Project Title
Can fluoxetine mitigate the mental health decline seen in patients with musculoskeletal trauma?

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Protocol

1. **Project Title**

   Can fluoxetine mitigate the mental health decline seen in patients with musculoskeletal trauma?

2. **Investigators**

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   Co- Investigators: Ludmilla Barbosa De Faria, MD**;** Marybeth Horodyski, EdD, Terrie Vasilopoulos, PhD, Thomas Krupko, MD; Matthew Patrick, MD; Andre Spiguel, MD; Michael Talerico, MD; Richard Vlasak, MD;

3. **Abstract**

Musculoskeletal trauma is one of the leading causes of disability in the United States and its negative quality of life impact extends beyond that of physical recovery. More than 50% of victims of musculoskeletal trauma suffer lasting mental health issues following their injury. These symptoms can develop across all spectrums of patients with a variety of injury severities. Previously, this research team developed a ten-step program with the aim of developing coping mechanisms in trauma patients. We were unable to demonstrate a measurable benefit to their mental health or physical function. This has been mirrored in other studies as well; talk therapy and support groups are not a strong enough intervention for some patients. The purpose of this pragmatic pilot study is to develop an effective, time-limited treatment strategy that could be safely implemented by non-mental health care providers for victims of musculoskeletal trauma. We will randomize patients 18-85 y/o who are admitted to UF Health Medical center for treatment of musculoskeletal injuries from trauma to Fluoxetine or Calcium. The patients' mental health, pain, medication adherence, self-reported functional outcomes and side effect profile will be recorded for a year. All patients will be taken off medication by nine months. We hypothesize that a subset of the trauma population would benefit from medical treatment for their depressive and anxious symptoms in the early recovery period

4. **Background**

   Over 50% of victims of musculoskeletal trauma suffer prolonged depressive and anxious symptomology following their initial injury. This is an independent risk factor for prolonged mental and physical disability. Support groups, self-help programs and talk therapy, while valuable, have not demonstrated measurable efficacy for this patient population. We hypothesize that a stronger, pharmaceutical intervention started immediately after injury would be effective at diminishing this negative symptomology.

5. **Specific Aims**

   Aim 1: Evaluate the efficacy of immediate Fluoxetine therapy vs standard of care Calcium treatment in improving mental health and wellbeing scores in the post-injury period for victims of musculoskeletal trauma.

Methodology: Patients 18-85 years of age admitted to UF Health with extremity or pelvic fracture(s) resulting from high energy trauma (more than ground level fall) will be enrolled during their index hospitalization. Following informed consent, baseline mental well-being surveys will be obtained (**Table 2**) and patient will be randomized to calcium supplementation or Fluoxetine (commonly known as Prozac®). The medications will be started during the hospitalization and prescribed upon discharge. The patient will be followed in the orthopedic clinic on a standard of care post-operative schedule (2 weeks, 3 months, 6 months, and 12 months). Serial mental well-being surveys will be administered at these time points. Post-operative complications such as infection, nonunion or any other reason for return to OR will be tracked.

Aim 2: Develop a safe Fluoxetine treatment protocol with a goal to be therapeutic by 6 weeks and taper completely off of treatment by 6-12 months.

Methodology: Dr. Barbosa De Faria will monitor symptoms and side effects of the Fluoxetine treatment study arm. Any evidence of escalation of depressive or suicidal ideology in either study population will result in immediate psychiatric evaluation and appropriate treatment. Dr. Barbosa De Faria, the PI Proxy and Co-Investigator, will determine if it is safe for the subject to continue enrollment in the study based on her clinical expertise. Common side effects, medication compliance and appropriate discontinuation will be tracked. Patient reported pain scales will be obtained at each clinic visit as well as documentation of narcotic and cannabis pain treatment during recovery. Patient will be informed of the finite nature of the medical management. We will assess how many patients in the Fluoxetine arm report worsening of symptomology after the cessation of therapy at 9 months and how many seek continued management.

