Weill Cornell Medicine

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Title: Depression, Obesity and Inflammatory Markers

Coordinating Center: Weill Cornell Medical College, Department of Psychiatry

Collaborating Institution: Weill Cornell Medical College –Qatar

Protocol Version	IRB Approval
Version 1.0	10/17/14
Version 2.0 (Current)	4/12/16

Background:

This project will focus on the comorbidity of bipolar disorder and obesity, a comorbidity that is also related to the risk of diabetes and coronary artery disease, particularly when accompanied by elevations of inflammatory markers such as C-reactive protein(CRP) and interleukin-6 (IL-6). Bipolar disorders are quite prevalent in both the United States and Qatar. The national comorbidity survey in the United States reported a 12 month prevalence of 2.6% for bipolar disorder in 2005 (1). A recently completed study of mental illness in Qatar found a prevalence of bipolar disorder of 4.3% (QNRF proposal number NPRP 30-6-7-38). Obesity is also quite prevalent in the USA. According to the Center for Disease Control and Prevention more than one-third of U.S. adults (35.7%) are obese. As for the rates of obesity in Qatar, a recent declaration by the Minister of Health indicates that 41% of Qatari citizens were obese (Qatar Tribune, Tuesday Nov 23, 2013; p1). (HE Abdullah bin Khalid al Qahtani: 41% of Qataris are obese: Minister; Qatar Tribune, Tuesday Nov 23, 2013; p1).

A secondary aim will be to pilot a novel treatment approach involving an anti-inflammatory antibiotic, minocycline, to treat depression in bipolar patients and comparing those having high versus low levels of the inflammatory biomarker CRP. The global psychiatric and public health importance of inflammation in depression and bipolar disorder lies in the implications for health comorbidity (obesity and heart disease) and responsiveness of depression to treatment. Benefits consistent with the priorities of the Qatar NPRP include questions of direct interest to public health (bipolar disorder, obesity, heart disease), collaboration between researchers in Qatar and international colleagues and international recognition due to the regional and global significance of the proposed research. Bipolar Disorder and Obesity In a recent review article McElroy and Keck (2) stated the following, Bipolar disorder (BD) is associated with obesity, overweight, and abdominal obesity, and BD individuals with obesity have a greater illness burden. Factors related to BD, its treatment, and the individual may all contribute to BD's association with obesity. Management strategies for the obese BD patient include use of medications with better metabolic profiles, lifestyle interventions, and adjunctive pharmacotherapy for weight loss. Obesity-related psychiatric and medical comorbidities should also be assessed and managed. Bariatric surgery may be an option for carefully selected patients. Greater research into the theoretical underpinnings and clinical management of the BD-obesity connection is needed. Bipolar disorder has clearly been associated with obesity in New York (3). Bond et al (4) prospectively observed the association of weight gain with symptom severity and degree of functioning in 19 patients with bipolar disorder and weight gain (defined as > 7% increase in body weight over 1 year) compared to 27 patients with bipolar disorder who did not gain > 7% body weight over one year. The Agency for Healthcare Research and Quality in the United States has recently completed enrollment of 484 bipolar patients into a 10 site comparative effectiveness trial called the Bipolar CHOICE study. Weill Cornell Medical College was one of the participant sites and one of us was the principal investigator at the site. The mean Body Mass Index (BMI) of the 484 subjects enrolled was 29.6, indicating that 50% of the sample met the definition of obesity.

Study Design:

This study will take place at Weill Cornell Medical Center in New York and also at Weill Cornell Medical Center in Qatar. The protocol will be identical at both sites. Recruitment for the study will involve local outreach to clinicians and advocacy groups in New York and Doha.

We plan to enroll 180 bipolar subjects (120 in Doha and 60 in New York over 24 months) for Aims 1-3 and 50 subjects (30 in Doha and 20 in New York) for Aim 4. (In order to achieve our aims we will recruit 60 manic, 60 euthymic, and 60 depressed bipolar individuals across the two sites. Depending on the local CRP results we may need to extend the sample of depressed subjects.) We have in place a network of referral sources

(including primary care providers and community mental health clinics) to facilitate enrollment of a diverse and representative group of patients.

