Treatment of Orthostatic Hypotension

NCT00581477

Informed Consent

Vanderbilt University Institutional Review Board
Informed Consent Document for Research

Principal Investigator: Emily M. Garland, PhD, MSCI
Revision Date: 12/11/17
Study Title: The Treatment of Orthostatic Hypotension
Institution/Hospital: Vanderbilt University

This informed consent document applies to Adult Patients (Dose Selection Trial)

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.

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. You have the right to ask what it will cost you to take part in this study. You may wish to contact your insurance company to discuss the costs further before choosing to be in the study as there may be added costs that you will be billed for if you agree to be in the study. You may choose not to be in this study if your insurance does not pay for the costs and your doctor will discuss other treatment plans with you.

1. What is the purpose of the study:
You are being asked to take part in this research study because you have problems with blood pressure regulation and other symptoms of an impaired involuntary (autonomic) nervous system. The autonomic nervous system controls blood pressure, heart rate, the size of your pupils, sweating, and other functions. Norepinephrine is an important chemical that can raise blood pressure. Another chemical, dopamine, can lower blood pressure. Dopamine can be converted into norepinephrine by a protein called dopamine-beta-hydroxylase (DBH). The amount of dopamine in your body, compared to the amount of norepinephrine, might be affected by the activity of DBH and might determine whether you have high, normal or low blood pressure in certain situations. You have participated in the study "The Pathophysiology of Orthostatic Hypotension", and the results from that study indicate that you might benefit from drugs that modify the level or activity of norepinephrine or dopamine. We would now like to treat you with one or more drugs and then do some tests to determine the effectiveness of the treatments. You might also be tested after taking an inactive substance (placebo). The study is designed to find the best dosage of the drug for you, in terms of safety and effectiveness. You will initially be given a low dosage and this will be increased gradually. Depending on the length of activity of the drug and its effect on you, you could be given the drug only one time or you could be given it more than one time. Similarly, you could receive the same dosage of the drug several times or you could receive several different dosages. You will be given a maximum of four increasing dosages of the drug in one day, and you will take each drug for a maximum of 7 days. Depending on the results of these trials, we might subsequently do some longer-term drug trials for which you will be asked to sign another consent form.

If you agree to participate in this study, the investigators in the Vanderbilt Autonomic Dysfunction Center and their collaborators will have access to your medical and research data.

2. What will happen and how long will you be in the study?
This study is being conducted at the Vanderbilt Clinical Research Center (CRC) and will take from approximately 1 to 7 days for each drug. Depending on where you live and the severity of your symptoms, you might be asked to stay in the hospital for a portion of or the entire study period. One of the investigators will explain the study to you and ask you to sign this consent form. The drug that you will take will be marked on the consent form, and its possible side effects will be discussed with you. A copy of the consent form will be given to you.

a. Continued drug withdrawal
You must remain off any medications that could affect blood pressure for three days prior to and during the study. This includes not only your usual scheduled medications, but also other drugs that might be taken intermittently. If your symptoms are severe enough that you or your physician have concerns that your

symptoms may worsen, you may be admitted to the hospital for observation during this portion of the study. While you are an inpatient on the CRC, we will check your general condition, blood pressure and heart rate regularly to reduce any risk.

b. Urine pregnancy test

If you are a female, we will perform a pregnancy test on a sample of your urine prior to the study. Pregnant females generally may not participate in research studies because we do not know how pregnancy might affect the results of the tests. We might also want to give you some medications that have not been studied in pregnant women. Very early in pregnancy, a pregnancy test can be negative. Therefore, we advise you to practice birth control, if you are sexually active, for two weeks before your study starts.

c. Diet

We will ask you to eat a standard diet with no caffeine and a controlled amount of salt for three days prior to and during the study. We will provide this food to you and ask you to eat all of it and no other food.

d. Drug testing

Medication trials will be started after at least 3 days of medication and diet restriction to assess your response to a drug that might be beneficial in your treatment. We will decide which drug to give you based on your clinical history and the results of testing that you underwent previously. Before we start drug testing, we will do a baseline Posture Study (see below) to determine your ability to stand in an unmedicated state. Blood pressure and heart rate will be measured with a cuff around your arm every 10 minutes for 30 minutes before you are given a drug. You will first be given a low dosage of the drug by mouth while you are seated in a chair or in your bed. Your blood pressure will be measured every 5-15 minutes for one hour after the drug. At 11/2 hours after the first dose each day, you may be asked to lie down for 30 minutes and then sit or stand, if you are able, for 5 minutes while we measure your blood pressure and collect blood samples to measure hormones involved in blood pressure control. During this day and following days, you will be given additional doses of the drug, with the amount of drug given at each time to be determined by your response to the previous dose. Before each dose of each drug, blood pressure and heart rate will be measured with a cuff around your arm every 10 minutes for 30 minutes, and your blood pressure will be measured every 5-15 minutes for one hour after dosing. Except for the first dose each day, blood pressure will also be measured at 2 hours after the drug, after 5 minutes of lying down and 5 minutes of sitting or standing. You will also be asked to report any changes in your symptoms and any discomfort you might experience. A Posture Study may be repeated at the end of the Dose Selection Trial.

