RESEARCH CONSENT FORM

Basic Information

Title of Project: Pilot Study of an Opioid-Receptor Antagonist and Gapabentin to Reduce Pain and Inflammation among HIV-Infected persons with Alcohol Problems

IRB Number: H-39162

Sponsor: National Institute on Alcohol Abuse and Alcoholism

Principal Investigator: Jeffrey Samet, MD, MA, MPH
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Study-Related Phone Numbers: Regular business hours: 7-812-234-4210
24 hours: 7-952-097-8173

Overview

We are asking you to be in a research study. A research study is an organized way of collecting information about scientific questions. This form will tell you what you should expect if you agree to be in the study. There are programs in place to make sure that investigators fulfill their obligations listed in this form.

It is your decision whether or not to join the study. We are doing the research to see if medications used to treat alcohol and opioid use disorders, gabapentin and low-dose naltrexone, improve pain, inflammation, and HIV outcomes among people with HIV and chronic pain, who also drink alcohol. If you agree, you will receive one of these two medications or a placebo. You will be in the study for 12 weeks if you decide to stay for the whole study. You will find more information about what will happen in this study later in this form.

The main risks of being in the study are stress from research assessment, bruising and minor pain from blood draw, withdrawal symptoms from naloxone challenge, and medication side effects. You will find more information about risks later in this form.

Purpose

The purpose of this study is to test if low-dose naltrexone and standard-dose gabapentin improve pain, inflammation, and HIV outcomes among HIV-positive persons with heavy alcohol use and chronic pain.

What Will Happen in This Research Study

You will be one of approximately 45 participants to be asked to participate in this study.

The study is being carried out at First St. Petersburg Pavlov State Medical University.

Although your participation will be at the above mentioned location in Russia, your data will be transferred to Boston, Massachusetts (US) and Seattle, Washington (US): Boston Medical Center/ Boston University Medical Campus and the University of Washington for evaluation with the collaborative Russian-US research team.

The ways we will protect your privacy and confidentiality are described in a separate section later in this form.

Screening Visit:

As part of the screening process, you will receive a rapid HIV test if you were not previously a participant in the Russia ARCH, St PETER, LINC-II or the PETER PAIN study. You will also be asked to complete a urine drug test and pregnancy test, if female. We will also collect a blood sample (4 ml [1 teaspoon]) to measure liver status and creatinine levels, all of which will be collected at First. St. Petersburg Pavlov State Medical University and sent for testing. If you brought in a copy of an ALT/AST and Creatinine result, dated within 4 weeks of your screening visit, to determine eligibility, then you will not require the blood draw. The results of these tests will not be put in your medical record and you will not receive any HIV medical care as part of the study. If a lab value for a test performed at the time blood is drawn is abnormal, the research assessor will share the result with you and will recommend to see your local provider to discuss the results. Your name will not be on the samples and samples will only be identifiable using a number code. The key to the code will be kept secure. If you are found not to be eligible for the study, we will keep the data we collect, but the data will not have your name on it. If you are found not to be eligible for the study, we may re-contact you to be re-screened.

Baseline Visit:
Once we have received your liver test results, we will notify you by phone and if eligible, you will be invited back to First St. Petersburg Pavlov State Medical University for your baseline study visit. At the baseline visit, if you are female, you will have a urine pregnancy test. All participants will be administered a naloxone challenge to make sure there are no opioids in your system, as taking study medication with opioids in your system will make you feel sick. Naloxone blocks the effects of opioids. It works only if it is injected and lasts about 30 minutes. It is used in hospitals and by emergency services to reverse the effects of a heroin or other opioid overdose. It will cause withdrawal if injected into someone who is currently physically dependent on opioids and will be administered to you as a way of making sure that you are not physically dependent on heroin or other opioids before you are given study medication.

