

The Use of Amitriptyline for Improving Hypoglycemia Course and Recognition

NCT03591458

Document Date: 04/24/2019

Consent and Authorization Document

You are being asked to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends and relatives if you wish. Ask the research doctor or staff if there is anything that is not clear or if you would like more information. Take time to decide whether or not to volunteer to take part in this research study.

BACKGROUND

Type 1 Diabetes mellitus can cause many devastating complications involving the heart, brain, eyes, kidneys and nerves. Tight blood glucose control will help stop or slow down the development of these complications. However, a tight blood glucose control can often cause low blood glucose events (hypoglycemia). Continuous glucose monitoring (CGM) devices, by providing the real-time glucose information, and alerting low blood glucose levels, have helped people with type 1 diabetes to avoid many low blood glucose events. However, despite the use of CGM, a lot of patients still spend a significant amount of time in low blood glucose on a day-to-day basis. In fact, previous studies have suggested that type 1 diabetes patients using CGM still spend in average about 45-80 minutes in hypoglycemia every day. Also, with frequent low blood glucose events, people can often lose their ability to sense low blood glucose; this is a condition called “impaired awareness of hypoglycemia” by medical doctors. People with impaired awareness of hypoglycemia is at a very high risk of developing severe hypoglycemia.

Calls for treatments that can further decrease the low blood glucose burden for people who have type 1 diabetes using CGM has been made. There currently exists no known treatment that can further lower the time spend in low blood glucose on top of CGM. Also, medical doctors and researchers have been trying to find a widely available treatment for the loss of ability to sense low blood glucose, as there is also no known drug treatment that can help bring back the awareness these patients have lost.

The goal of this study is to try to identify a drug treatment that can help people with type 1 diabetes using CGM to further decrease their low blood glucose burden and regain their ability ability of sensing low blood glucose. Scientists at the University of Utah have identified that amitriptyline completely recovers the ability to react to and treat low blood glucose in animal model. Also, amitriptyline has long been used for patients with diabetes to help their diabetic neuropathy, and has a good safety history. We are therefore testing to see whether a low dose amitriptyline can help decrease the low blood glucose burden and improve the ability to sense low blood glucose in patients with type 1 diabetes.

This study will be a Phase 2 pilot study, which aims to see if amitriptyline works to help improve the course of low blood glucose episodes and the ability to sense low blood glucose.

This study will be conducted at the University of Utah, and is sponsored by National Institute of Health (NIH) and Washington University at St. Louis and University of Utah Diabetes and Metabolism Center.

STUDY PROCEDURES



This study is a randomized, double-blinded, placebo-controlled trial. In such a trial, one group will be assigned to get one treatment and another group will get a different treatment (i.e. amitriptyline or placebo in this study). In a “randomized trial”, people are put in one group or the other by random chance. This means that a computer will decide by chance which group a person is in, not the doctors running the trial. In a double-blinded trial, neither you nor your doctor will know which treatment group you are in (although, if your doctor needs to find out for important medical reasons, he/she can do so).

A placebo is a dummy treatment such as a pill which looks like the pill that contains the study drug but is not. Placebos contain no drugs or active ingredients. In a placebo-controlled study, participants are given placebos so that the effects of a drug can be compared against no drug. Use of placebos also prevents the participant and the doctor from knowing whether or not the subject is getting the drug, and help the blinding of the study. There is a 50:50 chance you will be treated with amitriptyline or placebo.

In specific details, this study will have four outpatient visits and four telephone calls:

Screening visit/Visit #1: In this visit, you will be screened to evaluate whether you are a good candidate for this study. The initial screening process includes reviewing your medical, diabetes and CGM use history, previous blood test results and CGM download for the previous month. If the initial screening suggests that you are a good candidate for this study, we will obtain the consent from you for entering the study, collect other study information (including demographics, insulin regimen and other information related to the study), and conduct a physical examination and possibly a blood test. We will also discuss about the medications/devices which are prohibited or to be avoided during the study. You also will be expected to continue to wear your own CGM for the rest of the study. A discussion about contraception plan for the study period, and a pregnancy test, will be done (if applicable).