e. 24-Hour Urine Collection

You will collect your urine daily for 24 hours. The urine will be analyzed for

☐ sodium

☐ hormones that control blood pressure and heart rate.

f. Posture Study.

You will need to lie in bed for at least 30 minutes with nothing to eat for at least two hours. A small tube (catheter) will be placed in your arm vein in order to draw blood. We will draw two tablespoons of blood while you are lying down and two more after you have stood for 30 minutes (or for as long as you are able) to determine levels of hormones that regulate blood pressure. We will also monitor your blood pressure and heart rate during this study. Your blood pressure and heart rate will be monitored while you are lying down, immediately after standing, and at 3, 5, 10, 20, and 30 minutes of standing. The length of time that you are able to stand will be determined. You will be asked about your symptoms periodically during the study. You will undergo a Posture Study before any medication is given.

g. Orthostatic vital signs

Orthostatic vital signs will be measured several times a day while you are an inpatient. This testing consists of blood pressure and heart rate measured while you are lying down and then repeated after standing quietly for 10 minutes. Several readings are measured in sequence using the Dinamap, an automated blood pressure monitor that uses a cuff around your upper arm.

h. Blood sampling
It will be necessary to collect two samples of your blood during each Posture Study (a total of 4 tablespoons per study) for measurement of the hormones that control blood pressure. To avoid sticking you repeatedly, we will place a small plastic tube (catheter) in your arm vein.

Our goal is to find a dosage that results in a standing blood pressure of at least 100/70 mm Hg. The drug that you will take is checked below:

- ☐ L-DOPS, starting at 25 mg with increments as tolerated (for example, 50 mg, 100 mg, 200 mg, 300 mg…) given up to 4 times daily.
- ☐ L-Dopa, starting at 25 mg with increments as tolerated (for example, 50 mg, 100 mg, 150 mg, 200 mg, 250 mg), given three times daily.
- ☐ Carbidopa, starting at 25 mg with increments as tolerated to 25 mg four times daily.
- ☐ Metyrosine, starting at 62.5 mg with increments as tolerated (for example, 125 mg, 250 mg, 500 mg, 750 mg, 1000
- ☐ mg), given three times daily.
- ☐ Metoclopramide (Reglan), starting at 10 mg up to four times a day as tolerated.
- ☐ Alpha-methyldopa (Aldomet), starting at 62.5 mg with increments as tolerated to 250 mg given two times daily.
- ☐ Atomoxetine, starting at 10 mg with increments as tolerated to 20 mg and then 40 mg, given two times daily.
- ☐ Placebo

If you are given a trial with an additional drug, you will be asked to sign an additional consent form with that drug indicated.

3. Costs to you if you take 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 tests and treatments that are being **done only for research**. However, you are still responsible for **paying for the care you receive that is being done as part of treating your illness or condition and other health care**. This includes treatments and tests you would need whether you are in this study or not. These costs will be billed to you and/or your insurance.

4. Side effects and risks that you can expect if you take part in this study:

Stopping medications might worsen your symptoms of lightheadedness, palpitations, fatigue and others that accompany your condition. We will not ask you to stop any medication that will endanger your health and will admit you to the hospital if there is concern about your symptoms becoming too severe. We will communicate with you on a daily basis after stopping medications. While you are an inpatient on the CRC, we will check your general condition, blood pressure and heart rate regularly to reduce any risk.

Consuming a **sodium- and caffeine-controlled diet** that needs to be picked up at the CRC might be inconvenient. The low salt diet might be bland and not to your liking. If you drink caffeinated beverages regularly

and you stop caffeine intake suddenly, you might have headaches and fatigue for a few days. You can avoid these symptoms if you cut down gradually on the amount of caffeine in your diet.

Staying in the hospital might be an inconvenience for you.

Frequent blood pressure measurements with the cuff around your arm or finger may produce some discomfort and occasional bruising of the upper arm.

