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* Individuals who will be obtaining consent
† Individuals authorized to prescribe study medication

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**2. Title of Project:** An Investigation of the Effects of Riluzole in Patients with Post-Traumatic Stress Disorder (PTSD).

**3. Purpose:** To conduct a pilot study evaluating the efficacy of riluzole 50 mg twice per day in decreasing symptoms of PTSD in patients diagnosed with PTSD.

Post Traumatic Stress Disorder (PTSD) is a debilitating and chronic mental illness with limited treatment options. Currently, there are only two FDA-approved medications both of which are monoaminergic antidepressants. Rates of non-response to these medications are high. The current study aims to examine the efficacy of a novel drug, riluzole, in treating PTSD symptoms. Riluzole is an FDA approved medication for Amyotrophic Lateral Sclerosis. Preclinical studies have shown riluzole to modulate glutamate release and clearance, and to have potent neuroprotective properties, promoting neuro-resilience. Other preclinical data also show the drug to have anxiolytic-like and antidepressant-like effects in rodent models of stress used to screen for antidepressant and anxiolytic activity. In addition, several open-label clinical studies further suggest riluzole has anxiolytic and antidepressant properties, even in patients who do not respond to standard monoaminergic antidepressant and anxiolytic medications. However, to date, riluzole has not been studied in patients suffering from PTSD. The proposed study will provide pilot data on the efficacy of riluzole in PTSD.

**4. Hypothesis:** We predict that riluzole will significantly reduce the symptoms of PTSD (measured by the Clinician Administered PTSD Scale-CAPS scores).

**SPECIFIC AIM 1: To provide preliminary data about the efficacy of riluzole treatment in improving PTSD symptoms.** ***Hypothesis:*** PTSD subjects treated with

riluzole (50 mg twice per day for 12 weeks) will have reduction in PTSD symptoms. To examine the efficacy of riluzole we will compare the mean change in the CAPS total score over the course of 12 weeks of riluzole treatment.

**5. Background**:

*PTSD Is a Debilitating Illness with Limited Treatment Options*

The House Veterans Affairs Committee issued a report in mid October 2006 stating that the number of Iraq and Afghanistan veterans seeking help for PTSD has gone from 4500 to 9000 from October 2005 through June 2006. In the general adult population, PTSD has a lifetime prevalence rate ranging from approximately 5 - 10%[1, 2]. PTSD tends to be a chronic disorder with one third of sufferers having symptoms more than ten years after experiencing the traumatic event[3, 4]. The symptom profile for PTSD includes avoidance, arousal and re-experiencing symptoms.

Despite the disabling and chronic nature of PTSD, only two medications, both of them selective serotonin reuptake inhibitors (SSRIs), have FDA-approval for PTSD treatment[5-8]. However, accumulating evidence highlights the limitation of SSRI treatment and the prevalence of SSRI-resistant PTSD[2, 9, 10].

*Riluzole Is A Glutamate Modulating Agent With Anxiolytic And Antidepressant Effects.*

Over the last two decades, convergent lines of research have demonstrated aberrant glutamatergic function in mood and anxiety disorders[11, 12]. These neurobiological findings have been underscored by preliminary trials showing promising results for novel drugs with glutamate-based mechanisms[13, 14]. One such medication is riluzole, an agent possessing neuroprotective properties [15-17] approved by the United States Food and Drug Administration for treatment of Amyotrophic Lateral Sclerosis. Riluzole is believed to exert its pharmacological effects primarily by reducing pre-synaptic glutamate release and potentiating glutamate reuptake [18]. In open-label trials at Yale and other institutions, riluzole showed significant anxiolytic properties in patients with major depression [19, 20], bipolar depression [21], obsessive-compulsive disorder [22], and generalized anxiety disorder (GAD) [23] (for review see references. [18, 24]). However, to date, riluzole was not studied in patients with PTSD.

**6. Significance of proposed research:** Our proposed study is the first to examine the effect and feasibility of riluzole treatment for PTSD. Data from this pilot study will inform the design of future larger double-blind controlled studies. For e.g., if PTSD veterans showed full early response to riluzole following 1-4 weeks, this will affect the design of future definitive (likely multisite) studies.While placebo-controlled studies are standard for FDA approval and definitive clinical trials confirming efficacy, an open label approach is appropriate for pilot studies seeking early signals of efficacy and optimal treatment regimen. Pilot open label studies are essential for early phase of drug development.

**7. Experimental subjects**: We anticipate approximately 20 male and female subjects with PTSD, between the ages of 18-75 years, to complete all study procedures. In order to account for screenings failure and subject drop outs, and retain a sample of 20 subjects completing the treatment phase, approximately 50 eligible subjects will be enrolled.

*Inclusion Criteria:*

- Male or female subjects between the ages of 18-75 years;
- Able to provide written informed consent;
- Current Post Traumatic Stress Disorder, as determined by the Clinician Administered Scale for PTSD, or the presence of sub-threshold PTSD. Individuals with sub-threshold PTSD will be included at the discretion of the PI;
- Clinician Administered PTSD Scale (CAPS) score of 23 or higher;
- Be able to understand and speak English.
- Subjects taking FDA-approved antidepressant medications may enter the study if they have been on a stable dose for at least 4 weeks prior to starting the study drug.

