NEW YORK STATE PSYCHIATRIC INSTITUTE

DOPAMINERGIC DYSFUNCTION IN LATE LIFE DEPRESSION (THE D3 STUDY)

Overview

Below is a summary of the study in which you are asked to take part in. This outline is meant to be a guide for you to use while considering the study and reading the consent form. It is not meant to replace the consent form, which you will have to sign if you decide to participate in the study. The study described is a double-blind placebo-controlled study, which means that you will be randomly assigned (like the flip of a coin) to study medication or else placebo (a sugar pill). Neither you nor the study doctor will be informed whether you are receiving study medication or placebo until the end of the study.

Participation is Voluntary

Participation in this research study is voluntary. If you decide not to participate, or if you later decide to stop participating, you will not lose any benefits to which you are otherwise entitled. A decision not to participate or withdraw your participation will not affect your current or future treatment at the New York State Psychiatric Institute or Columbia University Irving Medical Center.

Alternatives

You do not have to participate in this study to receive treatment for depression or slowed thinking and movement. Food and Drug Administration (FDA)-approved antidepressant medications such as Selective Serotonin Reuptake Inhibitors (SSRIs, e.g., Prozac, Zoloft, etc.) or Serotonin Norepinephrine Reuptake Inhibitors (SNRIs, e.g., Effexor, Cymbalta, etc.), in addition to other types of medications are effective in the treatment of depression. Additionally, psychotherapies that are supported by research such as Interpersonal Psychotherapy and Cognitive Behavior Therapy are available outside of this study to treat depression. Finally, exercise programs and cognitive remediation may be helpful for slowed thinking and movement and also are available outside this research project.

Procedures

- At the beginning of the study, you will be given a physical examination, an electrocardiogram (EKG), and have your blood drawn.
- Next you will have tests of your memory, concentration, and other thinking skills as well as a test of your walking.
- Subjects in this study will undergo two (2) magnetic resonance imaging (MRI) scans of the brain and one (1) positron emission tomography (PET) scan of the brain.

- MRI scans use strong magnetic fields and radio waves to take pictures of your brain.
- The PET scans require placement of an IV catheter and injection of a radioactive substance called [^{18}F]-DOPA. [^{18}F]-DOPA allows us to examine the uptake of dopamine by cells in the brain, which are important in some psychiatric diseases such as depression.
- In the medication part of the study, you will be randomly assigned to receive a medication called carbidopa/levodopa (Sinemet) or pill placebo (a sugar pill). We are using carbidopa/levodopa "off-label" in this study, which means that it is not approved by the FDA for the treatment of depression. Half of study participants first will receive Sinemet for 3 weeks, then after a 1 week washout period, will be switched to receive a placebo for 3 weeks. The other half of participants first will receive placebo for 3 weeks, then after a 1 week washout period, will be switched to receive Sinemet for 3 weeks. All participants will receive placebo at some point in the study, either in Step 1 or Step 2.
- You will be asked to return each week to see one of the study doctors, talk about how you are feeling and have tests of your thinking and walking speed.
- The research study will end after 8 weeks. You will fill out some more thinking tests and have your walking speed tested again.

Risks

This study includes some risks and discomforts (please refer to the consent form for further details and explanations of these risks). The main risk to you in this study is that carbidopa/levodopa is an experimental treatment, and it is not known yet whether it will be effective in treating low dopamine levels or symptoms of depression. Other risks are worsening of depression while you are assigned to receive placebo, side effects associated with carbidopa/levodopa (such as nausea, headache, abnormal movements of arms and legs, muscle stiffness, and vivid dreams), and radiation exposure from the [^{18}F]-DOPA tracer used in the PET scans.

Please alert study staff if you feel your depression is getting worse.

Benefits

This research study is not meant to benefit you directly. You may contact the study doctor, Dr. Bret Rutherford at 646-774-8660 with any questions.

