Official Title: Prediction of Clinical Response to SSRI Treatment in Bipolar Disorder using Serotonin 1A Receptor PET Imaging

Research Protocol

Last approved by Institutional Review Board: 11/27/2020

Lay Summary of Proposed Research

Bipolar disorder is associated with alterations of chemicals in the brain, including one named serotonin. Treatment of depression in bipolar disorder can be accomplished by increasing serotonin function by a type of medication named a selective serotonin reuptake inhibitor (SSRI). Serotonin signals in the brain occur through receptors in a way that is similar to a lock and key, where serotonin is a key and the receptor is a lock. One important receptor is the serotonin 1A (5-HT_{1A}) receptor. This receptor has been found to be abnormal in bipolar disorder during periods of depression, as measured by a type of brain imaging called positron emission tomography (PET).

The amount of brain 5-HT_{1A} receptor measured by imaging has also been associated with how well depressed patients with major depressive disorder respond to an SSRI medication. This project will measure the 5-HT_{1A} receptors in bipolar depressed individuals using PET with the radiotracer [^{11}C]-CUMI-101 and will evaluate the ability of this brain imaging signal to predict how patients respond to SSRI treatment when added to a mood stabilizer.

Background, Significance and Rationale

Bipolar disorder (BD) is a common psychiatric condition characterized by episodes of mania and depression. It is one of ten leading causes of disability worldwide and carries a significantly elevated risk for suicide. The pathophysiology of the disorder remains largely unknown and there are no imaging or diagnostic tests for the disorder. BD depression is the mood state most associated with disability and suicide, and patients typically spend more time in this phase. BD depression remains difficult to treat, with only three medications approved for its treatment. Moreover, treatment can only be given in a trial and error manner. For these reasons, there is a need for more knowledge of the pathophysiology of BD depression in order to design and select better treatment options. Several randomized, placebo-controlled clinical trials have demonstrated the efficacy of fluoxetine, a selective serotonin reuptake inhibitor (SSRI), when combined with an anti-manic agent, for BD depression. Clinical trials of other SSRI's have not demonstrated a class effect of the medications, however, despite their common use and clinical guidelines recommending their use. Treatment with SSRI's also carries risks. A test to determine which patient with BD depression will respond to SSRI treatment would therefore be clinically useful. Positron emission tomography (PET) imaging allows for the quantitation of serotonin receptor levels and affinity in the brain. The serotonin 1A (5-HT1A) autoreceptor regulates serotonin neuron firing and release, and thereby influences the function of brain serotonin signaling. Our group developed a novel PET radiotracer for the 5-HT1A receptor, [^{11}C] CUMI-101. This radiotracer has a straightforward and reliable synthesis process and is a partial agonist and therefore represents a technical improvement over [^{11}C]WAY-100635 that has been previously used to measure binding to the receptor. [^{11}C] CUMI-101 should be able to detect both upregulation and an increase in the proportion of high affinity agonist binding in the

autoreceptor. We found that PET imaging of the 5- HT1A receptor binding using [^{11}C] WAY-100635 in BD depression found that high autoreceptor binding was associated with clinical remission from the disorder after patients received 3 months of naturalistic treatment. PET imaging with this radiotracer also found high autoreceptor binding to be associated with clinical response to antidepressant treatment in subjects with major depressive disorder. This protocol aims to evaluate whether PET scanning with [^{11}C] CUMI-101 of autoreceptors in patients can predict clinical outcome after a protocol-driven six week treatment.

Specific Aims and Hypotheses

This protocol aims to evaluate whether PET scanning with [^{11}C] CUMI-101 in bipolar depressed patients can predict clinical outcome after a protocol-driven six week treatment with an SSRI medication when added to a mood stabilizer medication. We hypothesize that higher brainstem raphe binding of [^{11}C] CUMI-101 in the brain (BP) will predict a better clinical response to treatment. This result would be consistent with the finding that higher BP within the brainstem raphe of a similar radiotracer [^{11}C] WAY-100635 predicted clinical response to selective serotonin reuptake inhibitors in subjects with major depressive disorder. Our finding may be the first step to developing an imaging test to predict clinical response to SSRI treatment in BD depression.