*Exclusion Criteria:*

- Breastfeeding women and pregnant women, or women of child bearing potential who are not using a medically accepted means of contraception (to include oral, injectable, or implant birth control, condom, diaphragm with spermicide, intrauterine device, tubal ligation, abstinence, or partner with vasectomy);
- Current, ongoing serious suicidal risk as assessed by evaluating investigator or by scoring 5 or more on the item-10 of the MADRS.
- Unstable medical illness as determined by the investigator;
- Patients with schizophrenia or schizoaffective disorders (current or past);
- Substance use disorder during the 3 months prior to screening; except for Cannabis and Alcohol use Disorders.
- Clinical evidence of untreated hypothyroidism;
- Patients with any evidence of clinically significant liver abnormalities, or any liver transaminase level > 1.5 x ULN at initial screening, or > 5 x ULN during treatment;
- Axis II personality disorders that are the primary purpose of treatment, or would interfere with a patient's safety or compliance, as determined by the investigator during open-ended psychiatric interview;
- Patients currently being treated for a respiratory disorder (including asthma or COPD);
- For participants over the age of 60, evidence of dementia as determined by the St. Luis University Mental Status Exam (SLUMS; participants with total scores less than or equal to 20 will be excluded and referred to their Primary Care Physician for follow-up/dementia evaluation);

Structured psychotherapy focused on treatment of PTSD is exclusionary unless the subject has had at least 8 weeks of treatment prior to starting the study medication;

**8. Privacy:** All reports generated from the data obtained through this study will protect the confidentiality of the subjects who participate in this study. All subjects will be given a "wallet card" which identifies them as a study participant and lists the emergency contact numbers. If a subject shows clinical deterioration (worsening of PTSD symptoms), Dr. Abdallah will determine whether: 1) the subject can remain in the study, or; 2) a higher level of care (e.g. referral back to treating psychiatrist or referral to emergency or inpatient care) is needed.

**9. Selection**: Subject eligibility will first be assessed via telephone screening and if records are available, by a preliminary medical record review. If the subject seems to be a likely candidate for inclusion in this protocol, he or she will be evaluated for study eligibility in person. Telephone screens will occur by experienced research personnel adept with this process. Following a face-to-face evaluation and discussion with the research team, an experienced study investigator will determine suitability for enrollment.

**10. Recruitment:** Subjects will be recruited through flyers, public advertisement (newspaper, radio, internet posting), by word of mouth, contact with community service groups, our local IRB-approved screening protocol (KW0003), and clinics and local treatment facilities (e.g., VA Hospital, Community-Based Outpatient Clinics, local private practices). Subjects will be identified via their response to advertisementsand/or internal recruiting through the research clinics. Subjects will be asked to call us at the number provided on the flyers if they are interested in participating in the research study. Subjects will be contacted for follow-up appointments via the most convenient means and personal preference, e.g. telephone. All available research staff is responsible for recruiting potential subjects.

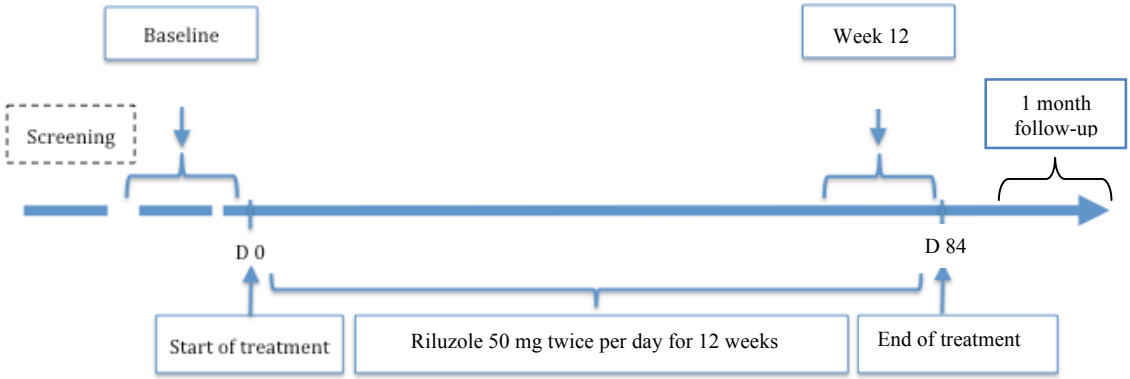
**11. Research Plan:** This study will be conducted at the VA Hospital, West Haven, CT.

*Overview*: This is a diagnosis-informed study designed to provide preliminary data regarding the efficacy and tolerability of riluzole to treat symptoms of PTSD. Subjects diagnosed with PTSD will receive riluzole, 50 mg taken twice daily (BID) for 12 weeks. PTSD subjects will be followed closely on a weekly basis and their liver function and pregnancy tests will be repeated (see Table 1).