6. Design & Methodology

All patients aged 18 -85under the care of the UF Orthopedic Trauma Division admitted to UF Health for trauma resulting in one or more extremity or pelvic fractures requiring surgery will be screened that meet inclusion/exclusion criteria provided in Table 1**.** Any patients with Traumatic Brain Injury or a past medical history of bipolar or other mental health conditions on current medical management will be excluded. Patients unlikely to follow up (live in at a distance from Gainesville, incarcerated etc.) will also be excluded. Please see table 1 for full inclusion/exclusion criteria. The patients will be approached for enrollment by research personnel during the initial hospitalization. If they consent to participate, they will be randomized to Calcium supplementation (1000mg by mouth per day) or Fluoxetine (10mg by mouth per day). The randomized drug will be prescribed by the orthopedic team on the day randomization so that the patient may be monitored for side effects during the remainder of their hospitalization. The patient will be prescribed the randomized medication on the day of discharge and a 90 day supply will be provided by the inpatient research pharmacy. Patients will be made aware of what drug they are randomized to after the informed consent process is completed.

Several self-administered mental health and patient centered outcomes surveys will be collected during the hospitalization, prior to the initiation of the medication. **(Table 2)**. This will be facilitated by the study team via data entry into portable tablet devices. Data will be immediately entered into a secure Redcap database. All surveys utilized are validated tools.

Inclusion	Exclusion
Patients 18- 85	Traumatic Brain Injury

Admitted to UF Health for trauma resulting in one or more extremity or pelvic fractures	Past medical history of bipolar or other mental health conditions (ie suicide or depression) on current medical management
Informed Consent obtained	Pregnancy
Patient enrolled in the hospital and consented prior to discharge	Incarceration
	Current or past medical history of substance abuse
	Expected injury survival of less than 90 days
	Unlikely to maintain follow up
	Any contra-indications to Fluoxetine or Calcium
	Medical or physical condition in opinion of the investigator that would preclude safe participation in the study
	Unable to provide informed consent due to language barriers or other barriers
	Fracture managed outside of the participating orthopaedic service (ie hand fracture managed by plastics) or transferred from an outside hospital

Table 1: Inclusion/Exclusion Criteria

	Baseline	2 weeks (14-27 days)	6 weeks (28-56 days)	3 months (57-137 days)	6 months (138 to 228 days)	1 year (229-412 days)
BDI-II	x	x	x	x	x	X
BAI	X	x	x	x	x	x
PSQI		x	x	X		
PSS-SR5	x	x	x		x	x
PEG	x	x	x	x	x	x
PROMIS			x	x	x	x
Morisky		x	x	x	x	
ASEC			x			

Table 2: Survey schedule [BDI-II- Beck Depression Inventory-II; BAI- Beck Anxiety Inventory; PSQI- Pittsburgh Sleep Quality Index; PSS-SR5-PTSD Scale-Self report for DSM-5 (pages 2-4); PEG-Pain, Enjoyment, General Activity Scale; PROMIS-Physical function; Morisky Medication Adherence Scale, ASEC- Antidepressant Side Effect Checklist].

The patients will be seen at 2 weeks post-hospitalization as per standard of care for post-surgical patients. During their orthopedic clinic visit they will be asked to complete several surveys to evaluate their mood, pain and to monitor for symptoms. At this visit, those patients randomized to Fluoxetine will have their dose increased to 20mg PO/day. The calcium group dose will remain the same. Subsequent prescriptions will be provided by the CTSI outpatient pharmacy and billed to the study. The study is funded by the Orthopaedic Trauma Research Fund.

Dosage will be standardized for all participants. Participants in the calcium arm will receive 500 mg of Calcium from the CTSI outpatient pharmacy. Participants in the Fluoxetine arm will receive 10 mg at their initial discharge from the hospital. After initial discharge subjects in the Fluoxetine group will be prescribed 20 mg Fluoxetine. The quantity prescribed will be based on time from randomization, distance of patient from OSMI and any perceived difficulties with prescription delivery.

Repeat surveys will be taken at the 6 weeks, 3 months, 6 months and a year follow up visit in the orthopedic clinic (standard of care). Patients in the Fluoxetine study arm that report improvement but incomplete resolution of their mental health symptoms at the 3 month visit will be further up-titrated to 40 mg PO qday. Use of narcotics, CBD/THC/cannabis supplements, illegal substances and alcohol consumption will be recorded. PDMP will be queried for other sources of narcotic prescriptions. Patient reported pain scores (PEG score) will be recorded at each visit. Any complications related to the surgery (i.e. Infection, nonunion, unplanned return to operating room) will be documented. If patients do not return to clinic for their follow-up appointment study personnel will call the patients to complete the survey's over the phone or by email.

