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AN EVALUATION OF ATPYICAL ANTIPSYCHOTIC USE, COSTS AND EFFECTIVENESS IN THE PEDIATRIC POPULATION

BY

KELLYE A. DONOVAN

A DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN

PHARMACEUTICAL SCIENCES

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2018

DOCTOR OF PHILOSOPHY DISSERTATION

OF

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UNIVERSITY OF RHODE ISLAND
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ABSTRACT

The pediatric mental health burden in the United States (US) is substantial, with more than 4 million children meeting diagnostic criteria for a mental health disorder. As of 2014, this number represented 20% of US children and adolescents. In 2010, mental health disorders are estimated to cost children and their families $247 billion dollars annually and severely impact quality of life for children and their families. From 2007 to 2010, inpatient admissions for mental health disorders in pediatric patients increased 24% and mood disorder admissions in pediatric patients increased 80% from 1997-2010. An estimated $11.6 billion was spent on pediatric mental health hospitalizations from 2006 through 2011, with public sources such as Medicaid and Medicare responsible for approximately 50% of the payments, leaving 50% to private payers. This economic and clinical concern has led pediatric medical associations and health quality agencies to increase support and funding for pediatric mental health research and treatment.

Medication therapy is a common intervention in mental health treatment and atypical antipsychotics are increasing in utilization, often becoming first-line therapy. Despite available data describing the need to treat pediatric mental health conditions, the available evidence for clinical effectiveness and economic impact of atypical antipsychotics (AAPs) has many shortfalls. Most available research is derived from patients utilizing publicly-funded medical care, such as Medicaid or Medicare resources, with little data available about patients with privately-funded care. To help address this gap in the literature, we used a large, privately-insured, US population for our analysis. We examined if the increased trend in AAP utilization from previous

research is also present in this pediatric population. Considering the payer perspective, we evaluated the cost of AAP medication therapy based on most recent utilization.

Available studies lack information about the direct costs of pediatric mental health treatment and efficacy of psychiatric medications in the pediatric population. Most efficacy studies are based on clinical trials necessary for pediatric indication approval from regulatory agencies such as the Food and Drug Administration (FDA). Many of the AAP medications do not have pediatric clinical trial evidence available and are frequently utilized without pediatric indications. The available data suggests that off-label prescribing is not an uncommon practice in the pediatric patient population.[3,4]

Approximately half of atypical antipsychotics do not have pediatric indications but are increasingly used, particularly in treating behavior disorders, due to such factors as improved patient compliance and improved side effect profiles. Limited formal studies examining atypical antipsychotic use compared to other agents in the class have been conducted. Studies with direct comparisons have yet to be conducted in the pediatric population with mental health disorders.

The manuscripts that comprise this dissertation aim to provide new insights into available trend and utilization patterns of atypical antipsychotic medication use in children. This research characterized the prevalence of atypical antipsychotic use in pediatric patient with mental health conditions in a large, privately insured US population, evaluating the diagnoses associated with treatment and estimate the cost of AAP medication therapy in this population. This research determined if the trends observed in publicly-insured children persist in the privately-insured, pediatric patient.

The analysis evaluated annual trends in prevalent use of atypical antipsychotic medication over 6-year period in this pediatric population and evaluated the appropriate use of AAPs for mental health diagnoses. Lastly, an evaluation determined if specific antipsychotic therapy delayed time to readmission among privately-insured children following a psychiatric hospital admission. The results of this dissertation will provide new insights regarding the trends and direct medication costs of atypical antipsychotic agents when utilized in pediatric patients with mental health disorders.

Manuscript 1: This analysis focused on characterizing the most recent (2015) AAP use in the pediatric population with mental health disorders, using a large, US population of privately- insured children. The study evaluated if the prevalence data observed among publicly insured children persists. Characterization of the prescribing trends for atypical antipsychotics and the medication costs of the use in this population were examined. Patterns of use across demographics and associated mental health diagnoses were characterized by the class of medication. This study focused on the prevalent use of AAPs in pediatric patients with a mental health diagnosis, evaluated the mental health diagnoses associated with AAPs and the direct cost burden of medication therapy associated with this use of AAP in the pediatric population to the private payer.

Manuscript 2: This research evaluated the trends in the prescribing of atypical antipsychotic medications from 2010 through 2015 in this privately-insured pediatric population. The trends of AAP use in the pediatric population over six years were examined. The associated mental health diagnoses corresponding with AAP

prescribing were described to examine the off-label diagnoses treatment prevalence in this population. This study hypothesizes that the prevalent use of AAPs is increasing in the privately-insured patients and off-label prescribing accounts for most clinical use in pediatric patients.

Manuscript 3: This analysis examined pediatric patients who utilized oral atypical antipsychotic therapy after an inpatient admission for mental health treatment. Readmission for mental health treatment was evaluated to determine the efficacy of using oral AAP medications in pediatric mental health patients. Some oral AAP agents have shown benefit in pediatric patients compared to placebo and have an official FDA indication for pediatric use. Many clinical providers believe that this entire class of medications can demonstrate benefit in pediatric patients, regardless of FDA indication. This study hypothesized that certain oral AAP medications are associated with delayed readmission in pediatric patients with an index admission for mental health treatment.

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This graduate program has been a blessing to our family and my own professional success. For anyone that is not directly mentioned, I apologize, but please know your support has been crucial to my achievements.

PREFACE

For this dissertation, a manuscript format will be utilized and will be comprised of three manuscripts, which examined (1) the current utilization and costs of atypical antipsychotic use in pediatric patients with mental health diagnoses, (2) the trend in atypical antipsychotic prescribing in the pediatric population and off-label prescribing of these agents, (3) the effectiveness of oral atypical antipsychotic agents in delaying inpatient readmission for mental health treatment in pediatric patients.

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MANUSCRIPT 1

Title: Atypical Antipsychotic Use in the Privately Insured Pediatric Population: Current Prevalence and Medication Costs.

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1.1 Abstract

BACKGROUND: Atypical antipsychotics (AAPs) are one of the most commonly prescribed classes of medication in the United States, representing 5% of all prescriptions among both pediatric and adult populations in 2012. The overall use of AAPs in pediatric patients with mental health disorders has been increasing over the last 20 years. Since 2007, almost double the number of AAPs have been approved on the US market and utilized in the pediatric population.[1] However, most available utilization studies are dated with the most recent completed almost ten years ago. The pediatric mental health burden in the United States (US) is substantial, with more than 4 million children meeting diagnostic criteria for a mental health disorder. As of 2014, this number represented 20% of US children. In 2010, mental health disorders are estimated to cost youth and families $247 billion. This study aims to provide a current (2015) assessment of atypical antipsychotic use in pediatric patients.

OBJECTIVE: This study will determine the prevalence and costs of atypical antipsychotic medication therapy in the privately-insured pediatric patient population with a mental health disorders. This study will also identify patient and clinical characteristics that influence the use of atypical antipsychotic medication in pediatric patients with mental health diagnoses.

METHODS: Healthcare claims data extracted from the Optum Clinformatics ® Data Mart; (OptumInsight, Eden Prairie, MN) database between January 2015 and December 2015 were analyzed. Children and adolescents (2-17 years) with a mental health diagnosis of interest, regardless of the presence of a paid claim for an atypical antipsychotic medication, were included. Baseline characteristics of patients by AAP

medication use (received AAP medications anytime during the year versus none during the year) were determined and prevalence of AAP use was calculated. Predictors of AAP medication use were evaluated using a logistic regression model. Twelve-month average costs for AAP therapy was calculated for the AAP medication cohort using a linear regression model.

RESULTS: The one-year prevalence in the privately-insured, pediatric population with a mental health disorder was 7% (67.5 per 1,000 children) in 2015. Despite being selected for inclusion in the cohort by mental health diagnosis of interest, we found that 29% of children treated with AAP medications did not have a mental health diagnosis at associated medical visit. Specialty providers were responsible for 41% of the AAP prescribing and found that primary care providers only prescribed 17% of the AAP paid claims. In the cost analysis, the average per member per month (PMPM) cost for the entire study population was $311.58. The total 12-month spend for 35,311 paid claims for AAP medication therapy was $12.5 million in 2015, representing 5,253 unique patients over the study period. Formulation of aripiprazole (generic and name brand) were the most commonly prescribed atypical antipsychotic medication (42%) followed by generic risperidone (25%) in 2015. The median cost of a paid claim for generic risperidone was $21.04 (Q1 = $12.39, Q3 = $31.55) per claim, representing almost the lowest cost per claim of all the AAP agents. The median cost of a paid claim for generic aripiprazole was $531.23 (Q1 = $519.79, Q3 = $668.89) per claim, representing the highest cost per paid claim compared with all other available generic AAP agents.

CONCLUSIONS: The prevalence of using atypical antipsychotic medications in pediatric patients with mental health disorders is significant in the privately-insured population. Individual costs vary greatly by AAP medication and further costs studies are warranted to determine the potential economic impact to a specific private payer.

1.2 Introduction

The pediatric mental health burden in the United States (US) is substantial, with more than 4 million children meeting diagnostic criteria for a mental health disorder.[2–4] As of 2014, this number represented 20% of US children. Pediatric patients are defined as children from 2 to 12 years and adolescents from 13 to 18 years.[5] In 2010, mental health disorders are estimated to cost youth and families $247 billion dollars annually and severely impact quality of life for children and their families.[2–4,6] An estimated $11.6 billion was spent on pediatric mental health hospitalizations from 2006 through 2011, with public sources such as Medicaid and Medicare responsible for approximately 50% of the payments, leaving 50% to private payers.[7] This economic and clinical concern has led pediatric medical associations and health quality agencies to increase support and funding for pediatric mental health research and treatment.[2,7]

Antipsychotic medication therapy is the gold standard of treatment for psychosis and related behavior disorders in adult patients. In the past decade, these medications have gained popularity as treatments for psychiatric and behavior disorders in adolescents (13-<18 years old) and pediatric patients (2-<13 years old), despite gaps in clinical efficacy and safety research.[8–10] Pediatric patients with behavioral and affective disorders, autism-spectrum disorders and mood disorders often benefit from pharmacotherapy with antipsychotic agents in conjunction with other nonpharmacological interventions.[10–13] While not all atypical antipsychotics have an Food and Drug Administration (FDA) indication for use in pediatric patients, atypical antipsychotics are considered first line agents by mental health experts and

clinicians, compared to typical antipsychotic medications, due to improved side effect and safety profiles, as demonstrated in adult clinical trials. [13] A Cochrane review of atypical antipsychotics in patients under the age of 18 years found only 13 suitable randomized, controlled trials appropriate for inclusion, representing 1,100 pediatric patients in total.[14] There is a lack of sufficient evidence regarding the comparative effectiveness of atypical agents over traditional agents in pediatric patients.[14] AAP medications offer the possibility of benefit in pediatric patients; however, there is limited evidence to support widespread use of these agents.

As of 2012, AAPs are one of the most commonly prescribed classes of medication in the United States, representing 5% of all prescriptions among both pediatric and adult populations and over $13 billion in drug expenditures.[13] The overall trend of use for AAP in pediatric patients with mental health disorders has been increasing over the last 20 years. From 1995 to 2002, multiple studies demonstrated a 5-fold increase of antipsychotic use in pediatric and adolescent patients in the United States.[14,15] This trend was largely due to the increased availability of atypical antipsychotics and the common misconception that atypical antipsychotics demonstrated lower risk of serious adverse events.[16,17] From 2007 to 2010, a study evaluating off-label use of AAP medications, found that 12% of outpatient medical visits documented the use of AAPs. This utilization study was based on medical visits where AAP medications were documented and not on paid claims data. More recent trend data utilizing administrative claims data in privately-insured children is unavailable. Cooper et al examined antipsychotic mediation use in publicly-insured youth and found that 53% of incident users were being treated for

mood or behavior disorders and not traditional psychiatric conditions.[8,15,16,18] Utilization and medication costs can vary over time based on market changes. Since 2007, almost double the number of AAPs have been approved on the US market and have been utilized in the pediatric population, according to claims database analyses.[1] However, most available measures of prevalent use are somewhat dated with the most recent completed studies analyzing data only as recent as 2011.[12]

Medication therapy is a common intervention in mental health treatment and atypical antipsychotics are increasing in use and often a first-line therapy.[3,7,9] Despite available data describing the need to treat pediatric mental health conditions, the available evidence for clinical effectiveness and economic impact of atypical antipsychotics (AAPs) has many shortfalls. As of 2010, most of the trend studies focused on publicly-insured children, such as Medicaid enrollees, with few studies including large, privately-insured populations. The available data suggests a growing trend in atypical antipsychotic use in pediatric patients with mental health diagnoses, but only a limited number of studies evaluated use of this medication class among privately-insured patients. It is unclear whether the available prevalence of AAP use among publicly insured children is also comparable to that among privately-insured pediatric populations with mental health diagnoses.[8,16,18,19]

The goal of this study is to characterize AAP use in the pediatric population with mental health diagnoses, using a large, US population of privately-insured children. Characterization of the prescribing prevalence for atypical antipsychotics and the medication costs of the use in this population will be examined. Examining this population for changes in prescribing over the most recent year can provide additional

insight into spending trends and changes in payer spending for AAP therapy. This study will evaluate how new market entries and new generic medications have possibly changed the spending profile and may provide additional data on the medication costs differences seen in this study compared to available literature. Patterns of use across demographics and associated mental health diagnoses will be described to better characterize the use of this class of medication in the pediatric population with mental health diagnoses. Considering the payer perspective, we evaluated the direct cost burden of AAP medication therapy for 2015, the most recent year of available data. We evaluated the overall utilization of these medications among privately-insured pediatric patients with mental health diagnoses. We discuss a comparison of the overall utilization observed in our study to available reported utilization among publicly-insured children.

1.3 Methods

Data Source and Study Design

This cross-sectional study was conducted utilizing administrative data (Optum Clinformatics ® Data Mart; OptumInsight, Eden Prairie, MN) for the period of January 1, 2015 to December 31, 2015. This data includes commercial health insurance claims (inpatient and outpatient medical records, laboratory data, facility information, and outpatient pharmacy) and enrollment data from large, private insurer across the United States.[20] This dataset provides healthcare information on 36 million beneficiaries and encompasses 1.2 billion individual medical records.

Sample selection

We conducted a cross-sectional study of atypical antipsychotic use among US pediatric enrollees to describe the use of atypical antipsychotic medication as most recently prescribed during the calendar year 2015. Our analyses were conducted using pharmacy claims data, outpatient medical claims data and patient eligibility data, which included patient age, gender, geographic region. Pharmacy claims data included medication information such as days' supply, quantity, prescribing physician and cost data. Outpatient medical visit provided clinical information on date of service, diagnosis codes at time of visit and provider type. **Figure 1** displays a flowchart of inclusion and exclusion criteria. Each patient was required to have at least one medical record present in 2015 with a mental health diagnosis of interest and information was aggregated to patient level (**Appendix A**). There were 87,503 pediatric patients with at least one mental health diagnosis enrolled in dataset in 2015. Pediatric patients (ages 2-17 years) represented 10% of the population available for analysis in administrative database. Before exclusion criteria were applied, 23% (20,732) of patients had a diagnosis of Disruptive or Aggressive Behavior (DAB) Disorders, 14% (11,870) had a diagnosis of Anxiety Disorders and 13% (11,611) had a diagnosis of Developmental Disorders (**Table 1**). Of the entire original cohort, 0.3% (210) of patients had a diagnosis of six mental health diagnostic categories documented at a medical visit claim during 2015.

Patients were excluded from study for the following conditions: 18 years or older during study period, did not have continuous enrollment during study period or incomplete information available for paid claims or medical visits for analysis. All

available dosage forms and atypical antipsychotic medications were included in the analysis, regardless of indicated use for the pediatric population.

Outcomes

For determination of atypical antipsychotic prescription use, the most recent dispensing of this medication type was used. Patients were identified as having an AAP medication paid claim using National Drug Codes (NDCs) as provided in **Appendix B**, for an available AAP medications on the US market. If patients had more than one paid claim for an AAP, we selected the most recent paid claim (latest fill date in 2015) to represent the paid claim of interest to best represent the most relevant clinical treatment plan.

For the cost analysis, the total cost of AAP medication therapy was determined as a summation of all paid claims for AAP medications for individual pediatric patients with mental health diagnoses over the calendar year 2015. To determine the 12-month average spend for atypical antipsychotic medication therapy, a per-member per-month (PMPM) variable was determined based on patient's overall days of exposure to AAP medication therapy and total cost of AAP therapy for each patient. The PMPM was calculated by totaling the cost for all paid claims for a given patients and dividing by total day supply of AAP medication therapy. This value was then multiplied by 30 days to represent the monthly cost associated with AAP medication therapy for each patient. This value provides a mean cost per patient for all AAP medications received per month, regardless of number of claims represented.

Statistical Analysis

The prevalence of AAP use was examined by age group (2 to 5 years, 6 to 12 years, 13 to 17 years), gender, geographic region (Northeast, Midwest, West and South), primary mental health diagnosis closest to the AAP paid claim date (**Appendix A**), provider category and concomitant medication use, including anxiolytics, antidepressants, antiepileptics and stimulants. Concomitant medication therapy was defined as the presence of a paid claim for the medication class of interest during the study period of 2015. This study focused on overall utilization of atypical antipsychotics and did not examine therapy switching between agents or overlap of multiple AAPs because this information is not needed to characterize the current utilization of any AAP agent. Mental health diagnoses were treated as a categorical variable, with an indicator variable for each condition as listed in **Appendix A**, using International Classification of Diseases, Ninth Revision, Clinical Modification (*ICD-9-CM)* and Tenth Revision (*ICD-10-CM*) diagnostic codes. Several studies examining mental health ICD-9 codes for research have been performed and indicate strong validity in using these codes in claims data mental health research.[21,22] Davis et. al found a positive predictive value (PPV) of 76% for mental health condition in administrative claims data.[22] Several previous research groups used these diagnostic categories for administrative data analysis of pediatric mental health conditions.[9,15,22] To determine the diagnosis associated with a specific AAP paid claim, a 60-day window (60 days before and after) around the date of prescription fill was established and the closest medical visit was selected to ascertain the diagnoses. If the 60 days window fell outside the study period, then patients were excluded for not having sufficient data for complete analysis. For patients that received no AAP therapy in

2015, the diagnoses from the most recent medical provider visits in 2015 were used. Per medical visit, only the first ten fields were used because these captured 95% of available diagnosis information in the database.

Among pediatric patients with mental health diagnoses, we determined the frequency and percentage of patients with AAP use compared to those without AAP therapy in 2015. Differences in patient characteristics and prescription claim information between the two groups were determined using the Chi-Square test. Prevalence was calculated as the number of pediatric patients with mental health diagnoses receiving a pharmacy dispensing for at least one AAP medication divided by the total number of children with a mental health diagnosis of interest during 2015. A logistic regression model was used to determine the factors associated with the use of AAP medication therapy. All pairwise interactions between covariates were tested and none were found to be statistically significant. No interaction terms were included in the final model due to lack of statistical significance. Collinearity between independent variables was tested using Variance Inflation Factors (VIF) test and no significant collinearity was found. No adjustments for collinearity were made in the final model. We evaluated the associations in both unadjusted and adjusted models that also included gender, age, geographical region, concomitant medication uses and provider specialty. Covariates with a P value < 0.20 in the univariate model were included in the final adjusted model, with primary mental health diagnosis forced into the model due to known clinical relevance for AAP therapy use.

The direct cost burden of medication therapy for pediatric patients with mental health conditions was analyzed as a percentage of the total spend for pediatric patients

with mental health disorders of interest over the study period. To assess the 12-month average cost for AAP medication therapy per patient, the PMPM variable was chosen, to represent the most accurate average cost per plan member from the payer perspective. A generalized linear model was used to evaluate patient or prescription level variables that were associated with PMPM spending. Each patient included had least one paid claim for an AAP during 2015. Patients with multiple claims in a given month had all claim costs for AAP medications totaled for each month, then the total days exposed per patient were determined. Patients with multiple claims for AAP medications were aggregated to one PMPM cost per month for analysis. PMPM was calculated as the total cost per month divided by the total days exposed per month multiplied by thirty days. Total days exposed to AAP therapy was determined by summing up the days' supply of all paid claims in a given month per patient. The PMPM variable was assessed for normality using a histogram and measures of skew. The distribution appeared to be non-normal, with a skewness 1.11 indicating a long right skewed tail and kurtosis value 2.1.[23–25] A modified park test was performed to determine the distribution for the cost model.[25,26] Test statistics revealed coefficient near two (lambda=1.76), which provides evidence the outcome to be modeled as a gamma distribution. A log-link with the gamma distribution fit better than other link options (log-link AIC=69,436, identity link AIC=69,448, logit link AIC=120,939) and was the model employed in the final analysis.[26] All statistical tests were two-sided and performed at a 0.05 significance level and conducted using SAS Enterprise Guide Version 7.1 (Cary, North Carolina, USA).

1.4 Results

Table 1 provides overall mental health diagnoses of the original pediatric cohort from 2015 prior to exclusion criteria, regardless of AAP medication therapy presence. In the original patient database of pediatric patients in 2015, 87,503 pediatric patients had a mental health diagnosis of interest in a medical recording during 2015. Before exclusion criteria were applied, 23% (20,732) of patients had a diagnosis of Disruptive or Aggressive Behavior (DAB) Disorders, 14% (11,870) had a diagnosis of Anxiety Disorders and 13% (11,611) had a diagnosis of Developmental Disorders. Of the entire original pediatric cohort, 0.3% (210) of patients had a diagnosis of six mental health diagnostic categories documented at a medical visit claim during 2015. This population included 71,630 children with mental health diagnoses of interest recorded in their medical claims in 2015 and continuous eligibility for all of 2015. The mean age of the entire study population was 11.7 (standard deviation [SD]=4.1) years. Of the entire population, 63% were male (P value <0.001). A total of 4,833 (6.8%; 95% CI=6.6, 6.9) patients received at least one paid claim for an AAP medication in 2015. The prevalence of atypical antipsychotic medication use was 67.5 per 1000 pediatric patients with mental health diagnosis of interest.