*Dosing*: Following confirmation of eligibility, the dosing regimen for the first week of study medication is 50 mg twice a day (BID). Subjects who are unable to tolerate the study medication will be allowed to take a lower dose. For these subjects, the dose may be lowered to 50 mg taken once a day (QD). Subjects who are unable to tolerate the once a day 50 mg (QD) dosing regimen will be discontinued from the study. Riluzole should be taken 1 hour before or 2 hours after a meal to avoid food-related decreases in bioavailability.

A schedule of the study events is provided in Table 1.

**Figure 1. Study Design**




*A.*

*Participants*: Twenty patients with a current diagnosis of PTSD or sub-threshold PTSD between the ages of 18-75 will complete the treatment phase of the study. Subjects will initially be pre-screened by phone interview and a preliminary medical record review. Eligible subjects will then be invited for an in-office visit and will complete the written informed consent process. Subjects will be thoroughly screened for inclusion and exclusion criteria as described below.

*B.* *Discontinuation of subjects*: Subjects may be discontinued from study treatment and assessments at any time. Specific reasons for discontinuing a subject from this study are:

- Voluntary discontinuation by the subject, who is at any time free to discontinue his/her participation in the study without prejudice to further treatment;
- Clinical deterioration: The following are objective criteria for clinical deterioration, (1) a 35% increase in CAPS scores at any time during the study, (2) Patients with a CGI-I score $\geq 6$ at any post-baseline visit, and (3) the onset of active suicidality as assessed by the study investigator or by scoring 5 or more on the item-10 of MADRS;
- Evidence of neutropenia (ANC $\leq 1500$) or other intolerable adverse reaction, or unable to tolerate study drug;
- Transaminase levels > 5x ULN;
- Safety reasons as judged by the investigator;
- Stopping birth control or positive pregnancy test;
- Evidence of illicit drug abuse (except for cannabis) or problematic alcohol use during trial;
- Non-compliance to protocol as judged by the investigator; Subjects who do not take between 75-125% of study medication for two consecutive visits are considered non-adherent and are withdrawn from the study medication.

A subject that prematurely discontinues (i.e. stops study medication or no longer wishes to participate) will always be asked about the reason(s) for discontinuation and the presence of any adverse events. If possible, they will be seen and assessed by the investigator. Adverse events will be followed up as medically necessary.

*C.* *Screening Procedures and Behavioral Assessments:* A waiver of HIPAA authorization and written informed consent will be obtained for a brief initial phone screen and preliminary medical record review. The phone screen and preliminary medical record review will be done to determine obvious exclusions from the study protocol and to prevent subjects from making unnecessary travel for screening as well as possibly delaying the start of other treatments. Potentially eligible subjects will then be invited for an in-office screening visit, sign the VA informed consent, the VA HIPAA, be personally interviewed and begin the medical assessments. All subjects will have an initial screening assessment that includes medical history, physical examination, laboratory testing, psychiatric history and standardized psychiatric assessments.

C.1. Historical and Demographic Information: Each subject will complete a demographic information form. This document will elicit information about the subjects' demographics including education level, socioeconomic status, race and ethnicity. In addition, it will also request information on the subject's family history of mental illness.

C.2. Screening Physical Exam and Laboratories: All subjects will have a standard physical examination (including neurological examination) conducted by a physician/APRN at the time of the initial screening. Routine laboratory studies include CBC, CMP, baseline HCG, TSH, fT4, RPR, ESR, CRP, urinalysis, and urine toxicology screen. An ECG will also be obtained. Additional tests will be requested as clinically indicated.

C.3. Screening and Behavioral Assessments: PTSD subjects will have an open ended psychiatric interview, in addition to a structured clinical interview (i.e. SCID or MINI). Baseline and follow-up ratings will also be obtained via assessment measures of PTSD, trauma, depression, anxiety, sleep, alcohol use, and adverse effects. Subjects will also complete a computerized neuropsychological test battery called 'Cogstate' (see Table 1).

It is estimated that the total amount of time required by the patient to determine screening eligibility will be 7 hours. It will require one hour of time to complete each of the scheduled CAPS interviews. Repeated follow-up visits (including rating scales, blood work, urine screens, etc.) without the above cited assessments, will last for approximately 45 minutes to one hour. If necessary due to time commitments or difficulties with scheduling, some visits may take place over more than one day during the study week.

Each of the psychiatric, behavioral and cognitive assessment instruments is briefly described below.