You then are ready to enter the “Run-in Period”. The purpose of this “Run-in Period” is to further assess whether you can be enrolled for the study drug testing. During this two-week Period, you will be asked to be adherent to wearing CGM, and to report information about your hypoglycemic events with an online/paper questionnaire (“Hypoglycemic Event Report”) for all hypoglycemic episodes.

Visit #2: Two weeks after Visit #1, you will be expected to return for this visit. The CGM data for the last two weeks will be downloaded and reviewed, together with the blood test done at Visit 1. An EKG assessment and repeated pregnancy test will be conducted if needed. Based on the review of these additional information, if you are still a good candidate to continue with this study, you will then be randomized to initiate a study drug (amitriptyline vs placebo). A blood test (hemoglobin A1C) and study questionnaires will also be done.

After Visit #2, you will be expected to start taking the study drug. You will be expected to take one capsule of the study drug once a day at bedtime for the first two weeks, and then increase to two capsules once a day at bedtime, and continue this for another eight weeks (i.e., until Visit #4). If you experience any potential side effect from the study drug, you will be encouraged to contact us to discuss about whether the symptoms are related to the study drug, and potentially how to titrate the medication dose. If we think it is safe to do so and you feel that you can tolerate the side effect, you may be asked to continue the same dose. You will also receive two telephone calls during this period to ask you whether you experience any side effect and remind you about study drug intake plan.

Visit #3: Eight weeks after Visit #2, you will be expected to return for this visit. We will download CGM data for the last month and ask you to fill some study questionnaires. Also, while asking you to continue to take the study drug, we will again ask you to start reporting information about your hypoglycemic events with an online/paper questionnaire (“Hypoglycemic Event Report”) for all hypoglycemic episodes, like you do after Visit #1, for the next two weeks.

Visit #4: Two weeks after the visit #3, you will be expected to return for this visit. We will download CGM data for the last two weeks. A blood test (hemoglobin A1C) and some study questionnaires will be done. We will also ask you to return all the unused study drugs. We will also dispense additional study drugs (if applicable) for study drug taper. If indicated, you will be asked to take one capsule of the study drug for up to another two weeks, and we will discuss how to stop the study drug.

Fourteen and twenty-six weeks after Visit #4, you will receive telephone call reminders to complete follow-up study questionnaires. The study is completed after the second follow-up telephone call.

We expect the duration between the Initial Visit and the completion of the study drug to be about 14 weeks. We expect the entire study, including the follow-up telephone calls, to last about 38 weeks.

RISKS

Amitriptyline has been approved by the US food and Drug administration (FDA) for medical use since 1961 and is considered to be a safe and generally well-tolerated medication. The following adverse events have been reported in patients using amitriptyline:

- Cardiovascular: Body/face swelling, high blood pressure, low blood pressure with body position change, passing out, fast or irregular heartbeat, heart attack, stroke
- Central nervous system: Headache, anxiety, excitement, restlessness, inability to concentrate, fatigue, drowsiness, abnormal thoughts, confusion, dizziness, difficulty speaking, hallucination, prickling sensation/numbness of skin/extremities, abnormal involuntary movements, increase in body temperature, insomnia, nightmares, seizure, coma, drug withdrawal (nausea, headache, fatigue, irritability, restlessness, dream and sleep disturbance, excitement [rare])
- Dermatologic: Allergic skin rash, hair loss, sweating, skin being sensitive to light, hives
- Endocrine & metabolic: Abnormal blood glucose, change in libido, milky breast discharge, breast enlargement, excessive water retention, weight gain/loss
- Gastrointestinal: Poor appetite, nausea/vomiting, dry mouth, abnormal/loss of taste, poor bowel movement/constipation, diarrhea, tongue color change/inflammation, salivary gland enlargement
- Genitourinary: Breast enlargement, erection difficulty, testicular swelling, urinary frequency/retention, urinary tract dilation
- Hematologic & oncologic: Abnormal bone marrow function (including low white blood cell and platelet count), increase in white blood cell number, bruising
- Hepatic: Liver inflammation (rare) or failure
- Hypersensitivity: Tongue swelling
- Neuromuscular & skeletal: drug-induced lupus, tremor, weakness