Informed Consent for Participation in Research

DOPAMINERGIC DYSFUNCTION IN LATE LIFE DEPRESSION (THE D3 STUDY)

PURPOSE OF STUDY

The purpose of this research study is to better understand the brain's dopamine system among older adults with depression. The dopamine system plays important roles in thinking, movement, motivation, and pleasurable or rewarding activities. In addition to performing brain scans and several different tests of your thinking and movement, we use a medication called carbidopa/levodopa (Sinemet) to investigate how the brain's dopamine levels influence behavior. Carbidopa/levodopa is approved by the Food and Drug Administration (FDA) for the treatment of Parkinson's Disease. We are using carbidopa/levodopa "off-label" in this study, which means that it is not approved by the FDA for the treatment of depression. We are interested in studying how carbidopa/levodopa affects the brain's dopamine levels as well as the mental and physical slowing that occur as people age.

In this study you will have brain scans using magnetic resonance imaging (MRI) and positron emission tomography (PET). We are performing these scans to understand more about how the brain's dopamine system may be different in older adults who are depressed. The MRI scans involve some parts where you will be asked to lie quietly in the scanner without doing anything and some parts where you will be asked to look at a screen and accomplish tasks by pressing buttons. The PET scan involves the use of a radioactive investigational drug called [^{18}F]-DOPA. It is an investigational drug that is taken up by parts of your brain that process dopamine. The drug contains a very small radioactive tracer that can be "seen" by the PET camera. The PET camera then takes "pictures" of the chemical activity in the brain by detecting the radioactive signal of [^{18}F]-DOPA. You will also be asked to take the drug carbidopa just before the PET scan so that the PET techniques can better measure the dopamine system in the brain.

This study is supported by a grant from the National Institute of Mental Health.

VOLUNTARY

Participation in this study is voluntary. If you do not wish to participate in this study or decide to discontinue your participation in this study later, you will not lose any benefits to which you are otherwise entitled, including current or future treatment at New York State Psychiatric Institute or Columbia University Medical Center. We will notify you of any significant new findings that may relate to your willingness to continue to participate.

ALTERNATIVE TREATMENT

You do not have to participate in this study. The alternative to participating in this study is to seek treatment outside the research project so that you would be certain of receiving a treatment approved for treatment of depression. Approved medications for depression are available (e.g., fluoxetine (Prozac), sertaline (Zoloft), etc.), and evidence based psychotherapies (Interpersonal Psychotherapy, Cognitive Behavior Therapy) also may be helpful with depression, whether on their own or combined with medication.

Although no treatments for mental and physical slowing have been formally approved by the FDA, other treatment approaches include exercise programs and cognitive training.

Information being collected is for research purposes only and is to learn more about changes in the brain's dopamine system with aging, not about you. It is not necessary to participate in this research study to have an MRI, and the MRI done as part of this study is not the same as one done for medical purposes.

STUDY PROCEDURES

Evaluation: If you decide to participate in this study, you will have blood drawn, complete some tests, and have your walking measured using a special mat. The total amount of blood taken at this study visit is about four tablespoons. Results of these blood tests will be available to you, should you request them. The tests measure thought processes such as memory, language, reasoning, and attention. These tests are paper-and-pencil as well as computer-based and take about two hours to complete. The results of these tests are for research purposes only and will not be shared with you.

Based on these tests, it will be determined whether you are eligible for the treatment portion of the study. If you are not eligible, you will be referred to appropriate options for further treatment. If you are eligible and continue to wish to participate, you will proceed with the next part of the study.

MRI scans: You will have an MRI scan at the beginning of the study (before you receive any carbidopa/levodopa or placebo) and again after the first part of the medication study (after you have taken carbidopa/levodopa or placebo for three weeks). Some parts of the MRI scans involve completing tasks while you are lying in the scanner machine. You will be trained for about 1 hour before each scan in the performance of two computer tasks by one of the study's research assistants. These tasks involve sitting at a desk, looking at pictures on a computer screen, and pressing buttons with your finger. You then will be asked to undergo the MRI scans, each of which lasts approximately one and a half hours.