The naloxone challenge will only be administered if your urine is negative for heroin or other opioids. The challenge will be done by administering 0.8-mg naloxone slowly intramuscularly. You will be observed by a research assessor for signs of withdrawal for 5-20 minutes. If you experience withdrawal after the naloxone test, your symptoms will be treated with clonidine or a benzodiazepine and will go away in 45-60 minutes. You will not be started on the study medication until you pass a naloxone challenge, which means that you have no signs or symptoms of opioid withdrawal after naloxone is administered.

After successful completion of the naloxone challenge, you will be asked about demographics (e.g., age, gender), general and mental health, and health-related behaviors such as drug and alcohol use. It will take approximately 60 minutes to complete. If you participated in the Russia ARCH, St PETER, LINC-II, or PETER PAIN study, information collected about you as part of that study will become part of the research data for this study. We will ask you to keep a daily diary on paper to record your pain, medication adherence, and alcohol use. We will ask you to bring this diary to all study visits.

We will ask to take a blood sample from you (up to 20 ml [or 1-2 tablespoons]), which will be done at a First St. Petersburg Pavlov State Medical University laboratory. It will be used to analyze your blood for markers related inflammation and HIV disease progression. The results of the tests will not be put in your medical record and you will not receive any HIV medical care as part of the study. If a lab value for a test performed at the time blood is drawn is abnormal, the research assessor, will share the result with you and will recommend to see your local provider to discuss the results.

You will also receive a cold-pressor test (CPT) at this visit. In brief, this test will see how long you can tolerate keeping your hand in a bucket of cold water. You will place your dominant hand and part of your arm in a tank

filled with cold water that is kept at a constant temperature of 0-2 degrees Celsius. You will tell the study staff when you first begin to feel pain/discomfort. When you can no longer tolerate the pain/discomfort, you can remove your hand from the water. The study staff will be measuring the amount of time from when you first put your hand in the water to when you felt pain and when you withdrew your hand. After the test, you will be asked to rate the pain you felt on a scale of 0-100. You will be asked to refrain from over the counter analgesic use (non-steroidal anti-inflammatory pain medications or acetaminophen) for 24 hours prior to your study visit, as this may affect your pain tolerance.

After completion of the baseline assessment and cold-pressor testing, you will be randomly placed in one of three study groups. Randomization means you will be randomly assigned to a group based on chance, like a flip of a coin. Neither you nor the researcher chooses your assigned group. You will have an equal chance of being in any group.

Group 1 – Low-dose naltrexone:

If you are in this group, you will receive low-dose naltrexone for a period of 8 weeks starting on the day of the baseline visit. You will be asked to take the medication once a day for the first week, and approximately three times a day (morning, afternoon, and evening) for 7 weeks.

Group 2 – Standard-dose gabapentin:

If you are in this group, you will receive gabapentin for a period of 8 weeks starting on the day of the baseline visit. You will be asked to take the medication once a day for the first week, and approximately three times a day (morning, afternoon, and evening) for 7 weeks.

Group 3 – Placebo

If you are in this group, you will receive drug capsules containing no active ingredient for a period of 8 weeks starting on the day of the baseline visit. You will be asked to take the medication once a day for the first week, and approximately three times a day (morning, afternoon, and evening) for 7 weeks.

Study medication will be provided by trained physicians, who will instruct you in proper medication administration and adherence. After you take the first dose of the study medication, you will stay at Pavlov for a 30 minute observation period. Neither you nor the study staff will know which of the three medications you will be taking. However, in an emergency situation, we can always find out which of the medications you're taking by contacting the study pharmacist.

Follow-Up Visits:

Medication check-ins
Participants in all groups will be asked to come in to First St. Petersburg Pavlov State Medical University for a short 15-20 minute medication adherence check visit 1, 2, 6, and 7 weeks after the baseline visit. During these check-ins, you will be monitored for any adverse events related to study medication. If you are experiencing any adverse events from the study medication, we may reduce your dose to one that you can tolerate better. We will administer a brief assessment of tolerability, side effects, and adherence. If you are female, you will be asked to provide a urine sample to check for pregnancy.