- Ophthalmic: Blurred vision, increased eye pressure
- Otic: Tinnitus/ringing in ears
- Postmarketing and/or case reports: Glaucoma, nerve dysfunction syndromes related to fever, confusion, irritability, muscle rigidity, tremor, sweating, diarrhea and other nerve dysfunction

The contraindications of amitriptyline are allergic reactions to amitriptyline or any component of the formulation; coadministration with or within 14 days of a special anti-psychiatric medication (“MAOIs”) and a special gastrointestinal medication (“cisapride”); acute recovery phase following heart attack.

Amitriptyline can be used as an antidepressant. Antidepressants increase the risk of suicidal thinking and behavior in children, adolescents, and young adults (18 to 24 years of age) with major depressive disorder and other psychiatric disorders. For the current study, patients with ongoing and recent history of depression or other major psychiatric disorders will be excluded from recruitment. Furthermore, short-term studies did not show an increased risk in patients >24 years of age and showed a decreased risk in patients ≥65 years.

Reproductive Risk

It is possible that if the treatment is given to a pregnant woman, it may harm the unborn child. Pregnant women must not take part in this study, nor should women who plan to become pregnant during the study. Women who have possibility becoming pregnant during the study will be asked to have a pregnancy test before taking part to exclude the possibility of pregnancy.

If you could become pregnant, you must use an effective contraceptive method during the course of this study. Acceptable methods of birth control include hormonal contraceptives (oral, patch or injection), intrauterine device, dedicated and correct condom use, birth control ring or diaphragm and female or male (partner) sterilization.

If you become pregnant while taking part in the study, you must immediately tell your research doctor. Options will be discussed with you at that time. Whether or not you remain on study treatment, we will follow the outcome of your pregnancy and we will continue to follow you according to the study plan.

Procedure Risk

We will conduct phlebotomy for Comprehensive Metabolic Panel and Hemoglobin A1C assessments. Localized pain, bleeding, bruising or infection can occur when blood samples are drawn. These risks and discomforts associated with the collection of a blood sample from phlebotomy include faintness, inflammation, pain, bruising or bleeding at the phlebotomy site. There is also a possibility of infection. Some subjects may feel dizzy from these procedures.

Risk of Loss of Confidentiality

There are risks associated with any loss of confidentiality of health information. This risk is very small because the sample will not be labeled with the subject’s name or other personal information that could identify them. Also, all data will be saved in encrypted computers or protected database. However, absolute confidentiality cannot be guaranteed.

The loss of confidentiality could lead to misuse of information. For example, it could be used to discriminate against a patient or could affect employment, insurance, or family relationships.

Unforeseeable Risk

Participation in the study may involve risks that are currently unforeseeable. You will be notified immediately of any new significant findings discovered during the course of the research that may affect your willingness to continue in the study.

BENEFITS

We cannot promise any benefits to you from you being in the study. However, possible benefits may include finding out your ability to recognize low blood glucose episodes; this information may be used for your clinical care after the completing the study. Also, if the treatment is effective, you may spend less time in low blood glucose and have an improve the ability of sensing a low blood glucose event.

ALTERNATIVE PROCEDURES

You may choose not to be in this study. If you do not want to take part in the study, you will continue to receive the same standard medical care from your care provider(s). Your decision will not affect your relationship with your doctor or the study team in any way.

PERSON TO CONTACT

If you have questions, complaints or concerns about this study, you can contact the Study Coordinator Sally Bradstreet at 801-581-4684 or Dr. Yu Kuei Lin, M.D. at 801-581-7761. If you think you may have been injured from being in this study, please call Dr. Yu Kuei Lin, M.D. at the above number. For any urgent need or concern about the study or study drug, please call the University of Utah Hospital Operator at 801-581-2121; an on-call Endocrinologist can be reached 24-hours a day.

