University Health Network

CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Title: **Anhedonia and the insulin pathway: a mechanistic nexus for the mood and metabolic disorders comorbidity**

Investigator: **Rodrigo B. Mansur, MD, PhD**

Office Number: **416-603-5133**

24-hour Number: **647-780-9533**

If you are transferred to an answering machine, please leave a message and the study team will call you back. If you do not receive a call back within 10 minutes, please call again.

Introduction

You are being asked to take part in a research study. Please read the information about the study presented in this form. The form includes details on study's risks and benefits that you should know before you decide if you would like to take part. You should take as much time as you need to make your decision. You should ask the study doctor or study staff to explain anything that you do not understand and make sure that all of your questions have been answered before signing this consent form. Before you make your decision, feel free to talk about this study with anyone you wish including your friends, family, and family doctor. Participation in this study is voluntary.

Background

You are being asked to take part in a study because you have been diagnosed by a health care professional with a mood disorder, either major depressive disorder (MDD) or bipolar disorder (BD), and are between the ages of 18 and 50. A diagnosis of MDD or BD means that you have had episodes of depressed mood and/or of abnormally elevated mood. This study will be completed at the University Health Network.

Mood disorders are usually treated with antidepressants, mood stabilizers and/or antipsychotics. There are many medications that have been shown to help with the symptoms of BD. However, for many individuals with BD these medications are insufficient or ineffective and, as a result, they continue to struggle with symptoms and with difficulties functioning.

Medical research has shown that many individuals with mood disorders experience difficulties with energy, motivation, and emotional processing, which interfere with their quality of life and their ability to function well at work and with their families. This might be due to an abnormal processing of sugar, the brain's primary source of energy.

Most people who take insulin for diabetes do so by injecting insulin into their skin with a needle. Although this helps their body use sugar, very little of the insulin makes it to the brain. Furthermore, injecting insulin into their skin carries the risk of dropping the blood sugar level too low, which could be dangerous. Insulin can also be administered by inhaling it from a spray that is placed into the nose - this is called intranasal insulin. It has been shown in various populations other than those with mood disorders that intranasal insulin goes directly to the brain and does not change sugar levels in the rest of the body. This suggests that intranasal insulin might help the brain use sugar more effectively.

Intranasal insulin is currently being tested as a new treatment option for many conditions such as Alzheimer's disease, depression, and obesity. However, intranasal insulin is an experimental treatment, which means that it has not been approved by Health Canada as a treatment for MDD or BD.

This is **not** a treatment assessment of intranasal insulin but a study of how intranasal insulin works in the body.

Purpose

Our research team is interested in using intranasal insulin to determine whether people with MDD or BD have a different response to brain insulin when compared to healthy individuals (i.e., individuals without psychiatric disorders), and how that would relate to mood, thinking, memory, and concentration. The research study that you have been asked to participate in will evaluate how your brain reacts to intranasal insulin with an exam called functional magnetic resonance imaging (fMRI). Through the results of this exam, the study will assess how the neurons in your brain, which are the cells that process and transmit information through electrical and chemical signals, are organized and connected. Our research team will check your memory, concentration, and ability to process emotional information by having you complete some tests. We will also analyze your body's metabolism through measurements of body weight, blood markers, and energy expenditure and heart rate through data collected from an accelerometer. An accelerometer is an instrument used to track acceleration and movement. The accelerometer in this study will be worn on the wrist, in the same way one would wear a watch. Finally, we will assess the expression of genes involved in the regulation of insulin using cells derived from your blood.

Study Design

A total of 75 participants with MDD or BD and 75 healthy controls will take part in this study. Most participants will come from the University Health Network hospitals, which

include the Toronto Western Hospital and Toronto General Hospital. The study design is referred to as a single administration, randomized, double-blinded, placebo-controlled, cross-over study. What this means is that you will receive insulin once and placebo once. A placebo looks just like insulin but contains no active medication. Whether you get the insulin first or the placebo first will be decided randomly (by chance) like flipping a coin or rolling dice. Neither you, your doctor or the research team will know if you are taking insulin or placebo (it is double-blinded) until the study is finished. This information can be found out in case of emergency.

