Study Protocol

Full Title: Sertraline for Preventing Mood Disorders Following Traumatic Brain Injury

Principal Investigator: Ricardo Jorge, MD

1. Summary:
Traumatic brain injury (TBI) is a leading cause of death and disability among young adults. The frequent cognitive, emotional and behavioral problems observed after TBI are major risk factors influencing the outcome of TBI patients. Mood disorders are the most frequent psychiatric complication of TBI, have a large impact on family functioning, interpersonal relationships, and return to work or school. Furthermore, a significant proportion of these disorders will progress to more chronic and treatment refractory forms. In spite of their clinical relevance, mood and anxiety disorders remain largely unrecognized and not adequately treated, contributing to greater disability and decreased participation in the aftermath of TBI. In this study, we will examine the efficacy of sertraline to prevent the onset of mood and anxiety disorders during the first six months after TBI. A group of 104 patients with closed TBI will be recruited immediately after resolution of posttraumatic amnesia and randomly assigned to receive six months of double-blind treatment with sertraline or placebo. Primary outcome measures will include time to onset of DSM-IV defined mood and anxiety disorders requiring immediate treatment intervention, and psychosocial outcome as measured by Community Integration Questionnaire (CIQ) scores. In addition, we will examine the effect of sertraline on frequent post-TBI behavioral disorders such as aggression, impulsivity, poor decision making and apathetic symptoms. MRI based volumetry and diffusion tensor imaging will be used to examine the structural correlates of mood and anxiety disorders as well biological predictors of treatment response and community reintegration. Early preventive treatment with sertraline would reduce sub-threshold mood and behavioral symptoms, prevent the occurrence of structural and functional brain changes associated with the onset of mood disorders, assure patient's access and participation in rehabilitation programs and, consequently, improve psychosocial outcome.

2. Specific Aims and Hypotheses:

Specific Aim 1: Determine whether treatment with sertraline beginning during the acute post-TBI period and continuing for 6 months, is more effective than placebo in preventing the occurrence of mood disorders following TBI.

Hypothesis 1: The time from baseline to onset of mood disorders will be significantly greater in the group of patients receiving sertraline compared to those patients receiving placebo.

Specific Aim 2: Determine the effect of treatment with sertraline compared to placebo on the extent of community reintegration and executive functioning at six months following TBI.

Hypothesis 2: When compared with patients receiving placebo, patients receiving sertraline will show significantly higher Community Integration Questionnaire (CIQ) scores and significantly better performance in a set of executive function tests.

Specific Aim 3: We have proposed that mood and anxiety disorders following TBI might result from abnormal prefrontal modulation of limbic and paralimbic structures located in the ventral aspects of the frontal lobe (e.g., subgenual cingulate cortex) and the medial temporal lobe (e.g., the amygdala). Structural damage of prefrontal areas and of white matter pathways that integrate these neural circuits might be important etiological factors of this abnormal modulation.
The principal neuroimaging aim of the current proposal is to identify predictors of the occurrence of mood disturbance during the first 6 months following TBI and examine whether chronic treatment with sertraline will modify this relationship.

**Hypothesis 3:** When compared with patients who do not develop a mood disorder six months after TBI, patients who develop a mood or anxiety disorder will present at baseline with lower fractional anisotropy (FA) value of the frontal white matter.

### 3. Study Design:

We will conduct a randomized, parallel group, double-blind study of the efficacy of sertraline versus placebo to prevent the onset of mood and anxiety disorders in patients who have sustained a TBI. Treatment with sertraline or placebo will be completed after 6 months. The screening for eligibility will be done before randomization (week 0) and will consist of a careful review of medical records, neurological exam and serial assessment of post-traumatic amnesia. The rest of the study protocol is shown in Table 1.

**Table 1**

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<thead>
<tr>
<th>Assessments</th>
<th>Randomization (week 0)</th>
<th>Week 2</th>
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Additionally to the evaluations listed in Table 1, a research assistant will call the patient every two weeks to assess psychiatric status, medication compliance and all interim adverse events. Psychiatric status will be assessed using the Mini International Neuropsychiatric Interview (MINI Plus)^1. Psychiatric symptoms will be reviewed by the PI who, if necessary, will schedule a full psychiatric evaluation at two weeks from the onset of symptoms. In the case of suicidality, the patient will be assessed on an emergency basis. Patients who develop a mood or anxiety disorder of at least 2 weeks duration during the study will be referred to their psychiatrist for initiation of treatment. At the time of termination, all of the measures will be taken and the data will be analyzed as part of the patients who terminated the study.