Institutional Review Board: Contact the Institutional Review Board (IRB) if you have questions regarding your rights as a research participant. Also, contact the IRB if you have questions, complaints or concerns which you do not feel you can discuss with the investigator. The University of Utah IRB may be reached by phone at (801) 581-3655 or by e-mail at irb@hsc.utah.edu.

Research Participant Advocate: You may also contact the Research Participant Advocate (RPA) by phone at (801) 581-3803 or by email at participant.advocate@hsc.utah.edu.

RESEARCH-RELATED INJURY

If you are injured from being in this study, medical care is available to you at the University of Utah, as it is to all sick or injured people. The University of Utah has not set aside any money to pay the costs for such care. The University will work with you to address costs from injuries. Costs would be charged to you or your insurance company (if you have insurance), to the extent those parties are responsible for paying for medical care you receive. Since this is a research study, some health insurance plans may not



pay for the costs. By signing this consent form you are not giving up your right to pursue legal action against any parties involved with this research.

The University of Utah is a part of the government. If you are injured in this study, and want to sue the University or the doctors, nurses, students, or other people who work for the University, special laws may apply. The Governmental Immunity Act of Utah is a law that controls when a person needs to bring a claim against the government, and limits the amount of money a person may recover. See sections 63G -7-101 to -904 of the Utah Code.

VOLUNTARY PARTICIPATION

Research studies include only people who choose to take part. You can tell us that you don't want to be in this study. You can start the study and then choose to stop the study later. We will still give you medical care and answer any questions you have. Your decision will not affect your relationship with your doctor or the study team in any way.

If you want to stop being in this study, please let the research doctor know. That way you can find out what should be done about your normal medical care outside of the study.

RIGHT OF INVESTIGATOR TO WITHDRAW PARTICIPANTS

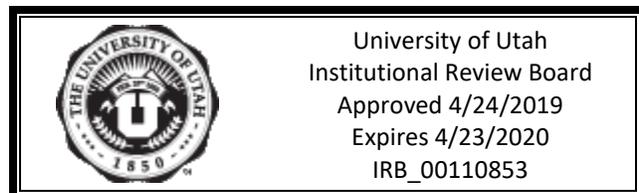
The research doctors can withdraw you without your approval. Possible reasons for withdrawal include the development of severe adverse event from the study drug, the inability/poor adherence in completing the study protocol such as CGM use, Hypoglycemic Event Report assessment, and the use of prohibited medication/device for this study.

If a participant withdrawal is considered, a review of the case will be conducted with all the major research doctors, and the decision will be informed to you. You will be asked to return the unfinished pills and the Hypoglycemic Event Report. The research data may still be used for study analysis, future study design and publication. Your compensation may not be provided to you if the withdrawal is due to a lack of adherences to the study protocol. If the withdrawal is due to an adverse event, for your health and welfare, a follow-up may be requested.

COSTS AND COMPENSATION TO PARTICIPANTS

You will not be charged, nor will your insurance company be charged, for the test drugs and any test or visit that is completed solely for the purpose of this study. The parts of your care that would normally be done as standard treatment or adverse event/research-related injury during the study period will be billed to you or your insurance company.

You may be offered financial participant support/compensation to help offset your time and travel expenses. Time and mileage will be reimbursed up to a total of \$200 if you complete the study, based on the current allowable government rate. You will only be reimbursed for completing visits and surveys. Please tell the study staff if you are in need of time and travel expenses compensation.



If you would like to be compensated for time and travel expenses, it is necessary for the University of Utah to collect your Social Security Number. You will provide this information for a Federal W-9 Form that is filed with our Accounts Payable Department at the University of Utah. The amount you receive for time/travel will be turned into the Internal Revenue Service (IRS) as taxable income. It may take a few weeks for the paperwork to be processed and then you will receive a check from the University of Utah. If you have any questions, please ask the study doctor or study staff.

You can choose not to provide us with your Social Security Number for this form and still participate in this study; however, we will not be able to pay you as outlined in this consent form.

