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Prevalence of Anti-diabetic and Antilipidemic Medications in Children and Adolescents treated with Atypical Antipsychotics in a Virginia Medicaid Population

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A Thesis submitted in partial fulfillment of the requirements for the degree of Master of Pharmaceutical Sciences at Virginia Commonwealth University

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Abstract

PREVALENCE OF ANTI-DIABETIC AND ANTILIPIDEMIC MEDICATIONS IN CHILDREN AND ADOLESCENTS TREATED WITH ATYPICAL ANTIPSYCHOTICS IN A VIRGINIA MEDICAID POPULATION

by

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A Thesis submitted in partial fulfillment of the requirements for the degree of Master of Pharmaceutical Sciences at Virginia Commonwealth University

Virginia Commonwealth University, 2013

Major Director: Cynthia K Kirkwood, Pharm.D., BCPP
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Objective: To determine if the prevalence of anti-diabetic and antilipidemic medication use among children treated with atypical antipsychotics is higher than those not treated with antipsychotics.

Methods: Virginia Medicaid beneficiaries (2-17 years) continuously enrolled from August 1, 2010 to July 31, 2011 with at least two prescription claims for atypical antipsychotics were the exposed group. All other subjects during the study period were the non-exposed group. Prevalence of anti-diabetic and antilipidemic medication use in both groups were computed and compared using Chi-square test (α=0.05).

Results: A total of 299,593 and 4,922 subjects were identified as the non-exposed and exposed groups, respectively. Prevalence of anti-diabetic medication use was 0.32% in the unexposed and 1.40% in the exposed group ($p<0.0001$). Prevalence of antilipidemic medication use was 0.09% in the unexposed and 0.35% in the exposed group ($p<0.0001$).

Conclusion: Prevalence of anti-diabetic and antilipidemic medication use in the exposed group was significantly higher.

CHAPTER 1: Introduction

A. Background

One in four adults experience a psychiatric disorder in any given year.[1,2] According to the National Survey on Drug Use and Health (NSDUH), 13.4% of adults in the United States (US) received treatment for mental illness in 2008.[3] Mental health disorders have also been an issue among children and adolescents. One in ten children have a serious emotional disorder.[1,4] Antipsychotics have become the mainstay of treatment for a number of psychiatric disorders (e.g., psychosis, mood disorders, tic disorder, disruptive behavior disorder).[5]

A national survey conducted on youth in 2002 by Olfson *et al.* showed that there was a 6-fold increase in the number of office visits which resulted in a prescription for an antipsychotic medication between 1993 and 2002.[5] Another survey conducted by Olfson *et al.* from 2005 to 2009 showed that there was a higher number of male patients among children and adolescents with office visits that resulted in the prescription of an antipsychotic agent.[6] A larger percentage of the children had antipsychotic visits for disruptive behaviors disorders in comparison with schizophrenia and bipolar mania. Only a small proportion of the diagnoses for children who received an antipsychotic prescription were for a Food and Drug Administration (FDA) approved indication. The most common off-label indication treated was attention-deficit/hyperactivity disorder. Risperidone was the most commonly prescribed antipsychotic agent.[6]

Use of second generation antipsychotics, or atypical antipsychotics, has increased because of the propensity to cause less adverse extrapyramidal symptoms (EPS) (i.e., dystonia, akathisia, pseudoparkinsonism, tardive dyskinesia) compared with the typical antipsychotics.[7] Typical antipsychotics have been replaced by atypical antipsychotics, for the treatment of schizophrenia.

Studies have shown that atypical antipsychotics are at least as effective as the typical medications in the treatment of psychiatric disorders such as schizophrenia and there has been a rapid rise in the use of atypical antipsychotics.[8-13] According to Olfson *et al.* of the total number of antipsychotics used by a pediatric population, about 92% was classified as atypical antipsychotics.[5]

With increased use of atypical antipsychotics among children and adolescents, the FDA has approved some of these atypical agents for use in the pediatric population. As of 2011, aripiprazole, olanzapine, quetiapine, and risperidone have been labeled for use in children with bipolar mania (age 10-17 years; olanzapine: 13-17 years) and schizophrenia (13-17 years of age). Paliperidone is indicated for adolescents with schizophrenia (12-17 years). Aripiprazole and risperidone also have an indication for irritability/aggression associated with autism (6-17 years of age).[14] Risperidone and aripiprazole were the first atypical antipsychotics to receive a pediatric indication in 2007.

Recently, there has been increased concern about the metabolic adverse effects profile of the atypical agents in both adults and children. Evidence from adult studies suggest that atypical antipsychotics are linked with metabolic disturbances; most commonly weight gain, hyperglycemia, diabetes, and hyperlipidemia.[15] Newer studies indicate that these effects are also seen among children and adolescents.[16] A study by Correll *et al.* showed that atypical antipsychotics were associated with weight gain, obesity, metabolic syndrome, dyslipidemia, glucose abnormalities, and decreased insulin sensitivity in children ages 4 through 19 years. Metabolic syndrome in children and adolescents is characterized by 3 or more of the following criteria: a blood pressure greater than 90th percentile, obesity with Body Mass Index (BMI) greater than or equal to the 95th percentile, triglyceride levels greater than 110 mg/dL,

fasting glucose greater than or equal to 100 mg/dL, and a high density lipoprotein (HDL) less than 40 mg/dL.[16]

Correll *et al.* reported that in children, atypical antipsychotics have the propensity to cause rapid weight gain and increases in BMI (>95th percentile) leading to complications such as obesity (>7% increase in weight), glucose abnormalities (i.e., hyperglycemia), dyslipidemia, and metabolic syndrome.[16] This is of concern as studies have shown that an increase in weight during childhood is a determinant of cardiovascular risk.[17] Weight has a direct correlation with cardiovascular disease. Childhood BMI, weight, and height were significantly correlated with increase in weight, BMI, height, insulin and lipid levels, and systolic blood pressure during adulthood.[17] Other studies showed that higher BMI during childhood was associated with increased fatal heart diseases as adults.[17,18] Childhood obesity is also a predictor of adulthood obesity and diabetes,[19] which are both risk factors for the development of type 2 diabetes mellitus and hyperlipidemia during childhood.[15] However the prevalence of anti-diabetic and antilipidemic medication use among children and adolescents using atypical antipsychotics has not been characterized.

B. Objective and Specific Aims

The objective of this study was to determine if the prevalence of anti-diabetic and antilipidemic medication use among children and adolescents treated with atypical antipsychotics is higher than the prevalence among children and adolescents not treated with atypical antipsychotics. Another goal of the study was to determine the odds of receiving an anti-diabetic or antilipidemic medication based on individual atypical antipsychotic therapy.

This study had the following specific aims:

Specific Aim IA:

To determine and compare the prevalence of anti-diabetic medication use in children and adolescents treated with atypical antipsychotics to those not treated with atypical antipsychotics.

Specific Aim IB:

To determine and compare the prevalence of antilipidemic medication use in children and adolescents treated with atypical antipsychotics to those not treated with atypical antipsychotics.

Specific Aim IIA:

To examine the relationship between the use of individual atypical antipsychotic agents and use of anti-diabetic medication in children and adolescents.

Specific Aim IIB:

To examine the relationship between the use of individual atypical antipsychotic agents and use of antilipidemic medication in children and adolescents.

C. Significance

The metabolic adverse effects of atypical antipsychotics have become problematic among children and adolescents. Increased weight gain and other metabolic effects are usually precursors to the development of diabetes and hyperlipidemia. There are studies in the adult population that observed the development of type 2 diabetes or hyperlipidemia after initiation of antipsychotic treatment.[12, 13] There is a similar study by Andrade *et al.* that evaluated the risk of development of type 2 diabetes mellitus in children and adolescents.[20] Our trial is innovative because no study to date has directly investigated the prevalence of anti-diabetic and antilipidemic medication use in children and adolescents less than 17 years of age treated with atypical antipsychotic agents. There are also no published data on the association between each atypical agent and the use of anti-diabetic or antilipidemic medications. The main objectives of our study were to determine the prevalence of anti-diabetic and antilipidemic medication use among children and adolescents receiving atypical antipsychotics, and to evaluate whether the prevalence of anti-diabetic and lipid lowering medication use differs among the atypical antipsychotic agents. Documenting the odds of receiving an anti-diabetic or antilipidemic medication based on individual atypical agent can help clinicians make informed decisions regarding drug selection among the various atypical antipsychotics. It will help clinicians decide which atypical agents have the least amount of risk, and should be considered for children and adolescents, and which of these agents should be avoided if possible.

