SUBJECT INFORMATION AND CONSENT FORM

Version 1.3 (March 20, 2024)

Measuring Psychomotor Response to L-DOPA Challenge as a Correlate of Clinical Response to Pharmacotherapy in Late-Life Depression

The Late-Life Depression – L-DOPA (LLDOPA) study

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In case of a serious medical event, please report to an emergency room and inform them that you are participating in a clinical study and that the following person can then be contacted for further information: Dr. Nicholas Ainsworth at the telephone number: 604-877-8371
24hr Emergency Number: 604-874-1141, ask to contact Dr. Nicholas Ainsworth

1. INVITATION

You are being invited to take part in this research study because you have been diagnosed with Major Depressive Disorder, are currently experiencing a major depressive episode, and are interested in pursuing a medication treatment. This study will involve the use of a medication, levodopa/carbidopa (e.g., Sinemet), which is often used in Parkinson's disease, to help understand why some people with depression in later life get better while others do not.

The study includes assessments of your mood and medication history, physical health, walking speed, cognitive assessments, and 2 weeks of treatment with levodopa/carbidopa followed by monitored medication treatment for depression.

2. YOUR PARTICIPATION IS VOLUNTARY

Your participation in this study is voluntary. You have the right to refuse to participate. If you decide to participate, you may still choose to withdraw from the study at any time without any negative consequences to the medical care, education, or other services to which you are entitled or are presently receiving.

You should be aware that there is a difference for both you and your doctor between being a patient and being a research participant. As a patient all medical procedures and treatments are carried out for your benefit only according to standard accepted practice. As a research participant you and your doctor also must take into account the requirements for the research study. These may include procedures and treatments that are not part of standard practice or are not yet proven. This consent form describes the diagnostic and treatment procedures that are being carried out for research purposes. Please review the consent document carefully when deciding whether or not you wish to be part of the research and sign this consent only if you accept being a research participant.

If you wish to participate in the study, you will be asked to sign this form. Please take the time to read the following information carefully and to discuss it with your family, friends, and doctor before you decide.

3. WHO IS CONDUCTING THE STUDY?

The study is being conducted by Dr. Nicholas Ainsworth at the University of British Columbia (UBC) in collaboration with Providence Health Care (PHC). This study is funded by the Institute of Mental Health at UBC. Should you have any questions about study funding or support, you may contact the Principal Investigator using the contact information above.

4. BACKGROUND

The standard or usual treatment for Major Depressive Disorder (MDD) is medication or counselling/psychotherapy. However, in older adults with MDD, it is difficult to predict who will respond to medication and who will not. Over the years, researchers have studied whether temporary exposure to certain medications, called "challenges", can show whether someone is likely to have their depression improve with medication.

Levodopa/carbidopa (L-DOPA) is a Health Canada-approved medication for Parkinson disease. It works by increasing levels of dopamine in the brain to treat symptoms of Parkinson disease. In MDD, it is theorized that low levels of dopamine may contribute to the symptoms of this condition as well. In particular, studies have shown that brain dopamine levels may be related to physical and cognitive slowing (called "psychomotor slowing") in later-life MDD. Psychomotor slowing is associated with more severe and difficult-to-treat depression, but it may improve with a medication such as L-DOPA. It is therefore possible that a medication that boosts dopamine such as L-DOPA will improve psychomotor slowing in people who are more likely to benefit from certain medications for MDD.

Identifying a link between improvement in psychomotor speed with L-DOPA and improvement in MDD symptoms following medication treatment is important, as this will potentially allow us to use this as a signal ("biomarker") of a person's likelihood of benefiting from a particular treatment for their MDD. The overall goal is to develop better precision and personalization of treatment for older adults with MDD.

Health Canada has not approved the sale or use of levodopa/carbidopa to treat major depressive disorder, although they have issued no objection for its use in this study.

