Metabolic Effects of Antipsychotics in Children (RO1MH072912)

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Protocol Amendment Timeline

Protocol 1.0 (6/22/06):
First approved protocol post-fundingAlready had the single-patient inclusion for age under 7 & addition of genetic samples prior to this

Protocol 1.1 (08/30/07):
Extra safety monitoring (3 and 9 week fasting blood draws and height/weight/WC, home urine glucose monitoring kit) for participants who have impaired fasting glucose at baseline or who develop impaired fasting glucose during participation; elevated triglycerides (>250 mg/dL); rapid weight gain (>10% of baseline by 6 weeks)
Changed allowable stimulant dose to 2 mg/kg/day MTP equivalent
Omitted 6 week fsOGTT for participants 55-93 lbs due to blood draw limitation (3 ml/kg per 2 months)
Added 3-month post-study follow up visit

Protocol 1.2 (7/11/08):
Changed inclusion age from 7-18 to 6-18

Protocol 1.3 (9/18/08):
Established the max blood draw as 3 mg/kg per 2 months to allow decreased minimum allowable weight for children under 94 lbs

Protocol 1.4 (7/16/09):
Added diet/exercise & psychotherapy questionnaires, Family Environment Scale
Additional data collection from schools for grades and suspension information 12 months prior to study inclusion

Protocol 1.5 (8/24/09):
Allowed concurrent treatment with atomoxetine
Added risk of agranulocytosis with aripiprazole

Protocol 1.6 (7/28/10):
Increase number of subjects from 240 to 325 due to high screen-failure and dropout rate

Protocol 1.7 (10/5/10):
Changed additional safety monitoring to be at PI discretion instead of limited to 3 and 9 weeks

Protocol 1.8 (6/16):
Fine-tuning analysis section to reflect that we had less missing data than expected
Eliminating items that were not tested/samples not run due to limited funding

Protocol 1.9 (3/18):
Clarification of primary versus secondary outcomes in the data analysis section

A. Specific Aims

The prevalence of overweight and obesity, insulin resistance and type 2 diabetes mellitus (T2DM) are increasing, particularly in children, with the Centers for Disease Control warning of epidemic rates of these conditions in children in the United States (US). Increased adiposity and related reductions in insulin sensitivity, also referred to as insulin resistance, are major risk factors for the development of dyslipidemia, metabolic syndrome, T2DM, cardiovascular disease (CVD) – e.g., risk of myocardial infarction and stroke, other adverse health outcomes, and reduced psychosocial function. Reductions in lifespan attributable to obesity impact younger, at-risk individuals most measurably.

Certain medications can increase regional adipose tissue mass and insulin resistance, contributing to both short-term and long-term metabolic risk. Antipsychotic medications are used extensively in children, with some agents producing larger increases in weight and adiposity than any other commonly used drugs in this age group. Recent studies also indicate that some antipsychotics may affect insulin sensitivity independent of adiposity, suggesting a potential additional mechanism for metabolic risk. The use of atypical antipsychotics in children is increasing, and has been stimulated by reported efficacy for aggression and irritability in a variety of childhood psychiatric disorders. However, no study in children has sensitively quantified the adverse metabolic effects of these agents despite reports of alarming levels of weight gain.

The proposed randomized clinical trial aims to assess the metabolic safety of atypical antipsychotic agents in antipsychotic-naive children with aggression in the setting of various childhood psychiatric disorders during 12 weeks of prospective, randomized treatment with olanzapine, risperidone or aripiprazole.

Primary Aim 1: To evaluate antipsychotic treatment effects on insulin action in skeletal muscle (glucose disposal), liver (glucose production) and adipose tissue (lipolysis). This study hypothesizes that treatments causing greater increases in adiposity (e.g., olanzapine) will be associated with reduced sensitivity to insulin effects on glucose disposal, glucose production, and glycerol/fatty acid release, in comparison to treatments producing less change in adiposity (e.g., aripiprazole). Hypotheses will be evaluated by measuring whole-body glucose and lipid kinetics with the use of stable isotope tracer methodology, using rate of disappearance of glucose (glucose Rd; primary), rate of appearance of glucose (glucose Ra), and rate of appearance of glycerol (glycerol Ra) as endpoints for the assessment of insulin sensitivity.

Primary Aim 2: To evaluate antipsychotic treatment effects on abdominal fat mass and total body fat. This study hypothesizes that the selected antipsychotic medications have significantly different affects on direct measures of fat mass (e.g., olanzapine > risperidone, olanzapine > aripiprazole). These hypotheses will be evaluated by measuring body composition using whole body dual energy x-ray absorptiometry (DEXA) and abdominal magnetic resonance imaging (MRI), quantifying percent total body fat (primary) and subcutaneous and visceral abdominal fat as endpoints.

The secondary aims of this study will be to evaluate the effects of selected antipsychotic treatments on 1) fasting plasma lipids and waist circumference, which are indirect or derivative surrogates for insulin sensitivity and abdominal fat, in order to assess the extent to which changes in the primary endpoints, measured directly with gold-standard tools, are also detectable using measures commonly available to clinicians, 2) effectiveness for treatment of symptoms of aggression and irritability, using the Clinical Global Impressions Scale (CGI) as the endpoint, and 3) (not for inclusion in the primary outcome paper) insulin secretion, using frequently sampled oral glucose tolerance tests (fsOGTT) to calculate post-load area-under-the-curve insulin..

Exploratory aims include the assessment of non-metabolic adverse events, and the assessment of metabolic effects with and without concomitant stimulant therapy. Children aged 6-18 will be studied, allowing exploration of age-related differences in vulnerability to treatment-induced adverse metabolic changes.

Relevant data on the primary aims are critically needed to assess the risks of antipsychotic therapy in children, to identify targets for additional basic research, and to guide clinical decision-making.

B. Background

Overview:

Soon after the launch of the second-generation antipsychotic medications, case reports of treatment-related severe hyperglycemia, hypertriglyceridemia, new-onset T2DM and diabetic complications like diabetic ketoacidosis entered the psychiatric literature. Based on early adverse event signals from FDA MedWatch post-marketing surveillance,[1-4] the FDA began to formally request regular updates from manufacturers beginning in the summer of 2000. In January of 2001, an NIDDK/NIMH workgroup focused on the association of mental disorders and diabetes incorporated evidence of antipsychotic medication effects on the risk for T2DM.[5] A recent comprehensive review of relevant reports cites three levels of evidence supporting the association between antipsychotic medications and metabolic risk: 1) case reports, case series and uncontrolled observational studies; 2) a series of retrospective database analyses using surrogate markers for incident T2DM (e.g., ICD codes, co-prescription of hypoglycemics); and 3) a small number of controlled analytic studies, including randomized clinical trials.[6] The PI/applicant contributed to the American Diabetes Association (ADA) Consensus Development Conference on this topic, which led to a position paper jointly sponsored by the ADA, the American Psychiatric Association (APA), the American Association of Clinical Endocrinologists (AACE), and the North American Association for the Study of Obesity (NAASO).[7] This review found “compelling evidence” that treatment with clozapine and olanzapine produces a risk of substantial weight gain, and a risk of T2DM and dyslipidemia. Risperidone and quetiapine were noted to produce less weight gain and discrepant results with respect to any association with T2DM or dyslipidemia, while ziprasidone and aripiprazole produced the least weight gain and no apparent association with T2DM and dyslipidemia based on reports to date. Unfortunately, this report and other reviews either fail to mention children or note only that the relative weight gain experienced by children during treatment with antipsychotics is much larger than that observed in adults, with no current evidence concerning the specific metabolic consequences associated with antipsychotic treatment.

Careful studies of antipsychotic-induced metabolic changes (e.g., changes in fat versus lean muscle mass, and changes in insulin action versus secretion) have just begun in adult humans. It remains unclear why children are especially vulnerable to weight gain with these medications, and how such metabolic change is associated with specific antipsychotics. Measurement of drug-specific treatment-induced changes in whole-body and regional fat mass, and tissue-specific changes in insulin actions relevant to glucose and lipid metabolism, are critical to predicting risk and planning interventions, particularly for children.

Children, Obesity, and T2DM:

The prevalence of obesity, insulin resistance and T2DM is increasing in the population in general and in children in particular, with the Centers for Disease Control (CDC) warning that one-third of U.S. children born in 2000 will develop T2DM (but up to one-half of African American and Hispanic children born that year will develop T2DM--Associated Press June 14, 2003). It is estimated that at least one-third of T2DM may be undiagnosed (6 million individuals), out of a total prevalence of 17 million in the U.S.[8] Prevalence increased by almost 50% between 1990 and 2000,[9] and the number of individuals diagnosed with diabetes is predicted to rise from 11 million to 30 million by 2050.[8] Currently, an additional 25 million individuals in the U.S. are estimated to have insulin resistance in the form of impaired glucose control below the diagnostic threshold for T2DM, typically related to increased adiposity and often accompanied by the metabolic syndrome. The metabolic syndrome can include increased abdominal adiposity, insulin resistance, hyperinsulinemia, hyperglycemia, dyslipidemia, hypertension, hypercoagulability, endothelial dysfunction and other features, sometimes alternatively defined under the terms insulin resistance syndrome or syndrome X. The National Cholesterol Education Program (NCEP) guidelines from the US Public Health Service provide the U.S. definition of the metabolic syndrome used for this project. Using these criteria, it is estimated that over 20% of the U.S. population, and approximately 60% of the obese U.S. population, has the metabolic syndrome.[10-12] In addition to the well-known risk of T2DM, obesity also has other well-established adverse health consequences, such as increased risk for cardiovascular disease, osteoarthritis, and breast, prostate, and colon cancers, with annual attributable costs in the U.S. that exceed $100 billion.[13] Annual costs related specifically to diabetes mellitus in the U.S. also currently exceed $100 billion.[14,15] Exemplifying high-cost morbidity, impaired glucose control and T2DM are the major cause in the U.S. of non-traumatic amputations, blindness and end-stage

renal disease. With respect to mortality, reductions in lifespan attributable to obesity and its consequences most measurably impact younger, at-risk individuals, with severely obese 20 year-old African American males, for example, expected to lose 20 years of life.[16]

NCEP recognizes the metabolic syndrome as a major risk factor and T2DM as a risk equivalent for cardiovascular disease.[12] Substantial evidence indicate a progressive relationship between hyperglycemia and cardiovascular event risk (e.g., myocardial infarction, stroke), beginning at glucose levels well below diabetic thresholds.[17-23] These reports indicate that treatment-induced hyperglycemia can have important clinical significance even when glucose levels do not reach "impaired" or diabetic thresholds. Hypertriglyceridemia, commonly associated with insulin resistance as detailed below, is also a strong predictor of cardiovascular events,[24-26] and the combination of hyperglycemia, dyslipidemia and abdominal adiposity is strongly predictive of increased cardiovascular morbidity.[24-27] One of the best-established effects of adiposity on cardiovascular risk occurs via perturbations of lipid metabolism. Increased adiposity, especially increased visceral abdominal adiposity, is associated with increased small, dense low-density lipoprotein (LDL) particles and decreased high-density lipoprotein (HDL) cholesterol.[28-30] Since LDL cholesterol comprises 60-70% of the total cholesterol level, total cholesterol has been used as a marker for increased LDL level in population studies. The National Health and Nutrition Examination Study III (NHANES III) provided prevalence data indicating that hypercholesterolemia (total cholesterol $\geq$240) increased with increasing BMI.[31] These increases in cholesterol are strongly associated with increased cardiovascular risk.[32,33] Recent meta-analyses have reported that hypertriglyceridemia is an independent risk factor for cardiovascular disease,[34,35] and current NCEP III recommendations state that greater emphasis needs to be placed on therapeutic lifestyle changes in people with hypertriglyceridemia.[36]

More recently, investigators have begun to assess the prevalence of the metabolic syndrome in children and adolescents. As part of the NHANES III, 2430 male and female adolescents aged 12-19 were examined for presence of metabolic syndrome.[37] The NCEP definition of metabolic syndrome was modified for age to include triglyceride level > 110, HDL < 40 and abdominal obesity was defined as a waist circumference > 90th percentile of the sample. High fasting glucose was defined as > 110 and high blood pressure was defined as > 90th percentile for the sample. They found an overall prevalence of metabolic syndrome in their adolescent sample of 4.2%. It was more common in males (6.1%) than females (2.1%). In addition, 41% of the subjects had at least 1 risk factor and 14% had 2 or more. Of those adolescents who had the metabolic syndrome, 73.9% were considered overweight by their BMI, defined as > 95th percentile. The authors concluded that up to 30% of overweight adolescents may meet criteria for metabolic syndrome, which would translate to approximately 1 million adolescents affected in the US.

Adiposity and insulin resistance:

A key risk factor for the development of the metabolic syndrome and T2DM is increased adiposity leading to decreased sensitivity to insulin actions, often referred to as insulin resistance. There is a well-characterized progression from insulin resistance to frank T2DM. Insulin resistance can be associated with simple hyperglycemia or dyslipidemia, impaired glucose tolerance, or the full complement of changes called the metabolic syndrome. All of these conditions are characterized by decreased sensitivity to insulin actions on skeletal muscle (glucose disposal), liver (glucose production) and adipose tissue (lipolysis), with T2DM also characterized by progressive secondary disturbances in insulin secretion. Decreased insulin sensitivity at adipose tissue tends to occur later in the course of naturally occurring diabetes, but potentially early during antipsychotic treatment, characterized by an impaired ability to decrease lipolysis with corresponding increases in the release of free fatty acids (FFAs) into circulation.[38] Increased plasma FFA (triglyceride + glycerol) is detected clinically as an elevation in plasma triglyceride.

