid-enrolled pediatric bipolar depression population in terms (1) mental-health related (nonmanic) hospitalization and (2) treatment augmentation.

Significance and Rationale

Depression is a highly prevalent state of BD (more prevalent than manic or hypomanic phase) (Post et al., 2003), and depressive phase is a major risk factor for suicidality, substance abuse, and poor social and academic performance. Well-established treatment guidelines are not available for pediatric bipolar depression patients; current psychiatric practice in this regard is dependent on extrapolation from research in adult populations and/or clinicians' experience. In general, relapse in bipolar disorder patients is widely prevalent – 40% in the 1st year, 60% in the 2nd year, and 73% over 5 years (Gitlin et al., 1995), and effectiveness of pharmacological treatment of bipolar disorder becomes suboptimal due to non-adherence to treatment (Crowe et al., 2010). Limited published data are available on psychotropic drug utilization patterns and adherence to medication regimens in pediatric bipolar depression patients. Evaluation of treatment adherence among bipolar depression patients is highly important, as treatment non-adherence has been cited to be associated with higher recurrence rates, hospitalizations, and suicidal events (Clatworthy et al., 2007). Unavailability of depression rating scales used in clinical trials, such as Hamilton Depression Rating Scale (HDRS), in retrospective claims data hinders direct studying of comparative effectiveness of pharmacological treatments in treating depression in a real-world patient population. As viable substitutes, comparative effectiveness of antidepressants, mood stabilizers, and antipsychotics will be investigated in terms of the risk of psychiatric disorder-related hospitalization and treatment augmentation. Moreover, antidepressant monotherapy is contraindicated in treating bipolar depression because of the risk of relapse of manic or hypomanic symptoms; however, our preliminary analysis has shown considerable use of antidepressant therapy in pediatric Medicaid bipolar depression patients. Thus, the other significant aspect of the proposed study will be evaluation of comparative safety

of antidepressant pharmacotherapy (monotherapy and combination therapy) in terms of risk of manic switch in pediatric bipolar depression patients. Knowledge gained from this study will provide a picture of medication utilization patterns and adherence to pharmacotherapy as reflected in a real-world pediatric bipolar depression population. Furthermore, this study will also aim to address comparative safety and benefits of antidepressant pharmacotherapy compared to antimanic (mood stabilizer and antipsychotic) agents among pediatric bipolar depression patients that will help policy-makers and clinician optimize drug regimen to treat BD in this population.

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MANUSCRIPT 1

The utilization of psychopharmacological treatment and medication adherence among Medicaid-enrolled children and adolescents with bipolar depression

Key Words: Bipolar Depression, Antidepressant, Mood Stabilizer, Antipsychotic, Monotherapy, Polytherapy

Conflict of Interest: There is no conflict of interest associated with this study. This study was unfunded.

NUMBER OF WORDS IN ABSTRACT: 290

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Abstract

Objective: To examine psychotropic medication utilization and to compare adherence to individual regimens in children and adolescents diagnosed with bipolar depression.

Methods: 2003-2007 MAX data from four geographically diverse states were used. Patients (6-18 years old) who received a minimum of 2 diagnoses of bipolar disorder other than bipolar depression followed by a bipolar depression diagnosis were identified. According to the regimen received by the patients in the first month after the bipolar depression diagnosis, the study cohort was categorized into 6 mutually exclusive groups. The month to month change of treatment regimen in each group was then assessed during the 2 months prior to and 6 months after the index bipolar depression diagnosis. Adherence to each regimen was measured as continuation of the initial regimen, switch to a new regimen, augmentation with medication from a different therapeutic category, and discontinuation of all pharmacotherapies. Repeated measure analysis was conducted to compare the trend of each adherence measure across the study groups.

Results: Of the 5,460 subjects identified, (1) 5.77% received antidepressant monotherapy, (2) 15.39% antipsychotic monotherapy, (3) 9.43% mood stabilizer monotherapy, (4) 22.51% antidepressant polytherapy, (5) 26.48% mood stabilizer-antipsychotic polytherapy, and (6) 19.89% antipsychotic-mood stabilizer-antidepressant polytherapy. More than one third of these regimens were continuations of the pharmacotherapies initiated before the bipolar depression diagnosis. Repeated measure analysis on utilization trends showed that antipsychotic monotherapy had the best adherence. Patients on antipsychotic monotherapy were more likely to continue the initial regimen (vs. antidepressant monotherapy and vs. mood stabilizer monotherapy) and less likely to receive treatment augmentations (vs. mood stabilizer monotherapy) than patients on other monotherapies. As compared to antipsychotic monotherapy, patients on combination regimens

(both antidepressant polytherapy and the combination of an antipsychotic and mood stabilizer) had even higher continuation rates and lower rates of augmentation. Switching to a new regimen was rare across all study groups, and most groups had a similar rate of discontinuing all psychopharmacotherapy except for the group taking a mood stabilizer plus antipsychotic combination.

Conclusions: Bipolar depression patients were predominantly treated with combinations of psychotropic drugs. Combination regimens had higher adherence rates as compared to monotherapies. Potentially questionable practices such as antidepressant monotherapy were used only in a small fraction of patients. Future research should be conducted to clarify the risk and benefit of existing regimens for pediatric bipolar disorder.

Introduction

Bipolar disorder (BD), also known as manic-depressive disorder or bipolar affective disorder, is a form of mood disorder characterized by presence of episodes of highly elevated mood (manic) and episodes of depressive phases. Worldwide prevalence of bipolar disorder was 5%[1], and in the USA were estimated to be 2.6% in adults and 1% in adolescents[2]. Early-onset bipolar disorder in childhood was associated with a higher number of lifetime episodes of manic and depressive phases, more comorbidities such as anxiety and substance abuse, rapid cycling between different phases, and higher incidence of suicide attempts compared to adulthood onset of bipolar disorder[3-5]. Lifetime prevalence of the depressive phase among bipolar disorder patients is 3-fold higher than the mania phase[6]. Untreated bipolar depression among all the phases of bipolar disorder, particularly in children and adolescents, is associated with a high risk of suicidality[7], substance abuse, functional disability, and poor academic and social performance among children and adolescents[8-14].

Medication utilization in treatment of pediatric bipolar disorder has been assessed under various setting such as specialty clinic, community service, national survey, private health insurance, etc.,[8,15-18] Despite the high prevalence of bipolar depression and its associated risk of morbidity and mortality, research on this particular phase of bipolar disorder is limited[19]. Ideally, the goals of pharmacotherapy in treating bipolar depression include symptomatic relief from depression, prevention or delaying a switch to the manic or hypomanic phase, and protection against future depressive relapse[19]. The treatment guideline for adults with bipolar depression advises the use of mood stabilizers (such as lithium and anticonvulsants like lamotrigine, valproate, etc.), second-generation antipsychotics (SGA) (such as olanzapine), and adjunct

therapy with antidepressants such as selective serotonin reuptake inhibitors (SSRI) and bupropion together with mood stabilizers[19].

Little is known about how bipolar depression is treated in real-world children and adolescents. This study aimed to examine the utilization trends and patterns for the treatment of pediatric bipolar depression in Medicaid-enrolled children and adolescents.

Methods

Data Source

2003-2007 Medicaid Analytic eXtract (MAX) files from the Centers for Medicare and Medicaid Services (CMS) were used to assess the utilization of psychotropic polypharmacy in children and adolescents with bipolar disorder. MAX is a set of person-level claims data files containing information on Medicaid eligibility, demographics, service utilization, and payments. Because it is difficult to analyze data from all 50 states, we used data from four geographically diversified states with large Medicaid enrollments of children and adolescents (CA, TX, IL, and NY).

Pharmacotherapy for Bipolar Depression

The pharmacotherapy of bipolar depression includes mood stabilizers (lithium, sodium divalproex/valproate, carbamazepine, oxcarbazepine, topiramate, lamotrigine and gabapentin); second-generation antipsychotics (risperidone, aripiprazole, olanzapine, quetiapine, clozapine, and ziprasidone), typical antipsychotics (chlorpromazine, fluphenazine, haloperidol, loxapine, mesoridazine, molidone, perphenazine, promazine, thioridazne, thiothixene, trifluoperazine), selective serotonin reuptake inhibitor (SSRI) antidepressants (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline) and other antidepressants (venlafaxine,

amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline, bupropion, mirtazapine, nefazodone, trazodone).

Study Population

Children and adolescents with bipolar depression were identified based on the following algorithm: (1) patients aged between 6 to 18 years (children and adolescents), (2) who received minimum 2 diagnoses of bipolar disorder other than bipolar depression (*International Classification of Diseases, 9th version, Clinical Modification* [ICD-9-CM]: 296.0, 296.1, 296.4-296.8, 301.11, 301.13) on different service dates, or 1 diagnosis of bipolar disorder that came from hospital discharge, followed by a diagnosis of bipolar depression (ICD-9CM: 296.5)[20] between 1st March 2003 and 30th June 2007, and (3) continuously eligible for Medicaid from 2 months before and 6 months after the initial bipolar depression diagnosis date (index date). Patients who received diagnoses of schizophrenia (ICD-9CM: 295.0-295.9) or epilepsy (ICD-9CM: 345.xx) were excluded from the cohort to make sure that the prescriptions were used for bipolar disorder. The 6-month follow up period was determined based on the recommendations of treatment guidelines for adults[20, 21]. The acute treatment phase of bipolar depression is generally considered to be 4 months[20]. After remission of depressive symptoms, bipolar disorder patients are recommended to receive additional 8 weeks (approximately 2 months) of maintenance therapy[21].

Psychotropic Utilization Pattern

Monthly medication use for each therapeutic class during the whole study period was computed based on prescription fill date and days of supply. Monotherapy was defined as if patients received medications from a single therapeutic class only, while polytherapy was defined as

receiving medications with a minimum 1 day overlap between prescriptions from two or three different therapeutic classes within a specific month. According to the regimen patients received in the first month after the bipolar depression diagnosis, the study cohort was categorized into 6 mutually exclusive groups; (1) antidepressant monotherapy, (2) antipsychotic monotherapy, (3) mood stabilizer monotherapy, (4) antidepressant polytherapy (antidepressant+antipsychotic, or antidepressant+mood stabilizer), (5) mood stabilizer-antipsychotic polytherapy, and (6) antipsychotic-mood stabilizer-antidepressant polytherapy.

Medication adherence

The adherence to each regimen were assessed. The monthly changes in medication adherence were described as four mutually exclusive patterns which include continuation, augmentation, switch, and discontinuation. *Continuation* was defined as continuously receiving the treatment regimen patients received in the first month after bipolar depression diagnosis. *Augmentation* was defined as the addition of an antidepressant, antipsychotic, or a mood stabilizer other than the index medication(s) to the treatment regimen patients received in the first month after bipolar depression diagnosis. For those who discontinued the original regimen, they could either discontinue all pharmacotherapy or switch to other regimen. S*witch* was defined as the patient did not continue the regimen prescribed in the first month and received any other monotherapy or polytherapy regimen. *Discontinuation* was defined as being devoid of any medication use for BD in the entire month.

Statistical Analysis

Repeated measure analysis was conducted to evaluate the monthly trends of treatment regimen continuation, augmentation, switch, and discontinuation, and to compare the trends across

treatment regimens received in the first month after bipolar depression diagnosis. SAS 9.2 statistical tool was used for the entire analysis, and $p < 0.05$ was considered statistically significant.

This study was approved by the Institutional Review Board of the University of Houston.

Results

A total of 88,668 children and adolescents with a bipolar disorder diagnosis were identified. After excluding patients with comorbid schizophrenia and epilepsy (n=8,731), those who did not receive other bipolar disorder diagnosis before the bipolar depression diagnosis (n=9,117), those with index bipolar depression diagnosis before 1st March 2003 or beyond 30th June 2007 (n=1,529), and those who did not have continuous Medicaid eligibility 2 months prior to and 6 months after the index date (n=978), there were 6,869 patients included in the cohort. Of these bipolar depression patients, 6,376 received pharmacotherapy for bipolar disorder during the 6-month follow up period and 5,460 received treatment within 30 days after the diagnosis.

Among the 5,460 patients who received pharmacotherapy in the first month, 1,670 (30.59%) were on monotherapy, 2,695 (49.36%) were on combinations of two medications, and 1,086 (19.89%) were on combinations of three medications. Among the monotherapy users, SGAs were the most commonly used (n= 836), followed by mood stabilizers (n=515) and SSRIs (n=208). For those on two drugs in combination, 1,229 (45.60%) received antidepressant polytherapy and 1,466 (54.40%) received mood stabilizer-antipsychotic concomitant treatment. Of those who received antidepressant polytherapy, 62.90% (n=773) received antidepressant-antipsychotic polytherapy and 37.10% (n= 456) had antidepressant-mood stabilizer polytherapy.

Continuation: As presented in Fig 1(a), the proportion of patients who continued the regimen received in the first month decreased during the follow up period. The slope of the downward trend, which represents how soon the treatment regimen was discontinued or modified, is the steepest for those who were on antidepressant or mood stabilizer monotherapies, followed by those on antipsychotic monotherapy, antipsychotic-mood stabilizer polytherapy, and antidepressant polytherapy. By the end of the six month follow up period, 58.39% of the mood stabilizer-antipsychotic polytherapy users and 56.91% of three class polytherapy users were still on the same regimens received immediately after the bipolar depression diagnosis. In contrast, only 27.94% of the antidepressant monotherapy users and 30.10% of the mood stabilizer monotherapy users stayed on the original regimen during the same follow up period. Repeated measure analysis using antipsychotic monotherapy as the reference group confirmed that the differences in trend slopes across the study groups were all statistically significantly different than antipsychotic monotherapy.

For those who did not continue the original regimen, they could either receive treatment modification (augmentation with an additional medication from a difference therapeutic category or switch to a different regimen) or discontinue all pharmacotherapy.

Augmentation: The most commonly seen modification on the monotherapy regimens was the addition of a medication from a different therapeutic category. As presented in Fig. 1(b), 24-27% of the monotherapy users and 11-12% of combination users received augmentation during the follow up period ($p<.0001$). For the monotherapy users, the vast majority (80%-90%) of the augmentations were observed in the second month after the index bipolar depression diagnosis. Consistent with the type of combinations used in the first month when augmentation was prescribed, the combination of antidepressant-antipsychotic (21.39%-25.36%), and mood

stabilizer-antipsychotic (26.46%-36.02%) were used more often than the combination of antidepressant-mood stabilizer (13.25%-15.05%).

Switch: The most common modification to combination regimens was a switch to a different regimen. By the end of the 6-month follow up period, 28.91% of the 3-class polytherapy group, 18.09% of the antidepressant polytherapy group, and 14.67% of the mood stabilizer-antipsychotic polytherapy group switched to a different regimen. Switch was mainly due to the discontinuation of one of the medications included in the combination regimen, especially the antidepressant. Switch to a different regimen was uncommon in the monotherapy groups. During the 6-month follow up period, only 4.52% of antipsychotic monotherapy and 7.57% of mood stabilizer monotherapy recipients switched to other regimens. Antidepressant monotherapy recipients had a slightly higher chance of switching to other regimens than the antipsychotic monotherapy group; the switch rate peaked in the 5th month of the follow up period (12.06%) and then dropped in the 6th month to 9.21% suggesting that some patients could be put back on an antidepressant after a switch to other medications.

Discontinuation of all pharmacotherapy: As presented in Fig. 1(C), during the follow up period, 16-30% of the children and adolescents discontinued all bipolar-related pharmacotherapy. Nearly half of the discontinuations occurred in the 3rd month after the index bipolar depression diagnosis. Repeated measure analysis suggested that, by using antipsychotic monotherapy as the reference group, the discontinuation rates were comparable across the study groups except for those who received mood stabilizer-antipsychotic polytherapy and 3-class polytherapy (p=.0008). The month to month discontinuation rates of the mood stabilizer-antipsychotic polytherapy group (1.5-15.89%) were only half of the discontinuation rate observed in the antipsychotic monotherapy group (4.40-25.95%).

A considerable proportion of the treatments identified after the bipolar depression diagnosis were continuations of the medication regimens initiated before the index bipolar depression diagnosis. Almost one-third (32.70%) of antidepressant and mood stabilizer monotherapies, 43.93% of antipsychotic monotherapy, and more than half of the combination regimens (52.89%- 59.07%) were initiated during of the pre-diagnosis period. (Table 1).

Discussion

According to our analysis, pediatric bipolar depression was treated predominantly (75%) by using two or three drugs in combination. The most commonly used combinations were antidepressant-antipsychotic and antipsychotic-mood stabilizer. Those who received two drugs in combination were more likely to stay on the initial regimen and less likely to receive treatment augmentation as compared to the monotherapy recipients.