There are minor risks and discomforts associated with **blood sampling**. We will insert a plastic catheter into the vein to allow drawing blood without repeated sticks during the study. This may cause a brief period of pain and possibly a small bruise at the site. Occasionally, a person feels faint when their blood is drawn. Rarely, an infection develops which can be treated. There is a small risk of bleeding after removal of the catheter and possibly a bruise at the site which can be prevented by tight compression on the site. Rarely, an infection develops which can be treated. As part of being in this study, you will have several blood draws that may worsen your anemia. Symptoms may include feeling faint, low blood pressure, and fatigue. This may require an increase in the length of time you are in this study, which may include additional visits to the CRC.

Collecting your urine might be inconvenient for you. We try to make it more convenient by fitting the toilet with a collection device and/or providing a urinal for your use.

When any medication is used in testing, there is a small risk of an unforeseeable life-threatening allergic reaction. Side effects associated with specific medications are listed below. Side effects are listed as common, uncommon, and rare.

α-Methyldopa – common: weakness, distention of lower abdomen, constipation, swelling of the lower extremities, fever and depression, anxiety, nightmares, being sleepy or drowsy, headache and dry mouth. Uncommon: dizziness, gas, diarrhea, chest pain, stuffiness of the nose, low blood pressure on standing, low heart rate, nausea or vomiting, abnormal liver function tests. Serious or life-threatening: extremely rare reactions are fatal liver damage and fatal inflammation to the heart.

Carbidopa – only reported to have adverse effects when it is given with the drug levodopa for Parkinson's disease. Common adverse events with the carbidopa-levodopa combination include dyskinesias (involuntary muscle movements) and nausea. Less common adverse effects are psychotic episodes, depression and dementia (confusion/memory loss).

Metyrosine – common: elevated blood pressure and heart rate, drowsiness, diarrhea, drooling, trembling and shaking of hands and fingers; trouble speaking. Uncommon: decreased sexual ability in men, dry mouth, nausea, vomiting, stuffy nose, anxiety, confusion, hallucinations, mental depression. Rare or life-threatening: crystalluria (the excretion of crystals in the urine resulting in urine retention), black, tarry stools, unusual bleeding or bruising, muscle spasms, painful urination, pinpoint red spots on skin, restlessness, shortness of breath, shuffling walk, skin rash and itching, swelling of feet or lower legs, tic-like movements

L-Dopa (levodopa) – common: abdominal pain, dry mouth, loss of appetite, nightmares, gas, abnormal thoughts, feeling overly excited/sensitive, anxiety, clumsiness, difficulty swallowing, dizziness, excessive watering of mouth, nausea and vomiting, uncontrolled body movements. Uncommon: Chest pain, mood or mental changes, discoloration of sweat or urine, constipation, diarrhea, flushed skin, headache, hiccups, increased sweating, muscle twitching, trouble sleeping, blurred vision, difficult urination, dilated pupils, dizziness or lightheadedness when getting up from a lying or sitting position, double vision, fast or pounding heartbeat, hot flushes, mental depression, skin rash, weight gain or loss. Rare: back or leg pain, black tarry stools, chills, convulsions, fever, high blood pressure, loss of appetite, swelling of feet or lower legs

Atomoxetine – common: headache, nausea, sleepiness, trouble sleeping, anxiety, dry mouth, loss of appetite, dizziness, constipation, flushed or warm sensation, rash. Uncommon: loose stools, excessive energy, excitement, stomach ache, fluttering sensation in chest, abnormal heart rhythm sensations, tingling, vomiting, aching muscles. Rare: abnormal blood tests, such as abnormal liver function tests

L-DOPS – The use of L-DOPS is under investigation and is not approved by the FDA. We have used it for many years in a small population of patients that lack dopamine-beta-hydroxylase, the enzyme that converts dopamine to norepinephrine. The initial dose is low and adjusted to treat low blood pressure without adverse effects. It is possible that there may be some side effects. The following rare side effects have been reported: increased blood pressure, nausea, headache, hallucination, anorexia, increased liver enzymes, dizziness/lightheadedness, heart fluttering, thirst, nervousness, stomachache, vomiting, abdominal pain, chest pain, and fatigue.

Metoclopramide – common: diarrhea, drowsiness, restlessness, insomnia, fast heart rate, confusion. Uncommon: chills, increase in blood pressure, dizziness, headache, nausea, rash. Rare: seizures, abnormal body movements, abnormal blood count, breast tenderness, increased flow of breast milk.

Placebo – The placebo is a pill or capsule that does not contain active ingredient. It should therefore have no side effects.