Using data from the National Health and Nutrition Examination Survey, Epidemiology Follow-up Study (1971-1992),[39] race- and sex-specific odds ratios of diabetes in relation to baseline BMI were calculated. The risk of diabetes increases as a function of BMI in all study groups. Family history, race, and ethnicity also play a role, and these variables will be measured for this project. However, substantial evidence indicates that increased central or abdominal adiposity, in contrast to femoral-gluteal fat, is a key predictor of decreased insulin sensitivity and the risk of T2DM.[40,41] For this project, visceral and subcutaneous abdominal fat will be

measured by MRI and total body % fat will be measured by DEXA, in order to sensitively characterize changes in fat mass and measure the effect of these changes on sensitive indicators of glucose and lipid metabolism.

Insulin resistance can be caused by increases in adiposity, but insulin resistance can also contribute to subsequent increases in fat mass. The relationship between insulin and body weight regulation is in part under central nervous system control, via widely distributed central insulin receptors and insulin signaling proteins.[42] The close relationship between insulin, lipids and adiposity is mediated in the periphery in part by lipoprotein lipase (LPL). LPL is bound to glycosaminoglycans at capillary endothelial surfaces,[43] with major LPL expression in adipose tissue, heart and skeletal muscle.[44] LPL can be thought of as a "gate keeper" enzyme, activated in response to hormonal (e.g. insulin), nutritional (e.g. carbohydrates), or mechanical (e.g. exercise) stimuli, which regulates the flow of fatty acids either toward muscle for oxidation or toward fat for storage depending on physiological circumstances. Skeletal muscle is usually the principal site of triglyceride clearance.[45-47] However, skeletal muscle LPL activity is strongly correlated with insulin sensitivity, i.e. those who are most sensitive to insulin (and have low circulating insulin levels) have the highest levels of skeletal muscle LPL activity.[48,49] In insulin resistant subjects with obesity, LPL activity can be elevated in adipose tissue and decreased in skeletal muscle, so that adipose tissue LPL becomes quantitatively dominant in terms of whole-body LPL activity, potentially steering additional fatty acids into fat storage. An underlying hypothesis for this project is that treatment-induced insulin resistance in children contributes to increased fatty acid storage.

Children and Antipsychotic Medication Use:

The use of antipsychotic medications in children is increasing. In addition to use in children with schizophrenia, clinical practice and recent studies have suggested additional indications, currently not approved by the FDA or fully informed by detailed risk-benefit considerations. Similar to other states, approximately 25% of the children treated with any psychotropic medication within Missouri Medicaid and the Department of Mental Health receive an atypical antipsychotic. Case reports, case series, and open label trials have described successful use of atypical antipsychotics for the treatment of aggression in children with a variety of psychiatric diagnoses.[50-55] Two recent double-blind, randomized, placebo-controlled trials have demonstrated the efficacy of risperidone in reducing aggression in children with a variety of diagnoses including autism, conduct disorder, oppositional defiant disorder, attention deficit disorder, disruptive behavior disorder, as well as subaverage intelligence.[56,57] These results are likely to further stimulate atypical antipsychotic prescriptions in children with aggression in the setting of a variety of psychiatric disorders. The proposed randomized, open-label study would address clinically relevant questions concerning both efficacy and safety in aggressive children with a variety of psychiatric disorders (see D.2. Methods).

Antipsychotic-induced changes in weight and adiposity:

While multiple environmental factors can contribute to increasing adiposity, certain medications can potently increase regional adipose tissue mass and insulin resistance, contributing to short-term and long-term metabolic risk. For example, investigators from Washington University School of Medicine have made major contributions to the study of agents like protease inhibitors that can increase central adiposity with related adverse changes in glucose and lipid metabolism.[58-60] However, these drugs receive limited use in children. In contrast, antipsychotic medications are extensively used in children and certain antipsychotics can produce greater increases in adiposity than any other commonly used drugs in this age group.

Antipsychotic treatments can produce weight gain of varying magnitude,[61-63] with more prominent effects linked to low-potency phenothiazines, clozapine,[63-66] and olanzapine.[66-68] Newer medications can have larger effects on weight gain than older agents, inducing excessive weight gain in up to 50% of adult patients,[69] with children and adolescents evidently susceptible to larger effects.[70] In general, reported weight change over specific periods of time has tended to underestimate the extent of weight gain observed with any of the medications by using last-observation-carried-forward (LOCF) data, rather than “completer” analyses.[71] FDA-approved weight loss agents are generally poorly tolerated in neuropsychiatric patients (e.g., due to events like activation, insomnia, and hallucinations), and initial efforts to identify tolerable augmentation strategies to attenuate antipsychotic-induced weight gain have been disappointing.[72,73]

Olanzapine induces clinically significant increases in short- and long-term weight gain. A comparative study of antipsychotic weight gain at 10 weeks of treatment showed a mean weight gain of 4.15 kg (9.15 lbs) with olanzapine, vs. 4.45 kg (9.81 lbs) with clozapine.[74] Within the first three months of treatment, weight increases approximate a mean of 4 kg (8.8 lbs).[63] Mean increases during 6-12 months of treatment with olanzapine or clozapine have been reported in the range of 14-26.4 lbs, with a mean of over 10 kg (22 lbs) at 12 months with olanzapine at 15mg/day, and individual patients experiencing 50-100 lb increases. U.S. package insert data show that 29% of patients taking olanzapine for 6 weeks (vs. 3% of placebo controls), and 56% of patients taking olanzapine long-term, gain greater than 7% of their baseline weight.

Although risperidone can produce more weight gain than some high-potency conventional agents and more than ziprasidone and aripiprazole, it produces relatively less short-term weight gain than olanzapine and clozapine,[75] ranging from 3 to 5 lbs. over the first 10 weeks of treatment.[63,76-78] In a 6-month comparison, Tran et al reported that mean weight gain on risperidone was 5 lbs versus 9 lbs with olanzapine treatment.[79] However, longer treatment with risperidone has been associated with greater gains (9 lbs) than those reported in the Tran study.[80] Interestingly, Ganguli et al. showed mean weight *loss* of 2 lbs with risperidone at a mean treatment duration of 125.3 days in unpublished data.[77] It may be critical to control for the previous treatment received, as switches from higher weight gain liability agents to lower liability agents can be associated with weight loss. Package insert data for risperidone indicate that 18% of patients gain 7% or more of their body weight over 6-8 weeks, vs. 9% of placebo controls.

Short-term clinical trial data from the aripiprazole package labeling indicate that aripiprazole is associated with approximately 2 times the incidence of clinically significant (7% or more) weight gain compared to placebo. Pooled data from five short-term studies indicate that 4 weeks of aripiprazole treatment is associated with 0.71 kg (1.6 lbs) of weight gain, similar to haloperidol.[81,82] Extrapolating this to 10 weeks for comparability with other agents, haloperidol is known to produce approximately 1 kg of weight increase over 10 weeks,[63] which may crudely approximate expected gain over the same period for aripiprazole. In a 26-week double-blind study, aripiprazole was associated with a 0.87 kg (1.9 lbs) *decrease* in weight.[83] Analysis of data from a 1-year double-blind study showed that aripiprazole was associated with 1.1 kg (2.4 lbs) of weight gain.[81] While published data are currently sparse for this relatively new agent, results suggest that aripiprazole compares favorably to other atypical antipsychotics associated with minimal weight gain.[84]

Special concerns regarding weight gain in children and adolescents

Weight gain in children can be associated with normal growth-related increases in lean muscle mass, or with increases in adiposity. The few studies in children that have attempted to address this distinction have compared treatment-induced weight gain to standardized growth curves rather than directly measuring changes in lean muscle versus fat mass, or calculating change in % body fat. Child psychiatrists have clinically noted substantial weight gain in children during antipsychotic treatment, providing anecdotal reports and early observations that this effect in children is even more pronounced than that observed in adults. However, no data are available to describe how treatment-induced changes in adiposity impact glucose and lipid metabolism in children.

The few studies that have reported changes in body weight in children treated with antipsychotics raise concern that weight gain may be significant in this treatment population. An open label study of olanzapine (mean dose 10.7 mg/day) in 25 children with pervasive developmental disorder demonstrated an average weight gain of 4.7 kg (10.3 lbs) after 12 weeks of treatment,[85] corresponding to nearly a 10% increase in body weight. Olanzapine treatment (mean dose 17.5 mg/day) of 8 psychotic adolescents resulted in an average 14% increase in body weight over an average of 9 weeks of treatment.[86] A retrospective study with 50 patients under age 18 treated with olanzapine (mean dose 13.9mg) found an average weight gain of 3.8 kilograms after an average duration of treatment of 39 days. [87] A study of 8 weeks of randomized treatment with either risperidone (up to 3 mg) or placebo in 26 children with Tourette's disorder resulted in an average weight gain of 2.8 kg (6 lbs) compared to no weight change during placebo treatment.[88] A multi-center double-blind study of 118 children ages 5-12 years with mental retardation and disruptive behaviors found a mean weight increase of 2.2 kilograms after only 6 weeks of treatment with risperidone (mean dose 1.16mg) compared to 0.9 kg with placebo.[56] A more recent study of 19 children aged 7-17 years with either Tourette's disorder or chronic motor tic disorder had an average weight gain of 1.9 kilograms over the 4-week treatment period with risperidone

(mean dose 2.5mg).[89] A similar open label study of risperidone treatment (mean dose of 1.26mg) in autistic children reported an average weight gain of 3.2 kg after 4 weeks of treatment.[90] A multi-site randomized, double blind trial of risperidone (mean dose 1.8mg) compared with placebo among 101 children ages 5-17 with autism found an average weight gain of 2.7 kilograms after 8 weeks of treatment compared to 0.8kg with placebo.[57] Sixty-three of these children treated openly for an additional 4 months had an average weight gain of 5.6 kilograms after a total 6 months, suggesting that, similar to adults, treatment effects on weight gain are not limited to the short-term.[91] Finally, Sikich et al randomized 50 psychotic children and adolescents to 8 weeks of treatment with haloperidol, olanzapine, or risperidone.[92] While significant weight gain was seen in all groups, between-group differences in weight gain and BMI were statistically significant, with olanzapine > risperidone > haloperidol. Risperidone-treated subjects had an average weight gain of 4.9 kg (10.9 lbs) compared to a mean weight gain of 7.1 kg (15.7 lbs) in olanzapine-treated subjects. All of these studies were limited by uncertain prior treatment.

Although the use of young adults rather than children might tend to minimize the effects actually observed in pediatric populations, treatment of antipsychotic-naïve first-episode schizophrenia patients may offer one of the best estimates of the potential weight gain in antipsychotic-naïve children. Recently analyzed data from an NIMH-funded study of first-episode schizophrenia patients (personal communication) suggests that olanzapine treatment is associated with a mean increase in body weight of 15.7% of baseline weight, while risperidone treatment is associated with a mean increase of 9.2% of baseline weight. Using recently analyzed data from a similar placebo-controlled first-episode schizophrenia study, aripiprazole induced a 2.7% increase in body weight from baseline (personal communication). In the absence of an available controlled antipsychotic-naïve treatment data in children, we used mean and S.D. data from these studies to estimate potential changes in percent body fat for this project.