Continuity of pharmacotherapy is an important measure of treatment acceptance and treatment success. In contrast, adjustments made to treatment regimens such as augmentation, switch, or discontinuation of all medication can be assumed to be due to ineffectiveness of the medications in treating the disorder emergence of drug-related adverse effects[3]. The better adherence associated with combination regimens observed in our study could be explained by better effects of combinations compared to monotherapies in the treatment of pediatric bipolar depression. Although no observational study has assessed the effect of any combination regimen specifically for the treatment of bipolar depression in pediatric population, a preliminary clinical trial in children and adolescents by Pavuluri et al. compared mood stabilizer and SGA monotherapy with combination therapy and concluded that monotherapy was not an effective treatment for long-term stabilization of symptoms in pediatric bipolar disorder[22]. Other studies

show that monotherapy does not appear to be efficacious and that combination therapy gives a better response[23,24].

Among the three monotherapy groups, antipsychotics and mood stabilizers are FDA-approved treatments for pediatric bipolar disorder. As compared to mood stabilizer monotherapy users, those who received antipsychotic monotherapy had higher continuation rates and required less augmentation. Although the antidepressant effect of antipsychotics has not been tested in the pediatric population, this effect of antipsychotics has been confirmed by RCTs using adult samples with unipolar depression. In 2008, the FDA approved the use of aripiprazole in combination with antidepressant medication for the treatment of major depression in adults[25]. In November, coinciding with the FDA approval of this supplemental New Drug Application for aripiprazole, a RCT demonstrated increased antidepressant effect from the addition of risperidone to antidepressant monotherapy[26]. The data specific to patients with bipolar depression are very sparse, but two reports with olanzapine involving a total of 18 adult patients found that 14 had a positive response[27,28].

There is no traditional mood stabilizer that possesses a similar degree of efficacy in treating both the manic and the depressive phases of bipolar disorder. Most of these drugs are purely antimanic agents except for lamotrigine and lithium[29]. However, lamotrigine is only approved by FDA for use in those over the age of 16. It is not commonly used in children because of the increased risk of fatal side-effects, such as Stevens-Johnson syndrome, in younger age groups. Lithium, despite an indication for pediatric bipolar disorder, was used less often in recent years due to its narrow therapeutic window and intensive monitoring requirements. Moreover, literature shows that diligent monitoring of serum levels and renal function might also

have caused earlier and more frequent discontinuation when lithium is used outside of controlled trials[30].

Until 2002, all bipolar treatment guidelines recommended an antidepressant as the first-line treatment of bipolar depression. In that year, the APA treatment guidelines relegated them to second-line use after initial treatment with lithium or lamotrigine monotherapy. It is commonly believed that the use of antidepressant monotherapy for bipolar depression could trigger a new manic episode. Therefore, it is recommended that antidepressant should always be used along with a mood stabilizer. However, in our study, a small fraction (5.77%) of bipolar depression patient still received antidepressant monotherapy immediately following the bipolar depression diagnosis. Unlike the treatments that could be used both in mania and depression, most antidepressant monotherapy (70%) were initiated after the bipolar depression diagnosis. Although polarity switch, if it happened, could lead to discontinuation of antidepressant or medication switch, neither treatment augmentation nor an increased risk of discontinuing, augmentation, or switch was observed in our study when compared to other monotherapies, especially mood stabilizers. Future research should be conducted to clarify the risk and benefit associated with antidepressant use in children and adolescents.

Limitations

One of the major limitations of this study is the absence of clinical validation of bipolar disorder and bipolar depression diagnosis, using DSM-IV criteria. To reduce the impact of possible misdiagnosis and miscoding, we used a strictly defined operational definition for bipolar depression by requiring two additional bipolar diagnoses prior to the index bipolar depression diagnosis to increase the reliability of diagnosis codes. Secondly, the diagnosis cannot be directly

linked to prescriptions in claims data. To ensure that prescriptions used were bipolar related, we excluded patients with other indications of psychotropic drugs under investigation and the analysis only included patients who received treatment within 30 days of the index bipolar depression diagnosis.

Despite the presence of the limitations, to our knowledge this is the first population-based study to explore the real-life practice for the treatment of bipolar depression in pediatric population. Findings from this study provide valuable data for the future evaluation of medication safety and effectiveness for this severe mental disorder in children and adolescents.

Conclusion

Most of the bipolar depression patients in this study received polytherapy rather than monotherapy. As compared to those who were on monotherapy, polytherapy users were more likely to continue the original regimen. Potentially questionable practices such as antidepressant monotherapy were only used in a small fraction of patients. Future research should be conducted to clarify the risk and benefit of existing practices for pediatric bipolar disorder.

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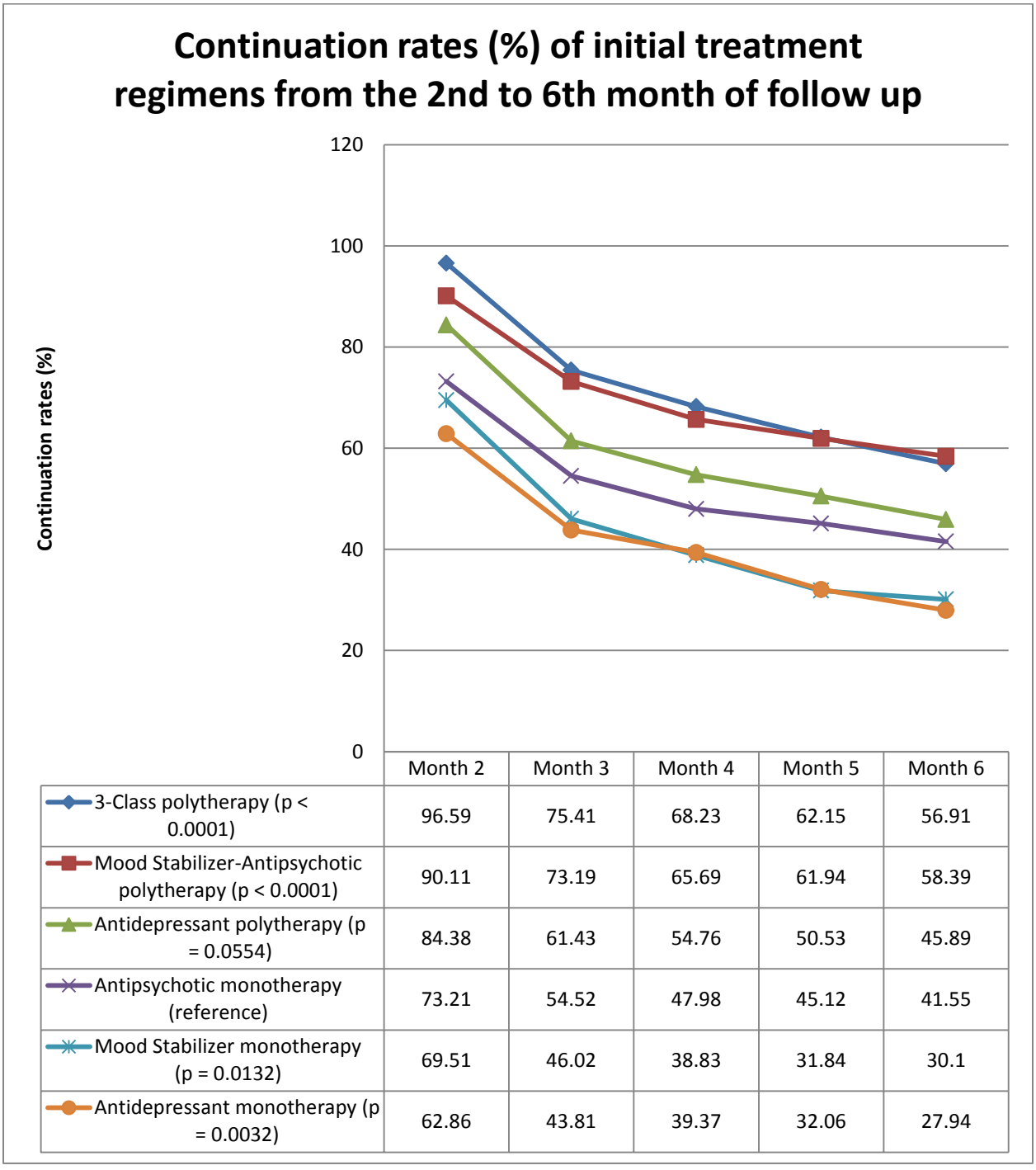
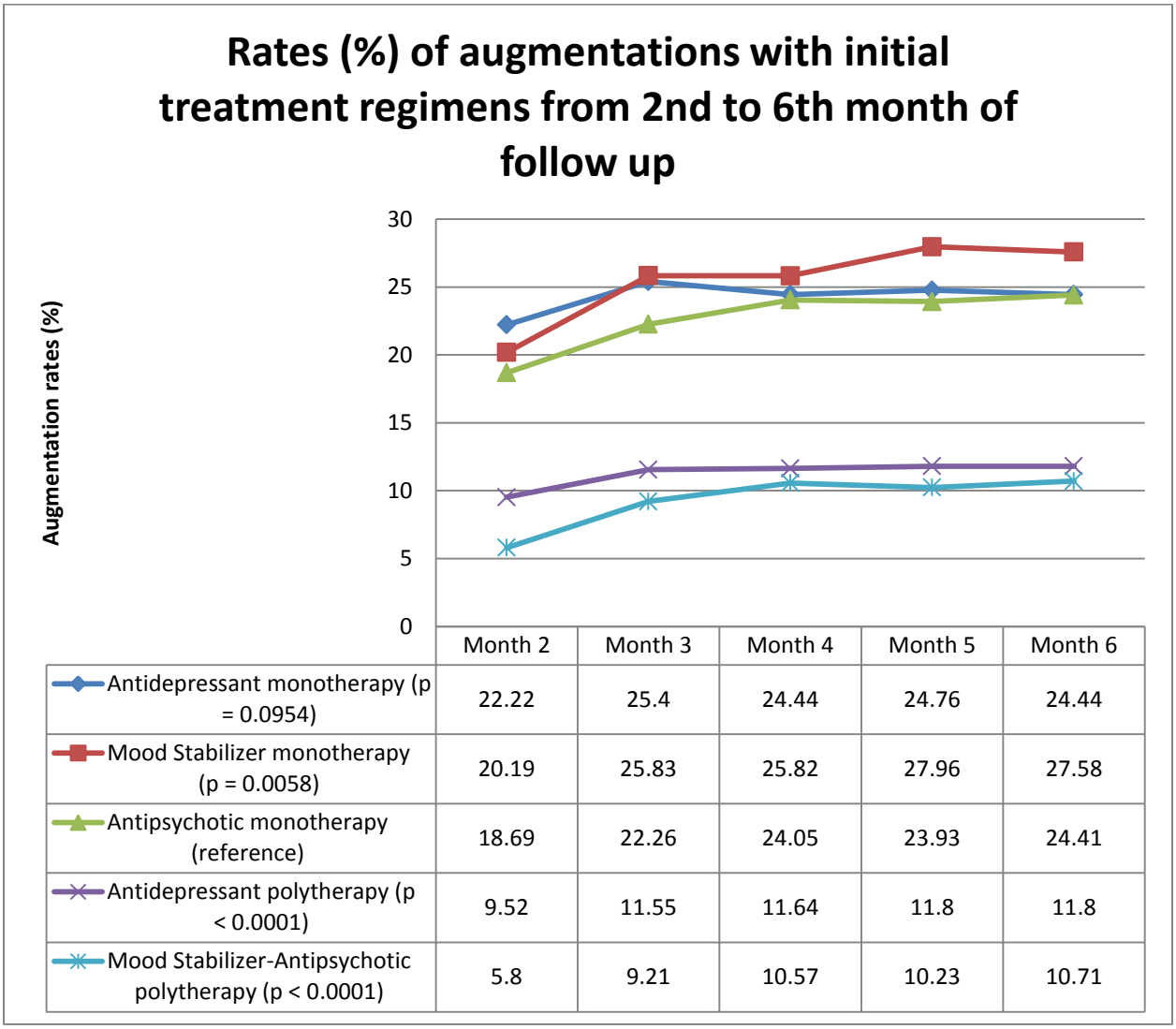
Figure 1(a). Continuation Rates (%) of Treatment Regimens from 2nd to 6th Month of Follow up Period among Bipolar Depression Patients



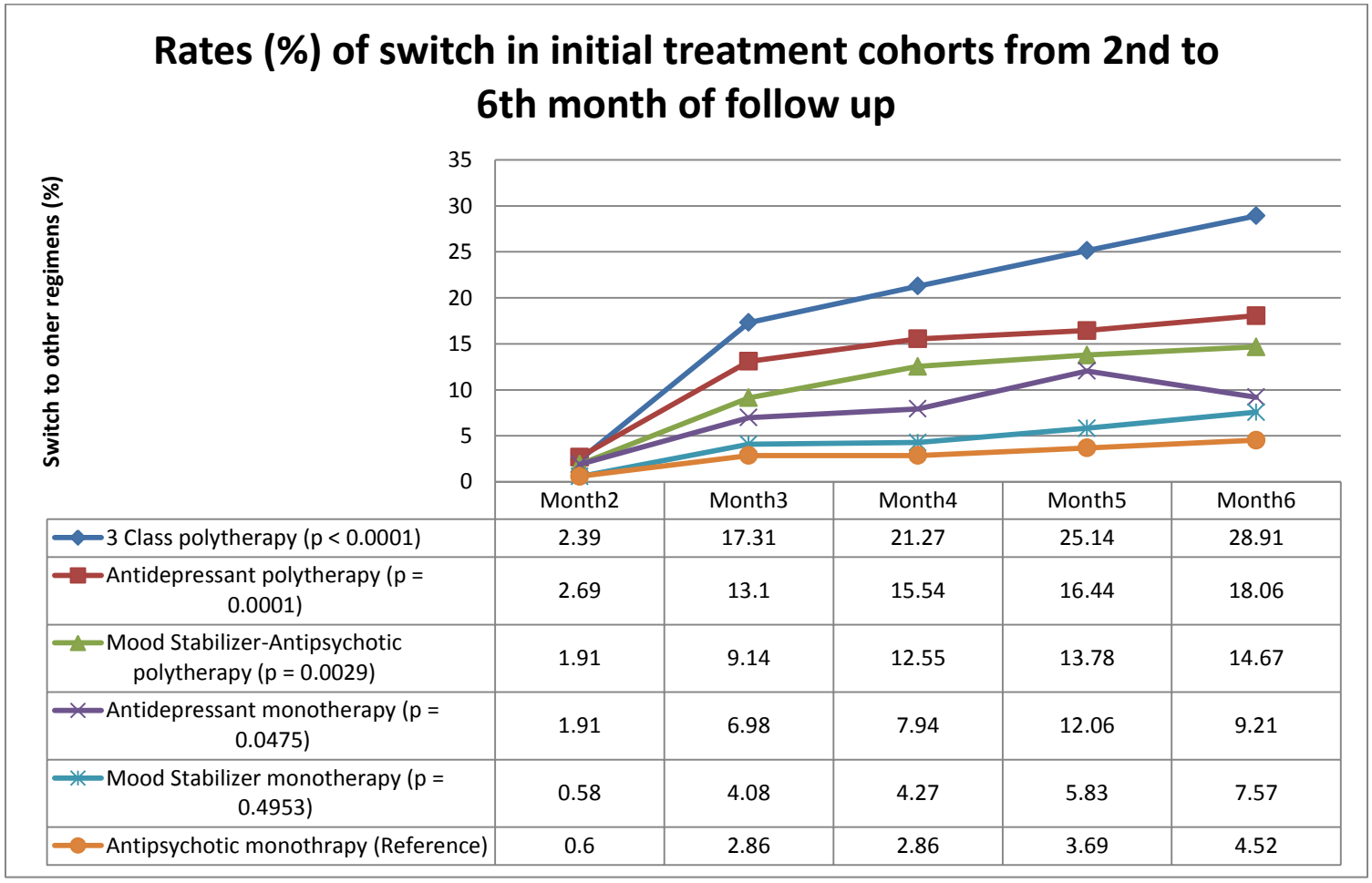
	Month 2	Month 3	Month 4	Month 5	Month 6
3-Class polytherapy (p < 0.0001)	96.59	75.41	68.23	62.15	56.91
Mood Stabilizer-Antipsychotic polytherapy (p < 0.0001)	90.11	73.19	65.69	61.94	58.39
Antidepressant polytherapy (p = 0.0554)	84.38	61.43	54.76	50.53	45.89
Antipsychotic monotherapy (reference)	73.21	54.52	47.98	45.12	41.55
Mood Stabilizer monotherapy (p = 0.0132)	69.51	46.02	38.83	31.84	30.1
Antidepressant monotherapy (p = 0.0032)	62.86	43.81	39.37	32.06	27.94

Figure 1(b). Augmentation Rates (%) from 2nd to 6th Month of Follow up Period among Bipolar Depression Patients