1. *Clinician Administered PTSD Scale* (CAPS): The CAPS is a standardized clinician-rated instrument to assess the presence and severity of PTSD symptoms.
2. *Post Traumatic Stress Disorder Checklist* (PCL): The PCL is used to measure PTSD symptoms and is a self-report questionnaire that shares similar reliability with the CAPS.
3. *The Combat Exposure Scale (CES):* The CES is a self-report instrument that measures reports of wartime stressors on a 5 point Likert Scale format.
4. *Early Trauma Inventory (ETI-SR)* The ETI-SR is a self-report instrument to assess childhood trauma and includes physical, emotional and sexual abuse as well as general traumas.
5. *Klein Loss Scale (KLS*): The KLS is a self-report of parental loss or separation during childhood.
6. *Global Perceived Early Life Stress (GPELS):* The GPELS is a self-report of perceived stress during childhood.
7. *Montgomery-Asberg Depression Rating Scale* (MADRS): The MADRS is a standardized instrument to ascertain depressed mood and neurovegetative signs and symptoms of depression.
8. *Quick Inventory of Depressive Symptoms – Self-Report* (QIDS-SR): The QIDS-SR is a patient-rated depression instrument.
9. *Massachusetts General Hospital Antidepressant Treatment History Questionnaire (MGH-ATRQ)*-This is a self-rated questionnaire used to determine treatment resistance in major depressive disorder.
10. *Clinical Global Impressions Scale* (CGI) and the Patient Global Impressions Scale (PGI): The CGI and PGI are widely used instruments, which assess overall severity of illness on a 1 to 7 point scale with 1 indicating "normal, not at all ill" and 7 indicating "among the most extremely ill patients." These instruments also assess global improvement on a 1-to-7 point scale with 1 indicating "very much improved," 4 indicating "no change" and 7 indicating "very much worse."
11. *Penn State Worry Questionnaire (PSWQ):* The PSWQ is a self-report questionnaire to assess for 'worry' symptoms that are typical of generalized anxiety.
12. *Pittsburgh Sleep Quality Index (PSQI):* The PSQI is a self-report questionnaire to assess sleep quality and sleep disturbance.
13. *Sheehan Disability Scale (SDS*): The SDS is a brief self-rated measure of disability and impairment.
14. *Columbia-Suicide Severity Rating Scale* (C-SSRS): The C-SSRS is a brief clinician administered and standardized measure that uniquely assesses essential information about suicide behavior, ideation, lethality and severity, and distinguishes between suicidal occurrences and non-suicidal self-injury.
15. *Cogstate* is a brief computerized neuropsychological test battery. We will administer the following subtests from this battery to assess working memory,

visual motor function, visual attention executive function,verbal learning/memory and visual learning/memory: One Back and Two Back Test, Chase Test, Identification Task, Groton Maze Learning Test (with delayed recall), the International Shopping List Task (with delayed recall) and the One Card Learning Task.

16. *St. Luis University Mental Status Exam (SLUMS)* – The SLUMS is a dementia screening instrument. It will be administered to participants who are 60 or older during our screening process.
17. *Modified Military Acute Concussion Evaluation (MACE)* - The MACE is a concussion screening tool for the acute assessment of service members involved in a potentially concussive event.
18. *Alcohol and Consumption Habits*- This is a brief measure that documents alcohol, caffeine and nicotine habits.
19. *Systematic Assessment for Treatment Emergent Events* (SAFTEE): The SAFTEE is a commonly used instrument originally developed by NIMH and adapted into a self-report instrument. It examines, in systematic fashion, possible treatment-emergent side effects and probes for specific adverse symptoms, including suicidal thoughts and behaviors, and self-injurious behavior.
20. *Drug Attitude Inventory- (DAI)*:The DAI evaluates how attitudes about medications may affect treatment adherence. The items with the most potential for discrimination between dosing compliance and noncompliance are related to subjective 'feeling' factors.
21. *Perceived Stress Scale (PSS):* This is a 10-item self-report questionnaire to assess the severity of perceived stress over the past month.
22. *Cumulative Adversity Interview (CAI):* A multifaceted semi-structured assessment of stressful life events and chronic subjective stress used in research on stress and psychopathology.

Due to the potential of Riluzole to cause elevations in serum aminotransferase levels, liver function tests will be reviewed and monitored for medical significance (marking NCS for results not clinically significant) by the PI, a co-investigator or other medical research personnel (A.P.R.N., R.N. etc.). If any liver transaminase level is > 5X the UNL, the study investigator will be informed and the patient will be discontinued from the study, with appropriate medical follow-up.

PTSD subjects receiving the study medication will be seen weekly. Compliance with study medication will also be assessed weekly and at each visit. Subjects will be given medication diary cards to record the medication that they have taken at each daily dosing interval and the medication that was missed at each dosing interval. Drug accountability will then be done between the medication that was returned and the medication recorded as being taken on the diary cards. A subset of the interviews and measures obtained throughout the study will be repeated at a one-month, in person follow-up. This follow-up will be used to evaluate any lasting effects of the treatment, if any.

The presence of any spontaneously reported side effect or adverse event is carefully documented. Reasons for premature discontinuation of study medication, including intolerable side effects, are recorded; however, all willing subjects continue to return for weekly evaluations as if they remain on study medication.

All concomitant medications taken during the study are also recorded in the paper research chart, along with dosage information and start and stop dates. Medication management and clinical ratings are performed by the study physician/APRN and the clinical rater, respectively.

Subjects who are unable to tolerate the study medication after adjusting the dosing regimen to the lowest dose of 50 mg QD are withdrawn from study medication. Treatment adherence is monitored by pill counts. In order to minimize risks, subjects are advised during the consenting process that if they discontinue the study medication prematurely, the researchers want them to continue study evaluations as if they were still on the study medication for reasons of safety monitoring (i.e. to evaluate the possibility of withdrawal effects from abrupt discontinuation of the study drug, worsening of psychological symptoms or other newly emergent medical symptoms after stopping the study drug). Non-adherent patients are classified as dropouts in the analysis.