We found that 1,378 (29%) of the 4,833 pediatric patients receiving AAP medication therapy did not have a psychiatric diagnosis of interest at the associated medical appointment ($\pm$ 60 days around AAP claim) during the study period (**Table 2)**. In patients receiving an AAP paid claim, across the entire study period, the leading diagnostic category present was 1336 children with Mood disorders (28%). Children

with Disruptive or Aggressive Behavior (DAB) Disorders were next frequent with 842 (17%) children.

Several patient characteristics varied between those who received AAP medications and those who did not (**Table 2).** Patients receiving AAP medications were on average 2.1 years older than those receiving no AAP medication therapy. Adolescents (age 13-17 years) received the most paid claims for AAP therapy (69%) compared to children aged 6-12 years (30%) and 2-5 years (1%) (P value<0.001). The distribution of region was comparable between the two groups. Concomitant medication therapy with stimulant, antiepileptic, antidepressant and anxiolytic medications was significantly different between the two groups. Children receiving AAP medication therapy had increased rates of concomitant use of stimulants (9% vs 8%, P value<0.001)), antiepileptics (2% vs. 1%, P value<0.001), antidepressants (7% vs. 4%, P value <0.001)) and anxiolytics (4% vs. 1%, P value<0.001) when compared to children receiving no AAP medication therapy. Category of mental health diagnosis of interest was significantly different between the patients receiving AAP medication therapy and those that did not, with most patients in both groups having no associated mental health diagnosis at most recent medical visit or associated with AAP medication paid claim. Significantly more pediatric patients reported an anxiety disorder as primary mental health diagnosis in the AAP medication group than in the no AAP therapy group (12% vs. 6%, P value <0.001). Similarly, in pediatric patients receiving AAP therapy, mood disorders were reported as the primary mental health diagnosis (28% vs. 3%, P value <0.001) in significantly more cases, than in patients with no AAP therapy. The prevalence of AAP use compared across patient

characteristics is displayed below in **Figure 2**. This figure presents the prevalence of characteristics in children with mental health diagnoses of interest, prescribed AAP medication therapy among the entire study population of children included in the analysis (N =71,630). The number of patients from the study cohort with that given characteristic that are included in the denominator, are listed at the top of the column. All patients included in this figure had a mental health diagnosis of interest during 2015, continuous eligibility during the study period and a medical visit associated with a paid AAP claim or medical visit available for analysis.

Results from the unadjusted and adjusted logistic regression models are displayed in **Table 3**. In the unadjusted model, several patient characteristics were found to have significant differences in AAP prescribing among children with mental health diagnoses of interest. Female children had 20% increased odds of being prescribed AAPs than male children (odds ratio (OR) = 1.2; 95% confidence interval (CI) = 1.1, 1.2). Children of an older age were 20% more likely (OR=1.2; 95% CI=1.1, 1.2) to have a paid claim for AAPs. In the unadjusted model, children aged 6-12 years of age were 9.8 times more likely to be prescribed AAPs than children aged 2-5 years (OR=9.8; 95% CI=7.2, 13). Adolescents (ages 13-17) were 19 times more likely to have a paid claim for AAP therapy (OR=19.0; 95% CI=14.0, 26.0). Patients in the Midwest (OR=1.3; 95% CI=1.1, 1.4) and the South (OR=1.2; CI=1.1, 1.3) regions of the US were significantly more likely to receive AAP therapy, compared to subjects in the Northeast region. Patients with a documented Mood Disorder diagnosis were 5 times more likely to receive an AAP paid claim (OR=23.0; CI=4.6, 5.8), compared to those with psychotic disorders as the primary mental health

diagnosis. Patients with a documented mental health disorder in the "Other" category were 2.8 times more likely to be prescribed AAPs (OR=2.8; 95% CI=2.2, 3.5) compared to patients with a Psychotic Disorder documented. Patients with documented Anxiety Disorder were 20% increased odds of having an AAP paid claim (OR=1.2; 95% CI=1.1, 1.4) compared to children with documented psychotic disorders. If the patient's primary mental health diagnosis was for an DAB or Developmental Disorder, the pediatric patient had 30% increased odds of having an AAP paid claim (OR=1.3; 95% CI=1.1, 1.4), (OR=1.3; 95% CI=1.1, 1.6), compared to patients with a Psychotic Disorder documented.

Concomitant use of several relevant medication classes was evaluated for significance as predictors of receiving AAP medication therapy. In the unadjusted model, a paid claim for stimulant medication during 2015 indicated 20% increased odds of receiving AAP medication therapy (OR=1.2; 95% CI=1.1, 1.3). Concomitant use of antidepressants in 2015 predicted 60% increased odds of being prescribed AAP therapy (OR=1.6; 95% CI=1.4, 1.8). The use of antiepileptic medications in pediatric patients with mental health diagnoses predicted they were 4 times more likely to be prescribed an AAP medication (OR=4.0; 95% CI=3.2, 5.1). Patients with a paid claim for anxiolytic medication in 2015 were 2.8 times more likely to also receive an AAP medication (OR=2.8; 95% CI=2.4, 3.3) during study period. Provider specialty was also evaluated as a clinically relevant predictor of AAP medication use. Patients seen by a specialty provider (psychiatrist) had 5 times the increased odds of receiving an AAP medication compared to patients seen by a primary care provider (OR=5.0; 95% CI=4.5, 5.3). Similarly, pediatric patients with a mental health disorder seen by a

specialist had 13 times increased odds of receiving a paid claim for AAP therapy than patients seen by a non-physician mental health provider (OR=12.5; 95% CI=11.0, 14.0).

In the adjusted final model, female pediatric patients with mental health diagnoses of interest had 11% decreased odds (adjusted odds ratio (aOR)=0.89; 95% CI=0.83, 0.95) of having a paid claim for AAP medication therapy. In the final model, age was a significant predictor in the prescribing of AAP medication, with a one-year increase in age having an associated 10% increased odds of receiving a paid claim for an AAP (aOR=1.1; 95%CI=1.0, 1.1). After adjusting for other patient and clinical characteristics, children 6-12 years of age were 10 times more likely than younger children to be prescribed AAP medication therapy, (aOR=10.3; 95% CI=7.5, 14.1). Adolescent patients with a mental health diagnosis of interest were 16 times more likely to receive AAP medication therapy, when compared to children ages 2-5 years (aOR=16.7; 95% CI= 12.2, 22.9). In the final model, patients with a mood disorder were 2 times more likely to receive an AAP medication, compared to patients with a documented Psychotic Disorder (aOR=2.2; 95% CI=2.0, 2.6). Also, patients with documented Developmental (aOR=1.4; 95% CI=1.2, 1.7) had a 40% increased odds and patients with documented Other Disorders (aOR=1.6; 95% CI=1.2, 2.0) had 60% increased odds of receiving an AAP, compared to pediatric patients with documented Psychotic Disorders. Patients with a documented Anxiety Disorder had 37% decreased odds of receiving a paid claim for an AAP (aOR=0.63; 95% CI=0.55, 0.73) compared to patients with a documented Psychotic Disorder. In the adjusted model, patients with DAB Disorders had 29% decreased odds of having a paid claim

for an AAP (aOR=0.71; 95% CI=0.62, 0.82) compared to patients with a documented Psychotic Disorder. Finally, adjusting for other covariates, patients with no mental health disorder documented had 80% decreased odds of receiving a paid claim for an AAP (aOR=0.20; 95% CI=0.18, 0.23) compared to a documented Psychotic Disorder. Once adjusting for other covariates, pediatric patients with concomitant use of stimulant medications had 48% decreased odds of being prescribed AAP medication therapy (aOR=0.52; 95% CI=0.46, 0.58) in the final adjusted model. Similarly, patients with concomitant antidepressant use had 55% decreased odds of being prescribed AAP medications (aOR=0.45; 95% CI=0.39, 0.50). After adjusting for other covariates, the use of antiepileptic medications during 2015 predicted 50% increased odds of having a paid claim for AAP medication during the study period (aOR=1.5; 95% CI=1.2, 2.0). After adjusting for other covariates, pediatric patients with mental health disorders demonstrating anxiolytic use during the study period no longer had a significant effect on likelihood of receiving an AAP paid claims. Overall, demonstrated use of other psychotropic medication classes were significant predictors in the prescribing or not prescribing of AAP medication therapy. Of note, in the adjusted model, several variable associations changed directions when adjusted for other covariates. In the adjusted model, female gender, use of stimulants and use of antidepressants were associated with a reduced risk of AAP use, which was a change from an increased risk in their respective univariate models. By adding one variable to the model at time, we determined that these estimates changed direction after adjustment for age group. This indicates that the age group of the patient at time

of paid claim demonstrates some unmeasured confounding affecting the other covariates, that is independent of the direct interaction of the variables.

In the adjusted model, prescriber specialty was a significant predictor for AAP prescribing. Patients seen by a specialty provider had 2.5 times the increased odds of receiving a paid claim for AAP medication than patients seen by a primary care provider (aOR=2.5; 95% CI=2.3, 2.7). Patients seen by a specialist had 5 times the increased odds of receiving an AAP medication paid claim than children seen by a non-physician mental health professional (psychiatric nurse practitioner, physician assistant) (aOR= 5.0; 95% CI=4.5, 5.6). After adjusting for other patient characteristics, region was no longer a statistically significant predictor of AAP prescribing in the final model.

Cost Model for AAP Medications Use in Pediatric Patients

The total 2015 annual expenditure for AAP prescriptions in the pediatric population with mental health conditions was estimated at $12,487,066.71, in a large US private payer. This expenditure represented 35,311 paid claims for AAP medication therapy and 5,253 unique patients over the study period. This corresponded to an average spending of $1.04 million per month for AAP medication in pediatric patients with mental health conditions for the private insurance plan. The average and median per-member-per-month (PMPM) costs of AAP medication therapy was $311.58 (standard deviation [SD]=$327.16) and $169.06 (quartile 1 to quartile 3 [Q1,Q3] = $$19.62, $556.32), respectively. The 12-month average AAP medication cost per patient was $3738.96 (SD=$3925.92).

The median cost per paid claim in 2015 is displayed by medication in **Table 4**. Generic risperidone was the most commonly prescribed atypical antipsychotic medication (25%) followed by generic aripiprazole (22%) and name brand Abilify® (20.0%). The median cost of a paid claim for generic risperidone was $21.04 (Q1=$12.39, Q3=$31.55) per claim, representing almost the lowest cost per claim of all the AAP agents. The median cost of a paid claim for name brand aripiprazole was $978.86 (Q1=$978.86, Q3=$978.86) per claim, representing the highest cost per paid claim compared with all other available AAP agents.

The cost data was then analyzed using a generalized linear model (GLM) to determine any covariates that were a significant predictor of PMPM costs. **Table 5** presents the results of the log-gamma regression of the per-member per-month (PMPM) costs during the 12-month study period adjusted for patient demographics. Using a gamma regression model with an identity link function, age group, gender, mental health diagnostic category and provider specialty were statistically significant predictors of total annual expenditure for AAP medication therapy. Children aged 6-12 years had overall adjusted mean spending for AAPs that was $90.22 (95% CI=-$14.40, $155.45) higher than patients aged 2-5 years. This corresponds with a PMPM that was 50% (adjusted odds ratio (aOR)=1.5; 95% CI=0.97, 2.1) higher than children aged 2-5 years. Adolescents aged 13-17 years had overall adjusted mean spending for AAPs that was $116.62 (95% CI=$12.48, $180.63) higher than patients aged 2-5 years. This corresponds with PMPM costs that were 60% higher (aOR=1.6, 95% CI=1.1; 2.3) than children aged 2-5 years. Older patients often require higher doses of medication therapy or more frequent administration and these dosing regimens often

cost more. Female subjects had overall adjusted mean spending for AAPs that was $30.69 (95% CI= $7.36, $54.67) higher than male subjects. Female gender represented a PMPM cost that was 10% (aOR=1.1;95% CI=1.0, 1.2) higher than male subjects. The adjusted difference in mean spending for AAPs between subjects from different US regions was only significant comparing patients located in the South to the Northeast. Pediatric patients located in the South region of the US had overall adjusted mean spending on AAPs that was $38.89 (95% CI= $0.78, $73.93) higher than patients in the Northeast US. This represented overall PMPM costs that were 10% (aOR=1.1; 95%CI=1.0, 1.3) higher than children located in the Northeast region.

1.5 Discussion

In privately-insured children and adolescents, the prevalence of atypical antipsychotic medication therapy was 67.5 per 1000 patients (6.75%; 95% CI=6.6%, 6.9%) with a mental health diagnosis of interest present in 2015. In our study, gender was associated with differences in prescribing AAP therapy, which aligned with previous research in private- and publicly-insured children.[11,15,27] These previous studies found that patients of male gender had increased odds of receiving AAP medication therapy. Our study found similar increased odds in male patients. The children receiving AAP therapy were significantly older (13.6 vs. 11.8 years) and older age was an important predictor of a patient receiving AAP therapy.

In our analysis, the 2015 prevalence of atypical antipsychotic use was higher than determined in previously studied research of privately-insured children and adolescents across the US.[15] Previous studies have found that publicly-insured youth have consistently lower AAP prevalence to that found in our study, at 1.9% in 2005

and 1.7% in 2010.[11] Since 2005, the AAP medication therapy options have doubled, as AAP medication approvals have increased dramatically in the US. Furthermore, previous studies in publicly insured population included all children, not only children with mental health diagnoses present in medical records for their analysis. [8,11,19] Including all children in the analysis could increase the population that is considered at risk for AAP medication use, leading to a possible underestimation of the proportion of study participants that received AAP medication therapy. These differences in study population could explain some of these observed differences. Private insurance payers have different formulary practices than public payer systems. Formulary approval and reimbursement practices could change the utilization and diversity of a medication class and represent the difference between our study and the results from studies analyzing publicly funded patients. Combination therapy with multiple AAP medications or therapy switching was not examined in this analysis. Combination therapy or medication switching is common in mental health treatment recommendations and represents a future direction that should be explored. Future research should also examine overlapping medication classes with AAP therapy or switching therapy to AAP as a significant factor in AAP medication use in pediatric patient with mental health diagnoses.

Our study found that 29% of pediatric patients treated with an atypical antipsychotic have no mental health diagnosis in an associated claim for medical visit within 60 days of the paid prescription claim. **Figure 2** shows the overall distribution of mental health diagnosis in the pediatric patients that supported their inclusion in the original study cohort. Among pediatric patients with a mental health diagnosis

present, Developmental disorders (13%), Anxiety Disorders (14%) and Disruptive or Aggressive Behavior (DAB) disorders (23%) were the leading diagnoses associated with AAP medication therapy. In the original database of pediatric patients with mental health diagnoses during calendar year 2015 (Figure 1), 0.3% (210 patients) of pediatric patients had all six mental health diagnostic categories present at a medical visit during the study period. The absences of mental health diagnoses in the associated medical visit around the paid claim for AAP medication therapy could be explained by the lack of coding in the medical visit for continued medication treatment by the visit provider. Lohr et al. analyzed AAP use in Kentucky Medicaid patients and found that 72% of subjects analyzed were missing a diagnostic code associated with paid claim and this issue was only resolved after 2006 once Medicaid rules required an appropriate code before paid claim would be fulfilled.[10] Other previous trend studies in public- and privately-insured pediatric patients categorized missing diagnoses as "other" or excluded patients with no diagnosis available completely.[8,28] The rate of missing mental health diagnosis found in our study was lower than previously published literature. A 2015 study found no mental health diagnosis present at an associated medication visit in 60% of pediatric patients treated with AAPs.[12] Previous research also found that in 75% of cases, all children with MH diagnoses of interest treated with AAP medications has multiple psychiatric diagnoses.[15] Similarly, we found that in the original cohort, 44% of children had multiple mental health diagnoses present during the study period.

We found that specialty providers were the leading prescribers (41%) associated with paid claims for AAP therapy. Olfson et al.[12] noted that specialists

were the provider associated with AAP therapy in approximately 69% of paid claims in 2010. The differences in associated prescriber characteristics could be related to coding differences between private insurers and their claims process. Prescribing physician requirements can differ between private and public payers. Formulary requirements for certain payers require specialist prescribing for certain populations or medication classes that may not be required of practices in our privatively-insured population.

Concomitant medication therapy was a significant predictor of a pediatric patient receiving AAP therapy. Use of stimulant and anxiolytic medications reduced the likelihood of a patient receiving a fill of an AAP medication in 2015. Sikirica et al. previously explored ADHD patients receiving stimulant therapy and the likelihood of receiving AAP medication therapy.[12] Their study identified 8.3% of stimulant treated children receiving an AAP in the 12-month study period.[13] Our study found a similar rate of concomitant use of stimulants with AAP medication therapy. Olfson et al. explored the overall rate of concomitant use of anxiolytics and antidepressants with antipsychotic medication treatment.[9] Their study found much higher rates of antidepressant use (33.7%) and anxiolytic use (9.7%) in patients on AAP medication therapy, than was identified in our current study. This previous analysis was based on medical office visits documenting the medication of interest and not based on individual paid claims for the relevant medication class. This methodology could explain the increased rates of concomitant use found in their study compared to results presented here. In this previous study, it is unclear if the patient was receiving the medication or the provider only discussed the medication therapy during the office

visit. The use of antidepressant and stimulant medications when analyzed alone, seemed to be a significant predictor of AAP use. However, in the adjusted model concomitant use of these two classes of medications showed lower odds of predicting use of AAP medications. This might indicate that some confounding is present and the other significant variables (age, gender, region, mental health diagnosis, provider specialty) are confounders for concomitant use of antidepressants and stimulants and their effect on AAP prescribing.

Our study is one of the first to describe the 12-month average medication cost of AAP therapy in the privately-insured pediatric patient population. The total 12-month cost burden for 35,311 paid claims for AAP medication therapy was $12.5 million in 2015, representing 5,253 unique patients over the study period. The average per-member per-month (PMPM) cost for the entire study population was $311.58. This study found that aripiprazole (name brand and generic) was the most commonly prescribed AAP medication in privately insured youth, with 44% of paid claims. Olfson and collegues[12] described risperidone as the most common AAP agent used in privately insured youth in 2010. This difference in choice of agents is most likely related to the pediatric indications granted by the FDA for aripiprazole and its dosage forms in 2009 and the availability of a generic formulation in 2015.[29]

In 2015, we estimated that $12.5 million was spent on atypical antipsychotic medication therapy among this privately-insured pediatric population. In a similar study of children enrolled in Florida Medicaid, researchers found that in Fiscal Year 2005 (FY2005) , $151 million was spent on AAP medication therapy. [30] This drastic difference compared to our study findings can most likely be explained by the peak

utilization that was seen for AAP medication therapy in 2005 and lack of generic formulations available on the US market. Their study adjusted dollar spending amounts to align with the medical care component of the consumer price index for the region during the FY2005.[30] Our study took direct costs paid by the payer from prescription claims data. Most of the available cost research focuses on publicly-insured children and our study is one of the first to explore the direct medication costs to a private, national payer. In 2004, the FDA issued advisory committee findings that recommended more conservative use of atypical antipsychotics in children and Pamer et. al examined a corresponding decrease in AAP medication use.[28,31] This research group observed a decline in AAP medication prescribing, but this decline did not achieve statistical significance nor did they examine overall spending or changes in average cost.[31] In 2016, Wang et al. performed a time-trend analysis examining AAP medication prescribing before and after supplemental pediatric indications being granted by the FDA. They found no statistically significant changes in AAP medication prescribing with the additional approved pediatric indications.[28] These studies provide limited evidence that the FDA medication safety alert and other prescribing decisions might have altered antipsychotic medication prescribing. Future studies that compare time trend utilization data against major clinical guideline recommendations or new FDA indications for AAP medications in larger population could provide stronger evidence of these influence of these administrative actions on prescribing habits.

1.6 Limitations

The analysis was conducted using insurance claims data; therefore, limited clinical information was available for patients that were included in the final analyses. Clinical information from claims data is limited to available medical documentation presented in the visit record as recorded by the documenting provider. Physical assessment information about the patient and laboratory information was limited and not included in the analysis. A mental health diagnosis of interest was not present in the medical visits associated with index AAP paid claim in 29% of the patients receiving AAP medication therapy. Prior studies have demonstrated the validity of ICD-9 codes for accurately representing a mental health diagnosis in the medical record.[21,22] However, other prevalence studies have found a similar rate of an absence mental health diagnosis associated with medication use. The window around the index claim for AAP therapy was expanded from +/- 30 days to +/- 60 days; however, this did not improve the capturing of diagnostic information from medical visits. This rate of incomplete mental health diagnosis documentation could make it difficult to interpret the proper clinical indication for AAP medication use. Miscoding in the practical setting could lead to variations in the results and make analysis by clinical disorder difficult to interpret. Furthermore, the observed study period may not have captured the incident mental health event for a patient, so we could be observing patients well after their initial diagnosis. The cost portion of this analysis only discussed the direct medication costs to the private healthcare plan and did not address other economic costs, such as utilization of other treatment resources, cost to caregivers and parents and lost school or work time. Finally, the prevalence and cost analyses both use the paid claim as the basis for evaluation. For concomitant

medication therapy and its significance as a predictive variable, only paid claims during study period was examined.