Drug cessation plan: At the six month visit, the patient will be prescribed one final 90 day supply of medication (either calcium or Fluoxetine). They will be instructed to complete the medication and then stop. Patients in both study arms will be called 6 weeks after their last dose to monitor for any change in symptoms. In patients from the Fluoxetine arm reporting worsening of mental health symptoms following cessation will be referred to their primary care for further treatment.

Loss to follow up: Every attempt will be made by the study team to retain patients for the entirety of the study period (12 months). If patients are unable or unwilling to come to in-person appointments at the orthopedic clinic, we will contact them via the telephone. Telemedicine appointments will also be offered to patients through the orthopedics clinics, when feasible/appropriate. We will routinely plan for phone survey follow up for the one year visit (unless patient reports surgery-related issues). Medications will be provided in three month supplies three times during the study (at hospital discharge, 3 months and 6 months). We will confirm and update address and phone number information at each study visit. If patients are unable to attend the six month visit, the study medication will be mailed to them.

Abrupt Stoppage: If subjects randomized to Fluoxetine no longer want to take the medication they can abruptly stop the medication safely. Fluoxetine has decades of clinical use and the safety profile is well established It has few side effects, is cost effective and has minimal withdrawal symptoms, if stopped suddenly. This makes it an ideal medicine for use by non-mental health providers, in a patient population with limited resources, such as the current.

Escalating psychiatric issues: Dr. Barbosa De Faria will monitor symptomology of both study groups for the duration of the study and will be the ultimate decider regarding titration of study medication. All patients will be started on 10 mg daily and titrated to 20 mg if medication is well-tolerated, which is the recommended therapeutic dose for adults The maximum dose for the study is 40 mg PO qday which will only be utilized if patients in the Fluoxetine study arm report

improvement but incomplete resolution of their mental health symptoms at the 3 month visit. If patients are unable to tolerate the dose, fluoxetine will be stopped. If Dr. Barbosa De Faria is out of town or unable to be reached then the Department of Psychiatry will be consulted for further evaluation. If the patient reported surveys are concerning for worsening psychiatric illness or evidence of suicidality, she will triage as appropriate. If any patient voices concern about their mental health or expresses suicidality at any of their surgical visits, they will be referred for immediate care at either UF Health emergency room or Meridian. The informed consent form contains both the UF Health Psychiatry number (352-265-4357 or 352-265-5481) and Meridian number (352-274-5600) for patients to call for further evaluation if needed. If the patient calls into the Orthopaedic clinic with mental health issues appropriate care will be provided and instructions given on next steps in accordance with the clinic policies and procedures.

Subjects may experience hesitancy to enrolling in the hospital as they do not appreciate their risk of symptom development and are afraid of being "labeled". Multiple patients have expressed regret at not consenting to randomization at their 2-week visit, once they start to develop PTSD symptomology, and we do not have a mechanism for including them. Additionally, many people do not realize the full impact of their injury until they return home and do not have 24-hour nursing assistance available to them. We have updated this protocol below to include those potential subjects.

DELAYED ENTRY PATH:

All patients aged 18 -85 under the care of the UF Orthopedic Trauma Division admitted to UF Health for trauma resulting in one or more extremity or pelvic fractures requiring surgery will be screened that meet inclusion/exclusion criteria provided in Table 1**.** Any patients with Traumatic Brain Injury or a past medical history of bipolar or other mental health conditions on current medical management will be excluded. Patients unlikely to follow up (live in at a distance from Gainesville, incarcerated etc.) will also be excluded. Please see table 1 for full inclusion/exclusion criteria.

Participants will then be approached for consent. Those patients that express interest in enrolling in the study but hesitancy at being potentially randomized to Fluoxetine, will be offered the "delayed entry" pathway. The delayed entry pathway will allow subjects to complete baseline surveys without being initially randomized to a study medication. Subjects will sign a shortened consent form detailing the delayed entry pathway and asking permission to take baseline study surveys. Subjects will also be given a full consent form to read and take home with them explaining the process for randomization. At the first post operative visit (around the two-week mark) subjects that have been entered into the delayed entry path will be approached by study personnel to follow up on any questions they may have. If at that point they would like to fully enroll, they will sign the full consent, be randomized in the clinic, and the study medication will be mailed to them. The remainder of their study experience will be the same. If subjects still express hesitancy at the first post operative visit no further enrollment will be offered. No further survey data will be completed but their initial baseline data will be kept for analysis.

