Medical Research Informed Consent

Title of Study: *Skeletal Muscle Molecular Mechanisms of Atypical Antipsychotic-Induced Insulin Resistance in Human Subjects*

Principal Investigator (PI): Kyle J. Burghardt, Pharm.D.
259 Mack Avenue
Suite 2190
Detroit, MI 48201
313-577-3132

Funding Source: National Institutes of Health
Wayne State University Eugene Applebaum College of Pharmacy and Health Sciences Faculty Research Award Program (FRAP)

Location(s): Wayne State University Clinical Research Center

Purpose

You are being asked to be in a research study on how medications called antipsychotics interfere with the body's ability to handle insulin because you are a healthy person. This study is being conducted at Wayne State University Clinical Research Center. The estimated number of study participants to be enrolled at Wayne State University Clinical Research Center is about 76. **Please read this form and ask any questions you may have before agreeing to be in the study.**

In this research study, we are looking at how an antipsychotic called olanzapine causes insulin resistance. Insulin is a hormone produced by the body to control sugar in the blood (blood glucose). Insulin resistance is a state when the body is not using insulin correctly, and more insulin is needed in order to maintain a normal blood glucose level. Insulin resistance is common in patients treated with antipsychotic medications. Long-term insulin resistance can lead to type 2 diabetes and heart disease.

The study doctors think that one possible explanation for insulin resistance caused by antipsychotics may be a change in the way the body utilizes its genetic code to control how its small molecules, like proteins, work within the skeletal muscle. We are looking at the skeletal muscle because it is a very important place where our body stores the sugar we eat. When our muscle is not able to store sugar properly it can lead to insulin resistance. The purpose of this study is to look at how an antipsychotic called olanzapine causes changes in our genes and small molecules in the skeletal muscle of healthy volunteers. Healthy volunteers are being used in this study in order to study these short-term changes more accurately without other factors like certain diseases or medications that could influence the outcomes. This study design is based off of 9 other studies that have given olanzapine to healthy volunteers for a short period of time safely and with no lasting effects. Participants in this study will take a blinded study drug (olanzapine or placebo) which will be administered by the study doctors. Neither you or the doctors will know what you have been given. Olanzapine is an FDA approved drug and we will be giving it for a short time period. It is hoped that information from this study will

help doctors find out how antipsychotics cause insulin resistance so that we can prevent antipsychotic side effects in patient populations that need these medications for treatment of their diseases.

Study Procedures

If you agree to take part in this research study, you will be asked to come to the Clinical Research Center at Wayne State University for three separate visits. On your first visit (Visit 1) you will come to the research center to read and sign the consent form. If you agree to participate in the study, we will continue with screening tests that will last for about 1 hour. If you meet all screening criteria you will be invited to come to the Clinical Research Center for two more visits. The second visit (Visit 2) and third visit (Visit 3) will include a measurement of several body variables, a measurement of how much energy you expend each day, an intravenous glucose test with blood draws and a muscle biopsy. Visit 2 and Visit 3 will last about 4-5 hours each. At Visit 2 you will be given a blinded study drug to take (either olanzapine or placebo). You will not know which drug you are taking. Visit 3 occurs exactly 7 days after Visit 2 and you will be asked to take home and wear an activity tracking wrist monitor and complete daily dietary logs at home between the two visits. The details of these visits are described below. Please note that if you have a medication that you have to take with food, you need to consult your own licensed physician to determine whether you can participate in this study and if you are able to skip or delay a morning dose on each visit day. Our licensed study pharmacist will also assess the medications you take to see if they effect glucose or can interact with the study drug. You will be able to take your dose of medication following the completion of each visit. If your physician or our licensed pharmacist determines you cannot participate in this study due to your medication or you cannot skip a dose, you will not be eligible for the study.

Visit 1: Consent & Screening

You will be asked to come to the clinical research center in the morning (within 1-3 hours of when you normally get up) for the screening tests and the visit will take about 1 hour. You will have to fast for this visit, which means you should not eat or drink anything but water after 10 p.m. the night before, and you should not eat breakfast the morning of the visit. The Screening/Consent visit procedures may be completed on two separate days if required. For example, if you do not fast, we will ask that you come back to finish the screening visit at another time. You will also have the option to take the consent form home and discuss with family, physician, etc. prior to signing at Visit 1 and participating in the study.

Once you have signed this consent form, a member of the research team will go through the procedures associated with Visit 1 to see if you qualify for Visits 2 and 3. For the rest of the study any information or samples collected from you will be given a coded identifier that is not related to your name or identifying information in any way. We do this to protect your information and privacy.