***Audio Recording:***

Clinician administered interviews may be audio recorded for inter-rater reliability and staff training purposes. Subject identifying information such as name, DOB, SSN, age, etc will not be on the audio recording. Recordings will be stored in a locked cabinet when not in use. Subjects will be asked on the consent form to indicate whether or not they agree to having their clinical interviews audio recorded. If subjects disagree to having their clinical interview audio recorded, it will not affect their eligibility to participate in study procedures.

**Data Analysis**

Descriptive statistics will be calculated prior to statistical analysis. Distributions of quantitative variables will be assessed for normality using normal probability plots and Kolmogorov-Smirnov statistics and transformations or non-parametric methods will be used as necessary. All statistical tests will be two-sided. Uncorrected alpha level of 0.05 will be used for testing the primary hypothesis. Pairwise post-hoc comparisons and tests of secondary outcome measures will be adjusted using Holm-Bonferroni procedure. All analyses will be intent-to-treat. We will using mixed effects regression models, with time effects for the primary outcome variable (CAPS). We do not expect significant moderating effects of alcohol use comorbidity but will assess the interaction between treatment and alcohol use comorbidity and perform follow-up tests as necessary. This approach will be applied to most secondary outcome measures as well. Mixed effects regression models use all available data on each subject, are flexible in modeling the correlation structure of the data and give unbiased results under missing at random

assumptions. In addition to testing the potential moderating effect of comorbid alcohol use described above, we will also perform exploratory analyses to the assess moderating effects of depression, medication status, substance abuse, age, and gender by adding these factors one at a time to the models above and testing interactions between each potential moderator and treatment group. Effects of intermittent missing data due to non-compliance with treatment schedule can also be assessed.

Table 1. Schedule of Study Events**

| Visit | Screening [a] | Baseline | 1 | 2&3 | 4 | 5,6,&7 | 8 | 9,10,11 | 12 | 1 month follow-up |
|---|---|---|---|---|---|---|---|---|---|---|
| Day | 0 | 0 | 7 | 14&21 | 28 | 35,42, & 49 | 56 | 63, 70, &77 | 84 | 114 |
| **Informed Consent [b]** | X | | | | | | | | | |
| **Demographics** | X | | | | | | | | | |
| **SCID / MINI** | X | | | | | | | | | |
| **C-SSRS baseline** | X | | | | | | | | | |
| **MGH ATRQ** | X | | | | | | | | | |
| **ETI-SR, KLS, GPELS, CES** | X | | | | | | | | | |
| **M-MACE** | X | | | | | | | | | |
| **Psychiatric Evaluation** | X | | | | | | | | | |
| **BP, Pulse, Resp., Wt., Temp.** | X | X | X | X | X | X | X | X | X | |
| **ECG** | X | | | | | | | | | |
| **Physical Exam** | X | | | | | | | | | |
| **CBC** | X | | | | X | | X | | X | |
| **CMP** | X | | | | LFTs | | LFTs | | LFTs | |
| **Serum Pregnancy (1)/ Urine Pregnancy (2)** | X(1) | X (2) | | | X(2) | | X(2) | | X(2) | |
| **Urinalysis** | X | | | | | | | | | |
| **Inclusion/Exclusion** | X | | | | | | | | | |
| **CAPS** | X | X [c] | | | | X (visit 6 only) | | | X | X |
| **MADRS** | X | X | X | X | X | X | X | X | X | X |
| **PCL, QIDS-SR, PSWQ, PSQI, SDS, SAFTEE** | | X | X | X | X | X | X | X | X | X |
| **Alcohol Consumption** | X | X | X | X | X | X | X | X | X | X |
| **Drug Accountability** | | X | X | X | X | X | X | X | X | X |
| **Concomitant Meds** | X | X | X | X | X | X | X | X | X | |
| **Collect AEs and SAEs** | | X | X | X | X | X | X | X | X | X |
| **CGI-S/I and PGI-S/I** | | X | X | X | X | X | X | X | X | X |
| **Urine Toxicology** | X | X | | | | | | | X | |
| **Ethanol Breath Test/DAI** | | X | | | | | | | X | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Cogstate** | Practice | X | | | | X (Visit 6 only) | | | X | X |
| **St. Luis University Mental Status Exam** | X | | | | | | | | | |