1.7 Conclusion

The prevalence of using atypical antipsychotic medications in pediatric patients with mental health disorders is significant in the privately insured population. The prevalence in the privately insured population was 6.75% (CI=6.6%, 6.9%) or 67.4 per 1000 children with mental health disorders in 2015. The total yearly spending by the private payer for atypical antipsychotic medications in pediatric patients was $12.5 million dollars in 2015. This represented an average per-member per-month cost of $311.58 for atypical antipsychotic medication therapy in pediatric patients with mental health diagnoses of interest. Individual costs vary greatly by AAP medication and further costs studies are warranted to determine the potential economic impact to a specific private payer. This study represents the most recent calendar year available for analysis.

Overlap or switching of therapy to or from AAP medication therapy was not examined but could be evaluated in future studies. Combination therapy with other AAP medications or other psychotropic medications is a common clinical practice and the possible impact on AAP utilization should be examined. Validation studies of the ICD-9 codes use for mental health diagnoses in the outpatient medical record warrant additional validation studies. Validation studies available are specific for claims data research in adults with mental health disorders. Providers may believe a stigma exists in documenting mental health conditions in the pediatric population and diagnostic code analysis may not be as reliable. These studies could provide additional insight in

to the use of diagnostic codes and the predictive value in mental health epidemiologic studies. Further studies about updated utilization and spending are needed to examine how more recent FDA decisions and safety alerts may have altered AAP prescribing and medication class utilization.

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Figure 1: **Selection of Patients for Analyses of Prevalence of Atypical Antipsychotic Medication Utilization and Cost of Atypical Antipsychotic Medication Therapy in Pediatric Patients (2 to 17 years) (2015).**
(Optum Clinformatics ® Data Mart; OPTUMInsight, Eden Prairie, MN)

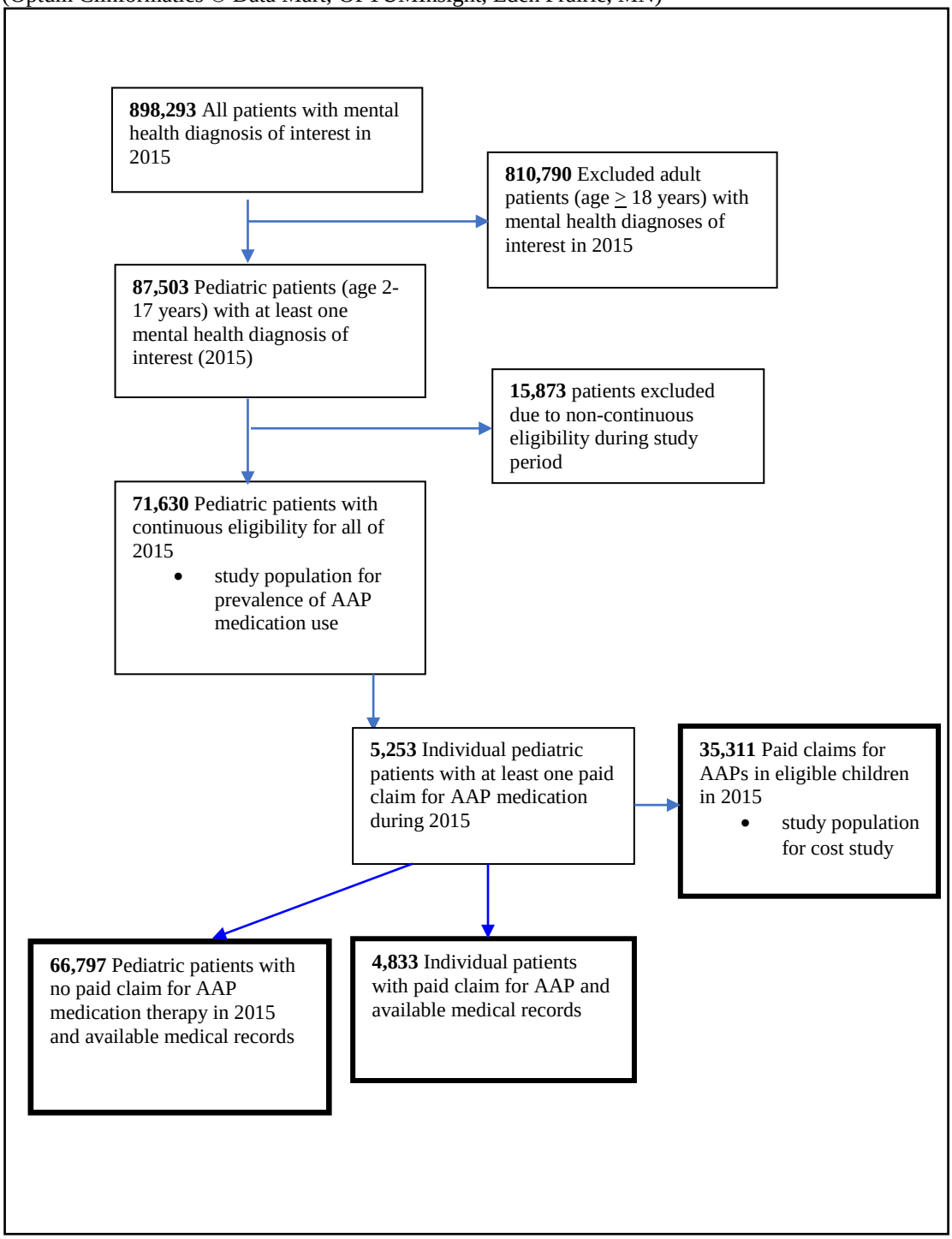


Table 1. Distribution of Mental Health Diagnoses in all Pediatric Patients (2 to17 years) Available in Study Cohort during 2015. *
(Optum Clinformatics ® Data Mart; OPTUMInsight, Eden Prairie, MN)

Primary MH Diagnosis of Interest	***All children (N, %) with Mental Health Diagnosis (N= 87,503)***
Disruptive or Aggressive Behavior Disorder	20732 (23)
Anxiety Disorder	11870 (14)
Developmental Disorder	11611 (13)
Three MH Disorders present	10192 (12)
Anxiety and Secondary MH Disorder	10187 (12)
Developmental Disorder with Secondary MH Disorder	6846 (8)
Disruptive and Aggressive Behavior with Secondary MH Disorder	2935 (3)
Mood and secondary MH Disorder	4087 (5)
Four MH Disorders Present	2929 (3)
Mood Disorder	2798 (3)
Psychotic Disorder	1315 (2)
Other Mental Health Disorder	1181 (1)
Five Mental Health Disorders Present	454 (0.5)
Six Mental Health Disorders Present	210 (0.3)
Psychotic Disorder with Secondary MH Disorder	156(0.2)

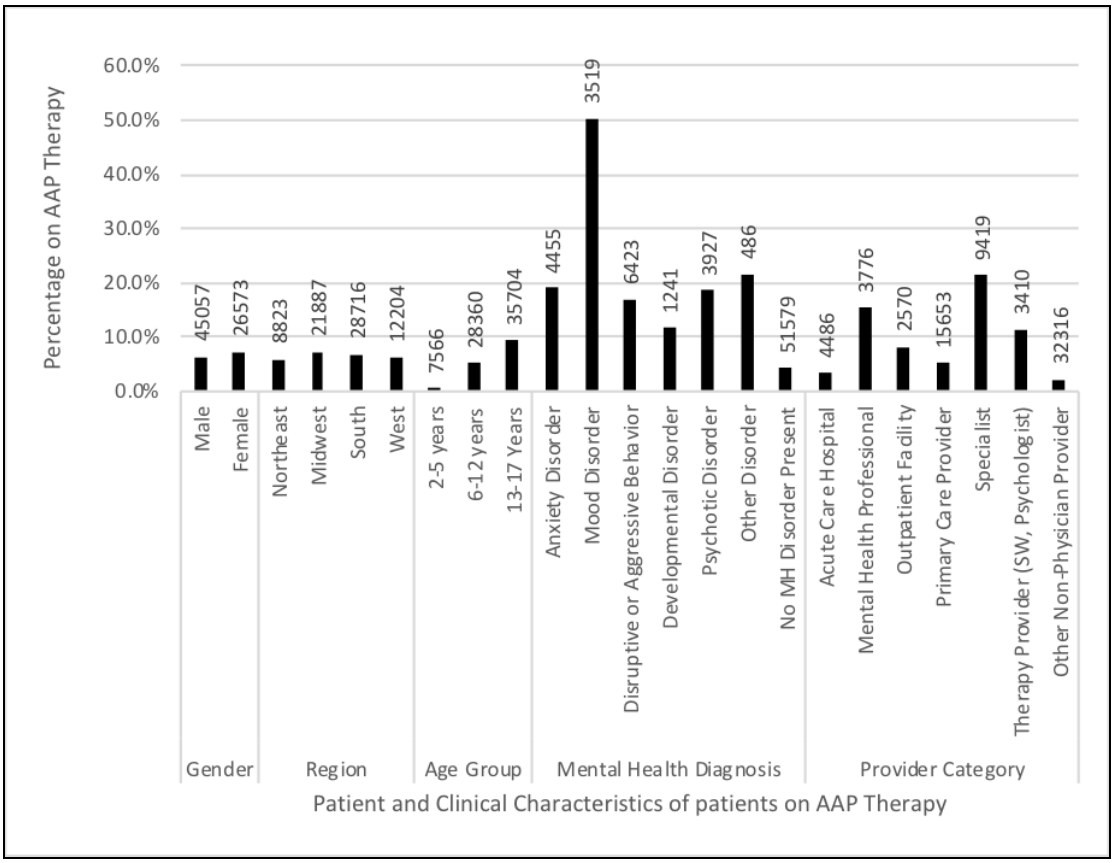
**No exclusion criteria applied. All pediatric patients with at least one MH diagnosis included in original cohort.*

Table 2. Demographic and Clinical Characteristics of Privately-Insured, US Children (2 to 17 years) with Mental Health Diagnoses of Interest during 2015 by AAP status (N =71,630)
(Optum Clinformatics ® Data Mart; OptumInsight, Eden Prairie, MN)

	Children with an AAP paid claim (N=4,833)	***Children with no AAP Treatment (N=66,797)***	***P value****
Patient Age, Years, Mean± SD	13.7 (3.0)	11.6 (4.2)	<0.001
Age Group (years) n(%)			<0.001
2-5 years (pre-school)	41 (0.9)	7525 (11.3)	
6-12 years	1439 (29.8)	26921 (37.6)	
13-17 years (adolescents)	3353 (69.4)	32351 (48.4)	
Patient Gender, n (%)			<0.001
Male	2891 (59.8)	42166 (63.1)	
Female	1942 (40.2)	24631(36.9)	
Patient Region, n (%)			<0.001
Northeast	523 (10.8)	8300 (12.4)	
Midwest	1609 (33.3)	20278 (30.4)	
South	1953 (40.4)	26763 (40.1)	
West	748 (15.5)	11456 (17.2)	
MH Diagnosis Category, n (%)			<0.001
Anxiety Disorder	571 (11.8)	3884 (5.8)	
Mood Disorders	1336 (27.6)	2183 (3.3)	
Disruptive or Aggressive Behavior Disorders	842 (17.4)	5581 (8.4)	
Developmental Disorders	169 (3.5)	1072 (1.6)	
Psychotic Disorders	417 (8.6)	3510 (5.3)	
Other MH Disorders	120 (2.5)	366 (0.6)	
No MH Diagnosis Present	1378 (28.5)	50201 (75)	
Use of Antiepileptics, n (%)			<0.001
Yes	92 (1.9)	319 (0.5)	
No	4741 (98.1)	66478 (99.5)	
Use of Antidepressants, n (%)			<0.001
Y	312 (6.5)	2817 (4.2)	
N	4521 (93.5)	63980 (95.8)	
Use of Anxiolytics, n (%)			<0.001
Y	181 (3.8)	922 (1.4)	
N	4652 (96.2)	65875 (98.6)	
Use of Stimulants, n (%)			<0.001
Y	444 (9.2)	5174 (7.8)	
N	4389 (90.8)	61623 (92.2)	
Provider Specialty, n (%)			<0.001
Acute Care Hospital	154 (3.2)	4332 (6.5)	
Mental Health Professional (non-physician)	578 (11.9)	3198 (4.8)	
Outpatient Facility	209 (4.3)	2361 (3.5)	
Primary Care Provider	810 (16.8)	14843(22.2)	
Specialist	2003 (41.4)	7416 (11.1)	
Therapy Provider (Social Worker, Psychologist)	384 (8.0)	3026 (4.5)	
Other Non-Physician Provider	695 (14.4)	31621 (47.3)	

**comparisons in baseline characteristics between children receiving AAPs and those that did not during study period using Chi-Squared tests or t-tests as appropriate.*

Figure 2. Prevalence of Privately-Insured Children (2 to 17 years) with Mental Health Disorders in the US Receiving AAP Medication Therapy in 2015 by Patient and Clinical Characteristics (n =71,630).*



**Number of children present in study cohort with given covariate listed at top of column (denominator)*

Table 3. Unadjusted and Adjusted Odds Ratios (ORs) with 95% Confidence Intervals (CIs) Based on a Logistic Regression Model for Patient and Clinical Factors Associated with Atypical Antipsychotic Medication Prescribing among US Privately-Insured Pediatric Patients (2 to 17 years) in 2015 (N=4,833).

	Unadjusted		***Adjusted****	
	ORs (95% CIs)	**P value**	**ORs (95% CIs)**	**P value**
Patient Age	1.2 (1.1, 1.2)	<0.001	1.1 (1.1, 1.1)	<0.001
Age Group (years)		<0.001		<0.001
2-5 years	**Reference**			
6-12 years	9.80 (7.20, 13.0)		10.3 (7.5, 14.1)	
13-17 years (adolescents)	19.0 (14.0, 26.0)		16.7 (12.2, 22.9)	
Gender		<0.001		<0.001
Female	1.20 (1.10, 1.2)		0.89 (0.83, 0.95)	
Male	**Reference**			
Region		<0.001		0.075
Midwest	1.3 (1.1, 1.4)		1.1 (1.0, 1.3)	
South	1.2 (1.1, 1.3)		1.1 (1.0, 1.3)	
West	1.0 (0.9, 1.2)		1.0 (0.9, 1.1)	
Northeast	**Reference**			
Mental Health Diagnosis		<0.001		<0.001
Anxiety Disorders	1.2 (1.1, 1.4)		0.63 (0.55, 0.73)	
Mood Disorders	5.2 (4.6, 5.8)		2.2 (2.0, 2.6)	
Disruptive or Aggressive Behavior Disorders (DAB)	1.3 (1.1, 1.4)		0.71 (0.62, 0.82)	
Developmental Disorders	1.3 (1.1, 1.6)		1.4 (1.2, 1.7)	
Psychotic Disorders	**Reference**			
Other MH Disorders	2.8 (2.2, 3.5)		1.6 (1.2, 2.0)	
No MH Diagnosis Present	0.23 (0.21, 0.26)		0.20 (0.18, 0.23)	
Provider Category		<0.001		<0.001
Acute Care Hospital	0.13 (0.11, 0.16)		0.19 (0.16, 0.23)	
Mental Health Professional (non-physician)	0.67 (0.61, 0.74)		0.42 (0.38, 0.47)	
Outpatient Facility	0.33 (0.28, 0.38)		0.68 (0.58, 0.81)	
Primary Care Provider	0.20 (0.19, 0.22)		0.40 (0.36, 0.43)	
Specialty Provider	**Reference**			
Therapy Provider (Social Worker, Psychologist)	0.47 (0.42, 0.53)		0.41 (0.4, 0.5)	
Other non-physician provider	0.08 (0.07, 0.09)		0.20 (0.2, 0.2)	
Use of Stimulants				
Yes	1.2 (1.1, 1.3)	0.003	0.52 (0.5, 0.6)	<0.001
No	**Reference**			
Use of Anxiolytics				
Yes	2.8 (2.4, 3.3)	<0.001	1.2 (1.0, 1.4)	0.12
No	**Reference**			
Use of Antidepressants				
Yes	1.6 (1.4, 1.8)	<0.001	0.45 (0.4, 0.5)	<0.001
No	**Reference**			
Use of Antiepileptics				
Yes	4.0 (3.2, 5.1)	<0.001	1.5 (1.2, 2.0)	0.002
No	**Reference**			

***adjusted for the following covariates at baseline: age group, gender, US region, Mental Health Diagnosis, Provider Category, Concomitant use of stimulants, anxiolytics, antidepressants and antiepileptics.*

Table 4. Median Costs (US Dollars) per paid claim and Total Spending for Atypical Antipsychotic Therapy for Privately-Insured, US Children (2 to 17 years) with Mental Health Disorders during 2015 (N=5,253 patients with 35,311 paid claims).

Medication Name	***Number of Paid Claims (%)***	***Median (Q1, Q3) ****	***Total Spending in 2015, $ (% of yearly total)***
Abilify (name brand)	7,094 (20)	978.86 (978.86, 978.86)	5,621,429.06 (45)
Aripiprazole (generic)	7,664 (22)	531.23 (519.79, 668.89)	4,614,370.15 (37)
Clozapine	307 (0.9)	46.57 (23.93, 121.66)	24,095.85 (0.2)
Fanapt	84 (0.2)	635.67 (317.84, 635.67)	41,647.13 (0.3)
Geodon (name brand)	34 (0.1)	635.94 (476.96, 771.74)	19,814.11 (0.2)
Invega (name brand)	406 (1.1)	665.48 (665.48, 998.22)	334,147.95 (2.7)
Latuda	1123 (3.2)	638.68 (638.68, 638.68)	758,792.30 (6.1)
Olanzapine (generic)	1624 (4.6)	23.89 (19.60, 33.16)	48,637.88 (0.4)
Olanzapine ODT	134 (0.4)	211.74 (112.06, 420.31)	38,568.81 (0.3)
Palperidone ER	79 (0.2)	641.99 (610.96, 800.97)	55,694.41 (0.5)
Quetiapine Fumarate (generic)	5343 (15)	19.50 (9.55, 32.37)	148,893.23 (1.2)
Risperdal (name brand)	42 (0.1)	613.91 (511.59, 1367.94)	31,340.74 (0.3)
Risperdal M-TAB	11 (0.03)	704.93 (704.93, 704.93)	7,754.23 (0.1)
Risperidone (generic)	8814 (25)	21.04 (12.39, 31.55)	241,841.20 (1.9)
Risperidone ODT (generic)	229 (0.7)	182.15 (95.89, 335.34)	51,671.77 (0.4)
Saphris	309 (0.9)	345.69 (345.69, 691.37)	155,686.00 (1.3)
Ziprasidone HCL (generic)	2010 (5.7)	96.92 (44.55, 197.64)	290,796.45 (2.3)
Zyprexa (brand name)	4 (0.01)	471.36 (471.36, 471.36)	1885.44 (0.02)
		Total Yearly Spending for AAP Medication Therapy	**$12,487,066.71**

**Quartile 1 (Q1) and Quartile 3(Q3) representing first and third quartiles for median value*

Table 5. Cost Ratios and Mean Cost Differences (US Dollars) with 95% Confidence Intervals (CIs) Based on a Gamma Generalized Linear Regression Model of Per-Member Per-Month (PMPM) Costs for AAP Medication Therapy in Pediatric Patients (2 to 17 years) with Mental Health Diagnoses of Interest in United States, 2015 (N=5,253 patients with 35,311 paid claims)

Independent Variable	***Unadjusted Model[b]***				***Adjusted Model[b,c]***		
	Mean Cost Difference, $[a], (95% CI)	**Cost Ratio**	**95% CIs**	**P-value**	**Cost Ratio**	**95% CIs**	**P-value**
Intercept	173.01 (102.52, 280.59)						
Age Group							
2-5 years	***Reference***	***Reference***			***Reference***		
6-12 years	90.22 (-14.40, 155.45)	5.8	5.7, 5.8	<0.001	1.5	0.97, 2.1	0.05
13-17 years	116.62 (12.48, 180.63)	5.3	4.9, 5.7	<0.001	1.6	1.1, 2.3	0.02
Gender							
Male	***Reference***	***Reference***			***Reference***		
Female	30.69 (7.36, 54.67)	5.8	5.7, 5.9	<0.001	1.1	1.0, 1.2	0.01
Region							
Northeast	***Reference***	***Reference***			***Reference***		
Midwest	12.45 (-26.00, 47.97)	5.7	5.7, 5.8	<0.001	1.0	0.92, 1.2	0.56
South	38.89 (0.78, 73.93)	5.8	5.7, 5.9	<0.001	1.1	1.0, 1.3	0.04
West	20.66 (-45.54, 95.96)	5.7	5.6, 5.8	<0.001	1.0	0.86, 1.1	0.86

[a] Unadjusted and adjusted mean costs per patient was estimated using the identity link function
[b]Unadjusted and Adjusted coefficients of gamma regression were estimated using the log link function and are reported as a ratio of average per member per month (pmpm) costs.
[c]The following covariates were adjusted for in the final model: age group, gender and US region.