Antipsychotic treatment and abnormal glucose metabolism:

Recent reports suggest that newer antipsychotic medications, perhaps even more than older agents, can contribute to the occurrence of clinically significant glucoregulatory abnormalities (e.g., new onset diabetes), dyslipidemia (e.g., increased plasma triglyceride) and increased weight and adiposity.[93] While phenothiazine treatment can contribute to abnormalities in glucose regulation, this association is not consistently observed at the same frequency for all older antipsychotics.[94] Hyperglycemia, exacerbation of existing T2DM, new onset T2DM, and diabetic ketoacidosis (DKA) have been associated with treatment using clozapine,[2,95-116] and olanzapine.[103,112,113,116-134] Fewer reports have been associated with quetiapine[116,130,135-137] risperidone,[116,138-142] and ziprasidone.[143] Random plasma glucose data from Pfizer's clinical trial dataset suggest that ziprasidone may be similar to haloperidol in the rate of associated hyperglycemia.[144] Aripiprazole has not been associated with published reports of impaired glucose metabolism at the time of protocol initiation, with fasting glucose and glycolated hemoglobin values comparable to placebo after 26 weeks of treatment in adults.[81] Deaths have been attributed to the induction of DKA or other hyperglycemia-related events during treatment with certain atypical antipsychotics.[2,125] The current published evidence for antipsychotic-associated hyperglycemia spans case reports and case series, FDA MedWatch data, case-control comparisons, prospective observational studies, retrospective database analyses and industry-initiated prospective randomized trials.[6] Glick et al.[145] reported that 6 weeks of randomized treatment with olanzapine produced a significant increase in adiposity, weight, plasma glucose, insulin and lipid as well as homeostasis model assessment (HOMA) insulin resistance,[146,147] in comparison to no significant change in these measures during ziprasidone treatment. Case reports suggest that children may be just as vulnerable to hyperglycemia during treatment with atypical antipsychotics.[1,148-150] The limited data from children precluded any mention of this at-risk group in the recent report from the ADA's Consensus Development Conference addressing second generation agents, co-sponsored by APA, AACE and NAASO.[7]

Insulin resistance with and without weight gain during antipsychotic treatment:

Weight gain producing increased visceral adiposity can increase insulin resistance and contribute to hyperglycemia,[40,151] so that treatment-related changes in glucose regulation are expected secondary to changes in adiposity. However, approximately 20-25% of cases of new onset T2DM in schizophrenia patients may occur in the absence of weight gain, suggesting potential direct effects on insulin secretion or action in a smaller subset of patients.[2,93,95,96,104,123,129] Recent studies also suggest the potential for drug effects on insulin

sensitivity independent of adiposity. Using fasting and post-load plasma measures from modified oral glucose tolerance tests (fsOGTTs), the P.I. and colleagues have reported that clozapine and olanzapine may be associated with disturbances in glucose regulation independent of differences in adiposity.[152] Similarly, a recent euglycemic clamp study in Wistar rats demonstrated acute impairments in insulin sensitivity associated with olanzapine and clozapine administration.[153] Henderson and colleagues[154] reported similar results with a frequently sampled intravenous glucose tolerance test (fsIVGTT) using Bergman's Minimal Model (MINMOD) analysis in subject groups similarly matched for adiposity, age and race.[155-160] MINMOD analyses have been used to assess insulin sensitivity and "glucose effectiveness" when gold-standard techniques are not possible.[156,157,160-162] The perspective gained to date in adults suggests commonly occurring, treatment-induced and largely adiposity-related increases in insulin resistance, with less consistent changes in insulin resistance independent of adiposity, and smaller or more sporadic defects in insulin secretion. Reports of sporadic cases of deaths associated with DKA underscore that large defects in insulin secretion may occur in some patients. No data are available from children to inform a similar understanding of the pattern of metabolic change during antipsychotic therapy. It is not clear at this time whether children experience primarily adiposity-related changes in glucose and lipid metabolism, or to what extent adiposity-independent effects may play a role. The answer to these questions is directly relevant to future efforts to establish prevention and intervention strategies to lower long-term metabolic risk for T2DM and CVD in children.

Antipsychotic treatment and abnormal lipid metabolism:

In early studies, phenothiazine treatment was associated with increases in measured plasma lipids.[163] Recent reports have similarly identified clinically significant increases in plasma triglycerides in patients treated with clozapine,[164-166] olanzapine,[124,167-169] and quetiapine.[167] Pfizer assessed fasting plasma triglycerides during brief randomized treatment with several newer and older antipsychotic agents[144] with groups ranging in size from 27 to 34 subjects. They reported increases in fasting plasma triglycerides during olanzapine, quetiapine and thioridazine treatment, and decreases during ziprasidone, risperidone and haloperidol treatment. A similar pattern of minimal effect on plasma lipids and other elements of the metabolic syndrome has been observed for aripiprazole during 26 weeks of randomized treatment, in comparison to both placebo and olanzapine.[170] While case reports indicate that children may also be vulnerable to abnormalities in lipid metabolism during antipsychotic treatment, no controlled or detailed studies have been performed.[171]

Interrelationship between lipid and glucose metabolism: The mechanism underlying treatment-related increases in circulating triglyceride levels remains unknown, but is hypothesized to involve changes in adiposity leading to decreased insulin sensitivity at adipocytes. Plasma lipoproteins are commonly classified as chylomicrons, very low density lipoproteins (VLDL), low density lipoprotein (LDL), and high density lipoprotein (HDL) based on their flotation in an ultracentrifuge. VLDL, produced by the liver, is the major endogenous triglyceride-rich lipoprotein. Triglycerides represent 65% of the lipids in VLDL particles and are formed by esterification of free fatty acids delivered to the liver from plasma, free fatty acids released from intrahepatic triglycerides, and fatty acids made *de novo* by the liver (*de novo* lipogenesis). Increased production of VLDL apoB and triglyceride is often causally related with hypertriglyceridemia associated with insulin resistance in other conditions.[172-174] Interrelationships between insulin, glucose, and fatty acid metabolism in regulating VLDL production are complex. Important basic methodological issues remain to be addressed in this patient population. Changes in adiposity can be strongly related to differences in lipid metabolism and circulating plasma lipoproteins. The most sensitive measure of treatment effects on glycerol and fatty acid kinetics is not changes in circulating plasma triglyceride levels, a complex function of rate-limiting hepatic apoB production and VLDL export, but rather a direct measure of glycerol and fatty acid kinetics as proposed in this application.

C. *Significance:*

T2DM and CVD are important disease targets for the NIH and the U.S. Public Health Service, with overweight and obesity, hyperglycemia and dyslipidemia identified as major modifiable risk factors. These risk factors can be altered by adverse changes in nutritional status and activity level, and by adverse medication effects. The identification of factors that contribute to the increased prevalence of medical illnesses such as T2DM and CVD in patients with major mental disorders is similarly a high priority. The critical evaluation of adverse events, as well as efficacy, is required for new medications seeking new on- or off-label indications. To our knowledge, the proposed Metabolic Effects of Antipsychotics in Children (MEAC) study would be the only

NIH funded study concerning adverse medication effects on direct measures of key metabolic risk factors for cardiovascular disease and T2DM in children (i.e., insulin sensitivity and adiposity). The broad generalizability of the results will be enhanced by the study of children with aggressive behaviors in the setting of a variety of disorders, with and without concomitant stimulant treatment.

Noted above, the recent ADA/APA Consensus Development Conference report concerning second generation antipsychotic medications makes no mention of use in children and no recommendations for risk management, due to the lack of relevant information from treated children. Relevant data are critically needed to assess the risks as well as benefits of antipsychotic therapy in children, identify needs for additional basic research, as well as guide administrative and regulatory decision-making.

D. Research Design & Methods

1. Study Site Resources and Timetable:

The proposed experiments will be conducted using existing dedicated research space at Washington University School of Medicine, including the Adult and Pediatric General Clinical Research Centers (GCRC), Diabetes Research and Training Center (DRTC) and Clinical Nutrition Research Unit (CNRU) where all previously reported experiments have been performed.

Year 1:

a. Subject recruitment;
b. Screen visit, (**Study Visit 1**) for 156 subjects;
c. Baseline evaluations (**Study Visits 2 and 3**) for 33 subjects;
d. 6-week post treatment evaluations **(Study Visit 4)** for 26 subjects;
e. 12-week post treatment evaluations (**Study Visits 5 and 6**) for 19 subjects;
f. Plasma sample analyses for substrate concentration and isotopic enrichment; data entry.

Year 2:

a. Subject recruitment;
b. Screen visit, (**Study Visit 1**) for 300 subjects;
c. Baseline evaluations (**Study Visits 2 and 3**) for 66 subjects;
d. 6-week post treatment evaluations **(Study Visit 4)** for 66 subjects;
e. 12-week post treatment evaluations (**Study Visits 5 and 6**) for 66 subjects;
f. 3-month post 12-week study evaluations for subset of subjects (Study Visit 7) estimated 22-42 subjects. Estimate is based on needs of current subjects: 17 out of 57 enrolled subjects (30%) vs 17 out of 27 subjects who have completed the study (63%);
g. Plasma sample analyses for substrate concentration and isotopic enrichment; data entry

Year 3:

a. Subject recruitment;
b. Screen visit, (**Study Visit 1**) for 300 subjects;
c. Baseline evaluations (**Study Visits 2 and 3**) for 66 subjects;
d. 6-week post treatment evaluations **(Study Visit 4)** for 66 subjects;
e. 12-week post treatment evaluations (**Study Visits 5 and 6**) for 66 subjects;
h. 3-month post 12-week study evaluations for subset of subjects (Study Visit 7) for estimated 22-42 subjects;
h. Plasma sample analyses for substrate concentration and isotopic enrichment; data entry.

Year 4:

a. Subject recruitment;
b. Screen visit, (**Study Visit 1**) for 300 subjects;
c. Baseline evaluations (**Study Visits 2 and 3**) for 66 subjects;
d. 6-week post treatment evaluations **(Study Visit 4)** for 66 subjects;
e. 12-week post treatment evaluations (**Study Visits 5 and 6**) for 66 subjects;
f. Plasma sample analyses for substrate concentration and isotopic enrichment; data entry.

g. 3-month post 12-week study evaluations for subset of subjects (Study Visit 7) for estimated 22-42 subjects;
h. Plasma sample analyses for substrate concentration and isotopic enrichment; data entry.

Year 5:

a. No additional subject recruitment;
b. No additional Screen visits (**Study Visit 1**);
c. Baseline evaluations (**Study Visits 2 and 3**) for 33 subjects;
d. 6-week post treatment evaluations **(Study Visit 4)** for 40 subjects;
e. 12-week post treatment evaluations (**Study Visits 5 and 6**) for 47 subjects;
f. Plasma sample analyses for substrate concentration and isotopic enrichment; data entry.
g. 3-month post 12-week study evaluations for subset of subjects (Study Visit 7) for estimated 22-42 subjects;
h. Plasma sample analyses for substrate concentration and isotopic enrichment; data entry.
i. Complete all data coding and entry; complete all final data analysis, write up results, presentation(s).

2. Subjects:

We will enroll 325 eligible subjects with clinically significant aggression symptoms, as defined by a score of ≥18 on the Irritability subscale of the Aberrant Behavior Checklist [205, 206] in the context of one or more Axis I DSM IV207 childhood psychiatric disorders, including conduct disorder, oppositional defiant disorder, disruptive behavior disorder, autism, pervasive developmental disorder, attention deficit disorder, bipolar affective disorder and schizophrenia, who assent to participate and whose guardian(s) give informed consent for participation in the study. Individuals with clinically significant suicidal ideation will not be included. We plan on screening up to four times the enrollment target number in order to achieve recruitment targets (**Study Visit 1**). All subjects will be 6-18 years of age and will include all races and ethnic groups **and both genders,** with targeted enrollment reflecting the overall gender distribution of males and females for "externalizing" disorders (i.e., 2.5:1, male:female).[208]. By initially enrolling 108 subjects in each of 3 treatment groups described below, we estimate this will enable us to obtain a study population of 80 subjects per group for a total of 240 analyzable subjects who complete the protocol (assuming 10% attrition). Recruitment will involve targeted community outreach to pediatricians, schools and family support groups, as well as screening potential subjects from the Child and Adolescent Psychiatry Clinic and the Barnes Jewish Christian [175] Behavioral Health System which have a combined annual total of 2,464 individual patients with a large number of potentially eligible subjects.

The inclusion criteria are: i) age 6-18 years ii) generally healthy and a score of ≥18 on the Aberrant Behavior Checklist for irritability in the context of one or more Axis I DSM IV childhood psychiatric disorder, including conduct disorder, oppositional defiant disorder, disruptive behavior disorder, autism, pervasive developmental disorder, attention deficit disorder, bipolar affective disorder and schizophrenia; iii) Children's Global Assessment Scale (CGAS) Score ≤ 60; iv) not previously treated with an antipsychotic; individual subjects with a remote (i.e., > 1 year), brief (i.e., < 1 week) prior antipsychotic exposure may be considered for enrollment on a case by case basis; v) patient assent and informed consent obtained from the parent or guardian; vi) no clinically significant (PI determination) changes in permitted medications (e.g., stimulants, SSRI's) for approximately 1 month prior to Baseline Evaluations;

The exclusion criteria are: i) active suicidality or a primary diagnosis of major depressive disorder; ii) any lifetime use of antipsychotics; individual subjects with a remote, brief remote prior antipsychotic exposure may be considered for enrollment as above; iii) the presence of any serious medical disorder that may confound the assessment of relevant biologic measures or diagnoses, including: significant organ system dysfunction; endocrine disease, including type 1 or type 2 diabetes mellitus; coagulopathy; anemia; or acute infection; all based on PI discretion; iv) subjects regularly taking within the last 3 months any glucose lowering agent, lipid lowering agent, exogenous testosterone, recombinant human growth hormone, or any other endocrine agent that might confound substrate metabolism, oral glucocorticoids (glucocorticoid nasal spray and inhalers are permitted), sedating antihistamines (non-sedating antihistamines such as but not limited to Claritin (loratadine) and Zyrtec (cetirizine) are permitted), and certain mood stabilizing agents, as some medications may

themselves worsen or otherwise alter weight gain, glucose and lipid regulation or otherwise make it difficult to assess the effects of the antipsychotic alone; (note that exposure to many psychotropic agents including stimulants and SSRI's is permitted in order to maintain the generalizability of the sample); v) IQ < 70 (based on school records and/or evaluation by clinician); vi) current substance abuse; vii) past history of, or current dyskinesia; viii) stimulant dosage significantly higher (per PI) than the equivalent of approximately 2 mg/kg/day methylphenidate equivalent dose.