5. WHAT IS THE PURPOSE OF THE STUDY?

This is a pilot study which is designed to help us understand whether it is feasible to use a levodopa/carbidopa challenge to help us determine who will benefit from medication treatment in later-life depression. A "pilot study" or "feasibility study" is done to test the study plan and to find out whether enough participants will join a larger study and accept the study procedures. This type of study involves a small number of participants, with a plan to enroll 50 people, and is not expected to prove safety or effectiveness. The results may be used as a guide for larger studies, although there is no guarantee that they will be conducted. Participation in a pilot study does not mean that you will be eligible to participate in a future larger study. Knowledge gained from pilot or feasibility studies may be used to develop future studies that may benefit others.

6. WHO CAN PARTICIPATE IN THIS STUDY?

You may be able to participate in this study if you:

1) Are an outpatient person capable of providing informed consent;

2) Are at least 60 years old;

3) Have a diagnosis of major depressive disorder.

4) Have moderate to severe symptoms of depression.

5) Are on stable doses of psychotropic medication, including antidepressant medication, for at least 4 weeks;

6) Are able to adhere to the study visit schedule;

7) Are able to walk safely unassisted.

7. WHO SHOULD NOT PARTICIPATE IN THIS STUDY?

You will not be eligible to participate in this study if you:

1) Have a current diagnosis of dementia;

2) Have current active psychosis;

3) Have an unstable medical illness;

4) Are feeling actively suicidal;

5) Have started or changed the dosage of a psychotropic medication in the past 4 weeks;

6) Are unable to complete neuropsychological testing in the English language;

7) Have a non-correctable clinically significant sensory impairment (i.e., cannot hear or see well enough to complete the neuropsychological tests).

8) A history of falls, with at least 1 fall per week during the past 4 weeks.

8. WHAT DOES THE STUDY INVOLVE?

Overall design of the study

The study will take up to 16 weeks to complete. It consists of an initial visit, during which study procedures will be explained to you, you will have an opportunity to discuss and review this consent form, and you will undergo screening for eligibility before having the opportunity to consent and enrol in the study; a baseline visit (which may be paired with the screening visit) where you will complete additional assessments; a challenge phase lasting 3-4 weeks, when you will be taking the study drug levodopa/carbidopa and completing assessments afterwards; and a treatment phase, when you will be offered standardized medication treatment for your depression.

If You Decide to Join This Study: Specific Procedures

If you agree to take part in this study, the procedures you can expect will include the following:

1) Questionnaires about your general and psychiatric health;
2) Questionnaires about your quality of life;
3) Questionnaires about your symptoms of depression, including any suicidal thoughts;
4) Tablet-based cognitive testing tasks;
5) A 2-week-long period of taking levodopa/carbidopa once to twice daily (the "challenge phase");
6) Regular assessments of your clinical status and vital signs;
7) Walking tests, where you will be asked to walk approximately 5 metres at a normal pace on flat ground;
8) Standardized medication treatment of your depression, following the challenge phase.

If you agree to join this study, the study doctor will look at your personal health information for clinical reasons only. Your personal health information will not be recorded in the study records. Personal health information is any information that could be used to identify you and includes your:

- name,
- address,
- date of birth,
- new or existing medical records, that includes types, dates and results of medical tests or procedures.

To determine if you meet the requirements to participate in this study, a member of the research team will need to access your Providence Health Care Electronic Medical Record.

Screening Visit/Before You Begin the Study

The first study visit will be a screening visit. At the screening visit, the study will be explained to you fully, and you will have the opportunity to decide if you wish to participate in the study or not. If you meet the requirements for the study and you would like to participate, you will be asked to sign this Informed Consent Form. Doing so shows that you have had everything explained to you and that you agree to participate. You may withdraw your consent to participate at any time.

A referral from your primary care provider (family physician or nurse practitioner) or your regular psychiatrist is required to enter the study. Once consented, we will send your primary care provider a notification that you have formally consented to participate in a clinical study. Your primary care provider will receive a copy of your initial psychiatric consult and a clinical summary of your progress at the conclusion of the study.

At the screening visit, we will conduct clinical assessments to determine if you are eligible to participate in the study. During the clinical assessment, you will be asked questions regarding your psychiatric history and your current symptoms of depression. You will also be assessed for your ability to safely receive the study medication (levodopa/carbidopa).