The following procedures will occur during visit 1:

- Questionnaires: We will collect information about your health and medication history including any medications you have taken or are currently taking. We will ask you about your lifestyle including how much you exercise, smoke and how much alcohol you drink. We will ask you about your past psychiatric history and how you think.

- We will measure your vital signs.
- We will measure your height, weight, and your waist and hips. We will also measure your body fat percentage using a very weak electric current. For this procedure, two small electrodes (like a small piece of tape with a wire connected to a meter) will be taped to your hand and your foot. A very weak electric current will be passed through your body by the electrodes in order to measure your body fat. You will not feel this current and there are no known effects on your body.
- You will have some blood (65 ml or about 4 and 1/3 tablespoons) and urine collected for laboratory tests. Female participants will be given a urine pregnancy test.
- We will not require you to take any study drug at this point. Visit 1 is only a screening visit to see if you qualify for the other study visits that include taking the study drug.

After Visit 1, a member of the research team will review the results from the screening tests and decide if you still qualify for visits 2 and 3. A member of the research team will contact you to let you know whether or not you qualify for visit 2.

Visits 2 and 3: Treatment Visits

If the results of the screening tests tell us that you are eligible for the rest of the study, you will be asked to come to the Clinical Research Center two more times. Visits 2 and 3 occur 7 days apart and will occur within 1-3 hours of when you normally get up. If you are a female we will ask you about your menses (cycles) to have you come in during a specific time. The hormones associated with menses can affect certain measures in our study so we do this to take our measurements at the same time of the cycle. You will have to fast for both visits, which means you should not eat or drink anything but water after 10 p.m. the night before, and you should not eat breakfast the morning of the visit. For each visit the following will occur: measurement of several body variables, measurement of your energy expenditure, an intravenous glucose test with blood draws and a muscle biopsy. Visit 2 and Visit 3 will last about 4-6 hours each.

To complete the biopsies at Visits 2 and 3, if you take anticoagulants on a regular basis you must stop using them for at least 7 days before each visit. You should also avoid taking them for 3-5 days after Visit 3. Anticoagulants include such things as aspirin, NSAIDS (e.g., ibuprofen, Motrin, Aleve, Advil), anticoagulants/antiplatelet medications (e.g., Coumadin, Plavix, Lovenox, Rivaroxaban, Apixiban, Dabigitran), herbs (e.g., red clover, ginger, black Cohosh and liquorice) and possibly supplements like vitamin E. If you are not able to stop taking any of these medications will you not be able to participate in Visits 2 and 3.

Prior to Visits 2 and 3 we will require you to refrain from intense physical exercise (anything more than light walking) for 7 days prior to Visit 2 and for 2-4 days following Visit 3. We ask that you do this so that it does not interfere with study measurements and because of the biopsies that we take from your leg. If you cannot refrain from intense physical exercise you will not be able to participate in the study.

Finally, if you take medications our study pharmacist will assess for any possible interactions with the study drug. If an interaction is identified, you will be excluded and cannot participate. Additionally, you will need to talk to your own physician to find out if you can participate in this study due to the study drug and because we require you to fast for all visits.

The following procedures will occur during visits 2 and 3 (once per each visit):

- You will be asked about any changes in your health since the previous visit. At visit 3 you will be asked about any suspected side effects from the drug therapy. We will also ask you questions about your health, your hunger, your lifestyle including alcohol intake and how much your exercise. We may collect a urine sample from you for lab tests. Female participants will be given a urine pregnancy test. We will also collect a mouth swab sample from you.
- We will measure your vital signs.
- We will measure your height, weight, and your waist and hips. We will also measure your body fat percentage using a very weak electric current. For this procedure, two small electrodes (like a small piece of tape with a wire connected to a meter) will be taped to your hand and your foot. A very weak electric current will be passed through your body by the electrodes in order to measure your body fat. You will not feel this current and there are no known effects on your body.
- We will measure how much energy your body expends each day using an "indirect calorimetry" machine. This machine measures how much oxygen and carbon dioxide you breathe by placing a plexi-glass canopy over your head while you are laying down. The canopy looks like a space helmet. The procedure will include a short 5 to 15-minute period where you will rest quietly and get used to the equipment. This will be followed by a 15 to 30-minute period where you continue to lay still and rest and we take measurements of how much you breathe. You will be required to stay still for about 20 to 40-minutes.
- A small sample of muscle and fat will be removed from the thigh of one of your legs using a special sterile needle and technique (a muscle biopsy) by a licensed medical doctor. We will conduct 2 muscle biopsies per visit (one at the start and one at the end). For the biopsy procedure, we will clean your thigh and use a numbing medicine (lidocaine) to numb a small area in your skin. Next, we will make a small cut in your skin (about one inch). A special needle will then be passed through this cut into the muscle, and a piece of muscle tissue about the size of a pea will be removed (See Figure 1). It can take up to 3 passes to collect the necessary amount of muscle tissue (~200mg). The doctor will also take a sample of fat (up to 100mg) from the same site. The place where we made the cut will be closed with a "steri-strip" which is like a "Band-Aid" and a pressure wrap will be applied to keep the incision closed. A cold pack will be placed over the cut for 10-15 minutes after the biopsy. We will provide you with specific instructions to take care of your biopsy.