There are four primary aims to this study as follows: Aim 1 will examine relationships between the levels of the inflammatory markers and current clinical state (depressed, manic or euthymic) with the hypothesis that Inflammatory markers will be higher in depression and mania relative to the euthymic state. Aim 2 will examine relationships between inflammatory markers and BMI in bipolar patients with the hypothesis that inflammatory markers will correlate positively with BMI. Aim 3 will examine the relationship between depression, obesity and inflammatory markers with the hypothesis that depressed (or manic) bipolar patients who are also obese will have higher inflammatory markers than either obese euthymic patients or non-obese depressed or manic patients. In order to achieve these aims we will need to diagnose and characterize a large sample of bipolar individuals in each of the above named clinical states, namely: -bipolar patients who are currently manic/hypomanic, euthymic or depressed for aim 1 -bipolar patients who are obese or nonobese for aim 2 -bipolar patients with or without elevated inflammatory markers for aim 3 and for aim 4 which we describe below. Pilot Study Of a Novel Treatment Approach for Bipolar Depression. Aim 4 will be to conduct a proof of concept add-on treatment study of the antibiotic minocycline for bipolar patients who are depressed, likely to be obese and likely to have elevated inflammatory markers and increased risk of heart disease.

This is a proposal to conduct a 2-site trial of 50 subjects to examine the value of minocycline augmentation in bipolar depressed patients who are incompletely responsive to initial treatment with anti depressants and/or mood stabilizers. We hypothesize that the patients with high baseline CRP levels will have a significantly better response to the addition of minocycline in terms of symptoms of depression, psychosocial functioning and indices of immune function. If results are promising we will design a larger placebo-controlled confirmatory trial in the future.

Primary Objectives:

This study would measure markers of inflammation in a cohort of patients with bipolar disorder. Inflammation has been thought to be elevated in both depression and obesity and to contribute to heart disease and poor response to antidepressants. Heart disease, obesity and bipolar disorder have significant prevalence in the populations of Qatar.

Aim 1 will examine relationships between the levels of the inflammatory markers and current clinical state with the hypothesis that inflammatory markers will be higher in depression and mania relative to the euthymic state.

Aim 2 will examine relationships between inflammatory markers and body mass index (BMI) in bipolar patients with the hypothesis that inflammatory markers will correlate positively with BMI in bipolar patients.

Aim 3 will examine the relationship between depression, obesity and inflammatory markers with the hypothesis that depressed (or manic) bipolar patients who are also obese will have higher inflammatory markers than either obese euthymic patients or non-obese depressed or manic patients.

Secondary Objectives:

A secondary aim will be to pilot a novel treatment approach involving an anti-inflammatory antibiotic, minocycline, to treat depression in bipolar patients and comparing those having high versus low levels of the inflammatory biomarker CRP.

Statistical Considerations:

For Aim 1, the sample size calculation is based on the comparison of inflammatory marker prevalences between the three MINI-defined groups (i.e., depressed, manic, and euthymic groups). A sample size of approximately 60 patients in each of the depressed, manic, and euthymic groups was calculated to have 80% power to detect pairwise effect sizes of 0.50 or greater, using two-group t-tests with a two-sided alpha level of 5%. Similar effect sizes can be estimated for Aim 3 with N=180 patients enrolled in the study.

For Aim 2, 95% confidence intervals for Pearson or spearman-rank correlation coefficients (for the relationship between inflammatory markers and body weight/BMI) can be constructed to have lower limits of 0.40 with N=180 patients enrolled in the study (this calculation assumes expected correlation coefficients of 0.50 or greater).

Aim 4 is a pilot proof of concept study and does not require formal sample size calculations. Groups for each aim will be compared on demographic, clinical and biological variables using two-sample t-tests or analysis of variance (ANOVA) tests for continuous variables (for nonparametric continuous variables, either Mann-Whitney tests or Kruskal-Wallis tests will be used) and chi-square tests or Fisher's exact tests Page 23 of 34 5/11/20 10:58 AM for categorical variables. Unless specified otherwise, each of the statistical tests above will use a two-tailed alpha-level of 0.05.

Inclusion/Exclusion Criteria:

Inclusion Criteria:

1. Patients with Bipolar Disorder and current depressive symptoms
2. Hamilton Depression Scale score >18
3. Failed an adequate trial of at least one antidepressant or mood stabilizer of at least 4 weeks duration. Medication history will be recorded using the Antidepressant Treatment History Form
4. 18 years or older
5. Fluent in English
6. Have the capacity to understand the nature of the study and sign the written informed consent.