Study Visits

Following your screening visit, you will conduct further baseline assessments, including questionnaires and cognitive testing. You will also complete a walk test prior to starting the challenge phase where you will be taking levodopa/carbidopa for 2 weeks.

During the challenge phase, you will start taking levodopa/carbidopa by mouth once daily in the morning at a dosage of 150/37.5mg, increasing to twice daily (at morning and noon) after the first seven days. You will be closely monitored for any side effects. You will have a visit at the 1-week mark to ensure that you are tolerating the medication and are not experiencing any troublesome side effects or changes in your blood pressure.

At the 2-week mark, you will stop taking the levodopa/carbidopa medication and will repeat your walk test. After one more week, to give time for the challenge medication to leave your system, you will return for a 3-week visit where you will complete additional questionnaires. Depending on the results of these questionnaires, you may be asked to start standardized medication treatment of your depression right away, or invited back after one more week to repeat the questionnaires. Depending on the results of this second set of questionnaires, you may be asked to start medication at this point or you may be asked to withdraw from the study. If you are asked to withdraw, you will be offered usual medical care.

During the standardized treatment phase, your treating physician will offer approved medication treatment options for your depression, depending on their clinical judgement and your preference. After 4 weeks following the start of this phase, you will be invited back to repeat several assessments, including questionnaires and cognitive testing. Finally, after 12 weeks following the start of this phase, you will be invited back for a final study visit to repeat these assessments once more.

Summary of study visits

Measure/ procedure	Screening	Baseline (Week 0; pre-challenge)	Week 1	Week 2 (post-challenge)	Week 3 (pre-treatment)	Week 7	Week 15
	1.5 hours	2 hours	1 hour	2 hours	1 hour	1 hour	1.5 hours
Levodopa/ carbidopa		X	X				
MINI	X						
Demographics	X						

Form							
Medical History Form	X						
Medication form	X	X	X	X	X	X	X
Adverse effects monitoring form			X	X	X		
MADRS	X			X	X	X	X
PHQ-9		X	X	X	X	X	X
Walk test		X		X			X
CORE		X		X			X
SRMP		X	X	X	X	X	X
Smell test	X						
NIH Toolbox-Cognitive Battery		X		X			X
PROMIS (physical functioning, social participation)		X		X			X
Vital signs		X	X	X	X		

MINI: Mini neuropsychiatric interview. This is a structured diagnostic interview completed on paper by a study physician to confirm a diagnosis of major depressive disorder.

Demographics form: This will gather basic information about you (age, gender, etc), completed by the participant (you).

Adverse effects monitoring form: This will gather information about any side effects or health changes you have noticed while on the study medication, administered by a study physician.

MADRS: This is a questionnaire assessing the severity of depressive symptoms, administered by a study physician.

PHQ-9: This is a questionnaire assessing the severity of depressive symptoms, completed by the participant (you).

Walk test: This is a short, timed test of your walking speed completed on flat ground at the study clinic.

CORE: This is an assessment of your speed of overall movement during normal activity, administered by a study physician.

SRMP: This is a Suicide Risk Monitoring Protocol, which is a list of questions that a study physician will ask you about any thoughts of harming yourself. It varies in length depending on your answers to each question. Your study physician may recommend treatment or care based on your answers to these questions.

Smell test: a brief test of your ability to smell and recognize common odours.

NIH Toolbox Cognitive Battery: This is a series of tasks completed on a tablet (e.g., iPad) that will allow you to demonstrate your thinking and memory skills.

PROMIS: This is a set of two questionnaires asking you about aspects of your quality of life that you will complete on a tablet.

Vital signs: This is a check of your heart rate and blood pressure using an automated device.

Expected Follow-up

Following your completion of the study, you will be offered usual clinical care. Your primary care provider will be informed of your completion of the study, and further recommendations may be sent to them.

9. WHAT ARE THE POSSIBLE HARMS AND DISCOMFORTS?

Known risks or potential harms associated with this protocol fall into the following categories:

1) Treatment delay

This study will require you to delay medication treatment of depressive symptoms by 3-4 weeks following enrolment, in order to enable completion of the levodopa (L-DOPA) challenge phase. As with any delay in treatment, there is a risk of worsening of your condition (i.e., depression) during this period of time. With depression specifically, the most serious potential risk associated with this worsening is the risk of becoming suicidal.

