

2-13-2014

# Factors Contributing to Weight Gain in Children Who Take Atypical Antipsychotics

Martha Faulkner

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**FACTORS CONTRIBUTING TO WEIGHT GAIN IN  
CHILDREN WHO TAKE ATYPICAL ANTIPSYCHOTICS**

by

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DISSERTATION

Submitted in Partial Fulfillment of the  
Requirements for the Degree of  
**Doctorate of Philosophy in Nursing**

The University of New Mexico

Albuquerque, New Mexico

December, 2013

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ABSTRACT

Children and adolescents with serious emotional disturbance (SED) who take atypical antipsychotics (AAs) gain significant amounts of weight. The purpose of this retrospective chart review study was to determine if type of AA, diagnosis, ethnicity/race, age, gender or months in treatment contribute to BMI  $z$  change score (weight gain). The sample was 110 children with SED who took AAs for 1-36 months,  $M$  age=10.5 years ( $SD=3.4$ , range 5-17), 67% male, 53% Hispanic or Latino. The average weight gain in the study was 22 pounds (0.33 BMI  $z$  change score). The percent of children classified as overweight or obese increased from 14% and 26% to 21% and 34%, respectively. Children on olanzapine, risperidone and quetiapine gained significantly more weight than children on aripiprazole or ziprasidone [ $t(106) = 1.16$ ;  $p = .01$ ;  $d = .23$ ]. Results of the hierarchical multiple regression (HMR) showed an interaction between type of AA and months in treatment. Months in treatment, the combined AA variables of olanzapine/quetiapine and aripiprazole/ziprasidone (with risperidone as the reference category), and the interaction terms for these variables together significantly explained

14% of the explained variance of the BMI  $z$  change score [ $F(5,103) = 3.40, p < .01$ ].

Distinct patterns of weight gain were revealed for each type of AA. The longer the child was on olanzapine, quetiapine, aripiprazole and ziprasidone, the more weight they gained. In contrast, children on risperidone lost weight over time [ $b = -.03, SE(b) = .01, p < .001$ ]. Diagnosis, ethnicity, age, and gender did not significantly contribute to BMI  $z$  change score. In conclusion, examining these demographic and treatment factors shed light on the unknown interaction between type of AA and pattern of weight gain over months in treatment and could support the development of time specific interventions to slow or halt weight gain.

## **Dedication**

To Gordon, my husband, and Jackson, my son for the multitude of sacrifices they have endured to support this dream.

To my sister Lu Ann and brother Keith for always supporting me and cheering me on no matter what!

To my parents, Jane Faulkner Coalson and Kenneth K. Faulkner for instilling in me a lifelong curiosity, the love of and thirst for learning...and to Robert Coalson for echoing those sentiments.

Finally to the children and adolescents of New Mexico who have and continue to struggle with mental illness, may your futures be brighter because of research done on your behalf.

## **Acknowledgments**

This has been a journey of unusual proportions that even I could not have predicted when Dr. Tigges interviewed me for the PhD program in 2003 and, asked me, “What is the likelihood that you will you finish this program?” I thought, “What a silly question I finish everything I start!” Yet here I am nine years later, grateful that I had the personal fortitude and unconditional support of my family and friends and my enduring chair and committee!

Challenges faced during this journey centered on balancing all things essential; my family, my 60+-hour workweek, and my ever-present doctoral research. As a novice researcher, the constantly changing design, hypothesis and analyses of my study were daunting.

My greatest appreciation and love are to my son Jackson and husband Gordon, as I learned to be flexible, to ask for help and accept it, to never give up and to believe in myself...no matter what!

Thank you to Dr. Beth Tigges for her enduring presence in my educational endeavors these past 13 years, as she was my thesis chair and now my dissertation chair. I appreciate her interest in my educational career as well as her patience and expert guidance in this process.

Thank you to Dr. Marie Lobo, for her steadfast reassurance and for consistently reminding me of the significance of and meaning in my research. Her expertise with vulnerable children and families, and PhD students was invaluable.

Thank you to Dr. Leah Albers whom I've long admired for her extensive international research career in all things midwifery. Thank you for sticking around after you retired to see this through and for your kind, abiding presence.

Thank you to Dr. Marcia Moriarta, the only member of my committee with expertise in child psychology, for giving well-considered advice and guidance throughout. Her unique perspective and warmth have enriched this dissertation.

Thank you to Blake Boursaw for jumping in with both feet to help me at a moment's notice on all things statistics! I so valued your time, energy and insights into my study. Your patience and quirky sense of humor were appreciated.

Thanks to Candace Schau, Ph.D., who helped me examine and correct my database for her encouragement and insights.

Thank you to Rashmi Sabu, M.D., for her never-ending support, collegial respect, and friendship and Marybeth Graham, Ph.D., who cheered me on long distance, and reminded me to "walk the dog" each and every day.

Thank you to Nichole Roesler, R.N., and Karen Leveille for your help in identifying and screening potential charts.

Thank you to my Ph.D. cohort, particularly Yolanda Morales, Ph.D., and Rebecca Mayo, Ph.D.

Finally thank you to the Gamma Sigma Chapter of Sigma Theta Tau International for a financial grant in support of my research in 2009.



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# **Chapter 1**

## **Introduction**

## **Purpose**

The purpose of this research was to determine whether or not various demographic, diagnostic, and treatment characteristics contribute to the amount of weight gain in children with serious emotional disturbance (SED) who take atypical antipsychotics (AAs). Little to no research has been done to study factors that might contribute to weight change or gain in children who take AAs. Rapid weight gain is a frequent side effect of AAs and predisposes these children to dyslipidemia and diabetes. Because SED is a chronic, lifelong disorder, unless more research occurs, the potential is high that obesity in children who take AAs will be chronic as well. Although childhood obesity is squarely in the radar of many health care researchers, children with a SED who have weight changes while taking AA medications seemed to have fallen off the radar in terms of current research. Other children gain minimal or no weight. It was hypothesized that there are demographic, diagnostic, and treatment characteristics that contribute to the amount of weight gain in this population.

A retrospective chart review of 110 purposively sampled children with SED on AAs was conducted to answer the question of whether type of AA, diagnosis, ethnicity, age, gender and months in treatment contributed to the amount of BMI z score change/weight change or gain that children experience when taking these medications. A hierarchical multiple regression analysis was run to answer this question. This chapter will begin with the theoretical framework that guided this study, continue with a brief discussion of key concepts, a clear statement of the problem, and conclude with the research questions, hypotheses and significance to nursing.

## Theoretical Framework

The *Bioecological Systems Theory*, created by developmental psychologist Uri Bronfenbrenner, is the theoretical perspective that guides this investigation.

Bronfenbrenner was one of the earliest theorists to assert that a child's development was shaped by the interactions of many interrelated and layered environments. Further, each environmental layer (ecology) or sphere of influence is characterized by its proximity to the child with the microsystem closest, followed by the mesosystem, the exosystem, and finally the macrosystem. The chronosystem is the overarching progression of historical time that affects the development and maturation of the child. Nested within each other, each ecology encircles the child in a dynamic atmosphere of multiple symbiotic systems. Relationships between the ecologies are bidirectional and shape the growth and development of the child and are affected by the child. Change at any level of the system causes change in other ecologies, causing a ripple effect.

The microsystem is the foundation upon which the development of the child is based, and contains the proximal processes of the child's biology, family, school, and peer group where social roles and interconnections occur in close proximity (Bronfenbrenner, 1979). The network of the connections and processes that transpire between two or more settings in which the developing child inhabits comprises a mesosystem. This would include the interface of the child with their school, community, pediatric and psychiatric provider. In contrast to the mesosystem, an exosystem is a network of the connections and processes that transpire between the child and in environments that do not contain the child. Events occur in these settings that indirectly influence the child and how they function within their immediate setting. An exosystem

for a child could be between home and a parent's workplace. The parent may be stressed within their workplace and carry that stress home to the child, indirectly impacting their environment. The macrosystem is the invariable form and content of the constellation of the micro-, meso- and exosystem. Even though cultures and subcultures are different, Bronfenbrenner argued that internally they are homogenous in the content of the settings, the roles and relationships played at successive life stages, the substance and organization of activities, and the nature and breadth of connections between settings that affect the developing person (Bronfenbrenner, 1979). This theory was well suited to this research because of the multiple interacting ecologies that surround the child and adolescent with SED who takes AAs.

## **Key Concepts**

### **Serious Emotional Disturbance**

Thirteen to 20% of children and adolescents have a mental disorder in any given year (Merikangas, He, Fisher, Bourdon, & Koretz, 2010b; O'Connell, Boat, & Warner, 2009; World Health Organization, 2011) and, for those adolescents who are 13 to 18 years of age, the lifetime prevalence for any mental health disorder is 46.3% and for a severe disorder is 21.4% (Merikangas et al., 2010). Twelve percent, or 4.3 million youth, have a serious emotional disturbance (SED) that significantly impairs their ability to function in their home, school, and the community (Costello, Egger, & Angold, 2005). These impairments adversely affect the way the adolescent develops socially and emotionally as well as the way they interact with their environment. As the child with SED grows into an adult, meeting normal cognitive, social, and emotional developmental tasks are often delayed and permanently altered. Consequently, these children are at an



increased risk for mental disorders in adulthood (O'Connell, Boat, & Warner, 2009) and have poorer life outcomes when compared to children with other disabilities or children without disabilities (Southerland, Casanueva, & Ringeisen, 2009; Wagner et al., 2005).

Vulnerable children and adolescents with SED may have an exceedingly different developmental journey from their peers without SED. Educational, employment, social, and health barriers develop for this population (Betz, 1998; Farmer, Clark, & Marien, 2003; Geenen, Powers, & Sells, 2003; Institute of Medicine (IOM), 2006; O'Connell, Boat, & Warner, 2009) placing them at jeopardy for involvement in high-risk behaviors (Davis, 2003; Vander Stoep et al., 2000; Wehmeier, Schacht, & Barkley, 2010). Many children with SED are reared in compromised family environments, with parents who also have SED, substance abuse, or low socioeconomic status. They are without the usual support systems and coherent perceptual and social skills available to children and adolescents without SED. Raised without protective factors that enhance resilience and self-esteem, such as supportive and involved parents, they are in danger of slipping into high-risk behaviors.

Exposure to and participation in crime (Constantine, Andel, & Robst, 2013; Southerland et al., 2009), violence, welfare, smoking, suicide, and unprotected sex are greater for children with SED, and for many at a younger age, than their peers without SED (Blum, Kelly, & Ireland, 2001; Southerland et al., 2009). As the mental health of children or adolescents deteriorates, they may become involved in illegal activities or harm others or themselves, possibly requiring a higher level of care such as hospitalization or incarceration. The families, psychiatric providers, and systems of care are often left to pick up the emotional and financial pieces. This is a vulnerable

population with few resources available for coordinated treatment and support.

Medications are one component of treatment for this population and assist in keeping them on a healthier developmental trajectory. Atypical antipsychotic medications are prescribed to manage disabling psychiatric symptoms in an effort to promote safety of the children and others, and to facilitate normal childhood psychosocial development.

**Weight change, weight gain, and body mass index.** Despite the epidemic of overweight and obesity, the experts cannot agree on a standardized definition of weight change or gain for children, adolescents, or adults (Correll & Carlson, 2006). Significant weight change for adults, however, is expressed as a percent of the body weight (Stevens, Truesdale, McClain, & Cai, 2006) and defined as less than +3% of body weight. Stevens et al. further distinguished clinically significant weight change for adults as +5% of body weight. How this weight change is measured is also a topic of debate. Techniques used to measure or estimate fat have been skin fold thickness, under water weight, dual energy x-ray absorptiometry, and body mass index (BMI), but all have problems with accuracy or practicality (Gallagher & Song, 2003). The accuracy of skinfold thickness has been questioned due to difficulty in reproducing those results and the limited sites of measuring on the body (Rodriguez et al., 2005). Also, underwater weighing and dual energy x-ray absorptiometry are often impractical and expensive.

The BMI, calculated as the bodyweight (in kilograms) divided by the square of the height (in meters) (Dudek, 2006), is practical, reproducible, and inexpensive.

Although universally applied in measuring adult obesity, there are certain problems that affect the use of BMI for assessing children's weight (Neovius, Linne, Barkeling & Rossner, 2004).

While growth in height and weight is a universal phenomenon in children and adolescents, BMI varies with sex, age, and different maturation patterns. Additionally, different growth spurts and accumulation of muscle increase the child's BMI and may not accurately reflect the measure of fat in the child's body. Widespread application of BMI to children is also problematic because ethnic differences abound that pertain to percentage of body fat. Overall, children's rate of weight and height change is low and steady until the growth spurt of puberty. During puberty, weight change, or gain and height increase are highly variable and dependent on individual maturational patterns, which account for about 15-20% of adult height and 50% of adult weight attained during this period (Dudek, 2006).

Mei et al. (2002), compared the CDC age and sex specific BMI for age reference to the Roherer index (where skinfold thickness is used in the formula), to the weight for height in screening for overweight children aged 2 to 19 years. A BMI, sex, and age-specific reference were better than the Roherer index and similar to that of weight for height. Furthermore, BMI was found to correlate to the direct means of measuring weight underwater, dual energy x-ray absorptiometry (Mei et al., 2002), and bioelectrical impedance analysis (BIA) (Phan, Maresca, Hossain, & Datto, 2012) and was superior to BIA when considering a child's age, race, and gender.

Body mass index is endorsed in the literature as the best clinical measure of weight change in children because it is specific to the individual's baseline weight and has high specificity (Ackerman & Nolan, 1998), thereby creating few false positives (Reilly, Wilson, Summerbell, & Wilson, 2002). Also, the BMI-for-age-growth charts are sex-specific (Centers for Disease Control (CDC), 2010) and are the most widely used tool

of measuring overweight for children. Recent efforts have been made to further refine the definition of weight change or gain for children and adolescents who take atypical antipsychotics.

The American Diabetes Association (ADA), American Psychiatric Association, American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity (2004) proposed guidelines for the care and monitoring of adults who receive atypical antipsychotics. Switching atypical antipsychotics was recommended if the patient's weight increased more than or equal to 5% of baseline weight (ADA et al., 2004). Criteria for the definition of significant weight change or gain in body composition in children and adolescents who receive atypical antipsychotics was proposed by Correll and Carlson (2006) as  $> 5\%$  gain during the first three months of treatment, due to its consistency with adult ADA recommendations and the assertion that this short time of normal growth should not contribute to weight change. Weiss et al. (2004) also examined weight change and maintained that an increase in the BMI z score of  $\geq 0.5$  increased the risk of metabolic syndrome by 55%.

Children in this research took atypical antipsychotics for a period of 3 months to 3 years. The body mass index (BMI z score) is standardized for the age and gender of the child and accounts for height as well as weight, therefore the BMI z score was used to assess whether the child had a weight change. The BMI z scores were calculated by obtaining the child's weight in kilograms from the chart review, the height in centimeters, and the child's gender and age in years and then entering this information at <http://www.bcm.edu/cnrc/bodycomp/bmiz2.html> into the children's BMI-percentile-for-age calculator. Weight change was calculated by taking the baseline BMI z score (prior

to initiation of the AA) and subtracting the BMI z score when the AA was discontinued (final BMI z score), no less than 3 months or more than 3 years from starting the AA. This calculation was labeled the BMI z change score or weight change. If, however, the child was switched to a different AA during that three-year period, those BMI z change scores were also recorded at the time of the switch.

**Atypical antipsychotics.** Antipsychotics are a class of medications that are often prescribed to individuals with SED in an effort to manage disabling psychiatric symptoms such as psychosis and extreme mood instability combined with extreme behavioral dyscontrol, and includes both typical and atypical agents (McDonagh, Peterson, Carson, Fu, & Thakurta, 2010). Biochemically, all antipsychotics target the flow of dopamine in four major pathways that innervate large areas of the brain to manage psychosis, extreme mood instability, and cognition. Typical agents block the production of dopamine and reduce symptoms but can produce potentially permanent involuntary movements and cognitive dulling. Atypical antipsychotics modulate the flow of dopamine and are much less likely to produce these side effects and can actually enhance cognitive functioning, thereby making them the preferred choice for children and adolescents.

Children with SED are often prescribed AAs to reduce or eliminate psychiatric symptoms in an effort to promote their safety and the safety of others, and to facilitate normal childhood psychosocial development. Atypical antipsychotics have been used more than typical antipsychotics to treat a variety of SEDs in children and adolescents because of the theoretically more benign side effect profile (Carroll & Carlson, 2008). Furthermore, the ease of once or twice a day dosing, and the ability to obtain therapeutic

levels without blood draws, enhance compliance. However, rapid weight gain, which most commonly occurs within the early months of administration (Correll et al., 2009; Correll and Mayaan, 2011; Vanina et al., 2002) is a significant problem causing statistically significant weight gain (Almandil et al., 2013). Although AAs appear to trigger significant weight gain, it is unknown to what degree other variables such as the type of AA, diagnosis, ethnicity/race, gender, age, SES, or time on AA might also contribute to the amount of weight change or gain in children and adolescents.

Most of the early research about contributing demographic, diagnostic, and treatment characteristics and behavioral variables for overweight, obesity, and weight change in this population had been done with adults, and incorrectly generalized to children. However, there is now a growing body of knowledge upon which to build, but this body of knowledge is incomplete.

Children are not little adults and have unique reactions to their environment that are multifactorial and exist beneath an ever-changing overlay of growth and development that persists across time. Therefore it is important to examine variables that might contribute to weight change or gain within the larger context of the developing ecologies and facets both proximal and distal to the child or adolescent: type of AA, diagnosis, ethnicity/race, gender, age, SES or length of time on the AA.

The type of AA may predict whether or not a child is predisposed to gaining more weight or having weight change. It has been postulated that the type of AA and its affinity for histamine is predictive of weight gain (Kroeze et al., 2003). Limited research however, has been conducted with children and adolescents regarding this issue. Aripiprazole is thought to have less affinity for histamine and therefore less weight gain,

but that has not always proven to be the case, as with one male adolescent who took aripiprazole and gained 25 pounds in a six-week period. Therefore, it is important to explore this issue further.

Adults with schizophrenia, even when medication naïve, are often genetically predisposed to overweight and obesity, lipid abnormalities, and diabetes (Allison et al., 1999; Saddichha, Ameen, & Akhtar, 2008; Thakore, 2004). Shrivastava & Johnston (2010) note that weight gain for adults with affective disorders is prevalent, but note that it appears to result from a combination of the illness and effects from medication. For children and adolescents, diagnosis may also be related to the potential for weight change or gain, but no data exists in the literature. Additional research must be conducted to determine whether early dietary and physical activity education and preventative treatment should be implemented for this population as part of normative treatment guidelines.

Socioeconomic status (SES) is inversely associated with overweight and obesity (Salonen et al., 2009) as cheap and available foods are often highly caloric, fat laden, and highly processed (Cohen, Sturm, Lara, Gilbert, & Gee, 2010) and children who take AAs and live in poverty may be vulnerable to metabolic challenges (Crystal, Olfson, Huang, Pincus, & Gerhard, 2009), but no definitive research has been done for this population on AAs. Native American, Hispanic, and African American children and adolescents without SED are more likely to gain weight than Caucasian or Asian children (Dixon, Pena, & Taveras, 2012; Eichner et al., 2008), but no research has been done with these specific populations. Research with self-identified African Americans with schizophrenia indicates that they have significant antipsychotic drug induced weight gain

(Chan, Zai, Monda, Potkin , 2013), but again no data of this nature in children and adolescents. Furthermore, although there are some data regarding the influences of age and gender on weight gain in children and adolescents, for this population no research has been conducted.

**Obesity in children.** Obesity is the most prevalent nutritional disease of children and adolescents in the United States (Strauss & Pollack, 2003) and a subject of vital epidemiological, economic, social and clinical concern. In 2009-2010, 16.9% of children and adolescents were obese (Ogden, Carroll, Kit, Flegal, 2012). One of the *Healthy People 2020*'s goals is to “promote health and reduce chronic disease risk through the consumption of healthful diets and achievement and maintenance of healthy body weights” (U.S. Department of Health and Human Services (USDHHS), 2013).

Significant weight gain is a serious side effect of AAs, which is more severe in children than adults and therefore an ideal area to study and target for intervention.

An earlier review of 10 studies indicates the range of weight gain is between 1.9 to 7.88 kg with varying types of AAs and over variable periods of time and with different diagnoses (Cheng-Shannon et al, 2004) however the greatest weight gain was with olanzapine and risperidone. These findings endure as De Hert et al. (2011) in their systemic review of 24 randomized controlled trials (RCTs) of olanzapine, risperidone, quetiapine, aripiprazole, and ziprasidone and Almandil et al. (2013) in their review of 21 RCTs of olanzapine, risperidone, and aripiprazole noted that all the studies reported statistically significant weight gain. The range of weight gain in these studies is seen in Table 1. Although it is unclear why weight gain is more severe in children with SED who take an AA, the impact of the weight gain is unmistakable.



Table 1  
*Current Meta Analyses of RCTs of AA and Weight Gain/Change*

Source/Sample	Range (kg)	Least Change	Most Change
De Hert et al. (2011) RTC	-0.04 to 3.45	ziprasidone	olanzapine
24 RCTs n= 3048			
Almandil et al. (2013)	.94 to 4.34	aripiprazole	olanzapine
21 RCTs n=2,455			

Children and adolescents who have an SED and are overweight or obese are three times more vulnerable and suffer physical and psychological effects, often for a lifetime (Pulgarón, 2013; Puhl & Brownell, 2003). Physical consequences are well known and include orthopedic problems, diabetes, cardiovascular disease, and cancer. Psychological effects are debilitating for children and adolescents due to the social stigma of overweight and obesity. Noted as “the last socially acceptable form of prejudice,” (Stunkard & Sorenson, 1993) obesity transmits the consequences of psychological and social import that can be as devastating as the physical cost (DePierre & Puhl, 2013; Zometkin, Zoon, Klein & Munson, 2004). The physical and psychological sequelae of overweight and obesity for children with SED can affect their quality of life (QOL). Research with this focus could significantly contribute to the knowledge base to develop tools for assessment and interventions for treatment.