Specify subject population

Patients with bipolar disorder, currently in a major depressive episode
Number of completers required to accomplish study aims
25
Projected number of subjects who will be enrolled to obtain required number of completers 40-45
Age range of subject population
18-60

Gender, Racial and Ethnic Breakdown

The target composition will be 75% White or Caucasian, 20% Black or African American, 5% Asian. Approximately 15% will be Hispanic and 85% will be non-Hispanic. 60% will be female and 40% will be male.

Describe settings where recruitment will occur

Patients will be recruited through referrals from treating outpatient psychiatrists, or from clinics, inpatient units and emergency department (ED) at Columbia University. Advertisements will be placed through the Columbia University website, on advertising sites such as Craig's List, social medial websites and in print newspapers such as AM New York. The study will be listed on Columbia's research study search engine, RecruitMe, and a website that describes the study will be created. Fliers will be posted around Columbia University Medical Center campus and the undergraduate campus at Morningside Heights. Outreach to mental health clinics, primary care clinics, support groups, community groups and facilities will be conducted in-person to best reflect the composition of the population in our city. Letters and fliers will be sent via mail or

email to clinic directors of outpatient mental health clinics describing the study and asking for referrals. Messages will be posted on email list-serves of mental health clinicians describing the study and asking for referrals.

How and by whom will subjects be approached and/or recruited?

Study staff and investigators will contact subjects who respond to advertising efforts to screen and recruit eligible individuals. For patients in the ED or inpatient unit, only subjects who the clinical staff has identified as appropriate will be approached. The clinical staff will first ask the patient if he or she can be approached by research staff. Only if the subject agrees to be approached will the staff from this study do so. All potential subjects will be given the telephone number of the research coordinators who will discuss the purpose and procedures of the research and screen the subjects for potential eligibility.

Inclusion criteria

1. Ability to provide informed consent.
2. Diagnosis of bipolar I disorder or bipolar II disorder and currently As defined by DSM-IV by means meet criteria for a major depressive episode.
3. Patients who were on psychiatric medication at presentation will have failed that regimen, as defined as not achieving at least partial remission after an adequate dose of medication for at least six weeks. Benzodiazepines are allowed up to 24 hours before neuroimaging and hypnotics are permitted throughout the study.
4. Depression of sufficient severity to score at least 16 on the first 17 Hamilton Depression Rating Scale items of the Hamilton Depression Rating Scale including the atypical depression items addendum
5. Age range 18-60 years
6. Females of child-bearing potential must be willing to use an acceptable method of birth control throughout the study. These include abstinence, birth control pill, male condom, IUD, depo-provera, Norplant, male sterilization, female sterilization
7. Subject agrees to discontinue all psychotropic other than those in Clinical interview, chart and urine the PSF and other types of drugs likely to interact with the 5-HT_{1A} receptors.
8. Subject is likely to tolerate medication cross-taper to monotherapy Clinical interview and assessment with a mood stabilizer (valproate, lamotrigine or lithium),

Exclusion criteria

1. Diagnosis of any other major psychiatric disorders such as lifetime schizophrenia, schizoaffective disorder, current psychotic depression or current drug or alcohol abuse (within two months before the study) or recent drug or alcohol dependence (within six months before the study); anorexia nervosa or bulimia nervosa within the last year; ecstasy use more than three times. Meet DSM-IV criteria for a manic episode at the time of screening.
2. Previous failed trial of fluoxetine and citalopram by themselves or in combination with an anti-manic agent, defined as at least six weeks of treatment at the dose of 20 mg per day or more. Failure of two trials of any SSRI or SNRI antidepressant medications.
3. If the patients are discontinuing medications as part of the washout period or are starting valproate, previous failed trial of the mood stabilizer that they will take alone, such that the patient experienced clinically significant symptoms of mania or increased rates of

cycling between mood states while taking a clinically therapeutic regimen in terms of dose and length of treatment.

4. Experienced intolerable side effects of both citalopram and fluoxetine in the past. Clinical interview If subject is not on medications, intolerable side effects of valproate in the past.
5. History of clinical deterioration when any of the medications that the patient is taking at presentation have been discontinued in the past with the exception of any of the medications that will be continued during the research protocol (eg. valproate, lithium or lamotrigine).
6. A first-degree family history of schizophrenia if the subject is less than 33 years old
7. Significant active physical illness, including blood dyscrasias, lymphomas, hypersplenism, endocrinopathies, renal failure, chronic obstructive lung disease, autonomic neuropathies, peripheral vascular disease, malignancy
8. Actively suicidal, as defined by expressing ideation with a plan for suicide or develops suicidal ideation that requires immediate medication or treatment intervention.
9. Pregnancy, abortion or miscarriage in the two months prior to enrollment or plans Clinical interview and serum pregnancy to conceive during the course of study participation
10. Lactating women
11. ECT within the past 6 months
12. Subjects who endorse a history of prior head trauma and score 1.5 standard deviations below the mean on Trailmaking A & B will be excluded from study participation.
13. Metal implants, pacemaker, metal prostheses, metal orthodontic appliances or shrapnel in the body
14. Current, past or anticipated exposure to radiation, including:

- Having been badged for radiation exposure in the workplace
- Participation in nuclear medicine protocols in the last year*.

*Subjects will be eligible, however, if the injected dose and dosimetry of the radiotracer are known and the cumulative annual exposure of the previous study and this study is lower than the annual limit for research subjects defined by the FDA (21 CFR 361.1)

15. History of claustrophobia that would prevent the participation in imaging scans
16. Obesity with weight >350 lbs or inability to fit into the MRI scanner**
    ** If there are doubts that the MRI scanner can accommodate the physical dimensions of the participant, the subject's circumference may be measured to determine if it is less than the MR scanner limit, 55 cm. The subject may also be brought to the MRI center and the MRI technologist will assess whether the subject will be able to fit into the MRI scanner. Metal screening and urine pregnancy testing will be done in this circumstance before the subject enters the MRI area.

<u>Research Procedures</u>

Valproate trial and medication washout: If patients are eligible to participate in the study, and if they are taking psychiatric medications at the time of recruitment, they will have all medications tapered off besides mood stabilizers indicated for the maintenance treatment of bipolar disorder (specifically, either lithium, lamotrigine or valproate). If the subject is on a combination of any of these three mood stabilizers, they will continue with this combination for the study. The doses of

the mood stabilizers will be changed as needed so that for one week before starting the SSRI medication one of the mood stabilizers will be in the therapeutic range - either serum level of lithium >0.6 mg/ml, serum level of valproate >40 mg/ml, or dose of lamotrigine greater or equal to 200 mg daily. If the subject is on no medications, valproate will be initiated. In that case, patients will be receive valproate monotherapy and have an effective anti-manic dose (serum level >40 mg/ml) for at least one week before starting SSRI medication. Benzodiazepines will be permitted up to 24 hours before the PET scan or MRI scan**,** and hypnotics will be permitted throughout the study. The patients will be off of all medications besides the mood stabilizer(s) for three weeks before PET scanning. This monotherapy treatment period is necessary to obtain imaging and clinical outcome data that are not significantly influenced by previous medications. This design also will allow us to measure the clinical response to an SSRI that is independent from a clinical response to starting valproate. Patients will meet with their psychiatrist at least weekly via phone or in person during this time. A CGI, HAM-D, YMRS and CSSRS will be performed at least weekly to detect new onset manic symptoms or clinical deterioration. Only patients who still meet the inclusion criterion of HAM-D>15, including the atypical depression items addendum, at the clinical appointment one week before the scheduled PET scan will continue. Patients who no longer meet inclusion criteria at the end of the period, including those that are no longer sufficiently depressed, will not continue with imaging and will be offered up to 6 months of open label outpatient treatment.

Frequency of clinical visits: Throughout the study, outpatients will meet with a treating MIND psychiatrist at least once a week either in-person or on the phone. This meeting will be in-person at least once every other week. Subjects will do the washout on the 4 Center or 5 South unit if clinically warranted. Inpatients will be evaluated by their physician at least three times weekly. In addition, all inpatients are monitored at intervals on an around-the-clock basis by ward clinical staff. During the wash-out period, inpatients will generally see a psychiatrist daily, except for weekends and holidays.

MRI/fMRI scans: All subjects will have an MRI of the brain prior to fluoxetine treatment to obtain information on brain structure and function. This information will help understand how brain structure, function and serotonin mechanism are inter-related. MRI scans will be obtained at the NYSPI MRI facility using a 3.0 Tesla GE scanner. Females of child bearing potential will have a urine hcg test within 24 hours of the scan. Subjects will have the option of visiting the MRI suite before the scan to enter a mock (fake) MRI scanner. The mock MRI scanner has the same dimensions as the real scanner so it allows participants to experience what it is like to be inside the actual magnet. The purpose of this is to have the subject be as comfortable as possible before the actual scan.