The MRI uses strong magnetic fields and radio waves to take pictures of your brain. MRI involves lying on a table that slides into a large magnet shaped like a cylinder. Before beginning the imaging procedure, we will determine whether you have a pacemaker or any unsafe metallic implants such as an aneurysm clip or heart valve and certain tattoos, and you will be asked to remove any metal or magnetized objects (such as keys, chains, jewelry, retainers, medication patches, hairpins and credit cards). You will be asked to lie flat on your back in the MRI scanner for about 90 minutes and to remain as still as possible. You will not feel anything, but you will hear a knocking noise. This is a normal sound produced by the MRI scanner and does not indicate that anything is wrong. If you feel nauseated during scanning, please immediately alert the MRI staff member. It could be dangerous to vomit while in the scanner due to a risk of aspiration.

PET scan: At the beginning of the study (before you receive any carbidopa/levodopa or placebo) you will also have a PET scan. The PET scan will likely happen after your first MRI scan and on a different day. On the PET scan day, we will ask you not to eat from 6 am until the study is over. We will also ask you not to drink caffeinated beverages, such as coffee, tea, and soda, that day.

For the PET scan, we will need to place an intravenous (IV) catheter in one of your veins, and we will inject the radioactive substance through it. After the catheter is inserted, we will begin the PET scan. For the scan, we will ask you to lie on the narrow table. We will also position your head with a chin strap or a polyurethane head holder that we will mold around your head to reduce head movement during the scan. Right before each PET scan we will perform a very short (~10-15 second) computerized tomography (CT, or "CAT") scan of the brain, which helps us make sure the PET scan is positioned correctly. We will then inject the radioactive substance [^{18}F]-DOPA through the catheter in your arm. Before this injection, you will be asked to take a pill containing carbidopa, which helps the [^{18}F]-DOPA be absorbed better by your body.

The scan will last up to 1 hour. In addition, if you move your head during the PET scan we may do an additional CT position scan at the end of the PET scan. If you feel nauseated during scanning, please immediately alert the PET staff member. It could be dangerous to vomit while in the scanner due to a risk of aspiration. After the end of the last scan, we will remove the catheter and you will be evaluated.

Medication study: The medication part of the study has two parts, Step 1 and Step 2. In Step 1, you will be randomly assigned to one of two different treatment options (like by flipping a coin). If you are assigned to the first option, you will receive the starting dose of carbidopa/levodopa (37.5mg/150mg). This dose will be increased each week to the final dose of carbidopa/levodopa 112.5mg/450mg. Taking the medication in this study will involve taking three pills per day, one in the morning, one at lunchtime, and one at night. If you are assigned to the second option, then you will receive pill placebo.

The placebo looks like the other treatments/pills, but does not contain any medicine (it is sometimes called a "sugar pill"). Neither you nor the researchers will know if you are getting the placebo, but they can find out in an emergency. You will receive free medication or placebo for the duration of the study.

Step 1 lasts three weeks, and at the end you will have the number of pills you are taken gradually reduced and then stopped over the course of one week. This is called a "washout period." After the washout period, you will begin Step 2, which has the same procedures as Step 1, except you will be assigned to the opposite pills to the ones you took in Step 1. If you were assigned to take carbidopa/levodopa in Step 1, then you will take pill placebo in Step 2. If you were assigned to take pill placebo in Step 1, then you will take carbidopa/levodopa in Step 2. The timing of the pill doses will be the same as Step 1, and the study will last three weeks followed by a one-week washout period.

In either Step, if you have trouble tolerating the study medication, we will lower your dose to one you previously tolerated. If you cannot tolerate any dose of the medication, your participation in the study will be discontinued. If the study doctor feels your condition worsens significantly, the current treatment will be stopped, and you will be offered different treatments for your slowed thinking and walking.

The study doctor may stop your participation in the study at any time without your consent if you do not comply with the study procedures or for other reasons. You will return each week to speak with the study doctor and have some tests. These appointments will last about 45 minutes. The research study will end after 8 weeks—three weeks for Step 1, a one-week washout period, three weeks for Step 2, and a second washout period. At the end of Step 1, you will have your second MRI scan and complete the same tests that you performed at the beginning of the study. At the end of Step 2, you will again complete the tests you performed at the beginning of the study, but you will not have another MRI.

