Information Sheet and Informed Consent Form
Does Xyrem® influence brain dopamine in patients with narcolepsy?
A PET imaging investigation

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Overview

You are invited to participate as a volunteer in a research project to determine whether a single oral dose of the medication Xyrem®, also known as Sodium Oxybate or Gamma-hydroxybutyrate (GHB), changes levels of a chemical called dopamine in the brain of patients with narcolepsy with cataplexy as compared with healthy controls.

Your participation in this study will not affect your treatment and the care provided to you.

This study is being funded through a grant from Jazz Pharmaceuticals, the company that produces Xyrem® in the US.

Xyrem® is a sedative drug that is now prescribed in Canada for treatment of narcolepsy with cataplexy. We do not fully understand how Xyrem® works in the brain, but suspect that the drug might reversibly slow down activity in brain of nerves that use dopamine as a chemical messenger. We want to test this hypothesis by conducting a brain imaging procedure called PET (positron emission tomography) before and after you receive a single standard oral dose of Xyrem®.

PET imaging uses a radioactive agent to obtain pictures of the brain. The agents that we are using in this study are called ^{11}C-Raclopride and ^{11}C-DTBZ, which will provide us with information about dopamine levels in the brain. **We want to find out whether a single dose of Xyrem® will change binding of ^{11}C-Raclopride and ^{11}C-DTBZ to your brain after receiving the drug.**

You will undergo PET sessions on two different days involving a total of five scans as well as an MRI scan. The MRI scan gives us information about the structure of the brain that helps us interpret the information from the PET scan.

You have been selected for possible inclusion into one of two study groups for this study:

Group a) Narcolepsy with cataplexy: You currently have a diagnosis of narcolepsy with cataplexy, but are otherwise healthy, and you have never used Xyrem® (Sodium Oxybate, GHB) in the past.

Group b) Healthy Controls: You are currently healthy with no neurological, medical or psychiatric issues (including drug or alcohol abuse), and you have never used Xyrem® (Sodium Oxybate, GHB) in the past.

In order to decide whether or not you wish to participate in this study, you should know about the risks and benefits to make an informed judgment. These sheets give you detailed information about the study and you should feel free to ask us or others any other questions that you might have. Once you understand the study and its risks you may choose to participate by signing the attached form.

Purpose of the Study
The ultimate goal of this research is to investigate whether a standard therapy dose of Xyrem® has any influence on the brain dopamine system in patients with narcolepsy with cataplexy and/or healthy controls.

Duration of Trial and Number of People Taking Part in the Study
Including you, we expect a total of a maximum of 15 subjects with narcolepsy and a maximum of 15 controls to complete this study. Typically it is expected to complete all study related procedures within 5 weeks from the time of enrollment.

You should not participate in the study if you have a past history of serious medical or psychiatric illness, alcohol abuse or regular use of illicit drugs, or have been exposed to other nuclear medicine scans (e.g. PET scans) which could exceed the maximum allowed annual amount of radiation.

What are the responsibilities of the study participants?
If you decide to participate in this study you will be asked to do the following:
1) Preliminary screening (3-4 hours, typically over 2 or more days): You will have a visit with a research staff member at CAMH to ensure that you meet the requirements to take part in the study. In this visit we will ask you about your medical, psychiatric, alcohol and drug use history.

You will be required to have an EKG (electrocardiogram or heart tracing) and to provide a blood sample (approximately two tablespoons or 30 mL) for complete blood cell count, routine blood chemistry and pregnancy test in females; and a urine sample for drug-screen.

As part of the screening procedures to ensure that it is safe for you to participate in this trial, a physician will review your medical history with you and perform a physical examination once the blood/EKG results are available. In some cases it may be helpful to speak with your own doctor and/or review your medical record if there are questions regarding your medical history or lab results. You can indicate whether you agree to this by checking and initialling below.

☐ yes
☐ no _____ (initial)

I give permission for the *Study Physician* to contact my doctor and/or review my medical records (if necessary).

If you are part of the narcolepsy group, you would have been referred to this study as someone who has a diagnosis of narcolepsy with cataplexy. With your consent, we will request information from your referring physician regarding your diagnosis and other relevant information required to characterize your disease.

☐ yes
☐ no _____ (initial)

I agree to allow Dr. _____ [referring physician] to communicate my diagnosis of narcolepsy with cataplexy, along with other relevant information with the study team.
☐ n/a – healthy control

The information collected from these screening visits will be reviewed by the doctors involved in the study to determine whether you qualify for the study, and ensure that it is safe for you to participate.