Avoidance of Coercion:

Healthcare providers will not be made aware if patients are in the study contemplative mode at the clinic visit, to avoid encouragement one way or the other

"Delayed entry" patients will be told during their initial contact with research personnel that they will be approached at the two-week visit so they do not feel over pressured or surprised.

7. Recruitment Strategy

All musculoskeletal trauma patients aged 18-85 admitted to UF Health are cared for by the orthopedic trauma team, of which Dr. Hagen is the Chief, so all will be under our clinical care at the time of study enrollment. Patients that consent to the study will be randomized during their in-patient hospitalization. No recruitment of non-hospitalized patients will occur.

Planned Enrollment Report

Racial Categories	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/ Alaska	1	1			**2**
Asian	1	1			**2**
Native Hawaiian or Other Pacific	1	1			**2**
Black or African	4	10			**14**
White	30	43	4	3	**80**
More Than One Race					**0**
Total	**0**	**0**	**0**	**0**	**100**

based on previous prospective study in this patient population [10]

8. Possible Discomfort and Risks

All patients will have surgery to treat their injury. Being in this study does not change the anesthetic risk or complication risks that patients would normally have following an orthopaedic trauma surgery. The potential surgical risks will be discussed with the patient as part of the surgical consent and are not directly related to the study. Many of these surveys ask questions about pain, mood, and feelings (including those of self-harm or suicide), and are of a personal nature and may be upsetting to some participants. All answers will be kept confidential and only viewed by the IRB approved study staff. If patients express they are experiencing expressing self-harm or thoughts of suicide, study personnel will address them. Questionnaires have been set up in RedCap to alert Dr. Barbosa de Faria if patients have exceeded a threshold where they may be experiencing harmful thoughts. Dr. Barbosa De Faria will triage issues, and appropriate care will be given.

Some patients taking **Fluoxetine** might experience GI distress (nausea, vomiting diarrhea), headaches, insomnia, nervousness and anxiety, sweating, abnormal dreams, dizziness. If patients experience these symptoms then Dr. Barbosa de Faria will decrease the dose or stop the medication.

Some patients taking **Calcium** might experience some minor side effects such as belching or gas. Calcium is **POSSIBLY UNSAFE** when taken by mouth in doses above the daily tolerable upper intake level (UL). The UL is 2000 mg for adults ages 19 and older and 1300 mg for adults aged 18. Our dosage of calcium for subjects in the calcium group is 1000 mg by mouth per day, well within the safety margins. Taking more than this amount of calcium daily can increase the chance of having serious side effects, such as milk-alkali syndrome, a condition that can lead to renal stones, kidney failure, and death.

This study may include risks that are unknown at this time.

9. Possible Benefits

It is possible patients could have improvement in depressive, anxious, and other negative mood symptoms if they are randomized to Fluoxetine. Patients in the calcium group will benefit from calcium's bone healing potential.

10. Conflict of Interest

None, no disclosures

11. Data and Safety Monitoring Plan

OVERSIGHT RESPONSIBILITIES

Day-to-day oversight of the trial is provided by the Principal Investigator (PI), Dr. Jennifer Hagen. Along with Dr. Hagen, Dr. Barbosa de Faria and Dr. Horodyski assure that informed consent is obtained prior to performing any research procedures, that all subjects meet eligibility criteria, and that the study is conducted according to the IRB-approved research plan. Drs. Hagen and Barbosa de Faria, review all study data and any adverse events (AEs) real-time, and report all AEs to the IRB according to the approved UF IRB and DSMP.

<u>Monitor</u>

Monitoring for the study is provided by an board certified psychologist at the University of Florida, including regular data monitoring at the site and regular review by Dr. Barbosa de Faria.

MONITORING PROCEDURES

An outside study staff member reviews study conduct (specifically patients' medication adherence and reported side effects) and AEs in aggregate on a yearly basis. Drs. Hagen and Barbosa de Faria review serious adverse events (SAEs), escalation of mood disturbance, and drug side effects in real-time. Study data are provided to the monitor prior to each yearly review and to Drs. Hagen and Barbosa de Fair before each monthly review. Data reports are prepared by the Clinical Research Coordinator.