5. Risks that are not known:
We cannot foresee any other risks, but there may be previously unknown or unforeseen risks. Because the medications might be harmful to an unborn child, adequate birth control measures (i.e., oral, implanted or barrier methods) must be used by all participants and their sexual partners while participants are enrolled in this study. If you become pregnant or father a child while in this study, you must notify your physician immediately. In addition, women must not breast feed while in this study. To rule out pregnancy prior to receiving treatment in this study, women of childbearing potential will have a pregnancy test.

6. 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 the costs of any additional care. There are no plans for Vanderbilt to give you money for the injury.

7. Good effects that might result from this study:
The potential benefits to science and humankind that may result from this study are that we might learn more about what causes disorders such as yours and possibly about treatments that might be effective for these disorders.

8. Other treatments you could get if you decide not to be in this study:
You may choose not to participate in this study. Along with your other doctors, we will still care for you even if you choose not to participate in this study.

9. Payments for your time spent taking part in this study or expenses:
You will not be compensated for your participation in this study.

10. Reasons why the study doctor may take you out of this study:
The investigators or Vanderbilt may stop you from taking part in this study at any time if it is in your best interest, if you do not follow the study rules, or if the study is stopped.

11. What will happen if you decide to stop being in this study?
If you decide to stop being part of the study, you should tell your study doctor. Deciding to not be part of the study will not change your regular medical care in any way.

12. Who to call for any questions or in case you are injured:
If you should have any questions about this research study or possibly injury, please feel free to contact [redacted], **David Robertson, M.D.** [redacted], **or Emily Garland, PhD,** [redacted].

For additional information about giving consent or your rights as a participant in this study, please feel free to contact the Vanderbilt University Institutional Review Board Office at (615) 322-2918 or toll free at (866) 224-8273.

13. Confidentiality
Much of the data will be entered into the password-protected Autonomic Dysfunction Center Database. Hard copies of research results are maintained by the Autonomic Dysfunction Center research nurses in a locked room. Data will be accessible to Dr. Robertson, other members of his research group, and his collaborators. All data and research specimens will be maintained for an indeterminate period of time. All the investigators have completed Vanderbilt training in compliance with the HIPAA regulations. Every effort will be made to protect and respect patient confidentiality and privacy within the limits of HIPAA.

14. Authorization to Use/Disclose Protected Health Information
Protected health information (PHI) is individually identifiable health information that has been entered into a medical record. Once this has occurred, use or disclosure of such information from the medical record must follow federal privacy guidelines. A decision to participate in this research means that you agree to let the research team use and share your PHI as described below.

As part of the study, Dr. Robertson and his co-investigators may report the results of your study and/or non-study related laboratory tests and electrocardiograms to other members of his research team and to his collaborators. If your research record is reviewed by any of these groups, they may also need to review your entire medical record. Your records may also be reviewed in order to meet federal or state regulations. Reviewers may include representatives from the Food and Drug Administration, representatives of the National Institutes of Health, the Vanderbilt University Institutional Review Board, or the research group headed by [redacted]. Once your health information is released to the persons or groups described above, there is no guarantee that those persons or groups will not in turn release your health information to others who may not be legally required to follow the procedures and limitations in this Informed Consent and Authorization Form.

The study results will be retained in your research record for at least six years after the study is completed. At that time the research information not already in your medical record will be kept indefinitely. Any research information in your medical record will be kept indefinitely.

If you decide to withdraw your authorization to use or disclose your PHI, we ask that you contact Dr. Robertson in writing and let him know that you are withdrawing your authorization. His mailing address is:

Dr. David Robertson
[redacted]

Principal Investigator: Emily M. Garland, PhD, MSCI Revision Date: 12/11/17
Study Title: The Treatment of Orthostatic Hypotension
Institution/Hospital: Vanderbilt University

At that time we will stop getting any more data about you. But, the health data we stored before you withdrew your consent may still be used for reporting and research quality.

You have the right to see and copy the PHI we gather on you for as long as the study doctor or research site holds this data. To ensure the scientific quality of the research study, you will not be able to review some of your research data until after the research study is finished.

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 PARTICIPATE IN THIS STUDY

[ ] I have read this consent form. All my questions have been answered, and I freely and voluntarily choose to participate. I understand that I may withdraw at any time.

[ ] I have read this informed consent document and the material contained in it has been explained to me verbally. All my questions have been answered, and I freely and voluntarily choose to participate.

_____ _____
Date Signature of patient/volunteer

Consent obtained by:

_____ _____
Date Signature

_____
Printed Name and Title