MANUSCRIPT 2

Title: Trends in Atypical Antipsychotic Prescribing for Pediatric Patients in a Commercial Health Plan: A 2010-2015 Claims Database Study

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2.1 Abstract

BACKGROUND: The overall trend of use for AAP in pediatric patients with mental health disorders has increased over the last 20 years. From 1995 to 2002, multiple studies demonstrated a 5-fold increase of antipsychotic use in pediatric and adolescent patients in the United States.[1–3] This treatment is often "off-label" or not for a specific Food and Drug Administration (FDA)-approved condition in children or adolescents.[1,2,4,5] Furthermore, 20% of pediatric patients prescribed an atypical antipsychotic medication had no FDA approved diagnosis associated with treatment.[6] As of 2010, most of the trend studies focused on publicly-insured children, such as Medicaid enrollees, with few studies evaluating large, privately-insured populations. The available studies suggest a growing trend in atypical antipsychotic use in pediatric patients, but only limited studies evaluated this medication class use in privately-insured patients.

OBJECTIVE: This study identified the trend in atypical antipsychotic medication prescribing in pediatric patients from 2010 to 2015. It also determined the rate of off-label prescribing by diagnosis of AAP medications in the same study population.

METHODS: An administrative dataset (Optum Clinformatics ® Data Mart; OptumInsight, Eden Prairie, MN) containing prescription claims between 2010 and 2015 was examined for all children 2 to 17 years of age who had a documented paid claim for an atypical antipsychotic medication. Patient demographic and clinical characteristics were analyzed using descriptive statistics. A generalized estimating equation (GEE) model with Poisson variance and a log-link was used to determine any demographic or clinical characteristics that predicted atypical antipsychotic use. To

characterize off-label diagnostic prescribing, a GEE model with a binomial variance and a log-link was employed to evaluate patient and clinical factors as predictors of off-label use in pediatric patients.

RESULTS: A total of 378,007 paid claims were evaluated, representing 40,750 individual patients aged 2 to 17 years old. The use of atypical antipsychotics within the entire pediatric population increased over the study period from 0.19% in 2010 to 0.28% in 2015. The rate of AAP paid claims per year for pediatric patients slightly increased with each calendar year: 57% in 2011, 63% in 2012, 79% in 2013, 73% in 2014. In 2015, pediatric patients had a 270% increase in the yearly rate of claim count per year during the study period (Rate Ratio (RR)=2.7; 95% confidence interval (CI) =2.6, 2.9), compared to 2010. Female patients had 10% reduction in the rate of paid AAP claims, compared to males (RR=0.90; 95% CI=0.89, 0.92). Our study found that both children 2-5 years old and children 6-12 years old had a 20% increase in the rate of paid AAP claims over the study period, compared to older children 13-17 years old (RR=1.2; 95% CI=1.1, 1.2; RR=1.2; 95% CI=1.1, 1.2).

Off-label prescribing by diagnosis of AAP medications represented 62% (95% CI=62%, 63%) of the paid claims evaluated. Children 2-5 years old were 43% less likely to be prescribed atypical antipsychotics for off-label diagnoses (adjusted odds ratio (aOR)=0.57, 95% CI =0.37, 0.90) than children 13-17 years old. Children 6-12 years old were 10% less likely (aOR = 0.90; 95% CI=0.77, 1.0) than adolescents (age 13-17 years) to be prescribed atypical antipsychotics for off-label indications. Female pediatric patients were 1.2 times more likely to be prescribed an AAP in an off-label manner (aOR=1.2; 95%CI=1.1, 1.3) compared to male children.

CONCLUSION: The use of atypical antipsychotic in children 2-17 years old increased overall from 2010 to 2015. This increase could be attributed to more atypical antipsychotic medications available in the US market. Over the study period, the number of AAP agents approved by the FDA increased substantially, from 7 agents to 13 available on the US pharmaceutical market. The practice of off-label prescribing by diagnosis is prevalent in the pediatric population, despite the lack of formal indications for pediatric use in this medication class.

2.2. Introduction

The overall trend of use for AAP in pediatric patients with mental health disorders has increased over the last 20 years. From 1995 to 2002, multiple studies demonstrated a 5-fold increase of antipsychotic use in pediatric and adolescent patients in the United States.[1–3] This increase was largely due to the increased availability of atypical antipsychotics and the common misconception that atypical antipsychotics demonstrated lower risk of serious adverse events.[7,8] Cooper et al examined antipsychotic mediation use in publicly-insured youth and found that 53% of incident users were being treated for mood or behavior disorders, rather than traditional psychiatric conditions.[1,4,7,9] This treatment is often "off-label" or not for a specific FDA-approved condition in children or adolescents.[1,2,4,5] Furthermore, 20% of pediatric patients prescribed an atypical antipsychotic medication had no FDA approved diagnosis associated with treatment.[6] The medications of interest and the corresponding FDA approval are listed in **Appendix B**.[10] As of 2010, most of the trend studies focused on publicly-insured children, such as Medicaid enrollees, with few studies including large, privately-insured populations. The available data suggests a growing trend in atypical antipsychotic use in pediatric patients; however, there have been few studies that evaluated this medication class use in privately-insured patients. More data in privately-insured children is unavailable and evaluation of the trend among privately-insured children has not been characterized nor compared to a population of publicly-insured children.[4,5,7,9,11] This study evaluated the overall utilization of these medications among privately-insured pediatric patients and discussed comparisons to publicly-insured children.

Clinical and demographic characteristics of youth receiving atypical antipsychotic medications are not fully understood. Available analyses of commercial and Medicaid prescription claims indicated that AAP treatment was significantly more common in boys than girls.[5,9,12,13] According to several state Medicaid studies, treatment of mood disorders, attention-deficit/hyperactivity disorder or disruptive and aggressive behavior disorders accounted for the majority of antipsychotic use.[4,5,14] One sample population of psychiatric outpatient visits found 77% of children had no diagnosis of any psychotic disorder associated with AAP medication therapy.[15] The data for commercial or privately-insured patients is limited and there remains uncertainty if the finding for publicly-insured children persists in the privately-insured population.

Utilization and medication costs can vary over time based on market changes. Since 2007, there has been a doubling in the number of AAPs approved on the US market with demonstrated use in the pediatric population.[10] However, most available measures of prevalent use are somewhat dated and based on data from before 2009. The increasing off-label use of medications, including AAPs, has been criticized and contested in legal cases, leading to changes in recommendations for such use by the FDA in 2009. Studies highlighting the off-label use of AAPs in the elderly has drawn criticism and concern, leading to Medicaid earning reimbursement for spending for off-label prescribing.[16,17] Policy makers anticipate similar off-label utilization in the pediatric population. The proportion of prescriptions authorized for off-label use in pediatric patients has not yet been evaluated in the privately-insured population.

Prior research that indicated increased use of atypical antipsychotic medication in children, coupled with the potential increase in off-label use, have led to public and professional uncertainty regarding recommended treatment regimens. The goal of this study was to evaluate annual trends in prevalent use of AAP medication over 6-year period from 2010 to 2015 in a large, privately-insured pediatric population and evaluate the appropriate use of AAPs for a given mental health diagnoses. Appropriate use was determined by labeled FDA indications for AAP medication referenced in the paid claim. We hypothesized that AAP medication utilization increased over the 6-year available study period and off-label prescribing of AAP medication represented the predominant use in pediatric patients.

2.3 Methods

This retrospective cohort study identified all paid prescription claims for AAP medications used in pediatric patients from 2010 through 2015. For each calendar year of the study period, patients were identified that were 2 to <18 years of age (as of the start of the year) and filled at least 1 prescription for an AAP agent during the year. We reported the number of patients who used any AAP overall and stratified by specific AAP agents. The utilization of AAPs was quantified as the prevalence of AAPs use; that is, the proportion of the pediatric population on AAPs during each year. Incidence of AAP therapy was also evaluated at the first year of follow-up to assess patients newly prescribed. All pediatric patients present for analysis in the administrative database (Optum Clinformatics ® Data Mart; OptumInsight, Eden Prairie, MN) were considered in the prevalence calculation.

Data Source and Study Design

This retrospective longitudinal study used the commercial data set (Optum Clinformatics ® Data Mart; OptumInsight, Eden Prairie, MN) from January 2010 to December 2015. This data includes commercial health insurance claims (inpatient and outpatient medical records, laboratory data, facility information, and outpatient pharmacy) and enrollment data from large, private insurer across the United States.[18] This dataset provides healthcare information on 36 million beneficiaries and encompasses 1.2 billion individual medical records.

Sample Selection

Patients aged 2 to 17 years of aged (at the start of the year with paid claim) that had a paid claim for an atypical antipsychotic were included in the analysis. Patients were then excluded if they lacked continuous eligibility during the claim year or did not have an associated medical visit in the time frame around the paid claim of interest. Continuous eligibility was applied as exclusion criteria to ensure all prescriptions claims and medical visits were available for analysis. Pediatric patients included in this analysis were not required to have continuous eligibility for the entire study period of six years, but only for year of paid AAP claim. Over the study period from 2010 to 2015 , 43,120 pediatric patients got an AAP paid claim, representing 490,123 paid claims. The final study cohort included 40,750 pediatric patients (378,007 paid claims for AAPs) with mental health conditions. Medical claims were collected for all types of services and the diagnoses were coded with the *International Classification of Diseases, 9th Revision and International Classification of Diseases 10th revision—Clinical Modification* (ICD-9-CM, ICD-10-CM). Medical claims associated within a 60-day window of the atypical antipsychotic (AAP) paid claim

were used to identify associated ICD-9-CM and ICD-10-CM diagnoses (**Appendix A)** associated with the prescription. For both analyses, patients and paid claims were excluded if they had no medical visit within the reference window (± 60 days around fill date) to provide clinical information for analysis. Ten diagnosis fields were queried for the associated reason for the medical visit. Medical visit data was carried forward for up to one year if it was missing at a particular medical visit. A one-year follow-up was used to ascertain all relevant clinical information for patients that were likely to be stabilized on AAP medication therapy and no longer presented to a provider for monthly medication refills. This ascertainment may explain repeated prescription paid claims for AAP medication therapy without a more recent medical appointment associated with the paid claim, since stable patients may be provided refills on an AAP prescription that do not require repeat monitoring by a provider. Pharmacy claims were recorded for all outpatient pharmacy plan claims and were coded with National Drug Codes (NDCs), with detailed information that included medication name, fill data, days' supply, quantity and drug strength. All pediatric patients were included in this analysis regardless of presence of associated mental health diagnosis at the associated medical visit.

Statistical Analysis

Overall AAP use prevalence was presented as a proportion of the pediatric population with mental health diagnoses prescribed AAPs in the cohort in the given year (no. of users per 1,000 children).[19] The total number of paid claims, unique patients and prevalence (represented as a percentage) is described in **Table 1.** The total number of children available in dataset was determined by examining all patients

with at least one paid claim in each year for patients age 2 to 17 years. The number of paid claims from 2010 to 2015 for AAP medication in pediatric patients were examined overall and by AAP medication (Figure 1). Among patients with at least one AAP paid claim and an associated medical visit available for analysis, we determined the frequency and percentage of baseline patient and clinical characteristics (**Table 2**).

We conducted a longitudinal analysis to evaluate the annual rates of AAP use, both overall and by medication class. Total counts of AAP paid claims per year was determined per patient. The unit of analysis for this section of the study was the medical visit for each patient associated with the AAP paid claim, which was then aggregated to a yearly count per patient. We examined a yearly count to better capture any market changes that may affect AAP prescribing, such as new drug approvals and generic formulations. Previous prescribing trends indicated that these market changes usually influence prescribing patterns over six to twelve months after the change is in effect.[3,4,11,12] The outcome of interest was the count of AAP claims per patients in each year. As mentioned above, 40,750 patients were included in the study cohort, representing 378,007 paid claims. The yearly claim count variable was determined by summing the individual paid claims for AAP medications for a given patient for each year during the study period. Mental health diagnosis associated with each paid claim was retained as the primary diagnosis for analysis unless a more recent paid claim was available with this information. Similarly, the provider details and specialty information were retained for each patient until a newer paid claim occurred with up-to-date information available.

Because there are multiple visits per patient, a generalized estimating equation (GEE) model was used to estimate the prevalence of children prescribed AAPs over time accounting for correlation within patient.[20] A GEE model with Poisson variance and a log-link was used to evaluate the association of covariates with annual claim count of AAP paid claims per patient over the study period.[20] No interaction terms were included in the final model due to lack of statistical significance of these terms. Collinearity between independent variables was tested using Variance Inflation Factors (VIF) test and no significant collinearity was found; thus, no adjustments for collinearity were made in the final model. Covariates that had a P value < 0.20 in the unadjusted model were included in the final adjusted model. No independent variables demonstrated a significant interaction with time over the study period, so no interactions with time were included in the final model.

We assessed the prevalence of possible off-label diagnostic use of AAPs for the study period of 2010 to 2015 as a percentage of total AAP prescriptions during that period. The unit of analysis for off-label use by diagnosis was each patient that received a paid claim for an AAP medication. Patients contributed multiple claims to the analysis over the study period and correlation within patient was addressed. To determine off-label diagnostic use, paid claims were only included if an associated medical visit of interest was found within the window mentioned above ($\pm$ 60 days). For paid claims that did not have enough time available in study period for complete analysis, the observation was excluded. For the off-label diagnostic use analysis, 74,841 paid claims (N=37,274patients) were included in the final cohort. A descriptive analysis evaluated off-label by diagnosis use and results were presented as

an overall percentage of off-label diagnostic use for each AAP medication. Any presence of diagnosis associated with AAP use that is off-label by diagnosis during the study period was considered off-label use, regardless if other diagnoses for a patient are indicated. Any use of clozapine (Clozaril), iloperidone (Fanapt) and ziprasidone (Geodon) was considered off-label diagnostic use in this patient population. As of December 2017, none of these agents have earned a pediatric indication for use from the FDA. Any off-label diagnostic prescribing was assessed for each paid claim and patient and provider characteristics associated with that claim were evaluated as predictors for off-label prescribing. Off-label use can also include use of agents for unapproved age groups or at doses not approved by FDA indication. For this analysis, possible off-label use was determined by diagnosis associated with AAP prescription.

Because multiple paid claims per patient were present, a generalized estimating equation (GEE) model was used to estimate the prevalence of off-label prescribing by diagnosis of children prescribed AAPs over time, accounting for correlation within patient.[20] A GEE model with binomial variance and a log link was used to evaluate the association of age, gender, region, provider category and associated mental health diagnosis as covariates for predicting the off-label diagnostic use of atypical antipsychotics in the study population.[20] This model used a robust estimator of variance to account for correlation between visits within a patient. No interaction terms were included in the final model due to lack of statistical significance of these terms. Collinearity between independent variables was tested using Variance Inflation Factors (VIF) test and no significant collinearity was found; thus, no adjustments for collinearity were made in the final model. Mental health diagnosis categories were

combined as follows due to low sample size in the original seven categories (Appendix A): Anxiety and Mood disorders; Developmental and Disruptive-Aggressive Behavior Disorders; Psychotic, Other Disorders or No Mental Health Diagnosis present. All covariates with P value < 0.20 were included in the adjusted model. The final multivariable model was examined for fit using the Hosmer-Lemeshow Goodness of Fit test, which indicated no evidence of a lack of fit (P value = 0.48). All statistical tests were two-sided and performed at a 0.05 significance level and analyses were performed using SAS Enterprise Guide Version 7.1 (Cary, North Carolina, USA).

2.4 Results

Trends in Atypical Antipsychotic Prescribing

From 2010 to 2015, there were 424,722 unique patients (ages 2 to 64 years) that received at least one atypical antipsychotic medications, with 4,647,014 paid claims for AAP medications over the entire study period. There were 490,123 paid claims for AAPs identified representing 78,481 individual pediatric patients (age 2 to 17 years) receiving at least one AAP paid claim over the study period. This represents an average number of 11.3 paid claims for AAP medications per pediatric patients over the six-year period.

In the final sample, 378,007 paid claims were evaluated, representing 40,750 individual patients. The use of atypical antipsychotics in this population increased over the years from 0.19% (2010) to 0.28% (2015). This percentage is out of all eligible children present in the dataset during the study period. **Table 1** and **Figure 1** below outline the yearly AAP medication claim count over the study period.

A full description of baseline characteristics for the study population is presented in **Table 2.** The mean age of pediatric patients receiving AAP therapy was 12.7 years (SD=3.7) at time of paid claim. Most patients (55%) were aged 13-17 years or adolescents. Specialty providers were the primary prescribers (40%) of AAP medication prescriptions. Primary care providers were the second most frequent prescribers (20%) of AAP prescriptions. At the medical visit associated with the AAP paid claims, 35% of patients did not have a mental health diagnosis present in the medical file. With a mental health disorder associated with the AAP paid claim, Mood disorders were the most common mental health diagnosis (28%), with Disruptive or Aggressive Behavior disorders the second most common (14%).

Based on the GEE model among the aggregated annual data, the rate ratios of claim count are presented in **Table 3**. The final adjusted model demonstrated that time, gender, age group, region and mental health diagnosis all demonstrated a significant effect on the rate of paid claims for AAP medications over time in years. Calendar time was found to have a significant association with the rate of pediatric patients receiving a paid claim for AAP medications over the study period. With 2010 (baseline) set as the reference point, pediatric patients had a 60% increase rate of claim count in 2011 (RR=1.6; 95% CI=1.5, 1.7). As the study period progresses, the rate of AAP paid claims per pediatric patient slightly increased with each calendar year 63% in 2012, 79% in 2013, 73% in 2014. In 2015, pediatric patients had a 270% increase in the rate of claim count compared to 2010 (RR=2.7; 95% CI=2.6, 2.9).

Female patients had 10% lower rates of paid AAP claims over the study period (RR=0.90; 95%CI=0.89, 0.92). Children 2-5 years of age had a 20% increased rate

(RR=1.2; 95%CI=1.1, 1.2) of paid AAP claims over the study period and children 6-12 years of age also had a 20% increased rate (RR=1.2; 95% CI=1.1, 1.2) compared to children 13-17 years old.

Geographic location of the pediatric patient has a small influence on the rate of paid claims over the study period. Patients living in the Northeast US were found to have a 4% increase in the rate of AAP paid claims (RR=1.04; 95% CI=1.0, 1.1) and patients located in the Midwest had a 3% increase rate (RR=1.03; 95% CI=1.0, 1.1) when compared to patients living in the western US. Overall, region of the US that patients were located did not have a significant effect on the rate of atypical antipsychotic prescribing over the study period (P value =0.13).

Mental health diagnosis associated with paid claims had a significant effect on the rate of AAP paid claims over the study period (P value <0.001). All comparisons were made to patients that had no mental health diagnosis associated an AAP paid claims. Patients with an Anxiety Disorder had 14% lower rate of AAP paid claims over the study period (RR=0.86; 95% CI=0.83, 0.89). Patients with Mood disorders were found to have a 9% lower rate of AAP paid claims and Disruptive or Aggressive Behavior (DAB) Disorders were found to have 6% lower rate of AAP paid claims compared to patients with no present mental health diagnosis (RR=0.91; 95% CI=0.89, 0.93 and RR=0.94; 95% CI=0.91, 0.97, respectively). Patients with "Other" mental health diagnoses (Tourette's Syndrome, Eating Disorders) had a 21% lower rate of paid claims for AAP medications during the study period (RR=0.79; 95% CI=0.75, 0.82) compared to patients with no present mental health diagnosis. Patients with developmental disorders and psychotic disorders did not have a

significantly different rate of paid claims for AAP medications over the study period, when compared to patients with no mental health diagnosis. Overall, the category of prescribing provider responsible for the AAP paid claim did not have a significant effect on the rate of AAP paid claims during the study period.

Off-Label Diagnostic Prescribing of Atypical Antipsychotic Medications

Off-label diagnostic prescribing of atypical antipsychotics was common in pediatric patients in our study. During the study period, 62% (95% CI=62%, 63%) of paid claims for atypical antipsychotics in pediatric patients were classified as off-label diagnostic use. Much of the off-label diagnostic use was due to the lack of mental health diagnosis present in the medical visit (35%) associated with AAP paid claim. No diagnostic code for a mental health condition at the medical visit associated with the paid claim was classified as off-label diagnostic use.

All covariates demonstrated significances as predictor in the univariate analysis (**Table 4**). In the final multivariable model, age group (P value=0.05), gender (P value =0.002), mental health diagnosis (P value<0.001), provider category (P value=0.08), and US region (P value<0.001) were significant variables in the likelihood of off-label diagnostic prescribing of AAPs. The adjusted odds ratios are presented in **Table 4**. In the adjusted model, children 2-5 years old were 15% more likely (aOR)=1.15; 95% CI=1.0, 1.3) than children 13-17 years old to be prescribed atypical antipsychotics for off-label diagnostic indications. Children aged 6-12 years old were 2% less likely to have off-label diagnostic (aOR=0.98; 95% CI=0.93, 1.0) use compared to adolescents (ages 13-17 years). Female pediatric patients were 10% times more likely (aOR=1.1; 95% CI=1.0, 1.2) to be prescribed an AAP in an off-label

diagnostic manner compared to male children. In the adjusted model, children located in the Midwest were 13% less likely (aOR=0.87; 95% CI=0.8, 0.97) to have an off-label diagnostic AAP paid claim, compared to children located in the Northeast. Similarly, children located in the South US were 16% less likely (aOR=0.84; 95% CI=0.76, 0.92) to have off-label diagnostic AAP use, compared to children located in the Northeast. The type of provider that a child received their AAP prescription from was not a significant predictor of off-label use by diagnosis in the adjusted model, when compared to prescriptions written by a specialty provider. After adjusting for other covariates, patients with a documented Mood or Anxiety Disorder were 95% less likely to receive an AAP medication for an off-label diagnosis (aOR=0.05; 95% CI=0.048, 0.053) compared to patient with psychotic, other or no mental health diagnosis present. Also, patients with a documented DAB or developmental disorder were 97% less likely to receive an AAP medication for an off-label diagnosis (aOR=0.03; 95% CI=0.03, 0.04) compared to patients with psychotic, other or no mental health diagnosis present after adjusting for other covariates.