** Day number reflects the approximate date, a window is allowed for scheduling and completion of the weekly study visits. **a.** Screening refers to the period between signing consent and completion of screening. As such this visit refers to one or multiple visits. **b.** Informed consent will be obtained prior to any study procedure. **c.** CAPS will be repeated at the discretion of the investigator or if 4 or more weeks elapsed since the prior CAPS. **Abbreviations**: Structured Clinical Interview for DSM (SCID), Mini International Neuropsychiatric Interview (MINI), Columbia-Suicide Severity Rating Scale (C-SSRS), MGH Antidepressant Treatment Response Questionnaire (MGH-ATRP), Early Trauma Inventory – Self Report (ETI-SR), Klein Loss Scale (KLS), Global Perceived Early-Life Stress (GPELS), Combat Exposure Scale (CES), Modified Military Acute Concussion Evaluation (M-MACE), Clinician Administered PTSD Scale (CAPS), *Post Traumatic Stress Disorder Checklist* (PCL), Montgomery-Asberg Depression Rating Scale (MADRS), Quick Inventory of Depressive Symptomatology – Self Report (QIDS-SR), Penn State Worry Questionnaire (PSWQ), Clinical Global Impression Severity/Improvement (CGI-S/I), Patient Global Impression-Severity/Improvement (PGI-S/I), *Systematic Assessment for Treatment Emergent Events* (SAFTEE), Pittsburgh Sleep Quality Index (PSQI), Electrocardiogram (ECG), Complete Blood Count (CBC), Comprehensive Metabolic Panel (CMP), Drug Attitude Inventory (DAI).

## 12. Risks and Benefits:

General: While subjects are participating in this study, they will temporarily forgo the opportunity to receive routine clinical psychiatric care in the community (i.e. patients are asked to maintain their treatment regimen throughout the study). This will be clearly explained to all patients, along with the treatment strategies that are generally used in patients with PTSD. Patients will also be told that riluzole is available for prescription by clinicians in the community; however, it has not received FDA approval for the indication of PTSD.

Screening and evaluation: The risks and discomforts of the screening and evaluations are minimal. No discomfort is expected to be associated with the physical examination or intake interview with the study staff other than the possible stress of answering personal questions. Subjects will be answering questions about their symptoms of PTSD and filling out questionnaires. They may find this process to be inconvenient, uncomfortable or upsetting. The psychological testing may include personal questions about previous experiences. The questions will be asked in a private room. Subjects will be informed that they do not have to answer any question that they do not want to answer. Subjects will also have the option to discuss their concerns with someone on the research staff. One or more individuals will be available to talk to the subjects should they become distressed during an interview or while filling out questionnaires.

Risks of ECG test: Sometimes the adhesive pads used to attach the leads for recording the electrical activity of the heart (ECG) can cause skin irritation. Such irritation usually clears without treatment.

Blood drawing: Blood samples are taken from a vein in the inside of the elbow or lower arm. Blood collection is done using a disposable needle or syringe. The risks or side

effects associated with taking blood from a vein are bruises, local irritation (swelling) with itching, slight bleeding and inflammation. In rare cases, it may result in thrombosis (blood clots) or an infection. Insertion of the needle can cause localized pain or pain at the needle puncture site. Subjects may feel slightly weak or lightheaded, or faint. Occasionally, in rare cases, inserting the needle can result in injury to a nerve. Subjects are closely monitored and checked for these or other symptoms and we will take appropriate measures if they occur. Normally these problems improve with time and no additional medical treatment is needed. Using trained personnel, as well as using sterile conditions minimizes these risks.

The total maximum quantity of blood that may be taken over the entire course of this study is less than 300 ml. This is 1.27 cups of blood. The blood is taken slowly over the course of the study. As a comparison, during a blood donor session, 450 mL (or less than 2 cups) of blood is taken in one visit.

Delay in treatment: By participating in this study, subjects are likely to experience a delay in starting other treatment due to the thorough diagnostic evaluation. Furthermore, since it is unknown whether riluzole is effective in the treatment of PTSD, participation in this trial could delay potentially effective therapy. During this period, it is possible that subjects' conditions could worsen and lead to increased disturbances in mood, sleep, appetite, and cognition. This could result in work loss, loss of social function, and possibly increased risk of suicide. However, the risk should be minimized as there are several safety precautions in place and subjects will remain in close contact with study clinicians.

Riluzole: Most side effects are usually mild and resolve after stopping the drug. The most commonly observed adverse reactions of riluzole, dosed at 100mg/day, in placebo-controlled trials were asthenia (19.2%), nausea (16.3%), decreased lung functioning (10.2%), headache (7.3%), rhinitis (6.4%), hypertonia (6.1%), hypertension (5.1%), abdominal pain (5.1%), weight loss (4.8%), vomiting (4.2%), dizziness (3.9%), dyspnea (3.8%), pruritus (3.8%), insomnia (3.5%), dry mouth (3.5%), arthralgia (3.5%), back pain (3.2%), anorexia (3.2%), peripheral edema (2.9%), diarrhea (2.9%), increased cough (2.6%), tachycardia (2.6%), flatulence (2.6%), urinary tract infection (2.6%), somnolence (1.9%), vertigo (1.9%), oral paresthesia, and, pneumonia. Cases of interstitial lung disease have been reported in patients treated with riluzole, some of them severe; upon further investigation, many of these cases were hypersensitivity pneumonitis. If respiratory symptoms develop such as dry cough and/or dyspnea, chest radiography should be performed, and in case of findings suggestive of interstitial lung disease or hypersensitivity pneumonitis (e.g., bilateral diffuse lung opacities), riluzole should be discontinued immediately. In the majority of the reported cases, symptoms resolved after drug discontinuation and symptomatic treatment.