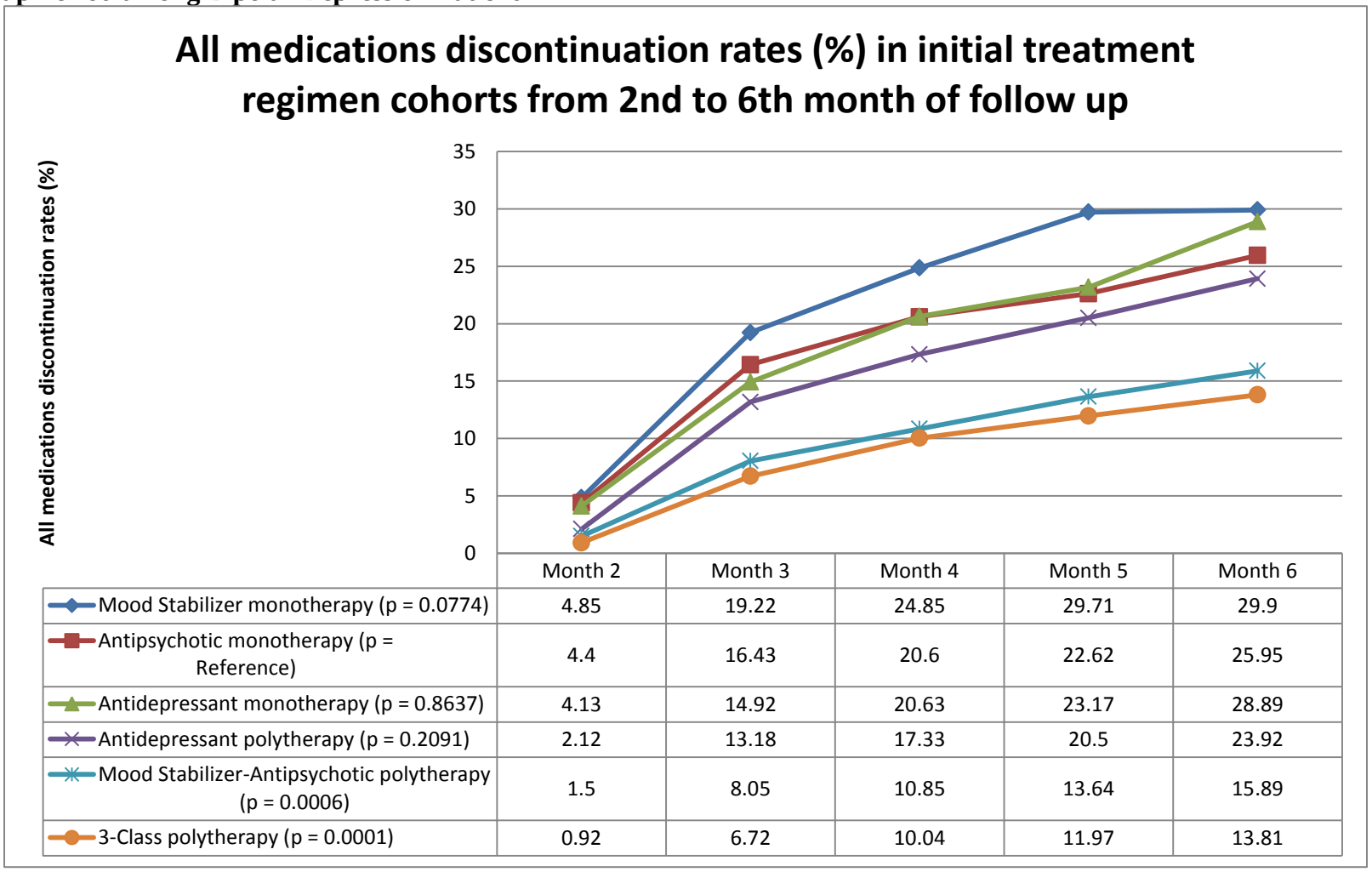
	Month 2	Month 3	Month 4	Month 5	Month 6
Antidepressant monotherapy (p = 0.0954)	22.22	25.4	24.44	24.76	24.44
Mood Stabilizer monotherapy (p = 0.0058)	20.19	25.83	25.82	27.96	27.58
Antipsychotic monotherapy (reference)	18.69	22.26	24.05	23.93	24.41
Antidepressant polytherapy (p < 0.0001)	9.52	11.55	11.64	11.8	11.8
Mood Stabilizer-Antipsychotic polytherapy (p < 0.0001)	5.8	9.21	10.57	10.23	10.71

Figure 1(c). Rate (%) of Regimen Switch in Each of the Treatment Regimens from 2nd to 6th Month of Follow up Period among Bipolar Depression Patients



	Month2	Month3	Month4	Month5	Month6
3 Class polytherapy (p < 0.0001)	2.39	17.31	21.27	25.14	28.91
Antidepressant polytherapy (p = 0.0001)	2.69	13.1	15.54	16.44	18.06
Mood Stabilizer-Antipsychotic polytherapy (p = 0.0029)	1.91	9.14	12.55	13.78	14.67
Antidepressant monotherapy (p = 0.0475)	1.91	6.98	7.94	12.06	9.21
Mood Stabilizer monotherapy (p = 0.4953)	0.58	4.08	4.27	5.83	7.57
Antipsychotic monothrapy (Reference)	0.6	2.86	2.86	3.69	4.52

Figure 1(d). All Medications Discontinuation Rates (%) in Each of the Treatment Regimens from 2nd to 6th Month of Follow up Period among Bipolar Depression Patient



	Month 2	Month 3	Month 4	Month 5	Month 6
Mood Stabilizer monotherapy (p = 0.0774)	4.85	19.22	24.85	29.71	29.9
Antipsychotic monotherapy (p = Reference)	4.4	16.43	20.6	22.62	25.95
Antidepressant monotherapy (p = 0.8637)	4.13	14.92	20.63	23.17	28.89
Antidepressant polytherapy (p = 0.2091)	2.12	13.18	17.33	20.5	23.92
Mood Stabilizer-Antipsychotic polytherapy (p = 0.0006)	1.5	8.05	10.85	13.64	15.89
3-Class polytherapy (p = 0.0001)	0.92	6.72	10.04	11.97	13.81

Table 1. Drug Utilization Pattern Two Months before Index Diagnosis among Bipolar Depression Patients

Pharmacotherapy type	Pharmacotherapy					
	1st Month	N	2nd Month Prior to Diagnosis	N (%)	1st Month Prior to Diagnosis	N (%)
Monotherapy	Antidepressant	315	Antidepressant	79 (25.08)	Antidepressant	103 (32.70)
	Antipsychotic	840	Antipsychotic	304 (36.19)	Antipsychotic	369 (43.93)
	Mood Stabilizer	515	Mood Stabilizer	164 (31.84)	Mood Stabilizer	189 (36.70)
Polytherapy	Antidepressant	1229	Antidepressant	466 (37.92)	Antidepressant	650 (52.89)
	Mood Stabilizer-Antipsychotic	1446	Mood Stabilizer-Antipsychotic	632 (43.11)	Mood Stabilizer-Antipsychotic	866 (59.07)
	Antipsychotic-Mood Stabilizer-Antidepressant	1086	Antipsychotic-Mood Stabilizer-Antidepressant	457 (42.08)	Antipsychotic-Mood Stabilizer-Antidepressant	641 (59.02)

MANUSCRIPT 2

Risk of manic switch with antidepressant therapy in a pediatric bipolar depression

Key Words: Bipolar Depression, Antidepressant, Mood Stabilizer, Atypical Antipsychotic,

Conflict of Interest: There is no conflict of interest associated with this study. This study was unfunded.

NUMBER OF WORDS IN ABSTRACT: 278

NUMBER OF WORDS IN MAIN TEXT: 4360

Abstract

Objective: To assess the risk of manic switch associated with antidepressants in Medicaid-enrolled pediatric bipolar depression patients.

Methods: In this retrospective cohort study, 2003-2007 MAX data from four geographically diverse states were used. Bipolar depression patients (6-18 years old) receiving antidepressant, second-generation antipsychotic (SGA), or mood stabilizer monotherapy or polytherapy during the 30 days before or after initial diagnosis and continuously enrolled in Medicaid throughout the study period were identified. Manic switch was defined using ICD9-CM codes 296.0, 296.1, 296.4, 296.81 observed in the diagnosis files during 6 weeks of follow up. Risk of manic switch was assessed using a Cox proportional hazard model and instrumental variable analysis.

Results: After applying all the selection criteria, 179 antidepressant monotherapy, 1047 SGA monotherapy, 570 mood stabilizer monotherapy, 445 antidepressant polytherapy, and 1906 SGA-mood stabilizer polytherapy users were identified in the analytic cohort. Instrumental variable analysis did not indicate endogeneity of the treatment variables. The Cox proportional hazard model identified history of bipolar subtype 1 as the most significant predictor of manic switch in all models. Antidepressant monotherapy exhibited significantly higher risk of manic switch [HR = 2.63 (95% CI: 1.02-6.83)] compared to SGA monotherapy, and insignificant association with manic switch [HR = 1.26 (95% CI: 0.48-3.30)] compared to mood stabilizer monotherapy. Antidepressant polytherapy exhibited insignificant risk of manic switch [HR = 1.52 (95% CI: 0.85-2.72)] versus SGA-mood stabilizer polytherapy.

Conclusions: Study findings indicate a possible higher risk of manic switch with antidepressant monotherapy versus SGA monotherapy in the pediatric population. Overall, the study findings support the clinical practice of cautious prescribing of antidepressants for brief periods. An

antidepressant combined with a mood stabilizer or SGA appears to be a safe regimen in this patient population. Special monitoring is suggested for those with history of bipolar I disorder.

Introduction

Bipolar disorder (BD) is a form of mood disorder characterized by the presence of episodes of highly elevated mood (manic) and episodes of depressive phases. Worldwide prevalence of bipolar disorder was 5%[1], and in the USA the prevalence was 2.6% in adults and 0-3% in adolescents[2]. The lifetime prevalence of depressive phase among bipolar disorder patients is 3-fold higher than mania phase[3], especially in youth. Untreated bipolar depression, among all the phases of bipolar disorder, particularly in children and adolescents, is associated with the highest risk of suicidality[4], substance abuse, functional disability, and poor academic and social performance[5-11].

Despite the higher prevalence of bipolar depression and associated risk of morbidity and mortality, research in treatment of the bipolar depressive phase is limited[12]. The Child and Adolescent Bipolar Foundation (CABF) expert panel advised use of mood stabilizers (such as anticonvulsants like lamotrigine, valproate, etc.), second-generation antipsychotics (SGA) (such as olanzapine), and adjunct therapy with antidepressants such as selective serotonin reuptake inhibitors (SSRI) and bupropion together with mood stabilizers, in treating pediatric bipolar depression[12,13]. However, uncertainty prevails over using antidepressants as a safe and effective medication class because of a possible increase in manic or hypomanic switch, rapid cycling, and long-term mood destabilization with the use of antidepressants while treating bipolar depressive phase[14-18]. Use of antidepressants has been suggested to induce short-term manic switch and long-term risk of mood destabilization[19]. Although potential risk of mood destabilization with antidepressants has been suggested historically, critical evaluation of the clinical trials suggested presence of bias and lack of control groups to accurately address this issue[20]. Systematic review

and meta-analysis of 12 randomized clinical trials published by Gijsman, et al[21], suggested antidepressants are safe and efficacious in acute care of bipolar depression.

The lack of prospective trials in the pediatric bipolar depression population hinders standardizing treatment guidelines, and psychiatric practice in this population is largely extrapolated from that of the adult population and physicians' experience and expertise. Subsequently, quantitative data on the safety of antidepressants and other medications (mood stabilizers and antipsychotics) in real-world pediatric bipolar depression is limited. This study aimed to examine the risk of manic switch with the use of antidepressant in Medicaid-enrolled children and adolescents with bipolar depression. Given the recommended use of mood stabilizers and SGAs in treatment of bipolar disorder manic or hypomanic phase, it was hypothesized that use of these two medication classes does not significantly increase the risk of manic switch while treating bipolar depression. This specific objectives of this study were to evaluate comparative risk of manic switch with (1) antidepressant monotherapy vs. SGA monotherapy, (2) antidepressant monotherapy vs. mood stabilizer monotherapy, and (3) antidepressant polytherapy (with SGA or mood stabilizer) vs. SGA-mood stabilizer polytherapy.

Methods

Data Source

In this retrospective cohort study, 2003-2007 Medicaid Analytic eXtract (MAX) files from the Centers for Medicare and Medicaid Services (CMS) were used. MAX is a set of person-level claims data files containing information on Medicaid eligibility, demographics, service utilization, and payments. Because it is difficult to analyze data from all 50 states, we used data

from four geographically diversified states with large Medicaid enrollments of children and adolescents (CA, TX, IL, and NY).

Pharmacotherapy for Bipolar Depression

The pharmacotherapy of bipolar depression includes mood stabilizers (lithium, sodium divalproex/valproate, carbamazepine, oxcarbazepine, topiramate, lamotrigine, and gabapentin); SGA (risperidone, aripiprazole, olanzapine, quetiapine, clozapine and ziprasidone), newer antidepressants (selective serotonin reuptake inhibitor (SSRI) antidepressants and others) (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine, and bupropion) and other antidepressants (amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline, mirtazapine, nefazodone, trazodone).

Study Population

Children and adolescents with bipolar depression were identified based on the following algorithm: (1) patients aged between 6 to 18 years (children and adolescents), (2) who received a minimum of 2 diagnoses of bipolar disorder other than bipolar depression (*International Classification of Diseases, 9th version, Clinical Modification* [ICD-9-CM]: 296.0, 296.1, 296.4-296.8, 301.11, 301.13) on different service dates, or only 1 diagnosis of bipolar disorder but that came from hospital discharge, followed by a diagnosis of bipolar or unipolar depression (ICD-9CM: 296.5, 296.2, 296.3)[22] anytime between January 2003 and December 2007, and (3) who received antidepressants, SGA, or mood stabilizers within 30 days of the depression diagnosis. The index date was defined as the date on which the first medication was filled during this period.

Exclusion Criteria

(1) Patients who received diagnoses of schizophrenia (ICD-9CM: 295.0-295.9) or epilepsy (ICD-9CM: 345.xx) were excluded from the cohort to ensure that the prescriptions were used for bipolar disorder.

(2) Patients without continuous Medicaid eligibility from 2 months before the index date until the end of the 3-month follow up period were also excluded.

(3) Patients who received antidepressant prescriptions during 60 days period prior to the index date were excluded to identify new users of antidepressants.

The remaining bipolar depression patients were divided into 5 mutually exclusive groups based on their medication use during 30 days around the index bipolar depression: (1) antidepressant monotherapy, (2) SGA monotherapy, (3) mood stabilizer monotherapy, (4) antidepressant-SGA or antidepressant-mood stabilizer polytherapy, and (5) SGA-mood stabilizer polytherapy. Monotherapy was defined as receiving medications from a single therapeutic class only, while polytherapy was defined as receiving medications from different therapeutic classes with a minimum of 1 day overlap between prescriptions from two or three different therapeutic classes, during the cohort selection period of 30 days around index bipolar depression.

Manic switch

Manic switch events were identified from the combined inpatient and other therapy MAX files, using the ICD-9CM codes of mania (296.0, 296.1, 296.4, 296.81) during the 6-week follow up[23] period after the index date. The follow up window was restricted to 6 weeks only to differentiate the manic event as treatment-emergent rather than a natural progression of the bipolar disorder itself. According to the nomenclature of the course and outcome of bipolar disorder defined by

the International Society for Bipolar Disorders (ISBD) task force[24], manic events during <= 8 weeks after treatment is a 'definite' measure of manic switch, while during <=12 weeks window is 'likely' or 'possible'. Sensitivity analyses were conducted with 8 weeks and 12 weeks follow up after index date to confirm the robustness of the primary estimate of the risk of manic switch.

Covariates

Covariates including information on demographics, comedications, and comorbidities were measured at 2 months baseline, prior to the index date. Comorbidities included substance abuse disorder (SUD), attention deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), anxiety, adjustment disorder, psychotic disorder, and history of diagnoses of bipolar subtypes at baseline. Comedications included stimulant, sedative, hypnotic, anticholinergic, and use of SGA and mood stabilizer at baseline. Psychotherapy use and all-cause hospitalization at baseline were identified as measures of disease severity. Among demographic characteristics of the selected patients, age (categorized as children if < 13 years age and adolescent if >= 13 years of age), sex, race (white, black, or other), state of residence (TX, NY, CA, or IL) were measured. Although all the patients were Medicaid enrolled, eligibility of patients in Temporary Assistance for Needy Families (TANF), and foster care setting were also identified, as these variables may indicate socioeconomic characteristics of the patients. Duration of disease computed as difference between index bipolar disorder and index bipolar depression was measured, as longer duration of disease may influence the future symptomatic outcomes such as mood destabilization. Finally, number of physicians available in each zip code was measured to adjust for psychiatric care availability for patients.

