VUMC Institutional Review Board
Informed Consent Document for Research

Study Title:	Pharmacologic Modulation of Hippocampal Activity in Psychosis
Version Date:	02/29/2020
PI:	Stephan Heckers, MD

Name of participant: _____ Age: _____

The following is given to you to tell you about this research study. Please read this form with care and ask any questions you may have about this study. Your questions will be answered. Also, you will be given a copy of this consent form.

Key information about this study:
You are being asked to take part in this research study because you are a healthy control subject. The purpose of this study is to test whether levetiracetam (otherwise known as LEV), a drug that alters brain activity, changes the activity of a brain region called the hippocampus when you use it during a MRI scan. This study will also test whether the drug affects memory performance using a brief memory test. Lastly, this study will test if this drug affects clinical symptoms of psychotic disorders. Previous studies in schizophrenia have shown that the hippocampus is hyperactive. An abnormal hippocampus can result in changes in memory performance and may be responsible for psychosis clinical symptoms. Therefore, the aim of this study is to understand the effects of LEV on hippocampus activity, memory, and clinical symptoms. We would like to enroll about 30 participants with schizophrenia and 30 healthy controls in this study at Vanderbilt. We will not be assessing you for any clinical symptoms of psychosis in this study because you are a healthy control subject.

You do not have to be in this research study. You may choose not to be in this study and get other treatments without changing your healthcare, services, or other rights. You can stop being in this study at any time. If we learn something new that may affect the risks or benefits of this study, you will be told so that you can decide whether or not you still want to be in this study. Your medical record will contain a note saying you are in a research study and may contain some research information about you. Anyone you authorize to receive your medical record will also get this information.

Side effects and risks that you can expect if you take part in this study:
Levetiracetam**:** Levetiracetam is an FDA-approved anti-epileptic medication. This study requires that you take this medication. Side effects have been well established in daily doses 2-6 times higher than the doses we will use in this study (1,000-3,000 mg/day): 10% of individuals experience headache, dizziness, asthenia (weakness, lack of energy or strength), neuropsychiatric symptoms (mild agitation, hostility, apathy, anxiety, or emotional lability), vomiting (occurs in 15%), or report infection while using this drug. Somnolence (sleepiness or drowsiness) occurs in 8-45% of patients. Very rarely, participants have experienced serious symptoms including hallucinations, suicidal ideation (thinking about or planning suicide), or psychosis (a mental disorder in which thought and emotions are so impaired that one

becomes disconnected from reality). Discontinuation of the drug led to resolution of symptoms. An exceedingly rare side effect of the drug is skin irritation and blistering.

Blood sampling**:** The blood draw may cause redness, slight discomfort, mild bruising, and possibility of infection. However this risk is low, as all blood samples will be taken by trained staff.

Risks of Neuropsychological Testing: It is not uncommon to experience some stress or frustration during the neuropsychological testing. However, you may stop or take a break from testing at any time if you wish.

Risks of MRI: There are no known major risks with an MRI scan. However, it is possible that harmful effects could be found out in the future. This is not an "open MRI" and the tunnel is closed and open only on either end, so it may bother you to be placed in a tight space (claustrophobia), and to hear the noise made by the magnet during the scan. You will be given earplugs to reduce the noise. You may also feel the table vibrate and/or move slightly during the scan. It may be hard to lie on the table during the scan. If you have any metal pieces in your body, they could move during the scan and damage nearby tissue or organs.

If you use a transdermal patch (medicated patches applied to the skin), you may need to take it off during the MRI scan. Transdermal patches slowly deliver medicines through the skin. Some patches have metal in the layer of the patch that is not in contact with the skin (the backing). You may not be able to see the metal in the backing of these patches. Patches that contain metal can overheat during an MRI scan and cause skin burns in the immediate area of the patch. Tell the study doctor that you are using a patch and why you are using it (such as, for pain, smoking cessation, hormones). Ask your doctor for guidance about removing and disposing of the patch before having an MRI scan and replacing it after the procedure. Tell the MRI facility that you are using a patch. You should do this when making your appointment and during the health history questions you are asked when you arrive for your appointment.

