CONSENT FORM COVER PAGE

STUDY TITLE: Dopaminergic Dysfunction in Late-Life Depression

NCT Identification Number: NCT04469959

Date of document: 12/11/2025

Institutional Review Board
Informed Consent Document for Research
MASTER CONSENT

Study Title: Dopaminergic Dysfunction In Late Life Depression (D3 Study)
Version Date: 12/11/2025

Part 1 of 2: MASTER CONSENT
Depressed Participants

Name of participant: _____ Age: _____

You are being invited to take part in a research study. This study is a multi-site study, meaning it will take place at several different locations. Because this is a multi-site study this consent form includes two parts. Part 1 of this consent form is the Master Consent and includes information that applies to all study sites. Part 2 of the consent form is the Study Site Information and includes information specific to the study site where you are being asked to enroll. Both parts together are the legal consent form and must be provided to you.

Key Information:
The first section of this document contains some key points that the research team thought you would find important. The study is described in more detail after this section. If you do not understand something, please ask someone.

Key information about this study:

What is the purpose of this study?

The purpose of this research study is to better understand how the brain's dopamine system may contribute to depression in older adults. Dopamine is a neurotransmitter, a chemical messenger released by nerve cells. Some medications used to treat depression affect dopamine but most do not.

This study is being conducted at Vanderbilt University Medical Center (VUMC) and the University of Pittsburgh Medical Center (UPMC). Across both sites, we plan to enroll up to 100 eligible participants with depression and 70 eligible participants with no history of depression for this study over five years.

In this study you will have tests of your memory, concentration, thinking, and walking. You will have brain scans using magnetic resonance imaging (MRI). We are performing these scans to understand more about how the brain's dopamine system may be different in older adults who are depressed.

What will happen and how long will you be in the study?

If you agree to be in this study, you will first be asked to sign and date this consent form. This study takes place over the course of at least 9 weeks. After an initial visit to determine if you are eligible for

the study, you will have at least 4 in-person and, 6 telephone or video conference visits. You will have up to 3 brain scans.

If you are eligible for the study and decide to participate, you will enter a baseline period. During the baseline period, we administer tests of your memory, concentration, and thinking. How you walk will be measured using a special mat. You will also complete one MRI scan and a blood draw.

If you are a participant at UPMC, while not necessary for many people, to confirm it is safe for you to have an MRI we may ask you to have an x-ray, which does use radiation, to see if there is metal in your body.

These baseline tasks, procedures, and assessments will be spread out over at least 2 visits over a period of up to 4 weeks. You can expect to spend about 10-12 hours total to complete them.

During parts of the MRI scans, you will be asked to look at a screen and accomplish tasks by pressing buttons.

After completing all the baseline period procedures, you will enter the medication phase of the study. The medication phase has two parts: Step 1 and Step 2. In Step 1 you will be randomly assigned (like by flipping of coin) to receive either carbidopa/levodopa (Sinemet) or placebo.

Carbidopa/Levodopa is approved by the Food and Drug Administration for the treatment of Parkinson's Disease. We are using carbidopa/levodopa off-label, meaning we prescribe this medication for a reason other than that which it has been officially approved. Carbidopa/levodopa changes into dopamine in the brain and allows us to investigate how increasing the brain's dopamine levels may influence beh avior. Carbidopa prevents breakdown of levodopa in the blood, so more levodopa gets to the brain. In this study we are examining how increasing dopamine levels with carbidopa/levodopa in individuals with depression affects brain function as well as mental and physical slowing that occur as people age.

Placebo is not an active drug. It looks like a study drug but it is not designed to treat any disease or illness. It is designed to be compared with a study medication to learn if that medication has an eff ect. Neither you, the study staff, nor the study clinician will know if you are receiving the placebo or study drug, although this can be determined in an emergency.

If you are assigned to active study drug, you will receive a starting dose of carbidopa /levodopa. The dose will be increased over three weeks. If you are assigned to placebo, you will receive pill placebo on the same schedule for 3 weeks. Because we allow for an extra week to safely increase the medication dose if necessary, the medication period may last for 4 weeks instead of 3 weeks.

Study Title: Dopaminergic Dysfunction In Late Life Depression (D3 Study)
Version Date: 12/11/2025

At the end of Step 1 you will have another MRI, repeat memory testing, and repeat the walking test. With a study clinician's guidance, you will reduce and stop the study medication over one week. This week is called the taper week.

After the Step 1 taper week is over, you will begin Step 2. This has the same procedures as Step 1, except you will be assigned to the opposite pills to the ones you received in Step 1. If you received active study drug in Step 1, you would receive placebo in Step 2. If you received placebo in Step 1, you would receive active study drug in Step 2. During both Step 1 and Step 2, you will have weekly check-ins with the study team to assure your safety and address any problems.

There is no cost to you for taking part in this research study. You will not have to pay for the brain scans or the tests and treatments that are being done only for research. The study medications will be free of cost throughout the study. You are still responsible for paying for the usual care you would normally receive for the treatment of your illness. This will be discussed in more detail later in this document.

