SUMMARY COVER SHEET
Serotonin 1A Receptor Binding in Bipolar Depression Determined by PET Imaging: Prediction of Clinical Response

Principal Investigator: Dr. Martin Lan (646-774-7610)

Overview: This outline is meant to be a guide for you to use while considering the study and reading the consent form. The consent form contains detailed information about the study and about the risks, which you will need to consider before making your decision. You are being asked to participate in research that looks at chemicals in the brain that are thought to be involved with bipolar disorder by having scans called MRI and PET. After the scans, for 6 weeks you will also receive medication treatment for depression that uses a selective serotonin reuptake inhibitor, either fluoxetine (Prozac) or citalopram (Celexa) added to mood stabilizer(s) (valproate, lithium, or lamotrigine). The goal is to determine whether "pictures" from PET scans can predict how effective the treatment will be.

Participation is Voluntary: As with all research, this is a voluntary study, and you do not have to participate if you do not want to. Also, you may stop participating at any time.

Alternatives: The alternative to participating in this study is to receive treatment with a physician outside of this study. Other medications used for depression in bipolar disorder include quetiapine (Seroquel), fluoxetine and olanzapine combination (Symbyax) or lurasidone (Latuda). You can also refuse treatment altogether.

Procedures

- Your medications will be changed so that you are on only mood stabilizers (either valproate, lithium, or lamotrigine). If you are not on any of these medications, valproate will be started and adjusted so that the levels in the blood are in the appropriate range; this will require drawing your blood several times over the course of about a week and treatment with this dose for three weeks.
- An MRI scan will use radiowaves and a large magnet to take a picture of the brain
- A PET scan will take a picture in the brain. It uses a small dose of a radioactive substance called [^{11}C]CUMI-101 that is given through a catheter (IV) placed with a needle into a vein. [^{11}C]CUMI-101 is an investigational drug approved by the FDA only for research use.
- After the scans, fluoxetine or citalopram will be added to the mood stabilizer(s) for six weeks of combination treatment. You will meet with a clinician regularly, and your mood and anxiety will be assessed during this time.
- You can receive free office visits with a psychiatrist for six months from starting the study

Risks

- Delay in starting antidepressant: During the delay before the study antidepressant is started, and when your current medications may be changed or stopped, there is a chance that your depression will worsen, including having new or more intense suicidal thoughts.
- MRI Scan: Metal implants or medicinal patches can dangerously interact with the machine.
- PET Scan: Exposes you to radiation but within limits set by FDA, a government regulatory agency. Intravenous (IV) line is needed and can cause discomfort, bruising or rarely bleeding or infection.
- Valproate side effects: You may experience headaches, weakness, nausea, vomiting, diarrhea, dizziness, weight gain, double or blurry vision. Rarely, liver or pancreas damage.
- Fluoxetine or citalopram side effects: You may experience nausea, sexual dysfunction, weight loss or gain, nervousness and/or difficulty sleeping, diarrhea or dry mouth. Fluoxetine or citalopram may not help your depression or may cause manic symptoms.

Benefits: This research study will not be of benefit to you.

Questions: Please contact the study doctors, Dr. Martin Lan at (646)774-7610 with any questions. You can also contact the physician on call at (646)774-7650 with any questions.

Columbia-Presbyterian Medical Center
New York State Psychiatric Institute

Informed Consent for Participation in Research

Serotonin 1A Receptor Binding in Bipolar Depression Determined by PET Imaging: Prediction of Clinical Response

Dr. Martin Lan (646 774 7610)

Patient Name: _____

Purpose and Overview

Fluoxetine (Prozac) and citalopram (Celexa) are antidepressant medications that can treat depression in people with bipolar disorder. They work, in part, by increasing a chemical in the brain called serotonin. Brain scans using positron emission tomography (PET) take "pictures" that give information on the activity of serotonin. These "pictures" seem to predict how well antidepressant medications like fluoxetine (Prozac) or citalopram (Celexa) work in patients with depression. We are trying to find out whether these "pictures" can predict how well the antidepressants work in bipolar disorder. You are being asked to participate in this study because you are depressed at this time, you have a diagnosis of bipolar disorder, you are between the ages of 18 and 60 years old, and you have agreed to be a part of a different study (IRB #4815). If you agree to participate in this study, and you are not currently taking a mood stabilizer (either lamotrigine, lithium, or valproate), you will first start valproate (Depakote), to prevent mania. After the mood stabilizer dose(s) is adjusted properly, and there is a period of time of treatment with just that medication, about three weeks altogether, you will receive imaging scans of the brain. After the scans, you will start either fluoxetine (Prozac) or citalopram (Celexa) to treat your depression. This antidepressant treatment will be for six weeks. There will be regular monitoring and follow-up of your mood, and especially depression, to determine the antidepressant effect. You can receive up to six months of free office visits after starting the research procedures with a psychiatrist at New York State Psychiatric institute. You will be responsible for the costs of your medications if they are not started as part of the research procedures. This study is funded by a grant from the National Institute of Mental Health.

