Washington University in St. Louis

Human Research Protection Office

Barnes-Jewish Hospital
St. Louis Children's Hospital
Washington University

October 4, 2010

John Newcomer, MD
Center For Applied Research Sciences
Box 8134

RE: 05-0264
Metabolic Effects of Antipsychotics in Children

Dear Dr. Newcomer:

The above-stated protocol was reviewed and approved by the Human Research Protection Office (HRPO). Following please find specifics of the approval:

Approval Date:	9/30/2010
Date released for accrual:	9/30/2010
Expiration Date:	9/29/2011
Research Risk Level:	Greater than Minimal
Type of Review:	Greater Than Minimal Risk (Full Board)
Reviewing Committee:	04 CRC
HIPAA Compliance:	Compliant with Authorization

WU HRPO has eleven duly appointed Committees established in accordance with 45 CFR 46.107 that review protocols for faculty and staff at Washington University School of Medicine, Barnes-Jewish Hospital, and Saint Louis Children's Hospital. The Committees have 20 – 25 members with varying backgrounds to promote complete and adequate review of research activities commonly conducted at WU. The names and qualifications of the members are on file with the Office of Human Research Protections.

The WU HRPO complies with the regulations outlined in 45 CFR 46, 45 CFR 164, 21 CFR 50, and 21 CFR 56. The OHRP Federal Wide Assurance numbers for WU, BJH, and SLCH are FWA00002284, FWA00002281, and FWA00002282 (respectively).

If further information is necessary, please contact the HRPO office at (314) 633-7400.

Sincerely,

Kathryn L. Vehe

Kathryn L. Vehe, PharmD
04 CRC Chair
CC: Westerhaus, Elizabeth

IRB- 04 Continuing Review Committee
FULL BOARD MEETING MINUTES
Continuing Review Project
Meeting Date: September 30, 2010

HRPO #:	**05-0264**
Principal Investigator:	**John Newcomer, MD**
Title:	**Metabolic Effects of Antipsychotics in Children**

IRB DECISION

The committee voted to **approve** the study.

REGULATORY DETERMINATIONS

- After assessing the risk/benefit ratio to subjects, the IRB determined that the study is approved for one year from the date of this meeting.

- The IRB determined that the study should be designated greater than minimal risk because the study involves the potential for risk of death.

- Overall, the IRB determined that the criteria for approval as described in 45 CFR 46.111 and 21 CFR 56.111 have been met.

- As this study involves children, the IRB has classified this study under **45CFR46.405/21CFR50.52** which means that the study poses greater than minimal risk but presents the prospect of direct benefit to subjects. The medicines used in this study may improve the patient's symptoms of aggressive behavior or conduct disorder. The IRB finds that: (a) The risk is justified by the anticipated benefit to the subjects; (b) The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and(c) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in 46.408.
    - The IRB requires the consent of one parent or legal guardian; however, an attempt should be made to obtain the signature of the second parent whenever possible

- In accordance with 45CFR46.408(a) the IRB determined:
    - Written assent will be obtained for children 6-17 by signing the assent signature line found on the consent form.

- This project has been granted a partial waiver of HIPAA Authorization per section 164.512(i) of the Privacy Rule to allow the research team to use appropriate Protected Health Information (PHI) to identify potential subjects. This determination is based on the documentation provided by the researcher in the Form K5.

    - This partial waiver of authorization for recruitment purposes satisfies the following criteria:
      (1) The use or disclosure of the requested information involves no more than a minimal risk to the privacy of individuals based on, at least, the presence of the following elements:
      (a) An adequate plan to protect the identifiers from improper use and disclosure
      (b) An adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research

justification for retaining the identifiers or such retention is otherwise required by law; and

(c) Adequate written assurances that the requested information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the requested information would be permitted by the Privacy Rule;

(2) The research could not practicably be conducted without the waiver or alteration; and

(3) The research could not practicably be conducted without access to and use of the requested information.

REQUIRED ACTIONS

No required actions.

SUMMARY OF BOARD DISCUSSION

The board found the study and the proposed modifications included with the renewal application acceptable as presented. There were no controverted issues.

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, with severely obese 20 year-old African American males expected to lose 20 years of life[1].

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 (Zyprexa), risperidone (Risperdal) or aripiprazole (Abilify).

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). Drug effects on insulin sensitivity that are independent of adiposity will also be detected, with the greatest effect hypothesized for olanzapine. 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), rate of appearance of glucose (glucose Ra), and rate of appearance of glycerol (glycerol Ra) as the primary endpoints.

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 (olanzapine > risperidone > aripiprazole), with significant increases in fat mass during olanzapine and risperidone treatment in comparison to aripiprazole treatment. 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 and subcutaneous+visceral abdominal fat as the primary endpoints.

The secondary aims of this study will be to evaluate the effects of selected antipsychotic treatments on 1) insulin secretion, using frequently sampled oral glucose tolerance tests (fsOGTT) to calculate post-load area-under-the-curve insulin, 2) resting metabolic rates, using indirect calorimetry to calculate rates of carbohydrate and fat oxidation, 3) 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, and 4) effectiveness for treatment of symptoms of aggression and irritability, using the Clinical Global Impressions Scale (CGI) as the primary endpoint. **Exploratory aims include** the assessment of non-metabolic adverse events (e.g. prolactin elevation), and the assessment of metabolic effects in children with and without concomitant stimulant therapy. Children aged 6-18 will be studied, exploring 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.

INFORMED CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Participant's Name _____ HRPO # **05-0264**

Principal Investigator **Newcomer, John W., MD** PI's Phone Number **(314) 362-5939**
Last First Credentials

Title of Project: **Metabolic Effects of Antipsychotics in Children (Treatment study,<18 y.o.)**

You may be eligible to take part in a research study. This form gives you important information about the study. It describes the purpose of the study, and the risks and possible benefits of participating in the study.

Please take the time to review this information carefully. After you have finished, you should talk to the researchers about the study and ask them any questions you have. You may also wish to talk to others (for example, your friends, family, or other doctors) about your participation in this study. If you to take part in the study, you will be asked to sign this form. Before you sign this form, be sure you understand what the study is about, including the risks and possible benefits to you.

Being in a research study does not take the place of routine physical exams or visits to your own doctor and should not be relied on to diagnose or treat medical problems.

1. **Why is this study being done?**
Use of antipsychotic medication in children and young adults has been shown to be an effective treatment for behaviors such as aggression, but doctors don't know as much about how they may affect weight, glucose (sugar), insulin (a hormone that controls blood sugar levels), and lipids (fats) in younger patients. Although these antipsychotic medications have been FDA-approved by the Food and Drug Administration (FDA) for adults and are now used commonly in children and young adults who have conduct disorder, aggression or other behavioral symptoms, they are not FDA-approved for children. The point of this research is to study side effects of these antipsychotic medications in younger individuals. We will be measuring how these drugs affect body weight and substances in the body such as glucose, insulin, and lipids. Dr. Newcomer and colleagues have performed more than 400 studies of this kind in adults to look at how different types of antipsychotic medications affect weight, glucose, insulin, and lipids. This study will include 325 children and young adults whose doctors want them to start taking antipsychotic medications to treat conduct disorder or other behavior symptoms. Your doctor has determined that one of these medications may be helpful to you.

For more information regarding minors in research see www.researchchildren.org.

2. **What am I being asked to do?**
All procedures described below are research-related *except* for the prescribing of an antipsychotic medication to treat a psychiatric diagnosis and a urine drug screen if there is a history of substance abuse.

Study Visit 1: Your child will be seen by one of our child psychiatrists for a full diagnostic evaluation. Based on the evaluation, if your child qualifies and you wish to participate, we will schedule the next two study visits. You and your child will be asked questions about feelings, emotions, and behavior, and about how your child gets along at home, school, or work, and with friends. We will first ask you these questions and then we will ask your child the same questions. These questionnaires will be administered by trained personnel over the telephone or at one of the initial study visits (study visit 2 or 3). The combined length of time for both parent and child for this phase of the study is approximately 4-5 hours.

a) **Study Visit 2:** Within a few days after Study Visit 1, your child will be scheduled to go to the Pediatric Clinical Research Unit (PCRU) or Clinical Research Unit (CRU) for blood tests, an EKG, a frequent sample oral glucose tolerance test (fsOGTT), an MRI and a DXA scan. This session will last approximately 3-4 hours. The blood tests, EKG and oral glucose tolerance test are considered standard clinical care for people taking antipsychotics. The DEXA body scan, MRI and insulin/glucose clamp are research related tests. For females of child-bearing age, a urine pregnancy test will be done at baseline and 12 week visits. If your child is pregnant or becomes pregnant during the study, she will be discontinued from the study because hormonal changes could alter test results. Your child may be asked to submit a urine sample for a drug screening if s/he and her/his doctor have been previously concerned about substance use. Each procedure is described below:

1. **EKG**: Your child will be given a routine resting electrocardiogram (EKG), where soft electrodes (like small pieces of tape) will be stuck to his/her chest to measure their heart rhythm.

2. **fsOGTT and Blood tests**: With an oral glucose tolerance test, your child will be given a sweet drink to see how his/her body handles extra sugar. On the night before this test, your child can't have anything to eat or drink except water after 10:00 p.m. In the morning, your child will go to the Pediatric Clinical Research UNIT (PCRU) or Clinical Research Unit (CRU) where he/she will lie in a hospital bed or reclining chair. If your child is a female of child-bearing age, before the procedure begins she will be given a pregnancy test. A small catheter (a plastic tube, also called an IV) will be inserted into a vein of your child's hand or wrist or bend in his/her arm. This feels like getting a shot, but we will numb your child's skin first with either a cream or an injectable local anesthetic to help it hurt less.

   Once the IV catheter is in your child's vein, it doesn't hurt and we will use the catheter to get blood samples during the study without hurting him/her. Your child's hand or wrist or arm with the IV will be heated in a routinely used temperature-controlled hand-warming box to increase the blood flow to the hand. This box is not FDA approved but is common in many centers.

   Your child will then drink a very sweet lemon- or orange-flavored drink. Blood samples will be taken from the catheter in your child's hand or wrist or arm at different times during the study to check sugar levels in your blood along with some other routine blood tests. He/she can watch cable TV or a video during this study.

   After this study, your child will be given breakfast.

3. **MRI**: Your child will also have a magnetic resonance imaging (MRI) scan to

measure the fat content in your belly. He/she will wear their clothes or a hospital gown during this scan. During the MRI scan, your child will lie on a table inside a tube while his/her stomach is scanned. The machine will scan your child's stomach three or four times, for about 30 seconds each time. Your child will need to hold still during the 30-second scans, but he/she can wiggle a little in between scans. The whole MRI study takes about 20 minutes. The machine makes some strange noises, but your child can't feel it scanning. Your child will wear earphones and listen to music while he/she is being scanned.

4. **DXA**: Your child will also have a dual-energy x-ray absorptiometry (DXA) scan to measure his/her body fat and body muscle content. The DXA scan involves lying still on a table in street clothes or a hospital gown (not in a tube this time) and having your child's body scanned by a machine for about 5 minutes. Your child won't be able to feel the DXA machine scanning, either.

b) **Study Visit 3: Insulin/Glucose Clamp:** About a week after Visit 2, your child will be come to the PCRU or CRU early in the morning (about 6:30 am) for a test called the Insulin/Glucose Clamp. This is a test that measures blood glucose (sugar), lipids (fats) and other hormones in your child's body while he/she is getting IV fluids that contain glucose (sugar) and insulin (a hormone that controls blood sugar levels).

Your child can't eat or drink anything except water after 10:00 p.m. the night before the test. Upon arrival to the PCRU or CRU, your child's height, weight, and vital signs will be measured. If your child is a female of child-bearing age, before the procedure begins she will be given a pregnancy test. Your child will then have two IV catheters inserted, one in each arm, using the injectable anesthetic or numbing cream first.

This large vein site in the one arm will allow us to give your child IV fluids that are non-radioactive stable isotopes (rare but natural forms of foods like fat and sugar). These isotopes are already present in your child's body and there will be no short-term or long-term side effects from the extra isotopes we give him/her. The second IV will be inserted into a vein of your child's other hand or wrist or bend in your arm. This IV site will be heated in a temperature-controlled box and blood samples will be taken from this IV at different times during the study. Your child will be able to watch cable or videos while lying in bed. The study doctor or research nurse and PCRU /CRU nurses will be present throughout the session. Twice during the session, your child will wear a special hood (called an indirect calorimeter) that measures your breathing and tells us how many calories you are burning. Your child will wear this two times during the study, each time for about 30 minutes. If he/she become uncomfortable wearing the hood, we will remove it. After the study, your child will receive a late lunch (around 2:30 p.m.), the IVs will be removed, and then you can take them home. The session will begin early in the morning following overnight fast and will take approximately 7 1/2 to 8 hours. Your child will be asked questions about how he/she is feeling during this session.

The amount of blood drawn during each test will depend on your child's weight at the time of each OGTT and Insulin/Glucose Clamp. We will follow Washington University School of Medicine Human Study Committee Research Protection Office's guidelines of drawing no more that 3 ml (3/5 teaspoon)/kg of body weight over a two month period of time. We will do this by decreasing the number of time points for each blood draw for each test.

(Under special circumstances, such as having trouble remembering not to eat after 10:00 pm the night before the test, your child might be asked to be stay overnight on the CRU on the night prior to the OGTT or the Insulin/Glucose Clamp.)

We will never sedate your child (give him/her any medication to make them sleepy or calm) for any of these procedures. <u>If your child becomes too uncomfortable, he/she can stop participating at any time.</u>

<u>Treatment Assignment:</u>

1) In coordination with your child's physician, after he/she has completed the baseline OGTT and Insulin/Glucose Clamp, he/she will be randomly (like the flip of a coin) assigned to receive one of the following newer antipsychotic medications for 12 weeks (3 months): aripiprazole (Abilify), olanzapine (Zyprexa), or risperidone (Risperdal). There is a one out of three chance of receiving one of the three medications. Your child's physician and the study personnel will closely monitor the addition of this medication. You and your child's physician will know what medicine your child has been assigned, and your physician will adjust the dose on an individual basis. If your child participates in this study, your child's physician will be asked not to use a second antipsychotic or certain other medications along with the antipsychotic, (e.g. antihistamines, tricyclic antidepressants, bupropion, clonidine, pemoline, and mood stabilizing agents). These medications may themselves worsen glucose and lipid control or otherwise make it difficult to assess the effects of the antipsychotic alone.

2) If more than six weeks have passed between your child's participation in the initial phase of the study and his/her random assignment to one of the medications, he/she will be asked to repeat the isotope infusion portion of the study (see c above for description).

3) If more than eight weeks have passed between your child's participation in the initial phase of the study and his/her assignment to a different medication, he/she will be asked to repeat the isotope infusion and repeat the MRI and DXA scans and routine blood tests (see b and c above).

4) Your child will be asked to refrain from donating blood for two months after the end of the study, since the amount of blood drawn will be close to the maximum guidelines suggested for children.

5) If at any time during the study your child's weight, blood sugar and/or blood lipid levels show a need to be watched more closely, the study doctor and staff may ask that your child come for visit at week 3 and /or week 9 of the 12 week study.

<u>Weekly Medication Check</u>

Your child will have weekly medication checks with the study doctor and research assistant. These visits may be over the telephone or as out-patient visits to research offices.

c) **Study Visit 4:** This visit will be approximately six weeks after the Insulin/Glucose Clamp (Study visit #3). This visit will include an fsOGTT and /or, blood tests and DXA as described in Study Visit #2. (There will not be a MRI at this visit). The fsOGTT may not be done if your child is younger and a small body size.

d) **Study Visit 5:** This visit will happen approximately 11-12 weeks after your child begins the study medication at Study visit #3. Study visit 5 will include an fsOGTT, DXA, MRI and all blood tests as described in Study visit #2.

e) **Study Visit 6:** This visit will happen approximately 1 week after Study Visit #5. This final visit will include a Insulin/Glucose Clamp and all blood tests as described for Study Visit #3.

f) **Extra study visits (safety checks) for some children/teens:** During the 12-week study, the study doctor will talk with you and your child about your child's weight and blood tests results. If the study doctor wants to watch your child's weight and/or blood tests more closely at any time during the study, you will be asked to come to the PRU/CRU for 1-2 extra study visits. These will be short visits lasting about 1-hour.

The safety checks will be approximately **3 weeks after starting study med (visit 3A) and/or 9 weeks after starting study med (visit 4A).** At the time, if it is decided that extra study visits will be helpful, your child will also be given a home monitoring kit that contains strips for testing urine sugar and ketones. You and your child will be given instructions on how to check your urine for sugar and ketones one or more times a week.

h) **3-month follow-up visit (after 12-week study ends)- Visit 7:** At the end of the 12-week study, the study doctors will make recommendations to you, your child, and your treating clinicians regarding the study-related treatment effects on your weight, blood lipids and blood sugar, and behavior. When the ending OGTT and Glucose/Insulin Clamp are completed, your child will be returned to the care of your treating physician (child psychiatrist or primary care doctor). If the study doctor recommends that he/she return for a follow-up visit (after the 12-week study ends) you will be asked to return for this brief follow-up visit in approximately 3 months. During the 3 months following the12-week study visits, your child will be under the care of your primary physician and no additional study visits will occur during that time. Your child's 3-month lab results will be shared with your treating physician.

For the safety checks and the 3-month follow-up, your child will need to be fasting after 10:00 p.m. the night before the study visit. He/she will have weight, height and waist measured and the PRU/CRU nurse will blood draw blood from his/her arm or hand for a fasting blood sugar and a fasting blood lipids (cholesterol and triglycerides). Less than one teaspoon of blood will be drawn at each visit; the amount will depend on his/her body size. During these study visits, the study staff will ask questions about your child's medications, how he/she feels and about any problems he/she might be having and look at the urine test results.

i) **Optional post-study phone questionnaires:** Someone from the research team may call you during or after your participation to ask about your child's eating and exercise patterns over the course of the study, as well as your own experiences and attitudes toward psychotherapy. Both questionnaires will be optional. You can choose to not answer any question, or not to take the questionnaires at all, without incurring any penalty and without jeopardizing your participation in the treatment study. These questions are for research purposes only and the final results of the questionnaires will not be traceable to you or your family.

j) **Optional post-study re-consent to release school records:** At the beginning of the MEAC study, you will be asked to provide permission for study staff to contact your child's school so that we may obtain information about your child's school performance as it relates to his/her

symptoms. Your decision whether to allow us to contact your child's school will not affect your child's treatment or you or your child's participation in the study in any way. The release will be good for 1 year, but in some cases, you may be contacted more than one year after your child's participation in MEAC has ended; this is to renew a release that is more than 1 year old.

How long will I be in the study?
Your child will be in the study approximately 3-4 months unless he/she has some changes in weight, blood sugar or blood lipid tests that need to be checked approximately 3-months after the 12-week study ends. If that happens, your child will be in the study for a total of 6-7 months, but your child psychiatrist or primary care doctor will be in charge of your child's behavioral/psychiatric treatment after the 12-week study ends. Study staff will assist with referrals to a child psychiatrist or primary care physician at the end of the 12-week study as necessary.

Financial Disclosure of Interest
The study sponsor is paying Washington University to conduct this study. The amount of payment is enough to cover the study doctor's and/or institution's expenses to perform the study.

Participating in Concurrent Studies
Your child may not be in any other medical studies while in this study.

3. **What are the costs?**
The procedures performed just for this research study are provided at no cost to you and your child. There are no extra charges to you or your insurance company for participating in this study. You or your insurance company will be charged for your antipsychotic medications. If your child has no current medical insurance, he/she will receive the medication for the study at no cost to you during your participation in the study. If your child has a history of drug or alcohol dependence, you or your insurance company may be charged for (standard of care) urine drug screening so that your child can receive the medical care needed for this condition.

Standard care and research may carry a co-pay or deductible. When insurance pays, you are responsible for the applicable co-pays and deductibles.

Your family will receive a total value of up to $700.00 (up to $775.00 if child has study visit at 3-months following the 12-week study) combined in gift certificates and monetary reimbursement for your participation in the 12-week research study. The child will receive payment in their choice of gift certificates. If you want to stop your participation at any time, you will receive part of the $700 value, based on how far in the study you are. You will receive $75.00 each for baseline and 6-week OGTTs (or 6-week fasting labs) and $100.00 for the 12-week OGTT; $50.00 for the first medication check visit with the study psychiatrist; $175 for the baseline Insulin/Glucose Clamp and $225.00 for the 12-week clamp. If you participate in the 3-month follow-up visit after the 12-week study ends, you will be paid an additional $75.00 in gift certificates and monetary reimbursement for that visit. All compensation will be for time and inconvenience. Gift cards and monetary reimbursement will be available at the next scheduled study visit - they will not be available during the child psychiatrist visits. You will not receive any payment for safety labs.

Because you will be receiving more than $600 in gift certificates, this amount will be considered extra income so you will receive an IRS Tax Form 1099 during tax season from Washington University so you can report it to the IRS.

4. **What are the risks?**
In this study, your child will get both routine and research procedures. The overall potential risks of this study are small. All key personnel involved in the design and conduct of the research involving human subjects have received the required education on the protection of human research participants prior to funding of this project. Some of the blood tests could be considered part of the routine diagnostic care of participants at greater risk for developing Type 2 Diabetes, for example, children who are overweight.

Taking part in the study will add the following risks to your care. Research related risks are:

♣ **Blood drawing:**
Likely: The risks of blood drawing and IV insertion include discomfort, bruising, and/or minimal bleeding.

Less Likely: Occasionally during blood drawing procedures, some people experience dizziness or feel faint.

Rare: Very rarely, the site of needle insertion could become irritated or infected. The side effects of the topical anesthesia are very rare. The most common side effects are irritation, redness, itching, or rash. There is also a very small risk of your child's hand becoming reddened or developing a small blister from warming his/her hand in the hand-warming box. Side effects associated with topical anesthesia used to numb the area of needle insertion infrequently cause side effects including irritation, redness, itching or rash.