NEW INFORMATION

Sometimes during the course of a research project, new information becomes available about the investigational drug or treatment that is being studied. If this happens, your research doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw at that time, your research doctor will make arrangements for your medical care to continue. If you decide to continue in the study, you may be asked to sign an updated consent form. Also, on receiving new information your research doctor might consider it to be in your best interests to withdraw you from the study. He/she will explain the reasons and arrange for your medical care to continue.

NUMBER OF PARTICIPANTS

We expect to enroll up to 80 patients at the University of Utah with eventually 24 eligible participants for study drug testing for this study.

AUTHORIZATION FOR USE OF YOUR PROTECTED HEALTH INFORMATION

Signing this document means you allow us, the researchers in this study, and others working with us to use some information about your health for this research study.

This is the information we will use and include in our research records:

- Demographic and identifying information like name, address and telephone number.
- Social Security Number – you can withhold their social security number and still participate
- Related medical information about you like family medical history, allergies, current and past medications or therapies, and information from physical examinations, such as blood pressure reading, heart rate, temperature, lab and EKG results
- All tests and procedures that will be done in the study

If you are enrolled in the study at the screening visit, but the other assessments before the study drug randomization (e.g., CGM data and questionnaires) show that you are not a good candidate for this study, the data collected may still be used for study analyses.

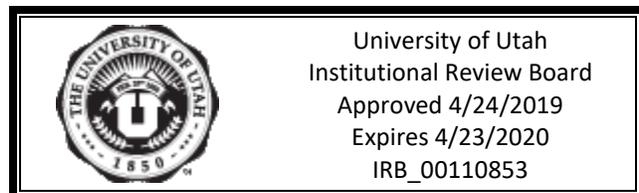
How we will protect and share your information:

- We will do everything we can to keep your information private but we cannot guarantee this. Study information will be kept in a secured manner and electronic records will be password protected. Study information may be stored with other information in your medical record. Other doctors, nurses, and third parties (like insurance companies) may be able to see this information as part of the regular treatment, payment, and health care operations of the hospital. We may also need to disclose information if required by law.
- A description of this clinical trial will be available on <http://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 website at any time.
- In order to conduct this study and make sure it is conducted as described in this form, the research records may be used and reviewed by others who are working with us on this research:
 - Members of the research team, including the study research coordinators;
 - The University of Utah Institutional Review Board (IRB), which reviews research involving people to make sure the study protects your rights;
 - University of Utah Department of Population Health Sciences, which will conduct the statistical analyses;
 - The Food and Drug Administration;
 - Potential future sponsors for further investigations, including, but not limited to: National Institute of Health, American Diabetes Association, Juvenile Diabetes Research Foundation;
 - Medical journals or meetings, that will publicize the research data and the new medical knowledge to the medical field.
- If we share your information with groups outside of University of Utah, we will not share your name or identifying information. We will label your information with a code number, so they will not know your identity.
- If you do not want us to use information about your health, you should not be part of this research. If you choose not to participate, you can still receive health care services at the University of Utah.

What if I decide to Not Participate after I sign the Consent and Authorization Form?

You can tell us anytime that you do not want to be in this study and do not want us to use your health information. You can also tell us in writing. If you change your mind, we will not be able to collect new information about you, and you will be withdrawn from the research study. However, we can continue to use information we have already started to use in our research, as needed to maintain the integrity of the research.

This authorization does not have an expiration date.



You have a right to information used to make decisions about your health care. However, your information from this study will not be available during the study; it will be available after the study is finished.

CONSENT

I confirm that I have read this consent and authorization document and have had the opportunity to ask questions. I will be given a signed copy of the consent and authorization form to keep.

I agree to take part in this research study and authorize you to use and disclose health information about me for this study, as you have explained in this document.

Participant's Name

Participant's Signature

Date

Name of Person Obtaining Authorization and Consent

Signature of Person Obtaining Authorization and Consent

Date

	University of Utah Institutional Review Board Approved 4/24/2019 Expires 4/23/2020 IRB_00110853
---	---