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. If you experience side effects of the medications that you cannot tolerate, you can stop participation in the study and will be able to receive other treatments.

You will be notified of any significant findings that may relate to your willingness to participate.

Alternative Treatments/Alternatives to Participation

The alternative to participating in this study is to receive psychiatric treatment elsewhere right away, without undergoing the procedures of this research protocol. The scans and other procedures will not help guide your treatment and will not provide information that will be used by the doctors caring for you. The tests are designed to learn more about bipolar disorder, not you, your diagnosis or which medications will help you.

The FDA approved approaches for treating depression in bipolar disorder include quetiapine (Seroquel), fluoxetine in combination with olanzapine (Symbyax) or lurasidone (Latuda). A variety of other medications and combinations of medications may be useful for bipolar depression. If your manic symptoms have never been severe in the past, and therefore you have a diagnosis of bipolar 2 disorder, using valproate in addition to either fluoxetine or citalopram may not be needed. Valproate is used here for bipolar 2 patients in part for scientific reasons, so that all people in the study receive the same medication treatment.

Procedures

Your psychiatric medications will first be changed to either one or a combination of mood stabilizers (valproate, lithium or lamotrigine). If you are not on any of these medications, valproate (Depakote) will be started and the dose will be changed so that the levels of the medication in the blood are within the correct range. This will require blood tests to measure the level of the medication every few days. Your other medications will be decreased and stopped gradually, a process that usually takes about a week. You will be treated with the correct dose of the mood stabilizer alone for about three weeks before the imaging. If you are still depressed at that time you will have imaging performed. It is important that you contact your study physician right away if your depression worsens, if you develop new or more intense suicidal thoughts, or if you have significant side effects.

There will be two days for brain imaging, one for an MRI and one for a PET scan. The MRI will happen at the New York State Psychiatric Institute (NYSPI). The MRI takes about 60 minutes. If the NYSPI MRI is not available, the MRI will be performed at another MRI facility at Columbia University Medical Center. In that case, the MRI will be only 30 minutes. The PET scan will take place at the Columbia Kreitchman PET Center (722 West 168th Street, New York, NY). A research assistant will meet you before the scans and will stay with you during the entire time you are there. The PET scan will take about 2 hours but may be shorter. In total, you will spend up to 3 hours in the PET suite to prepare for the scan and have the scan done.

The MRI (which stands for magnetic resonance imaging) takes a picture of the brain using a large magnet and radiowaves. It does not use X-rays. Before starting the test, you will be asked to take off any medicinal patches, metal or magnetized objects (like keys or credit cards) and change into a hospital gown. You will be asked to lie on a table that slides into a camera that is about 25 inches wide and 6 feet long. You will be asked to stay still for about 60 minutes. You will hear some loud banging noises. You may also feel tingling in your fingers or toes that can rarely be painful, sharp sensations. Within a month of the MRI, the scan will be read by a neuroradiologist for evidence of any obvious irregularities requiring follow-up. You or a physician of your preference will be informed if any significant abnormalities are detected. If you wish, we can also inform you if there are no obvious findings. Because of the research design of the scan, the lack of a finding does not mean that one is definitely not there.

On the day of the PET scan, you will be able to eat and drink as usual. Any women that have the potential of being pregnant will have a urine pregnancy test on the day of the PET scan to make sure that pregnancy has not occurred since the first screening visit. An IV catheter (intravenous) will be put into a vein in each arm using a needle. One IV will be used to inject the

"tagged" tracer and the other will be used to take two blood samples as part of the scan. A "tagged" tracer is a chemical that has radioactivity that allows the PET scanner to take pictures of where in the brain the chemical goes. A total of 2 blood samples (half of a teaspoon) will be taken during the PET scan.