In-person study visits
In addition to the short adherence check visits at 1, 2, 6, and 7 weeks, you will be asked to come to First St. Petersburg Pavlov State Medical University 4, 8, and 12 weeks after the baseline visit. During these visits, we

will administer a questionnaire, collect a blood (4 ml [1 teaspoon]) and urine sample (for female participants), and conduct the cold-pressor test. The urine sample will be used to check for pregnancy at the 2, 4, 6 and 7-week visits. The blood sample will be used to measure your liver status. If your blood test results at 4 weeks show that your liver enzymes are high, we will re-check your liver status at the 6-week visit, which means that we will collect a blood sample (4 ml [or 1 teaspoon]) during that visit. During the 8-week visit, additional blood will be collected (up to 20 ml or [1-2 tablespoons]). This blood sample will be used to analyze your blood for markers related to inflammation and HIV disease progression.

We will contact you via phone calls, text message, email, and/or letters to remind you about your follow-up appointments.

All data that we collect from you as part of this study will be placed in a repository for future HIV research. When investigators want to perform a study on repository data, they will submit a study plan for review and approval and will need to obtain any necessary approvals, such as approval from their IRB, to carry out the work with repository data or samples. Prior to receiving the data and/or samples, the researchers will agree not to share the data and not to attempt to identify any individual participants. In all cases the data and/or samples will be released from the repository in coded form (i.e., names and contact details will not be included and data/samples will be identified by a subject ID number).

Risks and Discomforts

You may experience stress from the research assessments, as you will be asked sensitive questions regarding substance use and HIV status. The risk of stress from interviews will be minimized by using trained interviewers and a standard interview process. You may be stressed by the length of the interviews (estimated 60 minutes). You will be allowed to stop at any time during the interviews to take a break and come back to complete them.

You may experience bruising and minor pain as a result of the blood draw. Other risks such as infection are rare. These risks will be minimized by using trained phlebotomists to draw your blood.

If you have opioids in your system, you may experience withdrawal symptoms after the naloxone challenge, such as feeling sick, stomach cramps, muscle spasms, feelings of coldness, heart pounding, muscular tension, aches and pains, yawning, runny eyes, and insomnia. The symptoms usually resolve untreated within 45-60min, but in rare occasions may require the use of clonidine and phenazepam. The most frequent side effects (which appear to be dose-related) of clonidine are dry mouth, drowsiness, dizziness, constipation and sedation. The most frequent side effects of phenazepam are drowsiness, sedation, muscle weakness, and ataxia. These side effects generally decrease on continued administration and are a consequence of CNS depression.

Some people have had side effects while taking these study medications.

The most common side effects (reported in more than 1 in 10 people) of naltrexone are difficulty sleeping, anxiety, nervousness, abdominal pain/cramps, nausea and/or vomiting, low energy, joint and muscle pain, and headache.

Uncommon side effects (reported in less than 1 and 10 people, but more than 1 in 100 people) of naltrexone are loss of appetite, diarrhea, constipation, increased thirst, increased energy, feeling down, irritability, dizziness, skin rash, delayed ejaculation, decreased potency, and chills.

Rare side effects (reported in less than 1 in 100 people) of naltrexone include nasal congestion, itching, rhinorrhea, sneezing, sore throat, excess mucus or phlegm, sinus trouble, heavy breathing,

hoarseness, cough, shortness of breath, nose bleeds, phlebitis, edema, increased blood pressure, non-specific ECG changes, palpitations, tachycardia, excessive gas, hemorrhoids, diarrhea, ulcer, painful shoulders, legs or knees; tremors, twitching, increased frequency of, or discomfort during, urination; increased or decreased sexual interest, oily skin, pruritus, acne, athlete's foot, cold sores, alopecia, depression, paranoia, fatigue, restlessness, confusion, disorientation, hallucinations, nightmares, bad dreams, eyes–blurred, burning, light sensitive, swollen, aching, strained ears–"clogged," aching, tinnitus, Increased appetite, weight loss, weight gain, yawning, somnolence, fever, and dry mouth.