4. Study Population:

We will recruit a series of 104 patients. Participants will be selected from TBI patients admitted to the Emergency, Neurosurgery and Rehabilitation Departments of the University of Iowa Hospital and Clinics (UIHC), Iowa City.

Inclusion Criteria
1. Aged 18 years or over.
2. Meeting the Center for Disease Control (CDC) criteria for TBI^2.
3. Mild, Moderate, or Severe TBI as categorized by initial Glasgow Coma Scale (GCS)^3 scores 13 to 15, 9 to 12, or 3 to 8, respectively. Accounting for the fact that there is a heterogeneous pathophysiology among patients with GCS scores in the 13-15 range, we will divide TBI patients with GCS scores within this range into mild head injury and high-risk mild head injury groups. Mild head injury is defined as a GCS score of 15 without acute radiographic abnormalities, whereas high-risk mild head injury is defined as GCS scores of 13 or 14, or a GCS score of 15 with acute radiographic abnormalities^4. Only those patients with high-risk mild head injury will be included in the study. In addition, patients with a GCS score in the 13-15 range but who underwent intracranial surgical procedures or presented with focal lesions greater than 15 cc, however, will be considered to have suffered a moderate head injury^5.
4. Complete recovery from Post Traumatic Amnesia (PTA) within 4 weeks of the traumatic episode.

Exclusion Criteria
1. Penetrating head injuries.
2. Clinical or neuro-radiological evidence of associate spinal cord injury.
3. Patients with severe comprehension deficits (i.e., those who are not able to complete part II of the Token Test^6) that precludes a thorough neuropsychiatric evaluation).
4. Evidence of previous cognitive decline consistent with a dementia diagnosis.
5. Presence of DSM-IV defined mood, anxiety or psychotic disorder at the time of enrollment to the study. However, patients with a history of alcohol abuse or alcohol dependence during the year preceding TBI will be included in the study.

6. We will exclude patients who were taking antidepressants at the time of TBI or during a six month period prior to the traumatic event. In addition, we will exclude those patients who have failed an adequate previous trial with sertraline or had side effects that prompted the discontinuation of this medication.

7. Pregnant women or women that plan to become pregnant during the period of the study. Women during their reproductive years who use effective contraceptive measures can be included in the protocol.

8. Severe complicating illness such as neoplastic disease or uncompensated heart, renal or liver failure.

5. Study Procedures:

Randomization and Masking
We will use permuted blocks randomization. Specifically, at the beginning of the study, the targeted sample size will be divided randomly (104 participants) into block sizes of 2, 4, and 6. Within each block participants will be randomly assigned using computer-generated random numbers of 1 or 2 to sertraline or placebo. This randomization scheme will provide a less unbalanced sample size at the end of the study than a simple randomization technique while helping to keep the professionals in charge of the patient examination from guessing the treatment allocation scheme. To further ensure this, the block sizes used will not be disclosed to the professionals in charge of the patient examination. The randomization tables will be physically separated from them and only members of the research team not requiring blinding will have access to them.

A research assistant that does not evaluate treatment outcomes will dispense medications and evaluate study drug compliance through sertraline blood levels. A physician that does not evaluate treatment outcomes will evaluate adverse events. All research assistants and physicians that assess study outcomes, patients, and caregivers will be blinded to treatment assignment.

Sertraline Administration and Adjustment
Sertraline and placebo will be given in a double blind fashion via an equal number of identical tablets administered once daily. Once stabilized in the targeted dosage, we will monitor sertraline serum levels twice during the course of the intervention. Blood samples will be obtained randomly, one during the first and one during the second trimesters of the protocol. We will not allow the use of other antidepressant medication. However, we will allow the use of small doses of a benzodiazepine or trazodone to treat initial insomnia.