Figure 1. Size of muscle tissue sample

- We will conduct an intravenous sugar (IV sugar) infusion test to see how your body handles sugar. A catheter will be placed in a vein in the back of your hand or in your arm, and your hand or arm may be warmed with a heating pad. We will draw baseline blood for labs and analysis of small molecules from this IV as well as measure sugar and insulin during the procedure.
- A second intravenous (IV) catheter will be placed in a vein in your opposite arm to give you infusions of solutions (glucose and insulin). After the second IV is placed you will be given an infusion of insulin followed by an infusion of glucose which we will adjust to keep your sugar level normal. We will take small blood samples to measure your sugar and other small

molecules every few minutes (anywhere from 1 to 20 minutes) for about 2-3 hours. The total amount of blood to be collected is about 170 mL (about 11 and 1/3 tablespoons) per visit.

- At the end of Visit 2 you will be given a blinded study medication to take for a total of 7 days. The medication will either be an antipsychotic called olanzapine or a placebo containing an inactive ingredient (sugar pill). You and the study staff will not know which medication you are taking. A licensed study pharmacist will counsel you on the medication including how to take it and what to expect. We also provide that information below and will give you a drug information sheet. The directions for the medication are: "Take one capsule by mouth daily on days 1-2, two capsules by mouth daily for days 3-7 and one capsule by mouth daily for days 8 and 9."
- At the end of Visit 3, you will be given two more days of study drug. We do this so that you decrease the dose before stopping it.

The Following will occur between Visits 2 and 3:

- We will have you complete a daily dietary log from visit 2 to visit 3. We will give you instructions on how to complete this log for each day starting at Visit 2 and ending at Visit 3. During our follow-up phone calls we will remind you to continue to complete your dietary logs.
- We will give you an activity monitor to wear on your wrist between Visits 2 and 3. We will give you instructions on how to wear the device along with an information sheet. We ask that you wear this device as much as possible. You are able to get the device wet so it can be worn in the shower or bath tub. We will collect the device from you when you come back from Visit 3.
- We will call you several times after Visit 2 (days 2, 4 and 6 after visit 2) to follow-up with you and ask about any changes in your health or side effects you may be experiencing since Visit 2. We will also follow-up with you about your dietary logging, activity monitor and preparing for Visit 3. We expect each call to last 5-15 minutes

The results of these tests from all visits will not appear in your medical record and will not be released to anyone unless required to do so by law. Please indicate if you would like us to send the results of any laboratory tests to you or your primary care provider. Information about genetic or other small molecule tests will not be released as they are entirely experimental.

□ No, I would not like the results of my laboratory tests sent to my physicians or me
□ Yes, I would like the results of my laboratory tests sent to my physicians or me

Name of Person to Send Tests to:
Address:

After Visit 3:

- You will be given two more days of study medication to take in order to discontinue the study medication after decreasing the dose safely.
- We will call you 2-3 days after Visit 3 to see how you are feeling and answer any final questions you may have.

Benefits

As a participant in this research study, there will be no direct benefit for you; however, information from this study may benefit other people that need to take antipsychotics for their well being now or in the future. We hope that the information we get from this study will help us prevent side effects and increase the length and quality of life for patients that take antipsychotics.

Risks

By taking part in this study, you may experience the following risks:

General Discomforts
You will have to fast for at least 10 hours before each visit and you may experience hunger symptoms during the study. This may cause some discomfort.

Skipping one dose of medication in the morning
If you have a medication that you have to take with food, you need to consult your own licensed physician to determine whether you can skip a dose on the visit day, and may take it after each visit is completed. If you cannot skip a dose, you will not be eligible for the study.

Refraining from intense physical exercise
In order to participate in this study, you must refrain from intense physical exercise 7 days before Visit 2 and 5 days after Visit 3. This is done because intense exercise may interfere with the measures we are performing in this study. Also, following the biopsies, you will have to allow your biopsy site time to heal before engaging in any intense physical activity. Light walking that is similar to what you have always done is allowed during the study. If you cannot refrain from intense physical exercise you will not be eligible for the study.