Study Visits and Procedures

There will be 3 visits over 3 weeks. During visit 1, you will undergo a clinical and psychiatric evaluation, including physical examination, MRI screening, **and** a **blood sample collection. During visit 2 and 3, you will undergo a blood sample collection and an fMRI scan after** the administration of insulin/placebo.

Visit 1 (Consultation and Screening)

- At the first visit (approximately 2 hours) our study coordinator will carry out an interview to make sure you are eligible for the study and to confirm your diagnosis of depression or bipolar disorder. After confirmation of your eligibility, you will meet with the research staff and he/she will carry out an interview about your mental and physical health.
- Your height, weight, heart rate, and blood pressure will be recorded.
- An MRI screening questionnaire will be administered to ensure your eligibility for undergoing an MRI scan (i.e., free of MRI contraindications such as having metal in or on body, being claustrophobic, etc.)
- A blood sample will be collected for laboratory tests to check your overall health. Male participants will be asked to provide 17.5 mL of blood which is equivalent to about 1 tablespoon. Female participants will be asked to provide 22.5 mL of blood which is equivalent to about 1.5 tablespoons. It is very important that every time you come to the clinic for a blood test that you come in the morning and that you not have any food after midnight the night before. This is called ‘fasting’. You are able to have water as you need. This is done so that the food you eat does not affect the blood tests. Women will also have a blood test to check for pregnancy.

Visit 2 and 3

You may or may not be invited to take part in visit 2 and 3. If you do not meet the eligibility criteria upon completion of visit 1, you will not be invited to visit 2 and 3. Participants who are eligible will receive intranasal insulin/placebo, and will undergo fMRI imaging.

Visit 2

You will come in at 7:00 AM for visit 2 (approximately 4 hours) after an overnight fast of at least 8 hours. The following will take place at this visit:

- We will start with a safety monitoring for blood sugar (glucose) and vital signs (pulse, blood pressure). The safety monitoring for blood sugar will involve a finger prick to test your blood sugar levels to make sure they are not too low.
- A blood sample will be collected from you (a total of 9 mL of blood, which is equivalent to 1.75 teaspoons or 2 tubes of blood).
    - All blood tests will be fasting. This means that you will be asked to <u>not</u> have food after midnight the night before. This is important to ensure that your blood test results are reflective of your health status.
    - Blood samples will be collected for a routine evaluation.
    - Blood samples will also be collected and stored for the analysis of biomarkers. Biomarkers are biological markers that may reflect the presence of an illness and/or the severity of the illness. Biomarkers of interest for exploratory research purposes consist of various proteins (e.g., inflammatory markers) that will be used to gain insight about the role of the biological substrates that are shared in metabolic and mental disorders.
- You will be randomized to receive either insulin or placebo. You will be under the direct observation of the research staff for a minimum of 1 hour post-spray.
- We will go through a screening questionnaire before the MRI scan to ensure there are no metal objects in/on your body (e.g., piercings, pacemakers).
- You will go through the first MRI scan, which will last for no more than 1 hour. An MRI scan uses magnetic waves to take pictures of your brain. You will have to lie still in the MRI machine but will be able to speak to someone at all times. You will be presented with a decision-making game during the MRI scan. The game consists of a series of repeated trials in which you are able to choose between performing a “hard-task” or an “easy-task” in order to earn varying amounts of monetary reward.
- Blood samples (i.e., finger prick) will be obtained at the time of the insulin/placebo spray administration and immediately after the second scan to determine blood glucose and insulin levels.
- You will receive your accelerometer wrist device which must be worn at all times until visit 3.
- You are to complete the “7-Day Accelerometer Wear Time Log” provided to you by research personnel, to track your daily wear of the device.

Your mood, thinking, memory, and concentration will be assessed after the scan and within 2 hours of insulin/placebo spray administration using approved questionnaires.

<u>Visit 3</u>
Visit 3 will be done exactly 1 week after visit 2. It will follow the same procedures of visit 2. If you received placebo during the second visit, you will then receive insulin during the third visit. Conversely, if you received insulin during the second visit, you will receive placebo during the third visit. You will be asked to return the accelerometer wrist device and the completed “7-Day Accelerometer Wear Time Log” at the beginning of this visit for data collection and analysis.