Rationale for Inclusion and Exclusion Criteria: The CGAS score corresponds to definite impairment that requires clinical intervention. Intelligence quotient cut-off is to ensure that subjects can comprehend the assessment questions. In order to aid recruitment, multiple psychiatric disorders including attention deficit disorder, bipolar affective disorder, conduct disorder, oppositional defiant disorder, and disruptive behavior disorder will be included, as long as participants meet screening criteria for aggression and are not actively suicidal or primarily depressed. Substance use disorders are excluded to avoid confounding mental status examinations and/or measures of metabolic factors. Stimulant drugs at a stable dose are permitted for some of the research subjects as at least half of these subjects will have comorbid ADHD. Not allowing stimulants would therefore likely decrease recruitment and would provide ecologically valid data. Children cannot be on a stimulant dosage significantly higher than the clinical standard of no more than 2mg/kg/day equivalent of methylphenidate. We choose to also study subjects off stimulants, in order to explore the effect of stimulant therapy on adiposity gain and metabolic change.

Subject recruitment and retention: Potential subjects will be recruited by Clinical Research Coordinator's in our unit, under the direction of the PI, from the clinics listed above, with additional outreach to sources such as pediatrician's offices and the school systems as needed. The names and contact numbers of these families will be sent to the PI and Clinical Research Coordinators, to do a telephone screen to rule out children who are unlikely to have the inclusion criteria or who have exclusion criteria. Those families not excluded by telephone screen will be given appointments for baseline assessments. Once subjects are enrolled, research staff will maintain at least weekly contact with subjects and relevant family members. The PI's Clinical Research Coordinators and staff have extensive experience working with neuropsychiatric populations and their families and efficiently performing recruiting, screening, and follow-up to maintain subject flow and high follow-up rates. Retention in this project will be further enhanced by the use of highly experienced clinicians, providing medication adjustments and monitoring, as well as supportive psychotherapy, throughout the course of the 12-week study (weekly visits for the first 4 weeks, followed by every other week visits for the final 8 weeks, with additional visits available as needed).

Subjects with Attention-Deficit Hyperactivity Disorder (ADHD) Not Already on Stimulants: If, at screening or during baseline, children are suspected of or diagnosed with ADHD, but are not already on treatment, they will be referred back to their community physicians for treatment. If the treatment is with a stimulant, and if the treatment has not alleviated the aggressive behaviors, these children can be referred back for the metabolic study of antipsychotic therapy. Reasons for excluding non-stimulant ADHD treatments and for the maximum dose of stimulant are provided above.

3. Study Outline and Randomization Plan:

All 240 eligible, recruited subjects completing the **Screen Visit (Study Visit 1)** will be randomized to prospective open-label treatment with one of three atypical antipsychotic medications. Specifically, a) 80 subjects will be randomized to open-label treatment with aripiprazole; b) 80 subjects will be randomized to open-label treatment with risperidone; c) 80 subjects will be randomized to open-label treatment with olanzapine. Recruitment and randomization will be further structured to target having half of the children in each treatment group aged 6-12, and half aged 13-18, using separate randomization schedules for each age group. In addition, within each of the 2 age groups in each of the 3 treatment conditions, recruitment and randomization will be further structured to target having half of the children on previously prescribed and ongoing stimulant therapy, and half not receiving stimulants. This plan targets the acquisition of 20 younger subjects on stimulants and 20 younger subjects off stimulants, as well as 20 older subjects on stimulants and 20 older subjects off stimulants, within each of the antipsychotic treatment groups. Targeted group size is

based on power estimates, described below, which will permit hypothesis testing for treatment group interactions with age and with stimulant therapy. Group composition will otherwise be monitored and matched to the greatest extent possible for disease severity, specific age, and ethnicity, by over-recruiting any under-represented groups identified in the active enrollment phase.

Randomized subjects will have **Baseline Evaluations (Study Visits 2 and 3)**, followed by assessments at **6 weeks** (**Study Visit 4**) and **3 months** (**Study Visits 5 and 6**) as described below and summarized in **Table 1** below. The 6-week **(Study Visit 4)** follow-up evaluation after the treatment change is selected to provide sufficient time for only initial changes in adiposity, glucose and lipid metabolism, without larger changes in adiposity predicted at this point in children. The 3-month follow-up is selected to measure predicted changes in adiposity, along with metabolic parameters. DXA scans at 6 weeks **(Study Visit 4)** and 3 months **(Study Visit 5)** will allow percent total body fat to be quantified for use as a covariate in the study analyses. The 3-month follow-up will include the MR scan **(Study Visit 5)** repeated from baseline, as sufficient time will have elapsed to permit larger changes in adiposity. Flexible antipsychotic dosing in the longitudinal follow-ups will enhance clinical outcomes and allow the possibility of exploring effects of dose, although there is currently no evidence for dose-dependent effects. Adverse events and aggression symptoms are rated, to assess status at baseline **(Study Visit 2)** and 12-weeks **(Study Visit 6)**, during the isotope clamp protocol. In addition, the Modified Adverse Event Checklist will be used during weekly contacts with all subjects. In order to evaluate clinical response to post-study recommendations, there will be a 3-month post study follow-up visit (**Study Visit 7 -** approximately 3 months after the end of the 12-wk study) for a subset of subjects who have had increases in metabolic risk factors (e.g. 10% or greater increase from baseline body weight, fasting triglyceride levels $\geq$ 250 mg/dl at 6 or 12 weeks, and/or a fasting or post-load glucose $\geq$ 100 or 140 mg/dl, respectively, at 6 or 12 weeks).

Quality of Care During the randomized treatment phase of the study, subjects will continue to receive care from their primary physician, with extensive supplemental contacts and monitoring as outlined above so that all subjects are monitored at a level that exceeds the standard of care. This site has extensive experience in the performance of clinical studies in children with psychiatric disorders, including interactions with children with acute and sometimes psychotic illness. This site also has extensive experience in performing complex metabolic assessments in pediatric populations, as well as in psychiatric patients with severe psychotic illnesses, maintaining an outstanding safety record and high retention rate in all of these endeavors.

Choice of Specific Treatment and Experimental Conditions: The antipsychotic medications selected for this project were chosen in order to compare specific newer antipsychotic medications needed to address the study questions, where the use in child populations is either well supported by current literature and/or the drug is used extensively for the treatment of aggression based on national and state prescribing patterns or showing rapid growth for this indication. Olanzapine and risperidone are the most frequently prescribed antipsychotic medications for aggression associated with psychiatric illness, with aripiprazole use increasing. Olanzapine is associated with the greatest amount of weight gain and metabolic effects in reports to date, making it an ideal positive control in this study. Risperidone is widely used in this population, and is the best supported by published literature, with intermediate weight gain and metabolic effects among the newer medications. Aripiprazole, most recently approved by the FDA, appears to have a favorable side effect profile in children, especially with respect to weight gain and minimal metabolic effects in adults. Although we could have chosen ziprasidone, concerns about QTc prolongation may have complicated recruitment and currently in the state of Missouri, aripiprazole is used in children within the Department of Mental Health at approximately twice the rate of ziprasidone. It is predicted to see extensive use in children in the coming months and years. Aripiprazole's favorable metabolic side effect profile in preclinical and early clinical trials make it a good candidate for a negative treatment control in this study.

4. Specific screening tests and procedures:

Table 1: Planned procedures

	MAGIC	Medical Exam/ ECG	Fasting Labs	fsOGTT	DXA Scan	MRI	Isotope Clamp	Hours of Participation
Study Visit 1 (Screen)	X							4-5
Study Visit 2 (Baseline)		X	X	X	X	X		3.5
Study Visit 3 (Baseline							X	8
Study visit 3A Extra safety visit at 3 wks			X					1
Study Visit 4 (6-weeks)			X for subjects ≥93 lbs	X for subjects 94+ lbs	X			2.5
Study visit 4A Extra safety visit at 9 wks			X					1
Study Visit 5 (12-week end of study			X	X	X	X		3.5
Study Visit 6 (12-week end of study.	X						X	8
Visit 7, 3-mo. post study follow-up for subset of subjects.			X					1

Medical examination and history: All subjects will be screened with a detailed history and physical examination performed by a study physician, routine blood tests including a glycated hemoglobin (A1C) level, and resting 12-lead electrocardiogram.

Assessment of Clinically-Available Parameters: fasting labs and anthropomorphic measures: In addition to the exploratory aim of assessing non-metabolic adverse events, a secondary aim of the study is to assess the extent to which changes in the primary endpoints, measured directly with gold-standard tools, are also detectable using surrogate or derivative measures that are commonly available to clinicians. For example, an indirect surrogate indicator of insulin sensitivity is triglyceride/HDL ratio.[176] Routine blood tests will be performed including A1C, complete blood count with differential, comprehensive metabolic panel,, and a fasting lipid panel. Blood pressure and a measure of waist circumference will also be obtained. Waist circumference is used to indirectly assess abdominal fat. Some studies have suggested the utility of anthropomorphic measures as proxies for abdominal fat as measured by abdominal computed tomography (CT), although concerns about reliability remain.[177-179]

Body composition analyses: Body composition will be evaluated at baseline, 6 weeks, and 3 months. Percent total body fat and percent total fat-free mass will be determined by DXA (Hologic QDR 1000/w, Waltham, MA).[180,181] The error of regional fat free mass determination by this technique, as compared with computerized tomography, is less than 5%.[180,181]

Magnetic resonance images of the abdomen will be obtained at baseline and 3 months to directly quantify abdominal (subcutaneous and intra-abdominal) adipose tissue mass.[182] Images will be acquired on a 1.5-T superconducting magnet (Siemens, Iselin, NJ) using a T_1-weighted pulse sequence with a TR of 500 msec and TE of 12 msec. The imaging matrix will be 256x256, and section thickness will be 8 mm with a 2mm intersection gap. Consistent slice localization will be accomplished by using a rigid landmark (i.e., the iliac crest) to position the subject in the machine and by using coronal scouting images to identify the site for image acquisition (i.e., the L_3-L_4 interspace). Three cross-sectional images at the level of the umbilicus, one above,

and one below the umbilicus section, will be obtained. Twenty-three slices are analyzed by selecting the first 8 sequential slices beginning at the inferior pole of the most superior kidney and continuing inferiorly. Visceral (VAT) and subcutaneous (SAT) adipose tissue surface area (cm^2) are calculated for each slice and reported as a mean value over the 8 slices. The image analysis will be performed by using NIH image software and a program constructed in the Mallinckrodt Institute of Radiology.

Isotope infusion clamp: Participants will be instructed to begin fasting, except for water, at 2000 the night before the study assessment, following a standard meal provided by their parent or caregiver. The following morning at approximately 0600, participants will be admitted to the Pediatric Clinical Research Unit for the clamp procedure. At approximately 0700, a catheter will be inserted into an antecubital vein of one arm to infuse stable isotopically labeled glucose, dextrose and insulin. Another catheter will be inserted into a contralateral hand or forearm vein heated to 55 °C using a thermostatically controlled hand-warming box to obtain arterialized blood samples.[183] At approximately 0800, prior to beginning the tracer infusion, blood samples will be taken to obtain baseline measurements of glucose and glycerol enrichments. Then, a 3-h primed-constant infusion of [6,6-$^2H_2$]glucose in 0.9% NaCl solution (22 μmol/kg prime and 0.25 $\mu mol.kg^{-1}.min^{-1}$ infusion rate) will be used to determine basal glucose kinetics. After 120 min of tracer glucose infusion, a 1-h primed-constant infusion of [1,1,2,3,3-$^2H_5$]glycerol (1.2 μmol/kg prime and 0.08 $\mu mol.kg^{-1}.min^{-1}$ infusion rate) will be used to determine basal glycerol kinetics. After the 180 minute basal tracer infusion period, a euglycemic, hyperinsulinemic clamp will be initiated and continued for 180 minutes.[161] During the clamp, insulin will be infused at a rate of 40 $mU.m^{-2}.min^{-1}$ for 180 minutes (initiated with a two-step priming dose of 160 $mU.m^{-2}.min^{-1}$ for 5 min followed by 80 $mU.m^{-2}.min^{-1}$ for 5 min), to achieve plasma insulin concentrations of approximately 90 μU/ml. This plasma insulin concentration provides an optimal level for evaluating insulin's effect on glucose production and lipolysis.[184] Euglycemia will be achieved by infusing a variable rate of 20% dextrose enriched to approximately 2.5% with [6,6-$^2H_2$]glucose to minimize changes in plasma glucose tracer to trace ratio.[185] The infusion of [6,6-$^2H_2$]glucose will be decreased by 50% of basal from 180-360 minutes to account for the expected decline in hepatic glucose production.[186,187] The infusion of [1,1,2,3,3-$^2H_5$]glycerol will also be decreased by 50% of the basal rate during the clamp to account for the expected decline in whole-body lipolytic rate.[188] Blood glucose will be measured every 5-10 minutes during the clamp procedure to inform adjustments to the dextrose infusion rate, using either a glucose oxidase method via a glucose analyzer (Yellow Springs Instruments, Yellow Springs, Ohio 45387 USA) or a validated portable blood glucometer when necessary to decrease the total amount of blood drawn in smaller individuals. Blood samples will also be collected every 10 min during the last 30 min of both the basal period and the insulin clamp periods to determine glucose and glycerol isotopic enrichments and the determination of glucose and glycerol kinetics, {Korenblat, 2008 #19307} {Deivanayagam, 2008 #19305} {Magkos, 2009 #19308} as well as plasma hormone (insulin, C-peptide, glucagon, growth hormone, epinephrine, norepinephrine, free fatty acid and leptin) concentrations. For children < 77 lbs, collection of plasma catecholamines, growth hormone, free fatty acid and leptin will be restricted to limit total blood draws to no greater than 3 ml/kg body weight. [183,189] Insulin-stimulated percent change for glucose and glycerol kinetics (Glucose Ra and Rd, Glycerol Rd) will be calculated as the absolute value of the difference between the kinetic rate calculated during insulin-stimulated versus basal conditions. The resulting value will be divided by the basal condition and multiplied by 100%. Primary Aim 1 endpoints from the isotope clamp protocol are: 1) Insulin-stimulated % change in Glycerol Ra; 2) Insulin-stimulated % change in Glucose Ra and 3) Insulin-stimulated % change in Glucose Rd.