2) Levodopa/carbidopa side effects

While levodopa/carbidopa is an approved medication for the indication of Parkinson disease and has an extensive track record of safety in people with that condition, there are known side effects and risks associated with its use. Common side effects include: nausea (30%), constipation (22%), dyskinesia (14%), and mood disturbance (11%). Less common side effects include hypertension, anxiety, sleep disturbance (including risk of sudden onset of sleep without warning signs), somnolence, and diarrhea. Rare but potentially serious complications include psychosis, impulse control disorder, and neuroleptic malignant syndrome.

You will be closely monitored by the study team during the challenge phase. If at any point you start to feel suicidal or experience any side effects that you think could be related to levodopa/carbidopa, please disclose this to the study team or your primary care provider. If you disclose suicidal thoughts, a study physician may ask you further questions about this. If you are assessed to be at risk of self-harm, you may be asked to go to the Emergency Department.

A drug information sheet provided by Health BC for levodopa/carbidopa can be provided to you by the study team on request.

Risks and Discomforts from Standard Treatment

The risks and side-effects of the standard or usual treatment of Major Depressive Disorder will be explained to you as part of your standard care. If you are unclear about what is standard of care and what is specifically part of this study, please discuss this with your study doctor.

10. WHAT ARE THE POTENTIAL BENEFITS?

There may not be direct benefit to you from taking part in this study.

We hope that the information learned from this study can be used in the future to benefit other people with major depressive disorder.

11. WHAT ARE THE ALTERNATIVES TO PARTICIPATION?

If you choose not to participate in this study or to withdraw at a later date, the following treatment options are available to you:

1) Medication treatment of depression under the supervision of a primary care provider or a psychiatrist;
2) Counselling or psychotherapy;
3) Alternative treatments such as lifestyle modification and natural remedies.

You can discuss these options with your doctor before deciding whether or not to participate in this research project.

12. AFTER THE STUDY IS FINISHED

You may not be able to receive the study treatment after your participation in the study is completed. There are several possible reasons for this, some of which are:

- The treatment may not turn out to be effective or safe.
- The treatment may not be approved for use in Canada for MDD.
- Your caregivers may not feel it is the best option for you.
- You may decide it is too expensive and insurance coverage may not be available.
- The treatment, even if approved in Canada for major depressive disorder, may not be available free of charge.

13. WHAT IF NEW INFORMATION BECOMES AVAILABLE THAT MAY AFFECT MY DECISION TO PARTICIPATE?

If you choose to enter this study and at a later date a more effective treatment becomes available, it will be discussed with you. You will also be advised of any new information that becomes available that may affect your willingness to remain in this study. You may be invited to sign an amended consent to indicate your continued consent to participate in the study.

14. WHAT HAPPENS IF I DECIDE TO WITHDRAW MY CONSENT?

You may withdraw from this study at any time without giving reasons. If you choose to enter the study and then decide to withdraw at a later time, all information about you collected up to the point of your withdrawal will be retained for analysis in order to protect the integrity of the research, which may benefit future research participants and patients. However, no further information will be collected.

15. CAN I BE ASKED TO LEAVE THE STUDY?

You may be asked to leave the study if the study doctor judges it is not in your best interest to continue, or if you are unable to fulfill the requirements for the study, or for any other reason. If you are asked to leave the study, the reasons for this will be explained to you and you will have the opportunity to ask questions about this decision. The study doctor will arrange for you to continue your care outside of the study. The study may also be stopped at any time by the Research Ethics Board or Health Canada if new information rises about the safety of the study treatment. The reasons for study stoppage will be explained to you by the study doctor.

16. HOW WILL MY INFORMATION BE KEPT CONFIDENTIAL?

Your confidentiality will be respected. However, research records and health or other source records identifying you may be inspected in the presence of the Investigator or his or her

designate by representatives of the Providence Health Care Research Ethics Board or Health Canada for the purpose of monitoring the research. No information or records that disclose your identity will be published without your consent, nor will any information or records that disclose your identity be removed or released without your consent unless required by law.