**Quality of life.** Children with only psychiatric illness and or only overweight or obese often struggle from social stigmatization (DePierre & Puhl, 2013; Puhl & Brownell, 2003). Weight gain for children and adolescents with psychiatric illness simply magnifies the social stigma of mental illness and it is anticipated that their QOL suffers. It is also difficult to determine what influences the QOL has in this sample of children on their SED or their overweight or obesity. Although there is an increasing body of research regarding the QOL of overweight and obese children and adolescents, no studies have been conducted with children who have SED and have gained weight.

### **Statement of the Problem**

Weight change and gain in children and adolescents with SED who take AAs to manage symptoms of their mental illness is a significant issue. Lifelong physical and psychological health is adversely affected, threatening their developmental trajectory and their ability to have a happy fulfilling life. However, no definitive cause for the weight gain is known. As children and adolescents develop within home, school, community and world environments, varying demographic, diagnostic, and treatment characteristics potentially contribute to gain weight. Furthermore, no research studying this problem could be found in the literature. Therefore, the aim of this study was to explore unexamined variables in the weight change or gain of children and adolescents with SED who take AAs. Type of AA, diagnosis, ethnicity/race and age, gender, SES and time on the AA were the variables under investigation. The majority of children in this study were on Medicaid, therefore analyzing the effect of SES on weight gain was not possible and it was removed from the analysis. Results from this research informs clinical assessment, practice, and interventions to possibly prevent or limit weight gain in this

population. This investigation targeted these issues through the following research questions and hypotheses.

### **Research Questions and Hypotheses**

#### **Research Question 1**

What demographic, diagnostic, and treatment characteristics (type of AA, diagnosis, ethnicity/race, gender, age, and months in treatment) contributed to BMI  $z$  change score (difference in baseline BMI  $z$  score and final BMI  $z$  score) in children who take AAs?

1.
  - a. H1 Children and adolescents who took olanzapine, risperidone, and quetiapine gained more weight than children who took aripiprazole and ziprasidone
  - b. H2 Children and adolescents who had mood/affective disorder, psychotic disorder, and anxiety disorder diagnoses gained more weight than children who had a diagnosis of disruptive behavior, pervasive developmental disorder, and tic disorder diagnoses.
  - c. H3 Children and adolescents from Hispanic or Latino, Native American, or Black or African American or Other (mixed race) ethnicity/race gained more weight than children who were from the White or Asian ethnicity/race.
  - d. H4 Children who are prepubescent (ages 9-13) gained more weight than children and adolescents who were ages 6 to 8 or 14 to 17.
  - e. H5 Females had more weight gain than males.

## **Research Question 2**

Does amount of time on an atypical antipsychotic affect the amount of weight a child gains?

2.

a. H6 The longer time the child or adolescent is in treatment the more weight they gain.

### **Summary of Procedures**

A retrospective chart review was conducted on a purposive sample of 110 children and adolescents with a DSM-IV<sup>TR</sup> diagnosis of psychiatric illness, from a university affiliated child psychiatric inpatient facility and outpatient clinic in a southwest state, who took an AA for three months to three years to evaluate if the type of AA, diagnosis, ethnicity, age, gender, and months in treatment had an effect on BMI  $z$  change score/weight change.

Charts were referred to the study by registered nurses, clinical social workers, child psychologists, a nurse practitioner or child psychiatrists, and were screened by the PI or a research assistant (RA) to assure that they met criteria for the research. Data were systematically collected using a Chart Review Form (CRF) and included the type of AA the child was taking; his or her diagnosis, ethnicity/race, age, gender, the date that the AA was initiated, the age, height, and weight of child at initiation; and the age, height and weight of the child when the AA was discontinued, switched to another AA, or at three years' time.

The BMI and BMI  $z$  score at date of initiation, when the AA was discontinued, switched to another AA or at three years' time was then calculated at

<http://www.bcm.edu/cnrc/bodycomp/bmiz2.html> and documented on the CRF. The BMI  $z$  change scores/weight changes were calculated by subtracting the baseline BMI  $z$  score from the BMI  $z$  score at AA discontinuation, at AA switch to a different AA, or at three years time. These BMI  $z$  change scores/weight change were documented on the CRF. Finally, the RA checked 10% ( $n = 11$ ) of the charts reviewed by the PI to assure accuracy in documentation.

To answer question one and test the associated hypotheses, data collected from the first trial of AAs were first analyzed using bivariate analyses ( $t$ -tests, ANOVA, Pearson correlations) of associations between the respective independent variables and BMI  $z$  change scores. The analyses were followed by a hierarchical multiple regression analysis to determine what demographic, diagnostic, and treatment factors contributed in combination to the amount of BMI  $z$  change score

For the hierarchical multiple regression, months in treatment was entered initially, followed by types of AA, interaction variables of types of AA by months in treatment, diagnosis, ethnicity/race, age, and gender. Categorical variables of type of AA, diagnosis, ethnicity/race, and gender were dummy coded; age and months in treatment were continuous variables. Descriptive statistics were also provided.

To answer question two, months in treatment was regressed upon BMI  $z$  change score to determine whether or not length of time on medication would influence amount of weight change.

### **Significance for Nursing**

Psychopharmacological treatment of children and adolescents with SED has primarily been guided by experience and research with adults. This is concerning

because conclusions drawn from adults' responses to AAs cannot be directly extrapolated to children and adolescents (Correll and Carlson, 2006; Correll et al., 2009). Children are more prone to developing side effects and accordingly more sensitive to the deleterious effect on their self-confidence (Farguas et al., 2011; Pringsheim, Lam, Ching, & Patten , 2011).

In the past 8 to 10 years, however, RCTs have been conducted with a greater number of children and adolescents on AAs, thereby adding to the incomplete knowledge base of earlier case studies and small open-label studies. Atypical antipsychotics are frequently prescribed in children and adolescents, therefore demographic, diagnostic, and treatment characteristics and their effect on weight change or  $z$  change score are important to assess, particularly since this population will continue to grow and develop into adults. It is postulated that dynamic variables in the environment impact weight change or a BMI  $z$  score change. This study provides a foundation from which future research can be completed, can assist in planning on which medication to prescribe to which child, and provides information regarding potential associations that were previously unknown.

This dissertation reviews the literature by examining the Bioecological Systems Theory and its applicability to this topic. Then the background and significance of children with SED are covered, along with AAs, their mechanism of action, and AA use in children and adolescents; obesity and the extent of weight change in this population; and the variables of type AA, diagnosis, ethnicity/race, age, gender, and time on medication that could contribute to BMI  $z$  score change in this population. The study design, research methodology, and analysis are then explained. The results of the data

analysis and a discussion regarding the findings and nursing implications of the research  
conclude the dissertation.

## **Chapter 2**

### **Review of Literature**



Psychopharmacological treatment for children and adolescents with serious emotional disturbance (SED) is flawed by a lack of rigorous empirical research within this population. Treatment is guided by research conducted with adults, with standards of care for children and adolescents limited and therefore controversial, even among child psychiatry providers. Atypical antipsychotics (AAs) are used in adults and children to manage severe illnesses such as schizophrenia and bipolar disorder. Children are born within a family surrounded by widening circles of interrelated spheres of influence. For children who have a SED, these spheres could include but are not limited to a child's psychiatric medication, the psychiatric diagnosis, the ethnicity/race, socioeconomic status, and gender. Research regarding the quality of life for children with SED indicates that they are prone to high risk behaviors and poorer life outcomes. In this chapter, an organizing theory is presented followed by a review of the literature concerning children with SED and treatment, obesity as a side effect of treatment, quality of life, along with other factors that are potential contributors to obesity in children with SED. The emphasis in this chapter is a critical review of the literature using a specific theoretical lens to provide a foundation for the proposed investigation.

### **Bioecological Systems Theory**

Developmental psychologist Uri Bronfenbrenner formulated the ecological systems theory to explain child development within the context of the many interrelated environments surrounding the child (Figure 1). *The Ecology of Human Development, Experiments by Nature and Design* (Bronfenbrenner, 1979), defined 'ecologies' as complex layers of environments nested within each other. A child's development was not purely psychological, but a "constellation of forces—cultural, social, economic,

political” (Ceci, 2006, p. 173). Each layer is distinguished by its proximity to the child, with the three main ecologies described as the microsystem, mesosystem, and exosystem. These spheres of influence interact with the developing organism, the child, to promote and shape growth. Change at any level of the environment causes change in other layers, causing a ripple effect that alters the child’s developmental trajectory, and in turn transforms the environment.

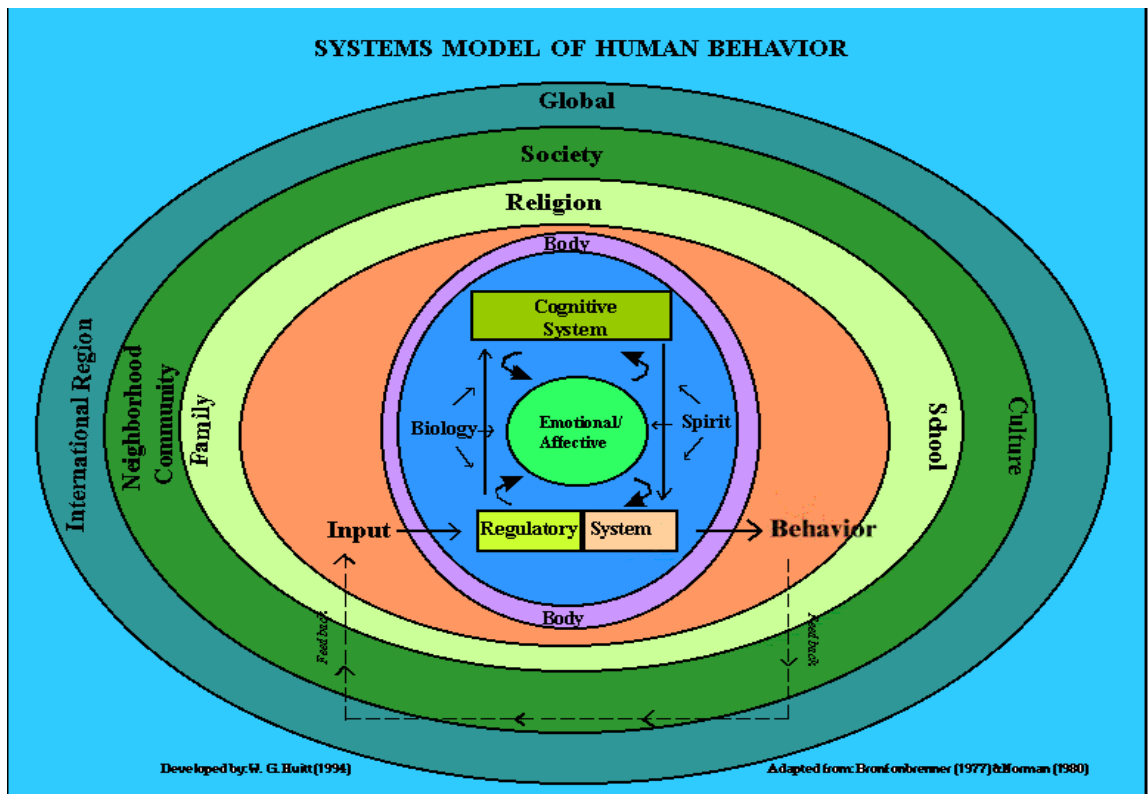


Figure 1. Ecological systems model developed by Urie Bronfenbrenner that demonstrates five nested structures that influence child development. These layers multidirectional influence on the child and on each other. Adapted from U. Bronfenbrenner (1979), W. G. Huitt (1994), and D. A. Norman (1980) on Web site: <http://chiron.valdosta.edu/whuitt/materials/sysmdl.html> downloaded November 19, 2009.

The microsystem is the foundation on which the development of the child is based. Most proximal, it contains the child’s biology, family, school, and peer group where social roles and interconnections occur. The child grows and learns to invite,

permit, or inhibit engagement in more complex interactions within the immediate environment. If relationships in the immediate microsystem break down, or are impaired, the child will not have the tools to explore other parts of his or her environment. For children who gain weight while taking AAs, the microsystem must be evaluated and supported to help children manage their weight.

A mesosystem is a network of microsystems, the connections, and processes that transpire between two or more settings that the developing child inhabits (home and school, home and neighborhood, or home and psychiatric provider, etcetera). Children, with SED who are given AAs, and their parents, ideally build a mutually trusting relationship with their psychiatric provider that influences the treatment compliance of the child. If the child gains weight while taking the AA, the child and their parents may then distrust the provider's intentions, believing that the AA is harmful to the child's body. Overweight children also need to have a connection with their school environment that supports their health by serving healthy, nutritious foods and providing adequate physical fitness activities. Socioeconomically, children are affected by the income that their parents bring into the home as financial support. When children live in poverty, their parents cannot buy expensive, less processed, foods, which limits children from making healthier food choices.

An exosystem is a network of the connections and processes that transpire *between* the child and environments that do not contain the child. Events that occur in these settings indirectly influence the child and how she or he functions within the immediate setting. An exosystem for a child could be between home and a parent's

workplace. The parent may be stressed within the workplace and carry that stress home to the child, indirectly impacting the surroundings.

Bronfenbrenner (2005) later enhanced the ecological systems theory by defining the overarching, consistent pattern of the micro-, meso-, and exosystems as the macrosystem. The macrosystem is based on the belief systems, bodies of knowledge, material resources, customs, lifestyles, opportunity structures, hazards, and life course options that make up a culture or subculture. This creates a dynamic entity that is the societal blueprint within which the child matures and evolves. Children who have mental illness and are overweight from taking AAs exist within a macrosystem that stigmatizes individuals with mental illness (Crisp, Gelder, Rix, Meltzer, & Rowlands, 2000; Pescosolido, Perry, Martin, McLeod, & Jensen, 2007) and overweight/obesity (Puhl & Brownell, 2001; Puhl & Latner, 2007; Schwartz, Chambliss, Brownell, Blair, & Billington, 2003). These children might incorporate messages conveyed by the culture such as: ‘obese people are lazy or bad’; or that ‘mental illness means you are crazy and unworthy.’

Advancing his theory further, in 1992 Bronfenbrenner considered the dimension of *time* and its effect upon the child and environment (Bronfenbrenner, 2005). The chronosystem is the dimension of time that occurs across all layers of children’s environments as they interact with each other simultaneously. This is a synergistic process that includes ontogenic, family, or historical time that represents a sustained change or movement in development. Ontogenic time is internal or the child’s biology such as puberty or serious illness. Family time is external to the child and might include a parent’s death, birth of new sibling, or moving to a new home. Historical time is also

external and might include war, famine, or socioeconomic depression. Changes internal to the child who is taking an AA and has gained weight might be related to the length of time the child took the medication or due to pubertal changes. An external time change might be that parents choose to separate, disrupting the child's family life, or that the child's medication is disrupted due to a socioeconomic depression in the country.

Bronfenbrenner renamed the theory, the bioecological systems theory in 2001 to emphasize the importance of the child's *biology* as the primary environment. As the most proximal environment, the child's biology fuels his growth and development and is the engine behind further maturation. Relationships between the child and his environment are bi-directional, each impacting and at times altering the other.

Two propositions define the structure and content of the bioecological model: 1. To develop intellectually, emotionally, socially, and morally, the child must participate in an increasingly more complex, reciprocal interaction within their immediate environment. These regular, enduring interactions are proximal processes, which are the primary engines of development; and 2. These proximal processes are not self-sustaining, but their form, power, content, and direction fluctuate as a conjoined function of the characteristics of the developing child and of the environment. These processes occur and are altered through the life course and historical period within which the child lives. The child's distinctive features serve both as an indirect creator as well as a consequence of development.

The Bioecological Theory presents one of the earliest representations of the impact of many interrelated environments upon children and their development. It builds on the premise that if early microsystems (relationships or biology) are not successfully

developed, it is impossible for the children to effectively explore their community or world. Bronfenbrenner's model and concepts are simply stated, logically deduced, and visually nested within each other. Children with mental illness exist and interact with the micro-, meso-, and exo- systems, the culture of their macrosystems, and are shaped by these experiences. The chronosystem represents the healthy neural growth that occurs with normal development across time as well as the positive and negative effects of AAs on their dopaminergic receptors.

This theory was applicable to my topic of weight change in children who take AAs because it addressed the *bioecological* and microsystem environment of the child. Children who are given atypical antipsychotics have a change in their primary biological environment, which often triggers weight change. In turn, this weight change affects their systems of relationships with others. Interactions with family may become conflictual as parents attempt to restrict their dietary intake. Peer interactions may become negative as friends turn away no longer wanting to play with the child. The child is then altered by these changes in relationships and may be stigmatized, developing low self-esteem and poorer quality of life. This investigation and the literature that follows focuses on the microsystem of the child's physiology with respect to the child's medication and its proposed mechanism of action, the diagnosis, gender, and ethnicity/race, and the mesosystem of the child's socioeconomic status.

Limited theory-based research has been conducted with obese individuals or those at risk of obesity (Baranowski, Cullen, Nicklas, Thompson, & Baranowski, 2003). Therefore, there is no theory-based research to cull evidence from within the obesity literature. However, the literature review and this investigation were conducted with an

eye to this theoretical perspective. A review of the literature concerning children with SED, antipsychotic medications, weight change and gain in children with SED, obesity in children, and contributing factors to overweight and obesity in children are addressed in the following sections.

### **Children with Serious Emotional Disturbance**

Serious emotional disturbance (SED) is a mental, behavioral, or emotional disorder that persists for an adequate length of time to meet diagnostic criteria specified in the Diagnostic and Statistical Manual of Mental Disorders IV TR (U.S. Department of Health and Human Services [USDHHS], 1999). Childhood onset of many psychiatric disorders is more common than previously thought (Costello, Egger, & Angold, 2005; Kessler et al., 2005; Kim-Cohen et al., 2003) and includes diagnoses of bipolar disorder, psychotic disorder, schizophrenia, depression, anxiety disorders, attention deficit hyperactivity disorder, disruptive behavior disorder, and autism spectrum disorders. Frequently indiscernible to the untrained eye, children with psychiatric illness are often invisible to the community. Several psychiatric disorders have their onset in childhood and impaired physiological, emotional, and psychological functioning often complicate their development. In this section, the incidence of SED among children, the pathogenesis of SED, and poor life outcomes for this population are reviewed.

#### **Incidence of SED in Children**

The National Comorbidity Survey Replication found that virtually half (46.4%) of all Americans have had a mental illness at sometimes in their lifetime (Kessler et al., 2005) prior to the age of 14, and 13 % to 20% have a mental disorder in any given year of their life (Merikangas et al., 2010b; O'Connell, Boat, & Warner, 2009; World Health

Organization, 2011) and 8% of adolescents have an SED (Kessler et al., 2012) in any given year. These numbers are seen as under representative of lifetime cases and risk, as evidenced in psychiatric research pointing to the reluctance of those with mental illness to participate in research of this type, along with a bias against reporting embarrassing behavior (Kessler et al., 2005). Early onset of SED forecasts difficulties for children academically and in the juvenile justice and child welfare systems (Constantine et al., 2013; Institute of Medicine, 2006). A worse prognosis is predicted for children who are diagnosed with psychiatric disorders compared to those diagnosed in adulthood (DelBello & Grevich, 2004). Two-thirds of psychiatric disorders that have pediatric-onset are moderate or severe (Correll, et al., 2009). As teenagers and young adults, they are at a higher risk of adverse life outcomes than are peers without psychiatric illness.

Nearly 21% (8.9 million) or 1 out of every 5 children and adolescents 9 to 17 years of age in the United States has a diagnosable mental health or addictive disorder (Shaffer et al., 1996). The Methodology for the Epidemiology of Child and Adolescent Mental Disorders (MECA) Study gathered data from 1,285 randomly selected children (ages 9 to 17) and their parents in four sites across the United States. Twelve percent, or 4.3 million youth, have an SED that significantly impairs their ability to function in the home, school, and within the community. The impairment in functioning can be pervasive in all settings or more problematic in one setting. In their review of three longitudinal studies examining the prevalence of mental illness, Jaffee, Herrington, Cohen and Moffitt (2005) noted by the time that children are 16, almost 40 percent have had at least one psychiatric disorder. Furthermore, the prevalence is increasing (Perou et



al., 2013) and is higher than that of adolescents with asthma (Akinbami, Schoendorf, & Parker, 2003) or diabetes (CDC, 2007).

As the child with psychiatric illness grows into an adult, meeting normal developmental tasks is delayed or altered. Cognitive, social and emotional development are often delayed and permanently affected. As a significant societal and public health burden, these results underscore the need to focus on research to determine the best methods of prevention, early diagnosis and treatment of psychiatric disorders in the young.

### **Pathogenesis of Serious Emotional Disturbance**

The pathogenesis of SED in children is suggested, but the ecological systems theory has complex bio-psycho-social origins that impair the trajectory of normal child development. Genetic and environmental influences predispose children and adolescents to psychiatric illness, causing functional impairment that considerably interferes with or limits one or more major life activities in an individual younger than age 18. Cognitive, social, and emotional development are often delayed and permanently affected. These children may be incapable of learning and progressing in school (McLeod & Fettes, 2007), building or maintaining satisfactory interpersonal relationships with peers, family and teachers or displaying appropriate behaviors or feelings under normal circumstances (DelBello & Grevich, 2004). Normal childhood development is impaired resulting in high risk behaviors, poor outcomes in life, and poor quality of life.

**Poor life outcomes.** Limited research, however, has been done regarding children with SED and poor life outcomes. One of the few studies on this issue was carried out by Wagner, Kutash, Duchnowski, Epstein, & Sumi (2005). They reviewed the Special

Education Elementary Longitudinal Study and the National Longitudinal Transition Study, which obtained data from teachers, school records, the students, and their parents. Multiple domains of functioning such as self care, communication, and academic achievement are also more likely to be impaired. Economic, social, and educational results are not as good for children with emotional disturbance as compared to children with other disabilities or children without disabilities.