Statistical Methodologies

Descriptive analysis was conducted to describe the demographics, treatment utilization, comedications, and comorbidities during the 2-month baseline period for the selected monotherapy and polytherapy users, separately. Chi-square tests and t-tests were conducted on covariates to examine the univariate differences across the monotherapy and the polytherapy cohorts for categorical variables and continuous variables, respectively. Standardized differences of the covariates, i.e. difference in means between the treatment groups divided by the standard error of the difference, were also computed.

Multivariable Cox Proportional Hazard Regression

Kaplan-Meier plot, log-minus-log survival plot, and Schoenfeld residual test were performed to test proportionality of hazard assumption. Also, log-rank test was performed with the time to manic switch outcome variables and the treatment groups to assess univariate association between the treatment and the outcome. Time to manic switch was analyzed using multivariable Cox proportional hazard regression method to assess the differential risk with antidepressant monotherapy compared to mood stabilizer or SGA monotherapy and antidepressant polytherapy compared to SGA-mood stabilizer polytherapy. All the covariates used in the descriptive analysis were incorporated in the regression models to adjust for those observed factors. Patients were censored in the model upon (1) discontinuation of the index treatment regimen, (2) augmentation with a newer medication other than the index regimen, and (3) end of follow up.

Instrumental Variable (IV) Approach

Instrumental variable analysis can address limitation of the traditional multivariable regression and propensity score analysis, as it ideally adjusts for both observed and unobserved covariate imbalances between the treatment groups and aims to explain variation in treatment

selection.[25]Important characteristics of instruments are (1) the instrument variable is significantly correlated with the treatment variable and explains a significant amount of variation in treatment, (2) the instrument theoretically does not cause the outcome except through the treatment variable, and (3) the instrument is not correlated with the observed and unobserved covariates associated with the outcome. In this study, IV analysis was performed to check the robustness of the estimates obtained from conventional Cox proportional hazard analysis. In this study, "misdiagnosis of index bipolar depression as unipolar depression (ICD9CM code: 296.2, 296.3)", "physicians' preference for prescribing antidepressant", and "year of cohort entry" were identified as instruments. Confirmed bipolar disorder patients experiencing a depressive episode and given a major depressive disorder (unipolar depression) diagnosis instead of a bipolar depression diagnosis (ICD9CM: 296.5) was suggested to be a misdiagnosis.[26] Also, major depressive disorder (MDD) diagnosis generally leads to higher prescribing of antidepressants rather than mood stabilizers or SGAs. Thus, MDD diagnosis as the index bipolar depression theoretically can influence the antidepressant monotherapy or polytherapy treatment utilization. On the other hand, as all the patients had confirmed bipolar disorder diagnosis and subsequent depressive symptoms, theoretically MDD misdiagnosis may not differentially influence the manic switch risk. Physicians' preference for antidepressant prescribing was identified if physicians prescribed an antidepressant during the first ever pediatric bipolar depression patient visit recorded. For all the subsequent patients who were treated with an antidepressant by those physicians, the value of the "physician preference" instrument was given as 1, while for patients who visited physicians who did not treat their first patient with antidepressant the value of the instrument was given as 0. The theoretical explanation of using this variable as an instrument is that physicians with a prior history of treating bipolar depression with antidepressants over mood

stabilizer or SGA may predict future use of antidepressants by those physicians while treating subsequent patients. First ever patients who visited the physicians were excluded from the analysis. The year the patients entered into the cohort, computed from their index date, was identified as the third instrument as it may explain yearly changes in Medicaid policy and formularies, which may predict treatment variation. The "physician prescribing preference" and "year of cohort entry" variables have been established as valid instruments for explaining psychotropic treatment variation in literature.[27,28,29]

As the treatment variables were binary (monotherapy or polytherapy) and the analytical model was nonlinear (hazard model), a two-stage residual inclusion (2SRI) approach[30] was applied.

Assumption Test

Strength of association between the instruments and the binary treatment variables were assessed by computing partial F-test and partial R-square[25,29]. Change in observed covariates imbalance was determined by comparing the covariate distribution across the treatment groups and the instruments. Fractional change in distribution[29] of each covariate between the treatment groups and the instruments was computed.

1st Stage Regression

Binary continuous treatment variables were regressed with all the covariates and the instruments in the 1st stage of the 2-SRI model, using a linear probability model.[31] Residuals (r) for each patient was computed as difference between the binary treatment variable and the predicted treatment variable from the linear probability model.

2nd Stage Cox Proportional Hazard Model

Time to manic switch associated with the treatment variables was assessed using a conventional Cox proportional hazard regression model adjusting for all the previously measured covariates, and r computed from the 1st stage. Association between the outcome and the treatment variable and all other covariates were reported as hazard ratio (HR) with 95% confidence interval. Statistical insignificance of r in the 2nd stage regression suggests exogeneity of the treatment variable and irrelevance of using the selected instruments.

SAS 9.2 was used for the entire analyses, and $p<0.05$ was considered to be statistically significant.

Results

The number of patients ages 6-18 years with mental disorders and receiving psychotropic medications was identified as 4216094 from 2003-2007 MAX files. Excluding those with schizophrenia or epilepsy (8731), 14009 patients were identified with bipolar depression diagnosis according to the diagnosis algorithm. Among those patients, 8397 patients were found to receive an antidepressant, mood stabilizer, or SGA, and initiated pharmacotherapy for bipolar depression during the 30 days before or after index bipolar depression, between March 2003 and September 2007. Among the pharmacotherapy recipients, 3271 patients were on monotherapy while 5126 patients received polytherapy. After applying the continuous Medicaid eligibility and 60 days wash-out period for baseline antidepressant prescriptions criteria, 5757 patients were left in the analytical cohort. After excluding the patients utilized to compute the "physicians' preference of antidepressant" instrument, 4326 patients were left in the final analytical cohort. Among 1975 monotherapy recipients in the final cohort, 179 patients were on antidepressant

monotherapy, 1047 were on SGA monotherapy, and 570 were on mood stabilizer monotherapy. Among 2351 polytherapy recipients in the final cohort, 445 were on antidepressant polytherapy, while the rest of the 1906 patients received SGA-mood stabilizer polytherapy (Figure 1).

Descriptive statistics

Among the comorbidities, attention-deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), anxiety, and adjustment disorder were found to be common among both the monotherapy and polytherapy cohorts. The most commonly seen comedications were stimulants and sedatives. Over 50% of the monotherapy and polytherapy users received psychotherapy and 16-30% percent had a history of all-cause hospitalization at baseline.

Almost 20-30% of monotherapy and polytherapy users were found to be in a foster care setting at baseline. Patients in the antidepressant monotherapy and polytherapy cohorts were found to most likely be adolescents (>=13 years), white, and residing in Texas. The SGA and mood stabilizer monotherapy and polytherapy users were observed to be most likely adolescents, white, and male. Descriptive statistics are reported in Table 1 and Table 2.

Risk Analysis

Multivariable Cox Proportional Regression Analysis

In the traditional survival analysis model, bipolar subtype I was the most significant predictor of manic switch within 6 weeks of follow up with a HR of 2.23 (95% CI: 1.30-3.85) in the antidepressant monotherapy compared to SGA monotherapy cohort and 2.39 (95% CI: 1.26-4.52) in the antidepressant monotherapy compared to mood stabilizer monotherapy cohort. Antidepressant monotherapy was found to significantly increase the risk of manic switch versus SGA monotherapy [HR = 2.63 (95% CI: 1.02-6.83)]. Increased risk of manic switch was not

associated with antidepressant monotherapy when compared to mood stabilizer monotherapy [HR = 1.26 (95% CI: 0.48-3.30)]. In the antidepressant polytherapy compared to SGA-mood stabilizer polytherapy analytical model with 6 weeks follow up, history of SGA use at baseline [HR = 1.40 (95% CI: 1.01-1.94)], and bipolar subtype I [HR = 2.95 (95% CI: 2.12-4.12)] were found to significantly increase the risk of manic switch. Antidepressant polytherapy did not raise the risk significantly compared to SGA-mood stabilizer polytherapy [HR = 1.52 (95% CI: 0.85-2.72)].

Instrumental Variable Analysis

Robustness of the treatment comparison estimates was examined by conducting instrumental variable analysis, using the same comparison as presented in table 3. The Partial F-statistic and partial R-square for the comparison between antidepressant and SGA monotherapy, antidepressant and mood stabilizer monotherapy, and antidepressant and SGA-mood stabilizer polytherapy ranged from 149-285 and 0.27-0.40, respectively. The results indicated strong association between the instruments and all the treatment comparison groups. Addition of instruments in the analysis seemed to reduce covariate imbalance as observed in the fractional change in standardized differences for most of the covariates (results not reported). The only variable that was observed to be significantly predicting manic switch during 6 weeks follow up in the monotherapy cohorts was the bipolar subtype I variable, with HR 2.32 (95% CI: 1.22-4.41) with antidepressant monotherapy compared to SGA monotherapy group, and HR 2.50 (95% CI: 1.18-5.28) with antidepressant monotherapy compared to mood stabilizer monotherapy group. The residual (r) from the 1^{st} stage regression were not statistically significant in the 2^{nd} stage regression, indicating exogeneity of the monotherapy treatments. Similar result from the IV analysis was also observed from the polytherapy cohort. Bipolar subtype I strongly predicted the

risk of manic switch during the 6 weeks follow up [HR = 3.01 (95% CI: 2.12-4.27)]. Residual (r) was statistically insignificantly associated with the outcome [HR = 1.18 (95% CI: 0.49-2.84)]. Results obtained from traditional Cox proportional hazard regression analyses and instrumental variable analyses are reported in tables 4-6.

Sensitivity Analysis

To assess the robustness of the findings from the primary analysis, additional sub-analyses were conducted with 2 months and 3 months follow up after the index date. In the antidepressant monotherapy against SGA monotherapy analytical model with 2 months follow up, antidepressant monotherapy [HR = 2.60 (95% CI: 1.06-6.36)], oppositional defiant disorder [HR = 1.64 (95% CI: 1.05-2.55)], and bipolar subtype I [HR = 2.39 (95% CI: 1.41-4.04)] were found to significantly increase the manic switch risk. During 3 months follow up, antidepressant monotherapy did not exhibit significant association with manic switch risk compared to SGA monotherapy [HR = 2.16 (95% CI: 0.96-4.84)]; but oppositional defiant disorder [HR = 1.62 (95% CI: 1.06-2.47)] and bipolar subtype I [HR = 2.56 (95% CI: 1.55-4.23)] continued to exhibit higher manic switch risk.

In the antidepressant monotherapy against mood stabilizer monotherapy sensitivity analysis with 2 months follow up, history of mood stabilizer use at baseline [HR = 1.94 (95% CI: 1.06-3.56)] and bipolar subtype I [HR = 2.72 (95% CI: 1.47-5.05)] exhibited higher manic switch risk, while use of antidepressant monotherapy was observed to be safe [HR = 1.61 (95% CI: 0.65-3.96)]. In the same analytical model with 3 months follow up, only bipolar subtype I exhibited higher manic switch risk [HR = 2.67 (95% CI: 1.44-4.94)].

In the antidepressant polytherapy against SGA-mood stabilizer polytherapy analytical model with 2 and 3 months follow up, bipolar subtype I continued to exhibit higher risk of manic switch [HR = 3.11 (95% CI: 2.25-4.30)] and [HR = 2.86 (95% CI: 2.10-3.89)], respectively. Antidepressant polytherapy was not found to significantly increase manic switch risk against SGA-mood stabilizer polytherapy during 2 months follow up [HR = 1.64 (95% CI: 0.93-2.88)] and 3 months follow up [HR = 1.09 (95% CI: 0.66-1.80)].

Discussion

Most bipolar depression patients received polytherapy as the treatment regimen, while antipsychotic monotherapy was the most commonly used monotherapy regimen. Most prevalent comorbidities and comedications seen among bipolar depression patients in previous literature[13] and clinical practice were also observed in this Medicaid enrolled pediatric bipolar depression cohort. The duration between receiving the first bipolar disorder diagnosis and index bipolar depression diagnosis varied among the patients, an average of 300 days for any of the 5 cohorts. This variable was included in the risk analysis models since patients with a prolonged history of bipolar disorder before receiving a depression diagnosis can be different from those promptly switching to depression after initially being diagnosed with other bipolar disorder.

"Misdiagnosis with MDD", "physicians' preference of antidepressant", and "year of cohort entry" exhibited strong prediction of antidepressant monotherapy or polytherapy in the 1st stage linear probability models of the instrumental variable analyses, providing evidence of reasonable selection of the instruments. They also exhibited strong association with the treatment variables with partial F-statistics more than 10 in all models, considerably high partial R-square values, and also reduced covariate imbalance. In the 2nd stage of the instrumental variable

analyses, statistical insignificance of the residual r indicated exogeneity of the treatment variables in all the models. In absence of endogeneity in treatment as highlighted by the instrumental variable approach taken in this study, risk of manic switch analysis adjusting only the observed factors should be emphasized.

After adjusting for all the covariates, antidepressant monotherapy and polytherapy did not demonstrate increased risk of manic switch in most of the models, except antidepressant monotherapy v/s SGA monotherapy cohort with 6 weeks and 2 months follow up period, where antidepressant monotherapy was found to be significantly increasing the manic switch risk in pediatric bipolar depression patient population. This data reflecting insignificant risk of antidepressant monotherapy and polytherapy in most of the models is in accordance with the most of the recent clinical trials in the general population[32] as well as systematic reviews and meta-analysis of randomized clinical trials[21,33]. All those randomized trials examined treatment emergent affective switch (TEAS) using symptomatic manic outcomes between antidepressant and placebo, or antidepressant and other medication, and most of the studies reported an insignificant association between antidepressant use and risk of TEAS. In our study, we defined a manic event during the follow up as a switch or mood destabilization event, and the results suggested that in the pediatric population the use of antidepressant does not bring a higher risk of mood elevation compared to the gold standard treatment regimens with mood stabilizer monotherapy or SGA-mood stabilizer polytherapy. However, antidepressant monotherapy users were observed to be at significantly higher risk of experiencing short-term manic switch (6 weeks and 2 months after initiation of bipolar depression treatment) compared to SGA monotherapy recipients. Based on the study findings, a higher likelihood of short-term manic switch resulting from antidepressant monotherapy cannot be ruled out. All these results provide

more support to the clinical guidelines and current psychiatric practice of not prescribing antidepressant monotherapy, and of combining an antidepressant with a first-line SGA or mood stabilizer.

The strongest prediction of manic switch by history of bipolar subtype I diagnosis accords with clinical rationale and previously published literature[34]. Bipolar subtype I, rather than subtype II patients are more prone to TEAS, as has been reported in systematic reviews on RCTs[35]. In accordance with the North American clinical practice guidelines, our study findings also suggest cautious prescribing of antidepressants for a brief period in treating acute depressive phase among patients with bipolar I disorder[34,36,37]. It was not possible to conduct sensitivity analysis on risk of manic switch with antidepressant only among those with bipolar subtype I at baseline because of a small sample size [61 (34.08%) in antidepressant monotherapy users, 307 (29.32%) in SGA monotherapy users, 151 (26.49%) in mood stabilizer monotherapy users, 131 (29.44%) in antidepressant polytherapy users, and 569 (29.85%) in SGA-mood stabilizer polytherapy users].

Use of SGA and mood stabilizer at baseline also predicted future mania in some of the models. This can be due to the fact that those who received these medications during the 2-month baseline period before the index date were experiencing either a manic episode or were on maintenance therapy after remission of a manic episode in the recent time before index bipolar depression. Presence of recent manic history can strongly predict the subsequent manic switch and mood destabilization.

Our study suffers from certain limitations. Use of claims data in this retrospective cohort study limited the identification of bipolar disorder and bipolar depression patients; without structured clinical evaluation using depression and manic rating scales, accurate classification of

the patients and inclusion in the study cohort cannot be confirmed. Because of the complicated treatment regimen pattern of bipolar disorder in general, it was difficult to identify the exact initiation of the bipolar depression treatment. The prescribed medications before or after index bipolar depression, especially mood stabilizers and SGAs, could be for treatment of acute depressive phase or could be a maintenance therapy of previous manic events. However, there is no theoretical reason to believe that any of this treatment selection-related and claims data-related limitations should differentially affect one treatment arm over another because of the comparative effectiveness study design. Also, the patient population was selected based on a minimum of 2 diagnoses of bipolar disorder and 1 diagnosis of bipolar depression; the multiple diagnoses criterion was used to confirm the bipolar nature of the disorder among the selected patients and to negate possibility of disease misclassification for using claims data in the absence of clinical evaluation to some extent. Another limitation of this study was the identification of the outcome. Randomized trials can accurately measure treatment-emergent mania by using manic rating scales. Treatment-emergent affective switch is not included in DSM-IV criteria of manic disorder and thus no specific ICD-9CM codes are available to differentiate switch from depression to mania because of the clinical features of the disease as opposed to the treatment. Our study could not assess TEAS but aimed to quantify risk of manic switch and mood destabilization with antidepressants. Also, the study findings will be generalizable only to the pediatric population enrolled in Medicaid. Despite all the limitations, this is the first study aimed to quantify safety of antidepressants in a real-world pediatric bipolar depression patient population, and this study also aimed to define acute bipolar depression phase, its treatment, and mood destabilization using diagnostic and pharmacy claims. Availability of detailed prescription fill information and outpatient and inpatient visit in the Medicaid claims data provided the

opportunity to conduct detailed longitudinal assessment of complex medication utilization patterns and manic switch outcomes in the patient population. Numerous claims data obtained from four states (CA, NY, TX, and IL) and for five years (2003-2007) provided a large sample size and sufficient statistical power to evaluate manic switch risk differences across multiple cohorts of medication regimen recipients. Self-report (recall bias) and differential self-selection in RCTs were not an issue because of using retrospective secondary data in this study. Finally, assessment of manic switch risk in a real-world pediatric population, who are generally excluded from clinical trials, was possible because of using claims data.