All study visits will be discussed in more detail later in this document.

Detailed Information:
The rest of this document includes detailed information about this study (in addition to the information listed above).

You are being asked to take part in this research study because you have depression, you feel you have slowing either in your thinking or movement, and are age 60 years or older.

You do not have to be in this research study. You may choose not to be in this study and get treatment 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.

Side effects and risks that you can expect if you take part in this study:
Diagnostic, Memory, and Motor Testing: We will ask you to complete some tasks that measure your memory, concentration, and your walking speed. Some of these will be done using pencil-and-paper while other tests will be done on a computer or iPad. It may take up to 4 hours to complete these tests.

You may experience boredom or discomfort during the clinical interview and evaluations when discussing symptoms and recent life events. You may also experience frustration with some tasks. Should you wish to stop or take a break, the study staff will allow it.

Walking Assessment: The walking assessment is done using a special mat. During the walking speed assessment or other physical movement measure you may feel unsteady and there is a risk of fall. During each performance-based assessment study personnel will be there to accompany you to ensure safety and provide support in case of a fall or if you are unsteady.

Risks of Carbidopa/Levodopa side effects: Carbidopa/Levodopa is approved by the Food and Drug Administration for the treatment of Parkinson's Disease. However, it is not approved for treating depression, so for this study is considered investigational.

Although carbidopa/levodopa is generally well tolerated, it does carry the risks of side effects. This drug combination has been well studied and in clinical use for many years. Possible common side effects may include nausea, headaches, vivid dreams, drowsiness, and dry mouth. You should be careful about drinking alcohol since it may have a greater effect on you in combination with carbidopa/levodopa. For people who use carbidopa/levodopa for longer periods of time, there is a possibility of developing abnormal movements of legs and arms.

Uncommon side effects include blood pressure changes, lower appetite, indigestion, constipation, trouble sleeping and a possible risk of developing hallucinations or delusions (hearing or seeing things that are not there or believing things that are not real).

In a recent study of older adults with depression, when carbidopa/levodopa was given similarly to how it will be given in this study, there was no evidence of severe adverse effects. The most common side effect was nausea, but this improved over the study. However, as people respond differently to medication, you will be monitored closely at each study contact. If you develop problems with nausea, uncontrolled movements, dizziness, or any other symptoms, you should contact study staff or your study clinician.

Risks of Magnetic Resonance Imaging (MRI): You will have two MRI scans: one during the baseline period and one after three weeks of study medication.

There are no known major risks with an MRI scan. But it is possible that harmful effects could be found out in the future. The tunnel is closed. It may bother you to be placed in a tight space (claustrophobia), and to hear the noise made by the magnet during the scan. You will be given earplugs to reduce the noise. You may also feel the table vibrate and/or move slightly during the scan. It may be hard to lie on

the table during the scan. If you have any metal pieces in your body, they could move during the scan and damage nearby tissues or organs.

If you use a transdermal patch (medicated patches applied to the skin), you may need to take it off during the MRI scan. Transdermal patches slowly deliver medicines through the skin. Some patches have metal in the layer of the patch that is not in contact with the skin (the backing). You may not be able to see the metal in the backing of these patches. Patches that contain metal can overheat during an MRI scan and cause skin burns in the immediate area of the patch. Tell study staff that you are using a patch and why you are using it (such as, for pain, smoking cessation, hormones). Ask your doctor for guidance about removing and disposing of the patch before having an MRI scan and replacing it after the procedure. Tell the MRI facility that you are using a patch. You should do this when making your appointment and during the health history questions you are asked when you arrive for your appointment.

Stopping Antidepressant medication: If you are eligible for the study and are currently taking a medication for depression, your study clinician will work with you on a plan to safely stop that medication. He or she will develop a schedule that will slowly reduce and stop your current antidepressant. Depending on your individual history, this may take several days or a few weeks. During this time, we will speak to you at least weekly by telephone to make sure that you are not having any problems coming off the medication and that your depression is not worsening. If you want to come for in-person visits, we can do this as well. There is a risk that your depressive symptoms may worsen during the time you are coming off an antidepressant or during the time you are taking study medication. If you are prone to develop thoughts of death or suicide when your depression gets worse, it is possible suicidal thoughts may develop.

Stopping antidepressants too quickly can lead to something called discontinuation syndrome. This may result in a variety of symptoms including dizziness, vertigo, trouble sleeping, tremor (shakiness), nausea, abdominal cramping, muscle aches, or tingling sensations. We will reduce the risk by a slow and careful taper of medication over time.

Loss of Confidentiality: There is also the potential risk of loss of confidentiality. Every effort will be made to keep your information confidential, however this cannot be guaranteed.

SMS/Text Medication Reminders: Later in this document, you will be able to choose a method to receive reminders to take your study medication. If you choose to receive text message reminders, SMS text messages aren't encrypted, meaning if a text message is intercepted by a third party the contents of the message can be read. If you don't want to receive medication reminders through text messages, you have alternative options.