Following the study, you will still receive 3 months of free doctor visits in the clinic. The medication used in this study is available from pharmacies, so it is an option to continue taking the medication following the study if you feel you have benefited from it. You will receive at least 1 month of free medication if you wish. Every effort will be made to provide free medication for 3 months total, but we cannot guarantee the availability of free medication beyond 1 month. If you do not wish to continue the medication after the study, the dose will be gradually decreased over 3 days before stopping it.

RISKS

Carbidopa/levodopa risk: The main risk to your participation in this study is that carbidopa/levodopa is an experimental treatment, and it is not known yet whether it will

be effective in treating low dopamine levels or symptoms of depression. The most common side effects reported for carbidopa/levodopa are nausea, headache, and vivid dreams. You should be careful about drinking alcohol, since it may have a greater effect on you in combination with medication.

In addition, you will be assigned to receive placebo for three weeks during the study. Therefore, you will not receive Food and Drug Administration (FDA) approved medication for your condition until after the 8 week study is over. Therefore, there will be a delay of 8 weeks (the time you are doing the study) before you will receive a treatment that is known to be effective for the treatment of depression (e.g., antidepressant medication). There is a chance your depression may worsen during the time you are receiving carbidopa/levodopa or placebo in this study.

It is not fully known how the normal slowing down that occurs during aging relates to the type of slowing that occurs in patients with Parkinson's disease. Some individuals who experience slowing with age may be at increased risk for Parkinson's disease. L-DOPA is a treatment for Parkinson's disease, but in patients with the illness it can be associated with increased risk for developing abnormal movements over time. You do not have Parkinson's disease right now. However, if you were to go on to develop Parkinson's disease later on and need treatment with L-DOPA, there is a small possibility that your participation in this study could increase your risk of developing abnormal movements. It is difficult to know the exact chances of your needing L-DOPA in the future or your risk of abnormal movements, but we would estimate the chances of this study causing you problems in the future as less than 1%.

PET risks: This research study involves exposure to radiation. This radiation exposure is not required for your medical care and is for research purposes only. The radiation exposure is necessary to obtain the research information desired. The total amount of radiation that you may receive in this study is approximately 4.71 mSv. The additional cancer risk from this research study is estimated to be up to 0.02% (1/4405 chance). At these low levels, scientists are uncertain as to the actual risk and there may be no risk at all.

Please tell your study doctor or other study personnel if you have taken part in other research studies at NYSPI or other places/hospitals that used radiation. This way we can make sure that you will not receive too much radiation. You should consider x-rays

taken in radiology departments, cardiac catheterization, and fluoroscopy as well as nuclear medicine scans in which radioactive materials were injected into your body. Before you take part in any future studies that use radiation, you should also tell those study doctors about your participation in this study.

The risk estimate is based on the subjects in the study population who are most sensitive to radiation exposure.

MRI risks: The long-term effects of being placed in a magnet of this strength (3 Tesla) are unknown, but you should be aware that there have been no reports of any ill long=term effects caused by magnets of the same or even higher strength, either here or elsewhere. Also, although there are no known risks associated with pregnancy, we will not scan someone who is pregnant. Therefore, you should understand that if you are a woman in your childbearing years, pregnancy testing will be used to assure that you are not pregnant.

Some people have reported sensations during MRI scans, such as "tingling" or "twitching" (or, very rarely, a painful sensation), which are caused by changes in the magnetic field that can stimulate nerves in your body. If you experience sensations and feel that these are uncomfortable, you can tell the MRI technologist, and he or she will stop the scan immediately. Occasionally, some people experience nervousness or claustrophobic feelings due to the scanner's small space. If you encounter any discomfort, you can tell the MR technologist, and he or she will stop the scan immediately. Despite these experiences, no one has ever had sensations from the scanning that did not stop as soon as the scanning stopped.