If you qualify for the study, you will participate in a total of five PET scans conducted on two different days.

2) Baseline scan day (1 MRI, 2 Baseline PET scans; approximately 7 hours):
i) MRI scan (up to approximately 1 hour): Magnetic resonance imaging (MRI) is a technology that uses strong magnetic fields ("magnetic") and radio frequency fields ("resonance") to produce detailed pictures of soft tissues in the body, including the brain. For this study, we will be using MRI to take pictures of your brain's structure to analyze the PET scans. The MRI machine looks like a big doughnut, and you will lie down on a bed with your head and shoulders in the tunnel made by the "doughnut hole". We will ask you to stay very still while we scan your brain. Movements will not be dangerous to you in any way, but will blur the picture of your brain. The MR technologist will be able to observe you at all times. You will be able to contact the MR technologist at any time during the scan session for any reason. You will hear moderately loud sounds when the MRI machine is scanning. This scan will be conducted at CAMH, and will take up to one hour for the scan itself, as well as setup time.

ii) PET Scans (approximately 1.5 hours each, 2 scans): PET scanning is a technique of making pictures of the brain to give information about where chemicals in the brain are distributed and in what amounts. The PET scans are done by injecting a very small amount of a radioactive substance into your arm vein and by taking pictures of your brain using a PET camera. This technique has been used for research and for clinical diagnosis in different centres around the world. We have also used this scanning technique in over 500 subjects at CAMH in recent years.

These scans will provide baseline values for comparison with the scans conducted after you take Xyrem®. You can eat a light breakfast or lunch and drink water (though not excessively so you do not have to go to the bathroom during the scan). For each PET scan, you will be asked to lie down on a scanning table such that your head is in the view of the PET camera. Because it is very important to make sure that you keep still during the study we will make a head holder out of plastic to minimize movements during the scan. We will keep this mask and re-use it for each subsequent scan. We will also collect a urine sample for drug-screen and, in females, a pregnancy test.

Prior to scanning, a single I.V. line or a fine needle-catheter (one per scan) will be inserted into an arm vein for the administration of a small amount of the radioactive substance ^{11}C-Raclopride for the first scan, and ^{11}C-DTBZ for the second. You will be asked to lie still on the bed in the scanner. The total length of the time in the scanner for each scan is approximately 80-90 minutes with 60 minutes of actual scanning time. A doctor will be available to answer any questions that you may have or to help if you feel any discomfort.

Transportation to and from CAMH will be provided (i.e., taxi) for this and subsequent visits if required.

3) Xyrem® scan day (three PET scans following 3.0 g oral dose of Xyrem®; approximately 10 hours): On the morning (approximately 8:30 am) of a different day you will drink a liquid containing 3.0 g Xyrem®. Because you are taking a sedative drug it is essential, for your safety, that you do not eat any solid food for breakfast that morning (including smoothies or instant breakfast drinks) and do not drink any liquids past 6:30 am (two hours before taking the drug).

Approximately 15 minutes after you take the drug, lasting up to approximately 3.5 hours, you will be sedated and during this time you may be actually be asleep. You will receive three PET scans, two

using ^{11}C-raclopride, one using ^{11}C-DTBZ, similar to the baseline scans. One of the ^{11}C-raclopride scans will take place while you are sedated (the scan begins approximately one hour after taking the drug), the second scan using ^{11}C-DTBZ will begin approximately five hours after taking the drug, the final ^{11}C-raclopride scan will start approximately seven hours after taking the drug. At five hours we expect that almost all or all of the sedation will have worn off.

Prior to taking Xyrem®, we will collect a urine sample for drug screen and, in females, a pregnancy test. Following that, an I.V. line will be inserted into an arm vein for the administration of the radiotracers (^{11}C-raclopride and ^{11}C-DTBZ), and also to allow for blood to be drawn for measurement of Xyrem® levels at different time points throughout the day including: just before taking Xyrem®, and at 0.5, one, three, five and seven hours after taking the drug. The total amount of blood drawn will be about 50 ml (3 tbsp). The I.V. line will stay in your arm for the day, with a saline drip attached in order to prevent blockage in the line.

Over the course of the sedation from Xyrem®, we will continuously monitor your heart rate, breathing and blood pressure using medical equipment. An anesthesiologist will be present with you for the duration of the time that you are sedated and will evaluate you and decide when it is safe for you to drink, eat, and to be discharged.