♣ **Interviews or Questionnaires:**
Likely: None

Less Likely: None

Rare: During these questionnaires you/your child may experience minor discomfort when answering some questions. In our experience this discomfort does not happen often, and when it occurs, it does not last long. No major upset has ever happened. All questionnaires are administered by highly trained research staff. Please let the staff know if you feel any discomfort so they may discuss this with you and your child. You/your child may choose not to answer any question that makes you uncomfortable.

♣ **Frequent sample oral glucose tolerance test** (fsOGTT):
Likely: None

Less Likely: None

Rare: There is a small risk of feeling some nausea when drinking the sweet liquid drink. This feeling should pass within a few minutes after drinking the liquid.

♣ **Magnetic resonance imaging (MRI) procedure:**
Likely: None

Less Likely: None

Rare: Having an MRI causes worry or fear for people with claustrophobia (fear of closed-in spaces), as some persons find the small space in the MRI machine confining and may feel uncomfortable. We find that "rehearsing" prior to the procedure helps to ease this. However, if your child should feel afraid or unable to continue, he/she can request the examiner to stop at any time. Magnetic resonance imaging (MRI) may also be harmful for people with certain kinds of metal in their bodies, especially: someone who had metal fragments in the eye, someone with electrical, mechanical, or magnetic activated implants, such as pacemakers and hearing implants.

This procedure will not be performed if your child has any of these kinds of metal. Therefore, it is important for your child to inform study personnel of any metal in his/her body. This will not affect payment for his/her participation. There are no other known risks of magnetic resonance imaging scans at this time.

♣ **ECG:**
Likely: None

Less Likely: There is a small chance that you will experience discomfort from the sticky pads temporarily attached to your child in order to perform the EKG.

Rare: None

♣ **Dual-energy x-ray absorptiometry:**
Likely: None

Less Likely: This research involves exposure to radiation from the DXA machine for body fat measurements. Your child may experience discomfort lying on DEXA scan table. This test has low–dose x-ray exposure (much less than a standard x-ray of your chest, technicians do not wear radiation monitors). The amount of radiation participants will receive from the scan is 1% of the amount of natural background radiation exposure people in the United States receive each year. The risk from the radiation exposure in this study is too small to be measured. If you would like more information about radiation exposure, we can provide you with a "Radiation Fact Sheet". If you want to know more about radiation exposure, please see the "Radiation Fact Sheet" located in the Guidelines section of the Human Research Protection Office website, at http://hrpo.wustl.edu, or ask the study staff for a copy.

Rare: None

♣ **Delta Trac:**
Likely: None

Less Likely: None

Rare: There are no physical risks associated with the Delta Trac. Wearing the special hood may cause worry or fear for people with claustrophobia (fear of closed-in spaces). We find that "rehearsing" prior to the procedure helps to ease this. However, if your child should feel afraid or unable to continue, he/she can request the examiner stop at any time.

♣ **Insulin/Glucose Clamp:**
Likely: None

Less Likely: None

Rare: There is a small risk of low blood sugar during the insulin infusion, which might lead to nausea, headache or feeling sweaty or shaky. The risks of infusing stable isotope tracers include the possibility of inflammation or infection. However, all solutions are tested for bacterial, molds, viruses, yeasts, and sterility before infusion and are administered under strict sterile conditions. There are no known short- or long-term risks associated with the infusion of the isotopes themselves. The special hood to measure breathing may contribute to some feeling of discomfort such as being too warm and/or facial sweating. It will be removed if your child is uncomfortable.

Risk of a breach of confidentiality:
With your written permission, we will obtain medical and hospitalization records from your child's doctors, results from prior blood, diagnostic, and laboratory tests and other information obtained from interviews or questionnaires related to your medical care. We keep this information in a locked area. The information you and your child give us will be given a code number. A master list linking the code number and your child's identity will be kept separate from the research data. Only the PI and people helping him will be able to see the list, and all staff involved with this project have been thoroughly trained in the protection of research participants. We will protect your child's information, but there is a chance somebody might see it.

One potential risk of participating in this study is that confidential information about you may be accidentally disclosed. We will use our best efforts to keep the information about you secure, and we think the risk of accidental disclosure is very small. Please see the *Confidentiality* section of this consent form for more information.

There is the possibility that your child will be contacted to see if you are interested in other parts of this study. Being in this part of the study doesn't mean your child has to participate in any additional parts. If your child is interested in future studies, we would give him/her a separate consent form to read and sign.

Risks of antipsychotic medications:
There are certain risks and discomforts that may be associated with each medication given in this research study **during the 12 weeks of treatment.** Risks of all medications are listed below, as are ways that we will minimize these risks, but your child will only experience risks of the medication treatment group that he/she is assigned to. These risks include:

Likely	Abilify/aripiprazole: Constipation, restlessness, headache, nausea, upset stomach, vomiting, agitation, anxiety, trouble sleeping, sleepiness, lightheadedness, weight gain. Zyprexa/olanzapine: dizziness, weakness, dry mouth, constipation, upset stomach, sleepiness, accidental injury, trouble sleeping, weight gain, increased appetite, thirst, tremor, depression, shakiness, involuntary movements and, weight gain., Children with borderline abnormal blood lipid levels prior to treatment with olanzapine (cholesterol or triglycerides) may develop abnormal levels while taking this medication. Risperdal/risperidone: sleepiness, trouble sleeping, agitation, anxiety, stiffness, involuntary movements, headache, upset stomach, runny nose, restlessness, dizziness, extra saliva, constipation, weight gain.
Less Likely	Abilify/aripiprazole: Accidental injury, edema, a non- or pre-diabetes increase in fasting blood glucose (below the level of diabetes), high blood pressure, muscle pain, involuntary movement, tremor, increased salivation, inflamed throat and upper digestive tract, cold and flu symptoms, blurred vision, weight gain, tremor, increased mortality and morbidity (cerebral vascular events, including stroke) in elderly patients with dementia-related psychosis, and adverse changes in blood lipids (cholesterol, triglycerides)., Children with borderline abnormal blood lipid levels (cholesterol, triglycerides) prior to treatment with aripiprazole may develop abnormal levels while taking this medication. Zyprexa/olanzapine: low blood pressure, a non- or pre-diabetes increase in blood glucose (below the level of diabetes), personality changes (non-aggressive objectionable behavior), restlessness, fever, back pain, chest pain, fast heart beat, high blood pressure, nausea & vomiting, rash, swelling, extremity pain or joint pain, abnormal gait, speech problems, cold and flu symptoms, vision changes, bed wetting, urinary tract infection, increased salivation, memory problems, numbness, confusion, extreme happiness, incoordination, sweating, acne, dry skin, menstrual period changes, vaginal infection, stiffness, dental pain, intestinal gas, joint or bone pain, twitching, abnormal dreams, delusions, emotional changes, eye infection, adverse changes in blood lipids (cholesterol, triglycerides). Risperdal/risperidone : nausea, vomiting, abdominal pain, a non- or pre-diabetes increase in blood glucose (below the level of diabetes), toothache, coughing, stuffy nose, sore throat, shortness of breath, back pain, chest pain, fever, skin problems, upper respiratory infections, abnormal vision, joint pain, fast heart beat, shakiness, decreased sensation, increased energy, dry mouth, fatigue, injury, coughing, acne, itching, muscle pain, generalized pain, weight increase, high blood pressure, low blood pressure, adverse changes in blood lipids (cholesterol, triglycerides). Children with borderline abnormal blood lipid levels (cholesterol, triglycerides) prior to treatment with risperidone may develop abnormal levels while taking this medication .
Rare	Abilify/aripiprazole: pain or tightness (including throat, abdominal, chest, pelvis, extremity, back pain, joint, muscle, jaw, neck or tongue), diarrhea, dry mouth, low appetite, behavioral & emotional changes including psychosis, infection, rash, menstrual periods changes, Neuroleptic Malignant Syndrome (fever, stiffness or involuntary movements, unstable blood pressure), fever, tiredness, migraine, chills, sensitivity to light, bloating, enlarged abdomen, head heaviness, aspiration or food or stomach reflux, heat stroke, enlarged heart, heart attack, heart failure, fast or slow heart beat and/or changes in heart rhythm, pounding heart beat felt by patient, low blood pressure, bleeding, blood clots, pale skin, sudden drop in blood pressure (e.g. when going from sitting or lying down to a standing position), inflamed blood vessels, heart-lung failure, increased

appetite, difficulty swallowing, tooth /gums infection or cavities, stomach or intestinal bleeding, rectal bleeding or hemorrhoids, stomach or intestinal gas, esophagus, intestinal or stomach inflammation or bleeding, inflamed gall bladder or gall-stones, ulcers, severe constipation or obstruction, hepatitis, blood in stool, enlarged liver, inflamed pancreas, thyroid changes, bruising of skin, changes in blood tests (various types of anemias or changes in white blood cells), weight loss, changes in metabolic blood tests (sodium, potassium, creatinine, bilirubin, albumin, alkaline phosphatase BUN, SGPT, SGOT, uric acid lactic acid), dehydration, edema, high or low blood sugar, high cholesterol, diabetes mellitus, high triglycerides, thirst, pale or bluish skin, gout, muscle paralysis, muscle tone abnormality, weakness or spasm, bursitis, inflamed tendons, abnormal dream, emotional ups and downs, twitch, rigidity, impaired concentration, dilated blood vessels and arteries, numbness, extremity tremor, hypersensitive skin, dizziness, slowed movement or response, lack of interest, panic attack, unsteady gait, visual hallucination, stroke, impaired memory, hyperactivity, slowed reflexes, restless leg, pain or numbness in nerves, increased reflexes, loss of voluntary movement, slowed thinking, blunted affect, extreme happiness, inability to rotate eyes, obsessive thought, decreased muscle tone or reflexes, bleeding in brain, sinus infection, difficult breathing or shortness of breath, pneumonia, asthma, bloody nose, hiccup, temporary voice loss from inflammation, aspiration pneumonia, decreased oxygen to lungs, respiratory failure, dry nasal passages, bloody sputum, skin ulcer, sweating dry skin, acne, skin discoloration, hair loss, dandruff, dermatitis, eye infection, ear pain, dry eye, eye pain, ringing in ears, cataract, ear infection, altered taste, inflammation of eyelid, eye bleeding, deafness, double vision, frequent blinking, lazy eye, poor vision in one eye, fear of light, bed wetting, difficulty or abnormal conditions of urination, vaginal bleeding, kidney failure, enlarged breasts, kidney stones, breast pain, female lactation, pain or tenderness in penis, severe allergic reaction (difficulty breathing, swelling and/or rash), diabetes mellitus, somnolence prolonged drowsiness or sleepiness, extrapyramidal movements (such as muscle rigidity, difficulty walking), orthostatic hypotension, tremor, fatigue, akathisia (muscle restlessness, blurred vision), producing more than the usual amount of salivary hypersecretion, increased risk of suicidal thoughts, potential for cognitive and motor impairment, difficulty with body temperature regulation, and dysphagia (difficulty swallowing), dizziness, and leucopenia, neutropenia, and/or agranulocytosis (abnormalities in your white blood cell count), especially in people with a history of a significant low white blood cell count. Seizure activity is a very rare risk with uncertain relationship to this medication.

Zyprexa/olanzapine: abdomen enlarged, chills, face edema, intentional injury, tiredness, infection, neck pain, pelvic pain, sensitivity to light, fever, hangover effect, cardiac (heart beat) changes, stroke, congestive heart failure, heart attack, hemorrhage, migraine, pallor changes in blood vessels and arteries, inflammation, blood clots, difficulty swallowing, inflammation of the esophagus, severe constipation, fecal incontinence, stomach pain or discomfort, inflamed gums, hepatitis, blood in stool, mouth ulceration, tooth abscess or caries, stomach gas, esophageal or stomach ulcer, intestinal obstruction, liver changes, high blood sugar, diabetes mellitus, diabetic acidosis, ketosis or coma, goiter, changes blood count, pale or bluish skin cast, acidosis, alkaline phosphatase blood test increased, bilirubinemia, dehydration, high cholesterol, high triglycerides, gout, high sodium, potassium, bilirubin, uric acid and/or protein in the blood, water intoxication, leg cramps, abnormal changes in muscle tissue, brittle bones, voluntary and involuntary movement disorders, antisocial behavior, ataxia, central nervous system stimulation, rigidity, delirium, dementia, speech and language disturbance, less sensitive or reactive to stimulation, slowed movement, loss of muscle tone or coordination, obsessive compulsive symptoms, extreme unfounded fears, physical symptoms of anxiety, alcohol, drug or tobacco misuse, stuttering, withdrawal syndrome, coma, any disorder of the brain, nerve pain or numbness, eyelid twitching, paralysis, bleeding in the brain, periods of difficult, decreased or absent breathing,

asthma, nose bleed, blood in sputum, sweating, hair loss, dry skin, dandruff, skin discoloration, skin ulcer, increased hair growth, difficulty adjusting to a situation or experience, cataract, deafness, double vision, dry eyes, ear pain, eye hemorrhage, various eye disorders breast pain, difficult or painful urination, female lactation, changes in urine or the process of urination, uterine fibroids enlarged, extreme vaginal bleeding, breast enlargement or inflammation, allergic reaction (can be severe with difficulty breathing, swelling, and/or rash), inflamed pancreas, pain & tenderness of penis, severe skeletal muscle disease potentially causing death, and blood clotting events. Seizure activity is a very rare risk with uncertain relationship to this medication.

□Risperdal/risperidone : increased dream activity, nervousness, trouble concentrating, depression, lack of interest, catatonic reaction, extreme happiness, increased libido, trouble remembering, sudden mood changes, nightmares, confusion, yawning, longer sleeping time, speech problems, spinning sensation, excess sedation, numbness or tingling, allergic reaction, leg cramps, stiff neck, coma, migraine, reflex changes, loss of appetite, reduced salivation, intestinal gas, diarrhea, increased appetite, swelling, flu-like symptoms, enlarged abdomen, skin irritations, fast breathing, pneumonia, asthma, trouble breathing, skin reaction to sunlight, increased sweating, acne, decreased sweating, hair loss, blocked veins or arteries in the heart, heart attack, eye pain, itchy eyes, low blood sodium or potassium or protein levels, blood chemical changes, increased thirst, weight decrease, diabetes mellitus (high blood sugar), anemia (low iron), dehydration, hyperphosphatemia (high phosphate levels in the body), hypertriglyceridemia (high triglycerides in the blood), hyperuricemia (high uric acid in the body), hypoglycemia (low blood sugar), increased urination/increased thirst, bed-wetting, hematuria (blood in urine), problems urinating, problems with the kidneys, joint pain, arthritis, missed menstrual periods, breast pain, bleeding, liver failure, hepatitis (liver inflammation), decreased blood clotting , blood clots, ringing in the ears, decreased hearing, ear problems, hormones problems, high prolactin levels in the blood, problems regulating body temperature, bitter taste, a change in the time it takes for the heart to conduct normal electrical signals (QTc prolongation) has also been associated with olanzapine use. Neuroleptic Malignant Syndrome (fever, stiffness or involuntary movements, unstable blood pressure). Seizure activity is a very rare risk with uncertain relationship to this medication.

It is important to note that these side effects do not occur in everyone. We expect that you, your child, and your child's doctor will be going over the side effects that you might watch for while taking any of these medications. The possibility of a suicide attempt is inherent in some psychiatric disorders, and close supervision of high-risk persons should accompany drug therapy.

Participants will be followed closely and monitored for side effects of medications and tests. Withdrawal of the study medication and/or treatment of medication side effects will be provided as indicated. Participants will participate in medication check-ups or telephone calls at least once per week and will be asked to report any concerns or adverse events during these times. To be sure that you/your child can always communicate with the research team, families will be provided with a 24-hour telephone number of a research clinician who will answer any questions and speak with any community physicians or dentists who the participants visit during the study. All families will also be instructed to tell any doctors or dentists they encounter that their children/adolescents are on the study medications.

The risk of your child's side effects will be minimized, or reduced should they occur, through the following steps:

1. Sometimes Abilify (aripiprazole), Zyprexa,(olanzapine) or Risperdal (risperidone) can cause nausea or vomiting. To prevent the nausea, it is best for your child to have something to eat in the morning before the a.m. dose.

2. Participants will be monitored for neuromuscular side effects at each weekly visit. Neuromuscular side effects include developing a walking style that seems to be shuffling along rather than lifting one's legs, stiffness in the movements of wrist and elbow joints, shaking of the hands when the hands are not busy and a loss of facial expression. Also, children/adolescents may also develop a problem that looks as if they are restless (called akathisia). These side effects can sometimes be reduced by lowering the dose of medication or adding an appropriate medication to treat the side effect. Participants will also be monitored for tardive dyskinesia (unusual movements of the mouth area, cheek, tongue or other parts of the body such as the shoulders and extremities). Study medications will be discontinued if tardive dyskinesia occurs.

3. Participants will be regularly monitored for changes in blood triglycerides or blood glucose. Problems with the way the body handles glucose (sugar) and lipids (triglycerides) can occur with Abilify, (aripiprazole), Zyprexa (olanzapine), or Risperdal (risperidone) potentially resulting in diabetes or a condition called the metabolic syndrome. These blood glucose and lipid problems can occur without any symptoms. That is why blood glucose and lipids are monitored in this study. If your child's fasting blood glucose becomes elevated at any point in the study to the level that is called diabetes, he/she will be withdrawn from the study. If his/her blood triglycerides become elevated to a serious degree that can increase the risk of an inflamed pancreas, then he/she will be withdrawn from the study. If your child's blood glucose or lipids become elevated during the study below the levels noted above, we will increase the frequency with which his/her blood is monitored for any further changes.

4. If your child's body weight increases 10% or more from when he/she first began taking the study medication, he/she will be monitored on a weekly or biweekly basis for other events that may occur in the setting of weight gain, especially hyperglycemia and hyperlipidemia.

During this study, your child/adolescent must avoid over-the-counter drugs and herbal supplements as these may interfere with treatment results.

Data and Safety Monitoring Committee

An independent group of medical and research professionals, called a Data and Safety Monitoring Committee (DSMC), has been established to monitor the data collected from this study and look for ways to continually improve the safety of all the procedures and medications administered as part of this project. The PI and study staff are responsible for sending regular reports to the DSMC detailing our findings, particularly highlighting any adverse or serious adverse events that occur. Having a DSMC makes sure that someone outside of the project knows about any problems and can provide an objective opinion about what needs to be done to fix or minimize them. It is the job of the DSMC to maintain the highest level of safety for our participants.

Study Discontinuation
When your child discontinues the study early due to an adverse event, or on schedule due to study completion, we will carefully work with him/her and their treating psychiatrist/physician to evaluate the risks versus the benefits of ongoing treatment with the medication your child was assigned to. At that time we can discuss the advantages and disadvantages of staying on that medication, switching to a different antipsychotic medication, or discontinuing antipsychotic medication. In all cases we will provide individualized consultation with parents and treating psychiatrist and/or pediatricians to provide the safest plan to continue the ongoing individualized therapy.

Breast Feeding
Your child must tell the study doctor if she is breast-feeding.

Certificate of Confidentiality
One potential risk of participating in this study is that confidential information about your child may be accidentally disclosed. We will use our best efforts to keep the information about him/her secure, and we think the risk of accidental disclosure is very small. Please see the *Confidentiality* (Item 7) section of this consent form for more information.

Coded Data
The information you and your child give us will be given a code number that includes your child's initials. A master list linking the code number and your identity will be kept separate from the research data. Only the PI and people helping him/her will be able to see the list. We will protect your child's information, but there is a chance somebody might see it.

Pregnancy/Childbearing Potential

If you are a woman of childbearing potential, please read and sign below.

Some parts of this study might cause physical or mental problems in an unborn baby. Your child must tell the doctor immediately if there is any chance she is pregnant. She must also tell the doctor if her birth control method fails while she is in the study.

To take part in this study, your child must have a pregnancy test before starting the study. She must use an acceptable method of birth control and must not become pregnant.

Please discuss with your child's research physician how long your child needs to wait before becoming pregnant.

By signing below, you agree to have your child follow these rules.

_____
Signature Date

As with any research procedure, unforeseen problems or side effects can occur. Your and your child will be told of any changes in the way the study will be done and of any newly identified risks to which your child may be exposed.

Participation in this study may cause all, some or none of the side effects listed above. In addition, there is always the risk of developing previously unknown side effects. The investigators are willing to discuss any questions you might have about the severity, frequency, and duration of these risks and discomforts.

Participation in this study may cause all, some or none of the side effects listed above which, if severe, may cause death.

What happens if you are injured because you took part in this study?
Washington University investigators and staff will try to reduce, control, and treat any complications from this research. If you feel you are injured because of the study, please contact the investigator (John Newcomer MD at 314/262-5939) and/or the Human Research Protection Office at (314) 633-7400 or 1-(800)-438-0445.

Decisions about payment for medical treatment for injuries relating to your participation in research will be made by Washington University. If you need to seek medical care for a research-related injury, please notify the investigator as soon as possible.

5. **Are there benefits to taking part in the study?**
These medicines may improve your child's symptoms of aggressive behavior or conduct disorder. In addition, your child will be checked for serious medical conditions that may not show any symptoms, such as high blood pressure or diabetes. Finding these conditions may improve your child's medical care. This study will help doctors to understand how antipsychotic medications may affect diabetes risk and ways to address the risk of diabetes in children with conduct disorder, aggression or other behavior problems.

6. **What other options are there?**
Taking part in this research study is voluntary. Your child may choose not to take part in this research study or he/she may withdraw consent at any time. Your child may withdraw by telling the study team he/she is no longer interested in participating in the study or you may send in a withdrawal letter. A sample withdrawal letter can be found at http://hrpo.wustl.edu under Information for Research Participants. Your child's choice will not at any time affect the commitment of your health care providers to administer care. There will be no penalty or loss of benefits to which you are otherwise entitled.

Other than not taking part in the research, your child may choose to have your doctor write a prescription for him/her if he/she feels it is in your best interest to receive this drug outside of the study. The study drugs, olanzapine, risperidone and aripiprazole are available to your child even if he/she does not participate in this study. Please discuss all alternatives with your child's doctor, including psychotherapy and behavior management.