Patients will receive a combination of structural and functional MRI scanning lasting not more than 90 minutes. Structural scans will include T1-weighted, T2-weighted FLAIR and diffusion tensor imaging sequences. Resting state fMRI and arterial spin labeling MRI will be obtained to assess baseline brain activity while patients relax and focus their attention on a cross-hair in the field of view. The procedure will be immediately stopped if the subjects report significant distress. If the NYSPI MRI facility is unavailable, the Neurological Institute's MRI Center will be used.

PET imaging: Each subject will undergo a PET scan with [^{11}C]-CUMI-101 at the Kreitchman PET Center, 722 West 168th Street, New York, NY 10032. A urine pregnancy test will be done on females on the morning of the PET scan before the scan to assure that pregnancy has not occurred between the time of laboratory tests at screening, during which a serum pregnancy

test is conducted, and the PET scan. The subject will have one intravenous line placed for radiotracer injection and one for obtaining two venous blood samples, one before radiotracer injection to determine radiotracer protein binding, one at 60 minutes to determine metabolite correction factor. Patients will have vital signs measured before radiotracer injection and after the PET scan is complete. Patients will have a urine pregnancy test conducted within 2 weeks of PET scanning.

The subject will be placed in a supine position on the camera bench. A head holder will be used to decrease head movement during the scan. A low dose computer tomography scan will be used to obtain data for attenuation correction. 16mCi or less of [^{11}C]CUMI-101 will be administered I.V. The emission scan will be initiated at the time of injection and emission data will be obtained for 120 minutes or less. If the patients need to get up from the scanner for any reason, the low dose computer tomography scan will be repeated once only per PET scan. Patients will have a clinical check in with a study physician within 48 hours of the PET scan for safety evaluation that will include an administration of the CSSRS.

Selective serotonin reuptake inhibitor treatment: After imaging, patients will have baseline clinical rating scales. They will be started on fluoxetine or citalopram 20 mg PO daily. Fluoxetine will be the first choice of SSRI treatment due to more clinical trial evidence of its efficacy in bipolar depression than citalopram. Clinical judgement will be used to determine if fluoxetine is not appropriate. After two weeks, the dose can be increased to 40 mg PO daily if the patient has not had a response to treatment at that time. If the dose is increased to 40 mg, the dose can be decreased again to 20 mg PO daily if the patient experiences side effects including any symptoms of hypomania. They will receive a clinical check-in with a research psychiatrist weekly throughout the valproate optimization/medication washout and treatment phases. At each appointment, the clinician will administer the clinical global impression scale-I, the SAFETEE-GI and the CSSRS. If subjects receive a CGI-I of 6 or higher at any visit, their clinical status will be evaluated by the clinical team for suitability to continue the treatment algorithm or the need to change the treatment in some other way such as medication adjustment. Subjects will receive Montgomerey Asberg Depression Rating Scale (MADRS), Beck Depression Inventory (BDI), Hamilton Anxiety Rating Scale (HAM-A), questions of BPRS related to psychotic symptoms, and Young Mania Rating Scale (YMRS) at weeks 0, 2, 4, 6. If subjects have no response in depression by week 4 of the study, the treating clinician will re-assess the plan to continue the research treatment protocol. Subjects will also have valproate or lithium levels checked at either weeks 1, 2 or 4 and will have fluoxetine or citalopram levels checked at either week 4 to check for adherence. Patients will be asked about the number of pills of fluoxetine or citalopram left each week to assess adherence. Patients without alcohol or benzodiazepine use disorders may receive benzodiazepines for insomnia or anxiety/agitation (maximum dose equivalent to 4 mg of lorazepam per day). All patients may also receive zolpidem or diphenhydramine for insomnia or agitation.

The medications that are started as part of study procedures (citalopram, fluoxetine or valproate) and all laboratory tests will be provided for free of charge to the participant. Patients will receive

six months of free outpatient treatment including the treatment obtained through this protocol, with treatment visits at least monthly. All outpatient follow-up visits and clinical assessments will be performed by Dr. Martin Lan unless coverage is needed.

The primary outcome of the study will be whether subjects have a greater than or equal to 50% change in MADRS score from baseline at any point in the six week trial. Subjects who achieve this will be considered “responders” and those that do not will be considered “non-responders”.