Chapter 2: Literature Review

A. Antipsychotic Medication Prescribing Trend

Studies that involved children enrolled in Medicaid programs and Health Maintenance organizations (HMO) have shown that there is a significant increase in the use of antipsychotics.[21-23] The study by Patel *et al.* showed that antipsychotic use was prominent among 10- to 19-year-olds but the greatest increase in use was seen among 5- to 9-year-olds.[23] The study by Cooper *et al.* reported that during 1995 to 2002, there were 5,762,193 outpatients visits, during which an antipsychotic was prescribed, by children in the United States less than 18 years of age. Two-thirds of these children were male and the mean age was 12.9 years. The frequency of antipsychotic prescriptions for children had increased from 8.6 per 1000 children in 1995-1996 to 39.4 per 1000 children in 2001-2002.[21] A very recent study by Zito *et al.* showed that the overall prevalence of antipsychotic use increased from 1.2% in 1997 to 3.2% in 2006.[24]

B. Metabolic Adverse Effects of Atypical Antipsychotics

As stated in the previous chapter, the majority of the antipsychotic prescriptions for children and adolescents are for atypical antipsychotics since these agents are associated with lower risk of EPS. Although atypical agents have lower propensity to cause EPS, there is an increasing concern about whether these agents induce serous metabolic adverse effects (i.e., weight gain, hyperglycemia and hyperlipidemia). A review by Newcomer showed that atypical antipsychotics are associated with increased weight gain, decreased insulin sensitivity, and changes in lipid profiles thus increasing the risk of patients to develop type 2 diabetes mellitus, hyperlipidemia, and metabolic syndrome.[25] Metabolic syndrome is common in obese patients and predisposes children to atherosclerotic cardiovascular disease.[26]

Weight: It has been shown that use of atypical antipsychotics has been associated with increased weight gain. Olanzapine and risperidone were commonly studied antipsychotics and though both cause increased weight gain, olanzapine seems to be associated with significantly greater weight gain. One of the largest cohort studies conducted in a pediatric population of first-time atypical antipsychotic users showed that olanzapine caused a mean increase of 8.5 kg (95% confidence interval [CI] = 7.4 - 9.7 kg) after a median of 10.8 weeks. The study looked at a wide array of antipsychotics and all caused varying degrees of weight gain in order of olanzapine> quetiapine> risperidone> aripiprazole. They also had a comparison untreated group which had minimal weight change of 0.2 kg (95% CI = -1.0 - 1.4 kg) within the same time frame.[16]

Another study showed that during the course of treatment (27 days), 7 new cases or 28% within the olanzapine group and 4 new cases or 17% within the risperidone group were overweight or at risk of being overweight with a BMI> 85%.[27] Another longitudinal study showed that even though there was a significant increase in the BMI z score in the olanzapine and risperidone groups ($p<0.05$), there was no significant weight gain in the quetiapine group. At the end of the 6-month, follow-up period 33% of the patients had significant weight gain, irrespective of group.[28]

The study by McIntyre *et al*. showed that the odds of excessive weight gain were significantly higher for girls and adolescents aged 13 years or older compared with boys. The mean age (standard deviation [SD]) at the onset of obesity was found to be 13.3 (3.7) years in this study.[29]

The study by Moreno *et al*. compared weight gain among young patients with bipolar disorder (psychotic and non-psychotic) who were prescribed atypical antipsychotics. Results showed that there was a gain of about 5.5 kg after the 3-month follow-up in the sample as a whole and no

significant differences were found in weight gain among patients with psychotic or non-psychotic disorders.[30]

Hyperglycemia: In a large cohort study, olanzapine was associated with the greatest increase in glucose levels (3.14 mg/dL, 95% CI = 0.69 - 5.59, p-value < 0.05). Following olanzapine was quetiapine, with moderately higher rates of hyperglycemia even though statistical significance was not acheived.[16] The study by Fraguas *et al*. did not show any statistically significant increase in the glucose levels among the various atypical antipsychotics.[28] This was similar to the results of other longitudinal studies. Changes in fasting glucose did not reach statistical significance.[27,30-32]

One study showed that girls were at an increased risk of developing diabetes mellitus (odds ratio [OR] = 1.79, 95% CI = 1.28 – 2.50) compared with boys. Similarly adolescents over 13 years of age and those who were exposed to multiple antipsychotics were at an increased risk of developing diabetes mellitus compared with younger children. The mean (SD) at the onset for incident type 2 diabetes mellitus was 13.8 (3.8) years.[29]

A possible mechanism could include antagonism of the serotonin 5-$HT_{1A/2A/2C}$ receptors, which results in the inhibition of insulin release, insulin resistance, or impaired glucose utilization. The effects of atypical antipsychotics on alpha adrenergic receptors could also affect the pancreatic beta cell function.[33]

Hyperlipidemia: A large cohort study showed that olanzapine and quetiapine had a statistically significant baseline-to-endpoint change in total cholesterol, triglycerides, and non-HDL. The levels of triglycerides with risperidone were raised significantly. Total cholesterol levels increased by 15.58 mg/dL (95% CI = 6.88 - 24.28) and 9.05 mg/dL (95% CI = 0.41 - 17.69)

within the olanzapine and quetiapine groups, respectively. Triglycerides levels increased by almost 37 mg/dL in the quetiapine group.[16]

A smaller cohort of 66 children also showed that total cholesterol levels had significantly increased in the group of patients who had received olanzapine (p-value = 0.047) and quetiapine (p-value = 0.016) but no significant changes were observed in the risperidone group.[28]

Interestingly, another cohort showed that the rate of dyslipidemia was higher in girls than among boys (OR = 2.08, 95% CI = 1.41 - 3.03) and among those who received more than one antipsychotic. The study also showed that the risk of patients with preexisting obesity and hypertension developing dyslipidemia was almost 4.5 times greater if they had taken an antipsychotic than if they were antipsychotic-naive.[29] Another longitudinal study showed that patients with bipolar disorder and other psychotic disorders had significant increase in cholesterol levels at the end of three months while HDL and triglycerides did not change within any group.[30]

One of the smaller studies in children with Tourette's disorder showed similar results. Thirty-three of the total seventy-three children had developed lipid abnormalities over the course of the study, 28 of the 33 had elevated low density lipoproteins (LDL) values, 8 had decreased HDL values, and some others had elevated triglyceride values.[31] In the study by Khan *et al*., fasting lipid profiles were obtained for 72% of the 25 patients in the olanzapine group and for 75% of the 24 patients receiving risperidone. In the olanzapine group, four of the patients had triglyceride levels equal to or exceeding 110 mg/dL with one patient exceeding 250 mg/dL. Similarly in the risperidone group, only one out of the 18 patients had triglyceride levels equal to or exceeding 250 mg/dL.[27]

Other Outcomes: Some of the studies also reported other outcomes that could be potentially related to metabolic disturbances. Fraguas *et al*. showed that quetiapine was associated with a statistically significant decrease in free thyroxine (FT4),[28] and the systolic blood pressure among patients taking olanzapine was higher than other antipsychotic groups.[27,28] Moreno *et al*. concluded that patients receiving second generation antipsychotics, especially higher doses, were vulnerable to adverse health outcomes (i.e., decrease in FT4, increase in thyroid stimulating hormone [TSH]).[30]

C. Risk of Metabolic Adverse Effects between Atypical Agents

Adult studies

A study was conducted by Lambert *et al*. to evaluate the association between antipsychotic treatment and type 2 diabetes in adult patients with a diagnosis of schizophrenia. It was a matched case-control study design conducted on California Medicaid beneficiaries. Patients with type 2 diabetes were identified using diagnosis codes and receipt of an anti-diabetic medication. Their results showed that the odds of developing type 2 diabetes were significantly higher in patients treated with olanzapine than in patients treated with risperidone. The study concluded that certain atypical antipsychotics (i.e., olanzapine and clozapine) are associated with significantly increased risk of developing new onset diabetes.[34]

Another similar study by Lambert *et al*. looked at the association between antipsychotic treatment and hyperlipidemia in patients with schizophrenia. The study concluded that the risk of developing hyperlipidemia was higher among olanzapine users compared to other atypical antipsychotics.[35] The study reported that patients who had developed hyperlipidemia were more

likely to have been exposed to olanzapine (OR = 1.20, 95% CI = 1.08-1.33). Exposure to risperidone and quetiapine were not significantly associated with developing hyperlipidemia.[35]

Pediatric Studies

Table 2.1 shows the studies that have compared some of the atypical antipsychotics and their propensity to cause metabolic adverse effects in children and adolescents. Except for one study there were no significant changes in the blood glucose levels. Correll *et al*. reported that olanzapine users did have a significant increase in their blood glucose levels.[16]

All the studies showed that olanzapine users had the highest weight gain when compared with other antipsychotics. Quetiapine and risperidone users did have some weight gain. Since obesity and weight gain are predictors for insulin resistance and glucose insensitivity, olanzapine users may be pre-disposed to developing diabetes mellitus.