Questionnaires
You will be interviewed about your past medical history, thoughts, and functioning, as well as having questions about your smoking, eating, physical activity, alcohol intake and medications. We will also ask you about your hunger and have you keep a log of what you eat every day. These interviews, questions and testing may cause you to feel emotionally uncomfortable and have some distress.

Blood drawing
Blood samples will be obtained from your veins. Possible side effects of obtaining blood samples are pain, bruising, bleeding, or infection at the blood draw site. Occasionally nausea, lightheadedness or fainting may occur. In order to minimize the number of needle sticks during visits 2 and 3 we will insert a catheter in your arm for the blood draws. For visit 1, we may insert a butterfly needle in order to collect the blood sample. On occasion, a catheter or needle may need to be replaced because we cannot draw blood from it or it falls out of the vein. We will attempt to insert a catheter up to a total of 5 times during a visit however you can decline to insert a catheter at any point. If the catheter cannot be placed within this amount of times, you may be excluded from the study or we may have you come back if we cannot place a catheter within those amount of tries. About 65 mL (about 4 and 1/3 tablespoons) of blood will be drawn during visit 1. In addition, another 170 mL (about 11 tablespoons) will be drawn per visit for Visits 2 and 3. The total amount of blood that will be drawn over the three visits is about 405 ml (~27 tablespoons or about 1 and ½ cups). This is less than the

amount needed for a single blood donation (500 ml). The risks are greatly reduced by having an experienced doctor or nurse placing the lines, by the use of sterile techniques to avoid infection and having skilled medical staff perform study procedures.

Biopsy during Visit 2 and 3

The numbing medication may burn or sting when injected (before the area becomes numb). After the anesthetic wears off, the area may be sore for about a week. You will feel some pressure or tugging in site where the tissue was obtained. About 1/3rd of people reported that they felt cramping or pain. The pain is mild to moderate and lasts 5-10 seconds. The pain usually stops when the needle is removed. Some discomfort, like a sore muscle, may be present for up to a week after the procedure. You will be provided information about caring for your biopsy site after the visit.

The most common discomforts from the muscle biopsy are:
-Pain and bruising (1-4%)
-Feeling lightheaded or faint during the procedure (about 3%)
-Bleeding at the site (less than 1%)
-Infection at the site (less than 1%)
-Allergic reactions to the numbing medicine which could include a skin sore, swelling, or hives (less than 1%)

Bleeding will be seen as bruising at the place on your leg where we take the muscle or fat was taken. The swelling or bruising usually goes away with rest within 2-3 days, although sometimes it may take a week. More severe bleeding is possible, but has occurred in less than 1 in 500 of these procedures. Very rarely some subjects may experience numbness or tingling at the biopsy site and damage to the tissues in the area is also very rare (2 in 1,600 cases). This usually is temporary and goes away in a few days. If pain, swelling, bruising, or numbness does not subside one-week after the procedure you should contact your physician immediately.

Use of anticoagulants, such as aspirin, NSAIDS (e.g., Motrin, Ibuprofen, Advil), anticoagulants/antiplatelet medications (e.g., Coumadin, Plavix, Lovenox), herbs (e.g., red clover, ginger, black Cohosh, liquorice) and possibly supplements, increase your risk of having increased bleeding during the biopsy procedure, and increased bruising (hematoma) after the procedure. Therefore, you must refrain from their use for a minimum of 18-21 days (7 days prior to Visit 2 and 3-5 days after Visit 3). You must consult your physician before stopping any medications taken on a regular basis. If you are unable to refrain from their use you will not be able participate in this study. If you experience one of these problems you should call the research center right away.

Lidocaine:

Allergic reaction is a possible side effect of the numbing medicine used for the biopsies. Symptoms of an allergic reaction may include a sore skin, swelling, or hives (less than 1%). You may experience tingling or burning sensations or lightheadedness when the lidocaine is first injected. If you have a history of allergic reaction to lidocaine you cannot participate in this study.

Indirect Calorimetry Test

The canopy that is placed over your head during this test may make you feel claustrophobic. If you are claustrophobic you may not be eligible for the study.

Intravenous Infusion Glucose Test

We will measure how your body handles sugar (glucose) and insulin with an intravenous infusion glucose test. For this test you will have a catheter placed in both arms. One catheter will be used to draw blood and the other will be used to give you infusion solutions of sugar and insulin.

SugarBolus: Regular glucose or sugar, is normally found in foods that you eat and is not harmful when infused.