Loss of Confidentiality: There is also the potential risk of loss of confidentiality. Every effort will be made to keep your information confidential, however, this cannot be guaranteed.

Risks that are not known:
As with any research, there may be risks of participation or from the study medication that we cannot predict. Because this treatment is investigational, meaning non-FDA approved, there may be risks that we do not know about at this time. If you experience any unpleasant effects during this study not mentioned in this consent form, please contact the study coordinator as soon as possible.

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Good effects that might result from this study:
The benefits to science and humankind that might result from this study: This study is designed to test a biological mechanism that may ultimately lead to new treatments for schizophrenia. Therefore, participation in this study may, in time, benefit both individuals with schizophrenia and society at large.

Procedures to be followed:
If you agree to be in this study, you will first be asked to sign and date this consent form. The study takes place over the course of about 2 weeks. After we determine if you are eligible to participate in the study, participation will involve the use and monitoring of LEV. Before starting LEV, you will have a brief neurocognitive (memory) test and a brain MRI scan. You will have another brain scan after taking your first dose of LEV. You will repeat the testing and brain scan after 2 weeks of receiving the medication.

Screening and Consent Visit: You are here today so we can evaluate if you are eligible for this study. If you agree to this consent form, we will need to take a blood sample to make sure this study is safe for you. If these levels come back within normal ranges, we will contact you about starting the study on a later day. If there is a problem where you cannot be in the study because of your blood levels, a research team member will discuss that with you.

Day 1 Visit: During the first visit, you will meet the study coordinator. Your medical, psychiatric, and social history will be carefully reviewed if we do not already have this information. We may assess your current and past medication use. You do not have to answer any questions you do not feel comfortable answering.

As a part of this visit, we will carefully evaluate you to determine if you have any metal in your body that could stop you from having the MRI. After we are sure that you are safe to complete the MRI, you will complete neuropsychological (memory) testing and the MRI scan.

Neuropsychological Testing: We will ask you to complete a task that measures your memory abilities. This will be done on the computer. This task will take about 30 minutes.

MRI: We will then continue the day 1 visit at the Vanderbilt University Institute of Imaging Science (VUIIS). A research team member will walk with you to and from the VUIIS. If you are unable to complete this walk, a research team member will instead accompany you on a Vanderbilt shuttle to and from the VUIIS. A MRI scan is taken in a large machine that is shaped like a tunnel. This scan does not use x-rays, but rather a strong magnet and radio waves to take pictures of your body. This will be a one-hour long session, and you will be asked to complete one task during the MRI. The first task involves the

presentation of pictures of faces and scenes, while in the MRI scan, and then pushing a button in response to various directions.

You may not be able to have this scan if you have a device in your body, such as aneurysm clips in your brain, heart pacemakers or defibrillators, or cochlear (inner ear) implants. Also, you may not be able to have this scan if you have iron-based tattoos or pieces of metal (bullet, BB, shrapnel) close to or in an important organ (such as the eye). If we determine that you cannot safely complete the MRI, we will withdraw you from the study.

Certain metal objects like watches, hairpins, credit cards, writing pens, etc. may be damaged by the machine or may be pulled away from the body when you are getting the scan. Also, metal can sometimes cause poor pictures if it is close to the part of the body being scanned. For these reasons, you will be asked to remove these objects before going into the room for the scan.

You will hear "hammering," clicking, or squealing noises during the scan. You will be given earplugs to reduce the noise. You will also be told how to alert the staff if you need them.

In this study, the MRI scan is for research only. However, if we see something that is not normal, you will be told and asked to consult your doctor.

After the MRI is complete, you will receive LEV tablets. On this first day, we will ask that you take two 250 mg tablets. A research team member will be present to monitor you when the study drug is administered. We will then wait for two hours. After two hours have passed, we will take another MRI scan. After this scan we will take another blood sample so we can check the LEV levels in your body. After the first day, you will take 250 mg tablets at two separate times in the day (in the morning and evening).