All the studies showed that children and adolescents using olanzapine had the highest increase in triglycerides and total cholesterol levels in comparison with other psychotics. None of the studies showed risperidone to have any significant effect on lipid levels.

The studies seem to indicate that olanzapine users have the highest risk of developing metabolic adverse effects (e.g., hyperlipidemia and hyperglycemia).

Table 2.1: Review of studies

Reference (year)	Drugs Studied	Glucose	Lipids	Weight Gain
Correll *et al.* (2009)[16]	A= Aripiprazole O= Olanzapine Q= Quetiapine R= Risperidone	O: significant increase by 3.14 mg/dL	O: significant increase in triglycerides, LDL and total cholesterol R,Q: significant increase in triglyceride	O (8.5 kg) > Q (6.1 kg) > R (5.3 kg)
Fraguas *et al.* (2008)[28]	R= Risperidone O= Olanzapine Q= Quetiapine	No significant increase	O: 10 mg/dL increase in total cholesterol	O (11 kg) > R (5 kg) > Q (2.5 kg).
Khan *et al.* (2009)[27]	O= Olanzapine R= Risperidone	No significant changes in fasting glucose	O: 4 patients with elevated triglycerides	O: BMI increase by1.7 kg/m^2 R: BM increase by 1.3 kg/m^2
Sikich *et al.* (2008)[32]	O= Olanzapine R= Risperidone	No significant changes in glucose profile	O: significant increase in total cholesterol (19.9 mg/dL) and LDL (14.7 mg/dL)	O: significant increase in weight (6.1 kg) R: increase of 3.6 kg

D. Type 2 Diabetes Mellitus in Children and Adolescents

Type 2 diabetes is characterized by insulin resistance and a decrease in insulin secretion. In children, it may lead to the early onset of cardiovascular disease, retinopathy, nephropathy, and neuropathy if uncontrolled.[36] Other chronic complications include end-stage renal disease and limb amputations. Because of these complications there is early morbidity and mortality among diabetic patients.[37] Type 2 diabetes is associated with other insulin resistant features (e.g., hyperlipidemia, hypertension and non-alcoholic fatty liver disease).[38] In youth, the mean age of onset is usually around 13.5 years and there is a greater prevalence among patients with non-white European descent.[39]

Diagnostic criteria for type 2 diabetes in children and adolescents (any one of the three):[39]

1) A fasting plasma glucose ≥ 126 mg/dL

2) The post challenge plasma glucose is > 200 mg/dL

3) Symptoms (polyuria, polydypsia, blurring of vision, and weight loss) of diabetes and a casual plasma glucose ≥ 200 mg/dL

The treatment of type 2 diabetes in children and adolescents is multifaceted. Non-pharmacologic therapy (e.g., diet, exercise, and lifestyle modifications) is encouraged before pharmacologic therapy is initiated. The first-line of therapy is metformin. It has similar HbA1c reducing properties to sulfonylureas with minimal risk of hypoglycemia. Metformin can also help with decreasing weight. Metformin is approved for pediatric use and other treatment options should be initiated only after failure of monotherapy with metformin.[39]

E. Hyperlipidemia in Children and Adolescents

Cardiovascular disease is one of the leading causes of death in the United States. A clinical report by Daniels *et al*. reports that even though the clinical burden of CVD occurs in adulthood, the process of atherosclerotic CVD starts earlier on in life during childhood years.[40] A clinical trial found that 15.6% of girls and 11.1% of boys had total cholesterol concentrations greater than 200 mg/dL.[41]

Ford *et al*. reported that only 0.8% of US teens had a LDL cholesterol level above the recommended threshold level (>190 mg/dL or > 160 mg/dL with risk factors) requiring pharmacotherapy. On the other hand, the study also reported that elevated cholesterol levels were found to affect 9-10% of US teens.[42]

According to the latest National Cholesterol Education Program (NCEP) guidelines, the following cut offs should be used to diagnose abnormal cholesterol concentrations in children and adolescents: [43]

1) Total cholesterol < 170 mg/dL and LDL < 110 mg/dL is acceptable

2) Total cholesterol 170-199 mg/dL and LDL 110-129 mg/dL is borderline

3) Total cholesterol ≥ 200 mg/dL and LDL ≥ 130 mg/dL is elevated

The NCEP does not recommend routine lipid screening for children 2-8 years of age and adolescents 12-16 years of age unless they have diabetes, hypertension, increased BMI (≥ 95th percentile for children and ≥ 85th percentile for adolescents), history of smoking, a strong family history of CVD, or a parent with total cholesterol greater than or equal to 240 mg/dL.[43] For children 9-11 years of age NCEP does recommend universal screening with a fasting lipid panel.[43]

According to the guidelines, hyperlipidemia should be initially treated using non-pharmacologic therapy (i.e., healthy lifestyle, dietary modifications). Dietary changes which focus on reducing calorie intake from total and saturated fat are recommended (except for children younger than 2 years). Pharmacologic therapy is reserved only for children greater than or equal to 10 years old with a LDL ≥ 190 mg/dL with no other risk factors, or ≥ 160 mg/dL with risk factors. Children younger than 10 years should not receive pharmacologic therapy unless they have severe primary hyperlipidemia or have a dramatic elevation in LDL ≥ 400 mg/dL or triglycerides ≥ 500 mg/dL. If pharmacologic therapy is warranted, statin therapy should be considered.[43] Statin therapies have been shown to be safe and effective in children.[44] The lowest available dose should be given

once daily and children taking statins should have routine monitoring for adverse effects related to muscle toxicity.[43]

F. Gaps in Literature

It is known that atypical antipsychotics can cause metabolic adverse effects in adults[45] and a study by Draeger *et al*. has reported the prevalence of anti-diabetic and antilipidemic medication use among antipsychotic users in an adult population.[46] Studies in the pediatric population have shown that atypical antipsychotics have the propensity to cause metabolic adverse effects (e.g., weight gain, dyslipidemia and insulin resistance).[16,27,28,32]

No study has looked directly at the prevalence of anti-diabetic and antilipidemic medication use among children and adolescents exposed to atypical antipsychotics. There is knowledge that atypical antipsychotics can cause type 2 diabetes and hyperlipidemia but there is no information about how many of these children are prescribed medications for these metabolic conditions.

Additionally, there are not studies that report the odds of receiving an anti-diabetic or antilipidemic medication among the various atypical antipsychotic agents. This information could help clinicians make informed decisions about which of the atypical antipsychotics is the safest to prescribe.

Chapter 3: Methodology

A. Study Design and Data Source

This was a cross-sectional study using the Virginia Medicaid pharmacy claims data. The dataset was obtained from the Department of Medical Assistance Services (DMAS), the agency that administers Medicaid and CHIP (Children's Health Insurance Program). Medicaid is the health program that is targeted to help families with low income and people with certain disabilities.

For the purpose of this study, Medicaid was an ideal source of data because medication information on children and adolescents could be obtained. All patient identifiers were removed by DMAS to protect the privacy of the patient. Each subject was assigned a unique identifier number by DMAS that was used to link the subject across files.

The study was approved by the Virginia Commonwealth University Institutional Review Board, Office of Research Subjects Protection in February 2012.

B. Study Population

Virginia Medicaid beneficiaries were included in the study if they met the following inclusion criteria:

(i) Subjects were between 2 and 17 years of age.

(ii) Subjects were continuously enrolled in the Medicaid system (Fee-For-Service and Managed Care) from July 31, 2010 to August 1, 2011.

(iii) Only subjects with at least two paid prescription claims for the atypical antipsychotics aripiprazole, quetiapine, olanzapine, risperidone, or ziprasidone were included to be in the

exposed group. The newer antipsychotic agents (i.e., lurasidone, paliperidone, iloperidone, asenapine) were not included in the study as substantial use of these atypical antipsychotic agents in the pediatric population had not been reported.

Subjects were excluded if they met any of the following criteria:

(i) They had juvenile diabetes identified using ICD-9-CM code 250.x1 or 250.x3.

(ii) They had paid pharmacy claims for a typical antipsychotic (e.g., haloperidol, thiothixene, chlorpromazine, fluphenazine, and perphenazine).