Study Title: Dopaminergic Dysfunction In Late Life Depression (D3 Study)
Version Date: 12/11/2025

Risks that are not known: As with any research, there may be risks of participation or from the study medication that we cannot predict. Because this treatment is investigational, meaning non-FDA approved, there may be risks that we do not know about at this time. If you experience any unpleasant effects during this study not mentioned in this consent form, please contact a study staff member or study doctor as soon as possible.

Good effects that might result from this study:
The benefits to science and humankind that might result from this study: You will be adding to the understanding of whether treatments that target dopamine may help treat depression in older adults, as well as the effects of carbidopa/levodopa on memory performance and movement. This information will help us determine if carbidopa/levodopa may be a useful approach to treating depression or mobility problems.

The benefits you might get from being in this study: By receiving carbidopa/levodopa, you may experience an improvement in your depression symptoms. In addition, you may experience an improvement in your walking speed or thinking performance. However, as people respond differently to treatments, personal benefit cannot be guaranteed.

Procedures to be followed:
Screening Visit (Total Time: about 3 hours):

The initial visit is called the screening visit and can occur across 1-2 separate visits. Your medical and psychiatric history will be carefully reviewed to make sure that you are eligible for the study. Additionally, we will assess your current depressive symptoms and your current and past medication use. You do not have to answer any questions you do not feel comfortable answering.

For your safety, you must tell study staff about all the medications you are taking, including over-the-counter drugs and herbals, before you start the study and before taking any new medications. If there is a problem where you cannot be in the study because of one of the medications you are taking, study staff will discuss that with you.

You will complete assessments at this visit that measure your walking speed, motor speed, and processing speed (how fast you think). These assessments must be conducted in person and will help determine whether you are eligible for the study.

As part of this visit, we will carefully evaluate you to determine if you have any metal in your body that could stop you from having the MRI. If you have had any surgeries that may have used

implanted metal objects, we may need to request medical records to assure your safety before you could proceed to MRI.

At the end of the screening visit, or during the baseline period, you will be asked to complete a series of questionnaires. These questionnaires can be completed in several ways.

1. We can email you a link that will allow you to complete the questionnaires on a device with internet access, such as a computer or smartphone. These questionnaires will be completed in a secure database in REDCap. REDCap is a secure web platform created for researchers where data for this study are collected and stored. VUMC is managing the REDCap database for this study.
2. If you do not have an email address, or if you prefer to complete the questionnaires on paper, you can be given a take-home packet of questionnaires to complete. We will ask you to complete them as soon as possible. If you are given paper questionnaires to complete at home, you will return them to us via the addressed, stamped envelope we will provide, or you can return them at your next in-person visit.
3. You can also complete the questionnaires during a study visit, using a study iPad or computer. This will not require your email address to be entered in the REDCap study database.

If you have any questions, you can contact us at any time.

Stopping Current Antidepressants: If you are eligible and taking a medication for depression, your study clinician will work with you on a plan to safely stop that medication that may take several days or a few weeks. During this time, we will speak to you at least weekly by telephone to monitor for any problems. Once you are off your current antidepressant medicine, you will return for the baseline period.

Baseline Period (Total time varies by site):

If you are eligible and would like to participate, after stopping your current antidepressants (if applicable) you will be scheduled for the baseline period. The baseline period will last up to 4 weeks. You will meet with study staff who will again assess your depressive symptoms. You will also complete neuropsychological (memory) testing, a gait (walking) assessment, and one MRI scan.

These baseline study procedures will be done over 2-4 separate visits. The symptom assessment portion of the baseline period may be done in-person or remotely using HIPAA compliant video conferencing (for example, Zoom). All other baseline assessments will be completed in-person.

N**europsychological (Memory) Testing:** We will ask you to complete some tasks that measure your memory, concentration, and problem-solving abilities. Some of these will be done using pencil-and-

paper while other tests will be done on a computer or iPad. The memory testing will take about two hours. Memory testing can be on the same day when you have the MRI scan, or on a separate day. Memory testing will be repeated at the end of each step, typically the Week 3 and Week 7 visits.

The memory tests are completed for research purposes only. They are not administered by a licensed clinical psychologist and thus, we are not able to provide a clinical interpretation of the results.

MRI: You will complete two MRI scans during the study. One will be during the baseline period before you receive study medication (carbidopa/levodopa or placebo) and the second will be after completing step 1 of the study medication phase. A health and medication review will be completed prior to the MRI scans.

Each MRI scan will take about 90 minutes. An MRI scan is taken in a large machine that is shaped like a tunnel. This scan does not use x-rays. Instead, they use a strong magnet and radio waves, like those used in an AM/FM radio to make pictures of your body.

During the MRI scan you will be asked to complete two tasks measuring your attention and decision-making abilities. You will see images on a screen and you will press buttons with your fingers to complete the tasks. You will be able to practice the tasks before entering the MRI scanner. Both tasks involve you responding to images on-screen to examine how people make decisions about rewards, such as choosing a high reward with a low chance of receiving it or choosing a low reward with a high chance of receiving it. Your performance on the tasks will determine how much compensation you receive for completing the MRI scan.