Sertraline will be given at 25 mg per day for 5 days, 50 mg per day for the next five days, and 100 mg per day, thereafter. We opted not to increase the dose of sertraline over 100 mg per day within this preventive strategy. Of note, the average dose of sertraline given in a previous successful prevention trial among stroke patients was 62.9 mg (range 50 to 150 mg). If a patient meets criteria for a mood disorder after 2 weeks on receiving sertraline (or placebo) at a 100 mg per day dose, she/he will be dropped out from the study and referred to standard psychiatric care. After completion of the study, sertraline dose will be tapered during a 2 week period and patients monitored for the appearance of withdrawal symptoms. If necessary they will be referred to standard psychiatric care. Adjustments of oral doses will be made immediately if sertraline is producing significant side effects (e.g., GI symptoms or sexual dysfunction). Side effects from sertraline will be registered in special forms including all side
effects enumerated in the drug’s monograph. In addition, we will complete a sexual side effects scale. A physician that does not assess study outcomes will review the adverse events and side effects. He will make the appropriate adjustments and termination decisions. In order to maintain the blind, an equal number of adjustments will be made in patients receiving placebo medication.

**Compliance with Treatment Medication**

In addition to monitoring blood levels of sertraline at follow-up visits, patients will be contacted at 2-week intervals to count the number of pills remaining in their supply of medication. Thus, patients will be asked about their compliance with their medication as well as a quantitatively determining their adherence at it through measurement of serum concentrations of sertraline. If serum concentrations indicate that they have not taken their medicine or if they have more pills than they should, patients will be encouraged to start taking their medication if they have missed only a few doses or stopped their medication for less than a week. If patients have stopped their medication for more than a week, the patient will be terminated from the study.

**Adverse Events Evaluation**

An adverse event will be defined as any undesirable medical event with new onset or significant exacerbation during the course of the study, regardless of whether or not considered to be related to the study medication. Adverse events will be graded on a three-point ordinal scale: 1) Mild = Discomfort noticed, but no disruption to daily activity; 2) Moderate = Discomfort sufficient to reduce or affect normal daily activity; 3) Severe = Inability to perform normal daily activity. Adverse events will be registered in ad hoc Case Report Forms and treatment will be stopped for all severe events and other events as indicated by necessity to alter pharmacological treatment.

We hypothesize that there will be significant differences between the sertraline and placebo groups in the frequency of adverse events attributable to the medication. Minor side effects of sertraline such as GI distress (e.g. nausea, vomiting, diarrhea) or sedation typically resolve with continued treatment. We will closely monitor the occurrence of sexual side effects (e.g., decreased libido, delayed ejaculation, anorgasmia, erectile dysfunction) that occur in up to 20% of patients treated with SSRIs. Sexual dysfunction will be assessed using the Arizona Sexual Experience Scale (ASEX). In the case that sexual side effects are serious and / or distressful for the patient, sertraline dose will be first reduced and, if symptoms are not alleviated, it will be discontinued. In the same way, we will carefully monitor for the presence of a bleeding tendency and abnormal coagulation tests. Hyponatremia can be alleviated by dose reduction but, in rare cases, will require discontinuation of the drug. Sertraline treatment can seldom produce or aggravate extrapyramidal signs and symptoms (e.g., akathisia, rigidity, or bradykinesia), particularly among patients with basal ganglia lesions. Assessment of these signs will form part of neurological examinations. Elevation of hepatic transaminases is uncommon and usually benign, but liver toxicity will be carefully monitored.

**Criteria for Early Termination of the Study**

The patient will be withdrawn from the study under the following circumstances:

1. Patient experiences an allergic or idiosyncratic reaction to the study drug.
2. Patient develops an intercurrent illness during the course of the study that requires treatment that is not consistent with the protocol requirements or represents too great a risk for continued participation in the trial.
3. Patient experiences a serious adverse event or presents a serious laboratory abnormality that constitutes an unacceptable risk for continued participation in the study.
4. Patient has a positive urine drug screen consistent with illicit drug use.

5. Patient requests to be withdrawn for the study.

6. Non compliance or refusal of treatment or assessment.

7. Development of a mood or anxiety disorder of at least 2 weeks duration (more than 4 days in the case of hypomania) that fulfills established DSM-IV criteria. All final assessments will be performed at the time of discontinuation. They will then be referred to their psychiatrist or family physician for appropriate treatment.

8. Patients who become suicidal. Family members and patients will be given the number to reach the PI and they will be instructed to bring the patient to the emergency room at UIHC or the other enrollment sites, if they become suicidal. To check for suicidal thoughts and developing depression, all patients will be contacted by phone every 2 weeks and their family will be instructed to bring them to the ER if they are suicidal. Finally, medications will be dispensed to patients on a 2 week basis so they will never have a large amount of medication on hand.

