Study Title: Dialysis Symptom Control Restless Legs Syndrome (DISCO-RLS) Trial

Investigators: Dr. Michael Walsh

Site of Investigation: St. Joseph's Healthcare Hamilton
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Sponsor/Funding: Population Health Research Institute (PHRI)
Canadians Seeking Solutions and Innovations to Overcome Chronic Kidney Disease (Can-SOLVE CKD)

INTRODUCTION

You are being invited to participate in a research study because you have kidney disease and are being treated with hemodialysis and have restless legs syndrome (RLS).

This form provides detailed information about this research study. A team member will also connect with you so that you can ask questions and to discuss the study. Please take your time to read this form carefully and ask the study doctor or the study team to explain anything that may not be clear to you. Once you fully understand and agree with the details of your participation, you will be asked to sign this informed consent form and you will be given a copy of this form to take home with you.

WHAT IS THE BACKGROUND INFORMATION FOR THIS STUDY?

RLS is a neurological disorder that causes an urge to move your legs (or other body parts) that begins or worsens during periods of rest or inactivity. It is relieved by movement, and only occurs or is worse in the evening or night rather than during the day. It is common and affects approximately 30 percent of patients with kidney disease and is associated with sleep disturbance, worse quality of life and potentially a greater risk of heart disease and death.

PURPOSE OF THIS RESEARCH STUDY

Research has shown that several different types of medications are effective in treating RLS in people without kidney disease, but only a few studies have been dedicated to studying therapies in individuals with kidney disease. This is important because medications may act differently in people with kidney disease, as safety and effectiveness could be different in those with decreased kidney function.

The purpose of this study is to test whether or not two different medications (gabapentin and ropinirole, alone or in combination) compared to placebo (pills that look, feel, smell and taste identical to the active medications) improve RLS symptoms as measured by scales.

WHERE IS THE STUDY BEING DONE AND NUMBER OF PEOPLE PARTICIPATING

This study will take part across several hemodialysis units in Canada. Approximately 80 people will participate in the study.

WHO CAN PARTICIPATE

To take part in this study, you must be at least 18 years old and receiving dialysis at least three times weekly. You must have been on dialysis for three months or more, and have been diagnosed with restless leg syndrome and experiencing symptoms more than 2 days per week. You must not participate if:

1. You have a kidney transplant from a living donor planned
2. If you will be travelling or relocating in the next 6 months
3. If you have anemia or iron deficiency
4. If your doctor has changed your medications for restless leg syndrome in the last 4 weeks

STUDY INTERVENTION

During a preliminary part of the study, you will be given a study medication for a time period of 2 weeks to determine if the study is right for you. After 2 weeks, you will be assessed to determine if the study is still suitable for you.

If the study is still suitable for you, you will then be "randomized" into one of the four groups described below. Randomization means that you are put into a group by chance (like "flipping a coin"). Neither you, the study staff, nor your doctor can influence which group you will be assigned to. You will have a 25% chance of being placed into either group. You and your doctor will not know which group you are in after you have been randomized in the study.

Group 1	Group 2	Group 3	Group 4
Gabapentin and Ropinirole	Gabapentin and Placebo	Ropinirole and Placebo	Placebo and Placebo

Group 1: If you are randomized to this group, you will receive a low fixed dose of gabapentin 100mg to be taken orally at night and a low fixed dose of ropinirole 0.50mg to be taken orally at night.

Group 2: If you are randomized to this group, you will receive a low fixed dose of gabapentin 100mg to be taken orally at night and a placebo pill to be taken orally at night.

Group 3: If you are randomized to this group, you will receive a low fixed dose of ropinirole 0.50mg to be taken orally at night and a placebo pill to be taken orally at night.

Group 4: If you are randomized to this group, you will receive two placebos pills to be taken at orally night.

You will go through all four groups (groups 1,2,3,4) in a random sequence that will not be disclosed to you or your doctor. You will be treated in each group for 4 weeks (period) after which you will "cross-over" to the next group for a total duration of 16 weeks.
If you have any side effects while you are on study drugs, you and your physician may decide to stop both medications and not complete that period of the study. You will immediately cross-over to the next period of the study.

If your symptoms are not adequately controlled on the study drugs, you and your physician might make other changes as appropriate. This may involve starting additional medications or pursuing other interventions with the potential to improve RLS symptoms (e.g. exercise, stretching, massage). If your symptoms are still not adequately controlled, you and your physician may decide to stop both medications and not complete that period of the study. You will immediately cross-over to the next period of the study.