You may not be able to have this scan if you have a device in your body, such as aneurysm clips in your brain, heart pacemakers or defibrillators, or cochlear (inner ear) implants. Also, you may not be able to have this scan if you have iron-based tattoos or pieces of metal (bullet, BB, shrapnel) close to or in an important organ (such as the eye). If we determine that you cannot safely complete the MRI, we will discuss whether you can participate in the study.

Certain metal objects like watches, credit cards, hairpins, writing pens, etc. may be damaged by the machine or may be pulled away from the body when you are getting the scan. Also, metal can sometimes cause poor pictures if it is close to the part of the body being scanned. For these reasons, you will be asked to remove these objects before going into the room for the scan.

You will hear "hammering," clicking, or squealing noises during the scan. You will be given earplugs to reduce the noise. You will also be told how to alert the staff if you need them.

During the scan, the MRI staff is able to hear and talk to you in between scans. You will also be able to hear the staff in between scans. They will be talking to you during your scan and may ask you to not move or other simple tasks. You may be asked to lie very still throughout the scan.

Medication Phase Step 1 & Step 2:

After the baseline period is complete, you will be randomly assigned by chance (like a flip of a coin) to receive either the study drug, carbidopa/levodopa or placebo. Placebo is not a medication and is not designed to treat any illness or disease.

Each step (Step 1 and Step 2) will last approximately 3 weeks.

In Step 1, if you are assigned to carbidopa/levodopa, during week 1 you will take a daily dosage of 150mg of levodopa and 25mg of carbidopa. During weeks 2 and 3 your dose will be increased to final doses of 450mg of levodopa and 75mg of carbidopa.

Neither you nor the study staff will know which study medication you are receiving, however this can be determined in case of emergency. You will be instructed to maintain the same timing of doses throughout the study.

To achieve these doses, during week 1 you will take study medication capsules once daily at 9 am. During week 2, you will take study medication capsules twice daily at 9am and 5pm. During week 3, you will take study medication capsules three times daily at 9am, 1pm and 5pm. If you are assigned to placebo, you will take capsules on the same schedule, but those capsules will not contain active medication.

Weekly Check-In Study Visits – Weeks 1 and 2

During the medication phase, we will schedule weekly study visits. Depending on your medical history, as well as your preference, these visits may be completed in person, by telephone, or using video conferencing. Your depression symptoms and any side effects will be assessed. These visits will last 30-60 minutes.

Vital signs such as blood pressure, weight, and pulse will be taken and recorded during each in-person visit. For visits you complete by telephone or video conferencing, while you are on the phone or video conference call, you will be asked to measure your blood pressure several times, both while you are lying down and then again when you are sitting up. If you are at not completing your visit in

person, you will need to be somewhere you can comfortably lie flat on your back and then sit up again, like on a couch or bed, during a portion of your telephone or video conferencing call. We will provide you with a study blood pressure cuff and written instructions to help you follow along if you are unable to take your blood pressure during the call. You will be asked to return the blood pressure cuff at the end of your study participation. If you have a blood pressure cuff at home, you may be able to use it instead of one provided by the study. Study staff will discuss this with you.

If you have difficulty tolerating a dose increase, you and your study clinician may decide to either keep you on your current dose or reduce your dose to the previous level for one week. If we do not increase your dose at a visit, we will either keep you at the same dose or try to increase the dose one more time at your next visit. If you cannot tolerate the dose increase a second time, you will stay on the lower dose for the remainder of the step. In this scenario, called a dose challenge, the medication period will last for 4 weeks instead of 3 weeks.

End of Step Study Visits – Week 3

After Week 3 of Step 1 (or Week 4 if you had a dose challenge during Step 1), you will have another in-person visit. Your depressive symptoms will be assessed, vital signs recorded, and any side effects will be assessed. You will complete study questionnaires and repeat the neuropsychological (memory) testing and the gait (walking) test.

You will also complete another brain MRI after Week 3 of Step 1 (or Week 4 if you had a dose challenge during Step 1) if it is safe for you to have an MRI scan. This Step 1 Week 3 visit will last about 5.5 hours. If you had a dose challenge during Step 1, these procedures will occur about 4 weeks after you started study mediation as you must be on either the maximum dose, or the maximum dose you could tolerate, for 7 days prior this visit.

Symptom and side effect assessments may be completed on a separate day through telehealth call or in-person visit. If the symptom and side effect assessments are completed on a separate day, they will be completed within 1-4 days of your Step 1 Week 3 (End of Step 1 visit).

Taper Week – Step 1 Week 4

After this final visit of Step 1, you will decrease and stop study medication capsules over a one-week period. This is called a taper week. If you have a dose challenge during Step 1, this visit will occur at Week 5. At the end of the taper week, you will complete another check-in visit.