MONITORING REPORT

The monitor provides a written report to the study team with recommendations for study

modification, study continuation/discontinuation as relevant.
The study team is responsible for forwarding the report to the IRB.

COLLECTION AND REPORTING OF SAEs AND AEs

For this study, the following standard AE definitions are used:

Adverse event: is any event that is not consistent with the current investigator brochure, protocol, consent form, or is not part of the normal disease progression. In addition, known adverse events may occur more frequently than expected. If so, then this event meets the definition of "unexpected" and must be reported to the IRB.

Serious Adverse Event: Any AE that results in any of the following outcomes:

- Death
- Life-threatening
- Event requiring inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect

AEs are graded according to the following scale:

Mild: An experience that is transient, & requires no special treatment or intervention. The experience does not generally interfere with usual daily activities. This includes transient laboratory test alterations.

Moderate: An experience that is alleviated with simple therapeutic treatments. The experience impacts usual daily activities. Includes laboratory test alterations indicating injury, but without long-term risk.

Severe: An experience that requires therapeutic intervention. The experience interrupts usual daily activities. If hospitalization (or prolongation of hospitalization) is required for treatment it becomes an SAE.

The study uses the following AE attribution scale:

Not related: The AE is clearly not related to the study procedures (i.e., another cause of the event is most plausible and/or a clinically plausible temporal sequence is inconsistent with the onset of the event).

Possibly related: An event that follows a reasonable temporal sequence from the initiation of study procedures, but that could readily have been produced by a number of other factors.

Related: The AE is clearly related to the study procedures.

AEs are identified during the index hospitalization when the medications are started and at each study follow up (2 weeks, 6 weeks, 3 months, 6 months and 12 months). At each patient encounter, study participants will be asked to complete a survey on medication compliance and surveys on their mood and behavior. Any worsening of psychiatric symptoms, instances of violence or self-harm, or hospital admissions for psychiatric-related issues will be identified and reviewed.

SAEs and specific procedure-associated AEs are reported to the PIs (Dr. Hagen and Dr. Barbosa de Faria) within 24 hours. In addition, all AEs are reported according to the UF IRB AE reporting guidelines.

MANAGEMENT OF RISKS TO SUBJECTS

<u>Expected AEs</u>

Expected AEs associated with *fluoxetine* include:

- GI distress (nausea, vomiting diarrhea),

- headaches,
- insomnia,
- nervousness and anxiety,
- sweating,
- abnormal dreams,
- dizziness

AE Management
Decrease dose or stop medication
Dose Escalation and Dose-Limiting Toxicities
All patients will be started on 10 mg daily and titrated to 20 mg if medication is well-tolerated. The maximum dose for the study is 20 mg daily, which is the recommended therapeutic dose for adults. If patients are unable to tolerate the dose, fluoxetine will be stopped.
Expected AEs associated with *Calcium* include:

- Belching
- Gas

AE Management
Decrease dose or stop medication

12. Data Analysis Plan

Drs. Hagen and Barbosa de Faria will review all subject reports side effects, mood scores and medication adherence on a monthly basis with the CRC. Any SAE will be identified and addressed, either with dose titration, medication stoppage, and/or mental health evaluation.
All SEAs will be reviewed in aggregate by the monitor on a yearly basis. Given the decades long safety record of Fluoxetine in the general population, we do not anticipate having to stop the trial. If individual patient are unable to tolerate Fluoxetine, they will no longer be given the medication but will be followed for the duration of the study (12 months) and analyzed as intent-to-treat. Data will contain column to indicate time of entry (baseline or 2 weeks). To assess "delayed entry" pathway statistically, sensitivity analyses will be conducted. First, everyone will be included in analysis, regardless of entry status. Then, we will stratify analyses by entry status, and compare results. Depending on these analyses, we may then include entry status as a covariate in final models.

13. Plan for Data Management

The monitor reviews study data on a yearly basis. No external site monitor will be used for this study. Confidentiality throughout the trial is maintained by assignment of a de-identified study number for each patient enrolled. The master link between their study number and personal identifiers will be kept in a secure location and accessible to study personnel only. All survey responses will be entered directly into a secure electronic device and fed directly into a secure Redcap database.

Supporting Literature:

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