7. **What about privacy and confidentiality?**
We will do everything we can to protect your privacy.

Providing your and/or your child's social security numbers is optional and you can fully participate in the study whether you disclose them or not. If you choose to provide your and/or your child's social security numbers, we will use them to locate you in the future if we are unable to locate you at your home address, and to search vital records. We will not share your and/or your child's social security numbers or leave them accessible to identity theft.

Protected Health Information (PHI) is health information that identifies you. PHI is protected by federal law under HIPAA (the Health Insurance Portability and Accountability Act). To take part in this research, you and your child must give the research team permission to use and disclose (share) your child's PHI for the study explained in this consent form.

In addition to health information that may be created by the study, the research team may access the following sources of your child's health information to conduct the study: hospital/physician medical records; lab, pathology and/or radiology results; information derived from biological samples (including blood); interviews/questionnaires; mental health and substance abuse records; physiologic imaging.

A Certificate of Confidentiality has been obtained from the Department of Health and Human Services. This will help further protect information that may identify your child. The Certificate prevents the investigator from being forced to disclose identifying information for use in court. The investigator may not even be forced by court subpoena. Courts that may be prevented from getting your child's information include any federal, state, local civil, criminal, administrative, legislative, or other court proceeding.

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. The investigator may not withhold information if you or your child give your insurer or employer permission to receive information about your participation in this research. This means that you and your family must also actively protect your own privacy.

The Certificate does not prevent the researchers from taking steps, including reporting to authorities, to prevent serious harm to yourself or others. Such disclosures will be made as described below.

The research team may share your information with:

- The Department of Health and Human Services (DHHS) to complete federal responsibilities for audit or evaluation of this study.
- Public health agencies to complete public health reporting requirements
- Hospital or University representatives, to complete Hospital or University responsibilities for oversight of this study.
- Your primary care physician if a medical condition that needs urgent attention is discovered
- Appropriate authorities to the extent necessary to prevent serious harm to yourself or others.

Once your health information is shared with someone outside of the research team, it may no longer be protected by HIPAA.

The research team will only use and share your information as talked about in this form. When possible, the research team will make sure information cannot be linked to you (de-identified). Once information is de-identified, it may be used and shared for other purposes not discussed in this consent form. If you have questions or concerns about your privacy and the use of your PHI, please contact the University's Privacy Officer at 866-747-4975.

This study is sponsored by National Institute of Mental Health (NIMH). Representatives of the sponsor will have access to your child's research and/or medical records for monitoring the study. The research team will also send study results to the sponsor. Information sent to the sponsor will be summarized and coded so that it cannot be associated with your child's PHI. The sponsor is not required to abide by the HIPAA regulations, but agrees to protect the confidentiality of your child's information. The sponsor reviews the study summary to verify that the research is progressing toward stated goals.

You/your child will always have access to his/her medical record. Some of the individual results from tests to be performed during this research study might be of interest to your child or your primary care physician. At your request, the researchers will share the medical information gained from this study with you and your referring and/or primary care doctors. If we become aware of any important health information during the course of your participation in this study, we may be obligated/required to share this information with your treatment team. You will not have access to your child's research record.

If you decide not to sign this form, it will not affect
your child's treatment or the care given by your health provider.
your child's insurance payment or enrollment in any health plans.
any benefits to which your child is entitled.

However, it will not be possible for your child to take part in the study.

If you sign this form:

- You authorize the use of your child's PHI for this research
  - Your signature and this form will not expire as long as your child wishes to participate.
  - Your child may later change your mind and not let the research team use or share your child's information (your child may revoke your authorization).

    - To revoke your authorization, complete the withdrawal letter, found in the Participant section of the Human Research Protection Office website at http://hrpo.wustl.edu (or use the direct link: http://hrpohome.wustl.edu/participants/WithdrawalTemplate.rtf) or you may request that the Investigator send you a copy of the letter.

    - **If your child revokes your authorization:**
      - The research team may only use and share information already collected for the study.
      - Your child's information may still be used and shared if necessary for safety reasons.
      - Your child will not be allowed to continue to participate in the study.

Please specify any contact restrictions you want to request for this study only.
(Example – no calls at home, no messages left for you, no e-mails, etc.)

_____

_____

Notice of Privacy Practices –

The Notice of Privacy Practices is a separate document. It describes the procedures used by WU to protect your child's information. If you/your child have not already received the Notice of Privacy Practices, the research team will make one available to you and your child.

_____ I have been offered a copy of the Notice of Privacy Practices.
Initial

8. Whom do I call if I have questions or problems?

Please contact the researcher listed below to:

- Obtain more information about the study
- Ask a question about the study procedures or treatments
- Report an illness, injury, or other problem (you may also need to tell your regular doctors)
- Leave the study before it is finished
- Express a concern about the study

Principal Investigator:	John Newcomer MD at 314/362-5939
Research Coordinators:	Martha Hessler at 314/362-2423 or Julie Schweiger at 314/362-3153
Mailing Address:	660 S. Euclid Ave., Campus Box 8134; St. Louis, MO 63110

If you wish to talk to someone else, or have questions or concerns about your child's rights as a research participant, call Washington University's Human Research Protection Office (WU HRPO) at (314) 633-7400, or 1-(800)-438-0445.

For questions about the Clinical Research Unit (CRU) or Pediatric Clinical Research Unit (PCRU) please call Michelle Jenkerson, Research Participant Advocate at (314) 362-5626.

Request Permission for Future Contact

May we contact you for future undetermined studies conducted by Dr. Newcomer, Haupt, and Nicol? If yes, we will need to look at your Protected Health Information (PHI) to check for study eligibility.	___ Yes	___ No
May other WU physicians conducting research contact you? If yes, your PHI will be shared with other WU physicians.	___ Yes	___ No

Taking part in future studies is optional. Your child can ask us at any time to take him/her off our contact list.

9. The Principal Investigator (PI) may withdraw your child from the study without your/his/her consent if considered appropriate (i.e. certain medical conditions, use of illegal drugs). It may be in your child's best interest to allow follow-up outside the study. The PI will share any new information that could change how you and your child feel about continuing in the study.

10. You will be given a signed copy of this consent form for your records.

Please mark all that apply. This section is optional.
[] Not Hispanic or Latino [] Hispanic or Latino [] Unknown
[] Asian [] Black or African-American [] Caucasian [] Native American or Alaskan Native
[] Native Hawaiian or Pacific Islander
[] Other [] Unknown
The Office of Management and Budget has declared that Hispanic/Latino is an ethnicity. National Institutes of Health, in an effort to ensure diversity in research, requests that you report your ethnicity. (http://grants.nih.gov/grants/funding/women_min/women_min.htm)

CONSENT FOR MINOR PARTICIPANTS

Parent or Legal Guardian: (If participant is less than 18 years of age.)
I have read this consent form and have been given the chance to ask questions. I give permission for my child to participate in this research described above, titled: **Metabolic Effects of Antipsychotics in Children (Treatment Study, 6-17 y.o.)**

HRPO does not require participants to re-sign the consent form unless a change is made; the investigator, however, may choose to re-consent participants at any time.

Signature: _____

Printed Name: _____Date of Signature: _____

Relationship to Child:
Father Mother Grandmother Grandfather Legal Guardian Other*: _____

***If the minor participant is in foster care or a ward of the State, please contact HRPO at 633-7400 for assistance.**

Signature of Second Parent or Legal Guardian: [Optional]

Signature: _____

Printed Name: _____Date of Signature: _____

Relationship to Child:

Father Mother Grandmother Grandfather Legal Guardian Other: _____

If Parent/Legal Guardian is also a Research Participant:
I have read this consent form and have been given the chance to ask questions. I agree to participate in this research described above, titled: **Metabolic Effects of Antipsychotics in Children (Treatment Study, 6-17 y.o.)**

HRPO does not require participants to re-sign the consent form unless a change is made; the investigator, however, may choose to re-consent participants at any time.

Signature: _____

Printed Name: _____ Date of Signature: _____

Principal Investigator (or Designee):

I have given this research participant information about this study that I believe is accurate and complete. The participant has indicated that he or she understands the nature of the study and the risks and benefits of participating.

Signature: _____ Title: _____

Printed Name: _____ Date of Signature: _____

DOCUMENTATION OF ASSENT (FOR PARTICIPANTS WHO ARE MINORS)

Participant's Assent:
The doctor or nurse has told me what will happen if I choose to be in this study. I understand what they have said, and I understand that my parents and I may later change our minds and stop being in the study.
Signature: _____

Printed Name: _____ Date of Signature: _____

ASSENT CONSIDERED INAPPROPRIATE (for minors)

We believe that requiring the signature of the minor is not appropriate for the following reason(s):

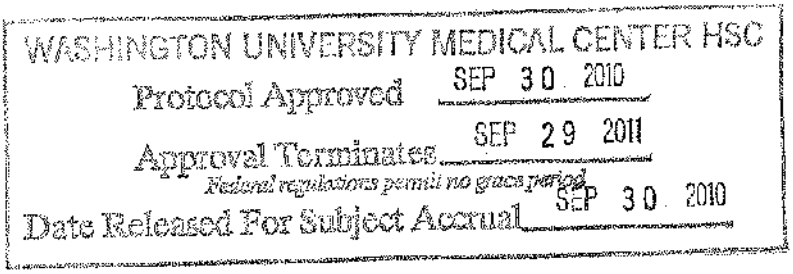
_____

_____

_____ _____

Physician Date Parent/Guardian Date

This form is valid only with the Human Research Protection Office's current stamp of approval.



INFORMED CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Participant's Name _____ HRPO # **05-0264**

Principal Investigator **Newcomer, John W., MD** (Last, First, Credentials) PI's Phone Number **(314) 362-5939**

Title of Project: **Metabolic Effects of Antipsychotics in Children (Treatment study,≥18 y.o.)**

You may be eligible to take part in a research study. This form gives you important information about the study. It describes the purpose of the study, and the risks and possible benefits of participating in the study.

Please take the time to review this information carefully. After you have finished, you should talk to the researchers about the study and ask them any questions you have. You may also wish to talk to others (for example, your friends, family, or other doctors) about your participation in this study. If you decide to take part in the study, you will be asked to sign this form. Before you sign this form, be sure you understand what the study is about, including the risks and possible benefits to you.

Being in a research study does not take the place of routine physical exams or visits to your own doctor and should not be relied on to diagnose or treat medical problems.

1. Why is this study being done?

Use of antipsychotic medication in children and young adults has been shown to be an effective treatment for behaviors such as aggression, but doctors don't know as much about how they may affect weight, glucose (sugar), insulin (a hormone that controls blood sugar levels), and lipids (fats) in younger patients. Although these antipsychotic medications have been FDA-approved by the Food and Drug Administration (FDA) for adults and are now used commonly in children and young adults who have conduct disorder, aggression or other behavioral symptoms, they are not FDA-approved for children. The point of this research is to study side effects of these antipsychotic medications in younger individuals. We will be measuring how these drugs affect body weight and substances in the body such as glucose, insulin, and lipids. Dr. Newcomer and colleagues have performed more than 400 studies of this kind in adults to look at how different types of antipsychotic medications affect weight, glucose, insulin, and lipids. This study will include 325 children and young adults whose doctors want them to start taking antipsychotic medications to treat conduct disorder or other behavior symptoms. Your doctor has determined that one of these medications may be helpful to you.

For more information regarding minors in research see www.researchchildren.org.

2. **What am I being asked to do?**
All procedures described below are research-related *except* for the prescribing of an antipsychotic medication to treat a psychiatric diagnosis and a urine drug screen if there is a history of substance abuse.

Study Visit 1: You will be seen by one of our child psychiatrists for a full diagnostic evaluation. Based on the evaluation, if you qualify and you and your parents wish to participate, we will schedule the next two study visits. You and your mom/dad will be asked questions about feelings, emotions, and behavior, and about how you get along at home, school, or work, and with friends. We will first ask your mom/dad these questions and then we will ask you the same questions. These questionnaires will be administered by trained personnel over the telephone or at one of the initial study visits (study visit 2 or 3). The combined length of time for both parent and child for this phase of the study is approximately 4-5 hours.

a) Study Visit 2: Within a few days after Study Visit 1, you will be scheduled to go to the Pediatric Clinical Research Unit (PCRU) or Clinical Research Unit (CRU) for blood tests, an EKG, a frequent sample oral glucose tolerance test (fsOGTT), an MRI and a DXA scan. This session will last approximately 3-4 hours. The blood tests, EKG and oral glucose tolerance test are considered standard clinical care for people taking antipsychotics. The DEXA body scan, MRI and insulin/glucose clamp are research related tests. For females of child-bearing age, a urine pregnancy test will be done at baseline and 12 week visits. If you are pregnant or become pregnant during the study, you will be discontinued from the study because hormonal changes could alter test results. You may be asked to submit a urine sample for a drug screening if you and your doctor have been previously concerned about your substance use. Each procedure is described below:

1. **EKG**: You will be given a routine resting electrocardiogram (EKG), where soft electrodes (like small pieces of tape) will be stuck to your chest to measure your heart rhythm.

2. **fsOGTT and Blood tests**: With an oral glucose tolerance test you will be given a sweet drink to see how your body handles extra sugar. On the night before this test, you can't have anything to eat or drink except water after 10:00 p.m. In the morning, you will go to the Pediatric Clinical Research Center (PCRU) or Clinical Research Unit (CRU) where you will lie in a hospital bed or reclining chair. If you are a female of child-bearing age, before the procedure begins you will be given a pregnancy test. A small catheter (a plastic tube, also called an IV) will be inserted into a vein of your hand or wrist or bend in your arm. This feels like getting a shot, but we will numb your skin first with either a cream or an injectable local anesthetic to help it hurt less. This is the only part of the study that hurts a little.

   Once the IV catheter is in your vein, it doesn't hurt and we will use the catheter to get blood samples during the study without hurting you. Your hand or wrist or arm with the IV will be heated in a routinely used temperature-controlled hand-warming box to increase the blood flow to the hand. This box is not FDA approved but is common in many centers.

   You will then drink a very sweet lemon- or orange-flavored drink. Blood samples will be taken from the catheter in your hand or wrist or arm at different times during the study to check sugar levels in your blood along with some other routine blood tests. You can watch cable TV or a video during this study.

After this study, you will be given breakfast.

3. **MRI**: You will also have a magnetic resonance imaging (MRI) scan to measure the fat content in your belly. You wear your clothes or a hospital gown during this scan. During the MRI scan, you will lie on a table inside a tube while your stomach is scanned. The machine will scan your stomach three or four times, for about 30 seconds each time. You will need to hold still during the 30-second scans, but you can wiggle a little in between scans. The whole MRI study takes about 20 minutes. The machine makes some strange noises, but you can't feel it scanning you. You will wear earphones and listen to music while you are being scanned.

4. **DXA**: You will also have a dual-energy x-ray absorptiometry (DXA) scan to measure your body fat and body muscle content. The DXA scan involves lying still on a table in your clothes or a hospital gown (not in a tube this time) and having your body scanned by a machine for about 5 minutes. You can't feel the DXA machine scanning you, either.

b) **Study Visit 3: Insulin/Glucose Clamp:** About a week after Visit 2, you will be come to the PCRU or CRU early in the morning (about 6:30 am) for a test called the Insulin/Glucose Clamp. This is a test that measures blood glucose (sugar), lipids (fats) and other hormones in your body while you are getting IV fluids that contain glucose (sugar) and insulin (a hormone that controls blood sugar levels).

You can't eat or drink anything except tap water after 10:00 p.m. the night before the test. Upon arrival to the PCRU or CRU, your height, weight, and vital signs will be measured. If you are a female of child-bearing age, before the procedure begins you will be given a pregnancy test. You will have two IV catheters inserted, one in each arm, using the injectable anesthetic or numbing cream first.

This large vein site in the one arm will allow us to give you IV fluids that are non-radioactive stable isotopes (rare but natural forms of foods like fat and sugar). These isotopes are already present in your body and there will be no short-term or long-term side effects from the extra isotopes we give you. The second IV will be inserted into a vein of your other hand or wrist or bend in your arm. This IV site will be heated in a temperature-controlled box and blood samples will be taken from this IV at different times during the study. You will be able to watch cable or videos while lying in bed. The study doctor or research nurse and PCRU /CRU nurses will be present throughout the session. Twice during the session, you will wear a special hood (called an indirect calorimeter) that measures your breathing and tells us how many calories you are burning. You will wear this two times during the study, each time for about 30 minutes. If you become uncomfortable wearing the hood, we will remove it. After the study, you will receive a late lunch (around 2:30 p.m.), and the IVs will be removed. You can then go home with your parent or guardian. The session will begin early in the morning following overnight fast and will take approximately 7 1/2 to 8 hours. You will be asked questions about how you are feeling during this session.

The amount of blood drawn during each test will depend on your weight at the time of each OGTT and Insulin/Glucose Clamp. We will follow Washington University School of Medicine Human Research Protection Office's guidelines of drawing no more that 3 ml (3/5 teaspoon)/kg of body weight over a two month period of time. We will do this by decreasing the number of time points for each blood draw for each test.

(Under special circumstances, such as having trouble remembering not to eat after 10:00 pm the night before the test, you might be asked to be stay overnight on the CRU on the night prior to the OGTT or the Insulin/Glucose Clamp.)

We will never sedate you (give you any medication to make you sleepy or calm) for any of these procedures. <u>If you become too uncomfortable, you can stop participating at any time.</u>

<u>Treatment Assignment:</u>

1) In coordination with your physician, after you have completed the baseline OGTT and Insulin/Glucose Clamp, you will be randomly (like the flip of a coin) assigned to receive one of the following newer antipsychotic medications for 12 weeks (3 months): aripiprazole (Abilify), olanzapine (Zyprexa), or risperidone (Risperdal). There is a one out of three chance of receiving one of the three medications. Your physician and the study personnel will closely monitor the addition of this medication. You and your physician will know what medicine you are assigned, and your physician will adjust the dose for you on an individual basis. If you participate in this study, you and your physician will be asked not to use a second antipsychotic or certain other medications along with your antipsychotic, (e.g. antihistamines, tricyclic antidepressants, bupropion, clonidine, pemoline, and mood stabilizing agents). These medications may themselves worsen glucose and lipid control or otherwise make it difficult to assess the effects of your antipsychotic alone.

2) If more than six weeks have passed between your participation in the initial phase of the study and your random assignment to one of the medications, you will be asked to repeat the isotope infusion portion of the study (see c above for description).

3) If more than eight weeks have passed between your participation in the initial phase of the study and your assignment to a different medication, you will be asked to repeat the isotope infusion and repeat the MRI and DXA scans and routine blood tests (see b and c above).

4) You will be asked to refrain from donating blood for two months after the end of the study, since the amount of blood drawn will be close to the maximum guidelines suggested for children.

5) If at any time during the study your weight, blood sugar and/or blood lipid levels show a need to be watched more closely, the study doctor and staff may ask that you come for visit at week 3 and /or week 9 of the 12 week study.

<u>Weekly Medication Check</u>

You will have weekly medication checks with the study doctor and research assistant. These visits may be over the telephone or as out-patient visits to research offices.

c) **Study Visit 4:** This visit will be approximately six weeks after the Insulin/Glucose Clamp (Study visit #3). This visit will include an fsOGTT and /or, blood tests and DXA as described in Study Visit #2. (There will not be a MRI at this visit). The fsOGTT may not be done if you are younger and a small body size.

d) **Study Visit 5:** This visit will happen approximately 11-12 weeks after you begin the study medication at Study visit #3. Study visit 5 will include an fsOGTT, DXA, MRI and all blood tests as described in Study visit #2.

e) **Study Visit 6:** This visit will happen approximately 1 week after Study Visit #5. This final visit will include a Insulin/Glucose Clamp and all blood tests as described for Study Visit #3.

f) **Extra study visits (safety checks) for some children/teens:** During the 12-week study, the study doctor will talk with you and your parents/guardian about your weight and blood tests results. If the study doctor wants to watch your weight and/or blood tests more closely at any time during the study, you will be asked to come to the PCRU/CRU for 1-2 extra study visits. These will be short visits lasting about 1-hour.

The safety checks will be approximately **3 weeks after starting study med (visit 3A) and/or 9 weeks after starting study med (visit 4A).** At the time, if it is decided that extra study visits will be helpful, you will also be given a home monitoring kit that contains strips for testing urine sugar and ketones. You will be given instructions on how to check your urine for sugar and ketones one or more times a week.

h) **3-month follow-up visit (after 12-week study ends)- Visit 7:** At the end of the 12-week study, the study doctors will make recommendations to you, your parents and your treating clinicians regarding the study-related treatment effects on your weight, blood lipids and blood sugar, and behavior. When the ending OGTT and Glucose/Insulin Clamp are completed, you will be returned to the care of your treating physician (child psychiatrist or primary care doctor). If the study doctor recommends that you return for a follow-up visit (after the 12-week study ends) you will be asked to return for this brief follow-up visit in approximately 3 months. During the 3 months following the12-week study visits, you will be under the care of your primary physician and no additional study visits will occur during that time.. Your 3-month lab results will be shared with your treating physician.

For the safety checks and the 3-month follow-up, you will need to be fasting after 10:00 p.m. the night before the study visit. You will have weight, height and waist measured and the PCRU/CRU nurse will blood draw blood from your arm or hand for a fasting blood sugar and a fasting blood lipids (cholesterol and triglycerides). Less than one teaspoon of blood will be drawn at each visit; the amount will depend on your body size. During these study visits, the study staff will ask questions about your medications, how you feel and about any problems you might be having and look at the urine test results.

i) **Optional post-study phone questionnaires:** Someone from the research team may call you during or after your participation to ask about your eating and exercise patterns over the course of the study. The questionnaire will be optional. You can choose to not answer any question, or not to take the survey at all, without incurring any penalty and without jeopardizing your participation in the treatment study. These questions are for research purposes only and the final results of the questionnaires will not be traceable to you or your family.

j) **Optional post-study re-consent to release school records:** At the beginning of the MEAC study, you will be asked to provide permission for study staff to contact your child's school so that we may obtain information about your child's school performance as it relates to his/her symptoms. Your decision whether to allow us to contact your child's school will not affect your

child's treatment or you or your child's participation in the study in any way. The release will be good for 1 year, but in some cases, you may be contacted more than one year after your child's participation in MEAC has ended; this is to renew a release that is more than 1 year old.