2.5 Discussion

The proportion of children receiving AAP medication therapy in a large private payer was small (<1%) but still meaningful. Previous studies that included all children available for AAP prescribing, not only ones with documented mental health disorders, found similar rates of AAP medication therapy (<1% for children ages 2 to 17).[11] This low percentage is still meaningful, because it represents thousands (N=51,699) of children over the six year study period that are exposed to medications that have documented metabolic and cardiac long-term effects in adult patients.[21,22]

This study included all pediatric patients available in the study dataset during the study period for the denominator, because all of these patients were at risk for receiving AAP therapy for any reason, off-label or on-label.

The exposure of these medications during childhood and the long-term effects on growth and metabolic measures are not clearly understood. Over the last six years, trends in atypical antipsychotic prescribing demonstrated an overall increase in use among the privately-insured pediatric population. The primary increase in AAP use occurred from 2010 to 2011. In 2010, 6,923 (0.19%) children received a paid claim for an AAP medication. Then in 2011, 8970 (0.25%) children received a paid claim for an AAP medication. For the remainder of the study years, the prevalence was stable as illustrated in **Table 1**. There was a slight increase in prevalence at the end of the study period, (2015), where 8,745 (0.28%) pediatric patients received AAP medication therapy. During the study period in our sample, AAP medication utilization peaked in 2011. This could be due to the increased availability of AAP medications on the US pharmaceutical market (**Figure 1**). Overall, by the end of the study period in 2015, pediatric patients had a 270% increase in AAP paid claim rate (RR=2.7; 95% CI=2.6, 2.9) compared to the start of the study period in 2010.

Several patient characteristics demonstrated an association with the rate of AAP paid claims per year over the study period. Gender had a significant association with the annual rate of paid claims over the study period, with female patients experiencing lower rates (RR=0.90; 95% CI=0.89, 0.92) of paid claims. Children ages 2-5 years (RR=1.2; 95% CI=1.1, 1.2) and 6-12 years (RR=1.2; 95% CI=1.1, 1.2) had an increase in the annual rate of paid claims over the study period, compared to older

children (ages 13-17). This may indicate that over the last six years provider began utilizing AAP medications in a young patient population as familiarity with the medication class grows. Geographic location of patient showed an association with the rate of AAP paid claims over the study period. These minor differences could be due to local treatment practices and clinical preferences.

Mental health diagnosis associated with the paid claim for an AAP demonstrated a significant association with the rate of AAP paid claims over the study period. Patients with Developmental Disorders and Psychotic Disorders did not have a significantly different rate of paid claims for AAP medications over the study period, when compared to patients with no mental health diagnosis. This is finding is surprising, because previous trend studies have shown that use of atypical antipsychotics for Developmental Disorders was increasing overall and represented the highest rate of utilization compared to other mental health disorders. Our study population had a much lower percentage of patients with Developmental Disorder (4%) compared to previous literature (53%).[4] All clinical categories of mental health diagnoses were compared to the absence of mental health diagnosis in the medical visit around the paid claim. In our study, 35% of paid claims did not have an associated mental health diagnosis. Providers may withhold the documentation of mental health diagnosis due to potential stigma that could follow a pediatric patient through to adulthood.[11,23] Some antipsychotics could be utilized for treatment for other conditions (insomnia, agitation) that do not meet clinical criteria as a mental health disorder.[11,24] Finally, provider specialty or category did not demonstrate an association with the rate of paid AAP claims over the study period. Our study found

that whether a patient is seen by a primary care provider or a mental health specialist, the rate of AAP prescribing is comparable.

Off-label prescribing can describe the use of medication therapy for indications that are not officially approved by the Food and Drug Administration. Off-label use also includes using medications for unapproved age groups and at unapproved dosing levels for certain populations. This study defined off-label diagnostic use as prescribing of an AAP medication with no documented mental health disorder or an unapproved mental health disorder. Future studies should explore dosing levels of AAP paid claims and differentiated age groups to examine all types of off-label prescribing. Off-label use of atypical antipsychotic agents in pediatric patients is heavily debated.[17,25] Many AAP medications have limited or no official FDA indication in children due to lack of research evidence in pediatric patients. Our study found that off-label diagnostic prescribing of AAP medications occurred in 62% (95% CI=62%, 63%) of all paid claims. This means that providers and patients were using AAP medications for other mental health diagnoses that have not been formally studied and approved by the FDA. Our study found that off-label prescribing of atypical antipsychotics is common in the pediatric population.

2.6 Limitations

Our study assumed that a paid claim for an AAP represents therapy adhered to by the patient. This assumes that the patient is exposed to a given medication because the paid claim was processed and therefore the patient adhered to the regimen. This could overestimate the actual exposure to AAP medication therapy because patients may have been prescribed the AAP medication, but never actually consume the

prescription. For the purposes of this study, only prescribing trends were evaluated, and outcomes based on patient exposure were not examined. Future research that explores outcomes related to exposure of AAP could perform patient surveys or pill count methods to confirm the exposure to AAP medication therapy.

A sizable percentage (35%) of paid claims for AAP medications was not associated with a mental health diagnosis of interest. All patients included in the original cohort had a mental health diagnosis of interest to warrant inclusion in the cohort. With so many patients missing a mental health diagnosis at associated medical visit, the rate of other categories of mental health disorder might be underrepresented. Many patients could have a diagnosis in one of the categories, but it is not documented and recorded in the "missing" category. This can underestimate the true rate of the mental health diagnostic categories that are used for off-label analysis. The lack of a mental health diagnosis associated with an AAP paid claim constituted off-label prescribing for the purposes of this study. This could be overestimating the rate of off-label diagnostic use of AAP medications in this study because provider could have simply failed to properly document the reason for AAP use and this undocumented reason could align with an approved FDA indication. Providers could justify this to protect a patient from the bias or stigma of mental health disease by not documenting a mental health diagnosis at medical visits.

2.7 Conclusions

Overall, the proportion of the pediatric population in a large privately-insured cohort receiving AAP medication therapy was small 0.28% (2015). From 2010 to 2015, atypical antipsychotic prescribing in privately-insured pediatric patients

increased from 0.19% in 2010 to 0.28% in 2015. At the end of the study period, pediatric patients had a 270% increase in the rate of atypical antipsychotic prescribing per year compared to 2010. Off-label prescribing represented 62% of atypical antipsychotic medication use and our study found it to be frequent practice in the pediatric population. Several AAP agents (clozapine, ziprasidone and iloperidone) with no pediatric indication at all were still found to be used in the study population (6.7%). Patients ages 2 to 5 years old were at an increased risk for using atypical antipsychotic medications for off-label diagnoses. Female patients were at increased risk for using atypical antipsychotic medications for off-label diagnoses. With these new insights, providers should consider more stringent use of atypical antipsychotic agents based on diagnosis until further safety studies are available specific to pediatric patients.

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Table 1. Atypical Antipsychotic Paid Claims for US Privately-Insured Children (2 to 17 years) from 2010 to 2015 (N=51,669 pediatric patients with 378,007 paid claims)

Group	*2010*	*2011*	*2012*	*2013*	*2014*	*2015*
Number of Eligible Pediatric patients in claims database	3,562,685	3,525,172	3,474,515	3,404,207	3,308,273	3,182,170
Number of AAP paid claims among children	50,976	67,586	71,712	70,077	62,416	55,240
Number of pediatric patients with at least one paid claim for an AAP medication	6923	8970	9507	9091	8433	8745
Percentage of Children receiving paid claim for AAP medication	0.19%	0.25%	0.27%	0.27%	0.25%	0.28%

Figure 1. Percentage of Total Paid Claims (displayed by medication) for US Privately-Insured Children (2 to 17 years) for an Atypical Antipsychotic (2010 to 2015).

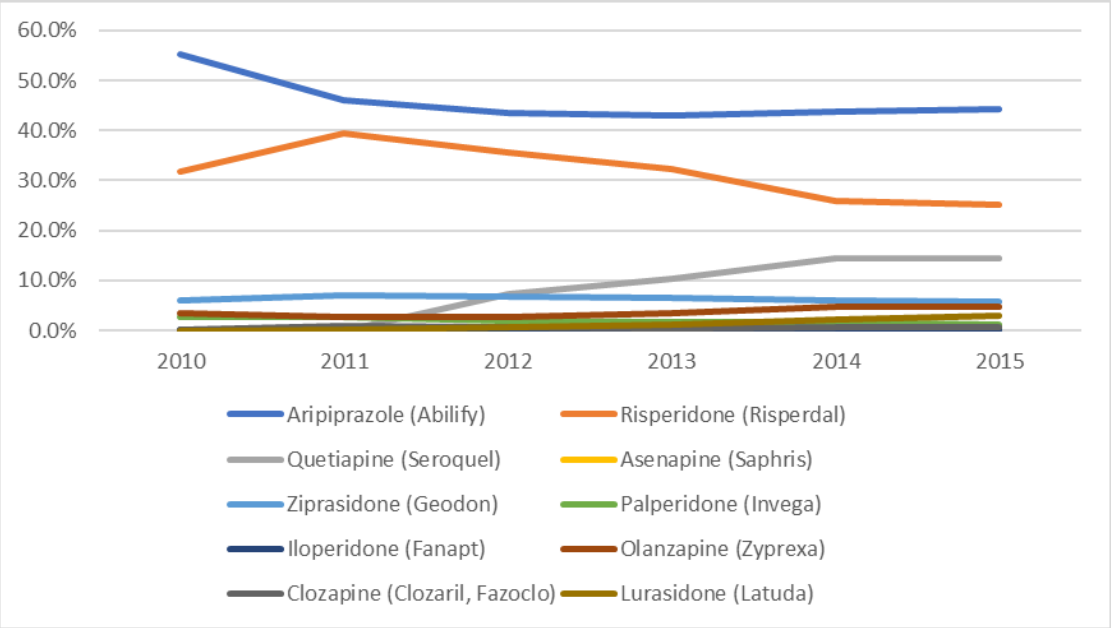

Table 2. Baseline Patient and Clinical Characteristics of US Privately-Insured Children (2 to 17 years) Receiving an Atypical Antipsychotic (AAP) Medication from 2010 to 2015 (N=40,750)

Characteristic	*Pediatric Patients with an AAP Paid Claim (N=40,750)*
Age, y (mean, SD)	12.7 (3.7)
Age Group, n (%)	
2-5 Years	2512 (6)
6-12 Years	15913 (39)
13-17 Years	22325 (55)
Male, n (%)	23139 (57)
US Region, n (%)	
Northeast	4261 (11)
Midwest	11802 (29)
West	7332 (18)
South	17355 (43)
Provider type, n (%)	
Acute Care Hospital	1910 (5)
Mental Health Professional (non-physician)	4089 (10)
Outpatient Facility	2368 (6)
Primary Care Provider	8029 (20)
Specialist	16077 (40)
Therapy Provider (Social Worker, Psychologist)	2450 (6)
Other Non-Physician Provider	5827 (14)
Diagnosis associated with AAP prescription, n (%)	
Anxiety Disorders	4465 (11)
Mood Disorders	11449 (28)
Disruptive or Aggressive Behavior Disorders	5509 (14)
Developmental Disorders	1495 (4)
Psychotic Disorders	1407 (4)
Other MH Disorders	2265 (6)
No MH Diagnosis Present	14160 (35)

Table 3. Rate Ratios (RRs) with 95% Confidence Intervals (CIs) Derived From an Adjusted GEE Model of Patient and Clinical Factors Associated with Prescribing of Atypical Antipsychotic Medication in US Privately-Insured Pediatric Patients (2 to 17 years) from 2010 to 2015. (N=40,750)

Variable	*Rate Ratios (95% CI's)*	*p-value*
Time (Study Year)		**<0.001**
2010	**Reference**	
2011	1.57 (1.5, 1.7)	
2012	1.63 (1.5, 1.7)	
2013	1.79 (1.7, 1.9)	
2014	1.74 (1.7, 1.8)	
2015	2.71 (2.6, 2.9)	
Gender		**<0.001**
Male	**Reference**	
Female	0.90 (0.89, 0.92)	
Age Group		**<0.001**
2-5 Years	1.2 (1.1, 1.2)	
6-12 Years	1.2 (1.1, 1.2)	
13-17 Years	**Reference**	
Region		**0.13**
Northeast	1.04 (1.0, 1.1)	
Midwest	1.03 (1.0, 1.1)	
South	1.0 (0.98, 1.0)	
West	**Reference**	
Mental Health Diagnosis		**<0.001**
Anxiety Disorders	0.86 (0.83, 0.89)	
Mood Disorders	0.91 (0.89, 0.93)	
Disruptive or Aggressive Behavior Disorders	0.94 (0.91, 0.97)	
Developmental Disorders	1.1 (0.99, 1.0)	
Psychotic Disorders	1.1 (1.0, 1.2)	
Other Mental Health Disorders	0.79 (0.75, 0.82)	
No Mental Health Diagnosis Present	**Reference**	
Provider Category		**0.35**
Acute Care Hospital	1.0 (0.97, 1.1)	
Mental Health Professional (non-physician)	1.0 (0.98, 1.1)	
Outpatient Facility	1.1 (1.0, 1.1)	
Primary Care Provider	1.0 (0.98, 1.1)	
Specialist	1.0 (0.99, 1.1)	
Therapy Provider (Social Worker, Psychologist)	1.0 (0.95, 1.1)	
Other non-physician provider	**Reference**	

**General estimating equations used with a Poisson variance and log-link. Final model adjusted for the following baseline covariates: Age group, gender, US region and Mental Health Diagnosis.*

Table 4. Odds Ratios (ORs) with 95% Confidence Intervals (CIs) Derived from an Adjusted GEE Model of Patient and Clinical Factors Associated with Any Off-Label Diagnostic Prescribing of Atypical Antipsychotic Medication in US Privately-Insured Pediatric Patients (2 to 17 years) from 2010 to 2015. (N=37,274 patients; 78,481 paid claims)

Variable	*Odds Ratios (95% CIs)*	*p-value*
Patient Age	1.0 (1.0, 1.1)	**0.05**
Age Group (years)		**0.05**
2-5 years	1.15 (1.0, 1.3)	
6-12 years	0.98 (0.93, 1.0)	
13-17 years (adolescents)	**Reference**	
Gender		**0.002**
Female	1.1 (1.0, 1.2)	
Male	**Reference**	
Region		**<0.001**
Midwest	0.8 (0.80, 0.97)	
South	0.84 (0.76, 0.92)	
West	0.99 (0.89, 1.1)	
Northeast	**Reference**	
Mental Health Diagnosis**		**<0.001**
Anxiety or Mood Disorders	0.05 (0.05, 0.06)	
DAB*** and Developmental Disorders	0.03 (0.03, 0.04)	
Psychotic, Other or NO MH Diagnosis Present	**Reference**	
Provider Category		**0.08**
Acute Care Hospital	1.1 (0.98, 1.2)	
Mental Health Professional (non-physician)	1.0 (0.97, 1.1)	
Outpatient Facility	0.98 (0.91, 1.1)	
Primary Care Provider	1.0 (0.98, 1.1)	
Specialist	**Reference**	
Therapy Provider (Social Worker, Psychologist)	1.0 (1.0, 1.2)	
Other non-physician provider	1.1 (1.0, 1.1)	

**General estimating equations used with a Binomial variance and log-link. Final model adjusted for the following baseline covariates: Age group, gender, US region, Mental Health Diagnosis, and Provider category.*
***Mental Health Diagnosis categories combined as described in above table. Patients receiving medication off-label did not have any diagnosis of Disruptive/Aggressive Behavior Disorders or Psychotic Disorders noted. Patients receiving medications "on-label" did not have any diagnoses of Anxiety Disorders, Developmental Disorders, Other Disorders or Missing.*
****Disruptive and Aggressive behavior (DAB)*

MANUSCRIPT 3

Title: Risk of Psychiatric Readmission in Pediatric Patients Treated with Oral Atypical Antipsychotics

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3.1 Abstract

OBJECTIVE: This analysis aims to determine the risk of readmission for mental health treatment for pediatric patients treated with oral atypical antipsychotics (AAPs) upon discharge from initial mental health inpatient admission. Examine patient and clinical characteristics that are associated with risk of readmission with oral atypical antipsychotic treatment.

METHODS: Inpatient hospitalization and pharmacy claims from the OPTUMInsight administrative dataset (Optum Clinformatics ® Data Mart; OptumInsight, Eden Prairie, MN) from 2010 to 2015 were analyzed. Children ages 2 to 17 years old with an inpatient admission for a mental health diagnosis of interest and discharged on an oral AAP were included in the study sample (N =3,028). A Cox proportional hazards regression model was used to evaluate if exposure to different oral AAPs agents, including risperidone, aripiprazole, quetiapine, etc., was associated with a delay in the time until readmission for mental health stabilization. Other patient and clinical characteristics and their association with delayed time until readmission was analyzed.

RESULTS: For all children with an index admission for mental health treatment, the mean age of the study cohort was 14.8 years (standard deviation (SD) = 2.3). Of all 3,084 patients, 85% of patients were aged 13-17 years old or in adolescence. The cohort had slightly more male patients than female patients, (59% vs. 46%, P value<0.001). In pediatric patients admitted for mental health treatment, 73% of patients had a Mood Disorder as their primary mental health diagnosis (P value= 0.02). In the study cohort, aripiprazole was the more frequently utilized discharge

AAP (42%). Overall, the Charlson Comorbidity Index (CCI) score for the entire cohort was not significantly different between the groups and most patients (92%) included in this cohort had a CCI score of zero. In the analysis examined by discharge AAP, patients receiving risperidone were younger (13.6, SD=2.8, P value <0.001) compared to other discharge AAPs. More male patients received risperidone as a discharge AAP, (70%, p<0.001) compared to other AAP agents. Children with a primary mental health diagnosis of Mood Disorders received aripiprazole, quetiapine or ziprasidone more often for discharge therapy (80%, 76%, 75%, respectively; P value <0.001) than other AAP agents. In the unadjusted model, quetiapine (hazard ratio (HR)=0.69, 95% confidence interval (95% CI)=0.47, 1.0) and ziprasidone (HR=0.52, 95% CI=0.28, 0.97) prescribed for a patient upon discharge form index admission demonstrated a significant lower risk of readmission, compared to risperidone.

In the adjusted Cox proportional hazards model**,** female gender was associated with a significantly higher risk (adjusted hazard ratio (aHR) =1.5, 95% CI=1.2, 1.8), of readmission for mental health treatment. Patients with no prior treatment with AAP medication before index admission were 8.9 times more likely (aHR=8.9, 95% CI=3.7, 21.8) to be readmitted for mental health treatment. In the adjusted model, patients receiving quetiapine (aHR=0.55, CI=0.37, 0.81) and ziprasidone (aHR=0.55, CI=0.29, 1.0) upon discharge had a lower risk of readmission, compared to risperidone. In the weighted cumulative incidence curves, 13% of patients receiving risperidone, 12.5% of patients who were taking aripiprazole and 10 % of patient receiving olanzapine were readmitted within the follow-up period. In comparison, 7%

of patient receiving quetiapine and 5.5% of patients receiving ziprasidone were readmitted within the follow-up period.

CONCLUSIONS: Patients receiving quetiapine and ziprasidone had a lower risk of readmission, compared to risperidone when used at discharge in pediatric patients. The cumulative incidence of readmission was lower in patients receiving quetiapine and ziprasidone upon discharge. Pediatric patients of a female gender had a significantly higher risk of readmission. Patients with no recent prior exposure to AAP mediation therapy in the 3-month prior to index admission were at a much higher risk of readmission for mental health treatment. Future studies should examine the adverse events of these agents in the pediatric population. This additional safety data can determine if these agents should be considered for increased use in clinical practice for in pediatric patients to reduce the risk of readmission for mental health treatment.

3.2 Introduction

Several randomized, controlled trials have demonstrated that atypical antipsychotic medications, such as risperidone, olanzapine, aripiprazole and quetiapine, produce fewer adverse effects and offer better psychotic symptom relief in a short course than other agents in pediatric patients with mental health disorders.[1–6] However, there is limited information available about the comparative effectiveness of these medications in clinical practice settings, specifically in pediatric patients.[7] A major indication of drug effectiveness in clinical practice is relapse. In regards to mental health disorders, this relapse is characterized by worsening symptoms or changes in behavior that become harmful to the patient and/or society.[8] Time to readmission for inpatient mental health treatment is a commonly used measure for assessing relapse and effectiveness of mental health therapies.[8,9] Available follow-up studies in adults indicate that up to 50% of patients with schizophrenia and other psychotic disorders are readmitted within one year post discharge.[10,11] This high rate of readmission is particularly concerning because a higher rate of relapse is associated with worse long-term prognosis in adult mental health patients.[11] . Poor adherence to antipsychotic therapy has been shown to increase risk of relapse and hospitalization with a related increase in related healthcare resource utilization and costs.[12–15] Patients often try several antipsychotic agents over the course of treatment due to side effects or varying efficacy in the individual patient. No studies are yet available comparing the rates of readmission with atypical antipsychotics in pediatric patients

According to 2008 research using data from the Healthcare Cost and Utilization Project (HCUP), there were 356,000 hospital admissions for psychotic

disorders in the US, representing 19% of all mental health hospitalizations.[16] These patients had an average length of stay of 11.1 days and average cost per admission was $7,500.[16,17] Patients who experienced a recent relapse (within previous 6 months) were found to have four times higher costs compared to patients without a recent mental health relapse.[17] This study focused primarily on adult patients and only included patients diagnosed with schizophrenia[12,13,16,17] A 2014 report analyzing admissions for mental health treatment in pediatric patients estimated the cost of hospital visits (inpatient and emergency department) to be $11.6 million from 2006 to 2011, based on HCUP data.[18] In 2014, 10% of all hospitalizations in children over the age of 3 years were for a primary mental health diagnosis.[19] Previous research followed adult schizophrenic patients for two years and found statistically significant differences between atypical antipsychotic agents in regards to risk of increased readmission rates.[9,20] To the best of our knowledge, no study has yet examined a direct comparison of oral atypical antipsychotic agents in privately-insured pediatric patients with mental health conditions to delay hospital readmission for mental health treatment.