(iii) They had paid claims for more than one atypical antipsychotic during the study period. Subjects using more than one antipsychotic during the study period were excluded so that the prevalence of the outcome could be attributed to the particular antipsychotic agent being studied.

C. Data Collection

After excluding subjects with ICD-9-CM codes for juvenile diabetes and those who had pharmacy claims for typical antipsychotics, two data files were obtained from DMAS. The exposed file included all the subjects who had paid pharmacy claims for atypical antipsychotics during the study period. The file also included all other paid pharmacy claims the subjects had during the year. The unexposed file included all subjects who had any pharmacy claims during the study period but were not included in the first file.

Variables: Both files contained the following variables:

- Unique patient identifier: Each subject was assigned a unique 7-digit number.

- Drug name and strength: Each claim was accompanied by the name of the drug and the strength. Each drug was identified using the Generic Code Number (GCN) which groups drugs with the same ingredients, strength, dosage form, and route of administration.

- Age: Age of the subjects was provided as a continuous variable measured in years. Categorical variables for age were created. Subjects were divided into three categories: 2-4 years, 5-11 years, and 12-17 years of age. The categories were based on the age categorization used by the Centers for Disease Control and Prevention (CDC) which approximates pre-schoolers, middle childhood, and teenagers.[47]

- Sex: Sex of the subjects was provided and treated as the categorical variables males and females.

- Race: This categorical variable included White, African-American, American Indian, Oriental/Asian, Hispanic, Native Hawaiian, Asian and White, African-American and White, Unknown, Asian and African-American, and Other. The classes were collapsed into White, African-American, and Others because of the smaller number of subjects among the other groups.

D. Specific Aim I

Identification of Groups

Unexposed group: From the unexposed file given by DMAS, only subjects who were continuously enrolled in Medicaid during the study period were included. These subjects composed the unexposed group. The demographic variables age, sex, and race were reported for the unexposed subjects.

Exposed group: From the exposed file, only subjects who were continuously enrolled during the study period and had at least two paid prescription claims for atypical antipsychotics were included. All subjects who had prescription claims for more than one atypical antipsychotic were excluded from this group. The remaining subjects comprised the exposed group. The demographic variables age, sex, and race were reported for all exposed subjects.

Specific Aim IA: To determine and compare the prevalence of anti-diabetic medication use in children and adolescents treated with atypical antipsychotics to those not treated with atypical antipsychotics.

Outcome: In the unexposed and exposed groups, subjects using anti-diabetic medications were identified from the pharmacy claims data using the GCN. The anti-diabetic agents included insulin, glimepiride, glyburide, glipizide, metformin, glipizide/metformin, glyburide/metformin, pioglitazone, pioglitazone/metformin, rosiglitazone, sitagliptin, acarbose, exenatide, and liraglutide. Subjects who had a prescription claim for an anti-diabetic medication were assigned outcome = 1 and other subjects without a prescription claim were assigned outcome = 0 . Demographic variables age, sex, and race were reported for all subjects in each group who had an anti-diabetic pharmacy claim. The prevalence of use of anti-diabetic medications was then computed in the unexposed and exposed groups:

$$\text{Prevalence} = \frac{\text{Number of subjects with claims for anti-diabetic medication in unexposed group}}{\text{Total number of subjects in unexposed group}}$$

$$\text{Prevalence} = \frac{\text{Number of subjects with claims for anti-diabetic medication in exposed group}}{\text{Total number of subjects in exposed group}}$$

Specific Aim IB: To determine and compare the prevalence of antilipidemic medication use in children and adolescents treated with atypical antipsychotics to those not treated with atypical antipsychotics.

Outcome: In the unexposed and exposed groups, subjects using antilipidemic medications were identified from the pharmacy claims data using the GCN. The antilipidemic agents included atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin, cholestyramine, colestipol, niacin, ezetimibe, fenofibrate, and gemfibrozil. Subjects who had a prescription claim for an antilipidemic medication were assigned outcome = 1 and subjects without a prescription claim for an antilipidemic medication were assigned outcome = 0. Demographic variables age, sex, and race were reported for all subjects in each group who had an antilipidemic pharmacy claim. The prevalence of use of antilipidemic medications was then computed in the unexposed and exposed groups:

$$\text{Prevalence} = \frac{\text{Number of subjects with claims for antilipidemic medication in unexposed group}}{\text{Total number of subjects in unexposed group}}$$

$$\text{Prevalence} = \frac{\text{Number of subjects with claims for antilipidemic medication in exposed group}}{\text{Total number of subjects in exposed group}}$$

E. Specific Aim II

Identification of Subgroups

Subjects who were identified as the exposed group in Specific Aim I were further classified into five subgroups based on the atypical antipsychotic agent they received. The subgroups were aripiprazole, olanzapine, quetiapine, risperidone, or ziprasidone users. The medications were identified using the GCN. The demographics of the subjects receiving each atypical antipsychotic subgroup were reported.

Specific Aim IIA: To examine the relationship between the use of individual atypical antipsychotic agents and use of anti-diabetic medication in children and adolescents.

Outcome: Within the five antipsychotic subgroups, subjects using anti-diabetic medications were identified from the pharmacy claims data. Subjects who had a prescription claim for an anti-diabetic medication were assigned outcome = 1 and subjects without an anti-diabetic pharmacy claim were assigned outcome = 0. The prevalence of use of anti-diabetic medications within each atypical antipsychotic subgroup was computed:

$$\text{Prevalence} = \frac{\text{Number of subjects with prescription claims for anti-diabetic medication}}{\text{Total number of subjects using atypical antipsychotic X}}$$

X = aripiprazole, olanzapine, quetiapine, risperidone, or ziprasidone

Specific Aim IIB: To examine the relationship between the use of individual atypical antipsychotic agents and use of antilipidemic medication in children and adolescents.

Outcome: Within the five subgroups, subjects using antilipidemic medications were identified from the pharmacy claims data. Subjects who had a prescription claim for an antilipidemic medication were assigned outcome = 1 and subjects without an antilipidemic medication pharmacy claim were assigned outcome = 0. The prevalence of use of antilipidemic agents by subjects within each atypical antipsychotic subgroup was computed:

$$\text{Prevalence} = \frac{\text{Number of subjects with prescription claims for antilipidemic medication}}{\text{Total number of subjects using atypical antipsychotic X}}$$

X = aripiprazole, olanzapine, quetiapine, risperidone, or ziprasidone

F. Statistical Analyses

Descriptive statistics were used to summarize the demographic variables age, sex, and race. Categorical data was described using percents and counts. Normal continuous data were described using mean and standard deviation. Chi-square test of homogeneity was performed to test for differences between age, sex, and race between the exposed and the unexposed groups. Fisher's exact test was used when there was inadequate cell size. The prevalence of outcomes between unexposed and exposed groups was compared using Chi-square test of independence. For the second specific aim, the number and percentage of subjects using each of the atypical antipsychotics was reported.

Logistic regression analyses were used to test the following:

Specific Aim IA: The relationship between exposure to atypical antipsychotics (Yes = exposed group, No = unexposed group) and outcome (1 = anti-diabetic claim, 0 = no anti-diabetic claim).

Specific Aim IB: The relationship between exposure to atypical antipsychotics (Yes = exposed group, No = unexposed group) and outcome (1 = antilipidemic claim, 0 = no antilipidemic claim).

Specific Aim IIA: The relationship between exposure to individual atypical antipsychotic agent (aripiprazole = 1, olanzapine = 2, quetiapine = 3, risperidone = 4, ziprasidone = 5) and outcome (1 = anti-diabetic claim, 0 = no anti-diabetic claim).

Specific Aim IIB: The relationship between exposure to individual atypical antipsychotic agent (aripiprazole = 1, olanzapine = 2, quetiapine = 3, risperidone = 4, ziprasidone = 5) and outcome (1 = antilipidemic claim, 0 = no antilipidemic claim).

In the first specific aim, the unexposed group was used as the reference. For the second specific aim, olanzapine was used as the reference. Since olanzapine had the highest propensity to cause weight gain, dyslipidemia and glucose imbalance, it was chosen as the reference.[16, 27, 30, 32] Logistic regression analyses were performed. Logistic regression analyses, controlled for age, sex, and/or race, were also performed if the variables were found to have a significant relationship with the outcome individually. The unadjusted and adjusted OR and 95% confidence intervals were reported for all logistic regression analyses. For the adjusted OR, 2-4 years, male, and White were used as the reference groups for age, sex, and race respectively. All tests were performed at a significance level of 0.05, and SAS 9.3 statistical package was used for all analyses.