Frequently-sampled oral glucose tolerance test (fsOGTT)**(Secondary analysis, not for inclusion in the primary outcome paper)*:** At baseline, 6 weeks and 3 months, after an overnight (12 h) fast, blood samples for plasma glucose, insulin, C-peptide, epinephrine, norepinephrine, glucagon, cortisol, concentrations will be obtained immediately at 0 (baseline), 10, 20, 30, 60, 90, and 120 min after ingesting a 75 g oral glucose load.[190] The new criteria of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus will be used to determine subject eligibility. Area under the curve insulin will be used as the endpoint in the secondary aim concerning treatment effects on insulin secretion. Subjects under 94 lbs will have fasting labs instead of a 6-week fsOGTT to decrease total blood volume drawn over 2-months.

5. Psychiatric/Medical Diagnostic Assessment Methods:

General Considerations and Time Frames: Instruments were selected to be comprehensive and to permit comparability to those used in other studies in federally funded research projects in child psychiatry. At baseline, the time frame will be lifetime. At follow-up appointments, the time frames will be the three-month interval since the prior assessment.

Need for Both Parent and Child Informants for Assessment of Child Psychopathology: In child psychiatry research, parent and child informants are both needed due to poor mother-child concordance.[191-199] Parent and child reports will be combined by using the most severe rating given by either, in accordance with the work of Bird et al.[200] Second informants for child aged subjects are usually biological mothers. If the mother is incapacitated (e.g., hospitalized for suicide attempt), the father or other guardian who lives with the child is the second informant. Different raters are used for the mother and child within each family. Scientifically this is important to avoid bias from knowing what the other informant has reported. This procedure also aids recruitment and retention, because families greatly appreciate mother and child interviews conducted in parallel by two raters, as this saves them time in the research unit.

Missouri Assessment of Genetics Interview for Children (***MAGIC):*** The MAGIC interview is a semi-structured standardized psychiatric diagnostic interview with six versions: Child, Adolescent, Young Adult and Adult are self-report versions, and the Parent and Parent of Young Adult are parent reports on siblings. The MAGIC is a revised version of the Diagnostic Interview for Children (5). All MAGIC versions are computerized for simultaneous administration and data entry. The MAGIC uses criteria of the DSM-III-R, DSM-IV and ICD-10 to diagnose child, adolescent, young adult, and adult psychiatric disorders. The interview can be administered by telephone or in person. A current paper version exists for all interviews should one be needed. The average length of time to administer the MAGIC is 2 hours for adults and 90 minutes for children or adolescents. The MAGIC has a lengthy companion specifications manual (Appendix 2) that is used to maintain consistency of administration across interviewers and across studies. An in-depth, 6-week training course with practice sessions is required for all interviewers, followed by a qualifying certification by an experienced certified interviewer or by one of the MAGIC authors. Diagnostic algorithms have been created, tested, and verified. The DSM-IV diagnoses include domain impairment and duration requirements. The specific sections included in the MAGIC interviews are: Demographics, Attention Deficit/Hyperactivity Disorder, Oppositional Defiant Disorder, Conduct Disorder, Alcohol Abuse, Tobacco and Glue-Sniffing Abuse, Marijuana and Street Drug Abuse, Gambling, Depression, Mania, Dysthymia, Separation Anxiety, Panic Disorder, Phobias, Generalized Anxiety Disorder, Obsessive Compulsive Disorder, Posttraumatic Stress Disorder, Eating Disorders, Premenstrual Dysphoric Disorder, Somatization, Psychosis and Schizophrenia, Psychosocial History, Home Environment, Peer and Sibling Relationships, Perinatal History, and Health Services Usage. Reliability and prospective stability studies have been completed on the MAGIC; in particular, for diagnosis of ADHD, inter-rater reliability for the Child, Adolescent, and Parent versions was excellent, (kappa >.9 for DSM-IV ADHD subtype diagnoses as well as for the endorsement of the 18 individual DSM-IV Criterion A ADHD symptoms). The 18-month prospective stability (done with raters blinded to the initial diagnosis) for a diagnosis of ADHD was also good (kappa =.78); kappas for population-defined ADHD subtypes including inattentive and combined subtypes were .76 and .67, respectively (6).

Achenbach Child Behavior Checklist/Adult Behavior Checklist (CBCL/ABCL): The CBCL/ABCL serves as a general screening measure of behavior problems, competencies, and school functioning, and has well-established norms. It obtains reports from parents, other close relatives, and/or guardians regarding children's competencies and behavioral/emotional problems. A shorter version of the CBCL/ABCL was created for the large Missouri sibship study, which does not include 20 competence items covering the child's activities, social relations, and school performance. These shortened versions will be used for this project. The revised CBCL/ABCL has 113/126 items that describe specific behavioral and emotional problems, plus one open-ended item for reporting additional problems. Parents rate their child for how true each item is now or within the past 6 months using the following scale: 0 = not true (as far as you know); 1 = somewhat or sometimes true; 2 = very true or often true. The subscales scored from the CBCL are Aggressive Behavior; Anxious/Depressed; Attention Problems; Rule-Breaking Behavior; Social Problems; Somatic Complaints; Thought Problems; and Withdrawn/Depressed. The six DSM-oriented scales are: Affective Problems; Anxiety Problems; Somatic Problems; Attention Deficit/Hyperactivity Problems; Oppositional Defiant Problems; and Conduct Problems.

Wechsler Intelligence Scale for Children, Version 4 (WISC-IV): To confirm the exclusion of mental retardation and to give a general estimate of intellectual ability all participants will be administered the Vocabulary subtest of either the WISC-IV (children/adolescents) or Wechsler Adult Intelligence Scale (WAIS-III) [201]. Normal scoring protocols will be used to create a standardized score.

Aberrant Behavior Checklist: [202,203] This instrument is a five-factor scale comprising 58 items under the categories of (I) Irritability, Agitation, Crying; (II) Lethargy, Social Withdrawal; [204] Stereotypic Behavior; (IV) Hyperactivity, Noncompliance; and (V) Inappropriate Speech. The 15-item Irritability subscale includes questions about aggression, self-injury, tantrums, agitation, and unstable mood on a scale of 0 to 45. It has been estimated that our cut-off of ≥ 18 on this subscale will identify individuals that are 1.3 to 1.5 SD above the mean.[205,206]

Social Responsiveness Scale (SRS): The SRS is a 65-item questionnaire with a 4-point rating scale ("Not true" to "Almost always true") designed for use by parents and/or teachers in which ratings of the frequency of typical autistic symptoms across all three DSM-IV symptom domains are obtained. It measures the severity of autism spectrum symptoms as they occur in natural social settings. The SRS provides a clear picture of a child's social impairments, assessing social awareness, social information processing, capacity for reciprocal social communication, social anxiety/avoidance, and autistic preoccupations and traits. It is appropriate for use with children from 4 to 18 years of age. The SRS has a major advantage over other instruments used to assess autism spectrum conditions. Rather than providing a "yes or no" decision about the presence of symptoms of a given disorder, the SRS measures impairment on a quantitative scale across a wide range of severity, from sub-clinical to severe—which is consistent with recent research indicating that autism is best conceptualized as a spectrum condition rather than an all-or-nothing diagnosis. Unlike most questionnaire instruments, SRS scores are highly correlated between parents and teachers (0.75-0.80), have minimal age differences in distribution, and show high test-retest reliability for at least 17 months (0.7-0.85). In addition, there are minimal associations between intelligence and SRS scores (correlations on the order of 0.1 to 1.2 in both normal and autistic children).

Children's Global Assessment Scale (CGAS): [207,208] This instrument is a global measure of severity based on psychiatric symptomatology and impairment of adaptation in family, social, school, and work areas. On this scale 0 is worst, 100 is best, and ≤ 60 is definite clinical impairment.

Clinical Global Impressions Scale (CGI): The CGI scale[209] is widely used in psychopharmacology research across the age span. It will be completed by a blinded rater. At baseline, the severity measure is used. At post-baseline assessment times, severity and improvement scales are used. At all time points, a severity score of 1 or 2 is little or no impairment, a score of 3 is mild and a score of ≥ 4 is moderate or greater psychopathology. At the three-month assessment, scores of 1or 2 are fully or almost fully recovered, score of 3 is minimal recovery and scores of ≥ 4 are almost no improvement or worsened from baseline. This is the endpoint for the secondary aim concerning effectiveness for symptoms of aggression.

Pubertal Status Questionnaire (PSQ):[210] This instrument is completed by subjects at least 10 years old. The PSQ has demonstrated high reliability with physical examination. Rather than a physical exam, the PSQ relies on participant self-report of Tanner Stage by endorsement of the appropriate cartoon representation of the respondent's pubertal status. The PSQ has been accepted by the Washington University IRB for the evaluation of pubertal status.

Modified Study Side Effects Scale (SE): This scale collects data on side effects such as sedation, galactorrhea and gynecomastia, and has been used in multiple NIH funded treatment studies.

Abnormal Involuntary Movement Scale (AIMS): This instrument is administered to the child and has been modified to include instructions on how to examine for cogwheeling and tongue dyskinesias in children.

Barnes Akathisia Scale (BAS): This instrument is administered to the child for the assessment of akathisia.

Simpson-Angus Scale (SAS): This instrument is administered to the child for the assessment of pseudoparkinsonianism.

Medical Records (MR) and Medical History Form: This information is obtained by telephoning to obtain mailing or faxing preference and then mailing or faxing consents to the various physicians, other health care providers, and hospitals. Consents accompany mailing materials with prepaid return postage or with instructions for faxing materials back to the investigators. The Medical History Form is administered to the mother about the child.

Locator Form: This form is completed at baseline to enhance the ability to locate subjects at the three-month follow-up. This form includes: (1) Social security numbers of the subject and each parent. (2) Work and home telephone numbers and addresses of both biological parents, step-parents and parents residing outside of the household. (3) Names, telephone numbers, and addresses of spouses, significant others, siblings, grandparents, close friends and neighbors of the participants. (4) The name, address and telephone number of the participant's school, and their teacher's name, as well as a check box option asking whether it is acceptable to contact the school. In our experience families do not object to supplying this information and understand that it will only be used to locate them without -under any circumstance- revealing why the University is looking for them other than that they are study participants.

Diet and Exercise Behaviors Questionnaire:
This retrospective phone questionnaire will assess participants' dietary habits and activity levels during the course of participation, and related changes. Study participants and their guardians will be given a 17-item questionnaire adapted from diet and exercise questionnaires used in similar research studies. [211] [212] [213] [214] [215] [216] [217] [218] [219] [220] Parents of subjects age 12 and under will be asked to complete the questionnaire, and, for subjects age 13 and up, the parent will be the default recipient of the questionnaire as well. Parents of subjects ages 13 and up will be asked at the beginning of the questionnaire whether their teenager has a significantly better idea of their own diet and exercise patterns, and, if they answer yes, their teenager will be contacted and asked verbal consent for the diet and exercise questionnaire at a later time. For subjects who have already enrolled in the MEAC study, consent will be implied via continuation of the phone interview, and verbal consent will be asked at the beginning of the phone call as well. All newly enrolled subjects will be formally consented for permission to be contacted during or after study participation. Subjects will be reminded that participation is voluntary, that their participation in the main MEAC study will be unaffected if they choose not to participate in this questionnaire, and that they may choose not to answer any question or end their participation in this segment at any time.

Psychotherapy Attitudes and Perceptions Questionnaire:
This retrospective phone questionnaire will assess parental attitudes and experiences with psychotherapy, and how these points of view might influence their decision to participate in optional family/individual psychotherapy offered to all study participants at the time of enrollment. Only guardians will be asked the 22-item questionnaire, adapted from questionnaires assessing attitudes and perceptions towards psychotherapy in similar studies of children with psychiatric diagnoses.[221] [222] [223] [224] [225] For subjects who have already completed the MEAC study, consent will be implied via continuation of the phone interview. All newly enrolled subjects will be formally consented for permission to be contacted during or after study participation. Subjects will be reminded that participation is voluntary, that their participation in the main MEAC study will be unaffected if they choose not to participate in this questionnaire, and that they may choose not to answer any question or end their participation in this segment at any time.

