Research Protocol: 18F-DOPA PET to Elucidate the Antidepressant Mechanism of Lurasidone in Bipolar Disorder

9/17/2019

Recruitment Procedures

Patients will be recruited through referrals from treating outpatient psychiatrists, or from clinics at Columbia University. Advertisements will be placed through the Columbia University website including the "RecruitMe" site and on advertising sites such as Craig's List. A website that describes the study will be created. Messages will be posted on email list-serves of mental health clinicians describing the study and asking for referrals. Subjects will be recruited by Depression Evaluation Service members through IRB#6669R.

Study staff and investigators will contact subjects who respond to advertising efforts to screen and recruit eligible individuals. For clinical patients at Columbia, 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.

Texts of written materials to be distributed via advertisements and websites will be submitted to the IRB for approval before they are distributed.

1. Initial screening will be completed as detailed in IRB#6879R or IRB#6669R.

2. If eligible, subjects will be asked to sign the consent form for IRB# 4815 (Sublette). Participants will then be given a physical exam, laboratory test (via blood draw) and psychiatric examinations as performed under IRB#4815. IRB#4815 allows for clinical assessments, a medical screening for significant illness, a screening for drugs of abuse, a developmental history and acquisition of blood samples for genetic analyses. IRB#4815 allows for the above procedures so that subjects can enter any of several different types of studies and protocols.

3. If eligible for IRB#4815, subjects will be given a detailed verbal explanation of this study by a research psychiatrist. During the consent process, the consenting psychiatrist will obtain a history of participants' past radiation exposure. Participants will then give written informed consent if they choose to participate in the study.

Inclusion Criteria

Criterion	**Method of Assessment**
1)Ability to provide informed consent	Clinical interview
2) Diagnosis of bipolar I disorder, bipolar 2 disorder or bipolar disorder NOS and currently meeting criteria for a major depressive episode	DSM-IV by means of SCID
3) Depression of sufficient severity to score at least 16 on the first 17 items of the Hamilton Depression Rating Scale including the atypical depression items addendum	Hamilton Depression Rating Scale
4) Age 18-50 years old	Clinical interview

5) 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 and hypnotics are allowed throughout the study	Clinical interview
6) Females of child-bearing potential must be willing to use an acceptable method of birth control throughout the study: abstinence, birth control pill, male condom, IUD, depo-provera, Norplant, male sterilization or female sterlization	Clinical interview
7) Subject is likely to tolerate medication washout if indicated	Clinical interview
8) Must be enrolled in IRB#4815	Review of records

Exclusion criteria

Criterion	**Method of Assessment**
1)Diagnosis of any other major psychiatric disorders such as 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 in the last year; Meet DSM-IV criteria for manic episode at the time of screening	As defined by DSM-IV by means of SCID; urine drug screen
2)Previous failed trial of lurasidone, defined by at leastv six weeks of treatment at the dose of 20 mg per day or more. Experienced intolerable side effects of lurasidone in the past. Taking any medications that are contraindicated with lurasidone unless there is a plan to stop these as part of the washout.	Clinical interview
3)History of clinical deterioration when any of the medications that the patient is taking at presentation have been discontinued in the past if they will be discontinued as part of the washout.	Clinical interview
4)First-degree family history of schizophrenia if the subject is less than 33 years old.	Clinical interview
5)Significant active physical illness, including blood dyscrasias, lymphomas, hypersplenism, endocrinopathies, renal failure, chronic obstructive lung disease, autonomic neuropathies, peripheral vasucalar disease, malignancy, neuromuscular disorder or tardive dyskinesia. Any medical diagnoses that would be a contraindication to lurasidone treatment. Hemoglobin <11 in females or <13 in males	Medical history by a physician, physical exam, screening lab tests (chemistry panel [SMAC20], CBC, HCG test for pregnancy, urinalyzsis and TSH under IRB#4815
6)Actively suicidal, as defined by expressive ideation with a plan for suicide or develops suicidal ideation that requires immediate medical or treatment intervention	Clinical interview and score of 5 or greater on CSSRS

7)Pregnancy, abortion or miscarriage in the two months prior to enrollment or plans to conceive during the course of the study participation	Clinical interview and serum pregnancy test at screening under IRB#4815
8)Lactating women	Clinical interview
9)ECT within the past six months	Clinical interview and chart review
10)Subjects who endorse a history of prior head trauma and score 1.5 standard deviations below the mean of Trailmaking A & B	Clinical interview and trailmaking A & B as needed
11)Metal implants, pacemaker, metal prostheses, metal orthodontic appliances or shrapnel in the body unless there is confirmation that the substance is MRI compatible	Clinical interview; written confirmation from health care provider if warranted
12)Current, past or anticipated exposure to radiation including a) Having been badged for radiation exposure in the workplace b) Clinical judgement that past lifetime radiation exposure is extensive enough to make exposure to PET scans in the current study inadvisable. c) 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 sutdy is lower than the annual limit fo research subjects defined by the FDA (21 CFR 361.1)	Clinical interview Study team will check our database to ensure that the subject has not participated in an imaging study within our Division in the past year.
13)History of claustrophobia that would prevent participation in imaging scans	Clinical interview
14)Obesity with weight >350 lbs or inability to fit into the MRI scanner	Medical evaluation and testing at MRI suite if needed
15)Inadequate understanding of English	Clinical interview
16)Concurrent anticoagulant or anti-platelet treatment including aspirin if it is needed daily	Clinical interview