Insulin Bolus: Low blood sugar (hypoglycemia) is a possible risk of the insulin bolus however this risk of this is very low for this test as the insulin bolus is very small and it will follow the sugar bolus. Symptoms of low blood sugar levels include hunger, sweating, heart pounding, drowsiness, anxiety, and trembling. Your blood sugar level will be checked every 2 - 20 minutes during the test. If your blood sugar level drops we will know immediately and we will give you glucose to keep your blood sugar normal. In the event that unanticipated complications occur, enough sugar will be given to you through one of the lines we will place in your veins to restore your blood sugar to normal levels.

Olanzapine (study drug)

During this study you will be assigned to receive a blinded study drug meaning that you will not know if you are taking olanzapine or placebo. We believe the risks of olanzapine based on previous similar studies is minimal. If you were assigned to olanzapine you would only take a total of 9 days of olanzapine doses (total = 70mg) which is a short time period. These 9 days include two days of building up the dose at initiation and two days of decreasing the dose at discontinuation to enhance safety even further. If you are on a medication our study pharmacist will check to see if any interaction is possible, if so you cannot participate. Risks of this amount of olanzapine may include the following: constipation, dry mouth, feeling weak, upset stomach, dystonia (muscle stiffness), akathisia (restlessness), tremors (shakes), dizziness, insomnia, blurry vision, irregular heartbeat, drowsiness and postural hypotension. There is also a risk for seizures however this risk is very small and we will further minimize the risk by not allowing you to participate in the study if you have a personal or family history of seizures. To date, there has been 9 studies administering olanzapine (at equivalent doses to our proposed study) and within these studies there has been no dropout due to adverse events and only one event of low blood pressure upon standing when a patient was stopping olanzapine. We will further minimize this risk by gradually decreasing the drug when we have you stop it. We will also not allow you to participate if you have a history of fainting and we will instruct you on standing slowly after sitting or laying for extended periods of time. Within the previous studies that are similar to ours, the most common side effects are sedation and dry mouth which we will minimize by having you take the study drug before bedtime and having you avoid any alcohol use during the study. Other risks of olanzapine include a syndrome caused by the drug where you have fever, sweating and unstable blood pressure and tardive dyskinesia (which are movement disorders) however the chance of this is very low with atypical antipsychotics like olanzapine. In summary, olanzapine is associated with some other adverse experiences (incidence 1%-10%) including: asthenia, increases in heart rate, palpitations, facial flush, sensory impairment, headache, nausea, vomiting, dry mouth, changes in appetite, easy laughing, euphoria, restlessness, panic attacks, anxiety/nervousness, paranoid reaction, confusion, dizziness, drowsiness, and impairment in coordination. We will provide you with a drug information sheet that you can look over. Our study pharmacist will go over this sheet in detail with you and answer any questions you may have. Should

you have questions at any time about the study or the study drug you can call the PI Dr. Kyle Burghardt, Pharm.D., at 313-577-3132.

Placebo (study drug)
The placebo will contain inactive ingredients and there are no known risks with taking placebo.

Risk for Pregnant Women
Participation in this study involves unknown risks to women who are or may become pregnant, to unborn babies, and to nursing infants. Therefore, to minimize the risks and to take part in this study, medically acceptable forms of birth control are required by (a) women during the study for at least 1 month after the study drug has been stopped and (b) men during the study and for at least 3 months after the study drug has been stopped. Men must wait longer to account for the time needed for sperm to fully mature compared to eggs in women.

Medically acceptable birth control may include the following methods: barrier protection—such as condoms used with contraceptive jelly, intrauterine devices (IUD), and abstinence (not having sex). Oral contraceptives may be used, but should not be the only means of protection. The use of medically acceptable birth control may not be necessary if the female partner has had permanent hysterectomy (sterilization) with some form of tubal occlusion, or if the male partner has had a vasectomy (so long as the female partner does not get a new partner). No birth control method completely eliminates the risk of pregnancy.

In order to participate in this study, you must use at least two forms of medically acceptable birth control. In addition to the pregnancy testing done prior to the start of the study, additional testing will be done at the following times: Visits 2 and 3.

Please state the two types of birth control that will be used during participation in this study

_____	_____	_____
Type 1 of Birth Control	Type 2 of Birth Control	Initials/Date

You should inform the study doctor (PI) immediately if you or your partner intends to get pregnant, or if you or your partner should become pregnant while participating in this research study, so that your choices and options can be explored and discussed.

Privacy and Economic
One risk of giving samples for this research may be the release of your name that could link you to the stored samples and/or the results of the tests run on their samples. There also is a risk of economic difficulty if their genetic information was released.