Eventually, “responders” will be compared to “non-responders” to evaluate differences in [^{11}C] CUMI-101 binding potential in the brain. Scores of anxiety on the HAM-A and manic symptoms on the YMRS will also be evaluated for correlation with [^{11}C] CUMI-101 BP in an exploratory manner.

Emergency procedures

A research psychiatrist will be available by cell phone at all times during the study. Patients requiring urgent admission at the time of a study visit will be brought to the CUMC Emergency Department by the study physician and if necessary, security assistance will be provided. The treating psychiatrist will arrange non-urgent hospital admissions, preferably to the NYSPI 5-South unit. If patients refuse hospitalization but the clinical team determines that this is needed, the team will arrange all necessary interventions including contacting the local crisis team, family or Emergency Medical Services

Patients lost to follow-up

Upon enrollment, patients will be asked to provide the name and phone number of at least two persons who will likely know their future whereabouts. These people will be contacted if the subject is lost to follow up.

Criteria for Early Discontinuation

1) Intolerable side effects of medications
2) Refusal to continue regimen and willingness to receive open treatment

3) DSM-IV criteria for a manic episode or score > 12 on the YMRS

4) During the washout/valproate monotherapy period, if subjects score a six (much worse) or seven (very much worse) on the CGI-I, the protocol will be discontinued. If the patients do not tolerate the washout because of marked agitation, severe anorexia such as inability to drink adequate amount of fluids or suicidal ideation or behavior with plan or intent, the protocol will be discontinued. In these cases, subjects will be offered open clinical treatment.

5) During the SSRI treatment phase, if there is clinical reason to change to open treatment, such as onset of psychotic symptoms, active suicidal ideation or a score on the CGI-I of 5 or 6 on two consecutive visits, the clinical team will evaluate whether the risks outweigh the benefits of continuing protocol.

6) If the patient requests withdrawal for any reason.

7) The PI judges that it is medically unwise to continue in the study, for example if the subjects are unable to comply with the study procedures and rules.

Clinical treatment alternatives

The proposed treatment is considered standard treatment. Several treatment guidelines for depression in bipolar disorder suggest a trial of either the olanzapine-fluoxetine combination pill or quetiapine before this regimen, however. Other anti-manic agents also exist that could be used in place of valproate, including lithium, carbamazepine or atypical antipsychotics. Valproate was chosen primarily because it has few effects on the serotonin signaling system, the scientific focus of the study.

Risks that could be encountered during the study period

1. Valproate initiation and washout period: Valproate has not been found to be effective on its own in treating depression in bipolar disorder. This medication needs to be started for patients not on any medications at the time of screening to limit the risks of precipitating mania or manic symptoms with SSRI treatment. It is possible that medications that patients are taking at the time of consent and that need to be tapered off as part of the research procedures are having a psychiatric treatment benefit. During this phase of changing medications to a mood stabilizer monotherapy, therefore, patients are at risk for worsening of the their depression or experiencing manic symptoms during the medication changes.

2. Discomfort during scanning (MRI and PET): It may be uncomfortable to lie motionless in the PET or MRI scanners and may cause some subjects to have anxiety.

3. MRI Scan: The MRI scanner takes images of the brain using a large magnet (3.0 Tesla). It is not associated with any known medical risks unless subjects have a heart pacemaker or metal in their body (ie. shrapnel or surgical prostheses) that can be affected by the magnet; medicinal patches can also cause burns in the magnet. There are no known risks associated with pregnancy but no one who is known to be pregnant will be scanned. Changes in the magnetic field of the scanner can stimulate peripheral nerves and sometimes cause sensations that are described as “tingling” or “twitching”, and can rarely cause a painful sensation. Some people feel nervous or claustrophobic feelings due to the scanner’s small space.

4. PET scan: There are some risks of exposure to radiation during the scan. For the [^{11}C]CUMI-101 compound, the single study exposure to the critical organ (pancreas in males) is 18.93 mGy (males) with the maximum proposed dose of 16 mCi (592 MBq). This is below the 5 Rem (50 mGy) single dose limit under the FDA guidelines 21CFR361.1. There is also a smaller exposure of radiation from the attenuation CT scan before the PET acquisition, significantly below the single dose limit under the FDA guidelines 21CFR361.1. The attenuation CT scan may have to be repeated only once if the subject leaves the scanner for any reason during the PET scan. In that scenario, the single study exposure will remain below the single dose limit under the FDA guidelines 21CFR361.1.