Compared to children with other disabilities or children without disabilities, children and youth with SED are more likely to have poorer outcomes in life (Wagner, 1995). Areas where youth are most affected are: education (Farmer et al., 2003; McLeod & Fettes, 2007); employment (Betz, 1998; Geenen et al., 2003); and crime (Constantine, et al., 2013; Davis, 2003). In 1999-2000, 51% of youth with SED did not graduate from high school, the highest for all students with disabilities (U.S. Department of Education, 2002). Within five years of dropping out, 73% of the former students were arrested (Chesapeake Institute, 1994), and in general adolescents with SED were more likely to be arrested than adolescents without SED (Constantine, et al., 2013). Adolescents with a psychiatric disorder were 4 times less likely to be employed or enrolled in a college or trade school, 3 times more likely to be involved in criminal activity, and 6 times more likely to have become pregnant or to have gotten someone else pregnant (Davis & Vander Stoep, 1997; Vander Stoep et al., 2000).

Blum, Kelly, and Ireland (2001) examined health risk behaviors among youth with SED. This population is more likely to display behaviors that expose them to health risks such as smoking, being a victim of violence, being on welfare, a history of family suicide, is more likely to have repeated a grade, and is more likely to have a gun in the

home. Youth with SED were more than 6 times more likely to report suicide attempts in the past 12 months than their peers and more likely to have had intercourse prior to the age of 12. Furthermore, they were subjected to protective factors such as family connectedness, lower parental expectation for school completion, fewer activities with parents, less parental presence at key times during the day, lower self-esteem, and lower GPA (Blum et al., 2001). This vulnerable population of children is often prescribed atypical antipsychotics to help manage their mental illness and obtain optimum cognitive and psychosocial development. However, the disturbing side effect of weight gain leads to overweight and obesity, which complicates their already burdened lives and leads to poor life outcomes. In the next section, antipsychotic medications as a class are examined, as is the mechanism of action, proposed mechanism of weight gain, and their use in children.

## **Antipsychotic Medications**

### **Mechanism of Action**

Antipsychotic medications are prescribed for not only their antipsychotic properties, but also for mood stabilization in children with SED who have schizophrenia, bipolar disorder, disruptive behavior disorders, pervasive developmental disorder, tic disorders, severe aggression, and anorexia nervosa (DelBello, & Grcevich, 2004; Findling & McNamara, 2004). Dopamine is one of many neurotransmitters indicated in the pathophysiology of mental illness and atypical antipsychotics modulate the hyperactive or hypoactive transmission of dopamine. Dysregulation of dopamine flow occurs in one of the four dopamine pathways located deep within the brain: nigrostriatal, mesolimbic, mesocortical, and tuberoinfundibular (Kapur & Remington, 2001; Kim,

Maneen, & Stahl, 2009; Meltzer, 2013; Seeman, 2002), can cause hallucinations, delusions, intense emotions, anhedonia, and cognitive dulling.

The nigrostriatal pathway controls movement; therefore, when a blockade of dopamine occurs, movement disorders such as akathisia, dystonia, extrapyramidal symptoms, and dyskinesias can occur (Kim et al., 2009).. The mesolimbic pathway is concerned with emotions and pleasure, and when hyperactive can cause psychosis, hallucinations, and delusions. The mesocortical pathway is thought to manage cognitive functioning, with a lack of dopamine in this area associated with the cognitive deterioration of schizophrenia. The tuberoinfundibular pathway inhibits prolactin release, and if blocked then hyperprolactinemia can occur, which causes amenorrhea and galactorrhea (Kim et al., 2009). Most antipsychotics are not pathway specific, and as a result block all pathways to produce unwanted side effects. Therefore, treating an overproduction of dopamine in the mesolimbic system, which targets psychosis, can cause problems in another pathway such as the nigrostriatal and cause movement problems.

There are two kinds of antipsychotics: typical (e.g., haloperidol, chlorpromazine) and atypical (e.g., clozapine, risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole). Both types of antipsychotics manage the ‘positive’ symptoms of schizophrenia such as auditory and visual hallucinations and delusions. Atypical antipsychotics, however, are significantly better at managing negative symptoms (Meltzer, 2013) such as “blunting of affect, poverty of speech and thought, apathy, anhedonia, reduced social drive, loss of motivation, lack of social interest, and inattention to social or cognitive input” (Tandon & Jibson, 2002).

Typical antipsychotics are dopamine 2 (D<sub>2</sub>) antagonists that bind tightly to the receptor, which causes mesolimbic, mesostriatal, and anterior pituitary dysfunction (Meltzer, 2013) resulting in a reduction of auditory and visual hallucinations, but potentiating movement disorders such as extrapyramidal symptoms (EPS) and/or tardive dyskinesias (TD) and galactorrhea, amenorrhea, and sexual dysfunction. Four types of EPS include dystonias (muscle spasms that produce an abnormal posture), akathisia (inner and observed restlessness), pseudoparkinsonian (muscle rigidity, tremors, drooling, a masked facial expression, and shuffling gait), and tardive dyskinesia (Stanilla & Simpson, 2009). These side effects result from a blockade of dopamine in the extrapyramidal tracts of the brain that coordinate movement, but TD can be reversible by reducing the medication or by adding anticholinergic or alpha antagonist medication. Tardive dyskinesia is a type of EPS that is potentially irreversible and can occur after months to years of antipsychotic use. Choreoathetoid movements of the head, mouth, neck, trunk, arms, legs, and fingers characterize TD and emerge as grimacing, lip smacking, tongue protrusion, twisting motions of the trunk, pill rolling movements of the fingers, and disturbances in gait (Jankelowitz, 2013). Neurochemically, AAs are distinctively different from typical antipsychotics as they are not only D<sub>2</sub> antagonists (Kim et al., 2009; Meltzer, 2013; Seeman, 2002), but also serotonin antagonists. The antagonists also have the potential to enhance cognitive functioning along the mesocortical dopaminergic pathway within the cerebral cortex.

The serotonergic and dopaminergic actions of atypical antipsychotics loosely bind to the receptors. This facilitates fast dissociation of the dopamine off the D<sub>2</sub> receptor (Kapur & Seeman, 2000), thereby reducing chances of EPS (Geddes, Freemantle,

Harrison, & Bebbington, 2003), TD, and prolactinemia (Seeman, 2002; Meltzer, 2013). There are two hypotheses behind this proposed mechanism of action (Stahl, 2003) in AAs. One hypothesis is based on the fact that AAs also bind to serotonergic receptors, and serotonin (5-HT<sub>2A</sub>) regulates dopamine release in the nigrostriatal pathway but has little to no effect in the mesolimbic pathway. Few 5-HT<sub>2A</sub> receptors are found in the mesolimbic pathways, so movement disorders are minimized while antipsychotic properties are preserved. When the serotonin receptors are blocked in the nigrostriatal pathway, dopamine levels increase, filling the D<sub>2</sub> receptors, which prevents total blockade by the antipsychotic medication. Reduced blockade in the nigrostriatal pathway means less motor side effects. The other hypothesis is that AAs quickly dissociate from the dopaminergic receptor to provide an antipsychotic effect without dopamine blockade and motor side effects. This allows the receptor to briefly be available to naturally occurring dopamine before the next dose of medication (Stahl, 2003).

Children are a special population that need to be monitored carefully for EPS and TD. The probability of EPS (Correll & Carlson, 2006; Wonodi et al., 2007) and TD is higher in children because the number of striatal dopamine D<sub>2</sub> receptors is greater in childhood, and then decreases as we age (Jucaite, Forssberg, Karlsson, Halldin & Farde, 2010). Children are also at a greater risk of developing EPS and/or TD because they may have to take these medications for an extended period, if not throughout their lives. Atypical antipsychotics present a reduced risk of EPS and TD (Correll et al., 2006; Pringsheim et al., 2011) compared to typical antipsychotics. Therefore, they have been the preferred antipsychotic medications when prescribing for children and adolescents (Findling & McNamara, 2004). Clinically significant weight gain ( $\geq 3$  kg), however, is a

particularly disturbing side effect of most AAs because of the physical consequences of obesity that can persist into adulthood.

**Proposed mechanism of weight gain.** The mechanism behind AA induced weight gain is not completely understood and due in part to the complex pharmacology of the medications (Casey & Zorn, 2001; Deng, Weston-Green, Xu-Feng, 2010; Kroeze et al., 2003). One hypothesis is that the intricate pharmacology of the antipsychotics interacts with multiple neuroreceptors: 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> serotonergic; H<sub>1</sub>-histamine receptors; α<sub>1</sub>- and α<sub>2</sub>-adrenergic receptors; and m<sub>3</sub>-muscarinic receptors (Deng et al., 2010; Kroeze et al., 2003) probably causing an increase in appetite (Baptista, de Mendoza, Beaulieu, Bermudez, & Martinez, 2004). After screening 17 typical and atypical antipsychotics and their binding to 12 neurotransmitters, Kroeze et al. discovered that medications with affinity for H<sub>1</sub>-histamine receptors were significantly correlated with weight gain. Olanzapine and risperidone have the highest H<sub>1</sub> affinity and the most weight gain with quetiapine, aripiprazole, and ziprasidone having decreased affinity respectively and the least weight gain (Kroeze et al., 2003; Casey & Zorn, 2001). Although direct metabolic effects of AAs such as insulin resistance have been observed, it is hypothesized that they occur as the result of body weight gain and not the direct effect of the AA (Baptista et al., 2004).

***Use in children and adolescents.*** There was a 6- to 20-fold increase in the utilization of AAs versus typical antipsychotics in younger children, adolescents, and males in both the Medicaid and privately insured populations from 1996-2001 (Patel et al., 2005). A sharp rise in the number of AA prescriptions for children and adolescents occurred between 1993 and 2009, with visits per 100 children growing from 0.24 to 1.83

for children and 0.78 to 3.76 for adolescents. Atypical antipsychotics were also prescribed to children at 31.1% of office visits, approximately the same rate as they were for adults (Olfson, Blanco, Liu, Wang, & Correll, 2012). Surprisingly, one population that has seen an increased use of antipsychotics is that of very young children. Among the privately insured, children 2 through 5 years old, antipsychotic prescriptions doubled between 1999/2000 and 2007, with 90% of the children prescribed AAs (Olfson et al., 2010). Similar to privately insured children, Medicaid insured children aged 10 to 17 years saw the prevalence of antipsychotic use increase from 1.2% in 1997 to 3.2% in 2006 with very young children ages 2 to 4 having a similar proportion of use (Zito, Burcu, Ibe, Safer, & Magder, 2013).

### **Weight Gain in Children With Serious Emotional Disturbance**

Weight gain has been documented among adults who take atypical antipsychotics for more than 20 years (Wetterling & MuBigbrodt, 1999), and most research has been done with adults (Newcomer, 2007). However, weight increases among children and adolescents who take these medications have been more severe (Almandil, et al., 2013; Correll, & Maayan, 2011; De Hert, Dobbelaere, Sheridan, Cohen, & Correll, 2011; de Hoogd, Overbeek, Heerdink, Correll, de Graeff, & Staal, 2012).

This is not a new problem. In 2004, Cheng-Shannon et al. observed that most of the available studies on AA use in children and adolescents were anecdotal or short-term open label trials that documented relative safety in children and adolescents. Only 15 studies were double blind, with 58 open-label trials, 18 retrospective chart reviews, and 85 case reports. Risperidone was studied most frequently with 76 reports, 11 that were double blind; however, olanzapine was the focus of 37 studies and quetiapine had 19



published studies with no double blind research. At that time, limited studies had been conducted with aripiprazole and ziprasidone because they were the latest AAs developed. Seen below is Table 2, which summarizes 10 key studies of AAs and their use in children, as well as one study on quetiapine (Cheng-Shannon, et al., 2004). Note that across these studies and given the different diagnosis and medications that the average weight gain was around 4 kg.

Cheng-Shannon et al. advocated for the cautious use of these agents in children, close monitoring of weight, lipids and fasting glucose at initiation, then and every 3-6 months thereafter, opinions that continue to be voiced today as well (Correll et al., 2009). Long and short-term studies to differentiate long-term clinical effects of these medications from the more chronic use have been encouraged (Correll et al., 2009; De Hert et al., 2011; Olfson et al., 2006). Youth with SED were increasingly being treated with atypical antipsychotics to manage their psychiatric illness.

Over the last eight to 10 years, increasing numbers of RCTs have been conducted and systematic reviews and meta analyses were compiled to assess the efficacy and safety of AAs and their, cardiometabolic and endocrine side effects (Almandil et al., 2013; Caccia, 2013; Correll et al., 2009; De Hert et al., 2011). Caccia (2013) reviewed AA use in children and adolescents to assess evidence of AA safety and pharmacokinetics. Citing literature that documents the effectiveness of all AAs, he noted that no one AA was more efficacious than another. Each AA has unique pharmacokinetics and distinctive binding properties at neuroreceptor sites, providing a slightly different side effect profile for each type. All AAs, however, had some degree of adverse endocrine and metabolic consequences including excessive weight gain.

Table 2 *Studies of weight gain in children who take atypical antipsychotics*

Investigator	Study Type	AA	Sample Size	Diagnosis	Avg Wt. Gain (kg)
Kemner et al. (2002)	Open label 12 wks	R	25	PDD	4.7
Ercan et al. (2002)	Case studies 9 wks	O	8	Schizophrenia Schizoaffective	7.88
Patel et al. (2004)	Retrospective treated ~39 d	O	50	“SED”	3.8
Scahill et al. (2003)	RCT 8 wks	R	26	Tourette’s	2.8
Aman et al. (2002)	Multicenter, double blind RCT	R	118	Disruptive Behavior Disorder & Mental Retardation	2.2
Gagliano et al. (2004).	Open label 4 wks	R	24	Autism	3.2
McCracken et al. (2002)	Multisite, RCT, double blind 8 wks	R	101	Autism	2.7
Martin & Leslie (2004)	Open 4 months	R	64	Autism	5.6
Sikich et al. (2004)	RCT 8 wks	H, O, R	50	Psychosis	H=3.5 O=7.1 R=4.9
Schimmelmann et al. (2007)	Prospective 12-week, multicenter	Q	56	Schizophrenia spectrum	6.2
<b>Total 10 studies</b>					<b>4.34 (1.90)</b>

*Note:* H=Haloperidol; Q=Quetiapine; O=Olanzapine; R=Risperidone; PDD = Pervasive Personality Disorder. \*conventional antipsychotic

Almandil et al. (2013), conducted a systematic literature review and meta-analysis, of 21 double-blind RCTs with children and adolescents aged  $\leq 18$  years on olanzapine, aripiprazole, and risperidone that examined metabolic adverse effects. The

range of disorders treated included ADHD, autism, bipolar disorder, conduct disorder, disruptive behavior, and schizophrenia. Three studies involved children on olanzapine, four for aripiprazole, and 14 of risperidone, with a total of 2,455 children and adolescents treated. Aripiprazole had the lowest mean statistically significant weight gain of 0.94 kg, then risperidone with 1.77 kg gained, and finally olanzapine with an increase of 3.45 kg. De Hert et al. (2011) systematically evaluated 24 randomized, placebo-controlled trials involving 3,048 children and adolescents and the cardiometabolic and endocrine side effects of AAs.

Although a meta-analysis was intended that included outcomes related to glucose, serum lipids, blood pressure, thyroid function, and prolactin, only weight change data were reported in sufficient amounts to enable a formal meta-analysis. Comparable to results obtained by Almandil et al (2013), olanzapine was associated with the most weight gain at 3.45 kg, risperidone with the second highest at 1.76 kg, followed by quetiapine, 1.43 kg, and ziprasidone with the lowest weight gain of 0.04 kg. Of note is that patients with the most significant weight gains were more likely to be younger, have an autistic disorder, and be antipsychotic naive. Diagnoses of children in the trials were behavioral disorder, bipolar, schizophrenia, autism, and pervasive developmental disorder.

Atypical antipsychotics can cause significant weight gain in this population, predisposing children and adolescents to lifelong consequences of physical illnesses and psychosocial stigma that are associated with overweight and obesity.

**Obesity in children.** Childhood obesity in the United States is at epidemic proportions as 17% of children and adolescents, aged 2-19 years are overweight (Ogden,

Carroll, Kit, & Flegal, 2012). Overweight and obesity can compromise quality of life (QOL), and physical and psychological health. In 2002, an increase of overweight and obese children was observed in all population groups. Between both genders, weight gain has more than doubled (to almost 9 million) since 1970 in the population of children and adolescents 6 to 19 years of age. (Ogden, Flegal, Carroll, & Johnson, 2002).

Disturbingly, the occurrence is increasing in minority populations, particularly among Mexican-American and non-Hispanic black adolescents (Ogden et al., 2012). Annual health care costs of obesity have been estimated at \$209.7 billion, or 20.6%, of the U.S. national health expenditures (Cawley, & Meyerhoefer, 2012) and childhood obesity accounts for \$14.1 billion in added outpatient costs, which include prescriptions and emergency room and outpatient visits (Trasande & Chatterjee, 2009).

Environmental organization and societal changes such as suburbs, fast food, television, and video games have adversely impacted this problem, especially as they pertain to children. Understanding obesity as a complex, multifactorial problem, particularly as it relates to childhood is critical to assessing the totality of the issue and for planning and evaluating interventions.

*Early antecedents of obesity.* Obesity significantly affects the physical and psychological health of children and adversely affects their future health trajectory as they grow into adolescents and adults (Campbell, Waters, O'Meara, & Summerbell, 2001; Freedman, Dietz, Srinivasan, & Berenson, 2005) as childhood BMI is related to adult adiposity (Freedman et al., 2005). Children have unique antecedents of obesity that extend into their adult lives, such as early development of sedentary habits, access to

heavily processed, highly caloric foods, and reduced activity levels due to living in communities where there are no parks or local stores.

Genetics, poor dietary habits of their parents, lack of exercise, watching television, and the higher fat and caloric value of fast foods are some of the primary contributors (Epstein, Paluch, Gordy, & Dorn, 2000; Goran & Treuth, 2001; Heitmann et al., 1997; Moran, 1999) to obesity in children. Although the mechanisms for weight gain in children taking atypical antipsychotics are not fully apparent, the problem of obesity for these children is very real and adds to the significant physical, mental, and emotional burden that many of these children have to bear.

One area of childhood obesity that has been neglected is that of children who have an SED who have gained weight while taking atypical antipsychotic medications. We do not know whether the antecedents of weight gain in children on atypical antipsychotics are the same or different as children in the general population.

Despite the evidence of the impact that cultural and environmental factors have on obesity, 75% of obesity research grants to the Center for Disease Control are funding genetic and metabolic studies, with less than 1% given to studies on environmental concerns (Farley & Cohen, 2001).

***Physical and psychological consequences of childhood obesity.*** Physical and medical consequences of childhood obesity include, but are not limited to: hypertension, dyslipidemia (Kiess et al., 2000), insulin resistance, orthopedic problems, skin fungal infections, acanthosis nigricans, and hepatic steatosis (Deckelbaum & Williams, 2001; Dietz, 1998; Koplan et al., 2005). The Bogalusa Heart Study (Freedman et al., 1999) revealed that 61% of overweight children ages 5-10 years had one or more cardiovascular

risk factor such as hyperinsulinemia, hyperlipidemia, or high blood pressure. In addition, more than 20% of overweight children had two or more cardiovascular risk factors.

Children and adolescents who are overweight and obese not only suffer future physical and medical sequelae of overweight and obesity, they also experience the immediate consequences of social and psychological stigma (Puhl & Brownell, 2003). Persistent obesity from childhood to adulthood was associated with poorer employment outcomes and a reduced likelihood of having a current partner for women (Viner & Cole, 2005). Wardle, Waller, and Jarvis (2008), in their research of sex differences in obesity and SES found that women and men who left school early were more likely to be obese than those who had more years of education.

Youth with SED who take atypical antipsychotics and are overweight or obese are three times more vulnerable due to being children who incur intensified social stigmatization and the physical consequences of mental illness and obesity. It is likely that these children may need to take these medications their entire lives. Therefore, a study of this kind could significantly contribute to the knowledge base and help develop tools for assessment and interventions for treatment.

### **Contributory Factors to Overweight and Obesity**

The origins of overweight and obesity are complex and multifactorial for children and adolescents and even more so for this population. Confounding this issue are the child's and adolescent's unique permutation of the type of AA, diagnosis, socioeconomic status (SES), ethnicity/race, age and gender. These spheres of influence could be interrelated. Although not totally determined, each facet has its own merits in

relationship to overweight and obesity and is presented in the order of proposed influence.

*Medication.* The type of AA is a factor in weight change and gain for this population and, as previously noted, all AAs can cause weight gain. Clozapine and olanzapine cause the most weight gain in children and adolescents, with risperidone and quetiapine following, and aripiprazole and ziprasidone causing the least gain (Almandil et al., 2013; Correll, & Maayan, 2011; De Hert et al., 2011; de Hoogd et al., 2012).

Although clozapine and olanzapine cause the most weight gain, specific research that looks at weight change over time for each type of AA is lacking. Furthermore, there are no known studies that compare and correlate the type of AA with these demographic, diagnostic, and treatment characteristics, as this research proposes.

The type of AA was initially operationalized as clozapine, olanzapine, risperidone, quetiapine, aripiprazole, or ziprasidone, but no child was prescribed clozapine, so this medication was removed from the AA variable. The type of AA was further dichotomized for analysis as olanzapine, risperidone, and quetiapine as one variable, which cause greater weight gain than aripiprazole and ziprasidone combined, which was another variable.

*Diagnosis.* Another possible contributing factor to weight gain concerns the diagnosis given to the child or adolescent. Research has suggested that adult patients with bipolar disorder or schizophrenia (Baptista et al., 2004), and specifically drug-naïve patients who have undifferentiated schizophrenia (Saddichha et al., 2008), may be genetically vulnerable to developing obesity. Tarricone, Gozzi, Serretti, Grieco and Beradi (2010) in their review and meta-analysis of weight gain in antipsychotic naïve

patients with first episode psychosis or schizophrenia under the age of 15 years found that weight gain is rapid and ongoing throughout antipsychotic treatment. Therefore, it is important to assess whether or not diagnosis contributes to weight gain in this population. Diagnosis was operationalized as having a primary mental health diagnosis from the Diagnostic and Statistical Manual of Mental Disorders IV TR, such as Disruptive Behavior Disorder, Oppositional Defiant Disorder, Conduct Disorder, Depressive Disorder, Mood Disorder, NOS, Bipolar Disorder, Psychotic Disorder, Schizophrenia, and Schizoaffective disorder. Diagnosis was further dichotomized for analysis as mood/affective disorder and psychotic disorder diagnoses (Depressive Disorder, Mood Disorder, NOS, Bipolar Disorder, Psychotic Disorder, Schizophrenia, and Schizoaffective Disorder) and disruptive behavior and pervasive developmental disorders (Disruptive Behavior Disorder, Oppositional Defiant Disorder, Conduct Disorder and Pervasive Developmental Disorders (PDD)).