How long will I be in the study?
You will be in the study approximately 3-4 months unless you have some changes in weight, blood sugar or blood lipid tests that need to be checked approximately 3-months after the 12-week study ends. If that happens, you will be in the study for a total of 6-7 months, but your child psychiatrist or primary care doctor will be in charge of your behavioral/psychiatric treatment after the 12-week study ends. Study staff will assist with referrals to a child psychiatrist or primary care physician at the end of the 12-week study as necessary.

Financial Disclosure of Interest
The study sponsor is paying Washington University to conduct this study. The amount of payment is enough to cover the study doctor's and/or institution's expenses to perform the study.

Participating in Concurrent Studies
You may not be in any other medical studies while you are on this study.

3. **What are the costs?**
The procedures performed just for this research study are provided at no cost to you. There are no extra charges to you or your insurance company for participating in this study. You or your insurance company will be charged for your antipsychotic medications. If you have no current medical insurance, you will receive the medication for the study at no cost to you during your participation in the study. If you have a history of drug or alcohol dependence, you or your insurance company may be charged for (standard of care) urine drug screening so that you can receive the medical care needed for this condition.

Standard care and research may carry a co-pay or deductible. When insurance pays, you are responsible for the applicable co-pays and deductibles.

Your family will receive a total value of up to $700.00 (up to $775.00 if child has study visit at 3-months following the 12-week study) combined in gift certificates and monetary reimbursement for your participation in the 12-week research study. The child will receive payment in their choice of gift certificates. If you want to stop your participation at any time, you will receive part of the $700 value, based on how far in the study you are. You will receive $75.00 each for baseline and 6-week OGTTs (or 6-week fasting labs) and $100.00 for the 12-week OGTT; $50.00 for the first medication check visit with the study psychiatrist; $175 for the baseline Insulin/Glucose Clamp and $225.00 for the 12-week clamp. If you participate in the 3-month follow-up visit after the 12-week study ends, you will be paid an additional $75.00 in gift certificates and monetary reimbursement for that visit. All compensation will be for time and inconvenience. Gift cards and monetary reimbursement will be available at the next scheduled study visit - they will not be available during the child psychiatrist visits. You will not receive any payment for safety labs.

Because you will be receiving more than $600 in gift certificates, this amount will be considered extra income so you will receive an IRS Tax Form 1099 during tax season from Washington University so you can report it to the IRS.

4. **What are the risks?**
In this study, you will get both routine and research procedures. The overall potential risks of this study are small. All key personnel involved in the design and conduct of the research involving human subjects have received the required education on the protection of human research participants prior to funding of this project. Some of the blood tests could be considered part of the routine diagnostic care of participants at greater risk for developing Type 2 Diabetes, for example, children who are overweight.

Taking part in the study will add the following risks to your care. Research related risks are:

♣ **Blood drawing:**
Likely: The risks of blood drawing and IV insertion include discomfort, bruising, and/or minimal bleeding.

Less Likely: Occasionally during blood drawing procedures, some people experience dizziness or feel faint.

Rare: Very rarely, the site of needle insertion could become irritated or infected. The side effects of the topical anesthesia are very rare. The most common side effects are irritation, redness, itching, or rash. There is also a very small risk of your hand becoming reddened or developing a small blister from warming your hand in the hand-warming box. Side effects associated with topical anesthesia used to numb the area of needle insertion infrequently cause side effects including irritation, redness, itching or rash.

♣ **Interviews or Questionnaires:**
Likely: None

Less Likely: None

Rare: During these questionnaires you may experience minor discomfort when answering some questions. In our experience this discomfort does not happen often, and when it occurs, it does not last long. No major upset has ever happened. All questionnaires are administered by highly trained research staff. Please let the staff know if you feel any discomfort so they may discuss this with you. You may choose not to answer any question that makes you uncomfortable.

♣ **Frequent sample oral glucose tolerance test** (fsOGTT):
Likely: None

Less Likely: None

Rare: there is a small risk of feeling some nausea when drinking the sweet liquid drink. This feeling should pass within a few minutes after drinking the liquid.

♣ **Magnetic resonance imaging (MRI) procedure:**
Likely: None

Less Likely: None

Rare: Having an MRI causes worry or fear for people with claustrophobia (fear of closed-in spaces), as some persons find the small space in the MRI machine confining and may feel uncomfortable. We find that "rehearsing" prior to the procedure helps to ease this. However, if you should feel afraid or unable to continue, you can request the examiner to stop at any time. Magnetic resonance imaging (MRI) may also be harmful for people with certain kinds of metal in their bodies, especially:
-- someone who had metal fragments in the eye
-- someone with electrical, mechanical, or magnetic activated implants, such as pacemakers and hearing implants.

This procedure will not be performed if you have any of these kinds of metal. Therefore, it is important for you to inform study personnel of any metal in your body. This will not affect payment for your participation. There are no other known risks of magnetic resonance imaging scans at this time.

♣ **ECG:**
Likely: None

Less Likely: There is a small chance that you will experience discomfort from the sticky pads temporarily attached to you in order to perform the EKG.

Rare: None

♣ **Dual-energy x-ray absorptiometry:**
Likely: None

Less Likely: This research involves exposure to radiation from the DXA machine for body fat measurements. You may experience discomfort lying on DEXA scan table. This test has low–dose x-ray exposure (much less than a standard x-ray of your chest, technicians do not wear radiation monitors). The amount of radiation participants will receive from the scan is 1.3% of the amount of natural background radiation exposure people in the United States receive each year. The risk from the radiation exposure in this study is too small to be measured. If you would like more information about radiation exposure, we can provide you with a "Radiation Fact Sheet". If you want to know more about radiation exposure, please see the "Radiation Fact Sheet" located in the Guidelines section of the Human Research Protection Office website, at http://hrpo.wustl.edu, or ask the study staff for a copy.

Rare: None

♣ **Delta Trac:**
Likely: None

Less Likely: None

Rare: There are no physical risks associated with the Delta Trac. Wearing the special hood may cause worry or fear for people with claustrophobia (fear of closed-in spaces). We find that "rehearsing" prior to the procedure helps to ease this. However, if you should feel afraid or unable to continue, you can request the examiner stop at any time.

♣ **Insulin/Glucose Clamp:**
Likely: None

Less Likely: None

Rare: There is a small risk of low blood sugar during the insulin infusion, which might lead to nausea, headache or feeling sweaty or shaky. The risks of infusing stable isotope tracers include the possibility of inflammation or infection. However, all solutions are tested for bacterial, molds, viruses, yeasts, and sterility before infusion and are administered under strict sterile conditions. There are no known short- or long-term risks associated with the infusion of the isotopes themselves. The special hood to measure breathing may contribute to some feeling of discomfort such as being too warm and/or facial sweating. It will be removed if you are uncomfortable.

Risk of a breach of confidentiality:
With your written permission, we will obtain medical and hospitalization records from your doctors, results from prior blood, diagnostic, and laboratory tests and other information obtained from interviews or questionnaires related to your medical care. We keep this information in a locked area. The information you give us will be given a code number. A master list linking the code number and your identity will be kept separate from the research data. Only the PI and people helping him will be able to see the list, and all staff involved with this project have been thoroughly trained in the protection of research participants. We will protect your information, but there is a chance somebody might see it.

One potential risk of participating in this study is that confidential information about you may be accidentally disclosed. We will use our best efforts to keep the information about you secure, and we think the risk of accidental disclosure is very small. Please see the *Confidentiality* section of this consent form for more information.

There is the possibility that you will be contacted to see if you are interested in other parts of this study. Being in this part of the study doesn't mean you have to participate in any additional parts. If you are interested in future studies, we would give you a separate consent form to read and sign.

Risks of antipsychotic medications:
There are certain risks and discomforts that may be associated with each medication given in this research study **during the 12 weeks of treatment.** Risks of all medications are listed below, as are ways that we will minimize these risks, but you will only experience risks of the medication treatment group that you are assigned to. These risks include:

Likely Abilify/aripiprazole: Constipation, restlessness, headache, nausea, upset stomach, vomiting, agitation, anxiety, trouble sleeping, sleepiness, lightheadedness, weight gain.

Zyprexa/olanzapine: dizziness, weakness, dry mouth, constipation, upset stomach, sleepiness, accidental injury, trouble sleeping, weight gain, increased appetite, thirst, tremor, depression, shakiness, involuntary movements and, weight gain. Children with borderline abnormal blood lipid levels prior to treatment with olanzapine (cholesterol or triglycerides) may develop abnormal levels while taking this medication.

Risperdal/risperidone: sleepiness, trouble sleeping, agitation, anxiety, stiffness, involuntary movements, headache, upset stomach, runny nose, restlessness, dizziness, extra saliva, constipation, weight gain.

Less Likely

Abilify/aripiprazole: Accidental injury, edema, a non- or pre-diabetes increase in fasting blood glucose (below the level of diabetes), high blood pressure, muscle pain, involuntary movement, tremor, increased salivation, inflamed throat and upper digestive tract, cold and flu symptoms, blurred vision, weight gain, tremor, increased mortality and morbidity (cerebral vascular events, including stroke) in elderly patients with dementia-related psychosis, and adverse changes in blood lipids (cholesterol, triglycerides)., Children with borderline abnormal blood lipid levels (cholesterol, triglycerides) prior to treatment with aripiprazole may develop abnormal levels while taking this medication.

Zyprexa/olanzapine: low blood pressure, a non- or pre-diabetes increase in blood glucose (below the level of diabetes), personality changes (non-aggressive objectionable behavior), restlessness, fever, back pain, chest pain, fast heart beat, high blood pressure, nausea & vomiting, rash, swelling, extremity pain or joint pain, abnormal gait, speech problems, cold and flu symptoms, vision changes, bed wetting, urinary tract infection, increased salivation, memory problems, numbness, confusion, extreme happiness, incoordination, sweating, acne, dry skin, menstrual period changes, vaginal infection, stiffness, dental pain, intestinal gas, joint or bone pain, twitching, abnormal dreams, delusions, emotional changes, eye infection, adverse changes in blood lipids (cholesterol, triglycerides).

Risperdal/risperidone : nausea, vomiting, abdominal pain, a non- or pre-diabetes increase in blood glucose (below the level of diabetes), toothache, coughing, stuffy nose, sore throat, shortness of breath, back pain, chest pain, fever, skin problems, upper respiratory infections, abnormal vision, joint pain, fast heart beat, shakiness, decreased sensation, increased energy, dry mouth, fatigue, injury, coughing, acne, itching, muscle pain, generalized pain, weight increase, high blood pressure, low blood pressure, adverse changes in blood lipids (cholesterol, triglycerides). Children with borderline abnormal blood lipid levels (cholesterol, triglycerides) prior to treatment with risperidone may develop abnormal levels while taking this medication.

Rare

Abilify/aripiprazole: pain or tightness (including throat, abdominal, chest, pelvis, extremity, back pain, joint, muscle, jaw, neck or tongue), diarrhea, dry mouth, low appetite, behavioral & emotional changes including psychosis, infection, rash, menstrual periods changes, Neuroleptic Malignant Syndrome (fever, stiffness or involuntary movements, unstable blood pressure), fever, tiredness, migraine, chills, sensitivity to light, bloating, enlarged abdomen, head heaviness, aspiration or food or stomach reflux, heat stroke, enlarged heart, heart attack, heart failure, fast or slow heart beat and/or changes in heart rhythm, pounding heart beat felt by patient, low blood pressure, bleeding, blood clots, pale skin, sudden drop in blood pressure (e.g. when going from sitting or lying down to a standing position), inflamed blood vessels, heart-lung failure, increased appetite, difficulty swallowing, tooth /gums infection or cavities, stomach or intestinal bleeding, rectal bleeding or hemorrhoids, stomach or intestinal gas, esophagus, intestinal or stomach inflammation or bleeding, inflamed gall bladder or gall-stones, ulcers, severe constipation or obstruction, hepatitis, blood in stool, enlarged liver, inflamed pancreas, thyroid changes, bruising of skin, changes in blood tests (various types of anemias or changes in white blood cells), weight loss, changes in metabolic blood tests (sodium, potassium, creatinine, bilirubin, albumin, alkaline phosphatase BUN, SGPT, SGOT, uric acid lactic acid), dehydration, edema, high or low blood sugar, high cholesterol, diabetes mellitus, high triglycerides, thirst, pale or bluish skin, gout, muscle paralysis, muscle tone abnormality, weakness or spasm, bursitis, inflamed tendons,

abnormal dream, emotional ups and downs, twitch, rigidity, impaired concentration, dilated blood vessels and arteries, numbness, extremity tremor, hypersensitive skin, dizziness, slowed movement or response, lack of interest, panic attack, unsteady gait, visual hallucination, stroke, impaired memory, hyperactivity, slowed reflexes, restless leg, pain or numbness in nerves, increased reflexes, loss of voluntary movement, slowed thinking, blunted affect, extreme happiness, inability to rotate eyes, obsessive thought, decreased muscle tone or reflexes, bleeding in brain, sinus infection, difficult breathing or shortness of breath, pneumonia, asthma, bloody nose, hiccup, temporary voice loss from inflammation, aspiration pneumonia, decreased oxygen to lungs, respiratory failure, dry nasal passages, bloody sputum, skin ulcer, sweating dry skin, acne, skin discoloration, hair loss, dandruff, dermatitis, eye infection, ear pain, dry eye, eye pain, ringing in ears, cataract, ear infection, altered taste, inflammation of eyelid, eye bleeding, deafness, double vision, frequent blinking, lazy eye, poor vision in one eye, fear of light, bed wetting, difficulty or abnormal conditions of urination, vaginal bleeding, kidney failure, enlarged breasts, kidney stones, breast pain, female lactation, pain or tenderness in penis, severe allergic reaction (difficulty breathing, swelling and/or rash), diabetes mellitus, somnolence prolonged drowsiness or sleepiness, extrapyramidal movements (such as muscle rigidity, difficulty walking), orthostatic hypotension, tremor, fatigue, akathisia (muscle restlessness, blurred vision), producing more than the usual amount of salivary hypersecretion, increased risk of suicidal thoughts, potential for cognitive and motor impairment, difficulty with body temperature regulation, and dysphagia (difficulty swallowing), dizziness, and leucopenia, neutropenia, and/or agranulocytosis (abnormalities in your white blood cell count), especially in people with a history of a significant low white blood cell count. Seizure activity is a very rare risk with uncertain relationship to this medication.

Zyprexa/olanzapine: abdomen enlarged, chills, face edema, intentional injury, tiredness, infection, neck pain, pelvic pain, sensitivity to light, fever, hangover effect, cardiac (heart beat) changes, stroke, congestive heart failure, heart attack, hemorrhage, migraine, pallor changes in blood vessels and arteries, inflammation, blood clots, difficulty swallowing, inflammation of the esophagus, severe constipation, fecal incontinence, stomach pain or discomfort, inflamed gums, hepatitis, blood in stool, mouth ulceration, tooth abscess or caries, stomach gas, esophageal or stomach ulcer, intestinal obstruction, liver changes, high blood sugar, diabetes mellitus, diabetic acidosis, ketosis or coma, goiter, changes blood count, pale or bluish skin cast, acidosis, alkaline phosphatase blood test increased, bilirubinemia, dehydration, high cholesterol, high triglycerides, gout, high sodium, potassium, bilirubin, uric acid and/or protein in the blood, water intoxication, leg cramps, abnormal changes in muscle tissue, brittle bones, voluntary and involuntary movement disorders, antisocial behavior, ataxia, central nervous system stimulation, rigidity, delirium, dementia, speech and language disturbance, less sensitive or reactive to stimulation, slowed movement, loss of muscle tone or coordination, obsessive compulsive symptoms, extreme unfounded fears, physical symptoms of anxiety, alcohol, drug or tobacco misuse, stuttering, withdrawal syndrome, coma, any disorder of the brain, nerve pain or numbness, eyelid twitching, paralysis, bleeding in the brain, periods of difficult, decreased or absent breathing, asthma, nose bleed, blood in sputum, sweating, hair loss, dry skin, dandruff, skin discoloration, skin ulcer, increased hair growth, difficulty adjusting to a situation or experience, cataract, deafness, double vision, dry eyes, ear pain, eye hemorrhage, various eye disorders breast pain, difficult or painful urination, female lactation, changes in urine or the process of urination, uterine fibroids enlarged, extreme vaginal bleeding, breast enlargement or inflammation, allergic reaction (can be severe with difficulty breathing, swelling, and/or rash), inflamed pancreas, pain & tenderness of penis, severe skeletal muscle disease potentially causing death, and blood clotting events. Seizure activity is a very rare risk with uncertain relationship to this medication.

Risperdal/risperidone : increased dream activity, nervousness, trouble concentrating, depression, lack of interest, catatonic reaction, extreme happiness, increased libido, trouble remembering, sudden mood changes, nightmares, confusion, yawning, longer sleeping time, speech problems, spinning sensation, excess sedation, numbness or tingling, allergic reaction, leg cramps, stiff neck, coma, migraine, reflex changes, loss of appetite, reduced salivation, intestinal gas, diarrhea, increased appetite, swelling, flu-like symptoms, enlarged abdomen, skin irritations, fast breathing, pneumonia, asthma, trouble breathing, skin reaction to sunlight, increased sweating, acne, decreased sweating, hair loss, blocked veins or arteries in the heart, heart attack, eye pain, itchy eyes, low blood sodium or potassium or protein levels, blood chemical changes, increased thirst, weight decrease, diabetes mellitus (high blood sugar), anemia (low iron), dehydration, hyperphosphatemia (high phosphate levels in the body), hypertriglyceridemia (high triglycerides in the blood), hyperuricemia (high uric acid in the body), hypoglycemia (low blood sugar), increased urination/increased thirst, bed-wetting, hematuria (blood in urine), problems urinating, problems with the kidneys, joint pain, arthritis, missed menstrual periods, breast pain, bleeding, liver failure, hepatitis (liver inflammation), decreased blood clotting , blood clots, ringing in the ears, decreased hearing, ear problems, hormones problems, high prolactin levels in the blood, problems regulating body temperature, bitter taste, a change in the time it takes for the heart to conduct normal electrical signals (QTc prolongation) has also been associated with olanzapine use. Neuroleptic Malignant Syndrome (fever, stiffness or involuntary movements, unstable blood pressure). Seizure activity is a very rare risk with uncertain relationship to this medication.

It is important to note that these side effects do not occur in everyone. We expect that you, your parents/guardians, and your doctor will be going over the side effects that you might watch for while taking any of these medications. The possibility of a suicide attempt is inherent in some psychiatric disorders, and close supervision of high-risk persons should accompany drug therapy.

Participants will be followed closely and monitored for side effects of medications and tests. Withdrawal of the study medication and/or treatment of medication side effects will be provided as indicated. Participants will participate in medication check-ups or telephone calls at least once per week and will be asked to report any concerns or adverse events during these times. To be sure that you/your child can always communicate with the research team, families will be provided with a 24-hour telephone number of a research clinician who will answer any questions and speak with any community physicians or dentists who the participants visit during the study. All families will also be instructed to tell any doctors or dentists they encounter that their children/adolescents are on the study medications.

The risk of your side effects will be minimized, or reduced should they occur, through the following steps:

1. Sometimes Abilify (aripiprazole), Zyprexa,(olanzapine) or Risperdal (risperidone) can cause nausea or vomiting. To prevent the nausea, it is best for you to have something to eat in the morning before the a.m. dose.

2. Participants will be monitored for neuromuscular side effects at each weekly visit. Neuromuscular side effects include developing a walking style that seems to be shuffling along rather than lifting one's legs, stiffness in the movements of wrist and elbow joints, shaking of the hands when the hands are not busy and a loss of facial expression. Also, children/adolescents may also develop a problem that looks as if they are restless (called akathisia). These side effects can sometimes be reduced by lowering the dose of medication

or adding an appropriate medication to treat the side effect. Participants will also be monitored for tardive dyskinesia (unusual movements of the mouth area, cheek, tongue or other parts of the body such as the shoulders and extremities). Study medications will be discontinued if tardive dyskinesia occurs.

3. Participants will be regularly monitored for changes in blood triglycerides or blood glucose. Problems with the way the body handles glucose (sugar) and lipids (triglycerides) can occur with Abilify, (aripiprazole), Zyprexa (olanzapine), or Risperdal (risperidone) potentially resulting in diabetes or a condition called the metabolic syndrome. These blood glucose and lipid problems can occur without any symptoms. That is why blood glucose and lipids are monitored in this study. If your fasting blood glucose becomes elevated at any point in the study to the level that is called diabetes, you will be withdrawn from the study. If you blood triglycerides become elevated to a serious degree that can increase the risk of an inflamed pancreas, then you will be withdrawn from the study. If your blood glucose or lipids become elevated during the study below the levels noted above, we will increase the frequency with which you blood is monitored for any further changes.

4. If your body weight increases 10% or more from when you first began taking the study medication, you will be monitored on a weekly or biweekly basis for other events that may occur in the setting of weight gain, especially hyperglycemia and hyperlipidemia.

During this study, your child/adolescent must avoid over-the-counter drugs and herbal supplements as these may interfere with treatment results.

Participation in this study may cause all, some or none of the side effects listed above which, if severe, may cause death.

As with any research procedure, unforeseen problems or side effects can occur. You will be told of any changes in the way the study will be done and of any newly identified risks to which you may be exposed.The investigators are willing to discuss any questions you might have about the severity, frequency, and duration of these risks and discomforts.

Data and Safety Monitoring Committee
An independent group of medical and research professionals, called a Data and Safety Monitoring Committee (DSMC), has been established to monitor the data collected from this study and look for ways to continually improve the safety of all the procedures and medications administered as part of this project. The PI and study staff are responsible for sending regular reports to the DSMC detailing our findings, particularly highlighting any adverse or serious adverse events that occur. Having a DSMC makes sure that someone outside of the project knows about any problems and can provide an objective opinion about what needs to be done to fix or minimize them. It is the job of the DSMC to maintain the highest level of safety for our participants.