Maximum Proposed Dose of Radiation per PET scan and FDA Dose Limit per Single Study Exposure

Male		Female	
Proposed	FDA limit	Proposed	FDA limit
16 mCi (592 MBq)	65 mCi (2406 MBq)	16 mCi (592 MBq)	80 mCi (2960 MBq)

Dosimetry Table for [C-11]CUMI-101 Exposure

Organ/Tissue	Absorbed Dose per Administration (mGy)	Total No. of Administrations per Study	Total Dose for Study (mGy)	Effective Dose per Study (mSV)
Brain *	2.69	1	2.69	
Liver	10.9	1	10.9	
Pancreas *	18.93	1	18.93	
Spleen	8.61	1	8.61	
Active Blood-Forming Organs (red marrow)	1.05	1	1.05	
Gonads	1.23	1	1.23	
Lens of the Eye	0	1	0	
Whole Body				3.16

* Critical organs

Summary Dosimetry Table for Entire Study

Organ/Tissue	Total Dose for Study (mGy)	Total Effective Dose for Study (mSV)
Active Blood-forming Organs (red marrow)	1.05	
Brain	3.69 or 4.69**	
Gonads	1.23	
Lens of the Eye	1.2 or 2.4**	
Liver	10.9	
Pancreas	18.93	
Spleen	8.61	
Whole Body		3.26 or 3.37**

* Critical organs

5. Vascular access during PET scan: There is a small risk of infection or bleeding associated with intravenous catheters. A vasovagal reaction, which can include light-headedness, dizziness or more rarely, syncopy can occur with venous line placement. Syncopy is estimated to occur in <1% of phlebotomy procedures, but we have not found reports in the literature of its incidence for catheterization specifically.

6. Side effects of medications initiated as part of study procedures

a. Fluoxetine or citalopram: Potential side effects include nausea, sexual dysfunction (decreased sexual desire, anorgasmia or abnormal ejaculation), weight loss or gain, nervousness and/or insomnia, diarrhea or dry mouth. There is some risk that the SSRI will induce hypomania, mania or a mixed state.

b. Valproate: Potential side effects include headache, weakness, nausea, vomiting, diarrhea, somnolence, tremor, dizziness, weight gain, double or blurred vision or flu-like symptoms.

Valproate also has risk for rare but more serious reactions of hepatic failure, pancreatitis, thrombocytopenia, hyperammonemia and multi-organ hypersensitivity reactions. Valproate is also teratogenic and is contraindicated in pregnancy.

c. Zolpidem: Potential side effects include diarrhea, dizziness, drowsiness, a drugged feeling and dry mouth

d. Lorazepam: Potential side effects include dizziness, drowsiness, a drugged feeling and some potential for tolerance or withdrawal symptoms

e. Diphenydramine: Potential side effects include dizziness, drowsiness, a drugged feeling and dry mouth

7. Interviews

Psychiatric interviews can be distressing at times, but some people find talking to a physician or psychologist helpful. All interviews will be performed by experienced clinicians.

8. Blood drawing: Drawing of blood will be performed with routine venipuncture procedures. These do carry minimal risk of physical discomfort, bleeding or bruising.

9. Pregnancy: Treatment with valproate is associated with teratogenicity and is considered contraindicated in pregnancy. For this reason, pregnancy is considered an exclusion criterion and will be evaluated at screening with a serum pregnancy test.

Describe procedures for minimizing risks

1. MRI scan: Subjects will have a screening interview before their scan with questions of whether they have a pacemaker or other metal in their body. Subjects will be asked to remove any medicinal patches from their body prior to scanning to avoid burns. Women of childbearing age will have a pregnancy test performed at the day of scanning. If the subject reports unpleasant sensations or feels uncomfortable during the scan, the MR technologist will stop the scan

immediately. Our research staff will be present at all times and a staff psychologist or psychiatrist will be available at all times should they be needed to comfort or treat the patient. From our experience, no subjects have had abnormal sensations that have persisted after stopping the scan. Because the MRI scan is designed for research purposes, it may not show problems that would be found on a clinical brain MRI scan ordered by a doctor for clinical purposes. However, the T1-weighted and T2-FLAIR images acquired in this study, will be examined by an appropriate qualified radiologist. These scans may demonstrate gross structural abnormalities such as the presence of mass effects or hydrocephalus. Upon request, results will be shared with research subjects or a physician designated by them.