*Socioeconomic status.* Socioeconomic status (SES) has been implicated in overweight and obesity in the general population (Ogden, Lamb, Carroll, & Flegal, 2010) but until the recent epidemic of obesity in this country, that relationship had both inverse and positive associations (Wang, 2001; Sobal and Stunkard, 1989). Shrewsbury and Wardle (2008) in their systematic review of 45 studies from 1990-2005, found consistent evidence of the inverse relationship between children's body mass index and their SES. Ogden et al. (2010) in their review of the National Health and Nutrition Examination Survey, 2005-2008, also found this inverse relationship to be true. For this population, SES is a factor that must be examined. However, in this chart review study, almost all participants were on Medicaid and it was not possible to analyze the effect of SES.



*Ethnicity/race.* No one ethnicity/race is immune to overweight and obesity, however ethnic differences are evident in the literature. Sundquist and Johansson's 1989 longitudinal study of young adults and adults found that ethnicity/race is an independent dynamic correlating to an increase in body mass index. Most recently, research within an ethnically diverse rural population in Oklahoma found that Native American children had the highest (53.8%) prevalence of obesity, followed closely by African American (51.7%), and Hispanic children (50.5%) (Eichner et al., 2008). In the National Health and Nutrition Examination Survey 2009-2010, 21.2% of Hispanic children and adolescents and 24.3% of non-Hispanic black children and adolescents were obese compared with 14% of white children and adolescents (Ogden et al., 2012). Ethnicity/race was operationalized by the standards outlined by the Office of Management Budget (1997) for ethnicity/race (American Indian or Alaska Native, Asian, Black or African American, Hispanic or Latino, Native Hawaiian or Other Pacific Islander, or White).

*Age.* Pubertal influence upon BMI could be a confounding issue in this study because it is a period of rapid height and weight gain. Body mass index gain could be falsely attributed to AAs even though the child may be undergoing normal pubertal BMI gain (Solorzano, & McCartney, 2010). Guo et al. (2000) examined the patterns of BMI during childhood, adolescence, and young adulthood.

Results indicated that pubescence was a critical period for the development of overweight across the lifespan. Furthermore, the maximum velocity of BMI across the lifespan, for both girls and boys, occurs during pubescence from 10.5 years of age to 13.5 years of age at an average of 0.6 kg/m<sup>2</sup>/year, or .05 kg/m<sup>2</sup> per month (Guo et al., 2000).

In the Guo et al. (2000) study, the effect of age as a proxy for puberty on BMI was assessed and controlled for in the analysis. Age was operationalized by self-report of years of age and by calculating the participants' age from their date of birth.

*Gender.* A lack of research regarding gender differences in overweight and obesity is evident in this population of children. Jerrell and McIntyre (2008), however, recently published data from a large retrospective cohort design that examined the adverse events with antipsychotics. Females were at higher odds of developing excessive weight gain and obesity, Type II diabetes, and dyslipidemia. Seeman (2008) systematically examined the literature regarding weight gain gender differences in adults taking AAs and found broad agreement that women have a greater vulnerability for weight gain, diabetes, and cardiovascular disease than men. Homel, Casey, and Allison (2001) in their review of national data regarding schizophrenic and non-schizophrenic patients of both gender determined that weight gain was significantly ( $p = .00$ ) greater for females aged 18 to 30. Gender is operationalized by self-report as female or male.

*Time in treatment.* The temporal relationship between length of time on the medication and the amount of weight gained is another factor to consider. Pai, Deng, Vella, Castle, and Huang (2012) have postulated that there are three different stages of weight gain that are caused by different underlying neural mechanisms. In their evaluation of clozapine, olanzapine and risperidone, Pai et al. (2012) found that there is an "initial rapid weight increase from baseline to 3 months (stage 1), a steady increase from 3 months to 18 months (stage 2) and a plateau after this point (stage 3) with continued antipsychotic treatment." They hypothesized that increased food intake promoted rapid weight gain in Stage 1 (1 to 3 months) and the chronic use of an AA

initiated a reduction in the energy, which produced an AA-induced hypometabolic state that contributed to the weight gain in Stage 2 (6 to 12 months). Prolonged effects of the AA H1 and 5 HT2 receptor expression, during the plateau of Stage 3 (12 or more months), sustains the weight gain.

In summary, it is hypothesized that these interrelated spheres of environmental influences can impact the development of overweight and obesity for this population of children. The type of AA, diagnosis, ethnicity/race, age, gender, and time in treatment may have an individual effect on overweight and obesity or synergistic effects, as suggested in the Bioecological Theory of Development. Furthermore, it is important to assess the effects of puberty upon BMI gain so as not to incorrectly attribute the cause to taking AAs.

## **Chapter 3**

### **Design and Methodology**

This chapter describes the original research design and methods of this study and then explains the altered design and amended methods that were implemented to answer revised research questions and hypotheses. First, the original research design and challenges with completing this proposal are explored and then the reorganized study design and final research questions and hypotheses are reported. Next the data analysis and data collection are described and finally the protection of human subjects is addressed.

### **Original Research Design and Challenges**

This study was designed as a quasi-experimental, cross-sectional, two group (participants and siblings) study with limited retrospective chart reviews. The purposes of the study were to determine whether or not various demographic, diagnostic, and treatment characteristics contribute to weight gain in children with SED who take AA, and whether the type of diagnosis and the amount of weight gain contributes to poor quality of life (QOL). Using a two-group design with a nonequivalent sibling control group would have strengthened the internal validity of the study by comparing the study participants to their siblings, who had equivalent environmental exposure. Despite multiple amendments to the study in an effort to enhance recruitment, major roadblocks hindered the enrollment of the planned 110 participants. Over a period of three and a half years, a total of five amendments were submitted to the Human Research and Review Committees (HRRC), with the aim to increase enrollment. Attempts were made to broaden and enhance criteria, more fully publicize the original study, add study personnel, and expand recruitment to sites outside of the university affiliated child psychiatric inpatient facility and outpatient .

Notwithstanding this varied and intensive effort to recruit, by September 2011 only 22 of the total 110 participants needed for this study had been enrolled. After consulting with the dissertation committee, the inclusion criterion for weight gain (0.5 BMI  $z$  score) was dropped, as was criteria that excluded Spanish-speaking and developmentally-delayed participants. A chart review of 110 children who met the remaining inclusion criteria was conducted and the QOL data from the 22 children that had been collected would answer the research question and hypotheses regarding QOL, using non-parametric statistics to do an exploratory analysis to look for trends.

This fundamentally altered the design and methodology of the research. Then, during a yearly renewal of the study with HRRC in April 2012, the Committee determined that another informed consent should be administered to the 22 participants who had provided QOL data or none of the data from those participants could be used in the analysis. Only 7 of the 22 participants who had provided QOL data could be located because the other 15 had moved out of state or had changed addresses and phone numbers.

Again, in consulting with the dissertation committee, it was determined that the research and dissertation should be completed within the designated timeframe, but the questions and hypotheses related to the QOL should be removed. In the end, the study was transformed into a chart review of a purposive sample, time on the medication was expanded from three months to three years, the weight gain criterion was dropped, Spanish-speaking and developmentally-delayed children were included and the QOL questions and hypotheses were removed. Finally, the study posed an additional question and hypothesis regarding the time on medication and the potential for weight gain.

## Final Research Questions and Hypotheses

1. What demographic, diagnostic, and treatment characteristics (type of AA, diagnosis, ethnicity/race, age, gender, and months in treatment) contributed to weight change (difference in baseline BMI  $z$  score and final BMI  $z$  score = BMI  $z$  change score) among children who took atypical antipsychotics (AAs)?
  - a. H1 Children and adolescents taking olanzapine, risperidone, and quetiapine gain more weight than children taking aripiprazole and ziprasidone.
  - b. H2 Children and adolescents with mood/affective disorders, psychotic disorders or anxiety disorder diagnoses gain more weight than children with disruptive behavior, pervasive developmental disorders, or tic disorders.
  - c. H3 Children and adolescents from Hispanic or Latino, Native American or Black, or African American or Other (mixed race) ethnicity/race gain more weight than children identified as White or Asian ethnicity/race.
  - d. H4 Children who are prepubescent (ages 9-13) gain more weight than children and adolescents age 6 to 8 or 14 to 17 years.
  - e. H5 Females gain more weight than males.
2. Does the amount of time on an atypical antipsychotic affect the weight a child gains?
  - a. H6 The longer a participant is on an atypical antipsychotic, the more weight they gain.

A detailed account of the design, methods, instrumentation, human subjects, data collection and analyses used in this investigation follow.

### **Study Design**

The completed study involved a non-experimental cross-sectional, retrospective one group design with retrospective chart reviews. Studying this vulnerable population of children with complex mental health problems was achieved by obtaining charts from a cross section of a population with the disease status already established. This design provided an adequate method of obtaining data, but also limited contact with the children. To answer the research questions, the PI reviewed 110 charts and documented the type of AA, diagnosis, ethnicity/race, age, gender, and months on medication on a non-identifiable Chart Review Form (CRF). The CRF enhanced internal validity by standardizing the method of the data collected. To further enhance internal reliability, a data location sheet (DLS) recorded the designated location of the data in the electronic medical record (EMR) and cross-referenced additional locations of the data in the EMR. To enhance rater reliability, the RA rechecked 10% of the charts reviewed by the PI. Data were examined by correlations, an ANOVA, independent *t*-tests, and a multiple regression analysis. More detail regarding data collection and analysis is given below.

### **Setting**

The charts for the study were from children receiving psychiatric care at a university affiliated child psychiatric facility and outpatient clinic in a southwest state. The annual inpatient population is 770 inpatient admissions, 14,064 inpatient days (9,588 acute with 35 beds, 4,476 residential treatment with 18 beds). The outpatient psychopharmacology clinic provides approximately 500 new psychopharmacology



evaluations per year and over 3,000 patient visits per year for psychopharmacology follow up. Children and adolescents are referred to the child psychiatric hospital from both metropolitan area, where it is located, and the entire state of New Mexico, but are referred to the outpatient clinic only from the metropolitan area. Referral sources include self, schools, and therapists in the community, group homes, day treatment programs, and inpatient psychiatric facilities.

Children with chronic, serious mental illness are often treated at a teaching university due to the severity of their symptoms and behaviors, the need for specialized, wraparound services, funding through Social Security disability and Medicaid, and the frequent inability to obtain comprehensive services in private, nonprofit facilities. Their extremely dangerous, aggressive, manic, and/or psychotic symptoms and behaviors are often treated with AAs. Therefore, at a university affiliated child psychiatric inpatient and outpatient clinic, a large number of participants were available for study recruitment and would subsequently have a higher incidence of weight gain because of taking AAs.

### **Sample**

- A purposive sample of charts from 110 children comprised the study group. A sample size of 103 was computed using the GPower 3 (Faul, Erdfelder, Lang, & Buchner, 2007) program, with the power set as .80 and alpha at 0.05 for a multiple regression with seven independent variables. Additionally, approximately 10% of the computed sample was added, which provided 110 charts from 110 participants in the study group. When the data was analyzed however, two more variables were added post hoc to the regression for a total of nine independent variables. Using the G power program ((Faul, Erdfelder, Lang, & Buchner, 2007), for a multiple regression with nine independent variables, a

sample size of 109, an alpha of .05, and a medium effect size of 0.15, the power for this study was .78. The study was slightly underpowered.

**Inclusion and exclusion criteria.** Inclusion criteria for the participants in the study group included:

1. Males or females
2. Between the ages of 5 to 18 years
3. Have a primary mental health diagnosis from the Diagnostic and Statistical Manual of Mental Disorders IV TR (American Psychiatric Association, 2000), such as:
  - a. Disruptive behavior disorder,
  - b. Autism disorder,
  - c. Oppositional defiant disorder,
  - d. Conduct disorder,
  - e. Depressive disorder,
  - f. Mood disorder, not otherwise specified (NOS)
  - g. Bipolar disorder,
  - h. Psychotic disorder,
  - i. Schizophrenia and schizoaffective disorder.
4. Have taken an atypical antipsychotic for a minimum of three months and a maximum of three years.
5. Weight changed since starting the atypical antipsychotics.

Exclusion criteria for the study were:

1. Chronic medical conditions that are known to influence weight, such as hyperthyroidism, hypothyroidism, and Prader-Willi Syndrome (Zametkin, Zoon, Klein, & Munson, 2004).
2. Diagnosis of anorexia nervosa, bulimia nervosa or binge eating disorder.
3. Children that began taking AAs at other systems of care and then switched agencies and began getting care in this system, as baseline weight, height and age could not be obtained.
4. Children that began taking AAs in this system of care but then left to obtain care in another agency as final weight, height and age could not be obtained.
5. Incomplete or inconsistent data (e.g. Different heights and weights recorded in 2 different places in the chart).

### **Data Collection**

The data collection section reviews the personnel training, obtaining access, recruitment, screening of charts, instrument overview, and step-by-step procedures of the chart review.

**Personnel training.** A research assistant (RA) was hired. The RA's primary responsibilities were to screen charts for the chart review and review 10% of the charts reviewed by the PI to strengthen the reliability of the charts reviewed by the PI. The RA had completed required human subjects training.

The PI met with the RA to review the purpose, methodology, data collection, and data analysis of the entire study. The RA was given a written job description of each element of the job. A written procedure and protocol for each element of the job was also provided (Appendix A).

**Obtaining access, recruitment and screening.** The PI met with the medical director, clinical director, and clinicians in PFCA and Cimarron Clinic and discussed the purpose, methods, and data collection and analysis for the study. Charts for enrollment were identified through referral by a participant's psychiatric provider or nurse, or were identified as taking an atypical antipsychotic by the PI/RA or MA who were all employees of university affiliated child psychiatric hospital or clinic. The PI and RA then screened all of the referred charts, along with the PI reviewing all 110 charts.

**Instrumentation.** The variables were operationalized as follows.

- 1) Weight change/gain – Weight gain is operationalized as the difference in the baseline BMI  $z$  score and the BMI  $z$  score after the first trial of AA (BBMI $z$ 1Change)
- 2) AA – Type of AA will be operationalized as olanzapine, risperidone, quetiapine, aripiprazole, or ziprasidone.
- 3) Diagnosis – Diagnosis will be operationalized, as has a primary mental health diagnosis from the Diagnostic and Statistical Manual of Mental Disorders IV TR (American Psychiatric Association, 2000), such as disruptive behavior disorder, oppositional defiant disorder, conduct disorder, depressive disorder, mood disorder, NOS, bipolar disorder, psychotic disorder, schizophrenia, and schizoaffective disorder.
- 4) Ethnicity – Ethnicity will be operationalized by the standards outlined by the Office of Management Budget (1997) for ethnicity (American Indian or Alaska Native, Asian, Black or African American, Hispanic or Latino, Native Hawaiian or Other Pacific Islander, or White).

- 5) Age – Age was operationalized as years of age by calculating the participant’s age from the date of birth.
- 6) Gender – Gender was operationalized by information in the chart that identified the child as female or male.
- 7) Months in Treatment – Months in treatment was operationalized as the number of months that the child was taking the atypical antipsychotic from the date it was prescribed to the date it was discontinued or the child stopped taking the AA, or 3 years.

The PI created two forms to document the data from each chart reviewed; The Chart Review Form (CRF) (Appendix B), and the Data Location Sheet (DLS) (Appendix C).

*Chart review form.* The following data from the chart review were documented on the standardized CRF:

- 1) Age
- 2) Gender
- 3) Ethnicity
- 4) Diagnosis
- 5) Other diagnoses
- 6) Weight and height at baseline before the AA was initiated, to calculate the BMI and BMI *z* scores
- 7) Weight and height at the time that the AA was discontinued to calculate the BMI, BMI *z* scores, and BMI *z* change score/weight change
- 8) Months in treatment for the AA

- 9) Type of AA
- 10) Other meds that were prescribed
- 11) Insurance status

**Data location sheet.** The PI created a standardized Data Location Sheet (DLS) to cross reference the data to all possible locations in the chart. This assured that the data obtained were valid and reliable. On the DLS, the primary and secondary locations (i.e., the physical assessment, graphic chart, and the medication administration sheet) of the data (i.e. weight, height, diagnosis, AA) were identified and a check was placed next to all the locations in the chart where that specific data were located.

### **Step-by-step Procedures**

#### **Screening charts.**

- 1) Charts were screened using the standardized Screening Form (Appendix D) created by the PI.
- 2) The PI/RA screened each chart for approximately 10 to 45 minutes in the following manner. The eligibility of a referred chart was confirmed by noting:
  - i) The child or adolescent was taking an AA
  - ii) The date of initiation of the AA was found in the chart
  - iii) An AA was taken for at least three months
  - iv) The date of AA discontinuation was 3 years or less from the date of initiation
  - v) The child or adolescent had a weight change
  - vi) The child or adolescent had a diagnosis that was in the inclusion criteria

- vii) The child or adolescent did not have a diagnosis of anorexia, hypothyroidism, or any diagnosis that would affect weight
- 3) Once charts were identified as eligible for inclusion in the study, the electronic medical record number (EMRN) was documented in the electronically-encrypted, password-protected Codebook and given a non-identifying code. The data from that chart were then known by the non-identifying code.

**Process for obtaining data from the chart.**

- 1) The non-identifying code of the chart was written at the top of the CRF and the DLS.
- 2) The age, date of birth, gender, and ethnicity/race of the child or adolescent were located on the *demographic form* (italicization denotes the different documents where the data were documented) in Power Chart Office (PCO) (electronic medical record program) and documented on the CRF. To ensure accuracy, these data were then cross-referenced and found on the *psychiatric or nursing assessment* and documented on the DLS.
- 3) The name and starting date of the AA, as well as other psychiatric medications if prescribed, were located on the *medication record* and then documented on the CRF. To ensure accuracy, these data were then cross-referenced and found on the *clinical therapy notes* and the *provider or psychiatrist progress note*, and then written on the DLS. If the AA was initiated when the child was an inpatient, these data were then cross-referenced and found by examining the

*ongoing physician orders, notes, and/or medication record* and then documented on the DLS.

- 4) The discontinuation date of the AA, or three years from the initiation date of the AA, was documented on the CRF and months in treatment were calculated and documented on the CRF.
- 5) There was no standardized protocol for follow up appointments. Therefore once an AA was initiated, each psychiatrist or nurse practitioner implemented varying intervals for follow up appointments and weights and heights. Also because children in these families were often from impoverished backgrounds, many times families often canceled because they did not have money for gas or a ride or simply did not show for appointments as they forgot.
- 6) The baseline (prior to AA initiation) height and weight were found in the *graphic chart* and *physical or nursing assessment* and then documented on the CRF. To ensure accuracy, these data were then cross-referenced and found on the *nursing assessment* or *provider or psychiatrist progress note*, then documented on the DLS.
- 7) Subsequent heights and weights when the child was switched to another AA, stopped taking the AA altogether because of resolution of symptoms or intolerable side effects, left the clinic to be treated elsewhere, or at the end of three years were located in the *graphic sheet* and then documented on the CRF. To ensure accuracy, these data were then cross-referenced and found on the *provider or psychiatrist progress note*, then documented on the DLS.



- 8) The BMI  $z$  change score in kilograms from AA initiation to AA discontinuation was calculated at <http://www.bcm.edu/cnrc/bodycomp/bmiz2.html> and then documented on the CRF.
- 9) The baseline BMI and BMI  $z$  scores (prior to initiating the AA) were calculated by entering age, gender, and height and weight into <http://www.bcm.edu/cnrc/bodycomp/bmiz2.html> and then written on the CRF.
- 10) The diagnoses on the day that the AA was initiated were located in the *psychiatric assessment, provider, or psychiatrist progress note*, and then documented on the CRF. To ensure accuracy, these data were then cross-referenced and found on the *admission note*, then documented on the DLS. Documented diagnoses, made by board-certified child psychiatrists or a certified nurse practitioner that specializes in child and adolescent psychiatry, were standardized from the DSM-IV TR (American Psychiatry Association, 2000). The child psychiatrists and the certified nurse practitioner are considered experts in diagnosing and treating psychiatric disorders for children and are employed by the university.
- 11) At discontinuation of the AA, or the end of three years, the BMI and BMI  $z$  scores were calculated by entering the age, gender, and height and weight into <http://www.bcm.edu/cnrc/bodycomp/bmiz2.html> and then documented on the CRF.

**Data entry and cleaning.** The PI created an electronically-encrypted and password-protected, Codebook (Appendix E) that included variable names, the EMRN,

and a non-identifying code for each participant, which was utilized to identify all data that pertained to that research participant. The PI visually examined the CRF and DLS, after the chart was reviewed, for any obvious errors or missing data.

The PI created a raw data file from the CRFs in the standard computer program IBM Statistical Package for the Social Sciences (SPSS) 20.0 for Mac, which was available to the PI on her personal computer. Data were screened, cleaned, and any errors were corrected. Recalculation of all weights, BMI, BMI  $z$  scores, and calculated BMI  $z$  change scores was done to assure the accuracy of data.

### **Data Analysis**

Descriptive univariate analyses were run in SPSS for all the categorical variables of AA, diagnosis, ethnicity/race, as well as gender and continuous variables of age, months in treatment, and BMI  $z$  change score. The frequencies were reviewed for each variable, and particular attention paid to any missed values. A descriptive analysis of mean, median, standard deviation, minimum, maximum, skewness, and kurtosis, as well as histograms was conducted. Normality plots were then run for the continuous variables of age, months in treatment, and BMI  $z$  change score. Each variable was reviewed for errors, missing data, extreme values, and normal distribution (test for the assumptions of linearity, normality, and homoscedasticity, and correct the data) (Appendix F). Table 3 presents the variables used in the analysis of the research questions.