6. Study Evaluations:

**Injury Severity and Baseline Neurological Variables**

A trained research assistant will be responsible for collecting this information during the acute in-hospital period. Data collection will be done following the guidelines and specific forms of the Traumatic Coma Data Bank\(^9\). Characteristics of the patient’s transport, time to admission, and mechanism of injury will be recorded on a special form. In addition, we will record details concerning pre-hospital treatment and complicating events such as significant hypoxia, aspiration or cardiopulmonary arrest. Admission blood alcohol levels and drug-screen results will also be recorded when available. During hospitalization, daily records of neurological assessment will be compiled by hospital personnel and will include GCS scores. A special emphasis will be placed in registering neurological (e.g. ischemia, delayed hemorrhage, edema, intracranial hypertension) and systemic (e.g. hypoxia, hypotension, anemia) complications associated with secondary brain damage during this period. Hypoxia will be defined as a PO2 less than 60 mm Hg, hypercapnia as PCO2 levels greater than 45 mm Hg, hypotension as mean arterial pressures less than 80 mm Hg, increased intracranial pressure when it is greater than 20 mm Hg, and anemia as an hematocrit of less than 30%. We will register the presence or absence of these complications as well as the number of times when they are registered. The type of treatment administered to the patient will be separately recorded.

Overall severity of traumatic injuries will be quantified using the Abbreviated Injury Scale (AIS)\(^10\). Severity of brain injury will be quantified as a function of the 24-hour GCS score and length of PTA.

**Neuroimaging Methods**

MRI scans will be obtained at the Radiology Department of Iowa using a Siemens Trio 3T scanner. Four different image sets will be acquired for structural MRI. The T1-weighted images will be acquired in the coronal plane using a 3D MP-RAGE sequence with the following parameters: TE=3.4ms, TR=2530ms, TI=1100ms, flip angle=10 degrees, NEX=2.0, FOV=26.0, matrix=256x192, slice thickness = 1.5mm. The T2-weighted sequence will be acquired using a 2D turbo spin-echo sequence with the following parameters: TE=77, TR=7000, NEX=1.0, FOV=26.0, matrix=256x256, slice thickness/gap=3.0/0.0mm, turbo factor=9. The FLAIR sequence will be acquired in the axial plane using the following parameters: TE=104, TR=9000, TI=2200, NEX=1.0, FOV=24.0, matrix=256x192, slice thickness/gap= 5.0/2.0mm. We will obtain an axial gradient-echo sequence (5mm thickness, 40% distance factor, 20 slices) with
TR/TE=500/10, flip angle= 20 degrees and voxel size=0.9 x 0.9 x 5 mm, in order to better assess the distribution of diffuse axonal injury. Diffusion tensor images will be acquired using an echo-planar double spin-echo sequence with the following parameters: TE=90ms, TR=9000ms, FOV=256x256, Matrix=128x128, slice thickness/gap=2.0/0.0mm, B-value=1000, number of directions=24, BW=1396Hz/Pixel, and NEX=1. Image analysis will be performed using the state-of-the-art tool available at the moment the collection of images has ended.

**Blood and Urinary Samples for Laboratory Tests**

They will be collected at baseline to ensure no undetected illness is present and will be reassessed at the 2nd week, 6th week, and 3rd and 6th month follow-up visits. Laboratory tests will consist of: a) Hematology: hemoglobin, hematocrit, red blood cell count (RBC), white blood cell count (WBC), differential count and platelet count; b) Blood chemistries: sodium, potassium, chloride, calcium, AST, ALT albumin, total bilirubin, glucose, creatinine, BUN, bleeding time and prothrombin time; and c) Urinalysis: color, appearance, volume, osmolarity, protein, glucose, specific gravity, pH, ketones, blood, leukocyte esterase, nitrite and microscopic examination. These tests are intended to identify any possible medical illness which would disqualify the patient and to monitor side effects related to sertraline therapy (e.g., hyponatremia). We will also randomly obtain urine screening tests of illicit drugs at baseline and at least twice during the follow-up period. If a patient has a positive urine drug screen consistent with illicit drug use, she/he will be discharged from the study and referred to appropriate care. Finally, serum pregnancy tests will be obtained at baseline or when clinically indicated during the follow-up period.