Please note that these side effects were reported among people taking 50mg of naltrexone. This study will use low dose naltrexone (4.5mg) and side effects are expected to be milder.

The most common side effects of gabapentin are lack of coordination, feeling tired, fever, feeling drowsy, jerky movements, nausea and vomiting, difficulty with coordination, difficulty with speaking, double vision, tremor, unusual eye movement, and swelling (usually of legs and feet).

You should not drive, use heavy machinery, or do other dangerous activities until you know how gabapentin affects you, as it can slow your thinking and motor skills.

You should avoid drinking alcohol while on study medication, as drinking alcohol while taking Gabapentin may make your sleepiness or dizziness worse.

Rare side effects of gabapentin (reported in about 1 in 500) include suicidal thoughts or actions. These may include thoughts about suicide or dying, attempts to commit suicide, new or worse depression, new or worse anxiety, feeling agitated or restless, panic attacks, trouble sleeping (insomnia), new or worse irritability, acting aggressive, being angry, or violent, acting on dangerous impulses, an extreme increase in activity and talking (mania), other unusual changes in behavior or mood.

Other side effects of gabapentin are serious or life-threatening allergic reactions that may affect your skin or other parts of your body such as your liver or blood cells. Symptoms may include skin rash, hives, difficulty breathing, fever, swollen glands that do not go away, swelling of your face, lips, throat, or tongue, yellowing of your skin or of the whites of your eyes, unusual bruising or bleeding, severe fatigue or weakness, unexpected muscle pain, frequent infections.

Be aware that in the event that gabapentin is used with opiates, it can increase the sedation side effects of opiates. Gabapentin when combined with CNS depressants, such as opioids, anti-anxiety medications, antidepressants, and antihistamines; can increase your risk of slowing or stopping your breathing. Your risk of slowing or stopping your breathing when taking gabapentin is also greater if you have an underlying medical condition, like chronic obstructive pulmonary disorder. You should seek or be brought to medical attention if you experience any of the following symptoms: confusion or disorientation, unusual dizziness or lightheadedness, extreme sleepiness, slowed, shallow or difficult breathing, unresponsiveness, or bluish-colored or tinted skin, especially on the lips, fingers, and toes.

In order to help prevent these adverse events, you will be asked not to take more medication than what is provided by the study. Study clinicians will also be monitoring for signs of medication overdose and misuse via pill counts and symptom monitoring. These adverse effects are not expected to be likely.

The test of pain sensitivity (cold-pressor test) may cause some discomfort and pain. However, the discomfort experienced during testing is relatively mild and should only last for the duration of the testing. You are asked

to withdraw your arm from the cold water bath when you feel pain. In order to avoid any cold injury, the cold-pressor test will be stopped after 3 minutes if you do not withdraw your hand by then.

In the event of an emergency, in which you may require acute pain management, opioids may not be a therapeutic option for acute pain management while on the study drug. A 72-hour washout period is generally needed prior to effective use of opioids, and monitored use under anesthesia, if needed emergently. In addition, we will provide you with a wallet card to be presented to your provider to indicate that you are receiving one of two study medications with potential impact on pain management.

There may be unknown risks/discomforts involved. Study staff will update you in a timely way on any new information that may affect your health, welfare, or decision to stay in this study.

If you suspect that you have become pregnant during the study, you must notify the study doctor immediately. If you become pregnant while you are participating in this study, it could be dangerous for the baby. You must use birth control if you are a woman having sex with men while you are taking study medication and for 8 weeks afterward. Some of the most effective birth control methods are: oral contraceptives (the pill), intrauterine devices (IUDs), contraceptive implants under the skin, contraceptive rings or patches or injections, diaphragms with spermicide and condoms with foam. You should not participate in this study if you are a woman who has sex with men and cannot use one of these birth control methods.

If at any time during a study interview you voice current suicidality, experience a psychiatric emergency, or express the intent to harm others, this will be reported to an on-site physician, immediately. That physician will determine the appropriate course of action, which will depend on location of the event and the clinical situation. You may be escorted to receive care by appropriate staff if deemed necessary.