Study Discontinuation
When you discontinue the study early due to an adverse event, or on schedule due to study completion, we will carefully work with you and your treating psychiatrist to evaluate the risks versus the benefits of ongoing treatment with the medication you were assigned to. At that time we can discuss the advantages and disadvantages of staying on that medication, switching to a different antipsychotic medication, or discontinuing antipsychotic medication. In all cases we will

provide individualized consultation with parents and treating psychiatrist and/or pediatricians to provide the safest plan to continue the ongoing individualized therapy.

Breast Feeding

You must tell the study doctor if you are breast-feeding.

Certificate of Confidentiality

One potential risk of participating in this study is that confidential information about you may be accidentally disclosed. We will use our best efforts to keep the information about you secure, and we think the risk of accidental disclosure is very small. Please see the *Confidentiality* (Item 7) section of this consent form for more information.

Coded Data

The information you give us will be given a code number. A master list linking the code number and your identity will be kept separate from the research data. Only the PI and people helping him/her will be able to see the list. We will protect your information, but there is a chance somebody might see it.

Pregnancy/Childbearing Potential

If you are a woman of childbearing potential, please read and sign below.

Some parts of this study might cause physical or mental problems in an unborn baby. You must tell the doctor immediately if there is any chance you are pregnant. You must also tell the doctor if your birth control method fails while you are on the study.

To take part in this study, you must have a pregnancy test before starting the study. You must use an acceptable method of birth control and must not become pregnant.

Please discuss with your research physician how long you need to wait before becoming pregnant. By signing below, you agree to follow these rules.

_____

Signature Date

What happens if you are injured because you took part in this study?

Washington University investigators and staff will try to reduce, control, and treat any complications from this research. If you feel you are injured because of the study, please contact the investigator (John Newcomer MD at 314/362-5939) and/or the Human Research Protection Office at (314) 633-7400 or 1-(800)-438-0445.

Decisions about payment for medical treatment for injuries relating to your participation in research will be made by Washington University. If you need to seek medical care for a research-related injury, please notify the investigator as soon as possible.

5. **Are there benefits to taking part in the study?**
These medicines may improve your symptoms with aggressive behavior or conduct disorder. In addition, you/your child will be checked for serious medical conditions that may not show any symptoms, such as high blood pressure or diabetes. Finding these conditions may improve your medical care. This study will help doctors to understand how antipsychotic medications may affect diabetes risk and ways to address the risk of diabetes in children with conduct disorder, aggression or other behavior problems.

6. **What other options are there?**
Taking part in this research study is voluntary. You may choose not to take part in this research study or you may withdraw your consent at any time. You may withdraw by telling the study team you are no longer interested in participating in the study or you may send in a withdrawal letter. A sample withdrawal letter can be found at http://hrpo.wustl.edu under Information for Research Participants. Your choice will not at any time affect the commitment of your health care providers to administer care. There will be no penalty or loss of benefits to which you are otherwise entitled.

Other than not taking part in the research, you may choose to have your doctor write a prescription for you if he/she feels it is in your best interest to receive this drug outside of the study. The study drugs, olanzapine, risperidone and aripiprazole are available to you even if you do not participate in this study. Please discuss all alternatives with your doctor including psychotherapy and behavior management.

7. **What about privacy and confidentiality?**
We will do everything we can to protect your privacy.

Providing your social security number is optional and you can fully participate in the study whether you disclose it or not. If you choose to provide your social security number, we will use your social security number to locate you in the future if we are unable to locate you at your home address, and to search vital records. We will not share your social security number or leave it accessible to theft.

Protected Health Information (PHI) is health information that identifies you. PHI is protected by federal law under HIPAA (the Health Insurance Portability and Accountability Act). To take part in this research, you must give the research team permission to use and disclose (share) your PHI for the study explained in this consent form.

In addition to health information that may be created by the study, the research team may access the following sources of your health information to conduct the study: hospital/physician medical records; lab, pathology and/or radiology results; information derived from biological samples (including blood); interviews/questionnaires; mental health records; physiologic imaging.

A Certificate of Confidentiality has been obtained from the Department of Health and Human Services. This will help further protect information that may identify you. The Certificate prevents the investigator from being forced to disclose identifying information for use in court. The investigator may not even be forced by court subpoena. Courts that may be prevented from getting your information include any federal, state, local civil, criminal, administrative, legislative, or other court proceeding.

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. The investigator may not withhold information if you give your insurer or employer permission to receive information about your participation in this research. This means that you and your family must also actively protect your own privacy.

The Certificate does not prevent the researchers from taking steps, including reporting to authorities, to prevent serious harm to yourself or others. Such disclosures will be made as described below.

The research team may share your information with:

- The Department of Health and Human Services (DHHS) to complete federal responsibilities for audit or evaluation of this study.
- Public health agencies to complete public health reporting requirements
- Hospital or University representatives, to complete Hospital or University responsibilities for oversight of this study.
- Your primary care physician if a medical condition that needs urgent attention is discovered
- Appropriate authorities to the extent necessary to prevent serious harm to yourself or others.

Once your health information is shared with someone outside of the research team, it may no longer be protected by HIPAA.

The research team will only use and share your information as talked about in this form. When possible, the research team will make sure information cannot be linked to you (de-identified). Once information is de-identified, it may be used and shared for other purposes not discussed in this consent form.

If you have questions or concerns about your privacy and the use of your PHI, please contact the University's Privacy Officer, at 866-747-4975.

This study is sponsored by National Institute of Mental Health (NIMH). Representatives of the sponsor will have access to your research and/or medical records for monitoring the study. The research team will also send study results to the sponsor. Information sent to the sponsor will be summarized and coded so that it cannot be associated with your PHI. The sponsor is not required to abide by the HIPAA regulations, but agrees to protect the confidentiality of your information. The sponsor reviews the study summary to verify that the research is progressing toward stated goals.

You will always have access to your medical record. Some of the individual results from tests to be performed during this research study might be of interest to you or your primary care physician. At your request, the researchers will share the medical information gained from this study with you and your referring and/or primary care doctors. If we become aware of any important health information during the course of your participation in this study, we may be obligated/required to share this information with your treatment team. You will not have access to your research record.

If you decide not to sign this form, it will not affect
-your treatment or the care given by your health provider.
-your insurance payment or enrollment in any health plans.
-any benefits to which you are entitled.

However, it will not be possible for you to take part in the study.

If you sign this form:

- You authorize the use of your PHI for this research
  - Your signature and this form will not expire as long as you wish to participate.
  - You may later change your mind and not let the research team use or share your information (you may revoke your authorization).
    - To revoke your authorization, complete the withdrawal letter, found in the Participant section of the Human Research Protection Office website at http://hrpo.wustl.edu (or use the direct link: http://hrpohome.wustl.edu/participants/WithdrawalTemplate.rtf) or you may request that the Investigator send you a copy of the letter.
      - **If you revoke your authorization:**
    - The research team may only use and share information already collected for the study.
      - Your information may still be used and shared if necessary for safety reasons.
      - You will not be allowed to continue to participate in the study.

Please specify any contact restrictions you want to request for this study only.
(Example – no calls at home, no messages left for you, no e-mails, etc.)

_____

_____

Notice of Privacy Practices

The Notice of Privacy Practices is a separate document. It describes the procedures used by WU to protect
your information. If you have not already received the Notice of Privacy Practices, the research team will make one available to you.

_____ I have been offered a copy of the Notice of Privacy Practices.
Initial

8. Whom do I call if I have questions or problems?

Please contact the researcher listed below to:

- Obtain more information about the study
- Ask a question about the study procedures or treatments
- Report an illness, injury, or other problem (you may also need to tell your regular doctors)
- Leave the study before it is finished
- Express a concern about the study

Principal Investigator:	John Newcomer MD at 314/362-5939
Research Coordinators:	Martha Hessler at 314/362-2423 or Julie Schweiger at 314/362-3153
Mailing Address:	660 S. Euclid Ave., Campus Box 8134; St. Louis, MO 63110

If you wish to talk to someone else, or have questions or concerns about your rights as a research participant, call Washington University's Human Research Protection Office (WU HRPO) at (314) 633-7400, or 1-(800)-438-0445.

For questions about the Clinical Research Unit (CRU) or Pediatric Clinical Research Unit (PCRU) please call Michelle Jenkerson, Research Participant Advocate at 314-362-5626.

Request Permission for Future Contact

May we contact you for future undetermined studies conducted by Dr. Newcomer, Haupt, and Nicol? If yes, we will need to look at your Protected Health Information (PHI) to check for study eligibility.	___ Yes	___ No
May other WU physicians conducting research contact you? If yes, your PHI will be shared with other WU physicians.	___ Yes	___ No

Taking part in future studies is optional. You can ask us at any time to take you off our contact list.

9. The Principal Investigator (PI) may withdraw you from the study without your consent if considered appropriate (i.e. certain medical conditions, use of illegal drugs). It may be in your best interest to allow follow-up outside the study. The PI will share any new information that could change how you feel about continuing in the study.

10. You will be given a signed copy of this consent form for your records.

Please mark all that apply. This section is optional.
[] Not Hispanic or Latino [] Hispanic or Latino [] Unknown
[] Asian [] Black or African-American [] Caucasian [Native American or Alaskan Native [] Native Hawaiian or Pacific Islander [] Other [] Unknown
The Office of Management and Budget has declared that Hispanic/Latino is an ethnicity. National Institutes of Health, in an effort to ensure diversity in research, requests that you report your ethnicity. (http://grants.nih.gov/grants/funding/women_min/women_min.htm)

SIGNATURES FOR ADULT PARTICIPANTS

Research Participant:
I have read this consent form and have been given the chance to ask questions. I agree to participate in this research described above, titled: **Metabolic Effects of Antipsychotics in Children (Treatment Study, ≥18 y.o.).**

HRPO does not require participants to re-sign the consent form unless a change is made; the investigator, however, may choose to re-consent participants at any time.

Signature: _____

Printed Name: _____ Date of Signature: _____

Principal Investigator (or Designee):

I have given this research participant information about this study that I believe is accurate and complete. The participant has indicated that he or she understands the nature of the study and the risks and benefits of participating.

Signature: _____ Title: _____

Printed Name: _____ Date of Signature: _____

This form is valid only with the Human Research Protection Office's current stamp of approval.

WASHINGTON UNIVERSITY MEDICAL CENTER HSC
Protocol Approved SEP 30 2010
Approval Terminates SEP 29 2011
Federal regulations permit no grace period
Date Released For Subject Accrual SEP 30 2010

INFORMED CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Participant's Name _____ HRPO # **05-0264**

Principal Investigator **Newcomer, John W., MD** PI's Phone Number **(314) 362-5939**
Last First Credentials

Title of Project: **Metabolic Effects of Antipsychotics in Children (Genetic Consent for Adult Parent or Guardian)**

You may be eligible to take part in a research study. This form gives you important information about the study. It describes the purpose of the study, and the risks and possible benefits of participating in the study.

Please take the time to review this information carefully. After you have finished, you should talk to the researchers about the study and ask them any questions you have. You may also wish to talk to others (for example, your friends, family, or other doctors) about your participation in this study. If you decide to take part in the study, you will be asked to sign this form. Before you sign this form, be sure you understand what the study is about, including the risks and possible benefits to you.

You are invited to take part in a research study by Dr. Newcomer and/or colleagues.

Please ask for an explanation of any words you do not understand.

Washington University will keep a copy of this consent form.

Being in a research study does not take the place of routine physical exams or visits to your own doctor and should not be relied on to diagnose or treat medical problems.

1. Why is this study being done?

Genetic studies compare genes from people who have illnesses to people who are not ill. Being part of a genetic study does not mean that you or your relatives have a genetic illness.

You are invited to participate in a research study conducted by Dr. Newcomer to find genes that may be linked with weight gain in children who are receiving certain medications given for emotional disorders. To best study this area, it is helpful to compare genes from families of children who have either gained weight or not gained weight and /or who have had changes in their blood lipids or blood sugar while taking various medications.

We are trying to learn what genes affect your child's behavior.
We hope to find new tests or treatments to help us understand conditions such as conduct disorder.

Your child can take part in Dr. Newcomer's treatment study even if you and/or your child decide not to participate in this genetic study.

2. **What am I being asked to do?** All procedures described below are research related, not standard-of-care.

When you come in for your child's Study Visit 2 (the Oral Glucose Tolerance Tests (OGTT)), you will have 10 ml (about two teaspoons of blood) obtained from a vein in your hand or wrist. Your name will not be on the blood sample. The blood sample will be identified (coded) with a number. The blood is for research only and will be stored in a freezer until the genetic tests are conducted (no longer than 20 years). These genetic tests may be conducted at other institutions, but the blood samples will only be identified by the code number. Other investigators will not receive your name, social security number or other identifying information.

How long will I be in the study?
Your blood for the genetic test will be drawn during one study day. The blood will be stored no longer than 20 years.

You and your physician will not get any study results. We will contact you if we learn you have a life-threatening medical disorder that current treatment can stop or lessen.

How many other participants will be in the study?
There will be approximately 325 participants invited to participate in the treatment study. Each participant's parent(s) or guardian(s) will be invited to participate in providing a blood sample for genetic testing.

Financial Disclosure of Interest
The study sponsor is paying Washington University to conduct this study. The amount of payment is enough to cover the study doctor's and/or institution's expenses to perform the study.

Future Use of Blood, Tissue, or Data
May I share your tissue and data? It will not have your name on it, only a code number, so nobody will know it was yours. I would like to share it with other investigators doing research in similar fields. These investigators may be at Washington University or at other research centers.
_____ Yes ____No

3. **What are the costs?**
There are no costs to you for drawing or testing the blood sample.
You will be paid $40 for your time and inconvenience for your blood draw.

4. **What Are The Risks?**
There are certain risks and discomforts that may be associated with this research. They include:

- **Blood drawing:**

Likely: The risks of blood drawing and IV insertion include discomfort, bruising, and/or minimal bleeding.

Less Likely: Occasionally during blood drawing procedures, some people experience dizziness or feel faint.

Rare: Very rarely, the site of needle insertion could become irritated or infected. The side effects of the topical anesthesia are very rare. The most common side effects are irritation, redness, itching, or rash. There is also a very small risk of your hand becoming reddened or developing a small blister from warming your hand in the hand-warming box. Side effects associated with topical anesthesia used to numb the area of needle insertion infrequently cause side effects including irritation, redness, itching or rash.

Certain genetic research may reveal that you are a carrier of a genetic disorder. This could mean that you or members of your extended family may have an increased likelihood of developing the disorder, or may be carriers. As pointed out in the material on Certificate of Confidentiality, no information about your family will be released unless you explicitly request us to do this. We need to caution you, however, that if you request that we release this information it may have the following effects on your future access to insurance for medical costs or to employability. If your participation in a genetic study becomes known outside of the research (for example, if your participation were to be noted in your medical record) you (and family members) may be unable to obtain health, life, or disability insurance. You might also be refused employment or be terminated from your current employment. This could happen if **you** choose to discuss your participation with your doctor without requesting that the information be kept out of your medical record. Inclusion of genetic (or any other) information in your medical record may allow insurance providers to access such information. Again, the Certificate of Confidentiality will protect the research records unless you request their release. It is Washington University policy that results of genetic testing, including paternity, are not given to any individual participants. Your blood samples will be coded with an identification number. The master list that links your name and the code number will be kept separate from the research materials. Every effort will be made to protect your research data; there is , however, always the possibility of a breach of confidentiality.

In the very unlikely event that genetic testing reveals that an individual has a treatable illness, the results of this will be given to parental guardians of children/adolescents or to adults about themselves. If you prefer that these results be given to a physician of your choice, before they are given to you, please let Dr. Newcomer know the name and telephone number of this physician at the time that she (or a designee) informs you of a result.

You will not hear from us unless we find information that may be clinically relevant.

What happens if you are injured because you took part in this study?
Washington University investigators and staff will try to reduce, control, and treat any complications from this research. If you feel you are injured because of the study, please contact the investigator, Dr. Newcomer, at (314) 362-5939 and/or the Human Research Protection Office at (314) 633-7400 or 1-(800)-438-0445.

Decisions about payment for medical treatment for injuries relating to your participation in research will be made by Washington University. If you need to seek medical care for a research-related injury, please notify the investigator as soon as possible.

- **Certificate of Confidentiality** One potential risk of participating in this study is that confidential information about you may be accidentally disclosed. We will use our best efforts to keep the information about you secure, and we think the risk of accidental disclosure is very small. Please see the *Confidentiality* (Item 7) section of this consent form for more information.

❖ **Coded Data**
The information you give us will be given a code number. A master list linking the code number and your identity will be kept separate from the research data. Only the PI and people helping him/her will be able to see the list. We will protect your information, but there is a chance somebody might see it.

5. Are there benefits to taking part in the study?
Taking part in this study will not benefit you directly. It may benefit others with your child's condition. You will not receive any medical or financial benefit from participating in this research. By agreeing to participate, you authorize the use of your blood for research that may benefit others. The study of your blood may one day result in new tests or treatments, or may help to prevent or cure diseases. In the future, medical or scientific products may result from research with you or your child's blood. Should this occur, you will not receive financial compensation related to those medical or scientific products. Scientific knowledge advances slowly, but it may greatly benefit future generations. Researchers at Washington University consider you an important partner in the battle against disease and are grateful to those who choose to participate.

6. What other options are there?
Taking part in this research study is voluntary. You may choose not to take part in this research study or you may withdraw your consent at any time. You may withdraw by telling the study team you are no longer interested in participating in the study or you may send in a withdrawal letter. A sample withdrawal letter can be found at http://hrpo.wustl.edu under Information for Research Participants. Your choice will not at any time affect the commitment of your health care providers to administer care. There will be no penalty or loss of benefits to which you are otherwise entitled.

Your child may choose to participate in the treatment study and you and your child may choose not to participate in the genetic study. Your choice will not at any time affect the commitment of your health care providers to administer care. There will be no penalty or loss of benefits to which you are otherwise entitled. Other than not taking part in the research, you may: your child may: participate in Dr. Newcomer's treatment study without participating in the genetic study described in this consent. If you choose to participate in this genetic study and later change your mind, the blood can be destroyed upon request. To withdraw your consent, please call Dr. Newcomer at (314) 362-5939.

7. What about privacy and confidentiality?
We will do everything we can to protect your privacy.

Notice of Privacy Practices –

The Notice of Privacy Practices is a separate document. It describes the procedures used by WU to protect your information. If you have not already received the Notice of Privacy Practices, the research team will make one available to you.

_____ I have been offered a copy of the Notice of Privacy Practices.
Initial

Protected Health Information (PHI) is health information that identifies you. PHI is protected by federal law under HIPAA (the Health Insurance Portability and Accountability Act). To take part in this research, you must give the research team permission to use and disclose (share) your PHI for the study explained in this consent form.

In addition to health information that may be created by the study, the research team may access the following sources of your health information to conduct the study: hospital/physician medical records; lab, pathology and/or radiology results; information derived from biological samples (including blood); interviews/questionnaires; mental health records; physiologic imaging.

A Certificate of Confidentiality has been obtained from the Department of Health and Human Services. This will help further protect information that may identify you. The Certificate prevents the investigator from being forced to disclose identifying information for use in court. The investigator may not even be forced by court subpoena. Courts that may be prevented from getting your information include any federal, state, local civil, criminal, administrative, legislative, or other court proceeding.

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. The investigator may not withhold information if you give your insurer or employer permission to receive information about your participation in this research. This means that you and your family must also actively protect your own privacy.

The Certificate does not prevent the researchers from taking steps, including reporting to authorities, to prevent serious harm to yourself or others. Such disclosures will be made as described below.

The research team may share your information with:

- The Department of Health and Human Services (DHHS) (including the Office for Human Research Protection or the Food and Drug Administration) to complete federal responsibilities for audit or evaluation of this study.
- Public health agencies to complete public health reporting requirements
- Hospital or University representatives, to complete Hospital or University responsibilities for oversight of this study.
- Your primary care physician if a medical condition that needs urgent attention is discovered
- Appropriate authorities to the extent necessary to prevent serious harm to yourself or others.

Once your health information is shared with someone outside of the research team, it may no longer be protected by HIPAA.

The research team will only use and share your information as talked about in this form. When possible, the research team will make sure information cannot be linked to you (de-identified). Once information is de-identified, it may be used and shared for other purposes not discussed in this consent form. If you have questions or concerns about your privacy and the use of your PHI, please contact the University's Privacy Officer at 866-747-4975.

This study is sponsored by the National Institute of Mental Health (NIMH). Representatives of the sponsor will have access to your research and/or medical records for monitoring the study. The research team will also send study results to the sponsor. Information sent to the sponsor will be summarized and coded so that it cannot be associated with your PHI. The sponsor is not required to abide by the HIPAA regulations, but agrees to protect the confidentiality of your information. The sponsor reviews the study summary to verify that the research is progressing toward stated goals.

You will always have access to your child's medical record. Some of the individual results from tests to be performed during this research study might be of interest to you or your primary care physician. At your request, the researchers will share the medical information gained from this study with you and your child's referring and/or primary care doctors. If we become aware of any important health information during the course of your participation in this study, we may be obligated/required to share this information with your treatment team. You will not have access to your research record.

If you decide not to sign this form, it will not affect

- your treatment or the care given by your health provider.
- your insurance payment or enrollment in any health plans.
- any benefits to which you are entitled.

However, it will not be possible for you to take part in the study.

If you sign this form:

- You authorize the use of your PHI for this research
- Your signature and this form will not expire as long as you wish to participate.
- You may later change your mind and not let the research team use or share your information (you may revoke your authorization).
    - To revoke your authorization, complete the withdrawal letter, found in the Participant section of the Human Research Protection Office website at http://hrpo.wustl.edu (or use the direct link: http://hrpohome.wustl.edu/participants/WithdrawalTemplate.rtf) or you may request that the Investigator send you a copy of the letter.
        - **If you revoke your authorization:**
            - The research team may only use and share information already collected for the study.
            - Your information may still be used and shared if necessary for safety reasons.
            - You will not be allowed to continue to participate in the study.