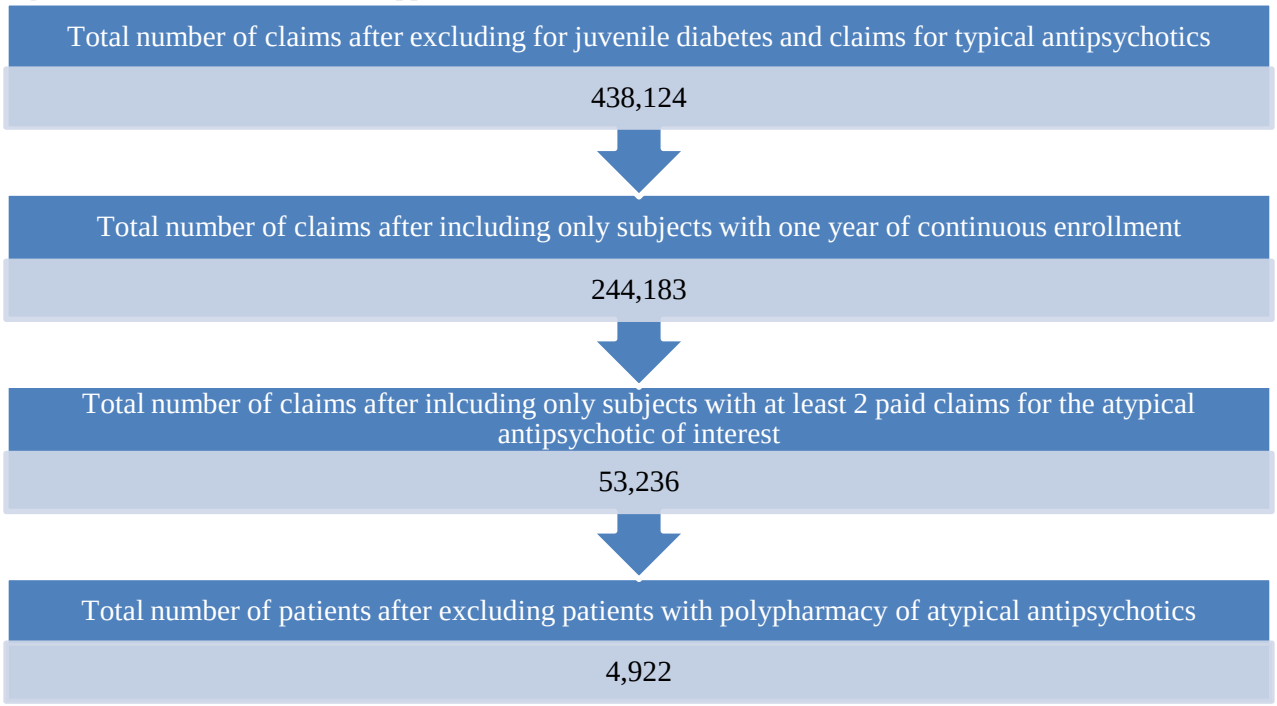
Chapter 4: RESULTS

A. Comparison of Subjects Exposed and Unexposed to Atypical Antipsychotics

DMAS provided two files after excluding subjects with a diagnosis of juvenile diabetes and subjects with pharmacy claims for typical antipsychotics. One file was for the unexposed group and the other for the exposed group. The unexposed file contained information on 2,502,643 pharmacy claims. After including only those subjects who were continuously enrolled in the Virginia Medicaid system during the study period, a total of 299,593 unique subjects with 2,286,629 claims were identified in the unexposed group.

The second file had information on the subjects who were exposed to atypical antipsychotics. It contained information on 438,124 pharmacy claims. As shown in Figure 4.1, 244,283 claims remained after including only subjects with one year of continuous enrollment. After including only those subjects who had at least 2 paid pharmacy claims per atypical antipsychotic, 53,236 claims remained. A total of 4,922 unique subjects were identified in the exposed group after excluding for subjects receiving more than one atypical antipsychotic.

Figure 4.1: Flow of claims after application of inclusion/exclusion criteria



(i) Baseline Characteristics of the Study Groups

Unexposed group: Table 4.1 illustrates the baseline demographic characteristics of the subjects by exposure to atypical antipsychotics. The mean age (SD) of the total sample of unexposed children was 8.23 (4.70) years with the highest percentage of children (43.34%) falling within the category of 5- to 11-year-olds. Approximately 38% of the subjects were White and African-American each and there was an equal distribution of males versus females.

Exposed group: Baseline characteristics of the subjects in the exposed group are shown in Table 4.1. The mean age of the subjects was 11.77 (3.65) years and almost 55% of the subjects were between 12 and 17 years of age. More than two-thirds of the subjects were male and the majority was White.

The unexposed and exposed groups were significantly different in their baseline demographics (Table 4.1). Therefore, age, sex, and race was controlled for in the logistic regression analyses.

Table 4.1: Baseline demographic characteristics of study subjects

Characteristic		Unexposed Group n (%) (N=299,593)	Exposed Group n (%) (N=4,922)	p-value
Age:	2-4 years	86,362 (28.83)	113 (2.3)	<0.0001
	5-11 years	129,838 (43.34)	2,088 (42.42)	
	12-17 years	83,393 (27.84)	2,721 (55.28)	
	Mean (SD)	8.23 (4.70)	11.77 (3.65)	
Sex:	Males	150,059 (50.09)	3,367 (68.41)	<0.0001
Race:	White	115,011 (38.39)	3,261 (66.25)	<0.0001
	African-American	113,671 (37.94)	1,187 (24.12)	
	Others	70,911 (23.67)	474 (9.63)	

(ii) Prevalence of Anti-diabetic Medication Use

In the unexposed group, 957 of 299,593 subjects had paid claims for an anti-diabetic medication during the study period. In the exposed group, 69 of 4,922 subjects had paid claims for an anti-diabetic medication. The prevalence of anti-diabetic medication claims was 0.32% among children and adolescents who were not exposed to antipsychotics and 1.40% in those exposed to atypical antipsychotics. The prevalence of anti-diabetic medication use was significantly higher among the subjects exposed to atypical antipsychotics compared with those who were not exposed (χ^2 = 168.96, df = 1, p-value < 0.0001). Demographics of subjects on anti-diabetic

medications are shown in Table 4.2. Because of the small cell sizes, Fisher's exact test was performed. Sex and race were found to be significantly different between the two groups. There were significantly more males in the exposed group who had claims for anti-diabetic medications. There was no significant difference in the ages between the groups (p-value = 0.3667). Of the subjects with claims for antidiabetic drugs, 92.75% in the exposed and 83.70% in the unexposed group had claims for metformin.

Table 4.2: Demographics of subjects with claims for anti-diabetic medications

Characteristic		Anti-diabetic claims		p-value
		Unexposed Group n (%) (N=957)	**Exposed Group n (%) (N=69)**	
Age:	2-4 years	4 (0.42)	1 (1.45)	0.3667
	5-11 years	175 (18.29)	13 (18.84)	
	12-17 years	778 (81.30)	55 (79.71)	
	Mean (SD)	13.82 (2.67)	13.86 (2.92)	
Sex:	Males	272 (28.42)	30 (43.48)	0.0131
Race:	White	445 (46.50)	49 (71.01)	<0.0001
	African-American	399 (41.69)	18 (26.09)	
	Others	113 (11.81)	2 (2.90)	

Logistic regression analyses: In the regression analysis, exposure to an atypical antipsychotic was found to be an important predictor to whether a subject received an anti-diabetic medication (χ^2 = 141.08, df = 1, p-value < 0.0001). The odds of having a claim for anti-diabetic medication for children and adolescents exposed to an atypical antipsychotic agent were 4.44 (95% CI = 3.47 - 5.68) times higher than in children and adolescents not exposed to these agents. Age (χ^2 = 679.04, df = 2, p-value < 0.0001), sex (χ^2 = 169.29, df = 1, p-value < 0.0001), and race (χ^2 = 85.32, df = 2, p-value < 0.0001) were found to have a significant relationship with receiving an anti-diabetic medication. Table 4.3 summarizes the results of the unadjusted and adjusted logistic regression analyses. After controlling for age, sex, and race the odds of having a claim for anti-diabetic medication for children and adolescents exposed to an atypical antipsychotic agent were 2.76 (95% CI = 2.15 - 3.55, p-value < 0.0001) times higher than children and adolescents not exposed to antipsychotics. Children between 5 and 17 years had higher odds of having anti-diabetic medications compared with 2- to 4-year-olds. Female children were at higher odds of being prescribed an anti-diabetic medication. White children had higher odds of anti-diabetic medication use compared with African American children or those of other race.