Because somnolence (sleepiness, drowsiness) has been reported in people who take LEV, we will require that you a) have someone drive you to and from Vanderbilt Psychiatric Hospital or b) take a brief test before and after you take LEV. This test will make sure that LEV is not making it dangerous for you to drive. If the test shows that LEV has affected your ability to drive, we will purchase a car service (Uber/Lyft) to drive you home and back to Vanderbilt Psychiatric Hospital on another day that works for you to pick up your vehicle.

This visit can last for the majority of a day. If needed we can spread the procedures out over two days. We will then schedule a follow up visit for about 14 days later.

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Time between visits: It is very important that you take the medication we give you twice a day. You will take one 250 mg tablet in the morning and another 250 mg tablet in the evening. Over the 14 days, we may periodically contact you and ask how you are doing. We want to make sure you are not experiencing any side effects and are taking the medication. We will also be available to ask you any questions about the study.

Day 14 Visit: You will be asked to complete the same neurocognitive and MRI tests. We also be asked to complete two additional surveys that will assess side effects and medication compliance. We will also take one final blood sample to check the levels of LEV in your body and make sure this medication has not changed any of your normal blood levels. We also ask that you bring any remaining LEV medication with you to this visit.

Over the course of this study, we will ask women to take a urine pregnancy test. The medication we are giving, LEV, can cause pregnancy complications. If this test is positive, we will stop the study immediately.

Payments for your time spent taking part in this study or expenses:
You will be provided $25 for completion of the baseline visit, which will be provided at the end of this visit regardless of your decision to enroll in the study. You will receive an additional $475 at the completion of the testing visit.

As an identifier for internal auditing purposes, your social security number is needed because you are receiving payment for taking part in this study. Vanderbilt University Medical Center is required to tell the IRS of any payments to you as a subject in research studies in a given calendar year totaling $600 or more. If that occurs, you will receive a 1099 form at the end of the year. No information identifying why you received this payment is given to the Hospital's accounting department or the government. This information is kept strictly confidential.

Costs to you if you take part in this study:
There is no cost to you for taking part in this study.

If you agree to take part in this research study, you and/or your insurance will not have to pay for the study medication or the tests and evaluations that are being done only for research.

However, you are still responsible for paying for the usual care you would normally receive for the treatment of your illness. This includes treatments and tests you would need even if you were not in this

study. This will also include any antipsychotic medication you are already taking. These costs will be billed to you and/or your insurance.

You have the right to ask what it may cost you to take part in this study. If you would like assistance, financial counseling is available through the Vanderbilt Financial Assistance Program. The study staff can help you contact this program. You have the right to contact your insurance company to discuss the costs of your routine care (non-research) further before choosing to be in the study. You may choose not to be in this study if your insurance does not pay for your routine care (non-research) costs and your doctor will discuss other treatment plans with you.

Payment in case you are injured because of this research study:
If it is determined by Vanderbilt and the Investigator that an injury occurred as a direct result of the tests or treatments that are done for research, then you and/or your insurance will not have to pay for the cost of immediate medical care provided **at Vanderbilt** to treat the injury.

There are no plans for Vanderbilt to pay for any injury caused by the usual care you would normally receive for treating your illness or the costs of any additional care. There are no plans for Vanderbilt to give you money for the injury.

Who to call for any questions or in case you are injured:
If you should have any questions about this research study or if you feel you have been hurt by being a part of this study, please feel free to contact the study coordinator, Maxwell Roeske, at (615) 875-1896, or the study doctor, Dr. Stephan Heckers, at (615) 322-2665.

For additional information about giving consent or your rights as a person in this study, to discuss problems, concerns, and questions, or to offer input, please feel free to call the Vanderbilt University Institutional Review Board Office at (615) 322-2918 or toll free at (866) 224-8273.

Reasons why the study doctor may take you out of this study:
Your study doctor may withdraw you from study participation if he or she determines that, based on the initial study interview, you are not eligible to continue the study. He or she may also withdraw you if you are having difficulty completing study procedures, if you need an immediate referral for clinical care, or if he/she decides that it is not in your best interest to continue in the study. If you are taken out of the study, you will be told the reason.