Family Environment Scale:
To characterize the family's perception of expressed emotion within the family during study participation, the Family Environment Scale (FES) will be included. FES form R, [226] which measures perceptions of family environment, is a 90 question True/False questionnaire with ten total scoring domains encompassing relationship (Cohesion, Expressiveness, Conflict), personal growth (Independence, Achievement Orientation, Intellectual-Cultural Orientation, Active-Recreational Orientation, Moral-Religious Emphasis), and system maintenance (Organization, Control). Caregivers of newly-enrolled MEAC subjects will be given the FES over the phone at baseline and in paper form

at the 3-month time point. Caregivers of patients who have already completed the MEAC study will be given the FES once as a retrospective phone questionnaire.

Establishing DSM-IV Diagnoses: All research materials (assessment instruments, school reports, agency records, pediatrician/medical charts), are reviewed in consensus conferences to establish final diagnoses.

STUDY ASSESSMENT INSTRUMENTS		
Instrument	**Second Informant**	**Child**
Missouri Assessment of Genetics Interview for Children (MAGIC)	X	X
Child Behavioral Checklist	X	
WISC-IV		X
Aberrant Behavior Checklist	X	
Social Responsiveness Scale	X	
Children's Global Assessment Scale	X	X
Clinical Global Impressions Scale	X	X
Missouri Adolescent Female Twin Study (MOAFTS), trauma subscale	X	X
Duke Pubertal Status Questionnaire		X
Modified Side Effects Scale	X	X
Abnormal Involuntary Movements		X
Barnes Akathisia Scale		X
Simpson-Angus Scale		X
Medical History Form	X	
Locator Form	X	
Diet and Exercise Behaviors Questionnaire:	X	X
Psychotherapy Attitudes and Perceptions Questionnaire:	X	X
Family Environment Scale	X	

Blinding, Training and Maintaining Interrater Reliability of Research Clinicians: Raters are blind to treatment group assignment. Families will be instructed not to reveal the drug that child has been on. This has worked well in multiple other studies. Research staff are trained to interrater reliability and recalibrated annually. Raters have virtual 100% agreement on diagnostic categories and symptom severity ratings five times in a row as both interviewer and observer.

Appointment Times and Reimbursements for Effort and Inconvenience: Reimbursements will be paid at a level commensurate with similar studies in the St. Louis area. Free parking is provided in a safe underground area. Each family receives reminder phone calls in the days and weeks prior to the follow-up visit from the research study staff.

6. Blood for Future Genetic Studies

Blood samples for future genetic studies will be obtained. These will only be obtained from families who specifically give permission on a separate genetic study consent form. These consent forms (child and parent/related guardian (e.g. grandparent)) will be separate from that of the metabolic study to reinforce that participation in the metabolic study does not mandate participation in the genetic study. Separate consents are also needed to accommodate the special language required in consent forms for genetic studies. For families consenting to future genetic studies, an RNA sample (2.5ml) will be obtained from the child at baseline and at 12 weeks. DNA samples, 10 ml each, will be obtained from the child and both parents when possible. All genetic samples will be stored at -80° C until processed or for up to 20 years. The samples will be labeled only with the subject study ID number.

7. Plasma Assays:

All analytical procedures are routinely performed in Washington University laboratories including the GCRC Core Laboratory.

a. Plasma metabolites: Plasma glycerol and glucose will be recovered in the aqueous fraction following solvent extraction of plasma lipids and converted to the HFB derivative for GC/MS. Plasma glucose concentration will be determined by the glucose oxidase method. Plasma and microdialysis glycerol concentrations will be determined by an enzymatic assay (Sigma). Plasma insulin and C-peptide,[227] glucagon[228] and cortisol[229] concentrations will be measured by radioimmunoassay. Plasma catecholamine concentrations will be determined by a radioenzymatic method developed by our GCRC core laboratory.[230] Amino acids will be isolated from plasma by cation exchange chromatography and converted to HFBPr derivatives[231] for GC/MS. Plasma fatty acids will be recovered by solid phase extraction as recently described, and analyzed by GC/MS and quantitative GC.[232] VLDL will be isolated from 3 mL of fresh plasma by ultracentrifugation at d=1.006 g/mL and stored at –70°C for further processing. VLDL triglyceride concentrations will be determined by enzymatic assay (Sigma Chemical Co., St. Louis, MO). TG will be isolated from the lipid extract by TLC, and fatty acids recovered as methyl esters and glycerol recovered as the HFB derivative for GC/MS analysis as previously described.[233,234]

b. GC/MS analyses of glycerol*:* Enrichment of HFB-[$^2H_5$]glycerol will be measured by electron impact (EI) by monitoring a fragment (M-O-HFB, m/z 467/472) which retains all 5 initial deuteriums in the [$^2H_5$]glycerol tracer. Washington University investigators have recently demonstrated that by incorporating concentration dependency into a standard curve approach one can decrease between-run variation in values to <1%.[235] HFB-glycerol and glucose will be analyzed by EI using ions at m/z 467/472 ([$^2H_5$]glycerol) and m/z 519/521 ([$^2H_2$]glucose). For all GC/MS analyses, instrument response will be calibrated using standards of known enrichment.

8. Calculations

a. Whole-body substrate (glycerol and glucose) Ra and Rd: During isotopic and physiologic steady state, Steele's steady state equation[236] will be used to calculate substrate Ra and Rd. Steele's non-steady-state equation[236] will be used to calculate substrate Ra during metabolic non-steady state conditions.

b. Whole body substrate oxidation: The rate of fat and glucose oxidation will be calculated using the stoichiometric equations described by Frayn.[237]

9. Data Management and Analysis Techniques:

Data management and quality control: The data management and quality control process will begin with the initial design of data collection forms (when needed) and data capture forms in SPSS (IBM SPSS; Armonk, NY). Quality control measures will include the flagging of out-of-range and inappropriately missing data items, the identification of forms that have not been completed for a particular subject, and confirmation that enrolled subjects satisfy eligibility criteria. To further ensure accurate and complete data, all data collection personnel will be asked to review forms as soon as they are filled out so that problems related to missing or illegible data items can be quickly corrected. Because forms will include the initials of the data collection person who completed the form, it will be easy to contact the appropriate individual when problems are identified.

Data analysis: Primary and secondary analyses for adiposity and insulin sensitivity outcomes were conducted using Intent-to-Treat (ITT) analyses (IBM SPSS; Armonk, NY) including randomized subjects. Primary outcomes were change in DEXA-measured adiposity (DEXA % total fat) and clamp-derived insulin sensitivity at muscle (percent change in Glucose Rd), with secondary outcomes of change in MRI measured adiposity and percent change in Glucose Ra and Glycerol Ra. Primary analysis for change in DEXA % fat used a likelihood-based mixed-effects model using time (0, 6 and 12 weeks) and medication group as independent variables, with Toeplitz covariance structure specified, based on Bayesian information criteria (BIC). The primary outcome analysis for insulin sensitivity, as well as the secondary outcome analyses for adiposity and insulin sensitivity, used repeated-measures analyses of covariance (ANCOVA) with baseline values of the dependent variables as the covariate (to address potential baseline influence on outcomes) and time and treatment condition as independent factors, testing for time by treatment condition as well as covariate interactions. When time by treatment interactions were significant, contrasts were used to test comparisons of interest; when not significant, treatment condition was removed from the model to calculate the main effect of time and any interactions. MRI abdominal fat models were run with compartment (subcutaneous versus visceral) as an additional 2-level factor, to test for time by compartment and time by treatment by compartment interactions. Exploratory analyses tested whether the effects of age, stimulant use, gender and race altered primary results, re-running primary analyses with an additional two- or three-level factor (e.g., yes/no stimulant); these exploratory analyses were corrected for multiple tests (Bonferroni; 0.05/4= 0.0125). Other exploratory analyses used ANCOVA as above (week 0 and 12) to support interpretation of primary/secondary measures (e.g., DEXA lean, clamped insulin concentration) or for clinical context (e.g., BMI %ile, psychiatric symptoms), with ANOVA used to test the effect of time within individual treatment groups. Effect sizes (Cohen's d) were calculated for primary and secondary outcomes.

Exploratory analyses include correlating the 12 week change in measures of insulin sensitivity and the corresponding change in percent fat with a view towards a more precise understanding of the degree to which changes in insulin sensitivity can be explained by changes in fat mass. Analyses of covariance that employ changes in insulin sensitivity as the dependent variable and include changes in percent fat as a predictor will provide estimates of the percent of variability explained (R^2) both by the change in fat mass alone and by the combination of this measure and the covariates already noted. These analyses will also provide information about the degree to which the covariates are independently predictive of changes in insulin sensitivity. Other exploratory analyses will involve the role of regulatory hormones such as cortisol, glucagon, and leptin. Since these hormones will be measured at baseline and at 6 and 12 weeks, mixed model repeated measures analysis of variance will evaluate the effect of treatment on these hormones and will provide information about the pattern of change during the 12 week follow up period. A final set of possible analyses will involve the use of logistic regression to determine factors that are associated with the presence of metabolic syndrome at baseline, to be performed only if baseline levels are meaningful. While we will also use logistic regression to explore factors that are predictive of the development of metabolic syndrome during follow-up and will evaluate between group differences in the incidence of syndrome development, we do not anticipate that large numbers of subjects who do not have this syndrome will develop it during the relatively brief 12-week follow-up. Thus, we expect that the statistical power associated with these latter analyses will be small and view them as exploratory hypothesis generating analyses.

In all of the analyses we perform, we will give careful attention to the appropriateness of the statistical procedures that are employed. Thus, all analyses will be preceded by graphical assessments of the data to evaluate the distribution of particular variables and to determine whether outliers are present. When we perform analyses of covariance, we will routinely evaluate regression residuals to ensure that the model is appropriate. Similarly, we will evaluate the Hosmer-Lemeshow goodness of fit statistic to assess the appropriateness of logistic regression models. When variables are poorly distributed and assumptions for a given analytic procedure are violated, we will explore and implement remedial measures that include data transformations and semi-parametric approaches based on the ranks of the data if satisfactory data transformations cannot be found. We have defined only two primary specific aims with the primary comparison being baseline to 12 weeks both because of the importance of those aims and to minimize multiple comparisons concerns. Because of the multiple comparisons issue, p-values associated with the secondary and exploratory analyses we perform will be interpreted cautiously as hypothesis-generating rather than as hypothesis-confirming.

Sample size and statistical power: The target sample size is 80 subjects in each of the three study groups. Prior data from young adults (i.e., NIMH and industry funded first episode studies where change in % body fat may be crudely estimated from known change in body weight and the assumption that increases occur in body fat rather than lean muscle), which may underestimate changes in children, suggests that percent body fat increases of 10 ± 4% may occur in the olanzapine group, 5 ± 4% in the risperidone group and 0 ± 4% in the aripiprazole group (e.g., 10 lbs fat increase in a 70 lb subject who starts at 20% body fat yields 30% body fat). Based on this, the power for a two-sided test at the 0.05 level of significance to compare any one group with any other group will be essentially 1. This substantial power will permit us to test hypotheses about changes in percent body fat in important subgroups that are defined by age, gender, race, and whether the subject is or is not taking stimulants (e.g., planned younger off-stimulant subgroup sample size is 20), as well as explore other predictors. Because we do not have reliable prior data on likely pooled baseline to endpoint or between-group differences in insulin sensitivity measures like the glucose disappearance rate, we base our power computations on the effect size that is detectable with 80 subjects per group. Using a two-sided test at the 0.05 level of significance, the target sample size implies that we can detect a between group difference in the mean disappearance rate equal to half of a standard deviation with a power of 0.88.

A secondary interest of the proposed research will be whether the younger prepubescent children between the age of 6 and 11 respond differently from children between the ages of 12 and 18. In our existing clinic system, a sample of 527 children who had the study eligible diagnostic codes indicated that 69.3% were in the younger age group. Even assuming a worst-case scenario that we fail in our planned efforts at over-recruitment to the older age groups and that these percentages continue as we recruit for the planned study, we anticipate that in each study arm, we will have about 56 subjects in the younger age group and 24 in the older age group. With these numbers and using within group analyses, we will have a power of 0.81 to detect a response rate difference in an outcome measure in younger as compared to older individuals that is 70% of a standard deviation, with the power increasing to 0.90 if the effect size is 80% of a standard deviation. If there are no statistical interactions between treatment group and age category, it will be reasonable to combine all three groups in asking about age-related differences so that worst case sample sizes will be 168 in the older group and 72 in the younger group. This dramatically increases statistical power to the extent that we will be able to detect an effect size equal to 40% of a standard deviation with probability of 0.81. The power increases to 0.94 under this no interaction assumption if the effect size comparing age differences is 50% of a standard deviation.