Step 2

After finishing the Week 4 (or Week 5 if you had a dose challenge during Step 1) taper visit, you will then start Step 2. In Step 2 you will receive an identical dosing regimen of the drug you did not receive in Step 1 (either carbidopa/levodopa or placebo). You will have weekly check-in visits as described above for Step 1. After Week 3 of Step 2 (or Week 4 if you had a dose challenge during Step 2), you will have another in-person, End of Step visit. Your depressive symptoms will be assessed, vital signs recorded, and any side effects will be assessed. You will complete study questionnaires and repeat the neuropsychological (memory) testing and the gait (walking) test. This visit will take about 3 hours. Symptom and side effect assessments may be completed on a separate day through telehealth call or in-person visit. If the symptom and side effect assessments are completed on a separate day, they will be completed within 1-4 days of your Step 2 Week 3 (End of Step 2 visit).

After finishing all study procedures for Step 2, you will be given a plan to safely stop the study medication. If an unblinded staff member is available during the visit, you will be informed about what study medication you have been receiving. If you were receiving placebo in Step 2, you may immediately stop taking the provided medication. If you were taking carbidopa/levodopa in Step 2, a study clinician will help you safely stop the medication over a final week. If an unblinded staff member is not available to unblind you during your in-person End of Step 2 visit, you may be unblinded over a phone call within about 7 days.

Medication Reminders

As you will need to take your medication up to three times per day, you will receive reminders to take your study medication.

You can choose between the following options for receiving reminders:

1. Text message reminders: You will receive a text reminder up to 3 times per day reminding you to take your study medication. The message will read: "This is a reminder to take your medication." The text message will not include any identifiable information, but we are using a third-party service called Twilio.com to send the medication reminders. This means that all text messages will go through Twilio's servers. Text message transcriptions do not stay in Twilio's logs, but are removed shortly after being completed, but your phone number will be temporarily logged on Twilio's servers. Standard text message rates/fees apply.
2. Pill organizer with alarms: If you choose this option, we will provide you with a 7 day pill organizer with an alarm. We will show you how to program the alarm to alert you 1-3 times a day when it is time to take your study medication. You will need to

Study Title: Dopaminergic Dysfunction In Late Life Depression (D3 Study)
Version Date: 12/11/2025

add the pills to the organizer each week. This pill organizer will be yours to keep upon completion of the study.

Please initial below to indicate how you would like to receive the study medication reminders if you are eligible for the study:

_____Option 1: I would like to receive text message reminders. I acknowledge that the SMS text messages I receive might be viewable by people who are not working on this study.

_____Option 2: I would like to receive a pill organizer that has alarms.

Reasons why the study doctor may take you out of this study:

Your study clinician may withdraw you from study participation if he or she determines that, based on the initial study interview, you are not eligible to continue the study. He or she may also withdraw you if you are having difficulty completing study procedures, if you need an immediate referral for clinical care, or if he/she decides that it is not in your best interest to continue in the study. If you are taken out of the study, you will be told the reason.

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 clinician or study staff. We may ask you to come in for a final study visit. Because you are receiving study medication, it is important to discuss a safe and effective plan for continuing, altering, or stopping the medication. If you withdraw or are withdrawn from the study early, you will be compensated for the parts of the study you have completed.

All participation in the study is voluntary, and there is no penalty for refusing to participate or for early withdrawal. Deciding to not be part of the study will not change your regular medical care in any way.

Clinical Trials Registry:

A description of this clinical trial will be available on 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 Web site at any time.

Confidentiality:

Study Title: Dopaminergic Dysfunction In Late Life Depression (D3 Study)
Version Date: 12/11/2025

All reasonable efforts will be made to keep the personal information in your research record private and confidential, but absolute confidentiality cannot be guaranteed. Your information may be shared with institutional and/or governmental authorities, such as the Institutional Review Boards for the University of Pittsburgh Medical Center or Vanderbilt University Medical Center. It may also be shared if you or someone else is in danger or if we are required to do so by law.

All data are labeled and coded for protection and confidentiality. Data are kept on secure, password protected networked computers, in secure REDCap databases, and in locked offices. Identification numbers are used instead of names for additional protection. Only research staff will have access to participant data. Source materials will be labeled and coded with an identification number that is not linked in any way to participant personal identifying information for purposes of additional protections and confidentiality. This number will be used to identify participants' self-reported questionnaires, memory test results, brain scans, and other data. Other than your date of birth, no other direct identifiers will be shared with our collaborators.

A list linking names to identification numbers will be available only to authorized personnel and will be kept separately from research charts. Only research personnel authorized by the Principal Investigator will have access to these records. The link between your identity and your identification number will not be shared with researchers in other institutions and will not leave your study site.

During the study, if we learn you are having thoughts about suicide or hurting yourself or others, the research staff will ask you more questions about your thoughts. Based on your response, the staff may provide you with help to get treatment. This may include:

- working with you to contact your doctor,
- contact a trusted family member, or a therapist to discuss your thoughts,
- or work with you on a plan that may include getting you to a hospital for safety.

In these cases, the research team may share information about your condition with other health care providers.