In conclusion, antidepressant monotherapy was associated an with increase in the risk of short-term manic switch compared to SGA monotherapy. Antidepressant monotherapy and polytherapy were observed to be safe regimens compared to mood stabilizer monotherapy or SGA-mood stabilizer polytherapy respectively. Thus, prescribing antidepressant monotherapy remains a controversial issue, especially among those with history of bipolar I disorder. The study findings support the current practice of combining antidepressant with mood stabilizers or SGA.

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Figure 1. Cohort Design

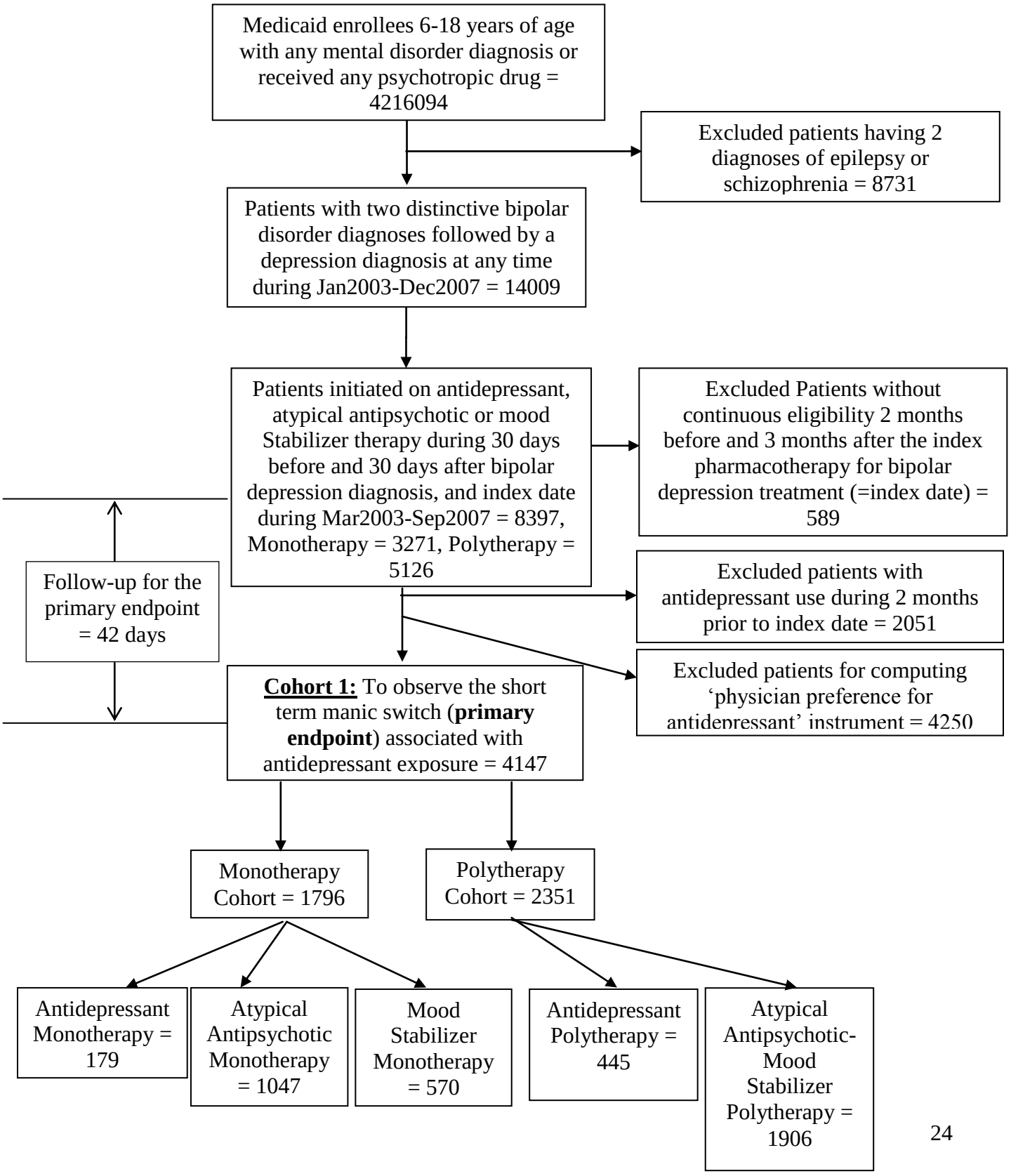

Figure 2. Study Time Frame Design

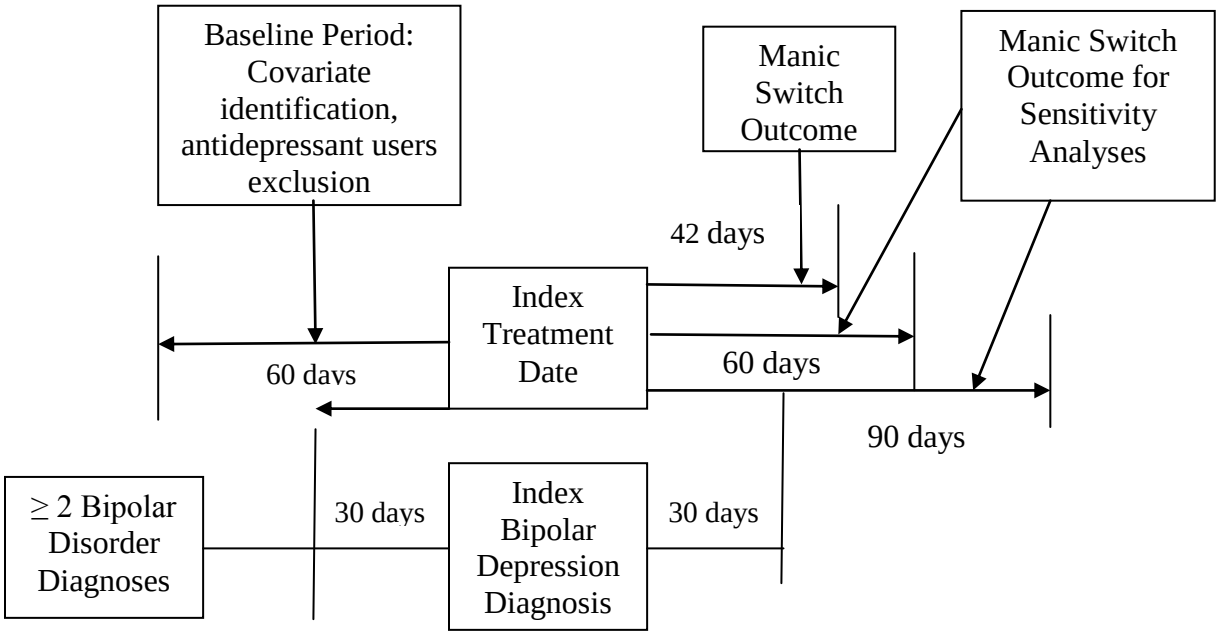

Table 1. Descriptive Results of the Monotherapy Cohort (N = 1796)

Covariates	Antidepressant Monotherapy (n=179) N (%) or Mean (±SD)	SGA Monotherapy (n=1047) N (%) or Mean (±SD)	Mood Stabilizer Monotherapy (n = 570) N (%) or Mean (±SD)
Duration of Disease	328 (±364)	334 (±372)	295 (±338)
Number of Physicians in Zip Codes	23 (±23)	31 (±29)	29 (±28)
Stimulant	29 (16.20)	209 (19.96)	105 (18.42)
Sedative	48 (26.82)	177 (16.91)	102 (17.89)
Hypnotic	4 (2.23)	50 (4.78)	16 (2.81)
Anticholinergic	4 (2.23)	71 (6.78)	22 (3.86)
Psychotherapy	102 (56.98)	543 (51.86)	309 (54.21)
Substance Abuse Disorder	15 (8.38)	73 (6.97)	44 (7.72)
ADHD	35 (19.55)	339 (32.38)	150 (26.32)
Suicidality	9 (5.03)	22 (2.10)	9 (1.58)
Oppositional Defiant Disorder	27 (15.08)	262 (25.02)	123 (21.58)
Anxiety	26 (14.53)	95 (9.07)	61 (10.70)
Adjustment Disorder	16 (8.94)	123 (11.75)	65 (11.40)
Psychotic Disorder	5 (2.79)	81 (7.74)	23 (4.04)
Bipolar			
SubType I	11 (6.15)	89 (8.50)	65 (11.40)
SubType II	13 (7.26)	55 (5.25)	26 (4.56)
SubType NOS	94 (52.51)	596 (56.92)	328 (57.54)
History of SGA	12 (6.70)	539 (51.48)	38 (6.67)
History of Mood Stabilizer	9 (5.03)	61 (5.83)	276 (48.42)
Prior Hospitalization	41 (22.91)	211 (20.15)	101 (17.72)
Foster Care	32 (17.88)	322 (30.75)	160 (28.07)
TANF	14 (7.82)	80 (7.64)	48 (8.42)
Age Category			
Children (6-13 years)	36 (20.45)	437 (42.55)	177 (31.83)
Adolescents (14-18 years)	140 (79.55)	590 (57.45)	379 (68.17)
Race			
White	89 (50.28)	461 (44.58)	260 (46.43)
Black	32 (18.08)	291 (28.14)	157 (28.04)
Sex: Male	71 (40.11)	650 (62.86)	321 (57.32)
State			
TX	76 (42.94)	320 (30.95)	164 (29.29)
CA	36 (20.34)	206 (19.92)	124 (22.14)
IL	51 (28.21)	340 (32.88)	201 (35.89)
NY	14 (7.91)	168 (16.25)	71 (12.68)
IV1: History of Major Depression	150 (83.80)	636 (60.74)	303 (53.16)
IV2: Physician Preference of	159 (88.83)	190 (18.15)	101 (17.72)

Antidepressant			
IV3: Year of Cohort Entry			
2003	9 (5.03)	78 (7.45)	93 (16.32)
2004	25 (13.97)	168 (16.05)	122 (21.40)
2005	37 (20.67)	210 (20.06)	113 (19.82)
2006	47 (26.26)	264 (25.21)	118 (20.70)
2007	61 (34.08)	327 (31.23)	124 (21.75)

Abbreviations: SGA: second-generation antipsychotic, ADHD: attention deficit hyperactivity disorder, Bipolar SubType NOS: not otherwise specified, TANF: temporary assistance for needy families, IV: instrumental variable; SD: standard deviation

Table 2. Descriptive Results of the Polytherapy Cohort (N = 2351)

Covariates	Antidepressant Polytherapy (n=445) N (%) or Mean (±SD)	SGA/Mood Stabilizer Polytherapy (n=1906) N (%) or Mean (±SD)
Duration of Disease	295 (±369)	392 (±377)
Number of Physicians in Zip Codes	26 (±24)	33 (±29)
Stimulant	61 (13.71)	442 (23.19)
Sedative	109 (24.49)	440 (23.08)
Hypnotic	20 (4.49)	93 (4.88)
Anticholinergic	27 (6.07)	175 (9.18)
Psychotherapy	286 (64.27)	1071 (56.19)
Substance Abuse Disorder	28 (6.29)	97 (5.09)
ADHD	128 (28.76)	602 (31.58)
Suicidality	10 (2.25)	31 (1.63)
Oppositional Defiant Disorder	87 (19.55)	487 (25.55)
Anxiety	65 (14.61)	145 (7.61)
Adjustment Disorder	58 (13.03)	238 (12.49)
Psychotic Disorder	32 (7.19)	149 (7.82)
Bipolar		
SubType I	30 (6.74)	254 (13.33)
SubType II	23 (5.17)	83 (4.35)
SubType NOS	261 (58.65)	1000 (52.47)
History of SGA	151 (33.93)	1375 (72.14)
History of Mood Stabilizer	67 (15.06)	1323 (69.41)
Prior Hospitalization	139 (31.24)	322 (16.89)
Foster Care	83 (18.65)	651 (34.16)
TANF	49 (11.01)	90 (4.72)
Age Category		
Children	156 (36.03)	808 (43.49)
Adolescents	277 (63.97)	1050 (56.51)
Race		
White	209 (47.83)	885 (47.33)
Black	86 (19.68)	487 (26.04)
Sex: Male	236 (54.00)	1268 (67.81)
State		
TX	228 (52.17)	747 (39.95)
CA	75 (17.16)	336 (17.97)
IL	112 (25.63)	485 (25.94)
NY	22 (5.03)	302 (16.15)
IV1: History of Major Depression	297 (66.74)	998 (52.36)
IV2: Physician Preference of Antidepressant	408 (91.69)	448 (23.50)
IV3: Year of Cohort Entry		
2003	26 (5.84)	271 (14.22)

2004	70 (15.73)	338 (17.73)
2005	117 (26.29)	452 (23.71)
2006	99 (22.25)	428 (22.46)
2007	133 (29.89)	417 (21.88)

Abbreviations: SGA: second-generation antipsychotic, ADHD: attention deficit hyperactivity disorder, Bipolar SubType NOS: not otherwise specified, TANF: temporary assistance for needy families, IV: instrumental variable

Table 3. Association Between Instruments and Treatment Cohorts

Treatment groups	Comparison groups	Partial F-statistics	Partial R-square
Antidepressant monotherapy	SGA monotherapy	149	0.28
Antidepressant monotherapy	mood stabilizer monotherapy	150	0.40
Antidepressant polytherapy	SGA-mood stabilizer polytherapy	285	0.27

Abbreviations: SGA: second-generation antipsychotic

Table 4. Cox Proportional Hazard Regression Analysis Results (Antidepressant Monotherapy V/S Second-Generation Antipsychotic (SGA) Monotherapy)

Variables	Hazard ratio (95% CI) from conventional Cox proportional hazard regression model	Hazard ratio (95% CI) from instrumental variable analysis
	Follow up: 42 days	
Antidepressant monotherapy (ref: SGA monotherapy)	2.63 (1.02-6.83)	2.34 (0.49-11.12)
Bipolar subtype I*	2.23 (1.30-3.85)	2.32 (1.22-4.41)
Bipolar subtype NOS*	0.46 (0.28-0.74)	0.45 (0.27-0.78)
	Follow up: 60 days	
Antidepressant monotherapy	2.60 (1.06-6.36)	2.37 (0.56-10.06)
Oppositional defiant disorder	1.64 (1.05-2.55)	1.63 (1.03-2.57)
Bipolar subtype I*	2.39 (1.41-4.04)	2.47 (1.34-4.56)
Bipolar subtype NOS*	0.52 (0.33-0.82)	0.52 (0.31-0.86)
	Follow up: 90 days	
Antidepressant monotherapy	2.16 (0.96-4.84)	1.51 (0.36-6.27)
Anticholinergic	0.26 (0.07-0.93)	0.18 (0.005-6.14)
Oppositional defiant disorder	1.62 (1.06-2.47)	1.58 (1.02-2.44)
Bipolar subtype I*	2.56 (1.55-4.23)	2.63 (1.48-4.69)
Bipolar subtype NOS*	0.55 (0.35-0.85)	0.54 (0.33-0.87)

*****Reference group: bipolar I single manic episode (ICD-9CM: 296.0), manic disorder recurrent episode (ICD-9CM: 296.1), chronic hypomanic personality disorder (ICD-9CM: 301.11), and cyclothymic disorder (ICD-9CM: 301.13)

Table 5. Cox Proportional Hazard Regression Analysis Results (Antidepressant Monotherapy V/S Mood Stabilizer Monotherapy)