Table 3

*Variable Overview*

<i>Variable</i>	<i>Source</i>	<i>Level of Measurement</i>	<i>Question Analyzed</i>	<i>Dependent (DV) or Independent (IV)</i>
Age	Chart – Demographic Sheet	Continuous	Q1	IV
Gender	Chart – Demographic Sheet	Categorical	Q1	IV
Ethnicity/race	Chart – Demographic Sheet	Categorical	Q1	IV
Diagnosis	Chart – Med Provider Note, Nurse’s Note, MAR	Categorical	Q1	IV
BMI $z$ change score*	Chart- Med Provider Note, Nurse’s Notes, Graphic chart	Continuous	Q1, Q2	DV
Type AA	Chart – Med Provider Note, Nurse’s Note, MAR	Categorical	Q1	IV
Months in treatment	Chart- Med Provider Note, Graphic chart	Continuous	Q1, Q2	IV

\*Difference in pre/post BMI  $z$  scores

**Data analysis for research question 1.** An analysis was conducted for Research Question 1: “What demographic, diagnostic, and treatment characteristics (type of AA,

diagnosis, ethnicity/race, age, gender, and months in treatment), contribute to weight gain in children who take atypical antipsychotics?”

***Hypothesis 1: Atypical antipsychotic and BMI z change score.*** It was hypothesized that children and adolescents taking olanzapine, risperidone, and quetiapine gained more weight than children taking aripiprazole and ziprasidone. An analysis of variance (ANOVA) was run to detect the effect of the AA on weight gained. Next, to test the hypothesis, AA was re-coded into two groups: The children given olanzapine, risperidone, and quetiapine were coded 0, with the children taking aripiprazole and ziprasidone coded 1. An independent samples *t*-test was conducted to compare the BMI z change score for the two groups.

***Hypothesis 2: Diagnosis and BMI z change score.*** It was hypothesized that children and adolescents who have a diagnosis of a mood/affective disorder, psychotic disorder, or anxiety disorder gained more weight than children who have diagnoses of disruptive behavior, pervasive developmental disorder, or tic disorder.

An ANOVA was run to detect the effect of diagnosis on weight gained. Next, to test the hypothesis, each diagnosis was re-coded into two groups as follows:

1. Participants with a diagnosis of mood/affective disorder and psychotic disorder were coded 0.
2. Those with a diagnosis of disruptive behavior disorder, pervasive developmental disorder, and tic disorder were coded 1.

An independent samples *t*-test was conducted to compare the BMI z change score for the two groups.

**Hypothesis 3: Ethnicity/race and BMI z change score.** It was hypothesized that children and adolescents from Hispanic or Latino, Native American, Black or African American, or Other (mixed race) ethnicity/race gained more weight than children listed as White or Asian.

An ANOVA was run to detect the effect of ethnicity/race on weight gained. Next, to test the hypothesis, ethnicity/race was re-coded into two groups as follows: those who were Hispanic or Latino; Black or African American; American Indian or Alaskan Native participants and Other (mixed race) were coded as 0, and those who were White or Asian coded as 1. Because no participants were Native Hawaiian or Other Pacific Islander, these categories were removed from ethnicity/race variable. Other (mixed) ethnicity/race always included Hispanic, Native American, or Black and therefore was placed in the composite variable 0 with Hispanic, Black, and Native American. An independent samples *t*-test was conducted to compare the BMI *z* change score for the two groups

**Hypothesis 4: Age and BMI z change score.** It was hypothesized that children who were prepubescent (ages 9-13) would have a greater BMI *z* change score than children and adolescents ages 6 to 8 years or 14 to 17 years. First, Pearson correlations were run to determine if there was a simple linear association between age and BMI *z* change score.

Next, to test the hypothesis, age was recoded into two groups: children 9 to 13 years who were coded 0 and ages 5 to 8 and 14 to 17 years of age, who were coded as 1. No participant was 18 years and was removed from the age variable. An independent samples *t*-test was conducted to compare the BMI *z* change score for the two groups.

***Hypothesis 5: Gender and BMI z change score.*** It was hypothesized that females would experience more weight gain than males. An independent-samples *t*-test was run to determine if there were differences in the BMI *z* change score distribution between males and females.

*Hierarchical multiple regression (HMR) analysis for research question 1.* The following is a summary of the HMR conducted. Greater detail regarding the procedures and decisions made is provided in the Results chapter. First, because of a possible interaction between type of AA and months in treatment, the five types of AA were reduced to two combined dummy AA variables using risperidone as the reference category for both. The first dummy variable OQ was created from the combination of olanzapine and quetiapine. The second dummy variable AZ was created from the combination of aripiprazole and ziprasidone. In addition, two interaction variables were created. The first interaction variable OQMO was created from OQ times months in treatment. The second interaction variable AZMO was created from AZ times months in treatment.

The HMR conducted included the following predictors for BMI *z* change score: the original demographic variables of gender, age, ethnicity/race; diagnosis; the new computed variables for AAs (OQ, AZ); months in treatment; and the new interaction variables for AA times months in treatment (QOMO and AZMO). Months in treatment was entered at Step 1, followed by the combined AA variables of OQ and AZ together at Step 2, the interaction variables of OQMO and AZMO together at Step 3, diagnosis at Step 4, ethnicity/race at Step 5, age at Step 6, and gender at Step 7. The same dummy variables computed for tests of Hypotheses 1 through 5 were used in the HMR.

### **Data analysis for research question two.**

*Hypothesis 6: Months in treatment and BMI z score change.* The longer the time that the child or adolescent is in treatment the more weight they will gain. First a Pearson correlation was run to determine if there was an association between months in treatment and BMI z change score. Then a bivariate regression was conducted. The DV was BMI z change score/ weight gain and the IV was the time on AA, or months in treatment.

### **Summary**

After obtaining HRRC approval, charts were enrolled for this study from the university affiliated inpatient and outpatient child psychiatric facilities. Data were then collected by the PI using a CRF. The data were analyzed through using bivariate analyses initially, then multivariate analysis. Statistical procedures included ANOVAs, *t*-tests, and a HMR to answer the research questions and test the hypotheses. The protection of human subjects is addressed in the next section.

### **Human Subjects Protection**

Human subjects' approval was obtained before data collection. Key issues that were addressed were vulnerability of children with psychiatric illness, confidentiality of the participants in the study, risks of, and benefits of participating

**Vulnerability of children with psychiatric illness who are overweight or obese.** Children with mental illness who are overweight or obese are in a threefold vulnerable population (Puhl, 2007; Spetie & Arnold, 2007) and often research with children is deferred due to these vulnerabilities. Children with mental illness should not become "research orphans" (Spetie & Arnold); however, because of this consideration,

researchers need to ethically address those vulnerabilities in studies of this population. Overweight and obese children are vulnerable due to the stigmatization they suffer from peers, parents, educators, and health care providers. Stigmatization is amplified by the inherently negative social, emotional, and physical consequences of overweight and obesity. Children and adolescents were not contacted in this retrospective chart review and the risk of harm was extremely low. Procedures to protect their personal health information were put into place to correct their confidentiality such as encryption of files and destructions of identifying information.

**Confidentiality of the participants in the study.** Several methods to protect the confidentiality of the participant's EMR and the collected data were put into place.

- a) All participant charts were given an identification number using the following procedures;
  - i) The EMRN of the participant was obtained from the hospital database, Power Chart Office (PCO) and written down in an electronically encrypted and password-protected Codebook
  - ii) Each EMRN was placed in the Codebook in sequential fashion and given a non-identifiable code, which was then the number that all data regarding that chart was referred (i.e., 1 - EMRN 123456, 2 - EMRN 223456, etc.).
- b) Then the electronic file of the EMRN key and referenced non-identifying code were separated from the Codebook and placed in a separate electronically encrypted and password-protected file in the PI's locked office that only the supervising faculty and PI could access.



- c) The electronic file of the list of non-identifying codes, along with the associated data, was kept in the Codebook.
- d) After the study was completed, the electronic file of the EMRN key and referenced non-identifying code was destroyed. No identifying information regarding the participants exists.

A Project Notebook was kept with all Human Research Review Committee (HRRC) approvals, which includes notes, forms, paperwork, and the names and numbers of all personnel involved with the study, as well as any and all information that pertains to this study. The Project Notebook was kept in a file cabinet in the PI's office when not in use by the investigator.

**Risks to the participants.** Because this was a retrospective chart review, there were no physical, psychological, social, or legal risks to the children because no contact was made with the participants. The data were obtained in a confidential manner from the EMR and any identifying data were destroyed after the research was concluded. The risks are extremely limited because no disclosure of personal information was made to anyone. Only one RA and one MA assisted with identifying potentially eligible charts, and only the RA reviewed 10%, or 10 of the 110, charts that were reviewed by the PI. Every effort was made to minimize the risks.

**Potential benefits of the proposed research.** Among the potential benefits is the possibility of making a contribution to the understanding of weight gain in children who take AAs. No subject directly benefitted from this investigation.

**Importance of the knowledge gained.** Knowledge gained in this investigation adds to the literature on BMI z change score/weight change and overweight and obesity

in children who take AAs. Furthermore, this research contributes to the understanding of demographic, diagnostic, and treatment characteristics and their potential contribution to BMI  $z$  change score/weight change and obesity in children who take AAs. It also may reduce potential health risks by adding to the body of research on adverse drug events. No collaborating sites were utilized and women and minorities were not specifically included in the research.

*Consent and safety.* No consents were obtained for this retrospective chart review. Monitoring the security of the data occurred throughout the research process. All data were kept in a locked file cabinet in the investigator's office. The study was never stopped because no personal safety concerns occurred. Results of the analyses of the data follow in the next chapter.

## **Chapter 4**

### **Results**

The results chapter is organized in the following manner. A description of the sample and variables will be given, and then the research questions will be examined as will the testing of the hypotheses. The key variables for this study were categorical variables of type of atypical antipsychotic (AA), diagnosis, ethnicity/race, and gender as well as continuous variables of age, total months of treatment, and the BMI  $z$  change score.

### **Sample Description**

For this study, approximately 600 charts were reviewed and 110 met eligibility criteria. Other than specific exclusion criteria, 91 charts were not eligible as the AAs were started in another system of care and no baseline heights or weights were available. Thirty-two children left the system of care and were lost to follow up, 14 had no baseline data as the medical assistant was out the day of the appointment and 7 were on two AAs, 7 were under the age of five and 5 did not start the AA after it was prescribed. Two children had diabetes, 1 was pregnant and 1 had a mitochondrial disease. Descriptive univariate analyses of 110 cases were run in SPSS (Pallant, 2007). One 15-year-old female, who was severely underweight at baseline, gained more than 24 kg (53 pounds) in eight months while taking aripiprazole. Her BMI  $z$  change score (6.28) was three standard deviations from the mean of this sample, and as an extreme outlier was removed from the final analysis. BMI  $z$  change score values under three standard deviations were included in the analysis, with  $N = 109$  in the final analysis.

To qualify for inclusion in this study, children had to be in treatment with an AA for at least three months and no longer than three years. Over the course of three years, no child had more than three trials of different AAs and all trials were for different

amounts of time (ranging from one month to 36 months). Because there were no more than three AA trials, the children were divided into three separate groups. A total of 109 children had an initial or first trial of an antipsychotic, 27 children (25%) had a second trial and only six children (1%) had a third trial. Only the data from the initial trial of medication were analyzed for this study because not enough children were in the second or third trials to run the analyses with any measure of statistical power.

### Age

The average age in this sample was 10.5 years ( $SD = 3.42$ , min/max = 5 /17 years). Approximately half of the sample ( $n = 56$ , 51.4%) was 5 to 10 years of age (See Table 4). Only 21 (19.2%) were ages 14 to 17 years. Age had a relatively normal appearing histogram, with a skewness of 0.11, kurtosis of -1.03, normal Q-Q and boxplot, and no outliers. Age met linearity and homoscedasticity assumptions, but the KS statistic was significant ( $p < .001$ ), indicating non-normality.

Table 4

*Age Frequencies (N = 109)*

Age	<i>n</i>	%
5	8	7.3
6	7	6.4
7	13	11.9
8	5	4.6
9	17	15.6
10	6	5.5
11	6	5.5
12	10	9.2
13	16	14.7
14	6	5.5
15	5	4.6
16	6	5.5
17	4	3.7

## Gender

Seventy-three (67%) of the sample were male and 36 (33%) were female.

## Ethnicity/Race

The sample consisted primarily of Hispanic or Latino children ( $n = 58, 53.2\%$ ), White children ( $n = 34, 31.2\%$ ), American Indian or Alaskan Native ( $n = 7, 6.4\%$ ), and Other (two or more races) ( $n = 5, 4.5\%$ ). Lastly, Black or African American children ( $n = 4, 3.7\%$ ) and Asian children ( $n = 1, 0.9\%$ ) comprised the fewest children.

## Diagnoses

Table 5 lists the primary diagnoses of the children in the sample.

Table 5

*Frequency and Percent of Children for Each Primary Diagnosis (N=109)*

<i>Diagnosis</i>	<i>n</i>	<i>%*</i>
Mood/Affective Disorder	66	60
Psychotic Disorder	20	18
Disruptive Behavior Disorder	10	9
Pervasive Developmental Disorder	3	3
Anxiety Disorders NOS	7	6
Tic Disorder	3	3

\*Does not add to 100% due to rounding.

For the children with a psychiatric diagnosis or diagnoses, the first diagnosis listed is the primary one, or the one with symptom clusters causing the greatest dysfunction. Then additional diagnoses are given for those symptom clusters that are not the primary issue but were identified as affecting the child. In this sample, 90% of the

children had a secondary diagnosis and 43% had a third diagnosis. The main secondary diagnoses were disruptive behavior disorders ( $n = 36, 37\%$ ), anxiety disorders ( $n = 21, 21\%$ ), and mood/affective disorders ( $n = 16, 16\%$ ) whereas disruptive behavior disorders ( $n = 13, 27\%$ ), anxiety disorders ( $n = 4, 8\%$ ) represented the top third of diagnoses, with pervasive developmental disorders ( $n = 3, 6\%$ ) close behind.

### **Atypical antipsychotics**

Table 6 shows the frequencies and percentages of the types of AAs that were first prescribed for children in this study. About half of the children were prescribed aripiprazole. Almost one-third was prescribed risperidone. Less than 10% were prescribed any one of the remaining three drugs.

Table 6

#### *Frequencies and Percentages of Atypical Antipsychotics*

Atypical Antipsychotic	$n$	%*
Olanzapine	6	6
Risperidone	32	30
Quetiapine	10	9
Aripiprazole	53	49
Ziprasidone	8	7

\*Does not add to 100% due to rounding.

**Months in treatment.** Time in months on any AA ranged from one to 36 consecutive months (See Table 7), with three children on an AA for one month and two on an AA for two months before being switched to another AA. The average time in treatment for an AA was just over one year ( $M=13.00, SD=10.28$ ). The histogram appeared somewhat normal (skewness=1.08, kurtosis = -0.08). Twelve children were on

an AA from 31 to 36 months. Five (42%) were either on risperidone or aripiprazole and one (8.3%) were either too quetiapine or ziprasidone, and none took olanzapine for this length of time.

Table 7

*Frequencies and Percentages of Months in Treatment on Each Atypical Antipsychotic (N=109)*

Atypical Antipsychotics						
Months in Treatment	Olanzapine <i>n</i> (%)	Risperidone <i>n</i> (%)	Quetiapine <i>n</i> (%)	Aripiprazole <i>n</i> (%)	Ziprasidone <i>n</i> (%)	Total <i>n</i>
1	-	1(33)	1(33)	-	1(33)	3
2	-	-	-	1(0.5)	1(0.5)	2
3	-	2(40)	-	2(40)	1(20)	5
4-6	3(11)	7(25)	1(4)	15(54)	2(6)	28
17-12	2(6)	9(28)	4(13)	16(50)	1(3)	32
13-18	-	5(39)	2(15)	5(38)	1(8)	13
19-24	-	1(12.5)	1(12)	6(75)	-	8
25-30	1(17)	2(33)	-	3(50)	-	6
31-36	-	5(42)	1(8.3)	5(42)	1(8.3)	12

The mean number of months on each AA is shown in Table 8. Risperidone had the highest mean number of months in treatment and ziprasidone had the smallest.

Table 8

*Mean Months in Treatment on Each Atypical Antipsychotic*

Atypical Antipsychotic	<i>M</i>	<i>SD</i>	min/max
Olanzapine	9.67	10.03	(4, 30)
Risperidone	14.28	11.63	(1, 36)
Quetiapine	13.40	9.55	(1, 36)



Aripiprazole	13.06	9.72	(2, 35)
Ziprasidone	9.38	11.60	(1, 36)

**Weight.** Although BMI is calculated in the same way for both adults and children, it is interpreted differently based on a child’s gender and age because the amount of body fat differs between girls and boys and changes with age. The (CDC) Centers for Disease Control BMI-for-age growth charts consider these differences by converting the BMI number into a percentile for the child’s sex and age. This is known as the children’s BMI percentile and it designates the comparative position of the child’s BMI number relative to other children of the same gender and age (Mei, et al., 2002). Therefore weight status categories are based on these percentiles and classified as follows: underweight (less than the 5th percentile), healthy weight (5th percentile to less than the 85th percentile), overweight (85th to less than the 95th percentile), and obese (equal to or greater than the 9th percentile) (Centers for Disease Control, 2011).

**Weight classifications and weight change.** At the initiation of AAs, in utilizing the children’s BMI percentile for age, 1 (1%) were classified as underweight, 60 (55%) were normal weight, 15 (14%) were overweight, and 28 (26%) were obese. Over the course of one to 36 months on AAs, 107 (98%) of the children gained weight, with the average weight gain across all children of 9.89 kg (SD = 8.33, min/max = -0.17/36.75) or 21.80 lb (SD = 18.37, min/max = -0.36/81.02). Only 2 (1.8%) of the children lost weight (-0.10 and -0.17 kg). The most weight gained was 36 kg by a nine-year-old Hispanic male with a diagnosis of disruptive behavior disorder that had one trial of aripiprazole for 34 months.

**BMI and BMI  $z$  change score.** An increase in BMI occurred in 95 (87%) of the children, with an average among all the children of 2.59 (SD = 2.63, min/max = -2.40/11.40). Twelve (11%) of the children had a decrease in BMI and two (2%) stayed the same. At the end of the initial trial of AAs, 1 (1%) of the sample was classified as underweight, 47 (43%) at normal weight, 23 (21%) overweight, and 37 (34%) were obese. The BMI  $z$  score, or standard deviation (SD) score, represents the number of SDs above or below the mean distribution of BMI scores for children or adolescents of the same gender and age. A positive BMI  $z$  score means a child is heavier than the mean and a negative BMI  $z$  score that the child is lighter than the mean.

The baseline BMI  $z$  score was calculated from the BMI at baseline, whereas the final BMI  $z$  score was derived from the BMI when the child either discontinued the initial medication or at three years' time. The BMI  $z$  change score, or weight loss or gain, is the difference of the baseline BMI  $z$  score from the final BMI  $z$  score. The mean BMI  $z$  change score for all children was 0.33 (SD = 0.62, min/max = -1.47/2.80). A majority of the children ( $n = 79$ , 72%) had an increase in their BMI  $z$  change score, which indicates that the standard deviation increased for their BMI based on their gender and age. Thirty-six (33%) of the children exhibited an increase of 0.5 or more in the BMI  $z$  change score, 20 (18%) had their BMI  $z$  change score decrease, and one child (1%) had no change in their BMI  $z$  change score.

## **Research Questions**

**Research question 1.** What demographic, diagnostic, and treatment characteristics (type of medication, diagnosis, ethnicity/race, gender, age, and months in treatment) contributed to the BMI  $z$  change score among children who take AAs?

Bivariate analyses were conducted with AA, diagnoses, ethnicity/race, age, gender, and months in treatment to examine their individual effects on the BMI  $z$  change score. Then a hierarchical multiple regression (HMR) was run to test the combined effects of the variables on the change score.

***Hypothesis 1: Atypical antipsychotic and BMI  $z$  change score.*** It was hypothesized that children and adolescents taking olanzapine, risperidone, and quetiapine would gain more weight than children taking aripiprazole and ziprasidone.

First, an ANOVA was conducted to detect the differences between each type of AA and the BMI  $z$  change score. In testing the assumptions for the ANOVA, AAs had a few outliers, none were extreme, and all appeared normal for this population. As assessed by the KS statistic, the distribution of the BMI  $z$  change score for olanzapine, quetiapine, and aripiprazole was normal as ( $p > .05$ ), but not for risperidone, ziprasidone ( $p < .05$ ). The skew and kurtosis of risperidone were not severe; however, ziprasidone (skew = 1.83,  $SE = 1.41$ ; kurtosis = 4.31,  $SE = 0.75$ ) had a severe skew and kurtosis. The assumption of homogeneity of variances was violated for AAs as assessed by Levene's Test of Homogeneity of Variances  $F(4, 104) = 4.50, p < .05$ . The ANOVA is robust to violations of assumptions, except in the case of unequal variances with unequal sample sizes. Because AA had unequal variances with unequal sample sizes, an adjusted version of the ANOVA was run for this variable.

Welche's  $F$  test was the statistical test used, which is robust to these violations and is considered more conservative. No significant differences were observed between types of AAs [ $F(4,20.55) = 2.10, p < .12$ ] and the BMI  $z$  change score, which indicates that the type of AA had no significant influence on whether or not a child gained weight.

Eta squared for the variable AA was  $\eta^2 = 0.03$ , or 3%, of the proportion of the variance explained of the BMI  $z$  change score, which is quite small.

Table 9 displays the means and standard deviation of weight change in kilograms and pounds and the BMI  $z$  change score for each type of AA. The greatest amount of weight gain occurred in a child who took aripiprazole (36.75 kg/81.02 lbs), while a child who took quetiapine actually lost weight (-.17 kg/-.38 lbs). In examining the BMI  $z$  change score means, large differences were noted, as with olanzapine ( $M = .61$ ), which had the greatest score, and ziprasidone ( $M = .09$ ), which had the least. A calculated Cohen's  $d$  from the means and standard deviation of olanzapine and ziprasidone revealed a very large effect size  $d = 1.3$ . However, the effect of olanzapine was not statistically significant because of its small group size ( $n = 6$ ). In examining the data, no pairwise comparisons were significant.