This study focused on pediatric patients who utilized oral atypical antipsychotic therapy after an initial admission for mental health treatment. Readmission for mental health treatment was evaluated to determine the efficacy of using specific atypical antipsychotics in pediatric mental health patients. Many randomized controlled trials and post-marketing trials demonstrated the efficacy of individual oral agents in the reduction in readmission in adults patients, compared to placebo or first generation antipsychotics.[21–23] Furthermore, clinical providers often

extrapolate the demonstrated benefit of these agents in adults to pediatric patients with limited direct evaluation among children.[24] This study evaluated the effectiveness of specific oral AAP agents in delaying readmission in pediatric patients.

3.3 Methods

Study Design

The study was a retrospective cohort study utilizing the administrative dataset (Optum Clinformatics ® Data Mart; OptumInsight, Eden Prairie, MN) from January 1, 2010 to December 31, 2015. This data set contains medical, including inpatient and outpatient, and relevant information about hospital admissions. This data included commercial health insurance claims (inpatient and outpatient medical records, laboratory data, facility information, and outpatient pharmacy) and enrollment data from large, private insurer across the United States.[25] This dataset provides healthcare information on 36 million beneficiaries and encompasses 1.2 billion individual medical records. Pediatric patients represent about 10% of this dataset or 3.5 million children. The inpatient admission file provided clinical information on date of admission, diagnosis codes for admission, length of stay (LOS) and discharge date. The inpatient file contains up to five diagnoses associated with an admission or encounter available for evaluation. Pharmacy claims data included medication information such as days' supply, quantity, prescribing physician and cost data. This dataset represents approximately 36 million covered patients across the United States. The index date was the date of the first hospital admission for a mental health diagnosis during the study period. A look-back period of 90 days from index admission date was examined to ensure no prior admission for mental health treatment

was present. Patients were followed for up to one year from the discharge date of the index hospitalization. According to studies evaluating inpatient mental health treatment in adults, the highest risk of readmission is in the first-year post-discharge, so this same follow-up period was chosen.

Inclusion Criteria

The study included all patients with an inpatient admission for a mental health diagnosis aged 2-17 years. Admission for a mental health diagnosis was determined by utilizing *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM) and International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM)* diagnostic codes listed in **Appendix A**. Eligible patients required at least 90 days or continuous health plan enrollment before index admission and 365 days after the index admission.[9, 24] Patients were included only if they received an atypical antipsychotic medication (AAP) upon discharge from index admission. Patients were identified as having an AAP medication paid claim using National Drug Codes (NDCs) as provided in **Appendix B**, for an available AAP medication on the US market. All available dosage forms and atypical antipsychotic medications were included in the analysis. Patients were determined to have received an AAP medication upon discharge if a paid claim was present for an AAP within 14 days post discharge date.

Exclusion Criteria

Patients will be excluded from the study if they were older than 17 years at index hospitalization and no paid claim within 14 days for atypical antipsychotic medication therapy.[9, 24] The 14-day post discharge date window was used to identify a

paid claim as representing a discharge prescription from the index admission. This window was defined based on clinical practice parameters from the American Academy of Child and Adolescent Psychiatry that recommend follow-up appointments post hospitalization occur within 7-14 days to provide continuity of care across levels of mental health treatment.[26] Patients who were hospitalized for mental health treatment during the study period in the recent months preceding the index admission were excluded. A look back period of 90-days was examined for any recent admissions for mental health treatment. Patients were included in study cohort if their index admission was for a mental health diagnosis. A 90-day look back period from index admission was performed to examine prior exposure to AAP therapy and patients were classified as having no prior exposure, exposure to same AAP as discharge agent or exposure to different AAP as discharge medication. **Figure 1** describes the study cohort with relevant exclusion or inclusion criteria.

Exposures and Outcomes

The exposure of interest was the use of atypical antipsychotic therapy at time of hospital discharge.[20] Exposure to specific AAP agents was evaluated and each agent was compared to risperidone. Risperidone was chosen as the reference agent because it was the first atypical antipsychotic to be awarded an Food and Drug Administration (FDA) indication for use in pediatric patients. The primary outcome evaluated was time from index hospital discharge to readmission for any mental-health related diagnosis **(Appendix A)**.

Covariates considered sufficient to adjust for confounding included the following at baseline: age, gender, admission diagnosis, length of hospital stay, Charlson Comorbidity Index (CCI) and AAP exposure (same AAP as discharge,

different AAP as discharge or no AAP therapy) prior to index hospitalization. Admission diagnosis was categorized in to groups listed in **Appendix A** and compared to diagnosis codes in the "other" category. The other category was used as the reference group because it contains mental health diagnoses that AAP agents do not have a FDA approved indication and should have the lowest exposure risk to AAPs since no official FDA indication is present. The CCI score was used to evaluate the severity of illness among patients at their index hosptialization.[27] The CCI score measures the severity of the presence of certain disease states, such as malignancies, HIV, and diabetes, in the patient's inpatient medical file at index admission and represents the overall health status of the patient. **Appendix C** provides a full listing of the disease states included in the CCI score and point values associated with each diagnosis. Length of stay (LOS) of index admission was examined as a covariate and represented in number of days as a continuous variable. Patients were followed to ascertain hospital readmission with a related MH diagnosis and were censored at the date of death (as recorded in a hospital claim), one-year post discharge of the index admission or end of the study period (31 December 2015), whichever occurred first.

Statistical Analysis

We reported descriptive statistics to characterize each outcome group of interest (readmission for mental health treatment or no readmission). Baseline characteristics were also examined by discharge AAP (exposure group) and presented in **Table 2.** Group comparisons on baseline sample characteristics were performed using chi-square tests or Fisher-exact tests for categorical variables and Analysis of Variance (ANOVA) for continuous variables. Baseline characteristics of patients at

index discharge were examined and included covariates age, gender and United States region. We used a Cox proportional hazards regression model to assess hazard (i.e., risk) of psychiatric readmission post-discharge within one year of index admission. Baseline covariates for adjustment in the models included age group, gender, index admission diagnosis, CCI score, region, pre-index AAP exposure and discharge AAP agent.[28,29] The Schoenfeld residuals were examined to determine if the proportional hazard assumption was violated.[29] All covariates except for age showed no evidence of a violation of proportional hazards through this statistical test [(LOS, P value=0.36), (Gender, P Value=0.84), (Region, P Value=0.26), (CCI Score, P Value=0.98), (MH Diagnosis, P Value=0.12), (Prior AAP exposure, P Value=0.37) and (Discharge AAP, P Value=0.14)]. The proportional hazard assumption for the covariate age group was not satisfied (P value = 0.02); therefore, the model was stratified by age group to allow for separate baseline hazards for each age group.[30] All pairwise interactions between covariates were not statistically significant in a single contrast (P value=0.56). These values indicated that none of the interactions of covariates were significant, so interaction terms were not included in the final model. Collinearity between independent variables was tested using Variance Inflation Factors (VIF) test and no significant collinearity was found; thus, no adjustments for collinearity were made in the final model. Covariates associated with the outcome with P value less than 0.20 in the univariate analysis were included in the final adjusted model.[28] Gender (P value<0.001), prior AAP mediation exposure (P value <0.001), mental health diagnosis (P value=0.11) and discharge AAP medication (P value=0.14) demonstrated a significant effect on risk of readmission during the study

period and all of these covariates were included in the adjusted model. CCI score was non-significant and was not included in the adjusted analysis. The length of stay (LOS) was not found to have a significant effect on risk of increased readmission and LOS was not included in the adjusted model. We used Efron's method to handle tied event times.[29,31] Cumulative incidence curves were generated using inverse probability weights to adjust for the baseline covariates. All statistical tests were two-sided and performed at the 0.05 significance level. Analyses were performed using SAS Enterprise Guide Version 7.1 (Cary, North Carolina, USA).

3.4 Results

During the study period 2010 to 2015, 3,215 pediatric patients were admitted with a mental health diagnosis documented as the reason for admission. After applying inclusion criteria of receiving an AAP medication upon discharge (within 14-day window), 3,084 patients had a qualifying index admission for mental health treatment during the study period. Of those subjects, 313 (10%) children had a readmission within one year of the index admission discharge date for a mental health diagnosis or readmission for mental health treatment. The study sample is presented in **Figure 1.**

Study Cohort disposition and characteristics

For the entire cohort, the mean age of the study cohort was 14.8 years (standard deviation (SD) = 2.3). Of all patients evaluated, 85% of patients were ages 13-17 years old or adolescents. The cohort had slightly more male patients than female patients, (53% vs. 47%). In pediatric patients admitted for mental health treatment, 73% of patients had a Mood Disorder as their primary mental health diagnosis (72.5%). In the study cohort, aripiprazole was the more frequently utilized

discharge AAP (41.8%). Overall the CCI score for the entire cohort was not significantly different between the groups (patients readmitted vs. patients not readmitted) and most patients (92%) included in this cohort had a CCI score of zero (**Table 1**). This was expected since the components of the CCI score are primarily chronic illnesses and these conditions are usually present in higher frequencies as a population ages.

Baseline characteristics of readmission versus no readmission patients are displayed in **Table 1.** Children readmitted for mental health treatment during the follow up period were slightly higher in age (15.2 years. vs. 14.7 yrs., P value=0.006). The group that was readmitted for mental health treatment has a significantly larger proportion of female patients (59% vs 46%, P value<0.001). The percentage of children with no prior AAP exposure in the three months preceding index admission was higher in readmitted group compared to the children not readmitted within the follow-up period (91.7% vs. 59.7%, P value<0.001). The admission mental health diagnosis differed significantly between the children readmitted for treatment, and those that were not (P value=0.007). Children readmitted for mental health treatment had a higher proportion of documented diagnoses for Mood Disorders (77% vs. 72%) than children not readmitted. Children readmitted for mental health treatment had a lower proportion of documented diagnoses for Disruptive or Aggressive Behavior Disorders (5% vs. 9%). The mean length of index hospital admission did not significantly vary between the two groups (8.2 days vs. 8.0 days, P value =0.85). The region of residence did not vary significantly between the two groups (P value=0.60).

The CCI score was zero in 92% of patients in both groups and was not significantly different (P Value =0.86).

Baseline characteristics of children in the cohort analyzed by exposure (discharge atypical antipsychotic agent) are presented in **Table 2**. Patients receiving risperidone were younger (13.6, SD=2.8, P value<0.001) compared to other discharge AAPs. More male patients received risperidone as a discharge AAP, (70%, P value<0.001) compared to other AAP agents (47%). Children receiving risperidone upon discharge had documented disruptive or aggressive behavior disorders as primary diagnosis more often than children receiving other AAP agents upon discharge (13% vs. 7%, respectively; P value<0.001). Children with a primary mental health diagnosis of Mood Disorders received quetiapine, aripiprazole or ziprasidone more often for discharge therapy (80%, 76% and 75%, respectively; P value <0.001) compared to other AAP agents. CCI score did not vary significantly between discharge AAP exposure groups at baseline.

Table 3 summarizes the results of the unadjusted and adjusted models. In the unadjusted model, several baseline patient characteristics displayed a significant association with the hazard of readmission for mental health treatment. Female patients had a 60% increased risk of readmission (hazard ratio, (HR) =1.6; 95% confidence interval, (CI) =1.2, 2.5) compared to male patients. Patients with a primary diagnosis of disruptive or aggressive behaviors disorders (DAB) had a 55% decreased risk of readmission (HR=0.45; 95% CI=0.23, 0.89) compared to children with a diagnosis of other mental health disorders. Similarly, patients with a primary diagnosis of Developmental Disorders had a 65% decreased risk of readmission

(HR=0.35; 95% CI=0.12, 0.98) compared to children diagnosed with other mental health disorders. Children with no prior AAP exposure in the three months prior to index admission were 10 times more likely to be readmitted for mental health treatment (HR=10.2; 95% CI=4.2, 24.7). Patients receiving quetiapine had a 31% decreased risk of readmission (HR=0.69; 95% CI=0.47, 1.0) compared to patients receiving risperidone. In the unadjusted model, patients receiving ziprasidone had a 48% decreased risk of readmission (HR = 0.52; 95% CI = 0.28, 0.97) compared to patients receiving risperidone. Finally, patients receiving "other" AAP agents (lurasidone, asenapine, clozapine, iloperidone and paliperidone) had a 71% decrease risk of readmission for mental health treatment (HR=0.29; 95% CI=0.11, 0.79) compared to risperidone. CCI score was zero in 92% in patients at baseline and was not included in Cox proportional hazard model. LOS (P value =0.70) and geographic region (P value=0.93) were not significantly associated with time to readmission.

In the adjusted Cox proportional hazards analysis, female patients had 50% increased risk of readmission for mental health treatment (adjusted hazard ratio (aHR)=1.5; 95% CI =1.2, 1.8). Patients with no prior treatment with AAP medication before index admission had 8.9 times the risk (aHR=8.9; 95% CI=3.7, 21.8) of readmission for mental health treatment. In the final adjusted model, choice of atypical antipsychotic agent for discharge therapy demonstrated a significant effect on the risk of readmission. Patients receiving quetiapine at discharge had a 45% decreased risk (aHR=0.55; 95% CI=0.37, 0.81) and patients receiving ziprasidone had a 45% decreased risk (aHR=0.55; 95% CI=0.29, 1.0) of being readmitted for mental health treatment, compared to patients receiving risperidone. In the adjusted model, primary

mental health diagnosis was no longer significantly associated with the hazard of being readmitted for mental health treatment during the follow-up period (P value = 0.14).

The unadjusted cumulative incidence of readmission is presented in **Figure 2** and the inverse probability weighted cumulative incidence curves are presented in **Figure 3**, examined by discharge AAP agents. In the unadjusted curves, 14% of patients receiving aripiprazole, 12% of patients taking risperidone, and 9% of patients receiving olanzapine were readmitted by one-year after discharge. In comparison, the unadjusted model shows that 8% of patients receiving quetiapine and 6% of patients receiving ziprasidone were readmitted within the follow-up period. After using inverse probability weighting, the adjusted curves show that 13% of patients receiving risperidone, 12.5% of patients who were taking aripiprazole and 10% of patients receiving olanzapine were readmitted by one-year after discharge. In comparison, 7% of patients receiving quetiapine and 5.5% of patients receiving ziprasidone were readmitted during the follow-up period.

3.5 Discussion

In the adjusted model, patients exposed to quetiapine and ziprasidone demonstrated a lower risk (aHR=0.55; 95% CI=0.37, 0.81; aHR=0.55; 95% CI=0.29, 1.0, respectively) of readmission, compared to risperidone. As represented in **Figure 3**, choice of discharge atypical antipsychotic does have a significant association with the risk of being readmitted for mental health treatment within the follow-up period in pediatric patients after adjusting for baseline covariates. Pediatric patients receiving quetiapine or ziprasidone also displayed a lower cumulative incidence of readmission

(**Figure 3**) over study period compared to patients receiving risperidone at discharge, after adjusting for baseline covariates Risperidone is one of the most frequently prescribed in the pediatric population for mental health treatment. This analysis suggests that patients might be at a lower risk of relapse when treated with quetiapine and ziprasidone and alternative AAP therapy may be more effective than risperidone. A longer follow-up period is needed to compare effectiveness of atypical antipsychotics.[8] In addition, discharge from the hospital does not imply adherence to the discharge medication therapy in the outpatient setting and this study did not consider adherence. Risperidone might be poorly tolerated in this patient population due to problematic side effects or poor therapeutic response. This could cause patients to discontinue discharge therapy prior to the completion of the prescription. If patients are no longer on risperidone discharge therapy, then the effect of this intervention on readmission risk can be unclear. Future studies should examine discharge therapy continuation to evaluate the role medication adherence in efficacy of discharge AAPs.[32]

Female patients demonstrated a higher risk of one-year readmission for mental health treatment compared to male patients. This differs from adult studies, that indicated that gender was not a significant predictor of readmission.[32,33] Patients who were recently naïve to AAP medication therapy or received no treatment for the three months prior to hospitalization were at a significantly higher risk of readmission at one-year that patients receiving therapy prior to index admission (aHR=8.9; 95% CI=3.7, 218). Often several therapies must be explored and tailored based on patient response and side effects before a maintenance therapy can be established. Patients

who had no recent exposure to AAP medication therapy could experience more adverse medication reactions or incomplete therapeutic response, which can require them to be readmitted for stabilization.

Our study focused on pediatric patients and many of the disease states evaluated using the CCI are chronic in nature and more prevalent as age progresses, so a majority of this pediatric study population (92%) demonstrated a CCI score of zero. This was expected since the components of the CCI score are primarily chronic illnesses and these conditions are usually present in higher frequencies as a population ages. Most of the disease states analyzed in the CCI are chronic in nature (diabetes complications, congestive heart failure, etc.) and do not occur frequently in children. No specific comorbidity index is available and sufficiently validated for use in pediatric patients, though there is forthcoming work for a pediatric-specific index.[34] Disease states that are more prevalent in children, such as asthma, childhood leukemia or autism, might be present in this cohort. However, the CCI index does not identify these diagnoses and they are not factored into the overall score that is intended to represent health status. Therefore, some underlying confounding by indication might be present if the patients that experience a readmission are sicker at baseline, but the disease severity is not fully captured by the CCI score. This study did not expressly evaluate cost of admission or treatment, but length of hospitalization was included as a covariate. Overall length of hospitalization can represent higher costs for the admission and poorer long-term clinical outcomes for mental health treatment, so overall length of stay (LOS) was examined as a covariate.[20] Overall length of hospitalization can represent higher costs for the admission and poorer long-term

clinical outcomes for mental health treatment, so overall length of stay (LOS) was examined as a covariate and was defined as a continuous variable for number of days of admission.[20]

Based on the weighted cumulative incidence curves, the "other" category of atypical antipsychotic agents trended toward a lower risk of readmission for mental health treatment, when compared to risperidone. This class represents lurasidone, asenapine, paliperidone, iloperidone and clozapine, all newer agents to the US market or agents with no pediatric indication for use. Evidence for the efficacy of these agents is limited in this study due to the low utilization of AAPs in this category. Further studies with higher utilization of these newer agents are needed to better understand this trend.

The model was stratified by gender and full results are presented in **Appendix D.** The adjusted model for the entire cohort indicated possible unmeasured confounding was present and some of underlying differences may be correlated with a patient's gender. After stratifying the model by gender, it was found that male patients had a higher rate of risperidone use as a discharge AAP (32%) compared to female patients (15%). Of note, male patients also had a higher rate of documented disruptive and aggressive behavior (DAB) (12%) disorders than compared to female patients (4%). Other demographics were similar between both groups in the study cohort. Previous research in pediatric patients found AAP agents were use more often in patients with documented DAB disorders (37.8%) compared to other mental health diagnoses.[1] Risperidone is one of the only AAP agents with a specific pediatric indication for use in DAB disorders. Both factors could explain the differences in

AAP selection and mental health diagnosis in the male portion of the study cohort. Overall, the findings of readmission risk were similar for all other covariates in the models separated by gender, except for discharge AAP. In the complete, adjusted model, the risk of readmission for patients given zisprasidone was 45% lower compared to risperidone (aHR=0.55, 95% CI=0.29, 1.0). Also, patients given quetiapine had a 45% lower risk of readmission compared to risperidone (aHR=0.55, 95% CI=0.37, 0.81). Once stratified by gender, female patients given zisprasidone had a 37% lower risk and male patients given zisprasidone had a 65% lower risk (aHR=0.63, 95% CI=0.30, 1.3; aHR=0.35, 95% CI=0.08, 1.4) , respectively). This decreased risk with zisprasidone compared to risperidone no longer reached the level of significant. When stratified by gender, female patients given quetiapine had a 48% lower risk of readmission and male patients given quetiapine had a 36% lower risk of readmission (aHR=0.52, 95% CI=0.31, 0.88; aHR=0.64, 95% CI=0.4, 1.0, respectively). This association remained significant, even when stratified by gender. The association between discharge AAP agent and risk of readmission was somewhat attenuated within each gender.