Potential Benefits

You may not receive any benefits from participating in the study. However, you may benefit from discussing your health with an assessor and society may benefit from a better understanding of the effects of these medications on the health of HIV-positive people.

Costs

There are no costs to you for being in this research study. You may incur costs traveling to and from study visits. All research procedures will be paid for by the study; these include assessments and tests. Outside of the study, you may choose to receive additional health services such as medical care, tests and/or medications. Payment for services outside of the study will not be paid for by the study.

Payment

You will receive 500 rubles in goods or cash for your participation in the screening visit, 1000 rubles in goods or cash for your participation in baseline, 800 rubles in goods or cash for your participation in 2-, 4-, and 6-week visits, and 1500 rubles in goods or cash for your participation in 8- and 12-week visits. You will also be compensated for completing short medication visits at weeks 1 and 7, for a total of 500 rubles per visit.

Confidentiality

We must use information that shows your identity to do this research. Information already collected about you will remain in the study record even if you later withdraw.

We will store your information in ways we think are secure. We will store biological samples taken from your body (such as urine, blood, or tissue) in a laboratory in St. Petersburg, Russia. Your name will not be on the samples and samples will only be identifiable using a number code. The key to the code will be kept secure. The repository has standard operating procedures to protect your confidentiality. We will store paper files in locked filing cabinets. We will store electronic files in computer systems with password protection and encryption. We will do our best to keep your information safe. However, we cannot guarantee complete confidentiality.

This study is covered by a Certificate of Confidentiality (CoC) from the National Institutes of Health. All studies funded by the National Institutes of Health that involve identifiable information or biological samples are covered by a CoC. The CoC provides how we can share research information or biological samples. Because we have a CoC, we cannot give out research information or biological samples that may identify you to anyone that is not involved in the research except as we describe below. Even if someone tries to get your information or biological samples in connection with a legal proceeding, we cannot give it to them. The CoC does not prevent you from sharing your own research information. The Certificate of Confidentiality applies to information and samples collected for this study which are sent to or kept in the United States of America.

If you agree to be in the study and sign this form, we will share information and biological samples that may show your identity with the following groups of people:

- People who do the research or help oversee the research, including safety monitoring.
- People from Federal and state agencies who audit or review the research, as required by law. Such agencies may include the U.S. Department of Health and Human Services, the Food and Drug Administration, the National Institutes of Health, and the Massachusetts Department of Public Health.
- People who will get your data and your biological samples as we described in the section **What Will Happen in This Research Study**. These people are expected to protect your information and biological samples in the same way we protect it.
- Any people who you give us separate permission to share your information.

Research assessment questionnaires will be completed with the majority of data entered directly into computers, which will require a username and password to logon to. Data will not have your name, only your unique study ID number. Locator contact information and the master enrollment list will have participant names. Paper forms will be kept in locked filing cabinets and electronic data will be stored on password protected computers. Study information will be accessible to study staff for purposes of conducting or monitoring the study.

We will share research data where we have removed anything that we think would show your identity. There still may be a small chance that someone could figure out that the information is about you. Such sharing includes:

- Publishing results in a medical book or journal.
- Adding results to a Federal government database.
- Using research data in future studies, done by us or by other scientists.
- Using biological samples in future studies, done by us or by other scientists.

A description of this clinical trial will be available on http://www.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.

Information from this study may be reviewed and photocopied by the National Institute on Alcohol Abuse and Alcoholism and/or state and federal regulatory agencies such as the Office of Human Research Protection and the Institutional Review Board of Boston University Medical Center. Information from this study and from your

medical record may be used for research purposes and may be published; however, your name will not be used in any publications.

Compensation for Injury

If you think that you have been injured by being in this study, please let the investigator know right away. Use the phone number on the first page of this form. You should seek treatment at your local medical center. There is no program to provide compensation for the cost of care for research related injury or for other expenses. Other expenses might be lost wages, disability, pain, or discomfort. If you do not go to a state-operated facility you will be responsible for paying for the medical treatment you receive. You are not giving up any of your legal rights by signing this form.