Next, to test the hypothesis, AA was re-coded into two groups: The group of children given olanzapine, risperidone, and quetiapine was coded 0, with the second group taking aripiprazole and ziprasidone coded as 1. An independent samples  $t$ -test was conducted to compare the BMI  $z$  change score for children in the two groups. A significant difference in the BMI  $z$  change score occurred for children taking olanzapine, risperidone, and quetiapine which indicated that they gained more weight than children taking aripiprazole and ziprasidone (see Table 12), with a Cohen's  $d$  of .23 indicating a small overall effect. Hypothesis 1 was supported.

An analysis of covariance was considered in order to examine the effect of months in treatment related to the effect of AAs on the BMI  $z$  change score, but the

assumptions of homogeneity of regression slopes and variances were violated, so the test was not conducted.

Table 9

*Means and Standard Deviations of Weight Change and BMI z Change Score for Each Type of Atypical Antipsychotic (N = 109)*

		Atypical Antipsychotic				
		Olanzapine	Risperidone	Quetiapine	Aripiprazole	Ziprasidone
		(n = 6)	(n = 32)	(n = 10)	(n = 53)	(n = 8)
kg/lb						
	<i>M</i>	13.75/30.31	9.21/20.30	11.51/25.38	9.88/21.78	7.70/16.98
	<i>SD</i>	11.73/25.86	7.03/15.50	10.55/23.26	8.38/18.47	8.04/17.73
	Min	5.80/12.79	.60/1.32	-.17/-.38	-.10/-.22	.90/1.98
	Max	33.90/74.74	28.90/63.71	33.7/ 74.3	36.75/81.02	25.90/57.10
BMI z						
Change Score						
	<i>M</i>	.61	.41	.44	.27	.09
	<i>SD</i>	.51	.94	.45	.41	.24
	Min	.02	-1.47	-.13	-.68	-.14
	Max	1.10	2.80	1.23	1.08	.63

**Hypothesis 2: Diagnosis and BMI z change score.** It was hypothesized that children and adolescents who have diagnoses of mood/affective disorder, psychotic disorder, or anxiety disorder would gain more weight than children who have diagnoses of disruptive behavior, pervasive developmental disorder, or tic disorder.

First, an ANOVA was conducted to detect the differences between each of the different diagnoses and the BMI z change score. In testing the assumptions for the

ANOVA, the diagnoses had a few outliers, but none were extreme and all appeared normal for this population. The distribution of the BMI  $z$  change score for psychotic disorder, disruptive behavior disorder, and anxiety disorders was normal as assessed by the KS statistic ( $p > .05$ ) but were not normal for mood disorders ( $p < .05$ ). However, the skew and kurtosis of mood disorders were not severe. The assumption of homogeneity of variances, which was assessed by Levene's Test of Homogeneity of Variances, was violated for diagnosis  $F(5, 103) = 2.74, p < .05$ . The ANOVA is robust to violations of assumptions, except in the case of unequal variances with unequal sample sizes, and the diagnoses had both. Therefore, the Welch's  $F$  test, an adjusted version of the ANOVA that is robust to these violations and considered more conservative, was run. The Welch's  $F$  test indicated no significant differences between diagnoses on the BMI  $z$  change score [ $F(5, 9.42) = 0.18, p < .96$ ]  $\eta^2 = 0.03$ , or 3%. Hence, the proportion of variance explained cannot account for the BMI  $z$  change score as noted in Table 7. In examining the data, children with pervasive developmental disorder had a far greater mean BMI  $z$  change score ( $M = .85$ ) than any other diagnoses ( $M_s = .07 - .38$ ), with tic disorders having the least ( $M = .07$ ) (see Table 8). In examining the data, no pairwise comparisons were significant.

Next, to test the hypothesis, each diagnosis was coded as follows: Participants with a diagnosis of mood/affective disorder and psychotic disorder diagnoses were coded 0. Those with a diagnosis of disruptive behavior disorder, pervasive developmental disorder, and tic disorder were coded 1. An independent samples  $t$ -test was conducted to compare the BMI  $z$  change score for children with mood/affective disorder, psychotic disorder, or anxiety disorder diagnoses to the score for children with disruptive behavior

disorder, pervasive developmental disorder, or tic disorder diagnoses. As shown in Table 10, there was no significant difference in the mean BMI  $z$  change score for children in the two groups. Therefore, Hypothesis 2 was not supported.

Table 10

*Means and Standard Deviations of BMI  $z$  Change for Diagnosis*

Diagnosis	$n$	$M$	$SD$
Mood/Affective Disorder	66	.30	.58
Psychotic Disorder	20	.38	.64
Disruptive Behavior Disorder	10	.37	.51
Pervasive Developmental Disorder	3	.85	1.75
Anxiety Disorders NOS	7	.29	.52
Tic Disorder	3	.07	.59

**Hypothesis 3: Ethnicity/race and BMI  $z$  change score.** It was hypothesized that children and adolescents from Hispanic or Latino, Native American, Black or African American, or Other (mixed race) ethnicity/race would gain more weight than children who are from White or Asian ethnicity/race. First, an ANOVA was conducted to detect the differences among different ethnic/racial categories and the BMI  $z$  change score. Ethnicity/race met the assumption of homogeneity of variances and all but the White category met the assumption of normality. Ethnicity/race had no statistically significant effect on the BMI  $z$  change score (see Table 11). The one child of Asian ethnicity/race had a greater mean BMI  $z$  change score ( $M = .57$ ) than all the children of other

ethnicities/ races ( $M_s = -0.60 - .41$ ) with Other ( $M = -.06$ ) having the least. In examining the data, no pairwise comparisons were significant. The ANOVA was not statistically significant  $F(5, 103) = 0.66, p = .66$ . The Eta squared was small,  $\eta^2 = 0.03$ , and 3% of the variance in the BMI  $z$  change score was accounted for by ethnicity/race.

Table 11

*Means and Standard Deviations of BMI  $z$  Change for Ethnicity/Race*

Ethnicity/Race	<i>n</i>	<i>M</i>	<i>SD</i>
American Indian or Alaskan Native	7	.20	.56
Asian	1	.57	-
Black or African	4	.18	.21
Hispanic/Latino	58	.34	.48
White	34	.41	.82
Other	5	-.06	.82

Next, to test the hypothesis, ethnicity/race was coded as follows: the Hispanic or Latino; Black or African American; American Indian or Alaskan Native participants and Other (mixed race) were coded as 0, and the children who were White or Asian were coded as:

1. An independent samples  $t$ -test was conducted to compare the BMI  $z$  change score of the children who were Hispanic or Latino, Native American, Black or African American or Other (mixed race) ethnicity/race to the score for the children who were White or Asian ethnicity/race. The BMI  $z$  change score did not statistically differ for the two groups (see Table 9). Hypothesis 3 was not supported and ethnicity/race did not affect outcome.



**Hypothesis 4: Age and BMI z change score.** It was hypothesized that children who were prepubescent (ages 9-13) would have a greater BMI z change score than children and adolescents ages 6 to 8 or 14 to 17. First, Pearson correlations were run to determine if there was a simple linear association between age and BMI z change score. However, age was not significantly correlated with the change score ( $r = .04, p = .66$ ). Next, to test the hypothesis, age was re-coded into two groups: ages 5 to 8 and 14 to 17 years were coded as 0, with the children 9 to 13 years old coded as 1. An independent samples *t*-test was conducted to compare the BMI z change score for prepubescent children (ages 9-13) and children and adolescents ages 6 to 8 or 14 to 17. No significant difference was found in the scores of the two groups (see Table 9). Hypothesis 4 was not supported and age was not related to outcome.

**Hypothesis 5: Gender and BMI z change score.** It was hypothesized that females would have more weight gain than males. An independent-samples *t*-test was run to determine if differences existed in BMI z change score distribution between males and females. A boxplot inspection did not detect any severe outliers. The distribution of the BMI z change score for gender was normal for females ( $p = .20$ ), but not for males, ( $p = .002$ ), as assessed by the KS statistic. There was homogeneity of variances, assessed by Levene's Test of Homogeneity of Variances  $F(4, 104) = 4.50, p > .05$ , which indicated equal group variance. The BMI z change score was not significantly greater for females than for males (see Table 12), which meant that females did not gain more weight than males. Hypothesis 5 was not supported.

Table 12

*Independent t-Tests of Effects of Independent Variables Specified in Hypothesis on BMI z Change Score*

			<i>M</i>	<i>SD</i>	<i>t(df)</i>	<i>p</i>	<i>d</i>
Atypical Antipsychotic	Group 1	Olanzapine Risperidone Quetiapine	.39	.74	1.16(106)	.01*	.24
	Group 2	Aripiprazole Ziprasidone	.25	.40			
Diagnosis	Group 1	Mood Disorder, Psychotic Disorder, Anxiety Disorder	.32	.58	-.50(107)	.35	-.11
	Group 2	Disruptive Behavior Disorder, Pervasive Developmental Disorder, Tic Disorder	.40	.82			
Ethnicity /Race	Group 1	Native American, Hispanic, African American Other	.29	.51	-1.01(107)	.16	.20
	Group 2	White, Asian	.42	.81			
Age in Years	Group 1	9-13	.33	.73	.02(107)	.07	.00
	Group 2	5-8 & 14-17	.33	.49			
Gender	Group 1	Male	.34	.68	.21(107)	.25	.03
	Group 2	Female	.32	.48			

***Building the hierarchical regression model.*** The initial proposed HMR design included a straightforward hypothesized model with only the demographic, type of AA and diagnosis variables. Because of the tremendous variability noted in the data

regarding time on medications (ranging from 1 month to 36 months), it became apparent that months in treatment should be considered as a covariate. Therefore, an exploratory analysis of the data was undertaken by conducting an ANCOVA of AA regressed upon BMI  $z$  score with a covariate of months in treatment. The ANCOVA assumptions were explored and the scatterplot and regression slopes inspected, which noted that the BMI  $z$  change score over months in treatment, differed for each type of AA (olanzapine, quetiapine, risperidone, aripiprazole, and ziprasidone). This result indicated a correlation between AA and months in treatment. However, the assumption of homogeneity of regression slopes was violated and the entire ANCOVA was not run.

The tests of between-subjects effects of the ANCOVA indicated that AAs and months in treatment had a statistically significant interaction  $F(4, 99) = 2.86, p = .03$ . Therefore an investigation of this interaction was done. A visual inspection of the regression slopes indicated that each type of AA had a different pattern of BMI  $z$  change score/weight change over time as seen in Figure 2. Risperidone had a distinctly different, negative trajectory of change than did olanzapine, quetiapine, aripiprazole, and ziprasidone.

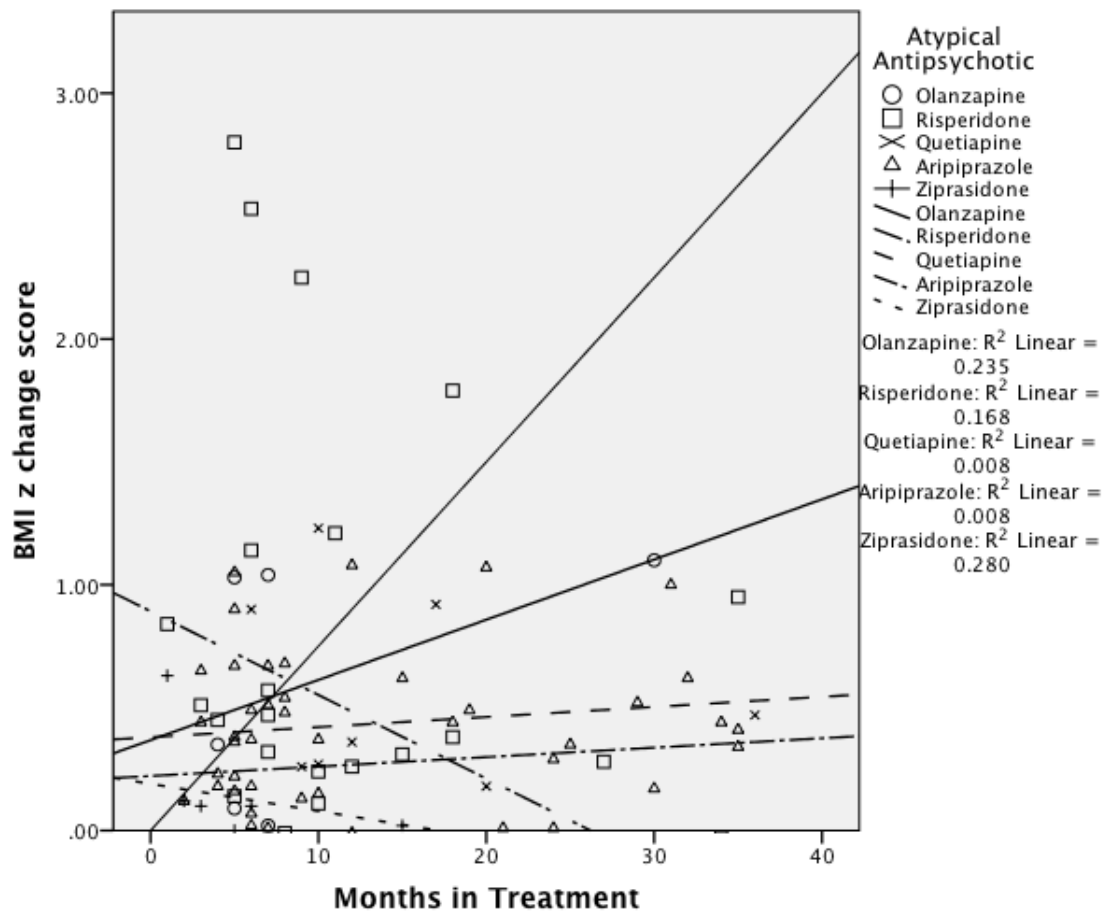


Figure 2. Scatterplot of regression slopes of olanzapine, risperidone, quetiapine, aripiprazole and ziprasidone of BMI z change score by months in treatment.

*Analyzing the interaction between AA and months in treatment.* Before conducting the HMR, the interaction between AA and months in treatment was explored further. To examine this more fully, the five types of AA were reduced to a new combined AA variable of three groups. One reference category created one group and two dummy variables created the second and third groups. Risperidone was chosen as the reference category, in part because it had a distinctly different pattern of BMI z change score/weight change than the other four types of AAs and it had a relatively large sample size. The first dummy variable OQ was created from the combination of olanzapine and quetiapine, because these two AAs represented the greatest BMI z change

score over time. The second dummy variable AZ was created from the combination of aripiprazole and ziprasidone, because these two AAs represented the lowest BMI  $z$  change score over time. In order to explore heterogeneity of the regression slopes, two interaction variables were created. The first interaction variable OQMO was created from OQ times months in treatment. The second interaction variable AZMO was created from AZ times months in treatment. An ANOVA was run for the new combined AA variable of 3 groups consisting of risperidone, OQ, and AZ to determine whether or not there were differences in BMI  $z$  change score for each group.

An ANOVA was conducted and in testing the assumptions, the new combined AA variable had a few outliers, none were extreme, and all appeared normal for this population. As assessed by the KS statistic, the distribution of the BMI  $z$  change score for OQ and AZ was normal as ( $p > .05$ ), but not for risperidone, ( $p < .05$ ). The skew and kurtosis of risperidone and AZ (skew =  $-.02$ ,  $SE = .31$ ; kurtosis =  $-.00$ ,  $SE = .60$ ) and OQ (skew =  $.26$ ,  $SE = .56$ ; kurtosis =  $-1.49$ ,  $SE = 1.09$ ) were not severe. The assumption of homogeneity of variances was violated for AAs as assessed by Levene's Test of Homogeneity of Variances  $F(2, 106) = 7.76$ ,  $p < .001$ . The ANOVA test is robust to violations of assumptions, except in the case of unequal variances with unequal sample sizes. Because AA had unequal variances with unequal sample sizes, an adjusted version of the ANOVA was run for this variable.

Welche's  $F$  test was the statistical test used, which is robust to these violations and is considered more conservative. There were no statistically significant differences in the BMI  $z$  change score as seen in Table 13 between risperidone [ $M(SD) = .41(.94)$ ], OQ [ $M(SD) = .50(.46)$ ], and AZ [ $M(SD) = .25(.40)$ ], [ $F(2, 34.76) = 2.15$ ,  $p = .13$ ]; no group

of new combined AAs had a significant influence on whether or not a child gained weight. Eta squared for the new combined variable AA was  $\eta^2 = 0.03$ , or 3%, of the proportion of the variance explained of the BMI  $z$  change score, which is quite small.

Table 13

*Welche's Analyses of Variance for New Combined AA Groups on BMI  $z$  Change Score (N = 109)*

	New Combined AA Variable	<i>M</i>	<i>SD</i>	<i>p</i>	<i>df1/df2</i>
Group 1	Risperidone	.41	.94	.13	2, 34.76
Group 2	OQ	.50	.46	-	-
Group 3	AZ	.25	.40	-	-

*Final hierarchical multiple regression for research question 1.* A reconfigured hierarchical multiple regression analysis was developed that included the following predictors for BMI  $z$  change score: the original demographic variables of gender, age, ethnicity/race; diagnosis; the new computed variables for AAs (risperidone, OQ, AZ); months in treatment; and the new interaction variables for AA times months in treatment (QOMO and AZMO). Despite the small, and largely insignificant, bivariate relationships between the demographic variables and BMI  $z$  change score, they were included in the final HMR analysis to examine their effects in combination with the other predictors.

Preliminary analyses were conducted to ensure there was no violation of the assumptions of normality, linearity, multicollinearity, or homoscedasticity for the independent variables. The same dummy coding used for the *t*-tests analyses was used in the HMR.

Table 14 provides a summary of the HMR results. Risperidone was again considered the reference category for the dummy AA variables. Months in treatment was entered at Step 1, followed by the combined AA variables of OQ and AZ together at Step 2, the interaction variables of OQMO and AZMO together at Step 3, diagnosis at Step 4, ethnicity/race at Step 5, age at Step 6, and gender at Step 7. Tolerance values for age, gender, and diagnosis were high but had no effect on the full model of the regression because they were insignificant.

The variable of months in treatment at Step 1 explained only 2% of the total variance in the BMI  $z$  change score and was not statistically significant. Combined AA variables OQ and AZ entered together at Step 2 explained 5% of the total variance in the BMI  $z$  change score.

However, interaction variables OQMO and AZMO, entered together at Step 3, proved statistically significant and explained 9% of the total variance in BMI  $z$  change score. The following four variables entered in the following order, diagnosis, ethnicity/race, age, and gender were not statistically significant. Each added less than 1% of the explained variance in BMI  $z$  change score, as documented in Table 14.

Model 3, shown in the regression model summary in Table 14, indicates that the proportion of the variance explained in the BMI  $z$  change score was statistically different from Model 2 (months in treatment and type of AA). Months in treatment, the combined variables of OQ and AZ together, and interaction variables of OQMO and AZMO together significantly explained 14% of the explained variance of the BMI  $z$  change score. Specifically, the addition of the interaction variables OQMO and AZMO to the overall regression model in model 3 led to a statistically significant increase and  $R^2$

change of .09. However, when all the variables were entered into the full Model 7, the proportion of variance explained increased by  $R^2$  change = .02, which was not statistically significant and indicated a poor incremental fit. Despite the poor incremental fit of Model 7, the overall model was statistically significant  $F(9, 99) = 2.01, p < .05, R^2 = .15$ . Model 3 was also statistically significant  $F(5, 103) = 3.40, p < .01$ .

Table 14

*Hierarchical Multiple Regression Analyses Predicting BMI z Change Score*

Model (Step)	R	R <sup>2</sup>	Adj R <sup>2</sup>	R <sup>2</sup> Chg	F Chg	df1	df2	p
1	.16	.02	.02	.02	2.67	1	107	.11
2	.23	.05	.02	.03	1.48	2	105	.23
3	.39	.14	.10	.09	5.42	2	103	.01
4	.38	.14	.09	.00	.05	1	102	.83
5	.39	.15	.09	.01	1.15	1	101	.29
6	.39	.15	.09	.00	.30	1	100	.59
7	.39	.15	.08	.00	.01	1	99	.92

Regression coefficients presented in Table 15 include the coefficient for the variable in that step of the model. Most of the coefficients for Model 3 were significant. The baseline value of the BMI z change score for AZ was significantly less (-.67) than the baseline value for risperidone, the reference category for the dummy variable. In contrast, the baseline BMI z change score for OQ was less (-.51), but not significantly so, than the baseline value for risperidone. Children on AZ and OQ gained less weight initially. The regression coefficients, or slopes, of .04 for AZMO and OQMO were both significantly different in than the slope of risperidone. Therefore the monthly change in BMI z score for AZMO and OQMO was .04 greater than that of the monthly change for risperidone, controlling for other variables in the model. The results of the HMR



indicated that when the dummy variable AZ and interaction terms AZMO and OQMO were added to the model, those variables contributed the most to the explained variance of BMI  $z$  change score when compared to OQ, months in treatment alone, AA alone, diagnosis, ethnicity, age, and gender.

Table 15

*Regression Coefficients and Standard Errors for Models 3 and 7*

	Model 3		Model 7	
	<i>b</i>	<i>SE(b)</i>	<i>b</i>	<i>SE(b)</i>
Constant	.89***	.17	.86***	.25
Months in Rx	-.03***	.01	-.03***	.01
OQ	-.51	.29	-.55	.31
AZ	-.67**	.21	-.68**	.22
OQMO	.04*	.02	.05*	.02
AZMO	.04**	.01	.04**	.01
Diagnosis	-	-	.07	.16
Ethnicity	-	-	.13	.13
Age	-	-	-.07	.12
Gender	-	-	.01	.13

Note.  $N=109$ .

\* $p < .05$ , \*\* $p < .01$ , \*\*\* $p < .001$ .

*Interaction of months in treatment and type of AA in predicting BMI  $z$  change score.* Regression Model 3 is appraised in a different way in Table 13, which examines the intercepts and slope of reference category risperidone and dummy variables OQ and AZ. The baseline intercept for risperidone can be seen as 0.89 with a change every month of -.03 BMI  $z$  score. Over a period of 30 months, the BMI  $z$  score changes significantly

by  $-0.90$  BMI  $z$  score. The baseline values (i.e. intercepts) for OQ and AZ were calculated by adding the coefficients for each respective dummy variable ( $-0.51$  and  $-0.67$ , respectively) to the constant term for Model 3 ( $.89$ ) in Table 16. As the reference category, the slope of risperidone ( $-0.034$ ) was then added to slope of OQ ( $.044$ ) and AZ ( $.036$ ) creating the slopes or BMI  $z$  changes of  $.01$  and  $.002$  respectively per month for each variable.