Variables	Hazard ratio (95% CI) from conventional Cox proportional hazard regression model	Hazard ratio (95% CI) from instrumental variable analysis
	Follow up: 42 days	
Antidepressant monotherapy (ref: SGA monotherapy)	1.26 (0.48-3.30)	1.06 (0.27-4.18)
Bipolar subtype I*	2.39 (1.26-4.52)	2.50 (1.18-5.28)
Bipolar subtype NOS*	0.49 (0.27-0.87)	0.46 (0.24-0.88)
	Follow up: 60 days	
Antidepressant monotherapy	1.61 (0.65-3.96)	1.29 (0.33-4.98)
History of mood stabilizer	1.94 (1.06-3.56)	1.85 (0.83-4.11)
Bipolar subtype I*	2.72 (1.47-5.05)	2.85 (1.36-5.99)
Bipolar subtype NOS*	0.48 (0.27-0.86)	0.45 (0.24-0.86)
	Follow up: 90 days	
Antidepressant monotherapy	1.46 (0.64-3.29)	1.14 (0.32-4.09)
Bipolar subtype I*	2.67 (1.44-4.94)	2.77 (1.35-5.67)
Bipolar subtype NOS*	0.46 (0.26-0.82)	0.43 (0.23-0.83)

*****Reference group: bipolar I single manic episode (ICD-9CM: 296.0), manic disorder recurrent episode (ICD-9CM: 296.1), chronic hypomanic personality disorder (ICD-9CM: 301.11), and cyclothymic disorder (ICD-9CM: 301.13)

Table 6. Cox Proportional Hazard Regression Analysis Results (Antidepressant Polytherapy V/S SGA-Mood Stabilizer Polytherapy)

Variables	Hazard ratio (95% CI) from conventional Cox proportional hazard regression model	Hazard ratio (95% CI) from instrumental variable analysis
	Follow up: 42 days	
Antidepressant polytherapy (ref: SGA polytherapy)	1.52 (0.85-2.72)	1.36 (0.59-3.11)
History of SGA	1.40 (1.01-1.94)	1.40 (1.00-1.97)
Bipolar subtype I*	2.95 (2.12-4.12)	3.01 (2.12-4.27)
Bipolar subtype NOS*	0.72 (0.52-0.99)	0.72 (0.52-1.01)
	Follow up: 60 days	
Antidepressant polytherapy	1.64 (0.93-2.88)	1.38 (0.63-3.03)
History of SGA	1.40 (1.02-1.92)	1.39 (1.00-1.93)
Bipolar subtype I*	3.11 (2.25-4.30)	3.17 (2.26-4.45)
	Follow up: 90 days	
Antidepressant polytherapy	1.09 (0.66-1.80)	0.75 (0.35-1.60)
Bipolar subtype I*	2.86 (2.10-3.89)	2.91 (2.10-4.03)

*****Reference group: bipolar I single manic episode (ICD-9CM: 296.0), manic disorder recurrent episode (ICD-9CM: 296.1), chronic hypomanic personality disorder (ICD-9CM: 301.11), and cyclothymic disorder (ICD-9CM: 301.13)

MANUSCRIPT 3

Effectiveness of Antidepressant Therapy in Medicaid-Enrolled Pediatric Bipolar Depression

Key words: bipolar depression, antidepressant, second-generation antipsychotic, mood stabilizer, monotherapy, polytherapy, nonmanic hospitalization, augmentation

Conflict of Interest: There is no conflict of interest associated with this study. This study was unfunded.

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Abstract

Objective: To assess effectiveness of antidepressants in treating pediatric bipolar depression.

Methods: In this retrospective cohort study, 2003-2007 MAX data from four geographically diverse states were used. Bipolar depression patients ages 6-18 years receiving antidepressants, second-generation antipsychotics (SGA), or mood stabilizers, monotherapy or polytherapy, during 30 days before or after initial diagnosis, and continuously enrolled in Medicaid throughout the study period were identified. Effectiveness was measured in terms of (1) mental health (non-manic) hospitalization and (2) treatment augmentation with a new class of medications other than the index regimen during 6 months of follow up. Effectiveness measures were assessed using multivariable a Cox proportional hazard model and instrumental variable analysis.

Results: After applying all the selection criteria, 171 antidepressant monotherapy, 923 SGA monotherapy, 547 mood stabilizer monotherapy, 405 antidepressant polytherapy, and 1742 SGA-mood stabilizer polytherapy users were identified in the analytic cohort. Instrumental variable analysis in most of the cohorts did not indicate treatment endogeneity. Both multivariable Cox proportional regression analysis and instrumental variable analysis suggested equivalent effectiveness of antidepressant compared to SGA and mood stabilizer in terms of preventing hospitalization. However, a higher likelihood of therapy augmentation associated with antidepressant regimens compared to SGA or mood stabilizers was suggested by both the survival regression and IV models.

Conclusions: Antidepressants were observed to be equally effective in preventing hospitalization in a pediatric bipolar depression cohort compared to SGA or mood stabilizers. Assessment of therapy augmentation suggested failure of treatment response achieved with

antidepressant regimens. Direct measurement of treatment effectiveness such as remission and relapse of depressive symptoms are required to be assessed using claims data incorporating standardized operational definitions.

Introduction

Bipolar disorder (BD), also known as manic-depressive disorder or bipolar affective disorder, is a form of mood disorder characterized by the presence of episodes of highly elevated mood (manic) and episodes of depressive phases. Worldwide prevalence of bipolar disorder was 5%[1], and in the USA the prevalence was 2.6% in adults and 0-3% in adolescents[2]. Early-onset bipolar disorder in childhood was associated with a higher number of lifetime episodes of manic and depressive phases, more comorbidities such as anxiety and substance abuse, rapid cycling between different phases, and higher incidence of suicide attempts compared to adulthood onset of bipolar disorder[3-5]. The lifetime prevalence of depressive phases among bipolar disorder patients is 3-fold higher than mania phases[6], especially in youth. Untreated bipolar depression among all the phases of bipolar disorder, particularly in children and adolescents, is associated with the highest risk of suicidality[7], substance abuse, functional disability, and poor academic and social performance among children and adolescents[8-14].

Despite the higher prevalence of bipolar depression and associated risk of morbidity and mortality, research in this particular phase of bipolar disorder is limited[19]. The treatment guideline for adults with bipolar depression advises the use of mood stabilizers (such as lithium and anticonvulsants like lamotrigine, valproate, etc., second-generation antipsychotics (SGA) (such as olanzapine), and adjunct therapy with antidepressants such as selective serotonin reuptake inhibitors (SSRI) and bupropion together with mood stabilizers[19]. Lack of prospective trials in pediatric bipolar depression population hinders standardizing treatment guidelines in this patient population, and psychiatric practice in this population is largely extrapolated from that of the adult population and physicians' experience and expertise. The goals of acute treatment of bipolar depression are relieving the depressive symptoms, protecting against future occurrence of

depressive symptoms, and protection against manic switch. Quantitative data on the effectiveness of antidepressants and other medications such as mood stabilizers and antipsychotics in real-world pediatric bipolar depression are limited. Some of the effectiveness measures used in clinical trials and observational studies are response, remission, recovery, relapse, recurrence etc[20]. All these outcomes in clinical trials are defined using symptom rating scales such as Hamilton Rating Scale for Depression (HAMD)[21] and Montgomery-Asberg Depression Rating Scale (MADRS)[22] at different time points of the bipolar depressive phase. For example, response and remission are measured based on the presence or absence of depressive symptoms during the 4-month acute treatment phase[20,23], recovery and relapse outcomes are measured during the 2-month maintenance treatment phase[20,24], while recurrence is identified after the maintenance phase[20]. The absence of such symptom severity scales in observational data hinders direct measurement of the effectiveness of pharmacotherapy in post-marketing comparative effectiveness studies. Some of the effectiveness outcomes evaluated in clinical trials and observational studies that can be measured using claims data are remission, relapse[23], hospitalization[23,25] (which has been used as a marker of relapse of symptoms and discontinuation of treatment), tolerability (defined as discontinuation of treatment)[26], and change in the level of psychiatric care (physician office visit or treatment)[25]. This study aimed to measure effectiveness of antidepressants in a Medicaid-enrolled pediatric bipolar depression population in terms of (1) mental-health related (nonmanic) hospitalization[23], and (2) treatment augmentation.

Methods

Data Source

In this retrospective cohort study, 2003-2007 Medicaid Analytic eXtract (MAX) files from the Centers for Medicare and Medicaid Services (CMS) were used to assess the utilization of psychotropic pharmacotherapy in children and adolescents with bipolar disorder. MAX is a set of person-level claims data files containing information on Medicaid eligibility, demographics, service utilization, and payments. In this study, data from four geographically diversified states with a large Medicaid enrollment of children and adolescents (CA, TX, IL, and NY) were used.

Pharmacotherapy for Bipolar Depression

The pharmacotherapy of bipolar depression includes mood stabilizers (lithium, sodium divalproex/valproate, carbamazepine, oxcarbazepine, topiramate, lamotrigine and gabapentin); SGA (risperidone, aripiprazole, olanzapine, quetiapine, clozapine and ziprasidone), newer antidepressants (selective serotonin reuptake inhibitor (SSRI) antidepressants and others) (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine, and bupropion) and other antidepressants (amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline, mirtazapine, nefazodone, trazodone).

Study Population

Inclusion criteria

Children and adolescents with bipolar depression were identified based on the following algorithm: (1) patients aged between 6 to 18 years (children and adolescents), (2) who received minimum 2 diagnoses of bipolar disorder other than bipolar depression (*International Classification of Diseases, 9th version, Clinical Modification* [ICD-9-CM]: 296.0, 296.1, 296.4-

296.8, 301.11, 301.13) on different service dates, or only 1 diagnosis of bipolar disorder but that came from hospital discharge, followed by a diagnosis of bipolar or unipolar depression (ICD-9CM: 296.5, 296.2, 296.3)[23] anytime between January 2003 and December 2007, and (3) who received antidepressants, SGA, or mood stabilizers during 30 days before and after the depression diagnosis. Index date was defined as the date the first treatment regimen was received during this time frame.

Exclusion criteria

1) Patients who received diagnoses of schizophrenia (ICD-9CM: 295.0x-295.9x) or epilepsy (ICD-9CM: 345.xx) were excluded from the study cohort to ensure that the prescriptions were intended for bipolar disorder treatment.
2) Patients without continuous Medicaid eligibility during 60 days prior to the index date were excluded.
3) Patients who received antidepressant during 60 days prior to the index date were excluded to identify new antidepressant users.

The remaining bipolar depression patients in the cohort were divided into 5 mutually exclusive groups based on the treatment regimens received during 30 days around initial depression diagnosis: (1) antidepressant monotherapy, (2) SGA monotherapy, (3) mood stabilizer monotherapy, (4) antidepressant-SGA or antidepressant-mood stabilizer polytherapy, and (5) SGA-mood stabilizer polytherapy. Monotherapy was defined as patients receiving medication from a single therapeutic class only, while polytherapy was defined as patients receiving medications from multiple therapeutic classes with a minimum 1 day of overlap between medications therapy from multiple classes, during the 30 days around the initial depression

diagnosis. The selected patients were followed longitudinally for a maximum of 6 months to assess treatment effectiveness.

Effectiveness outcomes

Mental Health (non-manic) Hospitalization

This outcome was defined using ICD-9CM codes inclusive of all mental health diagnosis (290.xx-319.xx) but excluding those of mania (296.0, 296.1, 296.4, 296.81). Mania diagnosis was excluded as it is a measure of safety of the bipolar pharmacotherapy. Time to mental health (non-manic) hospitalization was defined as interval between index date and the first occurrence of hospitalization with the above-mentioned diagnoses, during the 6-month follow up after the index date.

Augmentation

Augmentation is a measure of an increase in psychiatric care in the form of adding medications from a new class other than the index treatment regimen to the index pharmacotherapy. Prescribing a two-class polytherapy to the index monotherapy recipients, or prescribing a 3-class polytherapy to the index 2-class polytherapy recipients during the 6 months follow up were defined as augmentation. The most common reason for augmentation is ineffectiveness of the index treatment regimen. Time to augmentation was measured by subtracting the index date from the first date of augmentation during the 6-month follow up.

Covariates

Covariates, including information on demographics, comedications, and comorbidities, were measured at baseline 2 months prior to the index date. Comorbidities included substance abuse disorder (SUD), attention deficit hyperactivity disorder (ADHD), suicidality, oppositional defiant

disorder (ODD), anxiety, adjustment disorder, psychotic disorder, and history of bipolar subtypes at baseline. Comedications included stimulants, sedatives, hypnotics, anticholinergics, and use of SGA and mood stabilizers at baseline. Psychotherapy use and all-cause hospitalization at baseline was also identified as a measure of disease severity. Among demographic characteristics of the selected patients, age (categorized as children as < 13 years old and adolescent >= 13 years old), gender, race (white, black, or other), state of residence (TX, NY, CA, or IL) were measured. Although all patients were Medicaid enrolled, eligibility of patients in Temporary Assistance for Needy Families (TANF) and residing in a foster care setting were also identified, as these variables indicate socioeconomic status of the patients. Duration of disease computed as the interval between the index bipolar disorder and the index bipolar depression was measured, as longer duration of disease may influence future treatment response and subsequently the effectiveness of treatment. Finally, the number of physicians available in each zip code was measured to adjust for psychiatric care availability for patients.

Statistical methodologies

Descriptive analysis was conducted to describe the demographics, treatment utilization, comedications, and comorbidities during the 2-month baseline period for the selected monotherapy and polytherapy users, separately. Chi-square tests and t-tests were conducted on covariates to examine the univariate differences across the monotherapy and the polytherapy cohorts for categorical variables and continuous variables, respectively. Standardized differences of the covariates, i.e. difference in means between the treatment groups divided by the standard error of the difference, were also computed.

Comparative effectiveness of medications was assessed between (1) antidepressant monotherapy v/s SGA monotherapy, (2) antidepressant monotherapy v/s mood stabilizer monotherapy, and (3) antidepressant polytherapy v/s SGA-mood stabilizer polytherapy.

Multivariable Cox Proportional Hazard Regression

Kaplan-Meier plot, log-minus-log survival plot, and Schoenfeld residual test were performed to test the proportionality of hazard assumption for each of the comparison groups and effectiveness measures. Also, log-rank test was performed for each of the effectiveness end-points to assess univariate association between the treatment regimens and the outcomes. Time to effectiveness outcomes (hospitalization and augmentation) were analyzed using the multivariable Cox proportional hazard regression method to assess the differential effectiveness of antidepressant regimens compared to SGA or mood stabilizer regimens. All the covariates used in the descriptive analysis were incorporated in the regression models, to adjust for those observed factors. Different censoring criteria were used for the effectiveness measures. In time to mental health (non-manic) hospitalization analytical models, patients were censored during follow up for (1) treatment discontinuity, (2) manic switch, (3) discontinuity in Medicaid eligibility, and (4) end of follow up. In time to augmentation regression models, patients were censored based on the following criteria: (1) treatment discontinuity, (2) manic switch, (3) mental health (non-manic) hospitalization, (4) discontinuity of Medicaid eligibility, and (5) end of follow up. Censoring criteria were decided in this way to measure each effectiveness outcomes independently.

Instrumental variable (IV) approach

Instrumental variable analysis can address limitations of the traditional multivariable regression and propensity score analysis, as it ideally adjusts for both observed and unobserved covariate

differences between the treatment groups[27]. Important characteristics of instruments are that (1) the instrument variable is significantly correlated with the treatment variable and explains a significant amount of variation in treatment, (2) the instrument theoretically does not cause the outcome except through the treatment variable, and (3) the instrument is not correlated with the observed and unobserved factors associated with the outcome. Instrumental variable analyses were conducted in this study to examine the robustness of the effectiveness estimates obtained from the regular Cox proportional hazard regression models. In this study, "misdiagnosis of index bipolar depression as unipolar depression (ICD9CM code: 296.2, 296.3)", "physicians' preference of prescribing antidepressant", and "year of cohort entry" were used as instruments. Confirmed bipolar disorder patients experiencing a depressive episode and given a major depressive disorder (unipolar depression) diagnosis instead of a bipolar depression diagnosis (ICD9-CM: 296.5) was suggested to be a misdiagnosis.[28] Also, major depressive disorder (MDD) diagnosis generally leads to higher prescribing of antidepressants rather than mood stabilizers or SGAs. Thus, MDD diagnosis as the index bipolar depression theoretically can influence the antidepressant monotherapy or polytherapy treatment utilization. Physicians' preference for antidepressant prescribing was identified if physicians prescribed an antidepressant at the first pediatric bipolar depression visit recorded. For all the subsequent patients who were treated by those physicians, the value of the "physician preference" instrument was given as 1, while for patients who visited physicians who did not treat their first patient with antidepressant the value of the instrument was given as 0. The theoretical explanation of using this variable as an instrument is that physicians with a prior history of treating bipolar depression with antidepressants over mood stabilizers or SGA may predict future use of antidepressants by those physicians while treating subsequent patients. First-ever patients who visited the physicians were

excluded from the analysis. The year the patients entered in the cohort, computed from their index date, was identified as the third instrument as it may explain yearly changes in Medicaid policy and formularies, which may predict treatment variation. The "physician prescribing preference" and "year of cohort entry" variables have been established as valid instruments for explaining psychotropic treatment variation in literature[29,30,31].

As the treatment variables were binary (monotherapy or polytherapy) and the study outcomes were nonlinear (hazard model), a two-stage residual inclusion (2SRI) approach[32] was applied.