3.6 Limitations

This study only evaluated AAP medication therapy received upon discharge from a mental health hospital admission. The permanence of this therapy or switches in treatment was not evaluated. This study only evaluated the exposure to an agent at the time of discharge and other therapies within the follow up time were not evaluated. This could lead to exposure misclassification. Therapy switching and therapy permanence (PDC) between discharge and readmission should be analyzed to

determine if certain oral AAP therapies are more effective. This study examined the difference in one-year hazard of readmission after prescribed an atypical antipsychotic agent at discharge. The "other" category trended toward a lower risk of readmission, but the use of these newer agents was low, and the determination of efficacy warrants further study. Once these new agents are utilized in clinical practice, future studies can evaluate evidence in administrative claims databases and determine if these agents are effective at lowering the risk of readmission. Some unmeasured confounding might be present for variables that we were unable to capture or did not examine in this study. Combination therapy with multiple AAPs or compliance with counseling or behavioral therapy has been documented to improve clinical outcomes and prevent relapse.[15,17] This study focused on analyzing the impact of discharge medication therapy with AAPs on risk of readmission, so switching therapy or combination therapy was not evaluated at this time. Mental health treatment often includes counseling services and other behavioral therapy interventions. This study analyzed the impact of medication therapy interventions on readmission outcomes specifically and did not explore the impact of other treatment modalities. Mental health treatment is often multifaceted and patient success is dependent on many treatment modalities. Therapy services and group counseling provide support to the patient and play a vital role, along with medications, to treatment success. These treatment options and combinations of therapy with medications were not examined in this study but should be included in future research for their impact on mental health treatment success.

3.7 Conclusions

Patients receiving quetiapine and ziprasidone had a lower risk of readmission, compared to risperidone when used at discharge in pediatric patients. Newer atypical antipsychotic agents trended toward demonstrating a lower risk of readmission and future studies are warranted to see if these agents have a significant effect on readmission in pediatric patients. The cumulative incidence of readmission was lower in patients receiving quetiapine and ziprasidone upon discharge, compared to risperidone. Quetiapine and ziprasidone might want to be considered for increased use in clinical practice for in pediatric patients to reduce the risk of readmission for mental health treatment. Pediatric female patients had a significantly higher risk of readmission for mental health treatment. Patients with no prior exposure to AAP mediation therapy in the 3-month prior to index admission were at a much higher risk of readmission for mental health treatment. Further studies are warranted to evaluate factors, such as adverse events and therapy compliance, that might further mediate this increased risk.

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Figure 1. Selection of US Pediatric Privately-Insured Patients (2 to 17 years) for Analyses of Oral Atypical Antipsychotic Agents and Risk of Readmission for Mental Health Treatment (2010 to 2015)

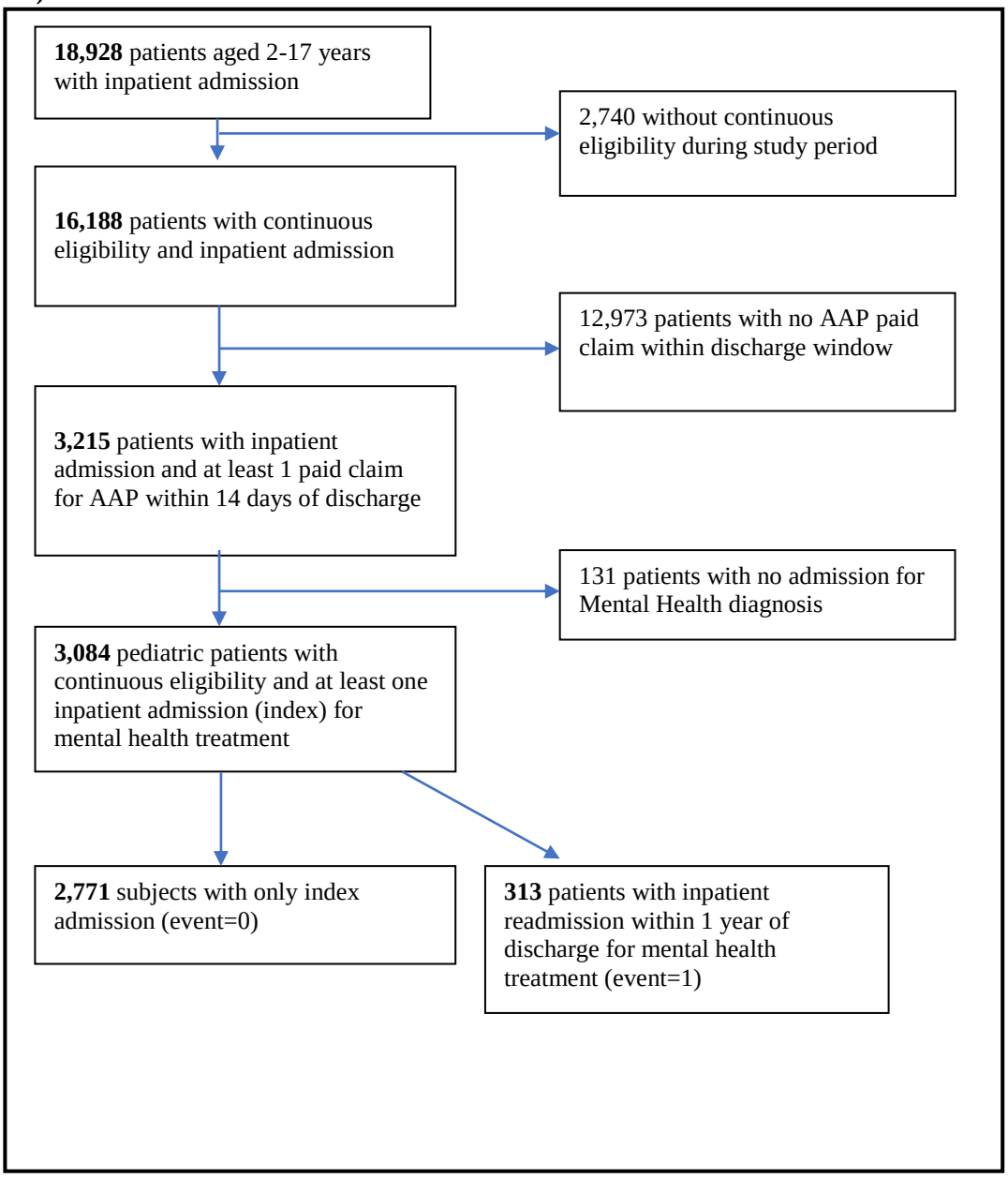


Table 1. Demographic and Clinical Characteristics of Privately-Insured, US Children (2 to 17 years) with an Index Inpatient Admission for Mental Health Treatment from 2010 to 2015 by Readmission Status (N=3,084)

Characteristic	*Children with readmission (N=313)*	*Children with no readmission (N=2,771)*	*p-value*
Patient Age, Years, Mean± SD	15.2 (15.0, 15.5)	14.7 (14.6,14.8)	0.002
Length of Stay (LOS, days)	8.2 (7.3, 9.1)	8.0 (7.5, 8.6)	0.85
Follow Time, (days), Median (Q1, Q3)	95.3 (84, 107)	308 (304, 312)	<0.001
Age Group (years) N (%)*			0.0032
2-12 years	30 (9.6)	441 (15.9)	
13-17 years (adolescents)	283 (90.4)	2330 (84.1)	
Patient Gender, N (%)			<0.001
Male	128 (40.9)	1489 (53.7)	
Female	185 (59.1)	1282 (46.3)	
Patient Region, N (%)			0.60
Northeast	36 (11.5)	264 (9.5)	
Midwest	87 (27.8)	810 (29.2)	
South	135 (43.1)	1247 (45.0)	
West	55 (17.6)	450 (16.2)	
MH Diagnosis Category, N (%)			0.002
Anxiety Disorder	21 (6.7)	145 (5.2)	
Mood Disorders	240 (76.7)	1996 (72.0)	
Disruptive or Aggressive Behavior Disorders	15 (4.8)	238 (8.6)	
Developmental Disorders	4 (1.3)	119 (43)	
Psychotic Disorders	3 (1.0)	78 (2.8)	
Other MH Disorders	30 (9.6)	195 (7.0)	
Prior AAP exposure			<0.001
No prior AAP exposure at index admission	287 (91.7)	1653 (59.7)	
Treatment with same AAP as discharge (index admission)	21 (6.7)	779 (28.1)	
Treatment with different AAP as discharge (index admission)	5 (1.6)	339 (12.2)	
Discharge Atypical Antipsychotic Agent			0.011
Risperidone (Risperdal)	82 (26.2)	653 (23.6)	
Quetiapine (Seroquel)	41 (13.1)	482 (17.4)	
Aripiprazole (Abilify)	157 (50.2)	1138 (41.1)	
Ziprasidone (Geodon)	11 (3.5)	175 (6.3)	
Olanzapine (Zyprexa)	18 (5.8)	205 (7.4)	
Other*	4 (1.3)	117 (4.2)	
Charlson Comorbidity Score (on Index admission)			0.86
0	289 (92.3)	2567 (92.6)	
1	24 (7.7)	202 (7.3)	
2	0 (0)	2 (0.08)	

**Other AAPs: lurasidone, asenapine, iloperidone, paliperidone, clozapine*

Table 2. Baseline Demographic and Clinical Characteristics of Privately Insured, US Children (2 to 17 years) with Index Inpatient Admission for Mental Health Treatment from 2010 to 2015, Analyzed by Discharge Atypical Antipsychotic. (N=3,084)

Variable	*Risperidone (N=735)*	*Quetiapine (N=523)*	*Aripiprazole (N=1295)*	*Ziprasidone (N=186)*	*Olanzapine (N=223)*	*Other* (N=121)*	*p-value*
Patient Age, Years, Mean (SD)	13.6 (2.8)	15.2 (2.1)	14.7 (2.3)	14.6 (2.2)	14.3 (2.5)	14.6 (2.2)	**<0.001**
Length of Stay (LOS, days),	7.5 (7.6)	7.9 (6.0)	7.9 (18.7)	8.5(8.0)	8.6 (6.1)	12.9 (29.0)	**0.006**
Follow time, Days, Mean (SD)	286 (126)	298 (118)	280 (125)	298 (117)	287 (126)	293 (118)	**0.05**
Age Group (years) n (%)							**<0.001**
2-12	204 (27.8)	46 (8.8)	159 (12.3)	21 (11.3)	31 (13.9)	10 (8.3)	
13-17	531 (72.2)	477 (91.2)	1136(87.7	165 (88.7)	192 (86.1)	111 (91.7)	
Patient Gender n (%)							**<0.001**
Male	514 (69.9)	226 (43.2)	618 (47.7)	82 (44.1)	124 (55.6)	53 (43.8)	
Female	221 (30.1)	297 (56.8)	677 (52.3)	104 (55.9)	99 (44.4)	68 (56.2)	
Patient Region, n (%)							**<0.001**
Northeast	83 (11.3)	45 (8.6)	141 (10.9)	14 (7.5)	8 (3.6)	9 (7.4)	
Midwest	246 (33.5)	162 (31.0)	341 (26.3)	56 (30.1)	54 (24.2)	37 (30.6)	
South	311 (42.3)	209 (40.0)	624 (48.2)	91 (48.9)	84 (37.7)	63 (52.1)	
West	95 (12.9)	107 (20.5)	189 (14.6)	25 (13.4)	77 (34.5)	12 (9.9)	
MH Diagnosis Category, n (%)							**<0.001**
Anxiety Disorder	55 (7.5)	23 (4.4)	61 (4.7)	3 (1.6)	17 (7.6)	7 (5.8)	
Mood Disorder	461 (62.7)	416 (79.5)	985 (76.1)	140 (75.3)	145 (65.0)	88 (72.7)	
DAB Disorders	101 (13.7)	20 (3.8)	91 (7.0)	16 (8.6)	17 (7.6)	8 (6.6)	
Developmental Disorders	44 (6.0)	6 (1.2)	38 (2.9)	12 (6.5)	18 (8.1)	5 (4.1)	
Psychotic Disorders	26 (3.5)	9 (1.7)	25 (1.9)	7 (3.8)	8 (3.6)	6 (5.0)	
Other MH Disorders	48 (6.5)	49 (9.4)	95 (7.3)	8 (4.3)	18 (8.1)	7 (5.8)	
Prior AAP Exposure, n (%)							**<0.001**
No prior AAP exposure	473 (64.4)	354 (67.7)	839 (64.8)	92 (49.5)	132 (59.2)	49 (40.5)	
Treatment with same AAP as discharge (index admission)	187 (25.4)	104 (19.9)	385 (29.7)	55 (29.6)	34 (15.3)	35 (28.9)	
Treatment with different AAP as discharge (index admission)	75 (10.2)	65 (12.4)	71 (5.5)	39 (21.0)	57 (25.6)	37 (30.6)	
Charlson Comorbidity Score (On Index Admission), n (%)							**0.41**
0	685 (93.2)	485 (92.7)	1189 (91.8)	171 (91.9)	212 (95.1)	113 (93.4)	
1	50 (6.8)	38 (7.3)	105 (8.1)	15 (8.1)	10 (4.5)	8 (6.6)	
2	0 (0)	0 (0)	1 (0.1)	0 (0)	1 (0.4)	0 (0)	

**Other AAPs: lurasidone, asenapine, iloperidone, paliperidone, clozapine*

Table 3. Unadjusted and Adjusted Hazard Ratios of Readmission derived from a Cox Proportional Hazards Model for Privately-Insured US Children (2 to 17 years) with an Index Admission for Mental Health Treatment, in database 2010 to 2015 (N=3,084)

Variable	***Hazard Ratio (95 CIs)***	***P-value***	***Hazard Ratios (Adjusted)***	***p-value***
Index Admission, Length of Stay (LOS)	1.0 (0.99, 1.02)	**0.88**		
Age Group		**0.007**		
2-12 years	1.7 (1.2, 2.5)		*Violated the proportional hazards assumption. Model stratified on age, so no hazard ratio generated*	
13-17 years	**Reference**			
Patient Gender		**<0.001**		**0.002**
Female	1.6 (1.3, 2.1)		1.5 (1.2, 1.8)	
Male	**Reference**		**Reference**	
Patient Region		**0.84**		
Northeast	1.1 (0.71, 1.7)			
Midwest	0.86 (0.6, 1.2)			
West	0.83 (0.6, 1.2)			
South	**Reference**			
MH Diagnosis Category		**0.35**		**0.14**
Anxiety Disorder	1.3 (0.77, 2.3)		1.1 (0.60, 1.9)	
Mood Disorders	1.0 (0.71, 1.5)		0.83 (0.57, 1.2)	
Disruptive or Aggressive Behavior Disorders	0.45 (0.23, 0.89)		0.58 (0.31, 1.1)	
Developmental Disorders	0.35 (0.12, 0.98)		0.37 (0.12, 1.1)	
Psychotic Disorders	0.50 (0.18, 1.4)		0.36 (0.11, 1.2)	
Other MH Disorders	**Reference**		**Reference**	
Prior AAP exposure		**<0.001**		**<0.001**
No prior AAP exposure	10.2 (4.2, 24.7)		8.9 (3.7, 21.8)	
Treatment with same AAP as discharge (index admission)	1.8(0.66, 4.7)		1.6 (0.6, 4.2)	
Treatment with different AAP as discharge (index admission)	**Reference**		**Reference**	
Discharge Atypical Antipsychotic Agent		**0.14**		**0.006**
Risperidone (Risperdal)	**Reference**		**Reference**	
Quetiapine (Seroquel)	0.69 (0.47, 1.0)		0.55 (0.37, 0.81)	
Aripiprazole (Abilify)	1.1 (0.84, 1.4)		0.93 (0.71, 1.2)	
Ziprasidone (Geodon)	0.52 (0.28, 0.97)		0.55 (0.29, 1.0)	
Olanzapine (Zyprexa)	0.72 (0.43, 1.2)		0.73 (0.43, 1.2)	
Other*	0.29 (0.11, 0.79)		0.35 (0.13, 0.97)	

**Other AAPs: lurasidone, asenapine, iloperidone, paliperidone, clozapine*

Figure 2. Unadjusted Cumulative Probability of Readmission from 2010 to 2015 for Mental Health Treatment by AAP Medication at Discharge, in US Privately-Insured Children (2 to 17 years) from 2010 to 2015 (N=313)

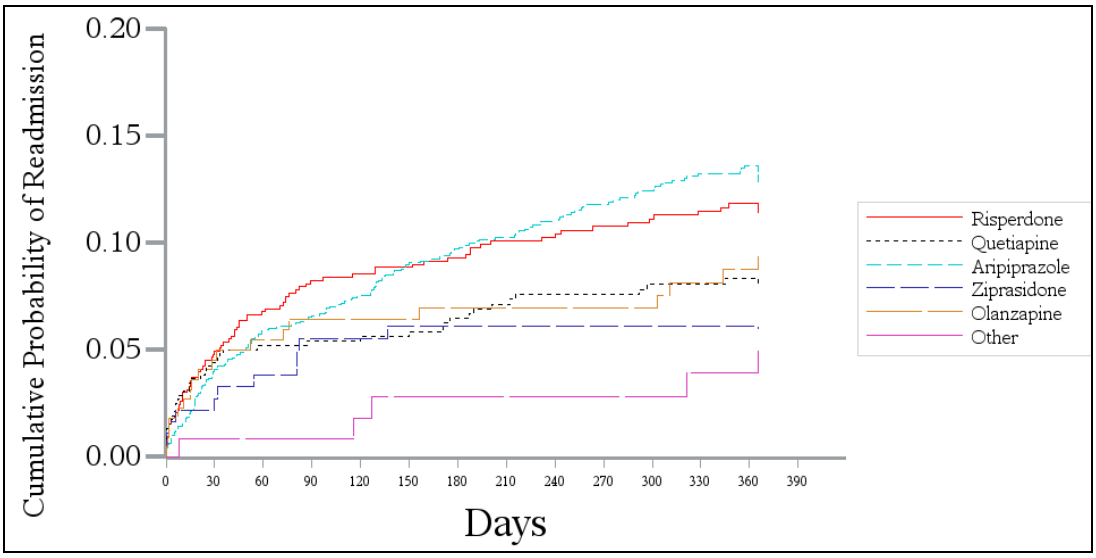
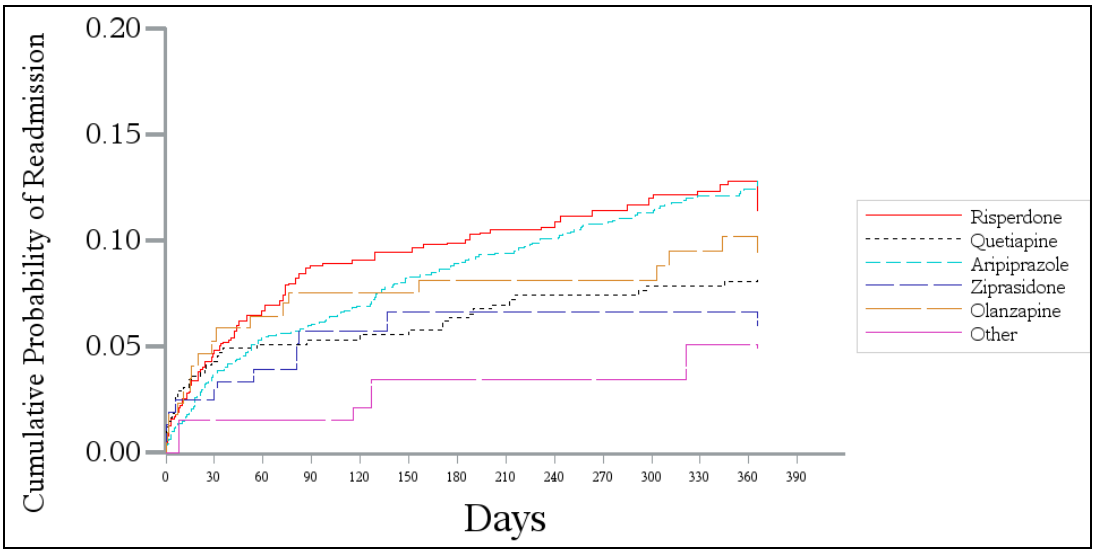


Figure 3. Weighted Cumulative Probability of Readmission from 2010 to 2015 for Mental Health Treatment by Atypical Antipsychotic Medication at Discharge, in Privately-Insured US Children (2 to 17 years) from 2010 to 2015 (N=313)



APPENDIX A

MENTAL HEALTH DIAGNOSES OF INTEREST FOR STUDY

POPULATION

International Classification of Disease 9th Edition [ICD-9] medical codes (2012)
International Classification of Disease 10th Edition [ICD-10] medical codes (2017)
(Halloran, Swindle, Takemoto, & Schnitzler, 2010; Olfson, King, & Schoenbaum, 2015; Patel, Crismon, & Shafer, 2006)

Diagnosis	**ICD-9-CM**	**ICD-10-CM**
Anxiety Disorders	300-300.3, 300.5-300.9, 309.2x, 309.4, 309.81, 313.0	F40-F48
Mood Disorders	296, 300.4, 301.1x, 309.0, 309.1, 311, 313.1	F30-F39
Disruptive/aggressive Behavior disorders	309.3, 312.xx, 313.81, 314.xx, V40.3, V40.9	F90-F98
Developmental Disorders	299.0, 315-319, V40.0-V40.2, V79.2	F70-F79, F80-F89
Psychotic Disorders	292.1x, 293-295.9, 297-298.9, 299, 299.1-299.91, 368.16, 780.1	F20-F29
Miscellaneous/Other Disorders	290-292.0, 292.2-292.2, 301-301.0, 301.2-307.59, 307.8-309, 309.8, 309.82-310.9, 313, 313.2-313.8, 313.82-313.9, 660-331.9, V66.3, V67.3, V71.0	F99, F50-F59, F60-F69

APPENDIX B

ATPYICAL ANTIPSYCHOTIC AGENTS AVAILABLE ON US MARKET

("Drugs@FDA: FDA Approved Drug Products," 2017)