Except for pacemakers and some types of metallic implants, we know of no health hazard from the MRI scan. The MRI scan is not painful, but lying still on the scanning table may be slightly uncomfortable.

Other risks: When your blood is drawn, there is a small risk you may be left with a bruise that will resolve within a few days. Results of blood tests taken for research purposes will remain confidential.

BENEFITS

You may not benefit from this study, and no benefit is in any way guaranteed as a result of your participation.

RESULTS OF YOUR MRI

While MRI scans are sometimes done for clinical purposes, the kind of MRI scans you will have as part of this study is for research purposes only. This means that the scans are not designed to provide clinical information that might be helpful to you or your

doctor and they may not show problems that would normally be found in an MRI ordered to evaluate a specific medical problem. It is likely that the MRI scan will not have the quality of those done for clinical purposes.

However, within a month of the MRI scans, the scans will be read by a neuroradiologist for evidence of any obvious irregularities requiring your follow-up. You, or a physician whom you may designate, will be informed only when significant abnormalities are detected. If you wish, we can also inform you if there were no obvious findings. Given the nature of the scans, the absence of a finding does not mean that one is not present.

CONFIDENTIALITY

Your records will be stored in a locked file. Records will be available to research staff, and to Federal, State and Institutional regulatory personnel (who may review records as part of routine audits). There are legal advocacy organizations that have the authority under State Law to access otherwise confidential records, though they cannot be redisclosed without your consent. All records will be kept confidential to the extent permitted by law. Your name and other personal identifying information will be stored in an electronically secure database at New York State Psychiatric Institute. Electronically stored data will be accessible only by password known to the study investigators and research assistants.

Your MRI will be interpreted and the results will be shared with you or a physician who you may designate. Your MRI report will be maintained as part of the clinical database at the New York State Psychiatric Institute or the Columbia University Medical Center along with your name and will be accessible to clinicians at the Medical Center. Your psychiatric diagnosis will not be a part of the report.

The data obtained for this study and biospecimens could be used for future research studies or may be distributed to another investigator for future research studies, however all information including biospecimens will be de-identified (this means information cannot be linked back to you) and will not include whole genome sequencing (i.e., sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen). Biospecimens will not be used for commercial profit. Clinically relevant research results, including individual research results may be available to you at you request but such request will be granted under the discretion of the study doctor. You may be contacted in the future by the study team for future studies.

Data from this study will be submitted to the National Institute of Mental Health Data Archive (NDA). NDA is a data repository run by the National Institute of Mental Health (NIMH) that allows researchers studying mental illness to collect and share de-

identified information with each other. A data repository is a large database where information from many studies is stored and managed. De-identified information means that all personal information about research participants such as name, address, and phone number is removed and replaced with a code number. With an easier way to share, researchers hope to learn new and important things about mental illnesses more quickly than before.

During and after the study, the researchers will send de-identified information about your health and behavior to NDA. Other researchers nationwide can then file an application with the NIMH to obtain access to your de-identified study data for research purposes. Experts at the NIMH who know how to protect health and science information will look at every request carefully to minimize risks to your privacy.

You may not benefit directly from allowing your information to be shared with NDA. The information provided to NDA may help researchers around the world treat future children and adults with mental illnesses so that they have better outcomes. NIMH will also report to Congress and on its web site about the different studies that researchers are conducting using NDA data. However, you will not be contacted directly about the data you contributed to NDA.

You may decide now or later that you do not want to share your information using NDA. If so, contact the researchers who conducted this study, and they will tell NDA, which can stop sharing the research information. However, NDA cannot take back information that was shared before you changed your mind. If you would like more information about NDA, this is available on-line at http://data-archive.nimh.gov.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. This means that the researchers cannot release or use information, documents, or samples that may identify you in any action or suit unless you say it is okay. They also cannot provide them as evidence unless you have agreed. This protection includes federal, state, or local civil, criminal, administrative, legislative, or other proceedings. An example would be a court subpoena.