Assumption Test

Strength of association between the instruments and the binary treatment variables were assessed by computing partial F-test and partial R-square[27,31]. Change in observed covariates imbalance was determined by comparing the covariate distribution across the treatment groups and the instrument. Fractional change in distribution[27] of each covariate between the treatment groups and the instrument was computed.

1st Stage Regression

Binary continuous treatment variables were regressed with all the covariates and the instruments in the 1st stage of the 2-SRI model, using a linear probability model[34]. Residuals (r) for each patient was computed as difference between the binary treatment variable and the predicted treatment variable from the linear probability model.

2nd Stage Cox Proportional Hazard Model

Time to effectiveness outcomes were assessed using a conventional Cox proportional hazard regression model adjusting for all the previously measured covariates, and r computed from the 1st stage. Association between the outcome and the treatment variable, and all other covariates was reported as hazard ratio (HR) with 95% confidence interval. Statistical insignificance of r in the 2nd stage of the IV analysis suggests exogeneity of the treatment variable and irrelevance of using the selected instruments for the treatment regimens.

SAS 9.2 was used for the entire analyses, and $p<0.05$ was considered to be statistically significant.

Results

From 4216094 patients with age (6-18) years, mental disorder, and receiving psychotropic medications identified from 2003-2007 MAX files, and excluding those with schizophrenia or epilepsy (8731), 14009 patients were identified with confirmed bipolar depression diagnosis according to the diagnosis algorithm. Among those patients, 7883 patients were found to receive antidepressant, mood stabilizer, or SGA, and initiating pharmacotherapy for bipolar depression during 30 days before and after index bipolar depression, between March 2003 and June 2007. Among the pharmacotherapy recipients, 3049 patients were solely on monotherapy while 4834 patients received polytherapy. After applying continuous Medicaid eligibility at the 2-month baseline, 60 days wash-out period for baseline antidepressant prescriptions criteria, and excluding patients used for computing the 'physician preference for antidepressant' instrument, 3788 patients were left in the analytical cohort. Among 1641 monotherapy recipients in the final cohort, 171 patients were on antidepressant monotherapy, 923 patients were on SGA

monotherapy, while 547 patients were on mood stabilizer monotherapy. Among 2147 polytherapy recipients in the final cohort, 405 were on antidepressant polytherapy, while the rest of the 1742 patients received SGA-mood stabilizer polytherapy (Figure 1).

Descriptive statistics

Among the comorbidities, substance abuse disorder (SUD), attention deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), and anxiety were found to be common among both antidepressant monotherapy and other monotherapies. Among polytherapy recipients, the most common comorbidities were ADHD, ODD, anxiety, and adjustment disorder. Stimulants and sedatives were the most commonly prescribed comedications among both monotherapy and polytherapy regimen recipients. Over 50% of the population in each of the monotherapy and polytherapy cohorts received psychotherapy at baseline. Also, 16-30% of patients had a history of all-cause hospitalization at baseline.

Around 16-34% of monotherapy and polytherapy users were found to be in a foster care setting at baseline. Patients in the antidepressant monotherapy and polytherapy cohorts were found to be most likely to be adolescent (>=13 years), white, and residing in Texas. SGA and mood stabilizer monotherapy and polytherapy users were observed to be most likely to be adolescent, white, and male. Descriptive statistics are reported in Table 1 and Table 2.

Effectiveness of antidepressant monotherapy compared to SGA monotherapy (Table 4)

(a) Mental health related hospitalization (non-manic):

Multivariable Cox proportional hazard regression analysis:

Antidepressant monotherapy was observed to be equally protective against hospitalization during the 6-month follow up compared to SGA monotherapy [HR = 1.07 (95% CI: 0.51-2.25)]. SGA

users and patients with a history of all-cause hospitalization at baseline were observed to be at higher risk of hospitalization during follow up, with HR = 2.07 (95% CI: 1.29-3.31) and HR = 3.84 (95% CI: 2.37-6.23), respectively. Residents of NY and TX were observed to be at lower risk of hospitalization compared to the residents of CA, with HR = 0.45 (95% CI: 0.22-0.94) and HR = 0.41 (95% CI: 0.20-0.82), respectively.

Instrumental variable (IV) analysis:

Similar results were obtained from IV analysis on risk of hospitalization between antidepressant monotherapy and SGA monotherapy. Antidepressant monotherapy was found to be equally effective compared to SGA monotherapy [HR = 1.60 (95% CI: 0.43-5.91)]. Patients with a history of SGA use and prior hospitalization at baseline were at higher risk of hospitalization during follow up, and residents of NY and TX were observed to be at lower risk of hospitalization in the IV analysis.

(b) Augmentation:

Multivariable Cox proportional hazard regression analysis

Antidepressant monotherapy recipients compared to SGA monotherapy users [HR = 4.10 (95% CI: 1.44-11.73)], psychotherapy recipients at baseline [HR = 1.92 (95% CI: 1.13-3.25)], those with history of mood stabilizer use at baseline [HR = 2.63 (95% CI: 1.40-4.95)], and those with bipolar subtype II at baseline [HR = 2.51 (95% CI: 1.25-5.04)] were suggested to be at higher likelihood of receiving treatment augmentation during the 6-month follow up period. Those with ODD at baseline were at lower risk of receiving treatment augmentation, HR = 0.52 (95% CI: 0.33-0.82).

Instrumental variable (IV) analysis

Dissimilar results were obtained from IV analysis while assessing the likelihood of treatment augmentation between antidepressant monotherapy and SGA monotherapy recipients. Residual (r) obtained from the 1st stage LPM model was observed to be statistically significant in the 2nd stage of the IV model [HR = 0.004 (95% CI: 0.0009-0.02)], implying possible endogeneity of the treatment variable. Antidepressant monotherapy and psychotherapy recipients at baseline continued to have a higher likelihood of receiving augmentation in the IV model. However, those with a history of mood stabilizer use, ODD, and bipolar subtype II at baseline were not found to be significantly at higher or lower risk of receiving augmentation. In the IV model, those with a history of SGA use at baseline were observed to be at higher risk of receiving augmentation during the 6-months follow up period [HR = 3.18 (95% CI: 1.76-5.77)].

Effectiveness of antidepressant monotherapy compared to mood stabilizer monotherapy (Table 5)

(a) Mental health related hospitalization (non-manic)

Multivariable Cox proportional hazard regression analysis

Antidepressant monotherapy was found to equally effective in protecting against hospitalization during the 6-month follow up compared to mood stabilizer monotherapy [HR = 1.64 (95% CI: 0.67-4.02)]. Those with a history of all-cause hospitalization at baseline were at higher likelihood of experiencing a hospital visit during follow up, HR = 2.79 (95% CI: 1.34-5.79). Residents of TX were at lower risk of hospitalization compared to CA residents, HR = 0.33 (95% CI: 0.12-0.93).

Instrumental variable (IV) analysis

IV analysis suggested similar conclusion in terms of risk of hospitalization during 6 months of follow up between antidepressant monotherapy and mood stabilizer monotherapy users. Antidepressant monotherapy was equally effective in preventing hospital visit compared to mood stabilizer monotherapy, while those with history of hospital visit at baseline and TX residents were at higher and lower risk of hospitalization during follow up, respectively.

(b) Augmentation

Multivariable Cox proportional hazard regression analysis

Antidepressant monotherapy use was not found to be significantly associated with treatment augmentation during 6 months follow up compared to mood stabilizer monotherapy, HR = 2.43 (95% CI: 0.90-6.60). Those with psychotherapy use at baseline and white patients had a higher likelihood of receiving treatment augmentation during follow up, with HR = 2.13 (95% CI: 1.17-3.89) and HR = 2.07 (95% CI: 1.10-3.90), respectively. Stimulant recipients at baseline were at lower likelihood of receiving bipolar depression-related medication combination regimens during follow up, HR = 0.39 (95% CI: 0.20-0.75).

Instrumental variable (IV) analysis

Antidepressant monotherapy recipients were observed to be at higher risk of receiving augmentation during follow up in the IV model, HR = 6.10 (95% CI: 1.41-26.47). Psychotherapy and stimulant recipients at baseline continued to be at higher and lower risk of augmentation, respectively. Race was not found to be significantly associated with augmentation during follow up in the IV model.

Effectiveness of antidepressant polytherapy compared to SGA-mood stabilizer polytherapy (Table 6)

(a) Mental health related hospitalization (non-manic)

Multivariable Cox proportional hazard regression analysis

Antidepressant polytherapy was found to be equally effective in preventing hospital visits during 6 months of follow up compared to a SGA-mood stabilizer polytherapy regimen, HR = 1.03 (95% CI: 0.64-1.66). Patients with a history of mood stabilizer use and hospitalization at baseline were at higher risk of hospitalization during follow up, HR = 1.64 (95% CI: 1.19-2.27) and HR = 2.28 (95% CI: 1.65-3.15), respectively. NY and TX Medicaid enrollees were observed to be at lower risk of hospitalization compared to the CA Medicaid enrollees.

Instrumental variable (IV) analysis

Similar results were obtained from IV analysis on risk of hospitalization between antidepressant polytherapy and SGA-mood stabilizer polytherapy. Antidepressant continued to exhibit equal effectiveness compared to SGA-mood stabilizer polytherapy regimen. Those with a history of mood stabilizer use and hospital visit at baseline were observed to be at higher risk of hospitalization during follow up. Residents of NY and TX were at lower risk of hospitalization compared to the residents of CA.

(b) Augmentation

Multivariable Cox proportional hazard regression analysis

Antidepressant polytherapy recipients compared to SGA-mood stabilizer recipients were observed to be at significantly higher risk of receiving add-on therapy with medications from a third therapeutic class, other than the initial combination regimen, during 6 months follow up,

HR = 10.54 (95% CI: 2.84-39.17). Male patients were observed to be at lower likelihood of receiving combination regimens, HR = 0.57 (95% CI: 0.35-0.91); and TX Medicaid population were more likely to receivie treatment augmentation compared to CA Medicaid population, HR = 3.01 (95% CI: 1.08-8.43).

Instrumental variable (IV) analysis

Dissimilar results were observed in the IV analysis, apart from the significantly higher risk of treatment augmentation among antidepressant polytherapy users compared to SGA-mood stabilizer polytherapy recipients. Sex and state were not found to be significantly associated with treatment augmentation in the IV model. However, in this model, ODD [HR = 2.86 (95% CI: 1.14-7.12)], history of SGA use [HR = 4.15 (95% CI: 1.32-13.01)], and history of mood stabilizer use [HR = 12.26 (95% CI: 3.75-40.05)] were observed to be significantly associated with treatment augmentation during follow up.

Discussion

Antidepressant monotherapy compared to SGA and mood stabilizer monotherapies, and antidepressant polytherapy compared to SGA-mood stabilizer combination, were found to be equally effective in protecting against mental health related (non-manic) hospitalization. Mental health (non-manic) hospitalization has been used as measure of the end of the depressive phase[23]; however, it has also been used as measure of discontinuation of therapy and relapse of symptoms in mental disorder-related studies[25]. Non-differential effectiveness between antidepressants and SGA and mood stabilizers in terms of risk of hospitalization offers equally effective treatment options to clinicians.

Antidepressant monotherapy and antidepressant polytherapy users were at significantly higher risk of receiving augmentation with SGA or mood stabilizer compared to SGA monotherapy and SGA-mood stabilizer polytherapy users, respectively. Viable explanation of this outcome trend can be ineffectiveness of antidepressant therapy compared to SGA or mood stabilizer in treating bipolar depression. Patients who a experienced manic switch during the 6-month follow up period were censored; treatment augmentation received by the antidepressant users may not be explained by bipolar depression treatment recommendation of combining mood stabilizer or SGA to antidepressant to protect against treatment emergent manic switch (TEAS).

Among the covariates adjusted for in the Cox regression and IV analysis models, history of SGA or mood stabilizer use and prior hospitalization at baseline exhibited statistically significant association with higher risk of hospitalization during 6 months follow up. Patients who received SGA or mood stabilizer at baseline were either being treated for acute mania or on maintenance therapy with the antimanic (SGA and mood stabilizer) at baseline. Patients with recent history of mania were reasonably at higher risk of future hospitalization, as manic patients often get hospitalized for hyperactivity and violent characteristics. All-cause hospitalization was used as a baseline severity measure, reasonably patients with high disease severity at baseline were observed to have a higher chance of hospitalization during follow up.

Psychotherapy recipients at baseline and in some of the models demographic factors such as whites and female population were observed to be associated with higher likelihood of treatment augmentation. Psychotherapy at baseline which was used as a severity measure of the bipolar depression patients in this study was reasonably found to be predicting higher utilization of polytherapy during the follow up period. The other demographic factors such as female sex or white population have been observed to utilize higher healthcare resource compared to the males

or black population, respectively, in previous healthcare resource utilization studies. In some of the models, history of mood stabilizer and SGA use at baseline was observed to be associated with future likelihood of treatment augmentation as well.

"Misdiagnosis with MDD", "physicians' preference of antidepressant", and "year of cohort entry" exhibited strong prediction of antidepressant monotherapy or polytherapy in the 1st stage LPM of the instrumental variable analyses, providing evidence of reasonable selection of the instruments. They also exhibited strong association with the treatment variables with partial F-statistics of more than 10 in all the models, considerably high partial R-square values, and also reduced covariate imbalance (not reported). In the 2nd stage of the instrumental variable analyses, statistical insignificance of the residual r indicated exogeneity of the treatment variables in most of the models. However, r was statistically significant in the 2nd stage IV model for augmentation outcome comparing antidepressant monotherapy and SGA monotherapy, indicating possible endogeneity in the treatment variable. In absence of endogeneity in treatment as highlighted by the instrumental variable approach taken in this study, comparative effectiveness analysis adjusting only the observed factors should be emphasized. Nevertheless, the effectiveness estimates obtained from the IV models served as comparators to the estimates obtained from the regular survival regression models.

This study suffers from certain limitations. Use of claims data in this retrospective cohort study limited the identification of bipolar disorder and bipolar depression patients; without structured clinical evaluation using depression and manic rating scales, accurate classification of the patients and inclusion in the study cohort cannot be confirmed. Because of the complicated treatment regimen pattern of bipolar disorder in general, it was difficult to identify exact initiation of the bipolar depression treatment. The prescribed medications before or after index

bipolar depression, especially mood stabilizers and SGAs, could be for treatment of and acute depression phase or could be a maintenance therapy from previous manic events. However, there is no theoretical reason to believe that any of this treatment selection related and claims data related-limitations should differentially affect one treatment arm over another because of the comparative effectiveness study design. Also, the patient population was selected based on a minimum of 2 diagnoses of bipolar disorder and 1 diagnosis of bipolar depression; the multiple diagnoses criterion was used to confirm the bipolar nature of the disorder among the selected patients and to negate the possibility of disease misclassification for using claims data in absence of clinical evaluation to some extent. Another limitation of this study was incapability to measure direct treatment effectiveness. Clinical trials accurately measure treatment effectiveness at different phases of bipolar depression, such as response, remission, recovery, relapse, or recurrence of depressive symptoms using severity rating scales such as MADRS or HDRS. Unavailability of such scales in the claims data impeded direct measurement of real-world treatment effectiveness. Proxy measures of effectiveness of treatment, such as hospitalization and therapy escalation in terms of treatment augmentation, were used in this study. Also the study findings will be generalizable only to the pediatric population enrolled in Medicaid. Despite of all the limitations, this study is one of the primary attempts to quantify effectiveness of antidepressants in a real-world pediatric bipolar depression patient population. This study also aimed to define the acute bipolar depression phase, its treatment, and therapy effectiveness using diagnostic and pharmacy claims. Availability of detailed prescription fill information and outpatient and inpatient visits in the Medicaid claims data provided an opportunity to conduct detailed longitudinal assessment of complex medication utilization patterns and effectiveness outcomes in the patient population. The quantity of claims data obtained from four states (CA,

NY, TX, and IL) and for five years (2003-2007) provided a large sample size and sufficient statistical power to evaluate comparative effectiveness across multiple cohorts of medication regimen recipients. Self-report (recall bias) and differential self-selection in RCTs were not an issue because of using retrospective secondary data in this study. Finally, assessment of effectiveness of pharmacotherapy in a real-world pediatric population, who are generally excluded from clinical trials, was possible because of using claims data.

In conclusion, antidepressant monotherapy and polytherapy was observed to be equivalently effective compared to SGA and mood stabilizer in terms of preventing hospitalization. However, antidepressants exhibited a higher chance of receiving treatment augmentation compared to SGA or mood stabilizers, suggesting failure to achieve intended treatment response with antidepressant regimens. A more direct measure of effectiveness of pharmacotherapy such as remission and relapse of depressive symptoms is subject to exploration in future studies using standardized operational definitions from claims data.