Medication	**FDA pediatric indication**	**Year of Indication Approval**
Risperidone	Schizophrenia (13-17 yrs.) Bipolar I (10-17 yrs.) Irritability with Autistic Disorder (5-16 yrs.)	2007 2007 2007
Olanzapine	Schizophrenia (13-17 yrs.) Bipolar I (13-17 yrs.)	2010 2009
Aripiprazole	Schizophrenia (13-17 yrs.) Bipolar I (10-17 yrs.) Irritability with Autistic Disorder (6-17 yrs.)	2007 2008 2009
Paliperidone	Schizophrenia (12-17 yrs.)	2011
Quetiapine	Schizophrenia (13-17 yrs.) Bipolar I (10-17 yrs.)	2009 2009
Ziprasidone	*None*	*none*
Lurasidone	Schizophrenia (13-17 yrs.)	2017
Clozapine	*None*	*None*
Iloperidone	*None*	*None*
Asenapine	Bipolar I (10-18 yrs.)	2015

APPENDIX C

CHARLSON COMORBIDITY INDEX, DIAGNOSTIC CATEGORIES

(Sundararajan et al., 2004)

Condition	Weights	ICD-9-CM Codes	ICD-10-CM Codes
Acute myocardial infarction	1	410, 412	121, 122, 125.2
Congestive Heart Failure	1	428	109.9, 111, 113, 113.2, 125.5, 142, 142.5-142.9, 143, 150, P29
Peripheral vascular Disease	1	441, 4439, 7854, V4334	170, 171, 173, 173.8, 173.9, 177.1, 179-179.2, K55.1, K55.8, K55.9, 295.8, 295.9
Cerebral vascular accident	1	430-438	G45, G46, H34, 160-169
Dementia	1	290	F00-F03, F05, G30, G31
Pulmonary disease	1	490, 491, 492, 493, 494, 495, 496, 500, 501, 502, 503, 504, 505	127.8, 127.9, 140-147, 160-167, J68.4, J70.1, J70.3
Connective tissue disorder	1	7100, 7101, 7104, 7140, 7141, 7142, 71481 (now 5171), 725	M05, M06, M31.5, M32-M34, M35.1, M35.3, M36.0
Peptic ulcer	1	531, 532, 533, 534	K25-K28
Liver disease	1	5712, 5714, 5715, 5716	B18, K70.0-K70.3, K70.9, K71.3-K71.5, K71.7, K73, K74, K76.0, K76.2-K76.4, K76.8, K76.9, Z94.4
Diabetes	1	2500, 2501, 2502, 2503, 2507	E10.0, E10.l, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9
Diabetes complications	2	2504, 2505, 2506	E10.2-E10.5, E10.7, E11.2-E11.5, E11.7, E12.2-E12.5, E12.7, E13.2-E13.5, E13.7, E14.2-E14.5, E14.7
Paraplegia	2	342, 3441	G04.1, G11.4, G80.1, G80.2, G81, G82, G83.0-G83.4, G83.9
Renal disease	2	285, 2830, 5831, 5832, 5833, 5835, 5836, 5837, 5834, 5855, 86588	I12.0, I13.1, N03.2-N03.7, N05.2-N05.7, N18, N19, N25.0, Z49.0-Z49.2, Z94.0, Z99.2
Cancer	2	14, 15, 16, 18, 170, 171, 172, 174, 175, 176,179, 190, 192, 193, 194, 1950, 1951, 1952, 1953, 1954, 1955, 1958, 200, 201, 202, 203, 204, 205, 206, 207,208	C00-C26, C30-C34, C37-C41, C43, C45-C58, C60-C76, C81-C85, C88, C90-C97
Metastatic cancer	3	196, 197, 198, 1990, 1991	C77-C80
Severe liver disease	3	5722, 5723, 5724, 5728	I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7
HIV	6	042, 043, 044	B20-B22, B24

APPENDIX D

STUDY 3 RESULTS: STRATIFIED BY GENDER

Demographic and Clinical Characteristics of Privately-Insured, Male, US Children (2 to 17 years) with an Index Inpatient Admission for Mental Health Treatment from 2010 to 2015 by Readmission Status (N=1,617)

Characteristic	*Children with readmission (N=128)*	*Children with no readmission (N=1,489)*	*p-value*
Patient Age, Years, Mean± SD	14.8 (14.3, 15.2)	14.3 (14.2, 14.5)	0.06
Length of Stay (LOS, days)	7.3 (6.2, 8.4)	8.4 (7.4, 9.4)	0.54
Follow Time, (days), Median (Q1, Q3)	97.2 (78.4, 116)	309 (304, 314)	<0.001
Age Group (years) N (%)*			0.11
2-12 years	21 (16.4)	335 (22.5)	
13-17 years (adolescents)	107 (83.6)	1154 (77.5)	
Patient Region, N (%)			0.12
Northeast	20 (115.6)	137 (9.2)	
Midwest	39 (30.5)	458 (30.8)	
South	50 (39.1)	645 (43.3)	
West	19 (14.8)	249 (16.7)	
MH Diagnosis Category, N (%)			0.13
Anxiety Disorder	10 (7.8)	66 (4.4)	
Mood Disorders	92 (71.9)	979 (65.8)	
Disruptive or Aggressive Behavior Disorders	12 (9.4)	186 (12.5)	
Developmental Disorders	3 (2.3)	95 (6.4)	
Psychotic Disorders	3 (2.3)	58 (3.9)	
Other MH Disorders	8 (6.3)	105 (92.9)	
Prior AAP exposure			<0.001
No prior AAP exposure at index admission	116 (90.6)	841 (56.5)	
Treatment with same AAP as discharge (index admission)	10 (7.8)	456 (30.6)	
Treatment with different AAP as discharge (index admission)	2 (1.6)	192 (12.9)	
Discharge Atypical Antipsychotic Agent			0.05
Risperidone (Risperdal)	50 (39.1)	464 (31.2)	
Quetiapine (Seroquel)	15 (11.7)	211 (14.2)	
Aripiprazole (Abilify)	54 (42.2)	564 (37.9)	
Ziprasidone (Geodon)	2 (1.6)	80 (5.4)	
Olanzapine (Zyprexa)	6 (4.7)	118 (7.9)	
Other*	1 (0.8)	52 (3.5)	
Charlson Comorbidity Score (on Index admission)			0.91
0	118 (92.2)	1375 (92.3)	
1	10 (7.8)	112 (7.5)	
2	0 (0)	2 (0.13)	

**Other AAPs: lurasidone, asenapine, iloperidone, paliperidone, clozapine*

Baseline Demographic and Clinical Characteristics of Privately Insured, Male, US Children (2 to 17 years) with Index Inpatient Admission for Mental Health Treatment from 2010 to 2015, Analyzed by Discharge Atypical Antipsychotic. (N=1,617)

Variable	*Risperidone (N=514)*	*Quetiapine (N=226)*	*Aripiprazole (N=618)*	*Ziprasidone (N=82)*	*Olanzapine (N=124)*	*Other* (N=53)*	*p-value*
Patient Age, Years, Mean (SD)	13.9 (2.7)	15.3 (1.9)	15.0 (2.1)	15.1 (1.9)	14.7 (2.2)	15.3 (1.8)	**<0.001**
Length of Stay (LOS, days),	7.5 (7.6)	8.5 (10)	7.2 (6.9)	7.8 (6.4)	8.6 (6.1)	11.1 (19.8)	**0.008**
Follow time, Days, Mean (SD)	289 (124)	299 (117)	292 (119)	289 (123)	298 (115)	291 (114)	**0.92**
Age Group (years) n (%)							**<0.001**
2-12	164 (32.0)	27 (12.0)	117 (29.0)	15 (18.3)	23 (18.6)	10 (18.9)	
13-17	350 (68.0)	199 (88.0)	501 (81.0)	67 (81.7)	101 (81.5)	43 (81.1)	
Patient Region, N (%)							**<0.001**
Northeast	56 (10.9)	20 (8.9)	67 (10.8)	5 (6.1)	5 (4.0)	4 (7.6)	
Midwest	177 (34.4)	70 (31.0)	173 (28.0)	23 (28.1)	33 (26.6)	21 (39.6)	
South	215 (41.8)	84 (37.2)	291 (47.1)	41 (50.0)	40 (32.3)	24 (45.3)	
West	66 (12.8)	52 (23.0)	87 (14.1)	13 (15.9)	46 (37.1)	4 (7.6)	
MH Diagnosis Category, n (%)							**<0.001**
Anxiety Disorder	32 (6.2)	5 (2.2)	31 (5.0)	1 (1.2)	4 (3.2)	3 (5.7)	
Mood Disorder	301 (58.6)	175 (77.4)	425 (68.8)	56 (68.3)	80 (64.5)	34 (64.2)	
DAB Disorders	87 (16.9)	12 (5.3)	70 (11.3)	9 (11.0)	14 (11.3)	6 (11.3)	
Developmental Disorders	33 (6.4)	5 (2.2)	35 (5.7)	9 (11.0)	11 (8.9)	5 (9.4)	
Psychotic Disorders	23 (4.5)	4 (1.8)	21 (3.4)	3 (3.7)	7 (5.7)	3 (5.7)	
Other MH Disorders	38 (7.4)	25 (11.1)	36 (5.8)	4 (4.9)	8 (6.5)	2 (3.8)	
Prior AAP Exposure, n (%)							**<0.001**
No prior AAP exposure	322 (62.7)	144 (63.7)	364 (58.9)	33 (40.2)	75 (60.5)	19 (35.9)	
Treatment with same AAP as discharge (index admission)	135 (26.3)	53 (23.5)	214 (34.6)	29 (35.4)	20 (16.1)	15 (28.3)	
Treatment with different AAP as discharge (index admission)	57 (11.1)	29 (12.8)	40 (6.5)	20 (24.4)	29 (23.4)	19 (35.9)	
Charlson Comorbidity Score (On Index Admission), n (%)							**0.39**
0	483 (94.0)	209 (92.5)	563 (91.1)	75 (91.5)	116 (93.6)	47 (88.7)	
1	31 (6.0)	17 (7.5)	54 (8.7)	7 (8.5)	7 (5.7)	6 (11.3)	
2	0 (0)	0 (0)	1 (0.2)	0 (0)	1 (0.8)	0 (0)	

**Other AAPs: lurasidone, asenapine, iloperidone, paliperidone, clozapine*

Unadjusted and Adjusted Hazard Ratios of Readmission based on a Cox Proportional Hazards Model for Privately-Insured, Male, US Children (2 to 17 years) with an index admission for Mental Health Treatment, in database 2010 to 2015 (N=1,617)

Variable	***Hazard Ratio (95 CIs)***	***P-value***	***Hazard Ratios (Adjusted)***	***p-value***
Index Admission, Length of Stay (LOS)	1.0 (0.98, 1.0)	**0.51**		
Age Group		**0.13**		
2-12 years	1.4 (0.90, 2.3)		*Violated the proportional hazards assumption. Model stratified on age, so no hazard ratio generated*	
13-17 years	**Reference**			
Patient Region		**0.08**		**0.02**
Northeast	**Reference**		**Reference**	
Midwest	0.61 (0.36, 1.0)		0.55 (0.32, 0.95)	
West	0.56 (0.33, 0.93)		0.44 (0.26, 0.74)	
South	0.56 (0.30, 1.0)		0.45 (0.23, 0.85)	
MH Diagnosis Category		**0.13**		**0.27**
Anxiety Disorder	2.0 (0.78, 5.0)		1.1 (0.60, 1.9)	
Mood Disorders	1.2 (0.58, 2.5)		0.83 (0.57, 1.2)	
Disruptive or Aggressive Behavior Disorders	0.84 (0.34, 2.0)		0.58 (0.31, 1.1)	
Developmental Disorders	0.41 (0.11, 1.5)		0.37 (0.12, 1.1)	
Psychotic Disorders	0.64 (0.17, 2.4)		0.36 (0.11, 1.2)	
Other MH Disorders	**Reference**		**Reference**	
Prior AAP exposure		**<0.001**		**<0.001**
No prior AAP exposure	12.2 (3.0, 49.4)		10.3 (2.5, 42.0)	
Treatment with same AAP as discharge (index admission)	2.1 (0.46, 9.6)		1.8 (0.4, 8.2)	
Treatment with different AAP as discharge (index admission)	**Reference**		**Reference**	
Discharge Atypical Antipsychotic Agent		**0.09**		**0.26**
Risperidone (Risperdal)	**Reference**		**Reference**	
Quetiapine (Seroquel)	0.67 (0.37, 1.2)		0.64 (0.4, 1.0)	
Aripiprazole (Abilify)	0.89 (0.60, 1.3)		0.90 (0.61, 1.3)	
Ziprasidone (Geodon)	0.25 (0.06, 1.0)		0.35 (0.08, 1.4)	
Olanzapine (Zyprexa)	0.48 (0.21, 1.1)		0.53 (0.22, 1.2)	
Other*	0.19 (0.03, 1.4)		0.29 (0.04, 2.1)	

**Other AAPs: lurasidone, asenapine, iloperidone, paliperidone, clozapine*

Demographic and Clinical Characteristics of Privately-Insured, *Female*, US Children (2 to 17 years) with an Index Inpatient Admission for Mental Health Treatment from 2010 to 2015 by Readmission Status (N=1,467)

Characteristic	*Children with readmission (N=185)*	*Children with no readmission (N=1,282)*	*p-value*
Patient Age, Years, Mean± SD	15.5 (1.8)	15.2 (1.9)	0.11
Length of Stay (LOS, days)	8.8 (8.9)	7.7 (6.6)	0.04
Follow Time, (days), Median (Q1, Q3)	93.9 (97.5)	307 (107)	<0.001
Age Group (years), n (%)*			0.11
2-12 years	9 (4.9)	106 (8.3)	
13-17 years (adolescents)	176 (95.1)	1176 (91.7)	
Patient Region, n (%)			0.60
Northeast	16 (8.7)	127 (9.9)	
Midwest	48 (26.0)	352 (27.5)	
South	85 (46.0)	602 (47.0)	
West	36 (19.5)	201 (15.7)	
MH Diagnosis Category, n (%)			0.033
Anxiety Disorder	11 (6.0)	79 (6.2)	
Mood Disorders	148 (80)	1017 (79.3)	
Disruptive or Aggressive Behavior Disorders	3 (1.6)	52 (4.1)	
Developmental Disorders	1 (0.5)	24 (1.9)	
Psychotic Disorders	0 (0)	20 (1.6)	
Other MH Disorders	22 (11.9)	90 (7.0)	
Prior AAP exposure, n (%)			<0.001
No prior AAP exposure at index admission	171 (92.4)	812 (63.3)	
Treatment with same AAP as discharge (index admission)	11 (6.0)	323 (25.2)	
Treatment with different AAP as discharge (index admission)	3 (1.6)	147 (11.5)	
Discharge Atypical Antipsychotic Agent, n (%)			0.01
Risperidone (Risperdal)	32 (17.3)	189 (14.8)	
Quetiapine (Seroquel)	26 (14.1)	271 (21.2)	
Aripiprazole (Abilify)	103 (55.7)	574 (44.8)	
Ziprasidone (Geodon)	9 (4.9)	95 (7.4)	
Olanzapine (Zyprexa)	12 (6.5)	87 (6.8)	
Other*	3 (1.6)	65 (5.1)	
Charlson Comorbidity Score (on Index admission), n (%)			0.79
0	171 (92.4)	1192 (93.0)	
1	14 (7.6)	90 (7.0)	
2	0	0	

**Other AAPs: lurasidone, asenapine, iloperidone, paliperidone, clozapine*

Baseline Demographic and Clinical Characteristics of Privately Insured, Female, US Children (2 to 17 years) with Index Inpatient Admission for Mental Health Treatment from 2010 to 2015, Analyzed by Discharge Atypical Antipsychotic. (N=1,467)

Variable	*Risperidone (N=221)*	*Quetiapine (N=297)*	*Aripiprazole (N=677)*	*Ziprasidone (N=104)*	*Olanzapine (N=99)*	*Other* (N=68)*	*p-value*
Patient Age, Years, Mean (SD)	14.6 (2.5)	15.4 (1.7)	15..4 (1.7)	15.5 (1.7)	15.2 (1.9)	15.7 (1.2)	**<0.001**
Length of Stay (LOS, days),	7.6 (7.3)	8.0 (5.7)	7.4 (7.2)	9.0 (8.2)	8.3 (6.4)	9.0 (7.1)	**0.16**
Follow time, Days, Mean (SD)	278 (128)	298 (119)	268 (130)	306 (112)	274 (137)	294 (122)	**0.003**
Age Group (years) n (%)							**<0.001**
2-12	40 (18.1)	19 (6.4)	42 (6.2)	6 (5.8)	8 (8.1)	0 (0.0)	
13-17	181 (81.9)	278 (93.6)	635 (93.8)	98 (94.2)	91 (91.9)	68 (100)	
Patient Region, N (%)							**<0.001**
Northeast	27 (12.2)	25 (8.4)	74 (10.9)	9 (8.7)	3 (3.0)	5 (7.4)	
Midwest	69 (31.2)	92 (31.0)	168 (24.8)	33 (31.7)	21 (21.2)	16 (23.5)	
South	96 (43.4)	125 (42.1)	333 (49.2)	50 (48.1)	44 (44.4)	39 (57.4)	
West	29 (13.1)	55 (18.5)	102 (15.1)	12 (11.5)	31 (31.3)	8 (11.8)	
MH Diagnosis Category, n (%)							**<0.001**
Anxiety Disorder	23 (10.4)	18 (6.1)	30 (4.4)	2 (1.9)	13 (13.1)	4 (5.9)	
Mood Disorder	160 (72.4)	241 (81.1)	560 (82.7)	84 (80.8)	65 (65.7)	54 (79.4)	
DAB Disorders	14 (6.3)	8 (2.7)	21 (3.1)	7 (6.7)	3 (3.0)	2 (2.9)	
Developmental Disorders	11 (5.0)	1 (0.3)	3 (0.4)	3 (2.9)	7 (7.1)	0 (0.0)	
Psychotic Disorders	3 (1.4)	5 (1.7)	4 (0.6)	4 (0.3)	1 (1.0)	3 (4.4)	
Other MH Disorders	10 (4.5)	24 (8.1)	59 (8.7)	4 (3.9)	10 (10.1)	5 (7.4)	
Prior AAP Exposure, n (%)							**<0.001**
No prior AAP exposure	151 (68.3)	210 (70.7)	475 (70.2)	59 (56.7)	57 (57.6)	30 (44.1)	
Treatment with same AAP as discharge (index admission)	52 (23.5)	51 (17.2)	171 (11.7)	26 (25.0)	14 (14.1)	20 (29.4)	
Treatment with different AAP as discharge (index admission)	18 (8.1)	36 (12.1)	31 (4.6)	19 (18.3)	28 (28.3)	18 (26.5)	
Charlson Comorbidity Score (On Index Admission), n (%)							**0.38**
0	202 (91.4)	276 (92.9)	626 (92.5)	96 (92.3)	96 (97.0)	66 (97.1)	
1	19 (8.6)	21 (7.1)	51 (7.5)	8 (7.7)	3 (3.0)	2 (2.9)	
2	0	0	0	0	0	0	

**Other AAPs: lurasidone, asenapine, iloperidone, paliperidone, clozapine*

Unadjusted and Adjusted Hazard Ratios of Readmission based on a Cox Proportional Hazards Model for Privately-Insured, *Female*, US Children (2 to 17 years) with an index admission for Mental Health Treatment, in database 2010 to 2015 (N=1,467)

Variable	***Hazard Ratio (95 CIs)***	***P-value***	***Hazard Ratios (Adjusted)***	***p-value***
Index Admission, Length of Stay (LOS)	1.0 (0.99, 1.02)	**0.88**		
Age Group		**0.16**		
2-12 years	1.6 (0.83, 3.2)		*Violated the proportional hazards assumption. Model stratified on age, so no hazard ratio generated*	
13-17 years	**Reference**			
Patient Region		**0.65**		
Northeast	**Reference**			
Midwest	1.1 (0.62, 1.9)			
West	1.1 (0.66, 1.9)			
South	1.4 (0.76, 2.5)			
MH Diagnosis Category		**0.13**		**0.41**
Anxiety Disorder	0.60 (0.29, 1.2)		0.70 (0.34, 1.5)	
Mood Disorders	0.62 (0.40, 0.97)		0.70 (0.42, 1.0)	
Disruptive or Aggressive Behavior Disorders	0.26 (0.08, 0.87)		0.33 (0.1, 1.1)	
Developmental Disorders	0.19 (0.03, 1.4)		0.41 (0.05, 3.1)	
Psychotic Disorders	0		0	
Other MH Disorders	**Reference**		**Reference**	
Prior AAP exposure		**<0.001**		**<0.001**
No prior AAP exposure	9.5 (3.1, 29.9)		8.9 (3.7, 21.8)	
Treatment with same AAP as discharge (index admission)	1.7 (0.47, 6.1)		1.6 (0.6, 4.2)	
Treatment with different AAP as discharge (index admission)	**Reference**		**Reference**	
Discharge Atypical Antipsychotic Agent		**0.02**		**0.035**
Risperidone (Risperdal)	**Reference**		**Reference**	
Quetiapine (Seroquel)	0.59 (0.35, 0.98)		0.52 (0.31, 0.88)	
Aripiprazole (Abilify)	1.1 (0.72, 1.6)		0.99 (0.66, 1.5)	
Ziprasidone (Geodon)	0.57 (0.27, 1.2)		0.63 (0.30, 1.3)	
Olanzapine (Zyprexa)	0.86 (0.44, 1.7)		0.87 (0.44, 1.7)	
Other*	0.30 (0.09, 0.96)		0.39 (0.12, 1.3)	

**Other AAPs: lurasidone, asenapine, iloperidone, paliperidone, clozapine*