Please specify any contact restrictions you want to request for this study only.
(Example – no calls at home, no messages left for you, no –emails, etc.)

_____

_____

8. **Whom do I call if I have questions or problems?**
Please contact the researcher listed below to:
- Obtain more information about the study
- Ask a question about the study procedures or treatments
- Report an illness, injury, or other problem (you may also need to tell your regular doctors)
- Leave the study before it is finished
- Express a concern about the study

Principal Investigator:	John Newcomer MD
Study Coordinator:	Martha Hessler
Mailing Address:	660 S. Euclid Ave., CB 8134; St. Louis, MO 63110
Telephone:	314-362-2423 (Ms. Hessler) or 314-362-5939 (Dr. Newcomer)

❖ If you wish to talk to someone else, or have questions or concerns about your rights as a research participant, call Washington University's Human Research Protection Office (WU HRPO) at (314) 633-7400, or 1-(800)-438-0445.

For questions about the Center for Applied Research Sciences, (Clinical Research Unit (CRU), Pediatric Clinical Research Unit (PCRU), Clinical Trials Unit (CTU), please call Michelle Jenkerson, Research Participant Advocate at 314-362-5626.

❖ **Request Permission for Future Contact**

1. May we contact you for future undetermined studies conducted by Drs. Newcomer, Haupt and Nicol? If yes, we will need to look at your Protected Health Information (PHI) to check for study eligibility.	___ Yes	___ No
2. May other WU physicians conducting contact you? If yes, your PHI will be shared with other WU physicians.	___ Yes	___ No

Taking part in future studies is optional. You can ask us at any time to take you off our contact list.

9. The Principal Investigator (PI) may withdraw you from the study without your consent if considered appropriate. It may be in your best interest to allow follow-up outside the study. For example, if your child withdraws consent from the treatment study, your genetic blood sample would no longer be needed for this genetic study. The PI will share any new information that could change how you feel about continuing in the study.

10. You will be given a signed copy of this consent form for your records.

SIGNATURES FOR ADULT PARTICIPANTS

Research Participant:
I have read this consent form and have been given the chance to ask questions. I agree to participate in this research described above, titled: "Metabolic Effects of Antipsychotics in Children (Genetic Consent Adult Parent or Guardian)".

HRPO does not require participants to re-sign the consent form unless a change is made: the investigator, however, may choose to re-consent participants at any time.

Signature: _____

Printed Name: _____ Date of Signature: _____

Principal Investigator (or Designee):

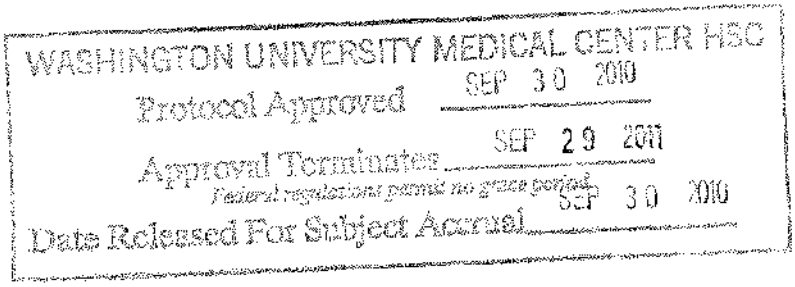
I have given this research participant information about this study that I believe is accurate and complete. The participant has indicated that he or she understands the nature of the study and the risks and benefits of participating.

Signature: _____ Title: _____

Printed Name: _____ Date of Signature: _____

Please mark all that apply. This section is optional.
[] Not Hispanic or Latino [] Hispanic or Latino [] Unknown
[] Asian [] Black or African-American [] Caucasian [] Native American or Alaskan Native [] Native Hawaiian or Pacific Islander
[] Other [] Unknown
The Office of Management and Budget has declared that Hispanic/Latino is an ethnicity. National Institutes of Health, in an effort to ensure diversity in research, requests that you report your ethnicity. (http://grants.nih.gov/grants/funding/women_min/women_min.htm)

This form is valid only if the Human Research Protection Office's current stamp of approval is shown below.



INFORMED CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Participant's Name _____ HRPO # **05-0264**

Principal Investigator **Newcomer, John W., MD** PI's Phone Number **(314) 362-5939**
Last First Credentials

Title of Project: **Metabolic Effects of Antipsychotics in Children (Genetic Consent for Children and Adolescents)**

In this consent form, "you" refers to the child or adolescent participating in this study.

You may be eligible to take part in a research study. This form gives you important information about the study. It describes the purpose of the study, and the risks and possible benefits of participating in the study.

Please take the time to review this information carefully. After you have finished, you should talk to the researchers about the study and ask them any questions you have. You may also wish to talk to others (for example, your friends, family, or other doctors) about your participation in this study. If you decide to take part in the study, you will be asked to sign this form. Before you sign this form, be sure you understand what the study is about, including the risks and possible benefits to you.

You are invited to take part in a research study by Dr. Newcomer and/or colleagues.

Please ask for an explanation of any words you do not understand.

Washington University will keep a copy of this consent form.

Being in a research study does not take the place of routine physical exams or visits to your own doctor and should not be relied on to diagnose or treat medical problems.

1. Why is this study being done?

Genetic studies compare genes from people who have illnesses to people who are not ill. Being part of a genetic study does not mean that you or your relatives have a genetic illness.

You are invited to participate in a research study conducted by Dr. Newcomer to find genes that may be linked with weight gain in children who are receiving certain medications given for emotional disorders. To best study this area, it is helpful to compare genes from children who have either gained weight or not gained weight and /or who have had changes in their blood lipids or blood sugar while taking various medications.

We are trying to learn what genes affect your behavior.

We hope to find new tests or treatments to help us understand conditions such as conduct disorder.

For more information regarding minors in research see www.researchchildren.org.

You can take part in Dr. Newcomer's treatment study even if you and/or your child decide not to participate in this genetic study.

2. **What am I being asked to do?** All procedures described below are research related, not standard-of-care.

During the first Oral Glucose Tolerance Test (OGTT), you will have approximately 2.5 ml (about 1/2 teaspoon of blood) obtained from a draw-line in a vein in your hand or wrist or arm. During the final Oral Glucose Tolerance Test (OGTT), you will have 12.5 ml (2 1/2 teaspoons) of blood drawn for genetic testing. A total of 15 ml (3 teaspoons of blood will be drawn for genetic testing over the entire study. Your name will not be on the blood samples. The blood sample will be identified (coded) with a number. The blood is for research only and will be stored in a freezer until the genetic tests are conducted (no longer than 20 years). These genetic tests may be conducted here and/or at other institutions, but the blood samples will only be identified by the code number. Other investigators will not receive your name, social security number or other identifying information.

How long will I be in the study?
Your blood for the genetic test will be drawn during one study day. The blood will be stored no longer than 20 years.

You and your physician will not get any study results. We will contact you if we learn you have a life-threatening medical disorder that current treatment can stop or lessen.

How many other participants will be in the study?
There will be approximately 325 participants invited to participate in the treatment study. Each participant's parent(s) or guardian(s) will be invited to participate in providing a blood sample for genetic testing.

Financial Disclosure of Interest
The study sponsor is paying Washington University to conduct this study. The amount of payment is enough to cover the study doctor's and/or institution's expenses to perform the study.

Future Use of Blood, Tissue, or Data
May I share your tissue and data? It will not have your name on it, only a code number, so nobody will know it was yours. I would like to share it with other investigators doing research in similar fields. These investigators may be at Washington University or at other research centers.
_____ Yes ____No

3. **What are the costs?**
There are no costs to you for drawing or testing the blood sample.

4. **What Are The Risks?**
There are certain risks and discomforts that may be associated with this research. They include:

- **Blood drawing:**

Likely: The risks of blood drawing and IV insertion include discomfort, bruising, and/or minimal bleeding.

Less Likely: Occasionally during blood drawing procedures, some people experience dizziness or feel faint.

Rare: Very rarely, the site of needle insertion could become irritated or infected. The side effects of the topical anesthesia are very rare. The most common side effects are irritation, redness, itching, or rash. There is also a very small risk of your hand becoming reddened or developing a small blister from warming your hand in the hand-warming box. Side effects associated with topical anesthesia used to numb the area of needle insertion infrequently cause side effects including irritation, redness, itching or rash.

Certain genetic research may reveal that you are a carrier of a genetic disorder. This could mean that you or members of your extended family may have an increased likelihood of developing the disorder, or may be carriers. As pointed out in the material on Certificate of Confidentiality, no information about your family will be released unless you explicitly request us to do this. We need to caution you, however, that if you request that we release this information it may have the following effects on your future access to insurance for medical costs or to employability. If your participation in a genetic study becomes known outside of the research (for example, if your participation were to be noted in your medical record) you (and family members) may be unable to obtain health, life, or disability insurance. You might also be refused employment or be terminated from your current employment. This could happen if **you** choose to discuss your participation with your doctor without requesting that the information be kept out of your medical record. Inclusion of genetic (or any other) information in your medical record may allow insurance providers to access such information. Again, the Certificate of Confidentiality will protect the research records unless you request their release. It is Washington University policy that results of genetic testing, including paternity, are not given to any individual participants. Your blood samples will be coded with an identification number. The master list that links your name and the code number will be kept separate from the research materials. Every effort will be made to protect your research data; there is , however, always the possibility of a breach of confidentiality.

In the very unlikely event that genetic testing reveals that an individual has a treatable illness, the results of this will be given to parental guardians of children/adolescents or to adults about themselves. If you prefer that these results be given to a physician of your choice, before they are given to you, please let Dr. Newcomer know the name and telephone number of this physician at the time that she (or a designee) informs you of a result.
You will not hear from us unless we find information that may be clinically relevant.

What happens if you are injured because you took part in this study?
Washington University investigators and staff will try to reduce, control, and treat any complications from this research. If you feel you are injured because of the study, please contact the investigator, Dr. Newcomer, at (314) 362-5939 and/or the Human Research Protection Office at (314) 633-7400 or 1-(800)-438-0445.

Decisions about payment for medical treatment for injuries relating to your participation in research will be made by Washington University. If you need to seek medical care for a research-related injury, please notify the investigator as soon as possible.

- **Certificate of Confidentiality** One potential risk of participating in this study is that confidential information about you may be accidentally disclosed. We will use our best efforts to keep the information about you secure, and we think the risk of accidental disclosure is very small. Please see the *Confidentiality* (Item 7) section of this consent form for more information.

- **Coded Data**
The information you give us will be given a code number. A master list linking the code number and your identity will be kept separate from the research data. Only the PI and people helping him/her will be able to see the list. We will protect your information, but there is a chance somebody might see it.

5. Are there benefits to taking part in the study?
Taking part in this study will not benefit you directly. It may benefit others with your condition. You will not receive any medical or financial benefit from participating in this research. By agreeing to participate, you authorize the use of your blood for research that may benefit others. The study of your blood may one day result in new tests or treatments, or may help to prevent or cure diseases. In the future, medical or scientific products may result from research with you or your child's blood. Should this occur, you will not receive financial compensation related to those medical or scientific products. Scientific knowledge advances slowly, but it may greatly benefit future generations. Researchers at Washington University consider you an important partner in the battle against disease and are grateful to those who choose to participate..

6. What other options are there?
Taking part in this research study is voluntary. You may choose not to take part in this research study or you may withdraw your consent at any time. You may withdraw by telling the study team you are no longer interested in participating in the study or you may send in a withdrawal letter. A sample withdrawal letter can be found at http://hrpo.wustl.edu under Information for Research Participants. Your choice will not at any time affect the commitment of your health care providers to administer care. There will be no penalty or loss of benefits to which you are otherwise entitled.

You may choose to participate in the treatment study without participating in the genetic study described in this form or you may withdraw your consent at any time. Your choice will not at any time affect the commitment of your health care providers to administer care. There will be no penalty or loss of benefits to which you are otherwise entitled. Other than not taking part in the research, you may: your child may: participate in Dr. Newcomer's treatment study without participating in the genetic study described in this consent. If you choose to participate in this

genetic study and later change your mind, the blood can be destroyed upon request. To withdraw your consent, please call Dr. Newcomer at (314) 362-5939.

7. What about privacy and confidentiality?
We will do everything we can to protect your privacy.

Notice of Privacy Practices –

The Notice of Privacy Practices is a separate document. It describes the procedures used by WU to protect your information. If you have not already received the Notice of Privacy Practices, the research team will make one available to you.

_____ I have been offered a copy of the Notice of Privacy Practices.
Initial

Protected Health Information (PHI) is health information that identifies you. PHI is protected by federal law under HIPAA (the Health Insurance Portability and Accountability Act). To take part in this research, you must give the research team permission to use and disclose (share) your PHI for the study explained in this consent form.

In addition to health information that may be created by the study, the research team may access the following sources of your health information to conduct the study: hospital/physician medical records; lab, pathology and/or radiology results; information derived from biological samples (including blood); interviews/questionnaires; mental health records; physiologic imaging.

A Certificate of Confidentiality has been obtained from the Department of Health and Human Services. This will help further protect information that may identify you. The Certificate prevents the investigator from being forced to disclose identifying information for use in court. The investigator may not even be forced by court subpoena. Courts that may be prevented from getting your information include any federal, state, local civil, criminal, administrative, legislative, or other court proceeding.

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. The investigator may not withhold information if you give your insurer or employer permission to receive information about your participation in this research. This means that you and your family must also actively protect your own privacy.

The Certificate does not prevent the researchers from taking steps, including reporting to authorities, to prevent serious harm to yourself or others. Such disclosures will be made as described below.

The research team may share your information with:

- The Department of Health and Human Services (DHHS) (including the Office for Human Research Protection or the Food and Drug Administration) to complete federal responsibilities for audit or evaluation of this study.
- Public health agencies to complete public health reporting requirements
- Hospital or University representatives, to complete Hospital or University responsibilities for oversight of this study.
- Your primary care physician if a medical condition that needs urgent attention is discovered
- Appropriate authorities to the extent necessary to prevent serious harm to yourself or others.

Once your health information is shared with someone outside of the research team, it may no longer be protected by HIPAA.

The research team will only use and share your information as talked about in this form. When possible, the research team will make sure information cannot be linked to you (de-identified). Once information is de-identified, it may be used and shared for other purposes not discussed in this consent form. If you have questions or concerns about your privacy and the use of your PHI, please contact the University's Privacy Officer at 866-747-4975.

This study is sponsored by the National Institute of Mental Health (NIMH). Representatives of the sponsor will have access to your research and/or medical records for monitoring the study. The research team will also send study results to the sponsor. Information sent to the sponsor will be summarized and coded so that it cannot be associated with your PHI. The sponsor is not required to abide by the HIPAA regulations, but agrees to protect the confidentiality of your information. The sponsor reviews the study summary to verify that the research is progressing toward stated goals.

You will always have access to your medical record. Some of the individual results from tests to be performed during this research study might be of interest to you or your primary care physician. At your request, the researchers will share the medical information gained from this study with you and your referring and/or primary care doctors. If we become aware of any important health information during the course of your participation in this study, we may be obligated/required to share this information with your treatment team. You will not have access to your research record.

If you decide not to sign this form, it will not affect

- your treatment or the care given by your health provider.
- your insurance payment or enrollment in any health plans.
- any benefits to which you are entitled.

However, it will not be possible for you to take part in the study.

If you sign this form:

- You authorize the use of your PHI for this research
- Your signature and this form will not expire as long as you wish to participate.
- You may later change your mind and not let the research team use or share your information (you may revoke your authorization).

- To revoke your authorization, complete the withdrawal letter, found in the Participant section of the Human Research Protection Office website at http://hrpo.wustl.edu (or use the direct link: http://hrpohome.wustl.edu/participants/WithdrawalTemplate.rtf) or you may request that the Investigator send you a copy of the letter.
    - **If you revoke your authorization:**
        - The research team may only use and share information already collected for the study.
        - Your information may still be used and shared if necessary for safety reasons.
        - You will not be allowed to continue to participate in the study.

Please specify any contact restrictions you want to request for this study only.
(Example – no calls at home, no messages left for you, no –emails, etc.)

_____

_____

8. Whom do I call if I have questions or problems?
Please contact the researcher listed below to:

- Obtain more information about the study
- Ask a question about the study procedures or treatments
- Report an illness, injury, or other problem (you may also need to tell your regular doctors)
- Leave the study before it is finished
- Express a concern about the study

Principal Investigator:	John Newcomer MD
Study Coordinator:	Martha Hessler
Mailing Address:	660 S. Euclid Ave., CB 8134; St. Louis, MO 63110
Telephone:	314-362-2423 (Ms. Hessler) or 314-362-5939 (Dr. Newcomer)

❖ If you wish to talk to someone else, or have questions or concerns about your rights as a research participant, call Washington University's Human Research Protection Office (WU HRPO) at (314) 633-7400, or 1-(800)-438-0445.

For questions about the Center for Applied Research Sciences, (Clinical Research Unit (CRU), Pediatric Clinical Research Unit (PCRU), Clinical Trials Unit (CTU), please call Michelle Jenkerson, Research Participant Advocate at 314-362-5626.

❖ **Request Permission for Future Contact**

1. May we contact you for future undetermined studies conducted by Drs. Newcomer, Haupt and Nicol? If yes, we will need to look at your Protected Health Information (PHI) to check for study eligibility.	___ Yes	___ No
2. May other WU physicians conducting contact you? If yes, your PHI will be shared with other WU physicians.	___ Yes	___ No

Taking part in future studies is optional. You can ask us at any time to take you off our contact list.

9. The Principal Investigator (PI) may withdraw you from the study without your consent if considered appropriate. It may be in your best interest to allow follow-up outside the study. For example, if your child withdraws consent from the treatment study, your genetic blood sample would no longer be needed for this genetic study. The PI will share any new information that could change how you feel about continuing in the study.

10. You will be given a signed copy of this consent form for your records.

Please mark all that apply. This section is optional.
[] Not Hispanic or Latino [] Hispanic or Latino [] Unknown
[] Asian [] Black or African-American [] Caucasian [] Native American or Alaskan Native [] Native Hawaiian or Pacific Islander
[] Other [] Unknown
The Office of Management and Budget has declared that Hispanic/Latino is an ethnicity. National Institutes of Health, in an effort to ensure diversity in research, requests that you report your ethnicity. (http://grants.nih.gov/grants/funding/women_min/women_min.htm)

CONSENT FOR MINOR PARTICIPANTS

Parent or Legal Guardian: (If participant is less than 18 years of age.)
I have read this consent form and have been given the chance to ask questions. I give permission for my child to participate in this research described above, titled: **Metabolic Effects of Antipsychotics in Children (Genetic Consent for Children and Adolescents)**

HRPO does not require participants to re-sign the consent form unless a change is made; the investigator, however, may choose to re-consent participants at any time.

Signature: _____

Printed Name: _____ Date of Signature: _____

Relationship to Child:
Father Mother Grandmother Grandfather Legal Guardian Other*: _____

***If the minor participant is in foster care or a ward of the State, please contact HRPO at 633-7400 for assistance.**

Signature of Second Parent or Legal Guardian (OPTIONAL):

Signature: _____

Printed Name: _____ Date of Signature: _____

Relationship to Child:

Father Mother Grandmother Grandfather Legal Guardian Other: _____

Principal Investigator (or Designee):

I have given this research participant information about this study that I believe is accurate and complete. The participant has indicated that he or she understands the nature of the study and the risks and benefits of participating.

Signature: _____ Title: _____

Printed Name: _____ Date of Signature: _____

DOCUMENTATION OF ASSENT (FOR PARTICIPANTS WHO ARE MINORS)

Participant's Assent:
The doctor or nurse has told me what will happen if I choose to be in this study. I understand what they have said, and I understand that my parents and I may later change our minds and stop being in the study.

Signature: _____

Printed Name: _____ Date of Signature: _____

ASSENT CONSIDERED INAPPROPRIATE (for minors)

We believe that requiring the signature of the minor is not appropriate for the following reason(s):

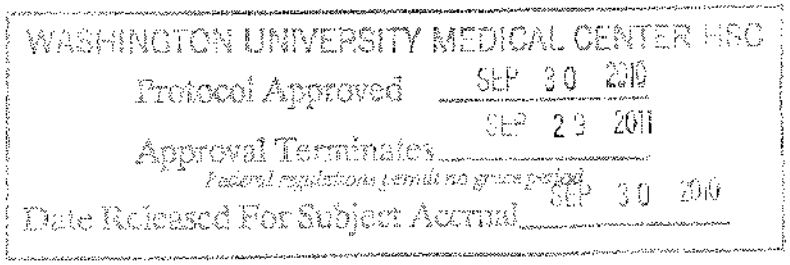
_____

_____

_____ _____

Physician Date Parent/Guardian Date

This form is valid only if the Human Research Protection Office's current stamp of approval is shown below.



A Study of Metabolic Effects of Antipsychotics in Children (HRPO Protocol #05-0264)
PI: John Newcomer MD

Source of Contact: _____ Screening number_____

Respondent Name:_____ Respondent's relationship to child: _____

Date:_____

Rater ID: _____

APPROVED
Jonathan M. Green, M.D.
Associate Dean and Executive Chair
SEP 30, 2010

Washington University School of Medicine
Children's Health Care Study Telephone Screening Script

Hello. My name is _____. I'm calling from the Children's Health Care Study at Washington University School of Medicine.

Did [*source of contact*] mention that I might be calling? Did you get a brochure or any details about the study?
If NO: Is this a good time to tell you about the study and ask some questions to see if your child is eligible to participate? IF YES: [Continue to I. Study Overview] [If asked, tell respondent it might take 20-30 minutes.

If YES: Good. Is this a good time to tell you more about the study and ask some questions to see if your child is eligible to participate? [okay for screener to explain their role in the study] *If YES:* Great. Thank you. [Continue to I. Study Overview] [If asked, tell respondent it might take 20-30 minutes.