Exclusion criteria:

1. Current diagnosis of Schizophrenia or other psychotic disorder, or Dementia Alzheimer Type or related cognitive disorders.
2. Principal diagnosis of Post-Traumatic Stress Disorder, Anorexia or Bulimia Nervosa, Obsessive-Compulsive Disorder. We define principal as the most pressing clinical problem.
3. Pregnant or nursing
4. Axis II diagnosis of antisocial, schizotypal or severe borderline personality disorder (defined as patients who are high risk for being unable to complete the study due to hospitalization, suicide attempts, significant self-mutilation, or other self-injurious or destructive behavior).
5. Patients who currently meet criteria for Alcohol or other Substance-Related Dependence Disorder (with the exception of nicotine dependence) who require detoxification.
6. Patients who are unable to read and write English or Arabic.
7. Patients having serious, unstable or terminal medical or neurologic illness that would compromise study participation (i.e., metastatic or advanced malignancy, chronic renal failure requiring dialysis, recent MI or unstable angina, or end stage chronic obstructive pulmonary disease).

8. People with common conditions such as hypertension, insulin dependent diabetes mellitus, asthma, compensated congestive heart failure, a malignancy in remission, treated hypothyroidism, or epilepsy will not be excluded from participation..
9. Autoimmune disease or chronic inflammatory diseases such as psoriasis or Crohn's disease
10. Chronic infection such as hepatitis B or C or HIV
11. Elevated antinuclear antibody or rheumatoid factor
12. Oral glucocorticoids in the past 6 months
13. Methotrexate or NSAID use in the past two weeks

Study Procedures

Informed consent, psychiatric evaluation, questionnaires, diagnostic interviews, height, weight, and urine pregnancy screening assessment (pilot female participants of child bearing potential only), lab tests, research blood draw, minocycline prescribed to the participants in the Aim 4 pilot study.

Assessing Safety and Efficacy

-Side Effects: Frequency and Intensity of Side Effects Ratings (FISER). A 3-item self-rated measure of medication side effects and burden will be obtained at each visit during the minocycline trial. The FISER was developed for and successfully used in the multicenter STAR*D study of depression.

- Safety: Assessments: At the beginning and end of treatment will include hematology, chemistries, and urine pregnancy screening prior to and at the end of treatment. - The Hamilton Depression Scale (HDS), which assesses depressive symptoms and severity of the depressive syndrome will be done by an independent blinded rater every two weeks.

Interim and Complete Stopping Rules

Site PIs will determine the action taken, if necessary, should an AE or SAE occur during the time the participant is in the study. The event will be documented by the site staff and will indicate if in response to the AE/SAE there was no change in procedure, procedure was interrupted, procedure was discontinued, other action was require, and if medical action was required. In the very unlikely case that severe SAE¿s occur due to participation in the minocycline study, the study will be stopped.

Termination or Dropout of Subjects

Though not expected, if a participant reports any adverse reaction to the minocycline medication in the pilot study, it will be stopped immediately. The standard treatment will be continued and will not be interrupted and participants will be removed from the study. If a participant becomes pregnant during the study it may be grounds for termination of subjects from this research protocol. Additionally, if a patient became medically or psychiatrically

unstable, termination of participation may become necessary. If psychiatrically unstable, the patient would be assessed for inpatient hospitalization by hospital staff.

Adverse Event Collection

Adverse Events (AEs) and Serious Adverse Events (SAEs) will be collected to assure the safety of the participants in the study and to comply with legally applicable documentation and regulatory requirements.

An AE is any unpleasant medical or psychiatric event observed in a patient that occurs in association with any of the study procedures or determined by the clinician. Medical conditions that are present prior to the study and worsen during a study may be considered adverse events. Examples of AEs may include an abnormal laboratory finding, adverse reaction to the minocycline, or excessive bleeding or bruising due to blood sample collection.

An SAE is a serious adverse event that is unexpected, related to or unrelated to participation in the research, and is harmful to the patient. SAEs include suicide attempt, death, a life-threatening experience, hospitalization, or as determined by a clinician. AEs/SAEs will be reported according to the IRB guidelines.