**Demographic Characteristics**

We will collect patients’ age, gender, marital status, education, and socio-economic status. We will carefully record employment level and school attendance, living situation, and primary source of income. We will obtain a complete account of patients’ previous medical history (including personal and family history of psychiatric disorders), personal history of alcohol abuse and dependence, as well as a list of medications regularly used by the patient before TBI.

**Psychosocial Adjustment**

We will assess psychosocial adjustment using the Social Functioning Examination (SFE) and the Community Integration Questionnaire (CIQ)\(^\text{11}\). SFE is a semi-structured interview assessing different aspects of psychosocial adjustment such as quality and satisfaction of interpersonal relationships, performance of home and family responsibilities, work experience, social activities, economic practices, stability of family income, living environment, spiritual beliefs, and use of community resources. Scores range from 0.0 to 1.0 with higher scores indicating greater impairment.

CIQ is an ordinal scale ranging from 0 to 29 in which higher scores reflect greater independence. It has 3 subscales assessing home competency, social integration, and productive activity. The CIQ is a reliable instrument with an extensive validation among TBI patients\(^\text{11}\).

**Disability and Activities of Daily Living Impairment**

At the time of the initial and 6-month evaluations we will assess disability and activities of the daily living impairment in all patients using the Disability Rating Scale (DSR)\(^\text{12}\).

The DRS is an ordinal scale from 0 to 30, which is divided in 4 subscales corresponding to responsivity and awareness, cognitive ability for self-care activities, dependence on others...
because of cognitive, emotional and/or physical disability, and capacity for employment. It is a validated scale with appropriate test-retest and inter-rater reliability\textsuperscript{12}.

**Psychiatric Examination**

Psychiatric assessment will be carried out after resolution of PTA by a psychiatrist blind to neuropsychological, neurological, and imaging data. Accounting for the fact that TBI patients might provide unreliable information (e.g., due to memory problems or unawareness of deficits), we will seek and encourage the participation of adequate informants. We will consider a relative, friend, partner or caregiver as an adequate informant if he/she has been in contact with the patient at least twice per week during the 6 months prior to the TBI. The assessment will include:

1) Mini International Neuropsychiatric Interview (MINI Plus)\textsuperscript{1}: which provides current (i.e. previous month), and lifetime DSM-IV diagnoses of major psychiatric disorders.
2) Hamilton Depression Scale (HDRS)\textsuperscript{13} and the Hamilton Anxiety Scale (HARS)\textsuperscript{14}: will be used to assess the severity of depressive and anxiety symptoms.
3) Young’s Mania Rating Scale (MRS)\textsuperscript{15}: will be used to assess the severity of manic symptoms.
4) Apathy Evaluation Scale (AES)\textsuperscript{16}: The 13-item AES measures patient withdrawal from social contacts and lack of interest and motivation in normal activity. It consists of a clinician version, an informant version, and a self-rated version. The AES conceives apathy as a psychological dimension defined by simultaneous deficits in the overt behavioral, cognitive and emotional concomitants of goal-directed behavior.
5) Overt Aggression Scale-Modified (OAS-M)\textsuperscript{17}: will be used to quantify the severity of aggressive behavior. In addition, we will record the frequency of aggressive episodes that resulted in police intervention and legal actions so as to assess pre-morbid aggressive behavior.

**Substance Use Disorders Assessment**

Alcohol consumption will be assessed following a previously reported timeline method\textsuperscript{18}. We will register the number of days per week and per month when the patient drank any alcoholic beverage, the average amount of drinks consumed on drinking days and the number of times when the patient drank five or more drinks. The time frame will be the month previous to the evaluation.

The substance abuse module of the MINI will be used to classify alcohol use disorders into the following DSM-IV categories: Alcohol Dependence and Alcohol Abuse. Alcohol Dependence Remission will be categorized as early (i.e., more than 1 month but less than a year) or sustained (i.e., more than a year) as well as partial or full (i.e., abstinence). Concurrent drug abuse will be categorized according to the DSM-IV criteria for amphetamine, cannabis, cocaine, hallucinogen, opioid, phencyclidine, sedative-hypnotic, or anxiolytic related disorders.