I. STUDY OVERVIEW

We are inviting kids and parents to join a medical research study about how medications can affect children's health. Joining the study is totally voluntary. The study will include kids who have been diagnosed by their doctor with various emotional problems such as aggression. Your child's doctor has recommended that your child take one of these medications: **Abilify** [aripiprazole], **Zyprexa** [olanzapine], or **Risperdal** [risperidone]. Joining our study will mean that your child will take one of these medications and receive extra medical care and attention for three months and beyond. For example, if one medication is not working for your child, our study doctor would immediately call your child's doctor to talk about the problem.

For this study we are interested in learning how these medications [Abilify, Ziprexa, Risperdal] might affect three things: weight gain, risk for diabetes, and cholesterol problems. To measure how these drugs might be affecting your child, we will ask your child to do two kinds of blood tests and two kinds of scanning tests. We'll do these tests before s/he starts medication, again about halfway through the study, and again when the study is over. We will see you five to six times for study tests plus medication visits with the study doctor. You can be with your child during all of these tests.

The first blood test is called an O G T T. That stands for oral glucose tolerance test. This test helps us find out how well your child's body can process sugar over a few hours. During this time your child can watch movies or cable TV.

The second kind of blood test is called a "clamp." There's no actual clamp involved—that's just the name of the test. In this test your child will be given sugar and insulin through a series of IVs in one arm. From the other arm very small amounts of blood will be taken periodically to measure their blood sugar levels. The clamp is a procedure that takes eight hours. During this time your child can sleep or watch TV or movies,

play video games, read, or listen to music. Both these blood tests are done in a section of the hospital that is set aside for this kind of specialized research.

The third test is an MRI of your child's tummy. These pictures are very safe, do not hurt, are taken from outside the body, and do not involve x-rays. This test measures your child's body fat. Your child will be asked to lie very still for a brief period of time.

The fourth test is called a DEXA scan. The DEXA scan uses an very small amount of x-ray energy, much less than for a dental film. It's so safe that the operator doesn't even have to wear a protective apron. It's the same machine that's used to measure bone density, but we'll be using it to measure body fat. Your child will lie flat while the machine takes pictures. This does not hurt and you cannot feel the machine taking pictures. For this test your child will also be asked to lie still.

We will pay you and your child for participating in the study. We will offer you a choice of gift certificate cards to many of the stores or attractions, like the zoo, in our area. The value of the gift cards you receive can total up to $775 depending on how many portions of the study you and your child are eligible to complete.

And, if you need it, we can arrange for a cab ride to and from your home for any part of the study.

Do you have any questions so far?
If NO: Continue to II. Screening Questions.
IF YES, answer any questions you can, or offer to call back after you've talked to the study doctor.
The next set of questions will help determine if your child is eligible to join the study. The questions ask about your child's health now and in the past. Okay if I go on?
If YES: Continue to II. Screening Questions. *Circle YES*
If NO: Is there a better time for me to call you back? _____
Or if it sounds like they may be refusing: **May I ask why? It might help us do our research better.** *Circle NO*

_____

_____

Thank respondent and discontinue call.

II. SCREENING QUESTIONS
First, if any of the questions I'm asking make you uncomfortable, please tell me and I will try to explain why I need to know this. All the information you provide will be kept strictly confidential.

1. How old is your child? _____ (under 7 and over 18 excludes) **1a. Date of birth?** ____ /____/ _____

2a. What is your child's height? _____ (in inches) [If needed: **Your best guess is fine.**]

2b. ....and weight? _____ (pounds) [Under 55 pounds would be a reason to call the study doctor and check]

3a. Does your child have Type 1 diabetes? YES NO *If YES,* child is excluded. "*Some of our tests use medications just like what your child is taking for diabetes, so we wouldn't be able to tell what's really happening during the study. We'll contact your doctor and let them know you won't be able to join the study.*" End call.

3b. What about Type 2 diabetes? YES NO
IF NO: Continue.

IF YES: Is your child taking medication for this? YES NO

IF YES on meds: What medication is s/he taking: _____
Child may be excluded, depending on medication. Check with Study doctor.

IF NO meds: Okay to continue. Ask for more information, to find out if treatment is starting soon, or if they've tried and given up, etc.

_____

_____

4. How about low blood sugar or any other problems with blood sugar? YES NO
IF YES: **Can you tell me more about that?**

_____

Note: This is something to check with the study doctor about.

5. Is your child currently taking any medications, including prescriptions, vitamins, herbs, supplements, or any over-the-counter medications? YES NO
IF NO, SKIP to #6
IF YES: **Can you tell me what they are and how much s/he is taking?** Record type and dosages:
[OK to suggest parent go and get medications to get accurate information. Also good idea to ask how medication is administered (by mouth, orally, nasal spray) in case it's not obvious from the name of the medication, or if parent doesn't know medication name for sure.]

_____ _____

_____ _____

_____ _____

_____ _____

Has you child EVER taken Risperdal, Zyprexa or Abilify? _____

_____

If yes, when and for what duration?* _____
*Check with study doctor to see if eligible.

Some inhalers are included and some are not. They need to be able to not take it for one month prior to treatment. If the inhaler is only for seasonal allergies and they do not currently need it, they can be included in the study. Glucocorticoids like Flonase [nasal] are exclusions. Oral steroids taken by mouth ARE exclusions, unless it's a short 5 day course for something like poison ivy. They would have to wait until the course is done before they can start the study. Inhalers are not exclusions.

I'll need to check with the study doctor about these, okay?"

6. Has your child had any medication changes within the last 3 <u>months</u>? YES NO
IF YES: **Please tell me more about this.**

-Medication changes within the last three months would exclude them temporarily, up until it has been three months since the change. The child may also have been taking medications within the last three months, so parent would have said NO to #5, so need to talk to study doctor. ***"I'll need to check with the study doctor about these, okay?"***

I have a few more detailed questions about your child's health.

7. Has he/she been dehydrated, nauseated, or running a fever in the past two weeks? That would be _____[mention date two week prior to date of phone call.] YES NO
IF YES: **Please tell me more about that.**

-An illness or fever in the past two weeks would exclude them, but only temporarily.

POSSIBLE TEMPORARY EXCLUSION EXPLANATION for parent: *"We just want to make sure your child is healthy before we begin treatment. Your child can join the study as soon as it has been two weeks. We'll call your doctor and let them know there will be a delay in joining the study. I'd still like to go on and ask the rest of the questions...would that be okay?"*

If child is female and over 9 years old: (otherwise, skip to next question)
8. Has your daughter begun having menstrual periods? YES NO

If YES: **She will have a routine urine pregnancy test when she comes in for the OGTT and Clamp testing I described before. This is because pregnancy hormones can change the results of the tests we do.**

9. Has your child ever had a seizure? YES NO
If yes: Please tell me more about that.

-Febrile seizures are not an exclusion. If the child has a seizure disorder that is being treated, this **is** an exclusion. If not being treated, check with study doctor.

Exclusion explanation for parent: *"With a seizure disorder that's being treated, it's hard for us to know what's related to the seizures or to something else, so we won't be able to have you join our study. We'll call your doctor right away to let them know."*

10. Has your child ever had a head injury? YES NO
IF NO, continue to #11.
If YES: **Was he or she unconscious for more than 5 minutes?** YES NO
IF NO: Continue to #11
If YES: **Could you tell me more about that? Did s/he go the emergency room or a doctor because of it? Or have any problems because of it?** Check with Study doctor to confirm if exclusion or not.

IF PERMANENT EXCLUSION, EXPLANATION for parent: *"With a head injury, it's harder to diagnose behavior problems, so we won't be able to have you join our study. We'll call your doctor right away to let them know."*

11. Has your child ever been hospitalized or had surgery? YES NO
If YES: **Please tell me more about this.** Get details for each event.

~Exclusions are major surgeries like transplants, heart surgery, brain surgery, etc.
POSSIBLE PERMANENT EXCLUSION: EXPLANATION for parent: *"It is really important to us to be sure your child is safe throughout this study. Knowing about any health conditions will help us decide if it's okay for your child to participate. We don't want to interfere with any other treatment s/he might be receiving."*

12. Has your child ever had any abnormal lab tests that your doctor told you about? YES NO
If YES: **Please tell me more about that.**

~*Exclusions would be any major illness like HIV, a heart condition, cancer, etc. It's determined on a case by case basis.*
POSSIBLE PERMANENT EXCLUSION, EXPLANATION for parent: *"It is really important to us to be sure your child is safe throughout the study , so we need to know as much as possible about his/her medical history. We'll discuss any abnormal lab tests with the doctor and he will decide if it's safe to give your child one of the medicines that we're studying.*

13. Has your child ever been treated for any serious medical conditions? YES NO
If YES: **Please tell me more about this.**

~Major illnesses or surgeries would exclude, (i.e., heart surgery, brain surgery, transplant, etc.
POSSIBLE PERMANENT EXCLUSION, EXPLANATION for parent: *"It is really important to us to be sure your child is safe throughout this study. Knowing about any health conditions will help us decide if it's okay for your child to participate. We don't want to interfere with any other treatment s/he might be receiving. We'll check with the study doctor and he will decide if it's safe to give your child one of the medicines that we're studying."*

14a. Does your child have any physical or mental challenges, such as a birth injury like cerebral palsy? YES NO
IF YES: **14b. Do you know your child's IQ level?** _____ ~Score of 70 or less excludes

[IF NEEDED TO CLARIFY] **14c. Is your child mentally retarded?**

~Mental retardation or any kind of brain damage would exclude.

PERMANENT EXCLUSION: EXPLANATION for parent: *"If a child is mentally retarded, s/he may not understand the purpose of the study, or not be able to answer our questions and follow directions safely."*

15. Does your child have serious difficulty learning, like a diagnosed learning disability? YES NO
If YES: **What grade is your child in?**_____ Look for more than one year behind typical grade level for age of child

Can you tell me more about this?

_____

_____

➡Any type of brain damage or complicated medical problem or MR would exclude.
IF MR: : *"If a child is mentally retarded, s/he may not understand the purpose of the study, or not be able to answer our questions and follow directions safely."*
IF OTHER: "We need to make sure we're not doing anything that could worsen any medical problems your child has."

16. Does your child have any permanent injuries from an accident? YES NO
(Mainly looking for brain damage or another complicated medical problem-check with study doctor)

IF YES: **Can you tell me about this?** _____

_____

POSSIBLE PERMANENT EXCLUSION, EXPLANATION for parent: *"We need to make sure we're not doing anything that could worsen any medical problems your child has."*

ASK#17 ONLY IF NOT ALREADY KNOWN. CODE SILENTLY IF ALREADY KNOWN.
17. **Who sees your child for the behavior problems that have brought you to the study? Is it...**
[Check one]
A PSYCHIATRIST? _____
A PEDIATRICIAN?_____
A FAMILY DOCTOR? _____
(Get name if not known) _____

18. When was he/she first diagnosed with a behavior problem? ____ _____ _____
[If not sure, probe for time of year, like school or summer.] mm dd yyyy

19. What is the name of your child's diagnosis? _____

20a. Has your child ever had problems with alcohol, street drugs, or abuse of prescription drugs?
YES NO
IF YES: **Please tell me more about that.**

_____

_____

IF NO, Skip to #21

20b. What substances have been a problem?_____

20c. Has this been a problem in the last 3 months, like at school or with friends, or at his/her job?
IF NO, Continue to #20d.
IF YES: **Can you tell me about this?** _____

_____

20d. Has he or she ever received any treatment for this? YES NO

20e. Is s/he currently having problems related to the use of alcohol, street drugs, or prescription drugs?
YES NO
IF NO: Continue to #21.
IF YES: **Can you tell me about this?** _____

_____

~ *If the child is currently abusing alcohol, street drugs, or prescription drugs, this would exclude. If child is not actively intoxicated or in withdrawal, it might be okay. Contact Study doctor to check.*

POSSIBLE PERMANENT OR TEMPORARY EXCLUSION: *"Drug or alcohol use can interfere with the tests we need to conduct in this study. If your child is currently having problems with using these substances, it won't be possible to have your child join the study right now. We'll call your doctor to let them know."*

21. Has your child ever been suspended from school?
IF NO: Continue to #22.
IF YES: **Could you tell me more about this?**

_____

22. Has your child ever been treated for depression? YES NO

23. Has your child ever threatened to hurt him/herself or attempted suicide? YES NO

IF NO: Continue to #24.
If YES: When did that happen? _____

~An exclusion only if in the present or within the last 30 days.

24. Has your child ever tried to harm someone else?
IF NO: Continue to exclusions/more information about the study.
IF YES: **Could you tell me more about this?**

_____

If the child has tried to seriously harm someone else, like stabbing with knife, this is an exclusion for the safety of study staff.

If a permanent exclusion applies, end call by saying: **"That's all the questions I have. From the information you have given me, your child will not be able to join the study. We will contact your referring doctor and let him/her know. Thank you very much for your time."**

If TEMPORARY OR POSSIBLE exclusion applies, end call by saying: **"That's all the questions I have for now. I need to check with the Study doctor about some of the information you gave me, to see if it's okay for your child to join the study. We will contact you very soon to let you know.** [IF TEMPORARY, like fever within

the last two week, make reference to temporary problem, and set timeline for calling back to see if eligible at another time. Tell parent we will call their doctor to let them know of the slight delay in joining the study.]

If not excluded based on above questions, continue.

MORE INFORMATION ABOUT STUDY

We'll be sending you a detailed description of the study in the mail, but if you have a few more minutes right now, I can give you an overview of the study. Would that be okay?

We're doing this study to learn more about how the side effects of three antipsychotic medications might affect kids. The study will take about 12 weeks. It's totally voluntary, and you can stop being in the study at any point. Of course, we hope you will complete the entire study, because that will give us the most helpful information. We'll work with your schedule and your child's school schedule to find times that will work.

A week before the study begins, we will go over the study consent forms with you on the phone. A copy of these consent forms will be mailed ahead of time so that you have time to read it carefully. The consent forms tell you all about the study in great detail, so you will know everything about the study before you start.

While we are talking about the consent forms on the phone, we want you to feel you can ask any questions you have about the study. Talking about the consent forms and answering your questions can take up to an hour. If you and your child decide to join the study, you will both be asked to sign the consent forms and return them to our office. We will send you an extra copy for you to keep.

We will then schedule a time to call again and ask more questions about you and your child. These questions take a bit longer, about an hour and a half. First, we will talk to you and ask questions about your child. Then we will call at another time to talk to your child and ask most of the same questions. If your child is 11 years old or younger, we may ask your child to come into our offices and answer these questions in person with one of our trained child interviewers. This combined length of time for both you and your child to answer these questions is about 3 to 4 hours.

Approximately one week after the phone questions are finished, your child will be asked to come to the General Clinical Research Center (GCRC), and have an Oral Glucose Tolerance Test (OGTT). With this test, your child will be given a sweet drink and will have some blood tests to see how his/her body handles the extra sugar. The night before you come in, your child will not be able to eat or drink anything overnight except tap water before arriving at the hospital, including gum, candy, or breath mints. When your child comes in, he/she will lie in a reclining chair or bed, and a nurse will place an IV into the vein in one arm. This feels a little like getting a shot, but we'll numb his/her skin first to help it hurt less. Once the IV is in, it shouldn't hurt much at all. Your child will then drink a really sweet orange or lemon flavored drink, and we'll use the IV to get very small blood samples during the next two hours. The blood samples check blood sugar and some other routine blood tests. Your child can watch cable TV or videos, or play video games, or listen to music during this study, and we'll give him/her lunch when he/she is finished, after about 2-3 hours.

When this test is over your child will also have a DEXA scan and EKG done. The DEXA scan uses an extremely small amount of x-ray energy, much less than a dental x-ray, to measure body fat. Your child will lie flat while the machine takes pictures. This does not hurt and you cannot feel the machine taking pictures. Your child will wear his/her own clothes or a hospital gown for the test. This takes about 10 minutes.

For the EKG, soft sticky pads will be placed on your child's chest and a machine will record how your child's heart is working. The EKG produces a printout of how your child's heart is functioning. This is a very short test, lasting 10 to 15 minutes.

On the next visit, your child will come back in to have a different kind of imaging scan or picture taken to measure body composition. This is called an MRI. Your child will lie on a table which is then placed in a tube to have his/her tummy scanned. He/She will need to lie still during this test to get the best picture. The entire MRI process lasts about 20 minutes. The scan does not hurt and your child can wear earphones and listen to music during the scan.

On the next visit, your child will come back to the General Clinical Research Center (GCRC) where he/she will lie in a reclining chair or bed, and a nurse will start two IV lines, one in each arm. This test is called a "clamp." There is no actual clamp involved, it's just a word doctors use to talk about keeping blood sugar "clamped" in a normal range. Just like the first visit, your child will not be able to eat or drink anything but tap water the night before and up until the test begins. This includes gum, candy, and breath mints like Tic Tacs. It's okay for your child to take his/her regular medications with water out of the faucet.

In one arm, an IV will be used to give your child insulin (a hormone found in the body that lowers blood sugar) and glucose (a type of sugar that will raise blood sugar), to keep your child's blood sugar in a very normal range (the clamp). The other arm will have an IV that will be used to take very small blood samples at various times to test your child's blood sugar level. The clamp part of the visit takes about six hours, plus 2 hours for preparation and discharge from the CGRC. Cable TV, videos, video games, and music will be available to keep your child occupied during this test. Your child will be provided with a late lunch before he/she goes home. This session will last about 8 hours total.

At the end of this visit, we'll work with your child's doctor to start your child on an antipsychotic medication. These medications have been FDA-approved for adults. Their use in children is now routine with symptoms of aggression or conduct disorder, but their use is considered "off-label".

We will monitor your child closely by telephone and/or doctor's office visits while he/she is taking the new medication, and you will have phone and beeper numbers to call the study staff and doctors with any concerns or questions. He/She will receive extra care and attention with regular visits with the study doctor and child therapist, who will maintain close communication with your regular doctor.

On the next visit, about halfway through the study, we will ask your child to return to the hospital to repeat the OGTT blood test, and DEXA and MRI scans.

After your child has been on the medication for about 12 weeks, your child will return to repeat all the tests: the OGTT, the DEXA scan, the MRI, the EKG, and the Clamp.

You and your child will be reimbursed up to $780 in gift certificates for your time and inconvenience, depending on how many portions of the study you and your child are eligible to complete.

Do you have any questions or concerns at this time?

_____

_____

If the parents and child are interested in the study and the child meets basic eligibility criteria, ask for contact information:

Mother's Name: _____

Father's Name: _____

Child's Name: _____ Child's DOB _____ [if not obtained earlier]

Address: _____

Phone number: _____ Best Day and Times to call: _____

Alternate phone: _____

Referring physician name: _____ Phone #_____

Thank you.

If need to check with study doctor: **I'll check with the study doctor and call you back as soon as possible.**

If eligible: **We'll be in touch very soon to set up your first appointment.** [okay to explain who will be calling them for the next step.]

For more information or a more detailed brochure please contact

Martha Hessler (888) 363-2423

Visit us on the web at www.childhealthstudy.org

SEP 30 2010

APPROVED

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Washington
WASHINGTON UNIVERSITY IN ST. LOUIS
School of Medicine

Children's Health Care Study

Washington University School of Medicine

The Children's Health Care Study

This study was designed by Dr. John Newcomer, MD, in response to a need for more information about the effects in children of a type of medication called atypical or second-generation antipsychotics. Second-generation antipsychotic medications are most often used in adults to treat certain emotional and mental problems. They're called atypical because they cause less of the "typical" nervous system side effects of the older, first-generation antipsychotic medications. These medications are being used more and more often in children to treat emotional and mental problems, although these uses are not currently approved by the FDA. Doctors and scientists want to learn more about the use of these medications in children, including how children's bodies respond to them. For this study we are interested in learning how these medications might affect three things: weight gain, risk for diabetes, and cholesterol problems. The specific antipsychotic medications we are studying are Abilify (aripiprazole), Zyprexa (olanzapine), and Risperdal (risperidone). Our study includes children ages 6-18 who have been diagnosed by their doctor with various problems that can result in increased aggressiveness.

A Growing Problem

The prevalence of obesity, insulin resistance and Type II diabetes mellitus are increasing, particularly in children, with the Centers for Disease Control warning of epidemic rates of these conditions in children in the United States. Increased weight and related metabolic changes are major risk factors for long term medical problems such as increased risk of heart attack and stroke as well as the development of high blood sugar, elevated lipid levels (cholesterol and triglycerides) and cardiovascular disease.

Led by Dr. John Newcomer at Washington University School of Medicine, The Children's Health Care Study, funded by the National Institute of Mental Health, will measure sensitive metabolic changes that can occur with some antipsychotic medications in children with aggressive symptoms related to various psychiatric conditions. Researchers will be looking at how three medications affect weight gain, risk for diabetes and cholesterol. Antipsychotic medications are extensively used in children, but with different outcomes. Some produce greater increases in weight and overall body fat than other drugs commonly used in this age group. It remains unclear why children are especially vulnerable to weight gain with these medications and how such metabolic change (changes in fat versus lean muscle mass and changes in insulin action versus secretion) are associated with specific antipsychotics. Until now, no study has measured the metabolic effects of widely used atypical antipsychotic medications in children.

Dr. Newcomer performed a pilot study last year in 11 children which showed that it was possible to obtain metabolic measures in children with behavior disorders related to psychiatric conditions. Children in the pilot study readily tolerated blood tests lasting longer than 6 hours. This study has provided evidence of the feasibility of using these measures in a larger study of antipsychotic drug effects on weight and metabolic factors in a population of children with aggressive symptoms related to psychiatric conditions. The current study will provide critical information and relevant data to guide pediatricians and child psychiatrists in clinical therapy and basic research, to identify medical risks for children receiving these medications, and to guide regulatory decisions regarding the use of atypical antipsychotic medications in children.

The Research Process

Measuring the changes in metabolism, blood sugar and body composition is an extensive process. Participants will make five study-related visits during the course of the study. The visits involve blood testing which measures how well the child's body metabolizes sugar, MRI and DEXA scans which tell us more about where and how much overall body fat the child has, and finally an EKG to monitor the child's cardiovascular functioning. These tests are done once at the beginning of the study and then again at the end to determine what effect the medication had on all of these measurements. Participants are closely monitored for twelve weeks and receive extra medical care and attention during this time. All testing is completed in a specialized unit of the hospital, called the General Clinical Research Center (GCRC).