Reminders

It is important to remember the following during this study:

- Do not change your medications, if any, without first discussing with your study doctor.
- You should not eat for 8 hours before all visits.
- Do not drink alcohol for 48 hours prior to all visits.
- Notify the research staff if you develop any illness or allergic reactions while enrolled in the study.
- Ask your study team about anything that worries you.
- Tell the study staff anything about your health that has changed.
- Tell the study team if you change your mind about being in this study.

Risks Related to Being in the Study

Taking part in this study has risks. Some of these risks we know about. There is also a possibility of risks that we do not know about and have not been seen in humans to date. Please call the study doctor if you have any side effects even if you do not think it has anything to do with this study.

The risks we know of are:

a) MRI risks: There are few potential risks of having an MRI scan, as it is a non-invasive procedure and does not involve any radiation. The main potential risk comes from loose metal objects, which, if taken near the scanner, could be dangerous. The combination of the noise of the scanner and confined space can also be stressful for people who feel uncomfortable in closed spaces.

   We are collaborating with an MRI facility that has access to new MRI methods from the scanner manufacturer. These new methods use investigational research scans that are not available on clinical scanners. All investigational scans are performed under strict safety guidelines and do not pose any additional risk to you.

b) Blood draw risks: Drawing blood may cause very mild pain, bruising, redness, and rarely infection at the needle stick.

c) Intranasal insulin risks: Intranasal insulin has been tested in healthy volunteers and in medical patients. It has been shown to be very well tolerated and safe. The primary concern is making sure that intranasal insulin does not change your blood sugar or insulin levels. If your sugar goes too low this can be very dangerous and is a medical emergency. Fortunately, this has not been reported in studies that have been conducted so far.

   The research team will be monitoring your blood glucose and insulin levels very closely, although low sugar (hypoglycemia) is not considered a major risk and has not occurred in the previous studies in which over 500 participants took part. You

should be familiar with the symptoms of hypoglycemia, which include: dizziness, sweating, vomiting, lightheadedness, confusion, disorientation, trembling, shaking, and change in your body temperature. If you experience these symptoms you should contact or visit the emergency room immediately. You can also call the 24-hour phone number of the clinical research staff.

Since you are administering a spray into your nose, you may notice some nasal congestion, nasal discomfort/irritation, or a nose bleed. The clinical research staff will help you on the proper administration of the intranasal spray so that the amount that is inadvertently swallowed is minimal. There is a bitter taste reported with the spray. Any of the intranasal insulin that is accidentally swallowed is digested by your stomach and does not circulate throughout your body.

d) Other risks: In addition to medical risks, being in this study may make you feel uncomfortable. You will be asked personal questions about your psychiatric and medical history. You may refuse to answer questions or stop the interview at any time if there is any discomfort. The cognitive testing may sometimes be frustrating particularly if you are not performing as well as you think you should, and it may also lead to mild mental and physical fatigue.

Risks Related to Pregnancy

It is unknown what effect intranasal insulin may have on the unborn baby or sperm; therefore, adequate birth control (oral contraceptives and/or condoms) must be used by both men and women three months prior to the study as well as while participating in this study. If you become pregnant while participating in the study, to protect the safety of your baby, your participation in the study will be discontinued.

Benefits to Being in the Study

You may or may not receive any direct benefit from being in this study. Information learned from this study may help other people with mood disorders in the future.

Voluntary Participation

Your participation in this study is voluntary. You may decide not to be in this study, or to be in the study now and then change your mind later. You may leave the study at any time without affecting your care. You may refuse to answer any question you do not want to answer, or not answer an interview question by saying “pass”.

We will give you new information that is learned during the study that might affect your decision to stay in the study.

Confidentiality

<u>Personal Health Information</u>

If you agree to join this study, the study doctor and his/her study team will look at your personal health information and collect only the information they need for the study. Personal health information is any information that could be used to identify you and includes your:

- telephone number
- email address
- month and year of birth
- new or existing medical records, that includes types, dates and results of medical tests or procedures.