2. PET imaging: To limit the risks of radiation exposure, subjects with radiation exposure in a research study in the previous year will only be included if the injected dose and dosimetry of

the radiotracer are known and the cumulative annual exposure of the previous study and this study is lower than the annual limit for research subjects defined by the FDA (21 CFR 361.1, see below).

We have performed a number of studies to evaluate the safety of [^{11}C] CUMI-101 including the FDA required toxicity study (intravenous) of CUMI-101 (CUNBID-101) in Sprague-Dawley rats sponsored by National Institute of Mental Health (NIMH) in the Toxicology Laboratory of SRI International. We proposed a total human dose of 10 microgram per injection and based on this dose male and female Sprague-Dawley rats (10/sex/group) were given a single iv dose of CUMI- 101 at 881 µg/kg (5286 µg/m2 , 1000 times the human dose, Group 2) or at 88.1 µg/kg (528.6 µg/m2, 100 times the human dose, Group 4), or 44.05 µg/kg (264.3 µg/m2, 50 times the human dose, Group 5) on Day 1 or twice a day at 440.5 µg/kg/injection (2643 µg/m2/injection, 500 times the human dose; total dose 881 µg/kg and 1000x human dose, Group 3). A control group (10/sex), Group 1, was given a single iv dose of vehicle, 5% ethanol in sterile saline, at an equivalent volume on Day 1. Animals were sacrificed on Day 3 or Day 15 (interim and terminal necropsy, respectively). The following parameters were evaluated for the toxicity evaluation: mortality/morbidity, clinical observations, body weights, food consumption, clinical pathology (hematology and serum chemistry), organ weights, and, at necropsy, macroscopic observation and microscopic histopathology. All animals survived until their scheduled necropsy. mid and high dose groups (Groups 2-4) displayed slight to moderate hypoactivity on Day 1 immediately after dose administration. The severity of the hypoactivity appeared to be dose dependent, with the highest severity observed in the high dose group (Group 2). The animals recovered quickly from the hypoactivity within a few hours and appeared normal by the last time point clinical observations were performed on Day 1. µg/kg (264.3 µg/mMale and female rats in the Rats in the low dose group at 44.05 2, 50x human dose) and the control group did not exhibit hypoactivity after dose administration. No drug-related effects were found for body weights, food consumption, organ weights, and macroscopic and microscopic evaluations. In conclusion, iv administration of CUMI-101 to male and female Sprague-Dawley rats for a single or twice a day administration did not produce overt biologically or toxicologically significant adverse effects except hypoactivity in the mid and high dose groups, which is not considered to be a dose limiting toxic effect. No adverse effects were observed in the low dose group. The no observed adverse effect level (NOAEL) is considered to be µg/kg (264.3 µg/m44.05 2) for a single iv dose administration. The maximum tolerated dose (MTD) is considered to be at least 881 µg/kg (5286 µg/m2) for a single iv dose administration. Although the groups with 1000-100 times human dose based on a 10 microgram showed only slight hypoactivity, we reduced the maximum injected mass of CUMI-101 to human subjects as 5 microgram per dose considering the no hypoactivity for a 50 times dose. Based on this dose the group 5 is now 100 times dosage based on a 5 microgram human dose and tolerate well in the toxicology studies. CUMI-101 has been successfully tested by us in more than 58 human volunteers, with >10 subjects receiving two doses of the tracer. No adverse effects were observed and the tracer gives a very reliable finding outcome measure with less than 10% CV on test retest. The total dose of [^{11}C]CUMI-101 used for the scan in this study is below 5 µg which is negligible and has no pharmacological effect. The safety of [^{11}C]CUMI-101 in humans is supported by SRI International Toxicology Report. Given a molecular weight of 371 g/mole, an injection of 13.0 to 20 mCi of [^{11}C]CUMI-101with specific activity of ~1 to 2 Ci/µmol would be 2.4- 7.4 µg. The risk of an idiosyncratic reaction is acknowledged in the consent form. A physician will be present at the time of each injection of the radiotracer. Any adverse reaction to the radioactive drug (radiation related or not) will be reported to the IRB and JRSC at Columbia, as specified in 21 CFR 361.1 (d8) and the NYPSI IRB. 16 mCi is the maximum dose and based on reviewing the quality of data from

scans with lower doses, given the requirement to have enough counts for reliable quantifications in lower binding regions, we seek an average dose of around 15 mCi.