You will be helped onto the scanner table and a plastic head support will be placed that helps to keep your head from moving during the scan. The scanner table will slide into the large doughnut shaped scanner machine. At the beginning of the scan, you will be injected with a tagged chemical named [^{11}C]-CUMI-101 and you will rest quietly on a table for two hours or less. To help you feel as comfortable as possible while lying still in the PET scanner or to help with any anxieties, our staff will be available the whole time during the scan to provide support. After the PET scan is done, we will take out the IV catheter and the head support. You will be asked to drink some extra fluids and urinate normally to decrease any exposure to radioactivity. You will be checked briefly and then you will be able to go home. You will have a clinical check-in with your treating doctor within 48 hours of the PET scan. Within two weeks of the PET scan, you will have another urine pregnancy test performed to be sure that no pregnancy was present during the PET scan.

After the PET and MRI scans are completed, you will start the antidepressant fluoxetine (Prozac) or citalopram (Celexa) at 20 mg per day. This dose will be increased to 40 mg per day after three weeks if you continue to be depressed. If you develop some side effects from the fluoxetine (Prozac) or citalopram (Celexa) at the 40 mg dose, the dose can be lowered back to 20 mg per day.

The levels of either valproate or lithium will also be measured at weeks 1, 2 and 4 while taking the fluoxetine (Prozac) or citalopram (Celexa) to make sure it is at the proper level to prevent mania from occurring. The level of fluoxetine (Prozac) or citalopram (Celexa) will also be measured at week 4. In total, there will be approximately 9 teaspoons of blood drawn for the laboratory tests in the study.

The treatment with either fluoxetine (Prozac) or citalopram (Celexa) will continue for a total of six weeks. You will meet each week with a study doctor during this treatment. Your mood and anxiety will be monitored with questionnaires every two weeks during the study. These will take about 90 minutes to complete. Valproate and either fluoxetine (Prozac) or citalopram (Celexa) will both be provided to you free of charge.

During the treatment, you will be able to take medications for sleep or anxiety, although these medications will not be paid for by our team.

After the six-week clinical trial, you will be offered up to 6 months of treatment with a psychiatrist, primarily involving medications, at the New York State Psychiatric Institute. Your doctor appointments will be free of charge during this time, but you will be responsible for the cost of your medications. This is different from the period of time during the research phase when your medications are paid for by the research team. If you do participate in this six months of treatment, and you still need treatment when this period ends, you will be given referrals for continuing treatment elsewhere.

Risks and Inconveniences

Delay to starting antidepressant: If you are not on one of the mood stabilizer medications, some time will be needed to adjust the dose of valproate until it is within the dose range that has been found to be effective at preventing manic symptoms. Medications other than the mood stabilizer

medications will need to be tapered off. These changes usually take about 1 week. There will then be about three weeks of treatment with just the mood stabilizer(s) before the scanning. Valproate does not have a significant antidepressant effect, so there may be a delay before your depression improves. If you are currently taking psychiatric medication, there is a chance that it is helping your mood even though you are depressed. Therefore, there is a risk that your condition will worsen when your medication is changed to just valproate, with more depressive symptoms, new or worse suicidal thoughts or manic symptoms.

MRI Scan: Some people have reported feelings such as "tingling" or "twitching" (or very rarely a painful sensation) that are caused by the large magnet used to take pictures of the brain affecting the nerves in your body. If you do have these sensations, and feel that they are uncomfortable, you can tell the MR technologist and the scan will be stopped right away. Some people have felt nervous or claustrophobic because of the scanner's small space. If you have any discomfort, you can also tell the MR technologist and he or she will stop the scan right away. From our experience, no one has had sensations from the scanning that did not stop as soon as the scan stopped. We know of no health risks from the MRI scan besides problems with pacemakers or other types of metal in the body. There is also a risk of burns from medicinal patches during the MRI, so you will be asked to take off any patches before the scan starts. Lying still in an enclosed space can also be uncomfortable for some people. The MRI scanner used here is considered to be experimental, but the FDA has determined that is a non-significant risk device that poses no more than minimal risk to humans. An MRI should not be done during pregnancy, however, because of possible risk to the fetus.