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Figure 1. Schematic Diagram of Effectiveness Cohort Build-Up

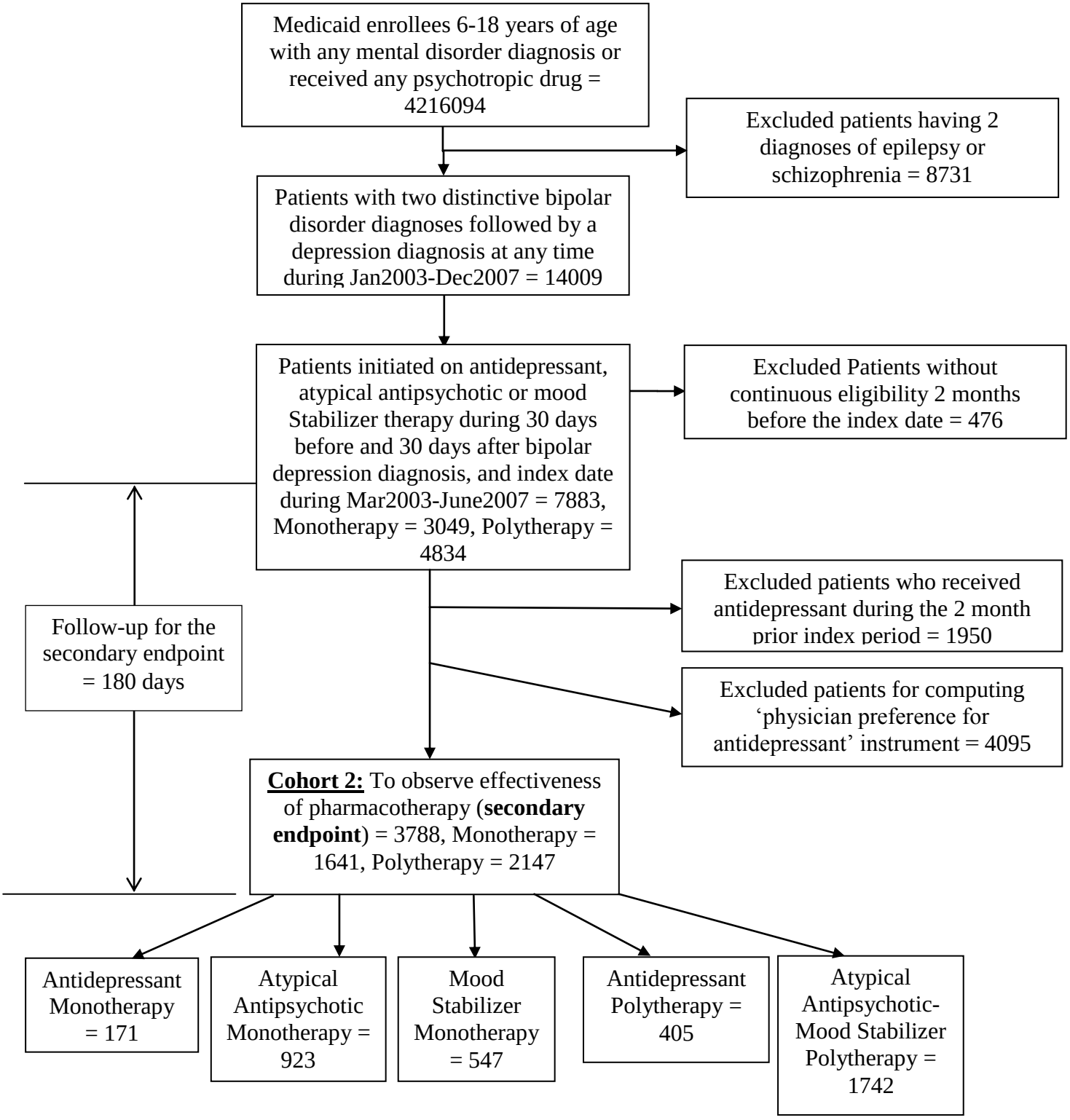

Figure 2. Study Time Frame Design

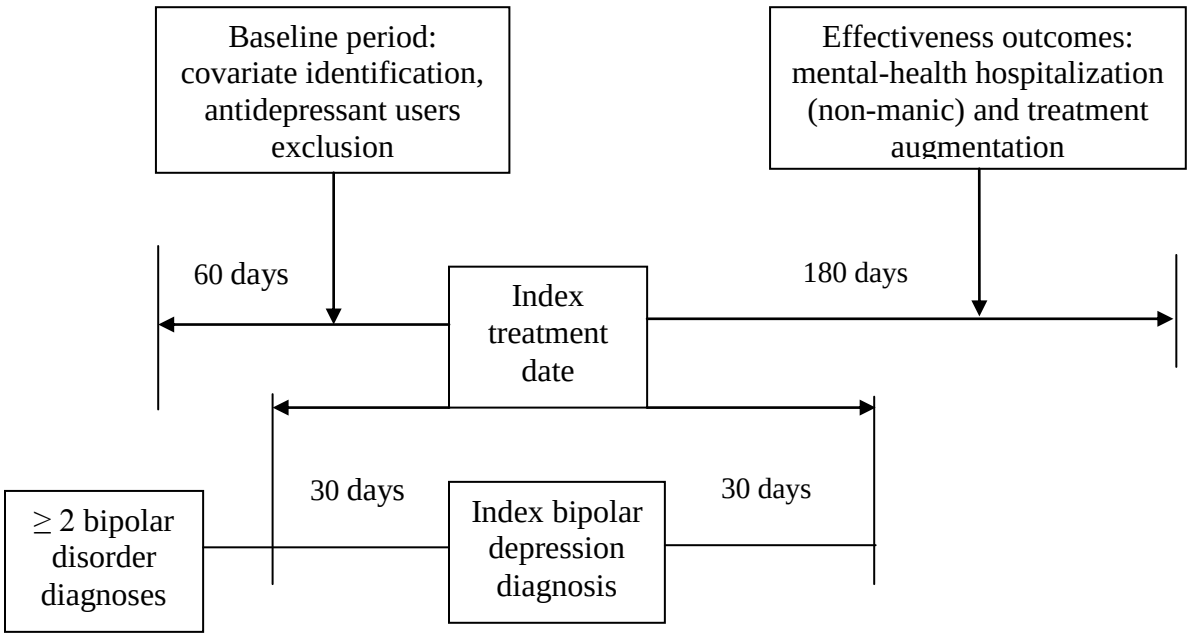

Table 1. Descriptive Results of the Monotherapy Cohort (N = 1641)

Covariates	Antidepressant monotherapy (n=171) N (%) or Mean (±SD)	SGA monotherapy (n=923) N (%) or Mean (±SD)	Mood stabilizer monotherapy (n=547) N (%) or Mean (±SD)
Duration of Disease	330 (±362)	314 (±349)	291 (±330)
Number of Physicians in Zip Codes	22 (±22)	31 (±28)	29 (±26)
Stimulant	29 (16.96)	194 (21.02)	102 (18.65)
Sedative	48 (28.07)	155 (16.79)	95 (17.37)
Hypnotic	3 (1.75)	45 (4.88)	15 (2.74)
Anticholinergic	3 (1.75)	61 (6.61)	20 (3.66)
Psychotherapy	95 (55.56)	487 (52.76)	292 (53.38)
Substance Abuse Disorder	18 (10.53)	61 (6.61)	44 (8.04)
ADHD	33 (19.30)	299 (32.39)	141 (25.78)
Suicidality	7 (4.09)	16 (1.73)	10 (1.83)
Oppositional Defiant Disorder	25 (14.62)	234 (25.35)	120 (21.94)
Anxiety	23 (13.45)	80 (8.67)	56 (10.24)
Adjustment Disorder	15 (8.77)	107 (11.59)	61 (11.15)
Psychotic Disorder	6 (3.51)	65 (7.04)	21 (3.84)
Bipolar			
SubType I	11 (6.43)	84 (9.10)	63 (11.52)
SubType II	13 (7.60)	48 (5.20)	26 (4.75)
SubType NOS	88 (51.46)	518 (56.12)	309 (56.49)
History of SGA	11 (6.43)	476 (51.57)	36 (6.58)
History of Mood Stabilizer	9 (5.26)	52 (5.63)	267 (48.81)
Prior Hospitalization	42 (24.56)	186 (20.15)	100 (18.28)
Foster Care	28 (16.37)	273 (29.58)	150 (27.42)
TANF	12 (7.02)	74 (8.02)	45 (8.23)
Age Category			
Children (6-13 years)	35 (20.71)	383 (42.60)	160 (30.08)
Adolescents (14-18 years)	134 (79.29)	516 (57.40)	372 (69.92)
Race			
White	92 (54.12)	414 (45.59)	249 (46.46)
Black	30 (17.65)	255 (28.08)	154 (28.73)
Sex: Male	66 (38.82)	577 (63.55)	311 (58.02)
State			
TX	74 (43.53)	296 (32.60)	154 (28.73)
CA	35 (20.59)	171 (18.83)	117 (21.83)
IL	48 (28.24)	284 (31.28)	197 (36.75)
NY	13 (7.65)	157 (17.29)	68 (12.69)
IV1: History of Major Depression	147 (85.96)	572 (61.97)	291 (53.20)
IV2: Physician Preference of	146 (85.38)	182 (19.72)	100 (18.28)

Antidepressant			
IV3: Year of Cohort Entry			
2003	10 (5.85)	75 (8.13)	92 (16.82)
2004	27 (15.79)	168 (18.20)	126 (23.03)
2005	41 (23.98)	213 (23.08)	118 (21.57)
2006	50 (29.24)	258 (27.95)	119 (21.76)
2007	43 (25.15)	209 (22.64)	92 (16.82)

SGA: second-generation antipsychotic, ADHD: attention deficit hyperactivity disorder, Bipolar SubType NOS: not otherwise specified, TANF: temporary assistance for needy families, IV: instrumental variable

Table 2: Descriptive Results of the Polytherapy Cohort (N = 2147)

Covariates	Antidepressant polytherapy (n=405) N (%) or Mean (±SD)	SGA-Mood Stabilizer polytherapy (n=1742) N (%) or Mean (±SD)
Duration of Disease	279 (±343)	376 (±368)
Number of Physicians in Zip Codes	37 (±34)	41 (±37)
Stimulant	60 (14.81)	405 (23.25)
Sedative	104 (25.68)	404 (23.19)
Hypnotic	20 (4.94)	80 (4.59)
Anticholinergic	26 (6.42)	149 (8.55)
Psychotherapy	266 (65.68)	989 (56.77)
Substance Abuse Disorder	23 (5.68)	86 (4.94)
ADHD	114 (28.15)	547 (31.40)
Suicidality	10 (2.47)	25 (1.44)
Oppositional Defiant Disorder	78 (19.26)	445 (25.55)
Anxiety	65 (16.05)	137 (7.86)
Adjustment Disorder	56 (13.83)	223 (12.80)
Psychotic Disorder	23 (5.68)	132 (7.58)
Bipolar		
SubType I	27 (6.67)	224 (12.86)
SubType II	22 (5.43)	80 (4.59)
SubType NOS	237 (58.52)	919 (52.76)
History of SGA	136 (33.58)	1260 (72.33)
History of Mood Stabilizer	65 (16.05)	1210 (69.46)
Prior Hospitalization	123 (30.37)	282 (16.19)
Foster Care	71 (17.53)	600 (34.44)
TANF	45 (11.11)	75 (4.31)
Age Category		
Children	141 (36.06)	751 (44.41)
Adolescents	250 (63.94)	940 (55.59)
Race		
White	193 (48.86)	804 (47.24)
Black	73 (18.48)	446 (26.20)
Sex: Male	236 (54.00)	1268 (67.81)
State		
TX	208 (52.66)	695 (40.83)
CA	63 (15.95)	287 (16.86)
IL	102 (25.82)	448 (26.32)
NY	22 (5.57)	272 (15.98)
IV1: History of Major Depression	297 (66.74)	998 (52.36)
IV2: Physician Preference of Antidepressant	280 (69.14)	946 (54.31)
IV3: Year of Cohort Entry		
2003	365 (90.12)	424 (24.34)
2004	73 (18.02)	351 (20.15)

2005	121 (29.88)	442 (25.37)
2006	104 (25.68)	414 (23.77)
2007	81 (20.00)	276 (15.84)

SGA: second-generation antipsychotic, ADHD: attention deficit hyperactivity disorder, Bipolar SubType NOS: not otherwise specified, TANF: temporary assistance for needy families, IV: instrumental variable

Table 3: Association Between Instruments and Treatment Cohorts

Treatment groups	Comparison groups	Partial F-statistics	Partial R-square
Antidepressant monotherapy	SGA monotherapy	111	0.24
Antidepressant monotherapy	mood stabilizer monotherapy	119	0.35
Antidepressant polytherapy	SGA-mood stabilizer polytherapy	236	0.26

Abbreviations: SGA: second-generation antipsychotic

Table 4: Cox Proportional Hazard Regression Analysis Results (Antidepressant Monotherapy V/S Second-Generation Antipsychotic (SGA) Monotherapy)

Variables	Hazard ratio (95% CI) from conventional Cox proportional hazard regression model	Hazard ratio (95% CI) from instrumental variable analysis
Outcome: mental health hospitalization (non-manic)		
Antidepressant monotherapy	1.07 (0.51-2.25)	1.60 (0.43-5.91)
History of SGA	2.07 (1.29-3.31)	2.32 (1.33-4.07)
State: NY v/s CA	0.45 (0.22-0.94)	0.42 (0.17-1.02)
State: TX v/s CA	0.41 (0.20-0.82)	0.37 (0.17-0.80)
Prior hospitalization	3.84 (2.37-6.23)	4.02 (2.33-6.93)
Outcome: augmentation		
Antidepressant monotherapy	4.10 (1.44-11.73)	362.52 (49.24-2669.09)
Psychotherapy	1.92 (1.13-3.25)	1.93 (1.03-3.60)
History of mood stabilizer	2.63 (1.40-4.95)	2.40 (0.98-5.88)
History of SGA	1.23 (0.81-1.88)	3.18 (1.76-5.77)
Oppositional defiant disorder	0.52 (0.33-0.82)	1.70 (0.99-2.91)
Bipolar subtype II*	2.51 (1.25-5.04)	2.30 (0.93-5.68)
Residual (r)	-	0.004 (0.0009-0.02)

*****Reference group: bipolar I single manic episode (ICD-9CM: 296.0), manic disorder recurrent episode (ICD-9CM: 296.1), chronic hypomanic personality disorder (ICD-9CM: 301.11), and cyclothymic disorder (ICD-9CM: 301.13)

Table 5: Cox Proportional Hazard Regression Analysis Results (Antidepressant Monotherapy V/S Mood Stabilizer Monotherapy)

Variables	Hazard ratio (95% CI) from conventional Cox proportional hazard regression model	Hazard ratio (95% CI) from instrumental variable analysis
Outcome: mental health hospitalization (non-manic)		
Antidepressant monotherapy	1.64 (0.67-4.02)	1.31 (0.26-6.70)
State: TX v/s CA	0.33 (0.12-0.93)	0.30 (0.10-0.95)
Prior hospitalization	2.79 (1.34-5.79)	3.12 (1.27-7.65)
Outcome: augmentation		
Antidepressant monotherapy	2.43 (0.90-6.60)	6.10 (1.41-26.47)
Stimulant	0.39 (0.20-0.75)	0.34 (0.16-0.72)
Psychotherapy	2.13 (1.17-3.89)	2.33 (1.16-4.68)
Race: White v/s Black	2.07 (1.10-3.90)	1.97 (0.89-4.40)

Table 6. Cox Proportional Hazard Regression Analysis Results (Antidepressant Polytherapy V/S SGA-Mood Stabilizer Polytherapy)

Variables	Hazard ratio (95% CI) from conventional Cox proportional hazard regression model	Hazard ratio (95% CI) from instrumental variable analysis
Outcome: mental health hospitalization (non-manic)		
Antidepressant polytherapy	1.03 (0.64-1.66)	1.60 (0.71-3.60)
History of mood stabilizer	1.64 (1.19-2.27)	1.89 (1.29-2.76)
State: NY v/s CA	0.25 (0.14-0.45)	0.24 (0.13-0.48)
State: TX v/s CA	0.42 (0.26-0.68)	0.41 (0.24-0.71)
Prior hospitalization	2.28 (1.65-3.15)	2.23 (1.58-3.15)
Outcome: augmentation		
Antidepressant polytherapy	10.54 (2.84-39.17)	4230994.35 (49353.89-362713317.01)
Sex: Male v/s Female	0.57 (0.35-0.91)	0.85 (0.43-1.68)
State: TX v/s CA	3.01 (1.08-8.43)	4.10 (0.68-24.81)
Oppositional defiant disorder	1.19 (0.65-2.16)	2.86 (1.14-7.12)
History of SGA	1.59 (0.86-2.94)	4.15 (1.32-13.01)
History of mood stabilizer	0.90 (0.49-1.64)	12.26 (3.75-40.05)