Table 16

*Intercept and Slope for Individual Regression Lines of Risperidone, OQ, and AZ on BMI  $z$  Change Score by Months in Treatment*

AAs	BMI $z$ Change score			
	Intercept		Slope/Change per month	
	<i>Estimate</i>	<i>SE</i>	<i>b</i>	<i>SE</i>
Risperidone	.89***	.17	-.03***	.01
OQ	.38	.24	.01	.02
AZ	.22	.12	.002	.01

\* $p < .05$ , \*\* $p < .01$ , \*\*\* $p < .001$ .

Figure 3 graphically represents the differences between risperidone, OQ, and AZ when plotted. As shown, a dynamic period of BMI  $z$  change score occurred in the first 10 months for all AAs. The pattern of change over time was significantly different for OQ and AZ than for risperidone. A rapid increase in the BMI  $z$  change score for children on risperidone peaked at three months, almost 2  $SDs$  above baseline, then began falling at 10 months and progressively tumbled. At 19 months however, the BMI  $z$  score of risperidone began a slower rate of decline, to finish at 36 months at 1.5  $SDs$  below

baseline. This indicates that, for this sample, the longer a child took risperidone, the more likely he or she was to lose weight. Children on OQ had slow, steady rate of weight

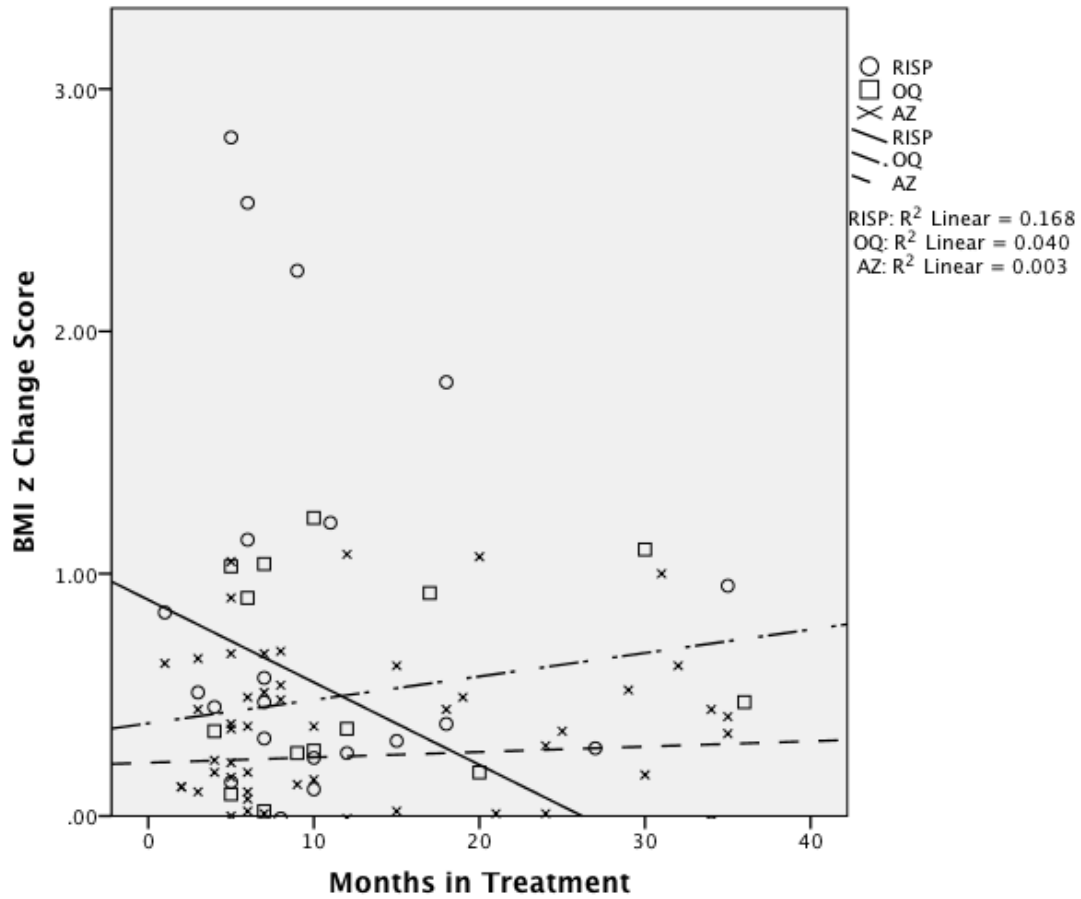


Figure 3. Regression slopes of new combined AAs of risperidone (RISP), olanzapine and quetiapine (OQ), and aripiprazole and ziprasidone (AZ), and BMI z score/weight change.

gain over months in treatment and children on AZ had an imperceptible increase in BMI z change score/weight change over time. These data revealed that children on OQ or AZ gained more weight the longer they were on these medications, albeit not at a rapid rate.

**Research question 2.** Does the amount of time on an AA affect the amount of weight that a child gains?

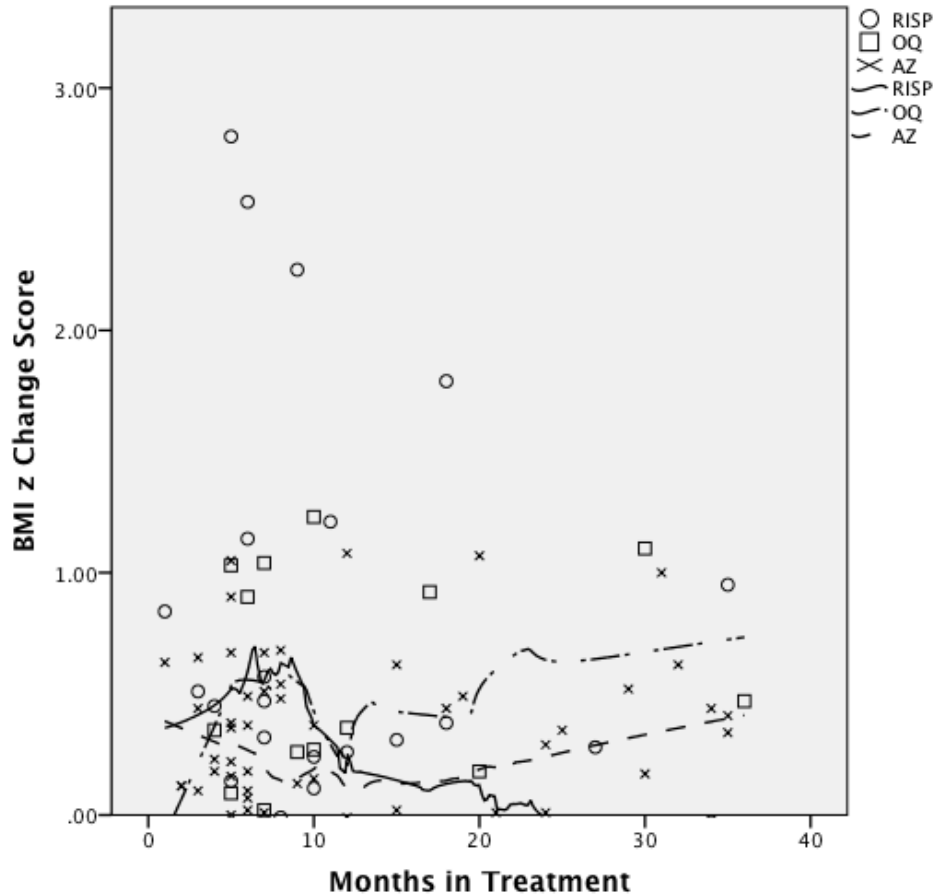
*Hypothesis 6: Months in treatment and BMI z change score.* The longer time that a child or adolescent is in treatment, the more weight they will gain.

First a Pearson correlation was run to determine if there was an association between months in treatment and BMI  $z$  change score. Months in treatment ( $r = -.16, p = .11$ ) did not significantly correlate with the BMI  $z$  change score, but was entered into the HMR to determine if it contributed to the model in combination with the other variables. As shown in Table 11, months in treatment alone claimed 2% of the total proportion of the variance explained for the BMI  $z$  change score,  $R^2 = .02, F(1, 107) = 2.67, p < .11$ ; adjusted  $R^2 = .11$  and was not significant. However, as previously discussed, an interaction was noted among months in treatment, the type of AA, and the BMI  $z$  change score, which indicated a different pattern of BMI  $z$  change score/weight change for each combination of AAs. In the HMR, the interaction terms QOMO and AZMO significantly predicted 14% of the total variance of BMI  $z$  change score explained in the model. The longer children were on olanzapine or quetiapine, the more weight they gained. Also, the longer the children were on aripiprazole or ziprasidone, the more weight they gained, although it was slow and incremental. However, the longer that children were on risperidone, the more they tended to lose weight. Hypothesis 6 was partially supported.

*Lowess or locally weighted scatterplot smoothing.* Locally weighted scatterplot smoothing (lowess or loess) is a nonparametric regression that provides a visual representation or underlying structure of the data to provide a clearer picture of the overall shape of the relationship of the variables (Anderson, 2009), but is purely descriptive and infers no conclusions. The lowess regression in Figure 4 depicts the detailed patterns of BMI  $z$  change score/weight change over 36 months for each dummy variable and the reference category (risperidone).

All three groups of combined AA variables indicated an initial increase in BMI  $z$

score/weight change, then risperidone's BMI  $z$  change score began to steadily decrease over an over time. The BMI  $z$  change score/weight change of children taking OQ sharply increased initially until about eight months, then dropped precipitously until about 14 months, before beginning a steady increase over the study period of 36 months. However, an initial weight gain among participants on AZ led to an unexpected and slight curvilinear relationship that resulted in a small weight loss before the weight increased at a very slow, almost imperceptible, amount over months in treatment. In contrast, the BMI  $z$  change score/weight change for children on risperidone sharply increased until eight months in treatment, at which point the weight plateaued until approximately 10 months. It then began a steady descent, ending well below baseline at 36 months in treatment.



*Figure 4.* A lowess scatterplot of the interaction of months in treatment with AA and BMI  $z$  change score/weight change. This demonstrates the individual pattern of weight change for each type of AA over time in treatment.

### Summary of Results

In this analysis, Hypothesis 1 was supported and Hypothesis 6 was partially supported.

Hypothesis 1, that children and adolescents taking olanzapine, risperidone, and quetiapine will gain more weight than children taking aripiprazole and ziprasidone, was supported. Hypotheses 2 through 5, which stated that a specific diagnosis, ethnicity/race, age, or gender would contribute to an increase in BMI  $z$  change score were not supported. Hypothesis 6, which theorized that the longer time a child was in treatment, the more weight they would gain, was partially supported. The HMR showed an interaction between type of AA and months in treatment that explained 14% of the variance in BMI  $z$

change score. Each group of combined AAs had a distinct rate and pattern of weight change over time in treatment. Children on olanzapine, quetiapine, aripiprazole, and ziprasidone gained more weight the longer they were in treatment. However, children on risperidone lost weight the longer they were in treatment.

## **Chapter 5**

### **Discussion**



Atypical antipsychotics (AAs) help children with SED function at home, in school, and in the community in a safer manner which enhances their ability to grow and develop socially and psychologically along as normal a trajectory as possible but may adversely affect their weight. The rapid weight gain for children who take AAs, along with the underlying demographic and treatment factors that may contribute to the weight gain, are not completely understood and served as the impetus for this dissertation. This study examined the type of AA, diagnosis, ethnicity/race, gender, age, and months in treatment and their effects on BMI  $z$  change score/weight change.

The chapter begins with a summary of the results of this research followed by a discussion of specific findings linked to the extant scientific literature. Then limitations of the research are considered, with particular emphasis on multiple threats of validity, the chart review design, and the difficulties in carrying out the originally proposed research. Implications for future research and clinical practice and a conclusion round out the chapter.

### **Summary of Results**

In this study, Hypothesis 1 was supported as type of AA contributed to the amount of BMI  $z$  change score. Children who took olanzapine, risperidone and quetiapine gained significantly more weight than children or adolescents who took aripiprazole and ziprasidone. Hypothesis 6 was partially supported as the longer time the child or adolescent was in treatment with olanzapine, quetiapine, aripiprazole, and ziprasidone the more weight they gained. However, children on risperidone lost weight the longer they were in treatment. Hypotheses 2 through 5, which stated that a specific

diagnosis, ethnicity/race, age, or gender would contribute to an increase in BMI  $z$  change score were not supported.

In testing the combined effects of the variables, months in treatment, the combined variables of OQ and AZ together, and the interaction variables of OQMO and AZMO significantly explained 14% of the variance of the BMI  $z$  change score. Diagnosis, ethnicity/race, age and gender contributed less than 1% of the explained variance and none were significant. An unexpected but interesting finding was the interaction of months in treatment and type of AA. Each type of AA had a distinct rate and pattern of weight change over time in treatment. Over time the rate of BMI  $z$  change score/weight change for children on risperidone, OQ and AZ was statistically significant.

### **Specific Findings and the Literature**

#### **Children on AAs**

This study is unique in several ways. First, it was conducted in the Southwest and 53.2% of the sample was Hispanic, as compared to New Mexico's Hispanic population of 54.9% (U. S. Census Bureau, 2009). No study of this type could be found in the literature that was conducted in the Southwest or with a predominantly Hispanic sample. The composition the ethnicity/race in this sample of children was slightly different for all but Hispanic children to that of New Mexico's population of children (U. S. Census Bureau, 2009). For this sample, as 29.1% of children were White compared to 39.8% of the state; 6.4% were American Indian versus 11.2% of the state; 4.5% were Other (two or more races) versus 5.1% of the state; Black or African American children were 3.7% versus 2.6% of the state; and lastly, Asian children 0.9% (1.5%) comprised the fewest children.

Second, consistent with FDA approved prescribing practices (Correll, Kratochvil, & March, 2011), children in this study were prescribed AAs for diagnoses of mood disorders and psychotic disorders. In contrast, in a recent review of national trends, Olfson and colleagues (2012) found that AAs were commonly prescribed to treat disruptive behavior disorder diagnoses in children (63%) and adolescents (33.7%) and are not FDA approved for these diagnoses (Harrison, Cluxton-Keller, & Gross, 2012; Pathak, West, Martin, Helm, & Henderson, 2010). New Mexico providers in this study appear to be practicing within the FDA approved guidelines. Very few children were prescribed olanzapine ( $n = 6$ ) as prescribers may have had a heightened awareness regarding AAs that cause more weight gain thereby prescribing an AA with less potential for weight gain.

And finally, in this study, aripiprazole (49%) was prescribed most often, followed by risperidone (30%), which was the reverse of the national trend (Olfson et al., 2012). No known reason could be elicited from the literature for this finding, but it is anticipated that different regional prescribing practices occur in part because of the ability of the drug companies to collaborate and provide certain medications at lower costs for certain states.

Similar to past research with this population, about two-thirds of the sample was male, with 55% of the males younger than 10-years-old. This suggests that more male children are treated with antipsychotics at earlier ages than females, which is consistent with the literature (Olfson et al., 2006; Zito et al., 2013). Males have a higher prevalence of externalizing disorders (attention deficit hyperactivity disorder, conduct problems, autism spectrum disorder, anxiety, and Tourette syndrome) than females (Perou et al., 2013), which results in a higher percentage of potentially aggressive behaviors. Still,

even when controlling for diagnoses of externalizing disorders, Olfson and colleagues reported that males were treated more frequently with AAs than females.

The proportion of children classified as normal weight, overweight and obese changed significantly over the course of treatment in this study. Fewer children (43%) at the end of treatment were considered normal weight than there were at baseline (55%). Children who were overweight (14%) or obese (26%) at baseline increased in number by the end of treatment (21% and 34% respectively).

Children and adolescents in this study gained an average of almost 22 pounds, which is double the average weight gain of 9.57 pounds in 10 studies cited by Cheng-Shannon et al. (2004). Furthermore, it is almost 3 times the average weight gain of 7.61 pounds in the meta-analysis of 21 double-blind randomized controlled trials (RCTs) conducted by Almandil et al. (2013) and the evaluation of over 20 RCT's by De Hert et al. (2011). Although these studies in the literature did not report the average BMI  $z$  change score, in this study the average BMI  $z$  change score was 0.33. One third (33%) of all children and adolescents in this study gained 0.5 BMI  $z$  score, a cut-off point that Weiss and colleagues (2004) estimated could possibly lead to a 55% increased risk of metabolic syndrome. Both the amount of weight gain for children in this study and the extent of the 0.5 BMI  $z$  change score across one third of the sample indicate a clinically significant impact.

**Interaction of type of AA and months in treatment.** Type of AA was the only variable that was significantly associated with BMI  $z$  change score by itself. Children and adolescents on olanzapine, risperidone, and quetiapine gained significantly more weight than children who took aripiprazole and ziprasidone, even with risperidone alone

having an overall negative relationship with BMI  $z$  change score. This finding is congruent with the majority of meta-analyses and reviews of RCTs in the literature (Almandil et al., 2013; de Fraguas et al., 2012; de Hert et al., 2011).

This study significantly adds to the literature in that it demonstrated an interaction between type of AA and months in treatment in predicting weight gain. No other authors have reported this result. Overall, the interaction of type of AA and months in treatment, in combination with diagnosis, ethnicity/race, age and gender explained 14% of the variance in BMI  $z$  change score. However, 14% of the variance was explained by type of AA (3%) and months in treatment (2%) alone and in interaction (9%). Individually, the combination of AZ had the largest effect size in relationship to BMI  $z$  change score. Although no specific literature focuses on this specific finding of time in treatment interaction with AA, children on aripiprazole (Almandil et al., 2013; Fraguas et al., 2011) and ziprasidone characteristically gain the least amount of weight (de Hert et al., 2011; Martinez-Ortega et al., 2013).

**Pattern of weight gain for each AA.** A unique pattern of BMI  $z$  change score/weight change was revealed for each type of AA over months in treatment. A steady increase in BMI  $z$  change score over months in treatment was seen for OQ and AZ, although AZ's pattern was initially curvilinear, where the weight change originally increased rapidly only to fall and then resume a slight increase at nine months progressively until the end of the study. Conversely, risperidone had a negative relationship to BMI  $z$  change during months in treatment as children lost weight after being on the medication for about 10 months. This is not consistent with the literature as weight gain is well documented with risperidone (Caccia, 2013). Risperidone is often

second behind olanzapine in the amount of weight gained (Almandil et al., 2013; de Hert et al., 2011) and there are no known reports of weight loss.

Pai et al. (2012) conducted the only extensive review of the literature that regards the temporal nature of weight gain with AAs in adults. No studies of this type were found in children. The authors postulated that a specific temporal course of weight gain during treatment is similar across clozapine, olanzapine and risperidone, albeit with differing magnitudes of weight gain.

- Stage 1, baseline to 3 months, an initial rapid increase in weight;
- Stage 2, 3 to 18 months, a steady rise of weight; and
- Stage 3, 18 months and beyond, weight plateaus with continued AA treatment.

Results from this dissertation somewhat illustrate Pai and colleagues' (2012) first stage because children on OQ and risperidone had a rapid increase in weight until about eight months. However, at this point, risperidone's trajectory diverged from OQ's and began a downward trajectory, creating a different pattern from the three stages that Pai et al. (2012) suggested. However OQ was associated with continuous weight gain until the end of the study at 36 months, whereas risperidone contributed to a steady weight loss until the end of the study. AZ behaved differently and advanced in the early months to develop a curvilinear relationship, where the trajectory of the weight change initially increased rapidly only to fall and then resume at nine months a slight weight increase until the end of the study.

Why children in this study on risperidone lost weight over time is unknown. It may be a finding specific to children who take AA over a longer period of time than

covered by most studies; most trials of AAs were an average of 8 weeks and the longest was 26 weeks (Almandil et al., 2013; de Hert et al., 201). Ultimately, it is an unusual finding that has no known support in the literature and it is unknown why the specific pattern of weight loss on risperidone or any other AA has not been reported.

Based on the unexpected weight loss with risperidone over time, it is also possible that reciprocal causality exists in the relationship between time in treatment and BMI z change score/weight change. Reciprocal causation is “when two variables cause each other” (Shadish, Cook, & Campbell, p. 511), thereby making it difficult to ascertain which variable caused the change in the other variable, because they affect each other. As with risperidone, the very dramatic weight gain in the first 3 months of treatment may have precipitated a reduced dosage of risperidone, the discontinuation of risperidone by the patient or a prescriber, or a change in the child’s prescription from one to another AA (Krantzler & Cohen, 2013) or medication. Indeed, poor compliance is also often a problem in antipsychotic treatment as one of the major concerns of patients is the fear of weight gain (Lett et al. 2012). Thus the pattern and amount of weight gain while on risperidone may have predicted the months in treatment and not the proposed hypothesis which implied that months in treatment would predict amount of weight gain.

### **Limitations and Threats to Validity**

The limitations of this study are explored and include those factors that might have influenced the interpretation of the research in ways that could restrict the conclusions reached and the generalizability of the results. Discussed are threats to the internal, external, and statistical conclusion validity. Challenges of chart review methodology are described as they pertain to the validity of the findings. Finally

approaches taken to address these threats are discussed

**Internal validity.** Internal validity refers to the strength of the study design to support assertions that there is a causal association between type of AA and BMI z change score (Shadish et al., 2001). Threats to internal validity in this study are related to the chart review methodology and include selection, small group sample size, instrumentation, history, ambiguous temporal precedence, as well as additive and interactive effects.

***Selection and instrumentation.*** A chart review methodology was selected for this study because it limited contact between vulnerable children with SED and research personnel and avoided exposure of the children to unknown risks (Gregory & Radovinsky, 2012). Selection bias was a threat because the PI did all of the chart reviews and was not blinded to the study; the lack of random selection of charts meant that the selection of charts and of the information in the charts might have been biased in some unknown manner. Another selection bias was the distinctly different characteristics of the sample in that it consisted of predominantly Hispanic and White children and adolescents and was therefore less generalizable to Native American, African American and Asian ethnicities/races. Specifically the percentage of Hispanic children reflected the composition of children in New Mexico as previously noted, however all other ethnicity/races were somewhat different. Children in this study were primarily prescribed aripiprazole for mood and psychotic disorders as compared to children nationally who are most commonly prescribed risperidone for disruptive disorders (Olfson et al., 2012). Although efforts were made to address selection bias through screening every referral to the study and every chart of each child identified as taking AAs, this had minimal impact.