Table 4.3: Regression analyses for prevalence of anti-diabetic medications

	Unadjusted Regression Model			Adjusted Regression Model controlling for Age, Sex, and Race		
	OR	95% CI		OR	95% CI	
		Lower	Upper		Lower	Upper
Exposure						
Unexposed	1 (reference)			1 (reference)		
Exposed	4.44	3.47	5.68	2.76	2.15	3.55
Age	N/A					
2-4 years				1 (reference)		
5-11 years				23.23	9.56	56.47
12-17 years				146.09	60.62	352.05
Sex	N/A					
Male				1 (reference)		
Female				2.34	2.04	2.67
Race	N/A					
White				1 (reference)		
African-American				0.91	0.79	1.03
Others				0.61	0.50	0.75

(iii) Prevalence of Antilipidemic Medication Use

In the unexposed group, 261 of the 299,593 subjects had paid claims for an antilipidemic medication during the year. Within the exposed group, 17 of the 4,922 subjects had paid claims for an antilipidemic medication. The prevalence of antilipidemic medication use among children

and adolescents who were not exposed to antipsychotics was 0.09% which was significantly lower than the 0.35% prevalence of antilipidemic medication use in those exposed to atypical antipsychotics ($\chi^2 = 35.41$, df = 1, p-value < 0.0001). Demographics of subjects on antilipidemic medication use are listed in Table 4.4. Fisher's exact test showed that sex and race were significantly different between the two groups. In the exposed group, significantly more males had claims for antilipidemic medications (p-value = 0.0416). There was no significant difference in the ages between the groups (p-value = 0.2909). A total of 64.71% of the subjects in the exposed and 55.17% subjects in the unexposed group had claims for statins.

Table 4.4: Demographics of subjects with claims for antilipidemic medications

Characteristic		Antilipidemic claims: Unexposed Group n (%) (N=261)	Antilipidemic claims: Exposed Group n (%) (N=17)	p-value
Age:	2-4 years	37 (14.18)	0	0.2909*
	5-11 years	58 (22.22)	4 (23.53)	
	12-17 years	166 (63.60)	13 (76.47)	
	Mean (SD)	11.82 (4.93)	13.94 (3.75)	
Sex:	Males	146 (55.94)	14 (82.36)	0.0416
Race:	White	142 (54.41)	14 (82.35)	0.0326
	African-American	61 (23.37)	3 (17.65)	
	Others	58 (22.22)	0	

*Non-significant

Logistic regression analyses: In the regression analysis exposure to an atypical antipsychotic was found to be an important predictor to whether a subject received an antilipidemic medication (χ^2 = 30.30, df = 1, p-value < 0.0001). The odds of having a claim for an antilipidemic medication for children and adolescents exposed to the atypical antipsychotic agent were 3.97 (95% CI = 2.43 - 6.50) times higher than children and adolescents not exposed to antipsychotics. Age (χ^2 = 148.01, df = 2, p-value < 0.0001), sex (χ^2 = 5.68, df = 1, p-value < 0.0171) and race (χ^2=36.24, df = 2, p-value < 0.0001) were found to have a significant association with whether the subjects received an antilipidemic medication. Table 4.5 shows the results of the adjusted and unadjusted logistic regression analyses. When controlled for age, sex, and race the odds of having a claim for an antilipidemic medication for children and adolescents exposed to an atypical antipsychotic agent were 2.12 (95% CI = 1.34 - 3.64, p-value = 0.0018) higher than children and adolescents not exposed to these agents. Subjects 12 to 17 years of age were found to have higher odds than 2- to 4-year-olds to receive antilipidemic medications. Unlike the results with anti-diabetic medications, females were found to have lower odds than males to receive an antilipidemic medication. White children had higher odds than African-American children of having antilipidemic medication claims.

Table 4.5: Regression analyses for prevalence of antilipidemic medications

	Unadjusted Regression Model			Adjusted Regression Model controlling for Age, Sex, and Race		
	OR	95% CI		OR	95% CI	
		Lower	Upper		Lower	Upper
Exposure						
Unexposed	1 (reference)			1 (reference)		
Exposed	3.97	2.43	6.50	2.21	1.34	3.64
Age	N/A					
2-4 years				1 (reference)		
5-11 years				1.07*	0.71	1.61
12-17 years				4.76	3.32	6.82
Sex	N/A					
Male				1 (reference)		
Female				0.73	0.57	0.93
Race	N/A					
White				1 (reference)		
African-American				0.44	0.33	0.59
Others				0.82*	0.60	1.11

*Non-significant

B. Comparison of Subjects Exposed to Atypical Antipsychotics by Drug

(i) Demographics of Subjects Using Select Atypical Antipsychotic Agent

Figure 4.2 shows the prevalence of subjects on each atypical antipsychotic agent during the study period. Among subjects who were exposed to any one of the five atypical antipsychotics (*n*=4,922), the largest number of the subjects had claims for risperidone while the fewest had claims for olanzapine. The demographics based on atypical antipsychotic use are found in Table 4.6. Subjects having claims for olanzapine, quetiapine, and ziprasidone had a mean age of 13 years while risperidone users were the youngest. Among each of the atypical antipsychotic users, there were more male than female users.

Figure 4.2: Percentage of subjects using each atypical antipsychotic agent

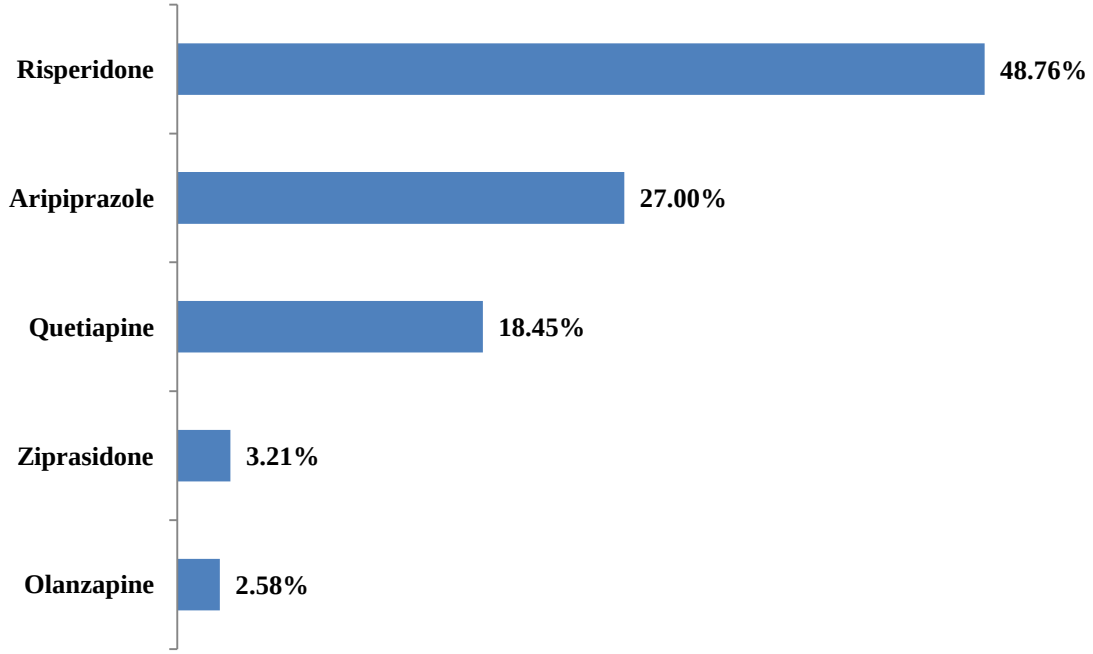


Table 4.6: Demographics of subjects using each atypical antipsychotic agent (*n*=4,992)

Drug	*n*	Sex	Age (years)				
		Males (%)	Mean (SD)	Range	2-4 (%)	5-11 (%)	12-17 (%)
Aripiprazole	1329	843 (63.43)	12.46 (3.35)	3-17	13 (0.98)	489 (36.79)	827 (62.23)
Olanzapine	127	107 (84.25)	13.02 (3.29)	5-17	0	43 (33.86)	84 (66.14)
Quetiapine	908	529 (58.26)	13.32 (3.12)	4-17	3 (0.33)	230 (25.33)	675 (74.34)
Risperidone	2400	1793 (74.71)	10.63 (3.67)	2-17	97 (4.04)	1286 (53.58)	1017 (42.38)
Ziprasidone	158	95 (60.13)	13.26 (3.08)	5-17	0	40 (25.32)	118 (74.68)

(ii) Prevalence of Anti-diabetic Medication Use

The prevalences of anti-diabetic medication use among the antipsychotic subgroups were computed and shown in Table 4.7. The highest prevalence of concomitant anti-diabetic medication use was among ziprasidone users (8.23%). Among olanzapine users, which were hypothesized to have highest prevalence of concomitant anti-diabetic medication use, only 3.15% had claims for anti-diabetic agents. Risperidone users had the lowest prevalence of concomitant anti-diabetic claims (0.46%).