Additional Risks
In addition, as with any research, there is some possibility that you may be subject to risks that have not yet been identified.

If a medical emergency were to occur during one of the tests, we will call "911" to bring emergency medical technicians to the clinical research center and you will then be transported to the Emergency

Room. If a licensed physician is not present in the room, he or she will then receive an emergency page. There will be a licensed physician within 3-5 minutes of the research unit at all times.

The researchers will try to minimize these risks in the following ways:

In order to minimize the risks during the blood draws, biopsies, and intravenous glucose test we are having experienced personnel (nurses and/or physicians) at the Clinical Research Center place IV lines and run the procedures. The PI and the Clinical Research Center personnel have performed many blood draws, intravenous tests and biopsies in the past. We will provide you with a snack and/or lunch after visits 2 and visit 3 to help with any light-headedness or upset stomach.

We have two Board-certified physicians on our protocol and they, or their physician designate(s), will be available on call during all intakes and between the visits to evaluate and recommend further evaluation and treatment for the emergence of any adverse events/side effects. Participants taking prescription or over-the-counter drugs that are known to interact with olanzapine will be excluded. We will exclude participants with a known sensitivity to the active drug or capsule excipients or to the numbing medication used during the biopsy. Pregnant participants will be excluded from participation because there is insufficient data to assure safety of the fetus during olanzapine exposure and pregnancy may introduce unintended influence on our study measures. In addition, nursing mothers will be excluded from the study due to unknown risks to an infant exposed to olanzapine through breast milk.

Olanzapine (Zyprexa®) is an FDA-approved prescription atypical antipsychotic used in the treatment of schizophrenia, bipolar disorder and major depressive disorder. For this study, olanzapine will be administered by the oral route. There is no evidence that participation in controlled, acute olanzapine studies such as this one increases the risk for significant side effects, including those conducted in laboratories (with 15+ years of experience) from which the current protocol is based. Should you desire to see these studies the study personnel will provide them to you at no cost. There are low social, legal or psychological risks associated with ingestion of olanzapine as a volunteer in this research study. Because you are a physically healthy volunteer, there are no alternative treatments. Participants will be fully de-briefed following the study. During debriefing, any questions participants may have will be answered. The study will not be un-blinded until it is complete so we will not be able to tell you whether you received placebo or olanzapine.

To minimize the risks associated with the interview, you can refuse to answer any questions that we ask.

To prevent the risks associated with release of information associated with this research, all study samples will be given a code. Only the study staff will know the code. The master list containing the name that belongs to the code will be kept on a secure password protected server in a password-protected file. Only Dr. Burghardt and approved study members will have access to your name and identifying information. **After completion of the study this list will be destroyed and your research record will no longer be identifiable for this study.** Additionally, the results from the genetic testing will not be made available to you. Your biological samples and the data obtained from the genetic and small molecule testing will be examined only in relation to how your body reacts to the study drug and not for the purpose of diagnosis of a medical condition. There have been some exceptions made when something is discovered about a gene that might significantly affect health

care, and research participants have been notified. However, we think that such a possibility with this study is very unlikely, and you should not expect to learn anything about yourself from these genetic tests. We consider all of the genetic and small molecule analyses from this study to be entirely experimental. However, we will let you know if you test positive for laboratory values outside of the normal range so that you can follow up with your primary care physician to continue the screening process.

The following information must be released/reported to the appropriate authorities if at any time during the study there is concern that:

- you disclose illegal criminal activities, illegal substance abuse or violence

There may also be risks involved from taking part in this study that are not known to researchers at this time.

Alternatives

The only alternative to this voluntary study is for you to not participate.

Study Costs

You will not be charged for the study drug however, your participation in this study could result in increased costs to you and/or your insurance company for additional monitoring and tests (for example, due to an adverse event that occurs during the study).

Compensation

For taking part in this research study, you will be compensated for your time and inconvenience. The following payment schedule will be used for compensation.