If the population had been more diverse ethnically/racially, the sample could have been stratified thus reducing this element of selection bias.

Although exactly equal group sizes are uncommon in clinical research, the atypical antipsychotic group sizes were extremely different as olanzapine had 6 children and ziprasidone had 8 whereas aripiprazole had 53 and risperidone at 32. This decreased the internal validity of the study as it indicates the changes in the BMI z change score might not have been due to the type of AA. However it is important to note that although only 6 children took olanzapine, those children had more weight gain than any other type of AA in this study.

In addition to selection bias, instrumentation bias was a threat because many different types of health professionals documented the data in the chart. As an example, weight, one of the key variables in this study, was not necessarily measured or documented in a consistent manner. The two medical assistants who measured the heights and weights often did not insist that the children take off their shoes, which resulted in inaccurate data.

In an effort to reduce selection and instrumentation bias, standardization of the data collection was achieved through use of a chart review template (CRT) and data location sheet (DLS) to enhance the reproducibility of the study methods. A step-by-step protocol was followed when conducting each chart review. Rater reliability was quantified by having the research assistant review 10% of the charts evaluated by the PI to assure that the information was accurate and there was 90% agreement.

**History.** Prescribing practices have changed over the five-year span of the study; therefore, history was a threat to internal validity. New information obtained through

research and experience in prescribing AAs demonstrated that olanzapine was associated with rapid and greater amounts of weight gain than the other AAs (Almandil et al., 2013; de Hert et al., 2011; Pai et al., 2012). Therefore, olanzapine was prescribed infrequently, as noted in this study, despite its excellent mood stabilizing and antipsychotic properties. It is postulated that prescribers began to offer more weight-neutral AAs, such as aripiprazole or ziprasidone, or switched AAs once rapid gain was recognized. In addition to the possibility that providers may have switched to more weight-neutral medications, children who started gaining weight over a period of time may have stopped the medication due to an adverse effect or because the drug was not managing symptoms. Additionally, there were approximately 10 different prescribers who each psychiatrically assessed and prescribed in a singular manner. No protocol was in place for how to prescribe the AA and if it had been, this would have limited threats of history as well as instrumentation. These changes in practice during the time period of the study and variations in prescribing by providers made it difficult to fully explore the association between type of AAs and BMI z change score.

*Ambiguous temporal precedence.* In analyzing the data, it was apparent that the length of time in treatment might have predicted the BMI z change score, but it is also plausible that the BMI z score might have predicted time in treatment as mediated by provider prescribing behavior or family decision-making. Once the child gained weight, he or she might have stopped the AA or the prescriber stopped or switched medications. The study design would have been stronger if it had been possible to include a process analysis of why medication changes occurred and if more than the first trial of AAs had been included in the data analysis.

**Additive and interactive effects.** Overall, 68% of the sample was on more than one medication that could have affected weight gain, such as stimulants, lithium, and anticonvulsants (for mood stabilization), and this presented additive and interactive effect threats. Consequently, it is difficult to ascertain whether the AA caused the weight gain or an unmeasured confounding variable that was not included in the regression analyses caused the change. It would, however, have been impossible to isolate the sample to only children on AAs. The study population was not large enough to draw from and children with SED frequently take more than one medication to manage their symptoms (Olfson et al., 2012). Secondly, and perhaps most importantly, children took these medications for different periods of time. In addition, the height and weight measurements were taken irregularly, when the family went in for a follow-up appointment with the prescriber, rather than at specific intervals. This inherent variability in real-world clinical practice generated a lack of specificity of measurement that might have interfered with detection of an accurate pattern and amount of change in weight across time. Each of the threats to internal validity, alone and in combination, contributed to limits in the validity of causal inferences about the relationship between type of AA and weight gain in this study.

**External validity.** External validity refers to whether or not one can generalize the study results to other populations, settings, treatment or measurement variables (Shadish et al., 2001). This study used a convenience sample, rather than a random sample of the population. Convenience sampling is the most common method for chart reviews and is the most time-efficient way to obtain a sample of charts. The study could have been strengthened by using quota sampling, selecting a specific number of participants for each category of a variable (e.g. type of AA or ethnicity/race) to assure

equal representation within each variable, and systematic sampling, which entails taking a specific case, for example every 5th (a predetermined number) chart to review. Also, because this sample was obtained from a predominantly Hispanic, Medicaid population in a not-for-profit health sciences center, the sample had few children with private insurance or with ethnicities/race other than Hispanic and White. The results cannot be generalized to the privately insured or Native American, Black, Asian or Other (mixed) populations.

**Statistical conclusion validity.** Statistical conclusion validity refers to the validity of inferences about the covariation between independent and dependent variables (Shadish et al, 2001). In this study, the main issues with statistical conclusion validity were violations of assumptions for statistical tests and what Shadish and colleagues label heterogeneity of units. Violations for an assumption of homogeneity of variances occurred for AAs and diagnoses when attempting to run an ANOVA, for AAs when attempting to run an ANCOVA, and for BMI  $z$  change score related to male gender when assessing for the  $t$  test. Although many statistical tests are robust to non-normality, this assumption was violated in several instances: for age, months in treatment, and BMI  $z$  change score for both risperidone and ziprasidone. This violation contributes to another threat, heterogeneity of the units. Heterogeneity of units refers to increased variability of the dependent variable, BMI  $z$  change score, within conditions (Shadish et al.). The resulting increase in error variance makes it difficult to detect relationships between the independent and dependent variables. Therefore, significant results may be inaccurate, such as the type of AA contributing to BMI  $z$  change score and the interactive effect of months and type of AA.

Strategies used in this study to strengthen statistical conclusion validity include calculating adequate power (.80) for this study to statistically identify significant relationships in the sample or to reject the null hypothesis when false. Another strategy was standardization of data retrieval from the chart through the CRT and DLS. Finally, the inclusion criteria of age, diagnosis and time on treatment as well as the exclusion criteria of rejecting diagnoses that could impact weight all were attempts at reducing the heterogeneity of units and aimed at strengthening statistical conclusion validity.

### **Implications for Research**

The findings of this study illuminated areas for future research. Research should focus on patterns of weight gain over a period of time for each type of AA because this is an area of research that is largely unexplored in the literature. Although Pai et al., (2012) proposed stages and neural mechanisms of AA weight gain, the researchers did not go further and determine whether or not each type of AA had a specific pattern of weight gain over time and if neural mechanisms contributed to this pattern. Any consistent patterns of weight gain that are detected might assist in finding additional behavioral or neural factors that underlie the patterns, which in turn might help to predict and develop interventions that could interrupt or modify these factors. In addition, study designs should address possible reciprocal causality when examining the relationship between time in treatment with AAs and BMI z change score/weight change.

Future research should also be prospective studies, designed with specific times for measurement of height and weight as well as abdominal girth, lipids, and fasting blood glucose. Such designs would allow not only the trajectory of weight change to be followed more precisely but would permit an analysis of metabolic changes that might

accompany changes in weight. This strategy could assist in quantifying these physical and physiological changes in tandem and again assist in developing methods of assessment and intervention. To enhance data collection at prescriber appointments, a standardized data collection template could be created. The template for data collection could serve not only a research purpose but also perform clinical and quality assurance functions. Trained medical assistants could then implement the template for all patients who are started on AAs.

**Changing horses (multiple times) in midstream.** The original planned dissertation was a quasi-experimental, cross-sectional two-group study design with limited retrospective chart reviews. The switch to a complete chart review methodology was a necessity, not a choice, in completing this dissertation. A number of barriers impeded the progress of the research from 2009 to 2012 and interfered with the effort to complete the research as originally proposed. Three areas, however, are the focus of this commentary: the inexperience of the researcher; the design of the research; and recruitment barriers. As these barriers are discussed, possible solutions are presented for addressing these issues in future research.

The inexperience of the PI could have been tempered by consulting with a psychiatric nurse practitioner, child psychiatrist, or child psychologist experienced in conducting research with this outpatient population. Such consults might have provided insight into the design and scope of the study, thereby possibly avoiding pitfalls. As a dissertation, the design of the study was too optimistic and broad. It would have been better to design a pilot study to explore inherent problems in the study design and characteristics of the population, such as potential problems with recruitment and data

collection. Inadequate knowledge of these dynamics and the enormous time to conduct research of this scope within this population created an unmanageable task.

Of importance for nurse-generated research is when the study was initiated in 2009, recruitment could only happen through direct referrals from a child's psychiatrist; the PI was not permitted by the HRRC to directly recruit. Recruitment was persistently hindered, despite the use of several recruitment strategies. Despite these efforts, a very limited number of children were referred to participate in the study. In 2012, a HRRC amendment was submitted along with literature from the National Institutes of Health that documented the appropriateness of an employee of an institution reviewing records to determine appropriate referrals for research. Once approved, this final strategy provided the most rapid recruitment and was used to identify participants for the chart review.

Recruiting from this population of children with SEDs had unique challenges. Families of these children had few financial and organizational resources and were often a vulnerable and transient population. Frequently, the parents had mental health issues of their own that made it difficult for them to schedule and keep appointments, and made it difficult to recruit. In an effort to collect the data, research appointments were coordinated at the same time that children were scheduled to come in for a follow-up appointment with their prescribers, but due to a high no-show rate this approach did not assist in gathering the needed data.

Consequently potential interventions to enhance recruitment and data collection in the future should center on gaining access to patients and their families. Most importantly the nurse researcher should obtain permission from the HRRC to access patients directly

or to examine their charts. A more comprehensive and ideal solution would be for the department of psychiatry at the university to develop a child and adolescent patient registry from which future participants for research could then be directly recruited. Prior permission from children and families encourages their active knowledge of and potential participation in a future research study.

Regarding data collection, although some families might be resistant to the idea, the simplest step would be to make home visits to obtain this data. In that way the information could be collected in a consistent, reliable manner. It is important to recognize however the struggles of doing research with an impoverished, vulnerable population. A portion of families would be unwilling to allow researchers into their homes or be unable to be organized enough to remember the date and time of the researcher's visit. The time and expense for the researcher in making home visits for data collection could be ameliorated through grant funding for the research.

In summary, findings from this study indicate that future research should include prospective studies that examine patterns of weight gain per type of AA in these children as well a ongoing documentation of metabolic indices. Potential strategies to enhance recruitment would concentrate on getting direct access to the family and child through the IRB or through a patient registry. Finally home visits are a possible strategy for a reliable data collection method. In planning research with vulnerable populations it is important to recognize potential inherent roadblocks that may arise.

### **Implications for Clinical Practice**

The findings of the study have a number of important implications for future practice. This includes prescribing with the realization that olanzapine, and quetiapine,



cause more weight gain than aripiprazole and ziprasidone and that over time weight loss would occur with risperidone. Understanding this risk prior to prescribing can help the prescriber and family weigh the risks and benefits of each type of AA. They should take into consideration that even though aripiprazole and ziprasidone have a more weight neutral effect, those drugs could be less efficacious antipsychotics than the more weight promoting and mood stabilizers for children and adolescents with psychotic or delusional disorders. Therefore, the more weight-promoting AAs may be the best AAs to manage psychotic or delusional symptoms. If this is the case, it is important to provide education on nutrition and exercise to the parents along with information about the indications, benefits, risks, and side effects of the AA.

Another implication relates to the interaction of time in treatment on the pattern of weight gain for each type of AA. Prescribers and other health care professionals such as nurses and medical assistants should look for, chart, and examine these patterns of weight gain over time. They could detect if there is a distinctive pattern of weight gain according to type of AA they prescribe. This deliberate assessment can help the prescriber and family track the child's weight and whether or not there is a pattern of weight gain. Then interventions aimed at ongoing nutritional education and physical health could be fine-tuned according to each child and family's needs.

### **Conclusions**

The aim of this dissertation was to determine whether or not various demographic, diagnostic, and treatment characteristics contributed to the amount of weight gain among children with SED who took AAs. Hypothesis 1 was supported, that type of AA contributes to overall BMI  $z$  change score children who took olanzapine,

risperidone, and quetiapine gained more weight than children who took aripiprazole and ziprasidone. Hypothesis 6 was partially supported as the although time in treatment did not contribute to the amount of weight gained, the longer time the child or adolescent was in treatment with olanzapine, quetiapine, aripiprazole, and ziprasidone the more weight they gained, however, the opposite was true of risperidone. Finally it was revealed that there is an interaction of months in treatment with type of AA that creates a distinct pattern of weight gain for each type of AA. Diagnosis, ethnicity/race, age, gender, or months in treatment were not associated with BMI  $z$  change score. These findings were surprising but may have been the result of building theoretical hypotheses from limited literature; many of the variables of interest had not, and still have not been well studied. Caution is warranted in the interpretation of the findings, as the sample was not randomized, group sizes were very different and some were very small, and 68% of children were on other medications that could have affected weight gain,

An unexpected finding was detecting different patterns of weight gain over time for each type of AA, as was the way months in treatment with the AA interacted with BMI  $z$  change score/weight gain. A study looking at patterns of weight gain over time related to AAs would be important if data collection for measurement could be completed at preassigned intervals for all participants. Then individual patterns of weight change over time could be charted and aid in identifying and developing potential moderators to these patterns. Moreover, it would be important to design studies to better understand the possible reciprocal causality between time and weight gained and the roles of clinician and family behavior.

There is limited research regarding factors that contribute to weight gain in

children who take AAs other than type of AA. Consequently it was important to implement and complete a study of this type.. Children with mental illness have often been labeled “research orphans” due the dearth of studies being conducted with this population because of risks and ethnical concerns related to its particular vulnerabilities. Both the positive and negative findings of this dissertation will add to the increasing, but incomplete, knowledge about this population of children with SED in the scientific literature.

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## **Appendix A: Written Procedure and Protocol**

### **Research Assistant Responsibilities**

1. Complete required human subjects training.
2. Meet with the primary investigator and the clinical director of the CPC-OS clinic and the clinicians in the clinic at a meeting to discuss the purpose, methods, and data collection and analysis for this study. Staff was encouraged to refer questions to the investigator if there was any confusion or questions regarding the study.
3. Screen charts for the chart review.
4. Reviewed 10% of the charts reviewed by the PI.
5. Communicating and meeting regularly with the primary investigator.

## Appendix B: Chart Review Form

1. Code: \_\_\_\_\_
2. Age \_\_\_\_\_
3. Ethnicity \_\_\_\_\_
4. DSM IVTR Diagnosis Code & Name
  - a. Primary \_\_\_\_\_
  - b. Secondary \_\_\_\_\_
  - c. Secondary \_\_\_\_\_
7. Baseline before meds WT (kg) \_\_\_\_\_ HT (cm) \_\_\_\_\_ BBMI \_\_\_\_\_ \*
- a. Baseline BMI z score (BBMI) \_\_\_\_\_ \*
8. a. First atypical antipsychotic (AA1):
  - \_\_\_01 =Clozapine
  - \_\_\_02 =Olanzapine
  - \_\_\_03 =Risperidone
  - \_\_\_04 =Quetiapine
  - \_\_\_05 =Aripiprazole
  - \_\_\_06 =Ziprasidone
  - \_\_\_07 =Other \_\_\_\_\_
- b. Months of time on first atypical antipsychotic (AA1) (months) \_\_\_\_\_
- c. Weight Gain (After 1st AA) WT1. (kg) \_\_\_\_\_ HT1 (cm) \_\_\_\_\_  
BMI1 \_\_\_\_\_
- d. BMI z score 1 (BMIZ1) \_\_\_\_\_ \*
- e. Difference in BMI z score 1 (DBMIZ1) = BMI z score baseline (BBMIZ – BMIZ1) \_\_\_\_\_
- f. If no change to second antipsychotic go to number 12d and  
DBMIZ1=DFBMIZ.



9. Second atypical antipsychotic (AA2): (if applicable)

- 01 =Clozapine
- 02 =Olanzapine
- 03 =Risperidone
- 04 =Quetiapine
- 05 =Aripiprazole
- 06 =Ziprasidone
- 07 =Other \_\_\_\_\_

a. Months of time on second atypical antipsychotic (AA2) (months)\_\_\_\_\_

b. Weight Gain (After second AA)= WT2 (kg) \_\_\_\_\_ HT2 (cm) \_\_\_\_\_  
\_\_\_\_\_BMI2\_\_\_\_\_

d. BMI z score 2 (BMIZ2) \_\_\_\_\_\*

e. Difference in BMI z score 2 (DBMIZ2) = BMI z score AA1 (BMIZ1–  
BMIZ2)\_\_\_\_\_

f. If no change to third antipsychotic go to number 12d and FDBMIZ=BMIZ2–  
BBMI.

10. Third atypical antipsychotic (AA3): (if applicable)

- 01 =Clozapine
- 02 =Olanzapine
- 03 =Risperidone
- 04 =Quetiapine
- 05 =Aripiprazole
- 06 =Ziprasidone
- 07 =Other \_\_\_\_\_

a. Months of time on third atypical antipsychotic (AA3) (months)\_\_\_\_\_

b. Weight Gain (After third AA)= WT3 (kg) \_\_\_\_\_ HT3 (cm) \_\_\_\_\_  
\_\_\_\_\_BMI3\_\_\_\_\_

c. BMI z score 3 (BMIZ3) \_\_\_\_\_\*

d. Difference in BMI z score 3 (DBMIZ3) = BMI z score AA3 (BMIZ3–BMIZ2)

\_\_\_\_\_

11. Final (3 months to 3 years after meds started) WT (FWT) (kg) \_\_\_\_\_ HT

(FHT)\_\_\_\_\_ (cm) Final BMI (FBMI). \_\_\_\_\_

c. \*Final BMI z score (FBMIZ) \_\_\_\_\_ \* Baseline BMI z score (BBMI)

\_\_\_\_\_\*

d. Final Weight Gain= Final Difference in BMI z score (FDBMIZ) = BMI z score

baseline (BBMIZ) –Final BMI z score (FBMIZ)\_\_\_\_\_

e. \*Calculated on <http://www.kidsnutrition.org/bodycomp/bmiz2.html>

5. Insurance Status

a. Medicaid

b. Private Insurance

c. University Based Insurance System

d. Self Pay

e. Other

## Appendix C: Data Location Sheet

### Recode

<b>Location in Chart</b>	<b>Data</b>
Face sheet	age, gender, and ethnicity
Physical assessment	height, weight,
Graphic chart	height, weight
Admission note	diagnosis
Admitting orders	date and initiation of the ATA
Physician orders	date and initiation of the ATA
Medication Administration Record (MAR) (if inpatient when started)	verify the physician's orders for ATA

## Appendix D: Screening Form

1. Child's name \_\_\_\_\_
2. Child's birthdate \_\_\_\_\_ Calculate Age: \_\_\_\_\_
3. Gender: G01 Male; G02 Female
4. Diagnosis (es) D01 ADHD; D02 Conduct Disorder; D03 Bipolar Disorder,  
D04 Depressive Disorder, D05 Disruptive Behavior Disorder, D06 Mood  
Disorder, D07 Oppositional Defiant Disorder, NOS, D08 Psychotic Disorder,  
D09 Schizophrenia and D10 Schizoaffective disorder, D11  
Other \_\_\_\_\_, D12 Don't know the diagnosis.
5. Atypical antipsychotic A01 olanzapine; A02 risperidone; A03 quetiapine;  
A04 ziprasidone ; A05 aripiprazole; A06 clozapine
6. Estimation of how much weight gained since started on  
medication? \_\_\_\_\_
7. Other medications 01 anticonvulsants \_\_\_\_\_; 02 antidepressants  
\_\_\_\_\_; 03 stimulants \_\_\_\_\_; 04 alpha2adrenergic  
blockers \_\_\_\_\_
8. Parent(s) name: Mother \_\_\_\_\_ Father \_\_\_\_\_
9. Address:
10. Home Phone:
11. Cell Phone
12. Sibling's Name:
13. Gender: SG01 Male; SG02 Female
14. DOB:

15. Type of Atypical Antipsychotic: 01 olanzapine; 02 risperidone; 03 quetiapine;  
04 ziprasidone; 05 aripiprazole; 06 clozapine.

16. Child's Psychiatrist/Nurse Practitioner:

17. Child's Therapist:

18. Other Medications:

### Appendix E: Codebook Sheet

MRN	ReCode

Recoded onto Data Sheet

ReCode	DOB	SEX	ETHN	AA	DX	SES	CWT	BWT

## Appendix F: Data Screening and Cleaning

### Steps in screening and cleaning the Data

**Monitor the N=number of valid cases for each variable to be sure none are missing**

1. Look for missing data or blanks, and typing errors on each variable.
2. To check categorical variables from the Data Sheet (AA, DX, ETH, SEX) in SPSS 20.0 click Analyze, Descriptive Statistics, and then Frequencies. Then move all of the categorical variables (AA, DX, ETH, SEX) into the Variables box. Then click on the Statistics button and tick minimum and maximum in the Dispersion section. Examine the output for each variable minimum and maximum values to assure they are in the range of possible scores. Check the number of valid and missing cases.
3. To check continuous variables from the Demographic Sheet (AGE, BMI  $z$  change score and Total Months in Treatment) click Analyze, then Descriptive statistics, then Descriptives. Then move all of the continuous variables (AGE, BMI  $z$  change score and Total Months in Treatment) into the Variables box. Then click on Options button and select mean, standard deviation, minimum, maximum, kurtosis, and skewness. Then click Continue and then OK. Then examine the output for each variable, check the minimum and maximum values and the mean score.
4. If error found, was it a dependent or independent variable. Both. Which case or variable was involved? How many errors are found? If few, might recode to “missing”. If many, check to see if values for independent and dependent variables are the same for missing and non-missing. If they are, then the chance of bias in the analysis was less. If errors are not the same for independent and dependent variables, then the variable may have a problem and consider not using it.

5. To find and correct errors in the data file, open Data Editor and click on the Data menu and choose Sort Cases. Then click on the variable that was identified as having an error and move it into the Sort By box. Choose either ascending or descending and then click on OK. Access the original Demographic Data Sheet, find the correct data, delete the erroneous value and enter the correct value. Then run the Frequencies again for that variable to double check.