In addition, the Alcohol Use Disorders Identification Test (AUDIT)\textsuperscript{19} will be used to identify harmful alcohol consumption. Those who score eight or more on the AUDIT but who are not classified as having alcohol abuse or dependence based on DSM-IV criteria will be defined as unhealthy consumers of alcohol. The reference period for the AUDIT will be the previous year or the heaviest period of consumption within that time if irregular patterns of consumption are reported. Thus, a patient will be categorized within the unhealthy alcohol use group if he meets DSM-IV criteria for alcohol abuse or alcohol dependence during the year preceding TBI or if he has and AUDIT score of 8 or more during the same period.
Neuropsychological Evaluation

Neuropsychological functioning will be assessed with a comprehensive battery tapping cognitive domains most affected by depression, declarative memory and frontal/executive functions. Performance will be analyzed including several measures per domain, which renders more reliable and valid results than individual observations. Standardized scaled scores or T scores in individual tests will be averaged to obtain a domain score.

Focused/selective attention: The capacity to concentrate and rapidly identify one type of perceptual stimuli. The score will comprise Ruff 2 and 7 Selective Attention Test Total Speed and Accuracy, and Digit-Symbol score from the WAIS III.

Inhibition/Executive Control: The ability to suppress competing distractors in perceptual and attentional input, to control behavior in case of conflicting tendencies, and resistance to interference. The index will be composed by Intrusions and False Positives scores from the CVLT-II, and Delis-Kaplan Color Word Interference Test Inhibition/Switching Total errors score.

Episodic memory: The ability to recall specific verbal and visual information, presented previously in the testing session, and to discriminate that information from related distractors. The index will be based on the California Verbal Learning Test - Short and Long Free Recall and Discrimination, and the Brief Visual Memory Test-R Delayed Recall.

Working memory: Capacity to maintain and simultaneously process immediate incoming information. The measure will be based on the Digit Span, Spatial Span, and Digit-Letter Subtests scores from the WAIS III.

General IQ: An index of general ability, general intelligence, or estimated cognitive level. Derived from Matrix and Similarities Subtests scores, WAIS III, and Wechsler Test of Adult Reading.

9. Primary Outcome:

Time to onset of DSM-IV defined mood and anxiety disorders. These disorders, including mood disorder due to TBI with major depressive features, anxiety disorder due to TBI with generalized anxiety features and post-traumatic stress disorder, will be associated with significant functional impairment and will require immediate therapeutic intervention.

10. Secondary Outcomes:

Total Community Integration Questionnaire scores at baseline, 3, and 6 months.

Inhibition/Executive Control will measure cognitive impairment. Our working hypothesis in this area will be that, when compared with patients treated with placebo, patients receiving sertraline will show improvement of executive control along the six month follow-up period.

Fractional anisotropy of frontal white matter will measure white matter integrity. Our main hypothesis concerning this outcome is that patients who do not develop a mood or anxiety disorder six months after TBI will present at baseline higher FA values of the frontal white matter than the patients who develop a mood or anxiety disorder.
Overt Aggression Scale-Modified total score will quantify the degree of aggressive behavior. We hypothesize that patients receiving sertraline will show significantly lower OAS-M scores than patients receiving placebo.

Working memory composite will measure cognitive impairment. Our working hypothesis in this area will be that, when compared with patients treated with placebo, patients receiving sertraline will show improvement of memory performance along the six month follow-up period.

Neuroimaging variables: We hypothesize that reduced prefrontal and hippocampal volumes will be associated with greater vulnerability to develop mood and anxiety disorders. Similarly, reduced fractional anisotropy of frontal white matter and limbic association pathways (e.g., cingulate bundle and uncinate fasciculus) will be significantly associated with the occurrence of mood disturbance. In addition, reduced prefrontal and hippocampal volumes will constitute an independent risk factor to poor vocational and social outcomes.

11. Statistical Methods:

We focused on specific aim 1 to adequately power this study. Based on the sample size needed to detect a clinically meaningful difference for specific aim one, specific aim 2 resulted over powered to detect what we consider a meaningful effect in this context.

Specific aim 1: We hypothesize that the time of onset of mood or anxiety disorders, as diagnosed by DSM-IV and requiring pharmacotherapy, will be significantly longer in the group of patients receiving sertraline compared to those patients receiving placebo. In order to assess this hypothesis, we will analyze these data using survival techniques (i.e., log rank test).

These data will also allow us to explore the effect of possible moderators and mediators such as alcohol use, substance abuse, previous history of mood disorders, or severity of the TBI. We will use proportional hazards Cox's regression using the time to onset of mood disorders as the dependent variable and group and all covariates of interest as well as all significant interactions as independent variables.