Investigators may share your information, without identifiers, to others or use it for other research projects not listed in this form. We will be sharing de-identified data with the University of Pittsburgh Medical Center, Vanderbilt University Medical Center, Emory University, Rutgers University, and University of North Carolina. We will comply with any and all laws regarding the privacy of such information. There are no plans to pay you for the use or transfer of this de-identified information.

This study is supported by the National Institutes of Health (NIH) and is protected by a Certificate of Confidentiality. This Certificate allows us, in some cases, to refuse to give out your information even

if requested using legal means. It does not protect information that we have to report by law, such as child abuse or some infectious diseases. The Certificate does not prevent us from disclosing your information if we learn of possible harm to yourself or others, or if you need medical help.

Privacy:

Any samples and information about you may be made available to others to use for research. Study information about you will be shared with study investigators across both sites, including Vanderbilt University Medical Center and the University of Pittsburgh Medical Center. To protect your privacy, other than your date of birth, we will not release your name or other direct identifiers.

De-identified data will also be shared with the University of North Carolina, Emory University, and Rutgers University.

You will not receive any benefit as a result of the tests done on your samples. These tests may help us or other researchers learn more about the causes, risks, treatments, or how to prevent this and other health problems.

Data from this study will be submitted to the National Institute of Mental Health Database (NDA) at the National Institutes of Health (NIH). NDA is a large database where deidentified study data from many National Institute of Mental Health (NIMH) studies is stored and managed. Deidentified study data means that all personal information about you (such as name, address, birthdate and phone number) is removed and replaced with a code number. Sharing your deidentified study data helps researchers learn new and important things about mental health and substance use more quickly than before.

During and after the study, the study researchers will send deidentified study data about your health and behavior to the NDA. Other researchers across the world can then request your deidentified study data for other research.

Every researcher (and institutions to which they belong) who requests your deidentified study data must promise to keep your data safe and promise not to try to learn your identity. Experts at the NIH who know how to keep your data safe will review each request carefully to reduce risks to your privacy. Sharing your study data does have some risks, although these risks are rare. Your study data could be accidentally shared with an unauthorized person who may attempt to learn your identity. The study researchers will make every attempt to protect your identity.

You may not benefit directly from allowing your study data to be shared with NDA. The study data provided to NDA may help researchers around the world learn more about mental health and

substance use and how to help others who have problems with mental health and substance use. NIMH will also report to Congress and on its website about the different studies using NDA data. You will not be contacted directly about the study data you contributed to NDA.

You may decide now or later that you do not want your study data to be added to the NDA. You can still participate in this research study even if you decide that you do not want your data to be added to the NDA. If you know now that you do not want your data in the NDA, please tell the study researcher before leaving the clinic today. If you decide any time after today that you do not want your data to be added to the NDA, call or email the study staff who conducted this study, and they will tell NDA to stop sharing your study data. Once your data is part of the NDA, the study researchers cannot take back the study data that was shared before they were notified that you changed your mind. If you would like more information about NDA, this is available on-line at http://nda.nih.gov.

Your samples may be used to make new products or tests. These may have value and may be developed and owned by the study staff, Vanderbilt University, Vanderbilt University Medical Center, and/or others. If this happens, there are no plans to provide money to you.

While you are participating in this study, we may want to discuss with you about possibly participating in other research studies at your study site. Please indicate below if you are willing to be contacted about other research studies. We will not contact you about future research studies once your participation in this study is complete.

O Yes, I agree to be contacted about other research studies.

O No, I do not want to be contacted about other research studies.

Study Results:

Study records will be maintained for at least seven years after all study procedures are complete, all subject contact has ended, and the study is closed with the IRB. After that time, study data may be destroyed or anonymized, meaning all links to direct identifiers will be destroyed. Any study data in the medical record will be kept indefinitely.

Institutional Review Board
Informed Consent Document for Research
MASTER CONSENT

Study Title: Dopaminergic Dysfunction In Late Life Depression (D3 Study)
Version Date: 12/11/2025

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.

Institutional Review Board
Informed Consent Document for Research
STUDY SITE INFORMATION

Study Title: Dopaminergic Dysfunction In Late Life Depression (D3 Study)
Version Date: 12/11/2025

Part 2 of 2: STUDY SITE INFORMATION
Depressed Participants

Site Name:	Vanderbilt University Medical Center
Site Principal Investigator:	Alexander Conley, Ph.D.
Site Principal Investigator Contact:	(615) 322-1073
Site Study Coordinator *(if applicable)*:	Carrie Williams
Site Study Coordinator Contact *(if applicable)*:	(615) 936-2162

This part of the consent form includes information about the site that is asking you to participate in this study and is specific to participation at your site only. Before making your decision, both the site-specific information and the general study information should be reviewed with you. Your medical record will contain a note saying you are in a research study and may contain some research information about you. Anyone you authorize to receive your medical record will also get this information.

Site specific key information:

Over the course of the study, you can expect to spend about 27 hours completing all study related procedures.