3. Vascular access during PET scan: Placement of IV's will be by trained physician or nurse. Any bleeding or hematoma formation will be treated with standard first aid procedures including application of pressure to the region. To reduce the risk of a vasovagal response, intravenous catheterization will be performed with subjects placed in a supine position, and subjects will be asked about a history of vasovagal responses with previous catherizations and blood draws.

4. Valproate optimization period: If the treating physician determines that treatment cannot be delayed safely, the patient will not be enrolled in the study.

5. Side effects of medications: Patients will be encouraged to report side effects of medications to their physicians. A rating scale for somatic symptoms, the SAFETEE-GI, will be administered regularly by the treating physician to monitor for these side effects systematically. If the dose of fluoxetine or citalopram is increased to 40 mg, the dose can be decreased again to 20 mg PO daily if the patient experiences any symptoms of hypomania. If patients have a YMRS >12 or meet DSM-IV criteria for a manic episode, they will be discontinued from the study and will be given appropriate anti-manic treatment.

6. Interviews: Patients will be informed prior to the interviews of the risks and the option of skipping particularly difficult interviews will be considered.

7. Blood drawing: Standard procedures for obtaining blood samples will be followed.

8. Pregnancy: Patients must agree at the time of consent to use a reliable form of birth control and to inform their treating psychiatrist if they become pregnant during the study. Pregnancy will be ruled out with a serum pregnancy test at screening. If the patient becomes pregnant during the study, they will not have imaging performed and all medications will be discontinued according to standard clinical practice, weighing the risks and benefits with the patient. Women will have a urine pregnancy test conducted on the day of the MRI scan to ensure pregnancy has not occurred since the screening. Women will also receive a urine pregnancy test at the time of PET scan to avoid radiation exposure in pregnancy and teratogenic effects of valproate. Women will also have a urine pregnancy test conducted within 2 weeks of PET scanning.

Describe methods to protect confidentiality

Access to research data will be allowed only to members of the research team or institutional personnel as part of a routine audit. Records may be reviewed by state or federal regulatory agencies and their personnel. 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 the subject's consent. All hard copies of records are kept in locked files. Coded computer files will be stored in a database which is password protected and behind an institute and department firewall. In addition, subject names and other personal identifying information will be stored in an electronically secure database at New York State Psychiatric Institute, the R2Net system for registration and tracking of research participants in the outpatient clinics. If information is transmitted electronically, it will be encrypted.

Once a patient enrolls in the project he/she is given a code number that is used for all subsequent computer data and/or lab forms. The code list and patient names as well as all data are kept in locked files in locked offices with access limited to those directly responsible for maintenance of these files by the research team. We will not apply for a Certificate of Confidentiality for this protocol.

The MRI report will be maintained as part of the clinical database at the New York State Psychiatric Institute or Neurological Institute along with the subject's name and will be accessible to clinicians. For patients (only), their psychiatric diagnosis will not be part of the report. All subjects will receive feedback

about their scans. All results will be shared with research subjects in a manner that is consistent with the acuity and certainty of the finding, and will be communicated by an appropriately qualified member of the research team in the form of a letter approved by the IRB and will be contacted by telephone if there is evidence of an abnormality. Results will be shared with the subject or a physician designated by the subject.

Compensation and/or Reimbursement

$250 for participation in the PET scan and $150 for participation in the MRI scan. Payment procedures are initiated at the time of completion of the scans. Payment is in the form of a check, usually received in the mail about 4-6 weeks after the research procedures.

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Statistical Analysis Plan

Statistics: Binding measures were analyzed first for the RN by fitting a linear model with log(BP_F) as outcome, using equal weighting of values. Predictors included relevant pretreatment clinical variables. Age and sex were considered as covariates, and they were removed from the model if they were not significant. For analysis of data from multiple regions, a similar modeling strategy was taken, but fitting linear mixed effect models with participant as the random effect, and region also included as a fixed effect. Prediction of clinical response was modeled linearly with MADRS score as outcome, controlling for initial MADRS score, and imaging or clinical predictors. Demographic or clinical differences between clinical groups were calculated with student t-test or Fisher's exact test. Associations between outcome measure components and clinical variables were calculated using Pearson Correlation. Significance was defined as p value less than 0.05 and all tests were two sided. SPSS 12 for Mac OSX (www.spss.com) or R (www.R-project.org) were used for calculations.