Re-Contact

1) Data and sample repository

We would like permission to store your research data, including samples, for future studies. Please indicate below if you will allow that.

My research data, including samples, may be kept for future clinical, virological, and immunological studies related to HIV disease and other associated illnesses. Yes [ ] _____(initial or sign) No [ ] _____(initial or sign)

If you would like to use my research data, including samples, for future studies not listed above, I am willing to be contacted about those studies for my permission. Yes [ ] _____(initial or sign) No [ ] _____(initial or sign)

2) Future studies
We would like to be able to contact you in the future about additional studies for which you may be eligible.

[ ] Yes, I agree to be contacted after my active participate in this study has ended_____(initial or sign)

[ ] No, I do not give permission to be contacted after my active participate in this study has ended. _____(initial or sign)

Subject's Rights

By consenting to be in this study you do not waive any of your legal rights. Consenting means that you have been given information about this study and that you agree to participate in the study. You will be given a copy of this form to keep.

If you do not agree to be in this study or if at any time you withdraw from this study you will not suffer any penalty or lose any benefits to which you are entitled. Your participation is completely up to you. Your decision will not affect your ability to get health care or payment for your health care. It will not affect your enrollment in any health plan or benefits you can get.

During this study, we may find out something that might make you not want to stay in the study. If this happens, we will tell you as soon as possible.

You may obtain further information about your rights as a research subject by calling the Ethical Committee of

First St. Petersburg State Pavlov Medical University at 7-812-338-6617.

Questions

The investigator or a member of the research team will try to answer all of your questions. If you have questions or concerns at any time, contact EDWIN ZVARTAU at 7-812-338-7023 during the day and EVGENY KRUPITSKY at 7-952-097-8173 after hours. Also call if you need to report an injury while being in this research.

You may also call 7-812-338-6617. You will be talking to someone at the St. Petersburg State Pavlov Medical University IRB. The IRB is a group that helps monitor research. You should call or email (spbgmutrials@yandex.ru) the IRB if you want to find out about your rights as a research subject. You should also call or email if you want to talk to someone who is not part of the study about your questions, concerns, or problems.

Protection of Subject Health Information

You have certain rights related to your health information. These include the right to know who will get your health information and why they will get it. If you choose to be in this research study, we will get information about you as explained below. You authorize Jeffrey Samet, Judith Tsui, and study staff at Boston Medical Center and the University of Washington, who are working on this research project and their employees to use and disclose information concerning you and your identity, medical history, and information collected during this study for the following purpose: to study alcohol use, chronic pain, and HIV disease progression. Such information may also be disclosed to or used by others involved in or overseeing the study including Boston University Medical Center Institutional Review Board and the study's sponsor, the United States National Institutes of Health (NIH). We share your health information only when we must. We ask anyone who gets it from us to protect your privacy. If you do not want to let us use your health information, you cannot be involved with this research study. This is because your health information is necessary to the conduct of this research. You may withdraw authorization to collect additional information about you at any time by writing to the local Principal Investigator, but information already collected may continue to be used and disclosed. This authorization has no expiration date.

Subject: _____
Printed name of subject

By signing this consent form, you are indicating that you have read this form (or it has been read to you), that your questions have been answered to your satisfaction, and that you voluntarily agree to participate in this research study.

_____ _____
Signature of subject Date

Researcher: _____
Printed name of person conducting consent discussion

I have personally explained the research to the above-named subject and answered all questions. I believe that s/he understands what is involved in the study and freely agrees to participate.

BMC and BU Medical Campus IRB
IRB NUMBER: H-39162
IRB APPROVAL DATE: 03/11/2021

_____ _____
Signature of person conducting consent discussion Date

To be completed by witness if researcher reads this form to the subject
This consent form was read to and apparently understood by the subject in my presence.

_____
Printed name of witness (a person not otherwise associated with the study)

_____ _____
Signature of witness Date