There are some important things that you need to know. The Certificate DOES NOT stop reporting that federal, state or local laws require. Some examples are laws that require reporting of child or elder abuse, some communicable diseases, and threats to harm yourself or others. The Certificate CANNOT BE USED to stop a sponsoring United States federal or state government agency from checking records or evaluating programs. The Certificate DOES NOT stop disclosures required by the federal Food and Drug Administration (FDA). The Certificate also

DOES NOT prevent your information from being used for other research if allowed by federal regulations.

Researchers may release information about you when you say it is okay. For example, you may give them permission to release information to insurers, medical providers or any other persons not connected with the research. The Certificate of Confidentiality does not stop you from willingly releasing information about your involvement in this research. It also does not prevent you from having access to your own information

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

COMPENSATION AND ECONOMIC CONSIDERATIONS

You will not be charged for any procedures that are a part of this study, including the study medication.

To compensate you for the time required for each study visit, we offer $35 for your initial screening visit and $50 for each of your three main assessment sessions (beginning, after Step 1, after Step 2). This money will be paid by cash at the conclusion of each of these visits.

To compensate you for the time required for the brain scans, we offer $100 for each MRI scan and $200 for each PET scan ($400 total if you attend all scans). This money will be paid in 1 lump sum payment at the end of the study. Payments typically require 1-3 weeks to process and will be mailed in the form of a check.

Thus, the maximum compensation in this study will be $585 for participants attending all study visits and doing all neuroimaging procedures.

In Case of Injury

Federal regulations require that we inform participants about our institution's policy with regard to compensation and payment for treatment of research-related injuries.

In case of injury, New York State Psychiatric Institute will provide short term emergency medical treatment, which has been determined to be necessary by New York State Psychiatric Institute's doctors, and which is within the capability of New York State Psychiatric Institute to provide. In addition, we will provide assistance in arranging follow up care in such instances.

New York State Psychiatric Institute and Research Foundation for Mental Hygiene do not provide compensation or payment for treatment of research related injuries. However, you should be aware that you do not give up your legal right to seek such compensation through the court by participating in this research.

Please be aware that:

1. The Research Foundation for Mental Hygiene, The New York State Psychiatric Institute, Columbia University and New York Presbyterian Hospital will furnish that emergency medical care determined to be necessary by the medical staff of this hospital
2. You will be responsible for the cost of such care, either personally or through your medical insurance or other form of medical coverage.
3. No monetary compensation for wages lost as a result of injury will be paid to you by the New York State Psychiatric Institute, Columbia University or by New York Presbyterian Hospital.
4. By signing this consent form, you are not waiving any of your legal rights to seek compensation through the courts.

QUESTIONS

If you have further questions about the research procedures, or about your response to the procedures research staff members are available to answer them to the best of their ability. You can reach Dr. Bret Rutherford at 646-774-8660 during general business hours. In an emergency, you may reach the on call doctor at 917-786-6940, 24 hours per day. If you have general questions, you may contact the research coordinator at 646-774-8664. We will notify you of any significant new findings that may relate to your willingness to continue to participate.

If you have any questions about your rights as a research participant, want to provide feedback, or have a complaint, you may call the NYSPI Institutional Review Board (IRB). (An IRB is a committee that protects the rights of human subjects in research studies). You may call the IRB Main Office at (646) 774-7155 during regular office hours.

You will be given a copy of this consent form to keep.

DOCUMENTATION OF CONSENT

I have read the above and voluntarily agree to participate in the research study described above. To the best of my knowledge, I am not pregnant. I have been informed that my participation is voluntary, and that I can withdraw from the study at any time without penalty or loss of benefits to which I am otherwise entitled.

Print name: _____

Signed: _____

Date: _____

I have discussed the proposed research with this participant including the risks, benefits, and alternatives to participation (including the alternative of not participating in the research). The participant has had an opportunity to ask questions and in my opinion is capable of freely consenting to participate in this research.

Print name: _____
Person Designated to Obtain Consent

Signed: _____

Date: _____