LENGTH OF PARTICIPATION

If you volunteer to participate in this study, we will ask you to do the following things:

1. You will be approached by a member of the research team to discuss your participation in the study. If you are eligible, the team member will explain the purpose of the study and the potential risks and benefits and allow you enough time to consider your participation. Should you agree to participate, you will be asked to sign the informed consent form located at the end of this document.
2. With your permission, research personnel will review your chart for information that is relevant to this study. They may also ask you some questions to clarify parts of your medical history.
3. If eligible, you will enter a preliminary part of the study where you will stop some of your current RLS medications and be placed on study medication for 2 weeks to make sure that you can tolerate it. The type of study medication you will be receiving will not be disclosed to you (but will be known to your treating doctor). This is because patients with RLS often report an improvement in symptoms even when taking a placebo. If your symptoms improve or worsen significantly during this period, or you develop any side effects, you or your doctor may decide to not continue the study.
4. You will be asked to complete a follow-up visit after being on study drug for 2 weeks and we will do a final assessment to ensure you are eligible to proceed. If eligible, you will be randomized into one of the four groups described above. You will then be seen by a member of the research team at 1 weeks, 3, weeks, 4 weeks, 5 weeks, 7 weeks, 8 weeks, 9 weeks, 11 weeks, 12 weeks, 13 weeks, 15 weeks, 16 weeks and 17 weeks during your regularly scheduled hemodialysis sessions. You will also be seen briefly every week to make sure you are tolerating the study drugs, your symptoms are under control and that you are willing to continue participating in the study. You will be seen in the dialysis unit and you will not be required to attend any study visits outside of your regularly scheduled hemodialysis sessions. However, you may be seen more often if the study doctor determines that this is necessary.
5. At each visit, you will be asked questions about whether you've had any new medical problems and any side effects related to the study medications or hospitalizations. You will be asked to bring your study medication to each visit so that pill counts can be performed.

6. You will be provided with questionnaires to complete at each study visit. The purpose of these questionnaires is to measure your RLS symptoms and their impact on your quality of life. All questionnaires collectively will take about 15-30 minutes to complete. The information you provide is for research purposes only. You may choose to not answer questions if you wish.

POSSIBLE RISKS OR SIDE EFFECTS OF TAKING PART IN THIS STUDY

Study Drug:

Reported side effects for ropinirole: getting dizzy when you stand up or change position suddenly (<25%), nausea/vomiting (10-40%), drowsiness (12%), dizziness (11%), worsening RLS symptoms over time (<10%), diarrhea (5%), abnormal movements (2%), lower impulse control (e.g. speeding, gambling, other risky behaviours) (<1%). All are temporary and typically resolve with stopping the medication.

Reported side effects for gabapentin: dizziness (10-30%), drowsiness (10-30%), abnormal thinking (1-10%), diarrhea (1-10%), nausea/vomiting (1-10%). All are temporary and typically resolve with stopping the medication.

BENEFITS

We cannot promise any personal benefits to you from your participation in this study. However, potential benefits include the possibility of adding to the medical knowledge about the use of these medications in the hemodialysis population and an improvement in your RLS symptoms with the introduction of these interventions.

ALTERNATIVE PROCEDURES OR TREATMENTS

You do not have to participate in this study. Of course, you may proceed with your current treatments without participating in this study.

WHAT WILL HAPPEN WHEN YOU COMPLETE THE STUDY

When the study is done, you will continue receiving dialysis and medications, as directed by your usual nephrologist. You will not have to continue taking study medication unless you choose to do so. At your request, you will be informed of the study results when they become available.

PARTICIPATION AND WITHDRAWAL FROM THE STUDY

Your participation in this study is purely voluntary. You may stop your participation in this study at any time without penalty or loss of any benefits to which you are otherwise entitled to or getting. Should you wish to stop participating, please notify the research staff at the telephone number listed on the first page of this consent form first so that a final visit may be arranged at your convenience and for your safety.

If you withdraw your consent, the information about you that was collected as part of the research project between the date you signed the current form, and the date you withdraw your consent will be kept and used by the research team unless you specifically ask to have it removed. This is to protect the quality of the research results. However, no new information about you will be collected and used.

The investigator, Hamilton Integrated Research Ethics Board (please see the section below titled "Research Ethics Board" to understand the role of a research ethics board) or the research team may stop your participation in the study at any time if they decide that it is in your best interest. They may also do this if you do not follow instructions. Your participation in the study may also be stopped if the sponsor determines that you or the investigator did not follow the study directions, or if the sponsor or regulatory agencies decide to stop the study, or if Hamilton Integrated Research Ethics Board stops the study at the participating site.

If the investigator determines that there could be a safety concern from a sudden withdrawal from the study, you may be required to remain under the investigator's care for a period of time until you can safely be taken off the study medications.

If you have other medical problems or side effects, the investigator will decide if you may continue in the research study.

LIABILITIES

All forms of medical diagnosis and treatment—whether routine or experimental—involve some risk of injury/illness. Side effects are possible in any research study despite the use of high standards of care and could occur through no fault of you or the study doctor involved. Unforeseeable harm may occur and may require care.