The side effects of the drug we will be using in the pilot study are listed below: The most common side effects from this medicine are gastrointestinal symptoms, dizziness and skin rash. Patients who take this medication for a long time may notice changes in their skin color, but this usually resolves after stopping the medication. Some women who take minocycline develop vaginal yeast infections. While this can occur with other antibiotics, it seems more common with minocycline and other tetracyclines. It is thought that minocycline kills bacteria that are normally present in the body and protect against yeast infections. Minocycline may increase sensitivity to sunlight, resulting in more frequent sunburns or the development of rashes following sun exposure. It is recommended that patients apply sunscreen (SPF 15 or greater) before outdoor activities or avoid prolonged exposure to the sun while taking minocycline. More rarely, minocycline can affect the kidneys or liver. Doctors may recommend periodic blood tests for long term users to check liver and kidney function. In equally rare cases, minocycline can induce lupus, but this condition usually improves after stopping the medication.

Site PIs will determine the action taken, if necessary, should an AE or SAE occur during the time the participant is in the study. The event will be documented by the site staff and will indicate if in response to the AE/SAE there was no change in procedure, procedure was interrupted, procedure was discontinued, other action was require, and if medical action was required.

SAEs will be systematically recorded to assess any life threatening events or hospitalizations. An SAE is defined as any adverse drug experience occurring at any dose or any event consistent with the underlying disease state that results in a life threatening including suicide attempts (suicide attempts must also be coded as a psychiatric hospitalization), death, hospitalization or prolongation of hospitalization, congenital anomaly, persistent or significant disability or incapacity, and or a required intervention to prevent permanent impairment or damage.

The following categories identify the intensity of an Adverse Event:

Mild: Awareness of a sign or symptom that does not interfere with the participants usual activity or is transient, resolved without treatment and with no sequelae;

Moderate: Interferes with the participants usual activity, but the patient is still able to function;

Severe: Events that interrupt a patient's usual daily activity and generally require a systemic drug therapy or other treatment. All AEs/SAEs will be evaluated as to its expected occurrence, or lack of expected occurrence:

Expected: An adverse event is expected when the specificity and severity of the event is consistent with the study procedures and Standard of Care, (e.g., the participant fainted in response to having his blood drawn) or underlying disease state, (the participant's depressive symptoms worsened).

Unexpected: An adverse event is unexpected when the specificity or severity of an adverse event is not consistent with the study procedures or Standards of Care, (e.g., the phlebotomist used the same blood collection needle on multiple participants, resulting in a participant acquiring Hepatitis C), or underlying disease state (e.g., the participant experienced a manic episode during the study). Unexpected as defined above refers to an adverse event that has not been observed before.

The PI at each site will determine the degree of AEs/SAEs suspected in association with any of the study procedures the participant engaged in. However, this must be related to our study procedures not just follow up information that we are collecting. AEs/SAEs will also be identified that are not related to the study procedures and indicated on the AE/SAE forms.

The following conditions will be used to define the relatedness of any study procedure to an AE/SAE.

Not related: The PI has determined that the event is not related to any study procedure. -Possible: The PI has determined that the event possibly has a reasonable relationship to the study procedures.

Probable: The PI has determined that the event probably has a reasonable relationship to the study procedures.

Definite: The PI has determined that the event is related to study procedures.

Unknown: The PI has determined it is impossible to determine the relationship of the event to the study procedures.

The clinical outcome of the AE/SAE will be characterized as follows:

Recovered/Resolved: The patient recovered from the AE/SAE.

Not Recovered/Not resolved: Patient did not recover and symptoms continue.

Recovered/Resolved with Sequelae: The patient has recovered but with clinical sequelae from the event.

Fatal: The event resulted in death. The SAE, Death, and Exit forms must be completed for this outcome.

Unknown: The clinical outcome of the patient remains unknown at the time of the report or the patient was lost to follow-up.

All AEs/SAEs will be followed until resolution or until the end of participation in the protocol. Participants may report AEs freely or in response to general questioning or through patient or clinician assessments. If it is determined that an AE has occurred, PI should be notified.

Events will be discussed among the PIs in the USA and Qatar. AEs will be reported to the IRB according to the WCMC IRB guidelines.