Dizziness, diarrhea, anorexia, and circumoral paresthesia occurred more frequently with 200 mg/day riluzole. In a study with approximately 4,000 patients given riluzole for ALS, three cases of neutropenia were reported within the first two months of treatment. Any

new medication has the potential for a rare, infrequent reaction of hypersensitivity, including anaphylaxis.

*Uncommon side-effects:* neutropenia – very rarely there is an abnormal drop in the number of white blood cells within the first two months of treatment. Rarely, jaundice is a side effect as well. Riluzole has also been found to cause elevations in serum aminotransferase even in patients without a history of liver disease. Experience with riluzole in 800 patients with ALS demonstrated that approximately 50% of riluzole treated patients experienced at least one ALT/SGPT level above the ULN, 8% had elevations > 3 x ULN, and 2% > 5 x ULN. A single non-ALS patient with epilepsy treated with concomitant carbamazepine and phenobarbital experienced marked, rapid elevations of liver enzyme with jaundice four months after starting riluzole that returned to normal seven weeks after treatment discontinuation. Another rare side effect is pancreatitis. It is estimated that pancreatitis can occur in 4.5/10000 treated patients. A recently published Cochrane Database Systems Review [68] states "Adverse effects from riluzole are relatively minor and for the most part reversible after stopping the drug" in the plain language summary.

Riluzole is Pregnancy Category C: Riluzole is detected in breast milk of rodents, and the recommendation from the PDR is for riluzole not to be used. Women who are breastfeeding will be excluded from enrollment. If a woman becomes pregnant during the study, the study medication will be discontinued.

Worsening of symptoms and suicide risk: At any time during the study, subjects may experience a worsening of symptoms and possibly have serious thoughts of suicide or of harming themselves.

Unidentified or unforeseen risks: Participation in this study may involve risks that are not known at this time.

**Minimizing Risks:** We describe below the manner in which the above-mentioned risks will be minimized.

Subject Recruitment and Consent: Subjects will be recruited through flyers, public advertisement (newspaper, radio, internet posting), by word of mouth, contact with community service groups, the NCPTSD's approved screening protocol (KW0003), and clinics and local treatment facilities (e.g., VA Hospital, Community-Based Outpatient Clinics, local private practices). Subjects will be identified via their response to advertisementsand/or internal recruiting through the research clinics. Subjects will be asked to call us at the number provided on the flyers if they are interested in participating in the research study. Subjects will be contacted for follow-up appointments via the most convenient means and personal preference, e.g. telephone. All available research staff is responsible for recruiting potential subjects.

After an initial phone screening, consent forms will be given to all prospective subjects, which detail all aspects of the project. The consent form will include the risks of

participation, assurance of efforts to maintain confidentiality, and will state that patients are free to refuse participation or to withdraw from the project and receive open uncontrolled treatment according to clinical indication, without loss of benefits to which they are otherwise entitled. The informed consent procedures will comply with the standards of the Institutional Review Boards at the VA.

A member of the research team will obtain written consent from the participants after explaining the procedures and risks involved. The original signed consent form is kept in a separate file from the subjects' research chart. The consent makes it explicit that the protocol involves return visits at specified times. Participants are informed of the amount of blood (less than 300mL or 1.27 cups) that will be drawn in the various procedures and the nature of the assays that will be performed. In particular, the consent form indicates that the nature of treatment is determined by the protocol, and that the study is a trial to evaluate efficacy of riluzole. Subjects will be informed that if their clinical condition deteriorates during the study, they may be hospitalized. The consent procedure is viewed as a process rather than a single event, and patients will be encouraged to discuss the study with the research team.

Protection Against Risks: All clinical raters have experience in clinical psychiatric assessment and will make every effort to implement protocol procedures in a sensitive and supportive manner. Research interviews will be interrupted if subjects become distressed or object to answering questions. Other measures to minimize risks include the careful assessment of each subject before the study, and close clinical scrutiny during all aspects of the study. Screening for suicide risk factors and suicidality is described in the research design.

Weekly contact is maintained throughout the clinical trial. A study staff member will call participants, during any week in which there is no clinic visits, to help ensure subject safety and protocol adherence.

We have included safety measures such as discontinuation of the study drug and transition to standard clinical treatment should subjects worsen to a sufficient degree. These precautions are likely to be highly effective in minimizing risks. Subjects may be hospitalized if they have a worsening of their symptoms, including becoming suicidal. In this case or if subjects discontinue study medication they will receive standard short-term clinical treatment as indicated.

Due to the potential of riluzole to cause elevations in serum aminotransferase levels, subjects will have liver function tests performed prior to initiating the trial and monthly for the duration of the study, or more frequently if clinically indicated. Patients with any evidence of clinically significant liver abnormalities or any liver transaminase level > 1.5 x ULN at baseline will be excluded from the study. Subjects will be discontinued from the study if any LFT measure rises above 5 x the ULN once treatment has been initiated. This is the recommendation in the PDR and is what has been used in previous studies. If treatment is terminated due to physical risks, subjects will be followed carefully until resolution of symptoms and treated with the follow up care described in the protocol.