Visit 1		**Visit 2**		**Visit 3**	
Questionnaires	$5	Questionnaires	$5	Questionnaires	$5
Blood Draw	$10	Biopsy	$75	Biopsy	$75
Clinical Measurements	$5	Infusion test	$75	Infusion test	$75
		Resting Energy Expenditure	$5	Resting Energy Expenditure	$5
		Clinical Measurements	$5	Clinical Measurements	$5
				Dietary Logging	total $25 possible (prorated on amount completed)
				Physical Activity Measurement	total $25 possible (prorated on time accurately worn)
				Took Study Medication	$50
Total Visit 1 Compensation	$20	Total Visit 2 Compensation	$165	Total Visit 3 Compensation	$265

The total compensation possible for completing the entire study is $450. You will be paid in cash for your participation and you may be paid in the form of gift cards, a "ClinCard" or checks for larger sums (>$60). Please note that check processing may take up to 10 weeks to complete. If your participation is stopped early for any reason you pay will be prorated based on what you have completed and/or based on the time you have spent in the study (defined by time spent in-person at the current visit) at a rate of $20/hour, whichever is larger. If you are not a U.S. citizen and/or not a U.S. tax payer 30% of the compensation will be withheld by WSU before a check is disbursed.

Research Involving the Future Use of Biological Specimens

Your volunteered time and samples are very valuable in our effort to reduce antipsychotic side effects. We would like to store the biological specimens and genetic material (or DNA) with the assigned numerical code specific for this study. No names will be used on these samples. The DNA and other samples will be stored within the Wayne State University Eugene Applebaum College of Pharmacy and Health Sciences in Dr. Burghardt's locked laboratory for future studies investigating antipsychotics and their effects. Only Dr. Burghardt and specific personnel (dictated by Dr. Burghardt) will have access to these samples which will be kept indefinitely. If you do not wish to give permission you can mark below to indicate that you do not want your biological samples or DNA used for future studies. Your samples will then be destroyed after the study ends and we have accomplished its objectives. You may also cancel your permission at any time before the end of the study by writing to the principle investigator listed at the top of this form. However, after the study ends, we will have no way of identifying your de-identified samples making it impossible for us to destroy your samples at that point.

☐ Yes, I would like my biological specimens and/or DNA to be used for future research.

_____
Initial and Date

☐ No, I would not like my biological specimens and/or DNA to be used for future research

_____
Initial and Date

Genetic Information Nondiscrimination Act (GINA):

A Federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.

- Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

Be aware that this Federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

Research Related Injuries

In the event that this research related activity results in an injury, treatment will be made available including first aid, emergency treatment, and follow-up care as needed. No reimbursement, compensation, or free medical care is offered by Wayne State University.

If a "research related injury" results from your participation in this research study, medical treatment will be provided. The costs for all your medical treatment will be billed to you and/or your insurance. A "research related-injury" means injury caused by the product or procedures required by the research which you would not have experienced if you had not participated in the research.

It is important for you to follow your physician's instructions including notifying your study physician as soon as you are able of any complication or injuries that you experienced.

You will not be paid for any other injury- or illness-related costs, such as lost wages. You are not waiving any legal rights and are not freeing the sponsor, Principal Investigator, or hospital of any malpractice, negligence, blame or guilt by participating in this study.

If you think that you have suffered a research related injury, contact the PI right away at 313-577-3132.

Confidentiality

All information collected about you during the course of this study will be kept confidential to the extent permitted by law. You will be identified in the research records by a code name or number. Information that identifies you personally will not be released without your written permission. However, the study sponsor, the Institutional Review Board (IRB) at Wayne State University, or federal agencies with appropriate regulatory oversight [e.g., Food and Drug Administration (FDA), Office for Human Research Protections (OHRP), Office of Civil Rights (OCR), etc.) may review your records.

When the results of this research are published or discussed in conferences, no information will be included that would reveal your identity.

A description of this clinical trial will be available on http://ClinicalTrials.gov as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Voluntary Participation/Withdrawal

Taking part in this study is voluntary. You have the right to choose not to take part in this study. If you decide to take part in the study you can later change your mind and withdraw from the study. You are free to only answer questions that you want to answer. You are free to withdraw from participation in this study at any time. Your decisions will not change any present or future relationship with Wayne State University or its affiliates, or other services you are entitled to receive.

If, for any reason, you withdraw your participation from the study and you are taking the study drug we will have you gradually stop taking the study drug for safety reasons.

The PI may stop your participation in this study without your consent. If you have any side effects that are very serious or if you become ill during the course of the research study you may have to drop out, even if you would like to continue. The PI will make the decision and let you know if it is not possible for you to continue. The decision that is made is to protect your health and safety, or because it is part of the research plan that people who develop certain conditions or do not follow the instructions from the study doctor may not continue to participate.

While taking part in this study you will be told of any important new findings that may change your willingness to continue to take part in the research.

Questions

If you have any questions about this study now or in the future, you may contact Dr. Kyle Burghardt or one of his research team members at the following phone number 313-577-3132. If you have questions or concerns about your rights as a research participant, the Chair of the Institutional Review Board can be contacted at (313) 577-1628. If you are unable to contact the research staff, or if you want to talk to someone other than the research staff, you may also call the Wayne State Research Subject Advocate at (313) 577-1628 to discuss problems, obtain information, or offer input.