If complications happen to you, the study staff will assist you in getting appropriate medical treatment. Unless covered by your own insurance, medical treatment will be provided at no cost to you for a "research-related illness or injury." The term "research-related illness or injury" means physical illness or injury caused by the study drug or procedures required by the study, which are different from the medical treatment you would have received if you had not participated in the study. This study does not provide financial assistance for additional medical care or other costs. You will not be compensated for side effects or harm that is not caused by the study drug or procedures required by the study, nor will you receive compensation for lost wages or lost time. However, by signing this form, you are not giving up any legal rights available to you if you are injured.

The above statement ("In Case of Research Related Injury") does not waive your legal rights or release the investigator, the institution, the sponsor or their representatives from legal responsibility of negligence.

CONFIDENTIALITY AND RELEASE OF PERSONAL INFORMATION

Records identifying you at this center will be kept confidential and, to the extent permitted by the applicable laws, will not be disclosed or made publicly available, except as described in this consent document. Data (information) derived from this study will be used for research purposes. The Investigator and study staff will only collect the information they need for this study. Health Canada, other regulatory agencies, the investigator and members of his/her research team, representatives of the sponsor, and Hamilton Integrated Research Ethics Board who oversees the ethical conduct of this study in Ontario will be granted direct access to your medical records and other records relating to this study for analysis to check that the study information is correct to the extent permitted by applicable laws and/or regulations. Representatives of Clinical Trials Ontario, a not-for-profit organization, may see study data that

is sent to Hamilton Integrated Research Ethics Board for this study. The Investigator and members of his/her research team and representatives of St. Joseph's Healthcare Hamilton have access to participant medical records. These records may include some or all of your medical records, including, but are not limited to: hospital records and reports; X-ray films and reports; operative reports; laboratory reports; treatment and test results; immunizations; allergy reports; prescriptions; consultations; clinic notes; notes relating to information obtained and any other records that are needed.

Any information that leaves the dialysis unit will be de-identified (i.e., identifying information will be removed from the documents). Your name, address, or other information that may directly identify you will not be used. The records received by these organizations may contain your participant code, initials, sex and date of birth.

In addition, the results of the study will be reported to the research team, Health Canada and possibly other regulatory agencies. In the event of any presentation or publication regarding this study, your identity will remain confidential. Your de-identified information and results will be archived by the investigator and sponsor as per applicable laws and/or regulations.

By signing and dating this informed consent form, you agree to such inspection and disclosure.

COSTS AND PAYMENT FOR PARTICIPATION

Your participation in this research project will not involve any additional costs to you. You will receive the study medication free of charge. Participants are not compensated for participating in this study.

You will not receive compensation for participating in this study. If you become ill or are physically injured as a result of participation in the study, medical treatment will be provided. It is important to know that by signing this informed consent form, you do not give up any of your rights. Moreover, you do not release the investigator and sponsor from their legal and professional responsibilities in case of a situation that has caused you illness or injury.

LEGAL RIGHTS

You will be told, in a timely manner, about new information that may be relevant to your willingness to stay in this study.

You have the right to be informed of the results of this study once the entire study is complete. The results of this study will be available on the clinical trial registry (see the "Will information about this study be available online" section for more details). We will also circulate a newsletter to participants summarizing the results of the study.

Your rights to privacy are legally protected by federal and provincial laws that require safeguards to ensure that your privacy is respected.

By signing this form you do not give up any of your legal rights against the study doctor, sponsor or involved institutions for compensation, nor does this form relieve the study doctor, sponsor or their agents of their legal and professional responsibilities

WHOM TO CONTACT

If you have questions about taking part in this study, or if you suffer a research-related injury, you can talk to your study doctor, or the doctor who is in charge of the study at this institution. That person is Dr. Michael Walsh (905) 522-1155 extension 35016. For any other study related questions, you can also reach a member of the research team at (905) 522-1155 extension 35368. Questions regarding your rights as a volunteer may be addressed to the committee that reviewed the ethical aspects of this study at (905) 521-2100 extension 42013.

CONSENT FOR DISCO-RLS TRIAL

-All of my questions have been answered
-I understand the information within this informed consent form
-I allow access to my medical records as explained in this informed consent form
-I do not give up any of my legal rights by signing this consent form
-I agree, or agree to allow the person I am responsible for, to take part in this study
-I will receive a signed copy of this form

_____	_____	_____
Signature of Participant/ Substitute Decision Maker	PRINTED NAME	Date

_____	_____	_____
Signature of Person Conducting the Consent Discussion	PRINTED NAME	Date

Complete the following section only if the participant is unable to read or requires an oral translation:

-The informed consent form was accurately explained to, and apparently understood by, the participants/substitute decision maker, and
-Informed consent was freely given the participant/substitute decision maker

_____	_____	_____
Signature of Impartial Witness/Translator *(If participant was unable to read/ required an oral translation)*	PRINTED NAME	Date