E. Human Subjects

Protection of Human Subjects

1. Risks to the subjects:

a) Human Subjects Involvement and Characteristics:

We will enroll 325 eligible subjects with clinically significant aggression symptoms, as defined by a score of ≥18 on the Irritability subscale of the Aberrant Behavior Checklist [205, 206] in the context of one or more Axis I DSM IV207 childhood psychiatric disorders, including conduct disorder, oppositional defiant disorder, disruptive behavior disorder, autism, pervasive developmental disorder, attention deficit disorder, bipolar affective disorder and schizophrenia, who assent to participate and whose guardian(s) give informed consent for participation in the study. Individuals with clinically significant suicidal ideation will not be included. We plan on screening up to four times the enrollment target number in order to achieve recruitment targets (**Study Visit 1**). All subjects will be 6-18 years of age and will include all races and ethnic groups **and both genders,** with targeted enrollment reflecting the overall gender distribution of males and females for “externalizing” disorders (i.e., 2:1, male:female).[208]. By initially enrolling 108 subjects in each of 3 treatment groups described below, we estimate this will enable us to obtain a study population of 80 subjects per group for a total of 240 analyzable subjects who complete the protocol (assuming 10% attrition).

The inclusion criteria are: i) age 6-18 years ii) generally healthy and a score of ≥18 on the Aberrant Behavior Checklist for irritability in the context of one or more Axis I DSM IV childhood psychiatric disorder, including conduct disorder, oppositional defiant disorder, disruptive behavior disorder, autism, pervasive developmental disorder, attention deficit disorder, bipolar affective disorder and schizophrenia; iii) Children's Global Assessment Scale (CGAS) Score ≤ 60; iv) not previously treated with an antipsychotic; individual subjects with a remote, brief prior antipsychotic exposure may be considered for enrollment by the PI on a case by case basis; v) patient assent and informed consent obtained from the parent or guardian; vi) no clinically significant (based on PI determination) changes in permitted medications (e.g., stimulants, SSRI's) for approximately 1 month prior to Baseline Evaluations based on PI discretion;

The exclusion criteria are: i) active suicidality or a primary diagnosis of major depressive disorder; ii) any lifetime use of antipsychotics; individual subjects with a remote, brief prior antipsychotic exposure may be considered for enrollment on a case by case basis by the PI; iii) the presence of any serious medical disorder that may confound the assessment of relevant biologic measures or diagnoses, including: significant organ system dysfunction; endocrine disease, including type 1 or type 2 diabetes mellitus; coagulopathy; anemia; or acute infection; all based on PI discretion; iv) subjects regularly taking within the last 3 months any glucose lowering agent, lipid lowering agent, exogenous testosterone, recombinant human growth hormone, or any other endocrine agent that might confound substrate metabolism, oral glucocorticoids (glucocorticoid nasal spray and inhalers are permitted), sedating antihistamines (non-sedating antihistamines such as but not limited to Claritin (loratadine) and Zyrtec (cetirizine) are permitted), and certain mood stabilizing agents, as some medications may themselves worsen or otherwise alter weight gain, glucose and lipid regulation or otherwise make it difficult to assess the effects of the antipsychotic alone; (note that exposure to many psychotropic agents including stimulants and SSRI's is permitted in order to maintain the generalizability of the sample); v) IQ < 70 (based on school records and/or evaluation by clinician); vi) current substance abuse; vii) past history of, or current dyskinesia; viii) stimulant dosage significantly higher (per PI judgment) than the equivalent of approximately 2 mg/kg/day methylphenidate equivalent dose.

All recruited subjects meeting inclusion/exclusion criteria will have Baseline Evaluations, followed by assessments at 6 weeks and 12 weeks. Subjects will be randomized to prospective treatment with one of 3 newer atypical antipsychotic medications that currently are either used extensively in children, or are showing rapid growth or growth potential in this population. Specifically: a) 40 subjects who have never been treated with an antipsychotic will be randomized to open-label treatment with risperidone (Risperdal). Of those subjects, 20 will be under the age of 11 years, 6 months and 20 subjects will be over the age 11 years, six months; b) 40 subjects who have never been treated with an antipsychotic but are receiving a stimulant will be randomized to open-label treatment with risperidone (Risperdal). Of those subjects, 20 will be under the age of 11 years, 6 months and 20 subjects will be over the age 11 years, six months; c) 40 subjects never treated with an antipsychotic will be randomized to open-label treatment with aripiprazole (Abilify). Of those subjects, 20 will be under the age of 11 years, 6 months and 20 subjects will be over the age 11 years, six months; d) 40 subjects who have never been treated with an antipsychotic but are receiving a stimulant will be randomized to open-label treatment with aripiprazole (Abilify). Of those subjects, 20 will be under the age of 11 years, 6 months and 20 subjects will be over the age 11 years, six months; e) 40 subjects never treated with an antipsychotic will be randomized to open-label treatment with olanzapine (Zyprexa). Of those subjects, 20 will be under the age of 11 years, 6 months and 20 subjects will be over the age 11 years, six months; f) 40 subjects receiving a stimulant but who have never treated with an antipsychotic will be randomized to open-label treatment with olanzapine (Zyprexa). Of those subjects, 20 will be under the age of 11 years, 6 months and 20 subjects will be over the age 11 years, six months.

b) Sources of Materials:

Research materials will be obtained by psychiatric interview, physical exam, medical record review, observation, indirect calorimetry by using a metabolic cart and a ventilated hood system (Vmax 29, SensorMedics, Yorba Linda, CA), DXA and MR imaging of body tissue, and collection of whole blood, as described in the Experimental Design Methods section of this application. The specimens will be obtained solely for research purposes. Although these generally will be obtained specifically for the purposes of the study, use will be made, where appropriate, of existing records and data obtained as part of routine clinical care. Study samples and data sheets will be coded with an identification number for each subject. All of the

data from individual subjects will be maintained confidentially and their names and identities will not be disclosed in any published document.

c) Potential Risks:

There are no physical risks associated with the psychiatric diagnostic and assessment procedures or clinical ratings. Some subjects may find the questions to be boring or difficult to answer and thus mildly distressing. Minimal risks exist for the collection of sensitive information on subjects. Although we will not ask about sexual function in this study, subjects will be asked by a physician or nurse to complete a Pubertal Status Questionnaire (PSQ). This is an IRB approved, age-appropriate questionnaire used to assess pubertal status. The potential physical risks of this study are small. The risks of blood drawing and catheter insertion include discomfort, minimal bleeding or infection at the site of insertion. However, sterile technique will be used and subjects with coagulopathy will be excluded. Prior to phlebotomy or placement of an intravenous catheter, a topical anesthesia will be offered to participants to minimize pain at insertion site and decrease the psychological affect associated with any invasive phlebotomy or intravenous catheter placements. The associated side effects of the topical anesthesia are very rare. The most common side effects are irritation, redness, itching, or rash. These side effects usually do not require medical attention. Regardless of the severity, a physician will evaluate all side effects. The risks of infusing stable isotope tracers include the possibility of pyrogen response or infection. However, all solutions are tested for pyrogens and sterility before infusion and are administered under strict aseptic conditions. There are no known short- or long-term risks associated with the infusion of the isotopes themselves. The risks of euglycemic clamping are transient hyper- or hypoglycemia that might lead to nausea, headache or feeling sweaty or shaky, however, glucose levels are very closely monitored and kept within $\pm$ 10 mg/dl of a target of 95 mg/dl, so that such adverse events have not occurred in any of the approximately 300 clamps conducted by the P.I. to date. The risks of DXA scanning include discomfort while lying on the scanning table, and low-dose x-ray exposure (less than a standard chest film). There are no known direct risks of MR scanning in the absence of having some metal in the body, a basis for exclusion from this aspect of the study. Some people who feel uncomfortable in small or confined spaces may feel similarly when they are positioned in the MR machine or under the indirect calorimetry ventilated hood. The hood may also cause some feelings of discomfort such as being too warm and/or facial sweating. The patients who are randomized to an antipsychotic medication will not do this exclusively for the purpose of this study, but for some clinical indication, and thus any risk associated with this switch is part of their routine clinical care, rather than research. Thus, they may be at risk for clinical adverse events associated with the newly started treatment, including the risk that their symptoms do not respond as well or temporarily worsen. The potential risk that subject reimbursement could be experienced as coercive has been addressed and minimized per our IRB. The cost for reimbursing subjects is based on our experiences recruiting patients into studies of similar complexity and inconvenience to subjects, with this level of reimbursement approved by our IRB and consistent with that of other similar projects in children at this institution. In addition, this project will be conducted on our GCRC, where a further layer of protection for human subjects is in place in the form of the Research Subject Advocate (RSA) Program, directed by NIH (NCRR) guidelines. The GCRC RSA will closely monitor this project, including the obtaining and maintenance of informed consent, through routine meetings with subjects and parents and attendance at some of the planned study visits.

2) Adequacy of Protection Against Risks

a) Recruitment and Informed Consent:

All key personnel involved in the design and conduct of the research involving human subjects will receive the required education on the protection of human research participants prior to funding of this project. Procedures to recruit subjects for the protocol and obtain their informed consent are conducted and supervised by the P.I. Targeted educational and recruitment in-services will be conducted at all appropriate facilities in order to make providers and administrators aware of this project and to assist in identifying eligible subjects. Clinicians and administrators at these sites are informed about the purpose, procedures, risks, and benefits of the protocol, as well as the inclusion and exclusion criteria, so that they can best discuss the research project with individual patients/guardians that might be eligible and interested, and make appropriate referrals for study

screening. The P.I. or Collaborators will discuss the study, including the risks and benefits of participation, with relevant potential subjects, their guardians, and relevant family members to obtain informed consent from interested individuals. Informed consent will be obtained from the patient/guardian whenever possible, or with assent from the patient and consent from the guardian. Guardians will be included in all informed consent processes. The consent form, which incorporates HIPAA authorization, contains a description of the purpose and procedures, risks, procedures to minimize them, and possible benefits. Subjects (and their guardians) are assured that they are free to withdraw consent and discontinue participation without prejudice to their current or future medical care. The objectives of the project, all of the requirements for participation, and any possible discomforts and risks will be clearly explained to the subjects orally and in writing in lay terms which they are able to comprehend. The subject/guardian must sign an informed consent form, approved by the Washington University School of Medicine Institutional Review Board, before they can participate in the study.

b) Protection Against Risk:

The risks of breaching confidentiality will be strictly limited by the use of locked and restricted access to data as well as numbers rather than names in the database that will be created for this project. No identifiers will be included in any computer files or reports generated by this study. All key personnel involved in the design or conduct of research involving the human subjects will receive the required education on the protection of human research participants prior to funding of this project.

Metabolic Measures-The discomfort associated with blood drawing or catheter placement is usually mild and brief; should it persist, participation will be discontinued. All blood will be drawn on the General Clinical Research Center (GCRC), a well-staffed medical inpatient and outpatient facility within the Washington University Medical Center. The risk of adverse events during the blood drawing and IV access procedures will be monitored by the nurse, who is in attendance at all times; treatment is facilitated by the extensive medical resources available on the GCRC. The risks of blood drawing and catheter insertion will be minimized by use of sterile technique and the exclusion of subjects with coagulopathy. The risks of infusing stable isotope tracers will be minimized by testing all solutions for pyrogens and sterility before infusion and will be administered under strict aseptic conditions. The risks of euglycemic clamping will be minimized by monitoring glucose levels very closely and keeping them within ± 10 mg/dl of a target of 95 mg/dl; no such adverse events have occurred in any of the approximately 300 clamps conducted by the P.I. to date. Should the need for medical attention arise, all the resources of a large teaching hospital are available for subject evaluation and treatment. Complete physical examinations will be performed to screen out subjects who may be at potential risk. The infusion studies will be conducted under the supervision of a licensed physician. The GCRC is equipped with a defibrillator and all appropriate emergency medications. Subjects with known or suspected heart disease will not be accepted into the study. A resting ECG will be obtained and read by a physician prior to the start of the studies. Any significant ECG abnormality at rest will lead to automatic exclusion of the subject from the project. Prior to participation in the MR scan, subjects are carefully screened for the presence of any metal objects in their body; the presence of metal objects are a basis for exclusion from this part of the study. Any physical or emotional discomfort with any procedures will be handled by allowing patients to stop and rest, or discontinue the procedure whenever they desire. Subjects enrolled into the randomized open-label treatment with risperidone, olanzapine, or aripiprazole will be chosen carefully in collaboration with treating physicians and psychiatrists, so that antipsychotics are added with adequate titration schedules and careful dose selection. These subjects will be closely monitored by their primary treating physician and supervised by Drs. Newcomer, Nicol, and Haupt, in order to minimize any adverse effects of adding antipsychotic therapy. Clinical care will be supplemented to a level above what is routine in clinical practice, using weekly safety visits either in person or via phone by the research staff in collaboration with Ms. Schweiger. Close follow-up will enhance compliance with prescribed medications and rapid clinical response to difficulties or need for medication adjustment. Subjects with increased risk factors at baseline or who have developed increased risk factors during the 12-weeks of study medication will have added study visits at 3-weeks and/or 9-weeks and will be given a home monitoring kit for weekly testing. (See Data and Safety Monitoring Plan). A Data and Safety Monitoring Committee has been developed for this protocol.

3-*month post study follow-up for a subset of subjects completing the 12-week study*

To assess end of study recommendations to parents and treating clinicians, a subset of subjects will be evaluated who have had increases in metabolic risk factors (e.g. 10% or greater increase from baseline body weight, fasting triglyceride levels greater than or equal to 250mg/dL at 6 or 12-weeks and /or a fasting or post-

load glucose of greater than or equal to 100 mg/dL or 140 mg/dL, respectively, at 6 or 12-weeks). Each subject will be evaluated individually for these criteria at the end of the 12-week study to determine which subjects would meet criteria for an additional safety visit. Those subjects meeting criteria and consenting/assenting would be scheduled for an interim medical history and measurement of weight, height, waist circumference, fasting glucose and fasting lipid profile. Clinically significant abnormal findings would be discussed with the parent(s) and relevant clinicians.