Table 4.7: Prevalence of anti-diabetic medication and antilipidemic medication use by drug

Atypical Antipsychotic Agent	Anti-diabetic (%)	Antilipidemic (%)
Aripiprazole (N=1329)	2.18	0.53
Olanzapine (N=127)	3.15	0.79
Quetiapine (N=908)	1.32	0.22
Risperidone (N=2400)	0.46	0.21
Ziprasidone (N=158)	8.23	1.27

Logistic regression analyses: Table 4.8 shows the results of the adjusted and unadjusted logistic regression analyses. The regression model showed that individual atypical antipsychotic agent use was significantly associated with whether the subject received an anti-diabetic medication (χ^2 = 53.57, df = 4, p-value < 0.0001). Risperidone users were found to have 0.14 (95% CI = 0.04 - 0.45) times lower odds than olanzapine users to receive an anti-diabetic medication. Ziprasidone users were found to have 2.76 (95% CI = 0.88 - 8.67) times higher odds than olanzapine to receive an anti-diabetic medication but this was not significantly different from olanzapine users (p-value = 0.0829). Since race was not found to be significantly associated with whether the subjects received an anti-diabetic medication or not in the exposed group (χ^2 = 3.19, df = 2, p-value = 0.2033), only age (χ^2 = 15.16, df = 2, p-value = 0.0005) and sex (χ^2 = 18.45, df = 1, p-value < 0.0001) were added to the regression model. After controlling for age and sex, antipsychotic use by agent was significantly associated with receipt of anti-diabetic medication claim (χ^2 = 44.54, df = 4, p-value < 0.0001). Risperidone users had 0.15 (95% CI = 0.04 - 0.47) times lesser odds of receiving an anti-diabetic medication compared with olanzapine users.

Ziprasidone had the highest odds but it was not significantly different than olanzapine users (p-value = 0.2158).

Table 4.8: Regression analyses of concomitant anti-diabetic medication use

	Unadjusted Regression Model			Adjusted Regression Model controlling for Age, and Sex		
	OR	95% CI		OR	95% CI	
		Lower	Upper		Lower	Upper
Atypical Antipsychotic						
Olanzapine	1 (reference)			1 (reference)		
Aripiprazole	0.69*	0.24	1.98	0.56*	0.19	1.63
Quetiapine	0.41*	0.13	1.30	0.29	0.09	0.94
Risperidone	0.14	0.04	0.45	0.15	0.04	0.47
Ziprasidone	2.76*	0.88	8.67	2.08*	0.65	6.65
Age	N/A					
2-4 years				1 (reference)		
5-11 years				0.44*	0.06	3.47
12-17 years				1.01*	0.13	7.64
Sex	N/A					
Male				1 (reference)		
Female				2.41	1.47	3.95

* Non-significant

(iii) Prevalence of Antilipidemic Medication Use

The prevalence of antilipidemic medication use among individual antipsychotic users is shown in Table 4.7. Risperidone users had the lowest prevalence of antilipidemic medication use (0.21%) which was similar to the prevalence of quetiapine (0.22%). Even though it was expected that olanzapine users would have the highest prevalence of antilipidemic medication use, ziprasidone users had the highest prevalence at 1.27%.

Logistic regression analyses: The logistic regression analysis was not able to show that there was a significant difference in the prevalence of receiving an antilipidemic medication between the different antipsychotic agents (χ^2=6.49, df = 4, p-value < 0.1653). Since age, sex, and race were not found to have a significant relationship with whether the subjects received an antilipidemic medication or not, they were not added into the regression model. The model showed that ziprasidone users had the highest odds of 1.61 (95% CI = 0.14 - 18.02), and risperidone and quetiapine users had the lowest odds of 0.26 (95% CI = 0.03 - 2.27) and 0.28 (95% CI = 0.02 - 3.09), respectively, but none were significantly different from olanzapine users for antilipidemic medication use.

Chapter 5: DISCUSSION

A. Main Findings

The use of atypical antipsychotics has been correlated with weight gain, insulin resistance, and lipid abnormalities in adult populations.[45] Draeger *et al*. assessed the prevalence of anti-diabetic and antilipidemic medication use among adult users of atypical antipsychotics, and reported that aripiprazole users had slightly higher odds than other atypical antipsychotic users of receiving an anti-diabetic or antilipidemic medication.[46]

Though similar studies on anti-diabetic and antilipidemic mediation use have not been done in the pediatric population there is evidence that atypical antipsychotics cause substantial weight gain, insulin resistance, and metabolic syndrome.[15,16,20,26,48,49] Studies have shown that increased weight gain and obesity during childhood are indicative of early development of metabolic syndrome, type 2 diabetes, and cardiovascular disease during adulthood.[17,19] There are clinical guidelines describing how to address and treat children and adolescents who have type 2 diabetes[39] or hyperlipidemia.[40] This raised the question of whether children on atypical antipsychotics who develop insulin resistance and lipid panel changes had to be started on anti-diabetic and antilipidemic medications.

To the best of our knowledge, this is one of the few studies that has evaluated the prevalence of diabetic medication use among children exposed to atypical antipsychotics[20] and the only study to evaluate the prevalence of antilipidemic medication use among children. The prevalence of anti-diabetic medication use was significantly higher among children and adolescents with claims for atypical antipsychotics than those children and adolescents who were not using atypical antipsychotics. We found that about 1.40% of atypical antipsychotic users had anti-

diabetic medications compared with 0.32% among non-antipsychotic users. The use of anti-diabetic medications among atypical antipsychotic users was more than four times the use of anti-diabetic agents among children not using atypical antipsychotics. This is similar to the results of the study by Andrade *et al*. which showed that the incidence of diabetes appeared to be more than four times higher among children and adolescents using atypical antipsychotics compared with those who were not.[20] In this study, we also estimated the odds of receiving anti-diabetic agents after controlling for demographic characteristics (i.e., age, sex, and race). We found that exposure to antipsychotics was still an important predictor of receipt of anti-diabetic prescriptions. Metformin was the most commonly prescribed anti-diabetic medication which is in accordance with the International Society for Pediatric and Adolescent Diabetes (ISPAD) guidelines on treating type 2 diabetes in children and adolescents.[39]

The prevalence of antilipidemic medication use was 0.35% among atypical antipsychotic users and 0.09% among non-users. The use of antilipidemic medications among children prescribed antipsychotics was almost four times higher than the prevalence of antilipidemic agents among non-users. Even after adjusting for demographic factors, the odds remained higher for antipsychotic users. According to the NCEP guidelines, pharmacotherapy should be reserved only for those children above 10 years of age with LDL levels exceeding 190 mg/dL.[43] Pharmacologic therapy should be reserved for children less than 8 years of age with a dramatic elevation in cholesterol values (i.e., over 500 mg/dL). A study by Ford *et al*. showed that 0.8% of teenagers in the United States had LDL values above the cut-off of 190 mg/dL thereby requiring pharmacotherapy.[42] This would imply that the true number of atypical antipsychotic users with hyperlipidemia is higher than 0.35% because only a small fraction of these children would have been started on a drug regimen.

Though the prevalence rates are relatively small, the clinical impact is relevant. Our study showed that 69 and 17 children out of the 4,922 subjects exposed to atypical antipsychotics were prescribed anti-diabetic and antilipidemic medications, respectively. These numbers came from only one Medicaid database during the period of one year, therefore the numbers at a national level would be higher and could be a cause for concern. Studies have shown that children and adolescents with abnormalities in their glucose or lipid levels are at higher risk to develop hypertension and dyslipidemia as adults.[39] Children and adolescents prescribed atypical antipsychotics could be predisposed to develop diabetes, hyperlipidemia, and hypertension as adults.

Most of the demographic results of this study are consistent with published trials. In previous reports, the majority of the atypical antipsychotic users were males[20, 28] and White[28] which was consistent with our results of 68% males and 66% White. The mean age of children receiving atypical antipsychotics in our study was about 12 years which is less than the mean age of 15 years reported by Fraguas *et al.*[28] This could reflect the fact that the Fraguas study was conducted between 2001 and 2005, before aripiprazole, risperidone, quetiapine, and olanzapine received FDA approval for pediatric use and the use of these agents might have been reserved for older chlidren.