Site specific procedures and risks:

Blood sampling: We will draw up to 10 mL (about 2 teaspoons) of blood one time. This blood sample will be used to measure inflammation. Pain, redness, soreness, bruising, or infection may occur at the needle stick site. However, this risk is low. Blood will be drawn by a phlebotomist using sterile technique. Rarely some people faint. The study staff may put some cream (called EMLA) on your skin to numb the area so you will not feel the needle stick as much. The numbing cream may make your skin have a change in skin color, but this is rare.

Risks of drug interactions: It is possible that receiving carbidopa/levodopa may change how your regular medications, vaccines, or supplements work. It is important that you tell the study staff about any medications, supplements, or vaccines before you take them during the study.

Risks that are not known: As with any research, there may be risks of participation or from the study medication that we cannot predict. If you experience any unpleasant effects during this study not mentioned in this consent form, please contact a study staff member or study doctor as soon as possible.

Site specific detailed Information

Your medical record will contain a note saying you are in a research study and may contain some research information about you. Anyone you authorize to receive your medical record will also get this information.

We are requesting that you provide the name and contact information of your primary care provider. If any clinically significant health findings arise from study procedures, we would like to inform you and your health provider of these findings. We ask that you designate your health care provider:

Name of health care provider _____

Phone number of health care provider_____

_____ I do not have a healthcare provider or do not want any information shared with my healthcare provider. If results are shared with me, I am encouraged to share them with a healthcare provider.

At the beginning of each virtual visit, you will be asked to confirm your location. Virtual study visits will need to occur when you are in a residence or work location. We ask that you keep your camera on for the duration of the visit. If you are unable to stay in one location for the entire visit, your visit may be rescheduled. If you are unable/unwilling to provide your location and keep your camera turned on for the entire visit, your visit will need to be rescheduled to a different time, rescheduled to an in person visit, or you may need to be withdrawn from the study.

Screening Visit:
During the screening visit, A blood sample may be collected. It will be discussed later in this document.

Baseline Period (Total Time: about 8 hours)

Blood Sample: We will collect up to 10 mL (about 2 tsp) of blood for one time during the study. The blood draw will occur either at an in-person screening visit or during the baseline period. You will not need to fast prior to the blood draw.

If you do not have a dose challenge week, the chart below shows a summary of what will occur during each visit:

Visit	Approx Time	Questionnaires/ Vitals	Blood Draw	MRI	Memory/ Walk Testing
Screening	3 hours	X			
Baseline	8 hours	X	X	X	X
Step 1 Week 1* - Weekly Check-In	1 hour	X			
Step 1 Week 2* - Weekly Check-In	1 hour	X			
Step 1 Week 3	5.5 hours	X		X	X
Step 1 Week 4* - Taper Week	1 hour	X			
Step 2 Week 1* - Weekly Check-In	1 hour	X			
Step 2 Week 2* - Weekly Check-In	1 hour	X			
Step 2 Week 3	3 hours	X			X

*= In-person, telephone, or video conferencing visit

Additional Information about MRI: The MRI scans are being done for research purposes rather than for diagnosis. The scans will not be routinely examined by health professionals for potential abnormalities. However, in the event an abnormality is detected by the investigators or the MRI technologist, the scans will be further examined by a radiologist and the investigator may encourage you to consult your physician or provider referrals for further evaluations. If your healthcare provider would like to use the MRI for comparison with another clinical scan that has already been

obtained or may obtain in the future, they may request a copy of the research scans if they are still available.

During the screening visit, you will have an option to complete a "mock" MRI scan. Although no actual scan is taken, you will be able to experience the process (getting on and off the table, being inside the scanning tube, hearing the sounds the machine produces during the scan) to make sure you are comfortable with having an MRI scan. Completing the "mock" MRI scan will take about 30-45 additional minutes.

This MRI scanner has been used with research animals. For your safety, we clean the scanner with bleach before and after your scan as we do with scanners used only for patients.

Additional Information about your Medical Record: Your medical record will contain a note saying you are in a research study and may contain some research information about you. Anyone you authorize to receive your medical record will also get this information.

Payments for your time spent taking part in this study or expenses:
You will be compensated for your participation based on how many visits/assessments you attend as well as your performance on the MRI tasks. You can receive up to $575. The table below shows how much you will receive for completing each visit:

Visit	Amount
Screening Visit	$25.00
Baseline Period	
Memory and Walk Testing	$75.00
MRI	Up to $150.00
Blood Draw	$25.00
End of Step 1 Visit	
Memory and Walk Testing	$75.00
MRI	Up to $150.00
End of Step 2 Visit	

Memory and Walk Testing	$75.00
Total Compensation	**Up to $575** if you return the blood pressure cuff
	Up to $500 if you do not return the blood pressure cuff

If you are given a blood pressure cuff to use at home for the study and do not return it, you will not be compensated for the Baseline Period Memory and Walk Testing.

You will receive up to $150 for completing each MRI scan. You will receive at least $90 as base pay for completing each scan. You can receive an additional $60 bonus per scan based on your performance during the tasks in the MRI scanner.