Behavioral Assessments- Only highly trained research staff or physicians will be utilized to collect data and these individuals will be experts in confidential and professional interaction with study participants. Participants will be informed in the informed consent document that any suicidal or homicidal information obtained from a child/adolescent will be shared with parent(s) to protect the life of the child/adolescent. If a child/adolescent is found to be suicidal or homicidal during any evaluation, the individual performing the evaluation will immediately notify the parent or guardian and will contact one of the study physicians. The research staff will provide the family with appropriate mental health care referrals, if the family does not already have a mental health caretaker. If the suicidal or homicidal participants are 18 years old, precautions and referrals will be given directly to the participant and to the participants' adult household members. If the participant is the sole adult household member and suicide/homicide is not deemed to be imminent, precautions and referrals, including emergency room contacts, will be provided. If any participant is deemed to be imminently suicidal and/or homicidal, 911 will be contacted as soon as possible. Participants will also be informed in the informed consent document that a request for a referral for professional care will be provided by the research staff. To protect against any misuse of knowledge about study participation, participants will be informed in the informed consent document that employers or insurers could act negatively if they learned of the study participation. Furthermore, participants will be informed that they may choose not to tell their health care providers or insurers about their study participation. Participants will also be told that the study will be covered by a federal certificate of confidentiality, which protects against subpoenas of the research materials.

3) Potential Benefits of the Proposed Research to the Subjects and Others:

There are minimal risks associated with participation in this protocol. Even though most subjects will derive little immediate benefit from participating in this study, they will receive both glucose and lipid evaluations, physical exams, and routine medical screenings that may supplement their usual level of clinical care, as well as compensation for their time and inconvenience. The potential benefits include gaining a better understanding of the effects of antipsychotic medications, glucose and lipid metabolism and adiposity in CD that may ultimately improve our ability to prevent and/or manage the adverse effects of newer, and otherwise beneficial, antipsychotic treatments as well as benefits from the knowledge that they have contributed to learning about childhood onset emotional illness. Such benefits far outweigh the relatively small risks involved in this protocol.

4) Importance of the Knowledge to be Gained:

This study will provide a much-needed understanding of the long-term effects of antipsychotic medications on glucose regulation, and ways to address the risk of diabetes and other cardiovascular disease in young patients treated with antipsychotics. Results of this investigation may also help to inform doctors about the risk of treatment-related changes in glucose regulation and cardiovascular risk associated with certain antipsychotic agents. These benefits to society as well as the benefits to the subject of gaining important information about his/her health status from the results of these tests far outweigh the minimal risks involved in this protocol.

Females and Minority Inclusion in Clinical Research

Inclusion of Females:

Females will be included.

Inclusion of Minorities:

All races/ethnicities represented in the St. Louis region will be recruited, and groups will be balanced for ethnicity based on the ethnic composition of the St. Louis area.

Patients will be recruited from clinics and private psychiatrists in the St. Louis area. In past studies at this university, 50% of our subjects have been recruited from St. Louis City (43.8% White, 51.2% Black or African American, 2.0% Asian, and 0.3% American Indian or Alaskan Native, 0.8% other race, 2.0% Hispanic or Latino origin; 2000 Census of Population and Housing, U.S. Census Bureau); and 50% have been recruited from St. Louis County (76.8% White, 19.0% Black or African American, 2.2% Asian and 0.2% American Indian or Alaskan Native; 1.4% Hispanic or Latino origin; 2000 Census of Population and Housing, U.S. Census Bureau). This 50/50 recruitment represents an over sampling of the less populous city population in the St. Louis area, but maintains the generalizability of our samples to most national metropolitan areas. Based on these percentages, the proposed enrollment is as follows: 60.3% White; 35.1% Black or African American; 2.1% Asian; 0.2% American Indian or Alaskan Native, and 1.7% Hispanic or Latino origin. Based on the gender and minority enrollment of past studies in this laboratory, we do not anticipate any difficulty with obtaining a subject sample of this composition using our proposed recruitment techniques. See "Targeted/Planned Enrollment Table" below.

Targeted/Planned Enrollment Table

Study Title: Metabolic Effects of Antipsychotics in Children

Total Planned Enrollment: 325

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	1	4	5
Not Hispanic or Latino	109	211	320
Ethnic Category Total of All Subjects*	110	215	325
Racial Categories			
American Indian/Alaska Native	0	1	1
Asian	3	5	8
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	39	77	116
White	68	132	200
Racial Categories: Total of All Subjects *	110	215	325

*The "Ethnic Category Total of All Subjects" must be equal to the "Racial Categories Total of All Subjects."

Participation of children

The proposed study is for children and young teenagers. Separate study of this age group is warranted because clinical, developmental, and neurobiological factors are sufficiently different in the pediatric age group.

Data and Safety Monitoring Plan

Although this proposal does not carry significant risk and is not a Phase III clinical intervention study requiring a Data and Safety Monitoring Committee (DMC), we have elected to appoint a committee as an added safeguard for our minor participants.

During the study, we have added extra safety measures and testing for those subjects who have at baseline or who have developed by 12 weeks on study medication the following:

a) Fasting blood glucose greater than or equal to 100 mg/dL or post-load glucose of greater than or equal to 140 mg/dL by SureStep Pro, Yellow Springs Instrument (YSI) or laboratory plasma glucose assay.
b) Rapid weight gain of greater than 10% of baseline weight by 6-weeks on study medication.
c) Increased fasting triglyceride levels of greater than or equal to 250 mg/dL.

Safety monitoring will be enhanced for these subjects by:

a) Adding fasting blood glucose, fasting blood lipid, TPR & B/P and weight/height/waist circumference measurements at 3–weeks, 9-weeks, or PRN at physician discretion, and
b) Providing a home study kit to measure urine sugar/ketones plus assess for adverse events that might require immediate treatment or a decision to discontinue study medication.

Subjects who are given the home study kits will be asked to check and document urine sugar and urine ketone measurements weekly or more often as directed. Although urine measurements will not provide the quantitative information provided by home blood glucose monitoring, it will potentially alert the investigators to increases in blood glucose levels above 180mg/dL and the presence of urine ketones. Urine measurements are less invasive for children and families who already facing added challenges of aggressive behavioral issues.

3-month safety visit post study for a subset of subjects completing the 12-week study

To assess end of study recommendations to parents and treating clinicians, a subset of subjects will be evaluated who have had increases in metabolic risk factors (e.g. 10% or greater increase from baseline body weight, fasting triglyceride levels greater than or equal to 250mg/dL at 6 or 12 weeks and /or a fasting or post-load glucose of greater than or equal to 100 mg/dL or 140 mg/dL, respectively, at 6 or 12 weeks). Each subject will be evaluated individually for these criteria at the end of the 12-week study to determine which subjects would meet criteria for an additional safety visit. Those meeting criteria and consenting/assenting would be scheduled for an interim medical history and measurement of weight, height, waist circumference, fasting glucose and fasting lipid profile. Clinically significant abnormal findings would be discussed with the parent(s) and relevant clinicians.

Role of the Committee- The DSMC's principal goal will be to ensure that participant risk-benefit ratio and study integrity are maintained at the highest possible standards. The following definitions and procedures will be used to monitor and follow any adverse events.

Adverse events (AEs) definition

AEs are defined conventionally as any untoward medical occurrence during the planned observation period in a research participant that develops during participation in the study. The AE and study participation do not have to be causally related.

Serious adverse events (SAEs) definition

SAEs are also defined conventionally, as any medical occurrence that results in death, is life threatening, requires inpatient hospitalization, results in persistent or significant disability, is a congenital anomaly or birth defect, or is an event requiring medical intervention to prevent any of these examples of an SAE.

SAEs may be mild (transient, easily tolerated by the participant), moderate (causes discomfort or interrupts the study or the participant's usual activities), or severe (causes considerable interference with usual activities) in severity.

Causality of adverse events

The causality of each AE in terms of relationship to administration of test drug will be assessed as definite (reasonable temporal relationship, with or without supporting laboratory data), probable (reasonable temporal relationship and other possible causes can be reasonably excluded), possible (reasonable temporal relationship and other possible causes are at least as or more likely), and unrelated (temporal relationship is not reasonable or other causes are reasonably more likely).

Collecting/reporting of adverse events

In the study, all adverse experiences, whether expected or unexpected, will be reported to the DSMC. Any adverse experience that occurs to a greater severity than expected will be reported to the Washington University Institutional Review Board (IRB) and the General Clinical Research Center (GCRC), and to the National Institutes of Health (NIH).

The IRB, GCRC, and the GCRC Research Subject Advocate (RSA), will be notified of any serious adverse experience within ten working days of occurrence.

If the event is fatal or life threatening, the DSMC, IRB, and RSA will be notified immediately, but not more than 24 hours after occurrence. The GCRC and NIH will be notified by telephone no later than three days after occurrence.

The IRB, GCRC, and NIH will receive annual reports regarding all adverse experiences.

Follow-up of serious adverse events

All SAEs will be followed until resolution or permanent outcome of the event or until stabilization. Some SAEs will require study discontinuation. For example, individual participants will discontinue the study in the rare case they develop diabetes mellitus, or experience triglyceride elevation of 400 mg/dl or greater. These participants will continue to undergo follow-up evaluation by the investigators, direct consultation between the investigators and the treating physicians and establishment of ongoing care plans. For subjects experiencing an SAE that does not require study discontinuation, continuing study participation will require discussions of the potential risks and benefits of continuing participation, involving the participant and their caregivers, the investigators, and the participant's treating physicians.

Follow-up of adverse events

Appropriate steps will be taken to minimize any AE. Specific examples include:

- Fasting blood sugar elevation above 99 mg/dl, but less than 126 mg/dl. In this case, participants will be monitored on a weekly, biweekly, or PRN basis for further increases in fasting blood sugar.
- Fasting triglyceride elevations above 250 mg/dl, but less than 400 mg/dl. In this case, participants will be monitored on a weekly, biweekly, or PRN basis for further increases in fasting triglycerides.
- Increase from baseline body weight of 10% or more. In this case, participants will be monitored on a weekly, biweekly, or PRN basis for other AEs that may occur in the setting of weight gain, especially hyperglycemia and hyperlipidemia.

DSMC Activities

The DSMC will include senior clinicians and investigators with expertise in child psychiatry, pediatrics, and statistics (see **Membership** below). The committee will make recommendations to ensure data integrity and the safety of the volunteers. DSMC activities will include:

- Review the research protocol and approve plans for data and safety monitoring.
- Evaluate the progress of the study, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, and other factors that can affect study outcome. Monitoring will also consider factors external to the study when interpreting the data, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the study. The principal investigator will make available to the DSMC any newly published information related to the use of atypical antipsychotic medications or the performance of the study procedures in adults or children that may affect patient safety.
- Issues regarding feasibility of the study will be evaluated by the DSMC who will make recommendations to NIH as needed regarding continuation of the study.
- Make recommendations to Washington University School of Medicine, its IRB, and investigators concerning continuation or conclusion of the study.
- Submission of an annual report to the IRB.
- Protect the confidentiality of the trial data and the results of monitoring.
- Review of data and safety issues (including any and all adverse events).
- The DSMC will be empowered to stop the study, at their discretion, for safety reasons.

DSMC Meeting Frequency

The DSMC will meet to review above listed information quarterly, with frequency to be adjusted as needed by the DSMC.

Stopping Rules:

- The study may be discontinued at any time during the study at the recommendation of the DSMC, IRB or NIH.
- If the study is terminated for any reason, the investigators will promptly inform the participants and provide appropriate therapy and follow-up.
- The study will be stopped *for any individual participant* in the case of any SAE which the PI or DSMC determines would be a contraindication to study participation. Noted above, if a participant is withdrawn from the study because of an adverse event, the participant will be followed and treated by the investigators until the abnormal parameter or symptom has resolved or stabilized, and care appropriately transitioned to the primary treating physician.
- New recruitment/enrollment will be discontinued after any SAE until satisfactorily reviewed by the DSMC, with recommendations, if any, for changes to recruitment practices, the informed consent document, or safety/monitoring practices. All such recommendations will be communicated to the GCRC and IRB.

Membership

The DSMC membership has been restricted to individuals free of apparent significant conflicts of interest. The membership for this DSMC is comprised of:

- George Vogler, PhD, Director, Center for Developmental and Health Genetics, Professor of Biobehavioral Health, Pennsylvania State University, with expertise in statistical analysis.
- Gordon Bloomberg, MD, Associate Professor of Pediatrics, Division of Allergy and Pulmonary Medicine, Washington University School of Medicine.
- TENTATIVE NEW MEMBER: Robert Berkowitz, MD, Chair, Department of Child and Adolescent Psychiatry, Children's Hospital of Pennsylvania; Associate Professor of Psychiatry; Attending Psychiatry, Weight and Eating Disorders Program.

F. Vertebrate Animals: N/A

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