It was reported by McIntyre *et al.* that the odds of developing type 2 diabetes mellitus were higher for girls and adolescents.[29] The Agency for Healthcare and Research and Quality (AHRQ) does state that women are at higher risk of developing diabetes and that weight gain is a risk factor. Our study showed that females and adolescents had higher odds of receiving anti-diabetic medications. A limitation in our findings is that metformin can also be used off-label to treat polycystic ovarian syndrome (PCOS) in female children and adolescents[50] and our study did not

exclude for subjects with PCOS. A study has shown that 5% of women develop PCOS and require pharmacotherapy.[51] In addition; metformin has been prescribed for the treatment and prevention of atypical antipsychotic–induced weight gain and metabolic changes.[52]

The same study by Fraguas *et al*. reported that the odds of developing dyslipidemia were higher for females and adolescents[28] but our study showed that the odds of receiving antilipidemic medications were significantly higher for males and adolescents. Larger studies using data from multiple states are needed to obtain robust results.

Atypical antipsychotics are being used in children and adolescents to treat various neuro-psychiatric disorders (e.g., irritability associated with autism, tics, bipolar mania, schizophrenia).[14] Even though some of the atypical antipsychotics are approved for pediatric use by the FDA, most are only approved for children as young as 10 years old. Risperidone is indicated for the treatment of irritability associated with autistic disorder in children as young as 5 years old.[53] Our study showed that atypical antipsychotics were being used in children as young as 2 years old which indicates that these agents were being prescribed off-label in this young pediatric population.

Our study showed that the most commonly prescribed atypical antipsychotic was risperidone while the least commonly prescribed was olanzapine during the study period. A retrospective study by Pathak *et al*. of a state's Medicaid administrative claims data from 2001-2005 reported that risperidone was the therapy initiated for most children while ziprasidone was the least common therapy initiated in new users.[54] A possible explanation for the high use of risperidone could be that risperidone has been commercially available for a longer period of time and had received its pediatric indication earlier than other atypical antipsychotics. The use of ziprasidone

during the study by Pathak *et al*. was off-label. Over the years, the increasing use of ziprasidone may be reflective of published literature supporting the use of ziprasidone over agents with a higher propensity to cause metabolic effects (i.e., olanzapine).[16,28] Our study has shown that the use of olanzapine among children was less frequent than risperidone which may be secondary to the number of studies reporting the harmful effects of olanzapine in children.[26]

A study by Seida *et al*. showed that there were no major differences among olanzapine, risperidone, and quetiapine in insulin resistance.[55] Another study by Correll *et al*. showed that olanzapine, and quetiapine had higher propensity to cause increase glucose levels.[16] In contrast, a study by Cohen *et al*. reported that risperidone caused a greater glucose imbalance than olanzapine.[56] There has been varying evidence on the propensity of each drug to cause glucose imbalance. Our study, which specifically looked at receipt of anti-diabetic medication, showed that risperidone users had the lowest prevalence of anti-diabetic medication use. Children and adolescents who were prescribed risperidone had lower odds than olanzapine users to receive an anti-diabetic medication. Interestingly, our study showed that ziprasidone users had a higher prevalence of anti-diabetic medication use than olanzapine users. However, the OR was not found to be significantly different between olanzapine and ziprasidone users. The small sample sizes in the ziprasidone and olanzapine groups are limitations; hence there may not have been enough power to detect a significant difference. Ziprasidone use among children has not been studied as extensively as the other antipsychotics. Most of the studies were very short term and the longer studies had very limited sample sizes.[26] Definitive conclusion regarding the metabolic effects of ziprasidone in children cannot be made until more studies are published in this area. Because of the cross-sectional nature of our study, it cannot be determined whether some of the ziprasidone users were children who had previously used olanzapine and were switched

secondary to metabolic adverse effects. Ziprasidone users in our trial were in a higher age category compared with olanzapine users. Because of these limitations, conclusions regarding ziprasidone cannot be made based on our data.

The studies by Correll *et al.* and Fraguas *et al.* have shown that olanzapine was associated with the highest change in lipid levels among children and adolescents.[16,28] Our study failed to identify differences in the odds of receiving antilipidemic medications among the various antipsychotic users. The prevalence was the highest among ziprasidone users, followed by olanzapine users, and the lowest among risperidone users. However, the differences were not statistically significant. The failure to show a statistical difference could be because of the small number of children with antilipidemic mediation use, and hence there may not have been enough power to reach statistical difference. It is interesting to note that with just 17 children having antilipidemic prescriptions among antipsychotic users, a significance level of 0.1653 was reached. It may be a worthwhile attempt to replicate this study in a larger setting with more power.

This study adds to the findings of the trials that have been published. To the best of our knowledge, this is the only study that has looked at antilipidemic medication use in children and adolescents and one of the few studies that evaluated anti-diabetic medication use.[20] There are studies that have looked at adverse effects of antipsychotics or have addressed the development of type 2 diabetes mellitus. Several studies have evaluated the development of hyperlipidemia in children and adolescents on atypical antipsychotics,[16] but none have reported actual antilipidemic medication use in this population. Since there were differences in the demographics between the groups, regression analyses controlling for these variables were done to see how they would affect the nature of the relationship. We also computed the prevalence of anti-diabetic and

antilipidemic medication use among a non-exposed group that was identified from the same Medicaid database to use as a comparator group. This is the only study that has assessed the odds of receiving anti-diabetic and antilipidemic medications among the various individual antipsychotics. Clinicians can use the prevalence and the odds of receiving anti-diabetic medication among atypical antipsychotic users to make informed decisions. The study has also set the groundwork for more studies in this area, possibly in larger, multicenter settings.

B. Limitations

Firstly, this is a cross-sectional study; hence we cannot establish any causal relationship between exposure to atypical antipsychotics and receipt of anti-diabetic or antilipidemic medications. This is not a longitudinal study looking at the long term effects of antipsychotic use. We have tried to address this limitation within the constraints of the study design by including only those subjects who had at least two paid claims for any one antipsychotic.

Secondly, because of the nature of the study, antipsychotic use is a crude measure. We cannot distinguish if subjects were switched from one antipsychotic before the study period. For example, if a patient developed diabetes while using olanzapine then was switched to ziprasidone and initiated on metformin, the anti-diabetic claim would have been included for this ziprasidone user. Also, it cannot be assumed that because a prescription for a medication was dispensed, it was consumed by the patient.

Thirdly, there were varying sample sizes between the antipsychotic users and a small number of subjects with the outcomes of interest. Some of the sample sizes may have been too small to reach statistical significance.

A fourth limitation is potential confounders that were not controlled for. Factors such as physical activity, diet, and family history could affect the risk of receiving anti-diabetic and antilipidemic agents. A survey-based design would be more appropriate to capture such variables. We also did not adjust for pre-existing diabetes or hyperlipidemia. Confounding by indication could also be a potential limitation because metformin could have been used to treat other disorders (e.g., PCOS), or used to treat or prevent weight gain or metabolic effects of atypical antipsychotics and not just diabetes.

Lastly, a major limitation is the limited generalizability of the study since this study used data from only a single state Medicaid pharmacy claims database. The results cannot be generalized to other pediatric populations, especially among those children not enrolled in Medicaid.

C. Future Directions

Further research should be done in this area to study the effects of all atypical antipsychotics. There is a need to carry out similar studies in a larger setting, i.e., a multi-state Medicaid study. This would ensure a larger sample and enough observations within each category to identify true differences. Studies should also examine the newer antipsychotics (e.g., lurasidone, asenapine) even though their use has not been significant among children and adolescents. Studies could also incorporate variables such as diet, physical activity, polypharmacy of antipsychotics, and concurrent use of other psychotropic medications, and study their individual relationship with the probability of receiving anti-diabetic or antilipidemic medications.

More longitudinal studies looking at long term effects of exposure to atypical antipsychotics in children and adolescents are needed after excluding for pre-existing diabetes and hyperlipidemia. The results of these studies could help clinicians with informed decision making.

D. Conclusion

In summary, the prevalence of anti-diabetic and antilipidemic medication use among children and adolescents using atypical antipsychotics (olanzapine, risperidone, quetiapine, aripiprazole, and ziprasidone) was almost four times higher than the prevalence among children and adolescents not treated with the atypical antipsychotics. Risperidone users had lower odds of receiving anti-diabetic medication compared with olanzapine users. There were no significant differences between the individual atypical antipsychotics and receipt of antilipidemic agents. We also found that age, sex, and race were significant predictors of whether children on atypical antipsychotics received anti-diabetic and antilipidemic medications.

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