The information that is collected for the study will be kept in a locked and secure area by the study doctor for 25 years. A list linking your study number with your name will be kept by the study team, in a secure place, separate from your study file. Only the study team or the people or groups listed below will be allowed to look at your records. Your participation in this study will also be recorded in your medical record at this hospital. This is for clinical safety purposes.

The blood samples will only be used for current study purposes. The samples will be labelled with your study ID and no personal identifiable information will be recorded on the samples. The samples will be kept in a locked and secure facility, as would all data related to this information, and will not be shared with any outside sponsor or external vendor.

The following people may come to the hospital to look at the study records and at your personal health information to check that the information collected for the study is correct and to make sure the study followed proper laws and guidelines:

- Representatives of the University Health Network (UHN) including the UHN Research Ethics Board
- Representatives of Health Canada, or other regulatory bodies (groups of people who oversee research studies) outside of Canada, such as the United States Food and Drug Administration.

Research Information in Shared Clinical Records

If you participate in this study, information about you from this research project may be stored in your hospital file and in the UHN computer system. The UHN shares the patient information stored on its computers with other hospitals and health care providers in Ontario so they can access the information if it is needed for your clinical care. The study team can tell you what information about you will be stored electronically and may be shared outside of the UHN. If you have any concerns about this, or have any questions, please contact the UHN Privacy Office at 416-340-4800, x6937 (or by email at privacy@uhn.ca).

Study Information that Does Not Identify You

Some study information will be sent outside of the hospital. Any information about you that is sent out of the hospital will have a code and will not show your name or address, or any information that directly identifies you.

All information collected during this study, including your personal health information, will be kept confidential and will not be shared with anyone outside the study unless required by law.

You will not be named in any reports, publications, or presentations that may come from this study.

Rights as a Research Participant

If you are harmed as a direct result of taking part in this study, all necessary medical treatment will be made available to you at no cost.

By signing this form, you do not give up any of your legal rights against the investigators, or involved institutions for compensation, nor does this form relieve the investigators, or involved institutions of their legal and professional responsibilities.

Withdrawal from Study

You may withdraw early from this study for reasons such as:

1. Voluntary discontinuation by you without prejudice to further treatment
2. Hypersensitivity (for example, an allergic reaction) to intranasal insulin
3. Worsening of symptoms and/or emergence of suicide thinking

If you decide to leave the study, you have the right to request withdrawal of information collected about you, your blood and your MRI scan, as well as of any information obtained from these samples. Let your study doctor know.

If you leave the study, the information that was collected before you left the study will still be used in order to help answer the research question. No new information will be collected without your permission.

Costs and Reimbursement

You will be provided the amount of money earned during the decision-making game.

Incidental Findings

Incidental findings are previously undiagnosed medical or psychiatric conditions that can be, potentially, discovered in the study assessments (e.g, the MRI scan). Results will be discussed with you, individually, in a separate visit. If necessary, additional tests and assessment will also be arranged by the study doctor.

Conflict of Interest

Researchers have an interest in completing this study. Their interests should not influence your decision to participate in this study. You should not feel pressured to join this study.

Questions About the Study

If you have any questions, concerns, or would like to speak to the study team for any reason, please call Dr. Rodrigo Mansur at (416) 603-5279 or the Research Coordinator at (416) 603-5133.

If you have any questions about your rights as a research participant or have concerns about this study, call the Chair of the University Health Network Research Ethics Board (REB) or the Research Ethics office number at 416-581-7849. The REB is a group of people who oversee the ethical conduct of research studies. These people are not part of the study team. Everything that you discuss will be kept confidential.

You will be given a signed copy of this consent form.

Consent

This study has been explained to me and any questions I had have been answered. I agree to the use of my information as described in this form. I know that I may leave the study at any time. I agree to take part in this study.

Print Study Participant's Name	Signature	Date

My signature means that I have explained the study to the participant named above. I have answered all questions.

Print Name of Person Obtaining Consent	Signature	Date

Signature of Investigator

Print Name of Principal Investigator	Signature	Date