Since you have taken a sedative drug <u>you cannot drive</u> or operate heavy machinery (including farm equipment), at any time that day or night and you will go home either by taxi (we will pay) or with an adult who would drive you home. You should <u>not</u> make any significant decisions (i.e., legal), engage in any strenuous activities or any activity that requires mental alertness, and also should not take any sedative drug (e.g., sleeping pill) or drink any alcohol for 24 hours after taking the Xyrem®.

4) Follow-up Telephone Call
The morning after taking Xyrem® someone from the research study (the head investigator of the study Dr. Kish and / or the Research Coordinator) will call you to ask about any experiences (positive or negative) that occurred since you left the PET Centre.

<u>Risks and Inconveniences</u>
From PET scanning: Please note that ^{11}C-raclopride and ^{11}C-DTBZ are investigational positron emitting radiopharmaceuticals (PER) used for research purposes and not yet marketed in Canada.

You will be exposed to a small amount of radiation from a brief transmission scan to measure how much radiation is absorbed by your head. You will also receive a radiation dose of approximately 10 mCi for each of the 5 PET scans. The radiation dose to you during a PET scan is comparable to other nuclear medicine scans and represents a very low risk. The radiation dose from each ^{11}C-DTBZ scan is less than 2.3 mSv, and less than 2 mSv for each ^{11}C-Raclopride scan, for a total of about 11 mSv. The amount of radiation received from natural sources during one year is about 3 mSv. The potential long-term risk from the radiation dose you will receive is uncertain, but these doses have never been associated with any definite adverse effects. While the radiation exposure from these PET scans is below the limits set by the PET Centre, **you must notify the investigator of any other radiation exposures which you have received over the past year**. The PET scan requires an injection.

It is also possible that you may find the scanning procedures stressful. You will be able to discuss any concerns with study staff at length at any time. On scan days, study staff will be available at all times, including during the scan (via call button and microphone in the scanner room). In addition, medical staff will be on call if you want to discuss matters with a doctor.

From PER injection: As with any injection or blood work, there is a small risk of bruising or swelling at the site of injection in your arm, and lightheadedness and feeling faint. If you feel faint, notify study staff.

From blood withdrawal: There will be slight discomfort from the insertion of the intravenous line as well as the possibility of bruising.

From MRI scanning: Metal Objects. Before you can participate in an MRI study, we need to make sure it is safe for you to do so. Because certain metal objects may lead to injuries during the MRI procedure, we will ask you to answer questions about any metal implants or objects you might have in your body and the location of any tattoos. If you have any metal implants or objects that are not safe for the 3T MRI at CAMH, you will not be allowed to be scanned. Some objects that are not safe for MRI include cardiac pacemakers, metal fragments in the eye, aneurysm clips in your brain. If there is a strong chance you may have metal fragments in your eyes, you will need to provide an x-ray report of your eyes before you can be scanned. The research study staff and the MR technologist will work together to make sure you will be safe in the scanner. We will also ask whether you are extremely uncomfortable in enclosed spaces (claustrophobia).

Based on the use of MRI in medicine for over 20 years, most experts believe there are no long-term negative health effects caused by the magnetic field strength used in this study. This MRI study does not involve any form of ionizing radiation or injections. Some people may feel uncomfortable lying still in the confined space of the MRI scanner, tingling sensations are felt by some people during certain scans or you may feel dizzy for a few minutes at the end of the MRI study. These are infrequent, but expected sensations. It is important you understand that you will be able to contact the technologist at any time during the scan. You may ask to be taken out of the scanner for any reason without any penalty or consequences.

From Xyrem®: Xyrem® is a sedative drug that is currently in use for patients with a diagnosis of narcolepsy with cataplexy. Patients typically take the drug, at their homes, twice nightly; once before bedtime (at least two hours after a meal) and again 2.5 – 4 hours later.

The dose you will be taking (3.0 g) is a common starting dose for a patient with narcolepsy with cataplexy. GHB is also often taken illicitly, unsupervised by any physician, by young adults in the Toronto area apparently because of the desired sedative action of the drug.

After taking **Xyrem®**, **you will feel sedated (like taking a strong "sleeping pill"), and may fall asleep for approximately 4 hours**. <u>You may find this sedation unpleasant</u> as it can be sometimes associated with dizziness, confusion, headache, nausea, vomiting, and involuntary urination and bowel movement (occurred in 8% of subjects in clinical trials).

Xyrem® can cause respiratory depression and, for this reason, even death in humans who overdose on the drug and who are not brought to a hospital to receive supportive care to help in their breathing. There are also risks that if you vomit it may enter your lungs or if you are over sedated this may depress your breathing. We believe that the risks of this happening to you are very low, but because it is possible, an anesthesiologist will be present during the entire time you are sedated to monitor your level of sedation and vital signs. If necessary they can provide additional care ranging in scope from simply providing oxygen, to placing a tube in your airway (intubate) assisting your breathing, and transporting you to another hospital for further care.