What will happen if you decide to stop being in this study?

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If you decide to stop being part of the study, you should tell your study doctor. We may ask you to come in for a final study visit. Because you are receiving study medication, it is important to discuss a safe and effective plan for continuing, altering, or stopping the medication. All participation in the study is voluntary, and there is no penalty for refusing to participate or for early withdrawal.

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

Confidentiality:

All reasonable efforts will be made to keep the personal information in your research record private and confidential, but absolute confidentiality cannot be guaranteed. Your records will be kept in locked filing cabinets within locked rooms, and only the research team will have access. Your information may be shared with institutional and/or governmental authorities, such as the Vanderbilt University Institutional Review Board, if you or someone else is in danger or if we are required to do so by law.

During the research, if we learn you are having thoughts about suicide or hurting yourself or others, the research staff will ask you more questions about your thoughts. Based on your response, the staff may provide you with help to get treatment. This may include working with you to contact a doctor, contacting a trusted family member or therapist to discuss your thoughts, or working with you on a plan that may include getting you to a hospital for safety.

Vanderbilt may share your information, without identifiers, to others or use it for other research projects not listed in this form. Vanderbilt, Dr. Heckers, and his staff will comply with any and all laws regarding the privacy of such information. There are no plans to pay you for the use or transfer of this de-identified information.

Privacy:
Any samples and information about you may be made available to others to use for research. To protect your privacy, we will not release your name. You will not receive any benefit as a result of the tests done on your samples. These tests may help us or other researchers learn more about the causes, risks, treatments, or how to prevent this and other health problems.

Study Results:

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Your individual study results will not be shared with you. The final results of the study will be made available through www.clinicaltrails.gov and potentially through publication in the scientific literature.

Authorization to Use/Disclose Protected Health Information
What information is being collected, used, or shared?
To do this research, we will need to collect, use, and share your private health information. By signing this document, you agree that your health care providers (including both Vanderbilt University Medical Center and others) may release your private health information to us, and that we may use any and all of your information that the study team believes it needs to conduct the study. Your private information may include things learned from the procedures described in this consent form, as well as information from your medical record (which may include information such as HIV status, drug, alcohol or STD treatment, genetic test results, or mental health treatment).

Who will see, use or share the information?
The people who may request, receive or use your private health information include the researchers and their staff. Additionally, we may share your information with other people at Vanderbilt, for example if needed for your clinical care or study oversight. By signing this form, you give permission to the research team to share your information with others outside of Vanderbilt University Medical Center. This may include the sponsor of the study and its agents or contractors, outside providers, study safety monitors, government agencies, other sites in the study, data managers and other agents and contractors used by the study team. We try to make sure that everyone who sees your information keeps it confidential, but we cannot guarantee that your information will not be shared with others. If your information is disclosed by your health care providers or the research team to others, federal and state confidentiality laws may no longer protect it.

Do you have to sign this Authorization?
You do not have to sign this Authorization, but if you do not, you may not join the study.

How long will your information be used or shared?
Your Authorization for the collection, use, and sharing of your information does not expire. Additionally, you agree that your information may be used for similar or related future research studies.

What if you change your mind?
You may change your mind and cancel this Authorization at any time. If you cancel, you must contact the Principal Investigator in writing to let them know by using the contact information provided in this consent form. Your cancellation will not affect information already collected in the study, or information that has already been shared with others before you cancelled your authorization.

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If you decide not to take part in this research study, it will not affect your treatment, payment or enrollment in any health plans or affect your ability to get benefits. You will get a copy of this form after it is signed.

STATEMENT BY PERSON AGREEING TO BE IN THIS STUDY

I have read this consent form and the research study has been explained to me verbally. All my questions have been answered, and I freely and voluntarily choose to take part in this study.

_____ _____
Date Signature of patient/volunteer

Consent obtained by:

_____ _____
Date Signature

_____
Printed Name and Title