For one task, you will receive 20% of the total amount you earned while completing the task (for example, if you won $80 during the task, you will receive 20% of that amount, which is $16). For the second task, you will complete several trials of the task that each contain several rounds. We will select three rounds from each trial and pay you the amount you won during those trials. Your total bonus payment of up to $60 will be given to you in cash immediately after the scan. The $90 base pay will be included in a check with the rest of your reimbursement.

The table below shows how much you will receive for completing each MRI scan:

Task	**Amount**
Base Pay	$90.00
Task Performance	Up to $60.00
Total:	**Up to $150 per MRI**

We will ask for your Social Security number and address before you are compensated for taking part in this study. You may receive up to $575 for taking part in this study. This amount may be taxable and will be reported to the Internal Revenue Service (IRS).

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 study drug, tests or assessments that are being done only for research. However, you are still responsible for paying for the usual care you would normally receive for the treatment of your illness. This includes treatments and tests you would need even if you were not in this study. These costs will be billed to you and/or your insurance.

You have the right to ask what it may cost you to take part in this study. If you would like assistance, financial counseling is available through the Vanderbilt Financial Assistance Program. The study staff can help you contact this program. You have the right to contact your insurance company to discuss the costs of your routine care (non-research) further before choosing to be in the study. You may choose not to be in this study if your insurance does not pay for your routine care (non-research) costs and your doctor will discuss other treatment plans with you.

Text Message Fees

If you choose to receive text message medication reminders, standard text message rates/fees apply.

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 any injury caused by the usual care you would normally receive for treating your illness or the costs of any additional care. There are no plans for Vanderbilt to give you money for the injury.

Who to call for any questions or in case you are injured:

If you should have any questions about this research study or if you feel you have been hurt by being a part of this study, please feel free to contact the study coordinator, Carrie Williams, at (615) 936-2162 or the principal investigator, Dr. Alexander Conley, at (615) 936-1552. If you cannot reach the research staff, please call the study doctor, Dr. Patricia Andrews, at (615) 875-3722.

For additional information about giving consent or your rights as a person in this study, to discuss problems, concerns, and questions, or to offer input, please feel free to call the Vanderbilt University Medical Center Institutional Review Board Office at (615) 322-2918 or toll free at (866) 224-8273.

Confidentiality:

Your paper research records will be kept in locked filing cabinets within locked rooms, and only the site research team will have access.

Blood samples will be leaving Vanderbilt University Medical Center for analyses of levels of inflammatory markers. They will be sent to Emory University to measure inflammation markers. These samples will be deidentified. This means they will only include your study-created identification number, the type of blood sample, and the date of blood collection.

Disclosures that you consent to in this document are not protected. This includes putting research data in the medical record or sharing research data for this study or future research. Disclosures that you make yourself are also not protected.

Authorization to Use/Disclose Protected Health Information:

What information is being collected, used, or shared?

To do this research, we will need to collect, use, and share your private health information. By signing this document, you agree that your health care providers (including both Vanderbilt University Medical Center and others) may release your private health information to us, and that we may use any and all of your information that the study team believes it needs to conduct the study. Your private information may include things learned from the procedures described in this consent form, as well as information from your medical record (which may include information such as HIV status, drug, alcohol or STD treatment, genetic test results, or mental health treatment).

Who will see, use or share the information?

The people who may request, receive or use your private health information include the researchers and their staff. Additionally, we may share your information with other people at Vanderbilt, for example if needed for your clinical care or study oversight. By signing this form, you give permission to the research team to share your information with others outside of Vanderbilt University Medical Center. This may include the sponsor of the study and its agents or contractors, outside providers, study safety monitors, government agencies, other sites in the study, data managers and other agents and contractors used by the study team. We try to make sure that everyone who sees your information keeps it confidential, but we cannot guarantee that your information will not be shared with others. If your information is disclosed by your health care providers or the research team to others, federal and state confidentiality laws may no longer protect it.

Do you have to sign this Authorization?

You do not have to sign this Authorization, but if you do not, you may not join the study.

How long will your information be used or shared?

Your Authorization for the collection, use, and sharing of your information does not expire. Additionally, you agree that your information may be used for similar or related future research studies.

The study results will be kept in your research record for at least six years after the study is finished. At that time, the research data that has not been put in your medical record will be kept for an unknown length of time. Any research data that has been put into your medical record will be kept for an unknown length of time.

What if you change your mind?

Unless told otherwise, your consent to use or share your PHI does not expire. You may change your mind and cancel this Authorization at any time. If you cancel, you must contact the Principal Investigator in writing to let them know. The mailing address is 1601 23rd Avenue South, Nashville, TN 37212. At that time, we will stop getting any more data about you. Your cancellation will not affect information already collected in the study, or information that has already been shared with others before you cancelled your authorization. The health data we stored before you withdrew your consent may still be used for reporting and research quality.

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.

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STATEMENT BY PERSON AGREEING TO BE IN THIS STUDY

I have read this consent form and the research study has been explained to me verbally. All my questions have been answered, and I freely and voluntarily choose to take part in this study.

Date	Signature of patient/volunteer

Consent obtained by:

Date	Signature
	Printed Name and Title

Time: _____