Our study doctors work closely with the participants' physicians and will make changes to the treatment as needed. Dr. Newcomer and colleagues are first and foremost concerned with the health and safety of each participant.

To refer a patient or if you have any questions, please call:

Martha Hessler-Study Coordinator
314-362-2423 (office)
314-740-2093 (cell)
hesslerma@psychiatry.wustl.edu
Julie Schweiger-Project Manager
314-362-3153 (office)
314-566-1532 (cell)
schweigj@psychiatry.wustl.edu
John Newcomer-PI
314-362-2461 (office)
314-378-0112 (cell)
newcomej@psychiatry.wustl.edu
Ginger Nicol MD
314-362-4290 (office)
314-283-9621 (cell)
nicolg@psychiatry.wustl.edu

Inclusion/Exclusion Criteria

-Ages 6 through 18
-Axis I diagnosis with aggressive symptoms (e.g. autism, pervasive developmental disorder, Asperger disorder, conduct disorder, ODD, ADHD, bipolar disorder, schizophrenia)
-About to start their first course of antipsychotic treatment
-Not currently treated with a stimulant higher than the equivalent of 2 mg/kg/day methylphenidate
-Presence of any serious medical disorder that may confound the assessment of relevant biologic measures (please call with specific d/o)
-Not currently treated with glucose or lipid lowering medication

bout Our Staff

John W. Newcomer, M.D.
Professor of Psychiatry, Psychology and Medicine
Medical Director, Center for Clinical Research

Bob Brady, M.D.
Research Physician

Ginger Nicol, M.D.
Research Physician

APPROVED
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Karen Flavin, RN
Nursing Manager

Julie Schweiger
Project Manager

PeChaz Clark
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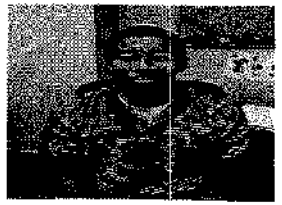

Jon Ken
Research Assistant

Children's Health Care Study

Funded by the National Institute of Mental Health

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Washington
WASHINGTON UNIVERSITY IN ST. LOUIS
School of Medicine

articipating in the Children's Health Care Study

brochure presents information designed to help you decide about your child's participation in e Children's Health Care Study at Washington University School of Medicine. It contains etailed information about the study, its staff and our interests in providing quality care for children through careful research.

nts: The research described in this brochure may be of interest *IF* you and/or family, your child's doctor, or teachers are concerned about your child's essive or irritable behavior, and current medication or behavioral therapy don't n to help. Specifically, this brochure may be of interest if your child's doctor, apist, or counselor has suggested that your child might benefit from taking one ie newer antipsychotic medications.

Study Background

study was designed by Dr. John Newcomer in response to a need for e information about the effects in children of a type of medication called ical or second-generation antipsychotics. (You'll read more about Dr. comer and the other staff involved in this study later in this brochure.) nd-generation antipsychotic medications are most often used in adults to treat in emotional and mental problems. They're called atypical because they cause of the "typical" nervous system side effects of the older, first-generation sychotic medications. These medications are being used more and more n in children to treat emotional and mental problems, although these uses are currently approved by the FDA. Doctors and scientists want to learn more it the use of these medications in children, including how children's bodies ond to them. For this study we are interested in learning how these ications might affect three things: weight gain, risk for diabetes, and esterol problems. The specific antipsychotic medications we are studying are ify (aripiprazole), Zyprexa (olanzapine), and Risperdal (risperidone). study includes children ages 6-18 who have been diagnosed by their doctor various problems that can result in increased aggressiveness. Your child's or may have suggested that your child start on one of these medications. ng our study will mean that your child will take one of these medications and ve extra medical care and attention for at least three months. Your child will ared for and monitored by a team of doctors and nurses who will stay in close act with your child's doctor. This study's goal is not only to learn new rmation, but to care for your child while doing so.

r child will be paid up to $780 in gift certificates to stores and local ctions, depending upon how much of the study your child completes. urally, we hope your child completes the entire study because that will ide us with the best information.

Visit Three

On the next visit, about halfway through the study (six weeks after beginning the new medication), we will ask your child to return to the PRU to repeat the OGTT test and DEXA scan.

Visits Four and Five

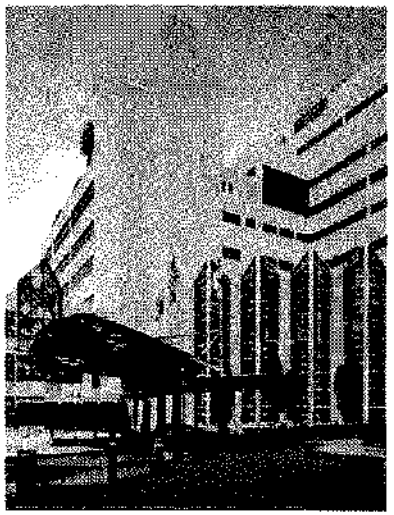
After your child has been on the medication for about 12 weeks, your child will return to repeat all the tests: the OGTT, the DEXA scan, the MRI, the EKG, and the insulin sensitivity test.

Our Research Facilities

The Washington University School of Medicine General Clinical Research Center at St. Louis Children's Hospital

Medical testing for this study will be done at The Washington University School of Medicine General Clinical Research Center (GCRC). This federally supported research resource, now in its 45th year, is made of an Adult and Pediatric Unit. Both are capable of providing care for children and both units are available for our use in this study. Making both units available gives us greater flexibility in scheduling a convenient time for you and your child. Both units are specialized areas available only to research participants.

The Adult Unit is located on the 4th and 5th floors of Barnard Hospital. The Pediatric Unit is located on the 11th floor of St. Louis Children's Hospital.



Washington University School of Medicine, including the pediatric, psychiatric and endocrinology contributions to this project, is a consistent leader in National Institutes of Health (NIH) funding. Washington University School of Medicine ranks 4th nationally in National Institutes of Health grant funding.

Visit Two

On the next visit, your child will come back to the Pediatric Research Unit (PRU) where he/she will lie in a reclining chair or bed, and a nurse will start two IV lines, one in each arm. This test is called an insulin sensitivity test. Just like the first visit, your child will not be able to eat or drink anything but tap water the night before and up until the test begins. This means no food after bedtime the night before, including no gum, candy, and breath mints like Tic Tacs. Again, it's okay for your child to take his/her regular medications with plain tap water.

During this visit, an IV will be placed in one arm to give your child insulin (a naturally occurring hormone produced in the body to control blood sugar) and glucose (a type of sugar found in many foods and drinks), to put your child's blood sugar into the normal range. The other arm will have an IV that will be used to take very small blood samples at various times to understand how your child's body responds to sugar. This part of the visit-a very important part of our study- takes about six hours, plus two hours for preparation and discharge from the PRU. Cable TV, videos, video games, and music will be available to keep your child occupied during this test. Your child will be provided with a late lunch before he/she goes home. This session will last about 8 hours total.

At the end of this visit, we'll work with your child's doctor to start your child on an antipsychotic medication. As noted above, these medications have been FDA-approved for adults. While their prescription by doctors for children with various mental conditions is now common and growing, this use is considered "off-label" or not FDA approved.

We will monitor your child closely during study visits, study doctor visits, and by telephone while he/she is taking the new medication. In addition, you will have phone and beeper numbers to call the study staff and doctors with any concerns or questions. Your child will receive extra care and attention with regular visits with the study doctor, who will maintain close communication with you child's regular doctor.

Usually during visit one, but sometimes during visit two, your child will have a different kind of imaging scan or picture taken to measure body fat, focusing on the abdomen (tummy). This is called an MRI (Magnetic Resonance Imaging). Your child will lie on a table, which is then placed in a tube to have his/her tummy scanned. He/She will need to lie still during this test to get the best picture. The entire MRI process lasts about 20 minutes. The scan does not hurt and your child can wear earphones and listen to music during the scan.

Does my child have to participate?

This study is totally voluntary and your decision will not affect the health care your child receives from his/her doctor. You always have the right to say "no" to a research study. If you do say "yes," you may take your child out of the study at any time. However, you should discuss this with the research team first, so your child can be withdrawn in the safest way possible.

Why Include Children in Research?

You may wonder why children are included in research at all. After all, research involves some uncertainty and some risks. Why not do research only on adults, who can decide for themselves if they want to participate? In fact, when possible, research IS usually done first on adults. However, this also means that many medicines and treatments have only been carefully studied in adults and remain less studied in children. Children often don't respond to medicines the same way adults do, so research in children is very important.

Sometimes children need treatment for a condition where the most promising and doctor-recommended medications have mostly been studied in adults. Those medications can also be given during a study that carefully measures benefits and side effects. When medicines are given in the setting of a study, scientists and doctors can learn more about them. At the same time, children, their families, and personal physicians can benefit from the close supervision provided by the study and information collected about an individual child's response to their medication can be used to guide future treatment decisions by families and physicians.

In addition to any personal benefit that may come from a study medication, or any benefit that comes from the careful monitoring involved in a research study, participation in research can also benefit others. Many children today are benefiting from research that was done on children in the past. For example, the current treatments for many childhood cancers and for cystic fibrosis are based on past research. Hopefully, the research done on children today will help children in the future in a similar way.

What will my child be asked to do?

We are interested in how these medications might affect weight gain, risk for diabetes, and problems with cholesterol. To measure these things we will ask your child to do two kinds of blood tests and two kinds of scanning tests. We'll do these tests before s/he starts medication, again about halfway through the study, and again when the study is over , about 12 weeks after the start of the medication. You will have between five and six study-related visits plus medication check-ups with the study doctor over the telephone or in person. You can be with your child during all of the testing.

All of these visits and tests are scheduled at the convenience of you and your child. We are able to work around school, work, sports, and other activity schedules as needed. If you need it, we can also arrange for a cab ride to and from your home for any part of the study.

Please read on for more information about each phone call, visit, and test.

Getting Started

The first contact you will have with the study staff will be a phone call.

During this call we will tell you about the study and ask a few general questions about your child's health to make sure it's okay for him/her to participare. (This takes about 20-30 minutes.) You can ask any questions you want at this time, in fact, we encourage you to do so. If the study sounds like something you're interesred in we will send out some consent forms to you and your child. Consent forms are similar to permission forms. They tell you about a study in writing and in great detail so you and your child know what is involved before you begin and asks for your permission to be included in the study. This process is designed to help parents understand the study before they decide whether or not their child should participate.

Our Study Coordinator, Martha Hessler, will go over the study consent forms with you on the phone. Again, we encourage families to ask questions. To continue with the study, you and your child will both be asked to sign these forms and return them to our office. We will also send you an extra copy for you to keep for your records.

Evaluation with a Child Psychiatrist

If your child qualifies for the study, the next step is an evaluation with one of our child psychiatrists (Dr. Robert Brady or Dr. Ginger Nicol). We will schedule this appointment as soon as possible. The child psychiatrist will do a full diagnostic evaluation. Based on the evaluation, if your child qualifies and you wish to participate, we will schedule the first two baseline visits.

Telephone Interview

One of our study coordinators will call to schedule a convenient time for you to answer more questions about your child over the phone. These questions take a bit longer, about an hour and a half, and ask more about your child's health, behaviors, and emotions. First, we will talk to you and ask questions about your child. Then we will call at another time to talk to your child and ask most of the same questions. The combined length of time for both you and your child to answer these questions is about 3 to 4 hours.

Visit One

For the first visit, your child will be asked to come to the Pediatric Research Unit (PRU) and have an Oral Glucose Tolerance Test (OGTT). With this test, your child will be given a sweet drink and will have some blood tests to see how his/her body handles sugar (glucose). The night before you come in, your child will not be able to eat or drink anything after bedtime except tap water before arriving at the hospital. This includes no breakfast, gum, candy, chewable vitamins, or breath mints. It is okay for your child to take his/her regular medication with plain tap water.

When your child comes in, he/she will lie in a reclining chair or bed, and a nurse will place a plastic tube (IV carheter) into a vein in one arm. This feels a little like getting a shot, but we use a special cream to numb the skin first to help it hurt less. Once the IV is in, it shouldn't hurt at all. Your child will then drink a very sweet orange or lemon flavored drink, and we'll use the IV to get very small blood samples during the next two hours. The blood samples check blood sugar and some other routine blood tests. Your child can watch cable TV or videos, play video games, or listen to music during this test, and we'll give him/her breakfast when he/she is finished, after about 2 to 3 hours.

On the same day, when this test is over your child will also have a DEXA (Dual Energy X-Ray Absorptiometry) scan and ECG (Electrocardiogram) done. The DEXA scan uses an extremely small amount of x-ray energy (so much less than a dental x-ray that no shield or apron is required for your child or even the operator who uses the machine every day) in order to measure total body fat. Your child will lie flat while the machine takes pictures. This does not hurt and you cannot feel the machine taking the pictures. Your child will wear his/her own clothes or a hospital gown for the test. This takes about 10 minutes.

For the ECG, soft sticky pads will be placed on your child's chest and a machine will record how your child's heart is working. The ECG is a standard test that many parents have had. It produces a printout of how the build-in electrical activity of your child's heart is performing. This is a very short test, lasting 10 to 15 minutes.

CHILDREN'S HEALTH CARE STUDY

The Children's Health Care Study at Washington University school of Medicine was designed by John W. Newcomer, MD and colleagues in response to a need for more information about the effects in children of medications called atypical or second-generation antipsychotics. These medications are frequently used in children to treat emotional and mental problems, although many of these uses are not currently approved by the FDA.

Doctors and scientists want to learn more about how children's bodies respond to these medications. We are especially interested in learning how these medications might affect weight, risk of diabetes, and cholesterol problems.

The specific antipsychotic medications are studying are **Abilify (aripiprazole), Zyprexa (olanzapine), and Risperdal (risperidone).**

Qualified Participants

This study includes children ages 6-18 who have been diagnosed by their doctor with various problems that can result in increased aggressiveness.

Benefits of Participation

- For their time and inconvenience, participants will be compensated with gift cards to stores and local attractions. Transportation for all study visits is provided as needed.
- Joining our study will mean that your child will take one of these medications and receive extra medical care and attention for at least three months.
- Your child will be cared for and monitored by a team of doctor, therapists, and nurses who stay in close contact with you and your child's doctor.
- This study's goal is to learn new information and to care for your child.

For more information or a more detailed brochure about the Children's Health Care Study at Washington University School of Medicine please contact

Martha Hessler
(888) 363-2423
660 S. Euclid
Campus Box 8134
St. Louis, MO 63110
www.childhealthstudy.org

Washington
WASHINGTON UNIVERSITY IN ST. LOUIS
School of Medicine

SEP 30 200

APPROVED

Jonathan M. Green, M.D.
Associate Dean and Executive Chair

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Jonathan M. Green, M.D.
Associate Dean and Executive Chair
SEP 30 200

Washington University in St. Louis
SCHOOL OF MEDICINE

August 24, 2010

Dear Community Members/Advocates:

If you are considering treatment with an antipsychotic medication for your child or for a child you care for, I would like you to know about the Children's Health Care Study at the **Washington University School of Medicine** as an option to receive additional medical care.

The Children's Health Care Study is funded by the National Institute of Mental Health to study the metabolic effects of antipsychotics in children, focusing on three second generation antipsychotic medications (Zyprexa, Abilify, and Risperdal) that are used in **children ages 6-18 for aggressive behavior**, in order to know more about the effect of these medicines on body weight, cholesterol and sugar. Reasons for interest and concern:

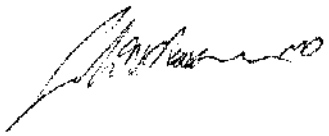
- Antipsychotic medications are often being used by doctors to treat aggresion and irritability in children, with FDA approval for some but not all uses, and growing use in the community (need NY Times links)
- The Centers for Disease Control (CDC) has noted an "epidemic" of childhood obesity and diabetes (blood sugar problems) (http://www.cdc.gov)
- The American Diabetes Association (ADA) has noted that antipsychotic medications can sometimes contribute to weight gain and increased risk of diabetes and cholesterol problems; ADA recommends regular measurement of weight/fat, and blood sugar and cholesterol during antipsychotic therapy (http://care.diabetesjournals.org/cgi/content/full/27/2/596)
- **Many persons can take antipsychotic medications and not get these problems**, but regular measurement of weight/fat and blood sugar and cholesterol is important to make sure that risk remains low during treatment, but this monitoring is often not done in the community
- This study provides careful and detailed safety monitoring of antipsychotic treatment, more than is available from doctor's offices and clinics
- Children in this study receive careful diagnosis and additional medical care and psychiatric support at no cost, and they are reimbursed for time and travel.
- We work closely with families and health care providers to give the best possible care for children in the study, offering supplemental visits and extra family attention required to stabilize children on the new antipsychotic therapy.
- We perform all needed assessments, while providing child's physicians and other important care providers with progress notes and the results of tests, as families and physicians direct.

The Research Process: Participation in this project is approximately 12 weeks. During that time, participants are evaluated at least weekly when they start medication, and have careful medical evaluations during five visits to the Washington University School of Medicine's Pediatric Clinical Research Unit (PCRU) and/or Clinical Research Unit (CRU) at Barnes-Jewish and Children's Hospitals. The medical tests are done once at the beginning of the study, again at 6 weeks, and then again three months after starting the medicine.

If you and your child's physician are considering treatment with an antipsychotic medication for the first time, please contact us for more information about the study. You can call our study coordinator, Martha

Hessler, at (314) 362-2423 or (888) 363-2423 or email at hesslerma@psychiatry.wustl.edu. You can also check our website at www.childhealthstudy.org for details.

Sincerely,



John W Newcomer, M.D.
Gregory B. Couch Professor of Psychiatry, Psychology and Medicine
Director, Clinical Trials Unit, Institute of Clinical and Translational Sciences (ICTS)
Co-Director, Regulatory Support Center, ICTS
Medical Director, Center for Clinical Studies

SEP 30 2010

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Washington University in St. Louis
SCHOOL OF MEDICINE

Jonathan M. Green, M.D.
Associate Dean and Executive Chair

August, 2010

Dear Colleague:

Greetings and thank you for your help in the continued success of the Children's Health Care Study (CHCS) at Washington University School of Medicine! As you may have already heard, **the CHCS**, funded by the National Institute of Mental Health, studies the metabolic effects of antipsychotics in children, focusing on three second generation antipsychotic medications (Zyprexa, Abilify, and Risperdal) that are used in **children ages 6-18 for aggressive behavior.** We are nearing the end of our fourth year, and have enrolled more than 200 participants towards our target goal of 240 over the course of 5 years.

Pediatric patients can experience changes in weight and metabolism during treatment with these medications, and more information regarding treatment-emergent effects in children is desperately needed. The goal of the CHCS is to ultimately produce the data needed to guide prescribing practices while at the same time providing safety monitoring for children who are currently in need of these medications. Since we know making the decision to use an atypical antipsychotic in a child is not simple, CHCS provides careful evaluation by highly trained doctors specializing in child and adolescent psychiatry, supplemented with the use of well-validated diagnostic assessments to ensure an accurate diagnosis.

Further:

- **In the last decade, there has been an alarming increase in the number of overweight children and adolescents in the U.S.** (Ogden et al, JAMA 2006; 295(13):1549-55, PDF attached). Many studies have shown that earlier onset of obesity leads to higher rates of morbidity and mortality from obesity-related illnesses, such as diabetes and cardiovascular disease.
- **Antipsychotic medications are increasingly prescribed to treat aggresion and irritability in children**, with FDA approval for some, but not all uses (New York Times, June 2006: Use of Antipsychotics in the Young Rose Fivefold). These medications have been associated with changes in weight, cholesterol and blood sugar in adults (Newcomer & Hennekens, JAMA 2007; 298(15): 1794-96, PDF attached). Children treated with these medications are showing concerning changes in these measures as well.
- **Rates of metabolic monitoring in patients treated with antipsychotics is alarmingly low,** despite clear evidence of increased cardiovascular risk and monitoring recommendations jointly endorsed by the American Diabetes Association (ADA) and the American Psychiatric Association (APA). Recently, a national study of monitoring rates in patients taking antipsychotics showed that children receive the least monitoring of all (Morrato et al, J Clin Psychiatry 2008; 69(2):316-22, PDF attached).
- **Many children can take antipsychotic medications without developing these problems**, but regular measurement of weight/body-fat, blood sugar and cholesterol are necessary to make sure that risk remains low during treatmet. CHCS provides more detailed safety monitoring of antipsychotic treatment than is available in most community clinic settings.

Benenfits of involvement in the CHCS include:

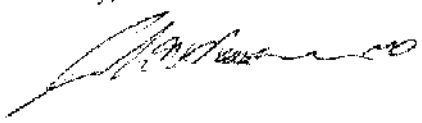
- Careful and timely psychiatric evaluation by child and adolescent psychiatrists with diagnosis using both extensive clinical assessments and validated diagnostic tools.

- Medical monitoring performed by study doctors and nurses using state-of-the-art techniques to assess for metabolic changes during treatment.
- Close communication with referring/treating providers regarding treatment response and side effects.
- Assistance with arranging appropriate treatment for those children who are not eligible for study participation, and referrals for follow-up treatment at study completion prior to exiting CHCS.
- Reimbursement for time and travel.

The Research Process: Participation in this project is approximately 12 weeks. During that time, participants are evaluated at least weekly when they start medication, and have careful medical evaluations during five visits to the Washington University School of Medicine's General Clinical Research Center (GCRC) at St. Louis Children's Hospital, recognized as a top-10 Children's Hospital by U.S. News and World Report (US News and World Report, August 2007). The medical tests are done once at the beginning of the study, again at 6 weeks, and then again three months after starting the medicine. Children who experience significant changes in metabolic parameters may be asked to return for a 6 month follow-up visit and fasting labs.

If you are considering treatment with an antipsychotic medication for the first time, please contact our study coordinator, Martha Hessler, at (314) 362-2423 or (888) 363-2423 or email at hesslerma@psychiatry.wustl.edu for more information. You can also check our website at www.childhealthstudy.org for details. We are looking forward to working with you!

Sincerely,



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