Because of the above risks you need to understand that **you cannot eat any solid food (including milkshakes, smoothies, or instant breakfast drinks) the morning you take Xyrem®, or drink <u>any</u> fluids during the 2 hours just before taking Xyrem®. Also, because other depressant drugs**

(alcohol, sleeping pills, tranquilizers) can interact with Xyrem® to cause further sedation, <u>you cannot take any of these drugs the day before or the same day that you take Xyrem®</u>.

<u>You should not take Xyrem®</u> if you have any unstable or uncontrolled medical condition such as heart or liver problems, high blood pressure, or a sensitivity to sedative drugs. To minimize risk, we will conduct a physical examination with the results of the examination evaluated by an investigator of our study who has experience in administration of Xyrem®.

A single case has been reported in separate study in which a participant receiving a drug similar to Xyrem® was hospitalized with elevated muscle enzymes after completing a multi-dose regimen of the drug [2.5 g 2x/day up to 4.5 g 2x/day, over a period of at least 3 months], and engaging in intensive exercise. As this is only a single case, we can't say for sure that whether the drug actually caused the muscle problem. However, to minimize this uncertain risk you should not engage in strenuous physical activity for ~24 hours after taking Xyrem®. If you experience significant muscle cramps after taking Xyrem®, please notify Dr. O'Leary, contact information provided below and on the wallet card you will be provided with, or go to your local Emergency Department.

Xyrem®/GHB can also be an abused drug with some individuals (we believe rarely) who take very high doses of the drug becoming addicted to the drug. To minimize this potential risk we will ask you questions about any past use of abused drugs. **<u>You should not take Xyrem® if you have a history of substance abuse.</u>**

From psychiatric interview: During the interview you may experience some emotional discomfort when answering some of the questions. If any particular question makes you feel uncomfortable, you may discuss its importance with the specially trained interviewer. You may choose not to answer any question with which you still feel uncomfortable.

***Women please note**:* It is advised that **pregnant women** avoid radiation from PET scans to minimize any risk to the fetus. Further, the risk of a single dose of Xyrem® to the developing fetus is unknown. You should not participate in this study if you are, could be, or plan to become pregnant during the study. Prior to your entering the study we will discuss with you the need to avoid becoming pregnant. If you change your mind about becoming pregnant during the study, please notify us immediately. As a precaution, we request that women of child bearing age provide a urine sample for a pregnancy test immediately prior to any PET scan.

<u>Safety</u>

To ensure your safety the following precautions will be taken:

i) All adequate precautions and procedures will be explained to you.
ii) Support will be available to you for the entire duration of the study. An anesthesiologist (MD) will be with you for the entire time you are sedated after taking the drug.

If you feel that you might require medical assistance resulting from any procedure in the study, please contact the study Anesthesiologist, Dr. Gerald O'Leary, study Sleep Clinician Dr. Colin Shapiro, your sleep clinician or family physician or, if none of the above are available, the emergency room of your local hospital for immediate assistance.

<u>Incidental Findings</u>

Research scans are not subject to clinical review and the psychological test and interviews are not used for a diagnostic purpose. However, any incidental findings will be communicated to you and, upon your request, to your physician.

<u>Benefits</u>

By participating in this study you will not have any direct benefit. Your participation will contribute to scientific knowledge about the neurotransmitter dopamine – and this knowledge may lead to developing better use of current medications or informing the search for newer medications for patients who have problems with brain dopamine.

Costs of Participating In This Study

Participation in this study will not involve any additional costs to you. By signing this consent form, you do not give up any of your legal rights.

Reimbursement for time and inconvenience

Study participants will receive a small honorarium to reimburse them for the time and inconvenience incurred during participation in this study. Incidental expenses such as travel costs, lunch on scan days, and any other costs directly related to participation in the study will also be reimbursed. The participants who complete the study will receive $850 as detailed below.

Visit	Compensation	Time	Description
Screening	$ 150	4 h	Determination of eligibility for the study and medical evaluation including blood and urine samples and EKG.
Baseline scan day	$ 250	7 h	1 MRI and 2 PET scans done on baseline day
Xyrem® scan day	$ 450	10 h	Xyrem® dose followed by 3 PET scans
Follow-up call		30 min	Interview with study staff about effects of Xyrem®
Total	$ 850	Up to 22 h	

No advance payment will be given; you will be reimbursed at the time of completion of the study. However, if your participation ends early for whatever reason, you will be compensated for the visits, blood sampling, and imaging sessions that have been completed as described above.