Radiation Exposure from PET scan: The PET scan involves exposure to imaging radiation with a substance or imaging agent called [^{11}C]-CUMI-101. It is a research drug that is approved by the Food and Drug Administration for use only in research studies. [^{11}C]-CUMI-101 will be given intravenously (IV) during the PET scan at very low doses. It has been tested in animals at 100 times the dose used in people and has been used in about 60 research subjects in our group without significant symptoms occurring. However, it is still possible that mild or even serious unknown side effects may occur. We will watch you closely during the study in the unlikely event that you may have an adverse reaction. If this does occur, we will treat you appropriately. The procedures involving radiation in this research study will expose you to a very small amount (3.16 mSv) of radiation in addition to the amount that you might receive from your normal medical care. There may be an increase in the chance of your developing cancer many years after this study. The additional risk from this research study is less than 0.0634%, or 1:1577. At this very low level, scientists are uncertain as to the actual risk from research and there may be no risk at all. Health hazards from such low amounts of radiation have never been shown. Radiation risk is cumulative over a lifetime, though, and any additional exposure should be carefully considered. Everyone is exposed to natural background radiation from sources such as radon, food, water and the sun's rays. To compare the amount of radiation exposure in this research study, the amount of radiation you get in one PET scan will be less than the amount you would receive in one year of natural background sources. It is not possible to tell whether the small additional radiation that you get through participating in this study will increase your long-term risk for diseases such as cancer.

To make sure that you do not receive more radiation than the maximum allowed for research purposes, you will be asked about any past radiation exposures including past CT scans or x-rays. In addition, we will check the records from our group to make sure you have not been a part of an imaging study using radiation here in the past year. Because we are only able to check our divisional database, you must inform the research staff of any other known radiation exposures (PET scans, CT scans, x-rays). Also, you should not take part in any other research

studies that use ionizing radiation for at least 12 months after you complete this study, unless it is approved by the appropriate regulatory authorities.

Side effects of Fluoxetine and Citalopram: You may experience side effects from fluoxetine (Prozac) or citalopram (Celexa). Side effects may include nausea, sexual dysfunction (problems with sexual desire, orgasm or ejaculation), weight loss or weight gain, nervousness, inability to sleep well, diarrhea or dry mouth. There is a small risk that either fluoxetine or citalopram will induce hypomania, mania or a mixed state, but it is thought that taking a mood stabilizer will decrease this risk. There is also some risk that fluoxetine (Prozac) or citalopram (Celexa) will not be effective in treating your depression and there is some risk that it may make things worse.

The FDA has warned that antidepressant medications may increase suicidal thoughts or actions in some children, teenagers, and young adults when the medicine is first started. You should pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings, especially when either fluoxetine (Prozac) or citalopram (Celexa) is first started or when the dose is changed. Call your doctor right away to report any new or sudden changes in mood, behavior, thoughts or feelings. Keep all scheduled follow-up appointment with your doctor. Call your doctor between visits if you have any concerns about symptoms. Do not stop taking your antidepressant medicines without consulting your doctor.

Side effects of valproate: Side effects may include headache, weakness, nausea, vomiting, diarrhea, sleepiness, tremor, dizziness, weight gain, double or blurred vision or flu-like symptoms. Please tell your doctor if any of these do arise. Treatment with valproate also has risk for rare but more serious reactions of liver or pancreas damage, low blood cells called platelets and high levels of a chemical called ammonia in the blood that can cause medical problems, and a rare allergy-type reaction that affects multiple organs. Valproate is also known to cause birth defects (teratogenic) and is not safe in pregnancy.

Please tell your doctor if any of these side effects occur. Do not stop taking the medications without consulting your doctor first.

Clinical visits and interviews: Psychiatric interviews can be upsetting at times, but some people find talking to their physician or psychologist to be helpful. During the research procedures, you may meet with your clinician more regularly and for longer periods of time than you would in typical treatment. The rating scales that assess your symptoms will take about 90 minutes to complete at each visit. This schedule has the potential to cause inconvenience. If you have no response in your depression by week 4 of the study, your clinician will reassess your clinical treatment course at that time.

Blood drawing and intravenous catheter: As a necessary part of treatment with valproate, venipuncture (drawing a blood sample) for routine blood laboratory tests is needed. These carry minimal risk of physical discomfort, bleeding or bruising. Putting in intravenous catheters can be briefly painful. Sometimes there is a bruise at the site after removal. A risk of catheter placement and blood drawing is feeling dizzy or light-headed. While rare, it is possible that you could pass out. Please let us know if you have experienced any reactions like this in the past while having blood drawn or having a catheter placed.