You will be assigned a unique study number as a participant in this study. This number will not include any personal information that could identify you (e.g., it will not include your Personal Health Number, SIN, or your initials, etc.). Only this number will be used on any research-related information collected about you during the course of this study, so that your identity will be kept confidential. Information that contains your identity will remain only with the Principal Investigator and/or designate. The list that matches your name to the unique study number that is used on your research-related information will not be removed or released without your consent unless required by law.

Your rights to privacy are legally protected by federal and provincial laws that require safeguards to ensure that your privacy is respected. You also have the legal right of access to the information about you that has been provided and, if need be, an opportunity to correct any errors in this information. Further details about these laws are available on request to your study doctor.

Primary Care Physician(s)/Specialist(s) Notification

Your family physician will be notified of your participation in the study so that your study doctor and your family doctor can provide proper medical care.

Because this is a treatment study, your signed consent form hard copy will be scanned and included in your electronic medical record, and your healthcare team will be alerted that you are on a study. This is to ensure your healthcare team has a little information about the study so that they can treat you safely according to the study protocol.

Disclosure of Race/Ethnicity

Studies involving humans now routinely collect information on race and ethnic origin as well as other characteristics of individuals because these characteristics may influence how people respond to different medications. You should be aware that providing this information is not mandatory.

17. WHAT IF SOMETHING GOES WRONG?

By signing this form, you do not give up any of your legal rights and you do not release the study doctor, participating institutions, or anyone else from their legal and professional duties. If you become ill or physically injured as a result of participation in this study, medical treatment will be provided at no additional cost to you. The costs of your medical treatment will be paid by your provincial medical plan.

In case of a serious medical event, please report to an emergency room and inform them that you are participating in a clinical study and that the following person can then be contacted for further information: Dr. Nicholas Ainsworth at telephone number: 604-877-8371.

18. WHAT WILL THE STUDY COST ME?

All research-related medical care and treatment and any related tests that you will receive during your participation in this study will be provided at no cost to you.

Reimbursement

We will fully reimburse you for parking and public transit expenses incurred by attending study visits (original receipts required).

Remuneration

As this is a pilot study with limited funding, we regrettably cannot offer payment for your time.

19. IF I HAVE QUESTIONS DURING THE STUDY, WHOM SHOULD I SPEAK TO?

If you have any questions or desire further information about this study before or during participation, or if you experience any adverse effects, you can contact 604-877-8371 and ask to contact Dr. Nicholas Ainsworth.

19. WHOM DO I CONTACT IF I HAVE ANY QUESTIONS OR CONCERNS ABOUT MY RIGHTS AS A PARTICIPANT?

If you have any concerns or complaints about your rights as a research participant and/or your experiences while participating in this study, contact the Research Participant Complaint Line in the University of British Columbia Office of Research Ethics by e-mail at RSIL@ors.ubc.ca or by phone at 604-822-8598 (Toll Free: 1-877-822-8598.) Please reference the study number (H23-02768) when calling so the Complaint Line staff can better assist you.

20. SIGNATURES

Measuring Psychomotor Response to L-DOPA Challenge as a Correlate of Clinical Response to Pharmacotherapy in Late-Life Depression

Participant Consent

My signature on this consent form means:

- I have read and understood the information in this consent form.
- I have had enough time to think about the information provided.
- I have been able to ask for advice if needed.
- I have been able to ask questions and have had satisfactory responses to my questions.
- I understand that all of the information collected will be kept confidential and that the results will only be used for scientific purposes.
- I understand that my participation in this study is voluntary.
- I understand that I am completely free at any time to refuse to participate or to withdraw from this study at any time, and that this will not change the quality of care that I receive.
- I understand that I am not waiving any of my legal rights as a result of signing this consent form.
- I understand that there is no guarantee that this study will provide any benefits to me.
- I authorize access to my health records as described in this consent form.

I will receive a signed and dated copy of this consent form for my own records.

I consent to participate in this study.

_____	_____	_____
Participant's Signature	Printed name	Date

_____	_____	_____	_____
Signature of Person Obtaining Consent	Printed name	Study Role	Date