Voluntary participation

Your participation is voluntary. You can choose to end your participation at any time without having to provide a reason. If you choose to withdraw, your choice will not have any effect on your current or future medical treatment or health care.

Can participation in this study end early?

The investigators may decide to remove you from this study without your consent for any of the following reasons: the investigators decide that continuing in this study would be harmful to you; you are unable or unwilling to follow the study procedures. If you are removed from this study, the investigators will discuss the reasons with you.

If you withdraw your consent the information acquired about you will still be used; however, no additional samples, tests or information about you will be acquired/performed. If you request, all previous samples (that is, urine and blood samples) will also be destroyed.

Blood samples

Your blood samples will be kept during the study period and beyond for subsequent and potentially pooled analysis; following completion of all analyses these blood samples will be destroyed.

Confidentiality

Your confidentiality will be maintained to the extent permitted by law. Under certain circumstances researchers are legally required to release confidential information by order of a court of law. Apart from such exceptional circumstances, all of the information obtained in this study will be kept confidential.

In the event that any reports or publications result from this study, no information will be revealed that will permit readers to identify you. Some of the samples collected from you during this study (including blood and/or urine) may be sent offsite (outside of CAMH) for analysis. In such cases, the samples will be coded so as to ensure confidentiality. If you would like to know the results of the study or your individual results on any of the measures we would be happy to reveal them to you after the data has been completely analyzed. According to Canadian Regulations, your records will be kept for 25 years.

As part of the quality assurance review of this research project, your study records might be examined by CAMH or Health Canada staff. A person from the CAMH Research Ethics Board staff may contact you to ask questions about the research study and your consent to participate. The person assessing your file or contacting you is obligated to maintain your confidentiality to the extent permitted by law.

A description of this research study might be published in public registries of clinical trials such as ClinicalTrials.gov (http://www.clinicaltrials.gov). No information that could identify you will be sent to these registries. At most these registries will publish a summary of the study results.

Some study information may be sent outside of CAMH as part of adverse event reporting. No information that directly identifies you will be included in these reports.

Your medical information and results could be sent to research collaborators working with us at sites around the world; if this occurs only your research identification code will be used, identifiable data (e.g., name and date of birth) will **not** be passed on.

New Information
If new information becomes available that is relevant to your participation to continue in the study, you will be informed in a timely manner.

Questions
We have used some technical terms in this form. Please feel free to ask about anything you don't understand and to consider this research and the consent form carefully – as long as you feel is necessary – before you make a decision.

Contact
If you have any further questions, please feel free to contact:

Head of the Study	Dr. Stephen Kish	416-535-8501 ext. 36256 (work) 647-409-4026 (cell)
Supervising Physician (Anesthesiologist)	Dr. Gerald O'Leary	416-500-6087 (cell)
Research Coordinator	Tina McCluskey	416-535-8501 ext. 36241

If you have any questions about your rights as a participant in a research study, you may contact Dr. Robert Levitan, Chair, Research Ethics Board, CAMH, at 416-535-8501 ext. 34020.

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Informed Consent Statement

The investigator or a member of the investigator's staff has discussed with me the requirements for participation in this study.

- I have not participated in any research nuclear medicine procedures that, including the dose received during participation in this study, will bring the total radiation dose over the currently approved guideline of 20mSv in a 12-month period.
- I have read all of the information in this Information Sheet, and I have had time to think about the information, and all of my questions have been answered to my satisfaction.
- I voluntarily agree to be part of this research study, to follow the study procedures, and to provide necessary information to the investigator or other staff members as requested.
- I am under no pressure to participate in the study, and **I understand that I may withdraw from the study at any time for any reason.** I also understand that my participation in the study may be terminated by the study investigator if necessary.
- By signing this consent form, I am not giving up my legal rights or releasing the investigators or sponsors from their legal and professional obligations.
- I will receive a copy of this signed consent form.
- I also consent to have the data collected from this study entered in an anonymized manner, that is, without information that could identify me as the subject, in a research database that is shared by other investigators. The purpose is to compare with data from those of healthy controls or subjects participating in future studies of similar disorders of the same sex and age.

❒ I agree to be contacted for future studies ❒ I do not agree to be contacted for future studies

We encourage you to keep a copy of this consent form.

_____	_____	_____
Print Participant Name	Date	Time

_____
Participant Signature

_____	_____	_____
Name of Individual Obtaining Consent	Date	Time

_____
Signature of Individual Obtaining Consent