Research Procedures

`Medication Washout: If patients are eligible to participate in the study, and they are taking psychiatric medications at the time of recruitment, they will have the psychiatric medications tapered off. The patients will be off of all medications for three weeks before PET scanning. This medication-free treatment period is necessary to obtain imaging and clinical outcome data that are not significantly influenced by previous medications. The design will also allow us to measure the clinical response to lurasidone that is independent from an interaction with the previous medications. Patients will meet with a psychiatrist from MIND or DES at least weekly

in person during this time. A CGI, HAM-D, YMRS, psychotic symptoms of BPRS and CSSRS will be performed at least weekly to detect new onset of manic symptoms or clinical deterioration. Only patients who still meet inclusion criterion of HAM-D>15, including 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 or DES psychiatrist at least once a week in-person. 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 washout period, inpatients will generally see a psychiatrist daily, except for weekends and holidays.

MRI Scans: All subjects will have an MRI of the brain to obtain information on brain structure to co- register PET data. 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 an MRI scan lasting not more than 30 minutes. Structural scans will include T1-weighted and diffusion tensor imaging sequences. The procedure will be immediately stopped if the participant reports significant distress.

PET Imaging: Each subject will undergo two PET scans with [18F]DOPA at the David A. Gardner PET Center at 722 West 168th Street, New York, NY 10032. One scan will be before lurasidone is initiated and the second will be four weeks (+/- one week) after starting lurasidone. Patients will not eat within 12 hours of the PET scan with the exception of a low-protein meal more than four hours before the scan. A urine pregnancy test will be done on females on the day of each 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. Patients will be given 150 mg of carbidopa PO within 120 minutes of the radiotracer injection. Carbidopa is used to prevent AAAD decarboxylation of the radiotracer so that it is bioavailable to cross into the brain. The subject will have an intravenous line placed for radiotracer injection. An arterial line will be placed in the radial artery of the other arm by an experienced physician, Dr. Ragy Girgis. Jayamole Kannamkzhiyil, RN will be present during the scan until the arterial line is removed. An MD clinician from the MIND Division will be on the CUMC campus and avilable during the scan via telephone. If Ms. Kannakuzhiyil is not available, Dr. Jeffrey Miller or Dr. Lan will be present during the scan until the arterial line removed. Patients will have vital signs measured before radiotracer injection and after PET scan is complete. If there is an complication with the arterial line placement, including patient refusal at the time of scan, the scan will proceed without blood sampling.

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. 5 mCi or less of [18F]DOPA will be administered I.V. over about 60 seconds. The emission scan will be initiated at the time of injection and emission data will be obtained for 90 minutes or less. During the emission scan, arterial samples will be drawn at 10 second intervals for the first two minutes and every 30 seconds for the second two minutes using an automated blood sampler. Thereafter, manual samples will be drawn at 6, 8, 10, 15, 20, 50, 75 and 90 minutes. Radioactivity in the plasma will be measured using a gamma counter. If the patients need to get up from the scanner for any reason, the low dose attenuation 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 CSSRS. Patients will have a urine pregnancy test conducted after the PET scan within 2 weeks of the scan.

Clinical Treatment: Open-label lurasidone will be taken by participants after a meal, beginning at 20 mg daily for the first two weeks. At that time, the dose can be increased to 40 mg daily for two weeks. Dosage will be raised only if the participant is tolerating the medication and has not been rated "much improved" or "very much improved" on the CGI improvement scale for that week. At week 4, blood samples will be drawn to measure blood glucose and lipids for safety monitoring. Treatment will be up to 4 weeks or until the second PET scan. Study visits will be weekly with a MIND or DES psychiatrist, unless the participant is rated much improved at week four, in which case visits will be biweekly thereafter. Additional visits can be scheduled at the study doctor's discretion for purposes of clinical management. At each visit, the study psychiatrist will complete the MADRS, YMRS, CGI, CSSRS, psychotic symptoms of BPRS, and SAFETEE-GI. Patients will complete self-rating forms at each visit. Participants with a Clinical Global Improvement (CGI) score of 6 ("much worse") or 7 ("very much worse") on two consecutive weeks during the trial will be terminated early from the study. Patients without alcohol or benzodiazepine use disorder 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.

Lurasidone and all laboratory tests will be provided for free of charge to the participant. Participants will receive six months of free outpatient treatment including the treatment obtained through this protocol, with treatment visits at least monthly.

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 lurasidone

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 period, if subjects score a six (much worse) or seven (very much worse) on the CGI- I, the protocol will be discontinued. If the participants 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 lurasidone treatment phase, if subjects score a six (much worse) or seven (very much worse) on the CGI-I for two consecutive weeks, the trial will be terminated early. If there is clinical reason to change to open treatment, such as onset of psychotic symptoms, manic symptoms of clinical concern, active suicidal ideation 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.

Radiotracer Information

Name of the radiolabeled drug/compound: [18F]DOPA

Manufacturer and other information: [18F]DOPA will be synthesized by the David Gardner PET Center at CUMC. IND 140398 is to use [18F]DOPA with lurasidone (latuda) as per this PSF. Lurasidone (Latuda) will not be used in an off label manner, however.

IND is approved IND# 140398. IND is held by PI/CU Investigator Lan, Martin, MD

Data Analysis Plan

The aim of the analyses is to provide feasibility data for a larger grant application. We will visualize all data to assess for trends that are not detectable in standard statistical analyses due to the small power of this preliminary study.