Power analysis: We consider that a 50% reduction in the incidence of mood and anxiety disorders in the group treated with sertraline when compared to the placebo group is a clinically meaningful difference. Our preliminary data for TBI subjects show that there is a 50% incidence of mood and anxiety disorders after six month of the injury. Thus, we expect to find that the patients treated with sertraline will have only a 25% mood and anxiety disorder’s incidence after 6 months of treatment. With 52 participants in each group, when comparing the sertraline group to the placebo group, we will have at least 90% power (at alpha 0.05) to detect a drop in the incidence of mood and anxiety disorders from 0.50 to 0.25 after the 6 months of trauma using the log rank test. This power analysis is assuming that we will have a 20% of participants lost to follow-up in both groups and that half of the participants will be already accrued at month 24 out of the 48 months allocated for accrual.

Specific aim 2:
Hypothesis 2.1: We hypothesize that, when compared with patients receiving placebo, patients receiving sertraline will show a significantly greater improvement in psychosocial outcome as measured by the CIQ. We will use a mixed model regression to analyze these data. The model will include the scores of CIQ as the dependent variable and variables such as group and presence of mood or anxiety disorders during the course of the study as well as other covariates of interest as independent variables. All interactions will be examined. In the case any of the
covariates interacts with the treatment group we will examine the simple effects for each group. The mixed-model analytical approach will allow us to model the correlation of observations the correlation of patient outcomes over time while including all the available data during the course of this study.

Hypothesis 2.2: We hypothesize that when compared with patients receiving placebo, patients receiving sertraline will show a significantly greater improvement in executive functioning as measured by the executive control composite score. We will use the same analytical approach detailed for hypothesis 2.1. The mixed regression model will include the composite scores as the dependent variable and variables such as group and presence of mood or anxiety disorders during the course of the study as independent variables.

Power analysis: Based on a comparison of a simple change score, we will have 90% power to detect an effect size of 0.5 or larger (i.e., standardized difference from the change score) using the standard 2-tailed t-test at alpha 0.05 given 41 subjects in each group. This sample size considers a 20% loss to follow-up. Since the mixed model proposed has greater power than a t-test over a change score, our analysis will have power $\geq 0.90$ for this moderate effect size. This power analysis is valid for the both hypotheses under the specific aim 2. Previous research indicates even larger expected effects sizes which will be more clinically relevant. Seale et al. showed in a similar sample that the increment in four points in the CIQ score at 6 months of follow-up is equivalent to approximately 60% of the patients showing a positive change. This corresponds to a standardized difference greater than 1.0. In the domain of executive functioning, Fann et al. found a clinically meaningful improvement on the executive control measures (i.e., Trail Making Tests A and B) before and after treating TBI patients with sertraline during 2 months. The authors report standardized effect sizes between 0.65 and 0.77.

Specific Aim 3: We hypothesize that when compared with patients who do not develop a mood or anxiety disorder six months after TBI, patients who develop a mood or anxiety disorder will present at baseline with lower fractional anisotropy (FA) value of the frontal white matter. We will use a logistic regression analysis to assess if the FA value of the frontal white matter is a significant predictor of the development of mood and anxiety disorders, after controlling for covariates that might confound this association (e.g., age, severity of the brain injury, and sertraline or placebo administration after TBI).

Power analysis: As mentioned before, we expect to have a 50% incidence of mood and anxiety disorders in the placebo arm and a 25% incidence in the active arm. Out of the 82 expected completers, we then estimate that 40% of the subjects will develop a mood disorder. This sample size will give us 90% power to detect a moderate effect size at alpha 0.05 using the presence of mood and anxiety disorders after 6 months of TBI as the dependent variable and FA value of the frontal white matter and various covariates of interest as the independent variables in a logistic regression analysis.

Covariates in all regression models proposed will be selected using the Akaike information criterion. Baseline characteristics will be described using means and SDs for continuous measures and analyses will be conducted using 2-independent sample t-test. Proportions, odds ratios (ORs), and hazard ratios (HRs) will be reported along with their respective 95% confidence intervals. Size of the effect will be assessed by reporting the number needed-to-treat and its CI following the recommendations by Kraemer and Kupfer. We will use Wilson score CIs for success rate difference as recommended by Newcombe and Bender.
All tests used will be two-tailed. We will analyze the data using the initial intention to treat sample for all the specific aims. We will test all assumptions for each of the statistical methods listed above and take appropriate actions in the case any of the assumptions does not hold.

12. References