Pregnancy: Treatment with valproate is associated with birth defects and is therefore not safe in pregnancy. Studies involving radiation should also not be conducted during pregnancy due to possible risk to the fetus. To participate in this study, women of child-bearing potential must agree to use an effective form of birth control such as: not having sexual intercourse, using

either birth control pills or another form of medication for birth control (Depo-Provera or Norplant), male condoms, an intra-uterine device (an implanted form of birth control), male sterilization or female sterilization. If female, you will also be required to have a blood pregnancy test at the time of medical screening, and urine pregnancy tests on the day of the PET and MRI scans. Within two weeks of the PET scan, you will have another urine pregnancy test. You will not be charged for the pregnancy test**s**. It is important to understand that even if your pregnancy test result is negative, you could still be pregnant because a urinepregnancy test cannot detect very early pregnancies (that is, within the first few days after conception), This study may convey risk to men because it is unknown if this radiation is harmful to sperm.

Benefits

This study has the potential for a benefit to the general public, as it may allow for better treatment of people who suffer from bipolar disorder in the future. The medications used in this study are standard medications for depression in bipolar disorder and may therefore help your depression. Because the MRI is designed for research purposes, you are not expected to benefit from the scan. You are not expected to benefit from the PET scan.

Costs and Compensation

You will not need to pay any costs associated with this research. You will receive monetary compensation of up to $400 for expenses in undergoing all the scans and interviews. If you do not complete the study, you will be given a partial payment that will relate to the amount that you participated in the study ($250 for PET scan session, $150 for the MRI). Payment is by check and arrives via mail about 4-6 weeks after completing the last scan. You will need to provide a W-9 form with your social security number in order for us to request the check that will be sent to you.

You will also be offered medication-based treatment for the six months from the beginning of the study. Medications will be provided by the research team during the research procedures, but you will be responsible for the costs of the medications after the research procedures are over.

Confidentiality

Your records will be kept in locked files and access will be allowed only to members of the research team or institutional personnel as part of a routine audit. Records may also be reviewed by state or federal regulatory agencies and their personnel (who may review records as part of routine audits). Research records, like other medical and clinical records, will be kept confidential to the extent permitted by law. There are legal advocacy organizations that have the authority under state law to access otherwise confidential subject records, though they cannot disclose this information without your consent.

Once you are enrolled in the project, your records are given a code number which is used for subsequent data and/or lab forms. This de-identified data may be shared with other researchers within our division only for research purposes. The code list and names of participants as well as all other data are kept in locked files with access limited to those directly responsible for maintenance of these files by the research team. Your name and other personal identifying information will be stored in an electronically secure database at New York State Psychiatric Institute protected by a “firewall” requiring a password.

Your MRI report will be maintained as part of the clinical database at the New York State Psychiatric Institute or Columbia’s Neurological Institute along with your name. Your PET

report will be maintained as part of the clinical database at the Columbia Kreitchman PET Center along with your name. These reports will only be accessible by clinicians and your psychiatric diagnosis will not be part of the reports.

In Case of Injury

Federal regulations require that research participants be informed about our institution's policies with regard to the provision of treatment and compensation for research related injuries. If you believe that you have sustained injury as a result of participating in a research study, you may contact the Principal Investigator, Dr. Martin Lan at 646-774-7610 so that you can review the matter and identify the medical resources which may be available to you. Please be aware that:

- 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
- You will be responsible for the cost of such care, either personally or through your medical insurance or other form of medical coverage.
- 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.
- By signing this consent form, you are not waiving any of your legal rights to seek compensation through the courts.

Questions

The physician who has reviewed this consent form with you will answer to the best of his or her ability any questions that you may have now or in the future about the research procedures, or about your response to the procedures. You can also contact Dr. Martin Lan (646) 774-7610, the principal investigator of the study, with any questions.

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 participants 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 signed consent form to keep.

Documentation of Consent

I voluntarily agree to participate in the research study described above.

Participant print name: _____

Participant signature: _____

Date: _____

MRI Results

Initial “Yes” or “No” below:

_____ YES, tell me my MRI results even if there are no significant abnormalities

_____ NO, do not inform me of my MRI results if there are no significant abnormalities

Physician Documentation of Consent

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.

Researcher Print Name: _____

Researcher Signature: _____

Date: _____