Consent to Participate in a Research Study

To voluntarily agree to take part in this study, you must sign on the line below. If you choose to take part in this study you may withdraw at any time. You are not giving up any of your legal rights by signing this form. Your signature below indicates that you have read, or had read to you, this entire consent form, including the risks and benefits, and have had all of your questions answered. You will be given a copy of this consent form.

Signature of participant / Legally authorized representative*	Date
Printed name of participant / Legally authorized representative *	Time
Signature of witness**	Date
Printed of witness**	Time
Signature of person obtaining consent	Date
Printed name of person obtaining consent	Time

*Remove LAR reference if you don't intend to consent participants that have or may have LAR.

**Use when participant has had this consent form read to them (i.e., illiterate, legally blind, translated into foreign language).

APPROVAL PERIOD

JUL 12 2018 APR 04 2019

WAYNE STATE UNIVERSITY
INSTITUTIONAL REVIEW BOARD

Signature of translator	Date
Printed name of translator	Time

Continue to HIPAA Authorization on next page

HIPAA Authorization

A federal regulation, known as the "Health Insurance Portability and Accountability Act (HIPAA)" gives you certain rights concerning the use and disclosure (sharing with others) of your Protected Health Information (PHI). This regulation provides safeguards for the privacy and security of your information. Your permission (authorization) is required for the use and sharing of any protected health information collected as part of this research study. If you are not willing to sign this authorization to use and/or disclose your PHI by the research team, you will not be eligible to take part in this research study.

The principal investigator (PI) and his research team will use your medical records and information created or collected as part of this research study. Your PHI is important for the PI and his research team in order to collect information about you during the study, to be able to contact you if needed, and to provide treatments to you during the study, if required. The PI may send out your study related health information to the sponsor or other entities involved in this study.

Your medical records, which may contain information that directly identifies you, may be reviewed by representatives from groups identified below. The purpose of these reviews is to assure the study is being conducted properly, that data is being obtained correctly or for other uses authorized by law. These reviews occur at the study site or in the PI's research office and can take place anytime during the study or after the study has ended.

The PHI that will be "USED" for this research includes the following: name, address (street address, city, state and zip code), e-mail address, elements of dates, telephone numbers and Your unique study identifier code and associated study data while you are actively in the study

The PHI that will be "DISCLOSED" or shared with others for this research includes the following: No PHI will be disclosed

Your study information may be **used** with the following people or groups:

- The PI, co-investigators, and key personnel of WSU associated with the research project
- WSU's Institutional Review Boards (IRB)
- Authorized members of WSU's workforce who may need to access your information in the performance of their duties. [*For example, to provide treatment and services, ensure integrity of the research, or for accounting and/or billing matters.*]
- Federal agencies with appropriate regulatory oversight (e.g., FDA, OHRP, OCR, etc.) may review your records

Once your information has been released according to this Authorization, it could be released again and may no longer be protected by the HIPAA regulations.

This Authorization does not expire. The research team may need to correct it or provide missing information about you even after the study has ended, and your medical records may be needed to assist in this process.

- During your participation in this research project you will not be able to access that part of your medical record involved in the research. This will be done to prevent the knowledge of

the research results from affecting the reliability of the project. Your information will be available to the treating physician should an emergency arise that would require for him/her to know this information to best treat you. You will have access to your medical record when the study is ended or earlier, if possible. The PI is not required to release research information that is not part of your medical record.

You may withdraw (take back) your permission for the **use** and **disclosure** of your PHI for this research at anytime, by **writing** to the PI at the address on the first page of this form. Even if you withdraw your permission, the PI for the research project may still use your PHI that was collected prior to your written request if that information is necessary to the study. If you withdraw your permission for use of your PHI, you will also be withdrawn from the research project. Withdrawing your authorization **will not** affect the health care that will be provided by the Detroit Medical Center and/or the WSU School of Medicine Practice Plans.

Authorization to use and disclose PHI

- By signing this document, you are authorizing the PI to **use** and **disclose** PHI collected about you for the research purposes as described above.

Signature of participant _____ Date _____

Printed name of participant _____

- For participants unable to give Authorization, the following individual is acting on behalf of the research participant (e.g., children, mentally impaired, etc.).

Signature of authorized representative _____ Date _____

Printed name of authorized representative _____ Relationship to the participant _____

Signature of person obtaining Authorization _____ Date _____

Printed name of person obtaining Authorization _____ Time _____