Subjects will also be asked to report any cough, difficulty breathing or chills to the study staff in order to monitor for the possible emergence of interstitial lung disease or hypersensitivity pneumonitis. The study investigator, physician/APRN, and rater ask patients about any new symptoms at every visit.

Suicidal Ideation and Imminent Harm: Despite treatment, people with PTSD may get worse. All communications about suicide and threats are taken seriously. It is important to assess the risk of suicide carefully when working with these individuals. Many subjects may admit to fleeting thoughts of death or briefly wishing for death; these thoughts need to be considered in context of the subject's overall history, along with a consideration of other risk factors for suicide. Study clinicians will assess patients at each visit for suicide risk and potential. Individuals at such risk will be treated appropriately, including options such as increased contact, more frequent clinical visits, or emergent psychiatric hospitalization. Subjects who score > 5 on the MADRS item 10 (suicide) at screening will be excluded from the study. In addition, a serious suicide or homicide risk, as assessed by evaluating clinician will be considered an exclusion criterion.

Throughout the study, any subject who scores ≥ 5 on the MADRS item number 10 will be discontinued from the study. Any subject with scores of ≥ 6 on the CGI-I will be discontinued from the study.

Subjects will be informed of any important discoveries made during this study, which may affect their condition or willingness to participate in this study by leaving a message (with subject permission) to contact the study team or by letter, if the subject cannot be reached by phone.

**Possible Benefits:**

Subjects may not receive any benefit from participating, though it may help patients in the future by giving important information about the study medication and PTSD. Subjects may benefit from initial screening procedures that will include careful examination of their physical status and psychiatric condition. In the event that clinical abnormalities are discovered, subjects will be informed of the finding and referred for appropriate care. Subjects' conditions may improve from taking the study drug. However, we cannot and do not guarantee or promise that they receive any benefits from participating in the study. Study personnel will offer a referral to treatment after completion of this study. The relative risks and inconveniences associated with participation in this study are balanced by the potential benefits to society, particularly patients suffering from PTSD.

**13. Data Safety Monitoring Plan:**

The investigator's assessment of the overall risk for subjects participating in this study is moderate.

**Moderate Risk DSMP**

**1. Personnel responsible for the safety review and its frequency:**

The principal investigator, Chadi Abdallah, M.D., will be responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency, which must be conducted at a minimum of every 6 months (including when reapproval of the protocol is sought). During the review process, the principal investigator (monitor) will evaluate whether the study should continue unchanged, require modification/amendment, continue or close to enrollment. Either the principal investigator or the IRB have the authority to stop or suspend the study or require modifications.

**2. The risks associated with the current study are deemed moderate for the following reasons:**

1. We do not view the risks associated with riluzole as minimal.
2. Given the established safety and validity of the use of riluzole, we do not view the proposed study as high risk.

Although we have assessed the proposed study as one of moderate risk, the potential exists for anticipated and/or unanticipated adverse events, serious or otherwise, to occur since it is not possible to predict with certainty the absolute risk in any given individual or in advance of first-hand experience with the proposed study methods.

Therefore, we provide a plan for monitoring the data and safety of the proposed study as follows:

**3. Attribution of Adverse Events:**

Adverse events will be monitored for each subject participating in the study and attributed to the study procedures / design according to the following categories:

a. Definite: Adverse event is clearly related to investigational procedures(s)/agent(s).
b. Probable: Adverse event is likely related to investigational procedures(s)/agent(s).
c. Possible: Adverse event may be related to investigational procedures(s)/agent(s).
d. Unlikely: Adverse event is likely not to be related to the investigational procedures(s)/agent(s).
e. Unrelated: Adverse event is clearly not related to investigational procedures(s)/agent(s).

**4. Plan for Grading Adverse Events:**

The following scale will be used in grading the severity of adverse events noted during the study:

1. Mild adverse event
2. Moderate adverse event
3. Severe

**5. Plan for Determining Seriousness of Adverse Events:**

**Serious Adverse Events:**

In addition to grading the adverse event, adverse events are evaluated to determine whether they meet the criteria for a Serious Adverse Event (SAE). An adverse event is considered serious if it:

1. is life-threatening
2. results in in-patient hospitalization or prolongation of existing hospitalization
3. results in persistent or significant disability or incapacity
4. results in a congenital anomaly or birth defect OR
5. results in death
6. based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition, or
7. adversely affects the risk/benefit ratio of the study

An adverse event may be graded as severe but still not meet the criteria for a Serious Adverse Event. Similarly, an adverse event may be graded as moderate but still meet the criteria for an SAE. It is important for the PI to consider the grade of the event as well as its "seriousness" when determining whether reporting to the IRBs is necessary.

**6. Plan for reporting serious AND unanticipated AND related adverse events, anticipated adverse events occurring at a greater frequency than expected, and other unanticipated problems involving risks to subjects or others to the IRBs**

The investigator will report the following types of adverse events to the IRB: a) serious AND unanticipated events; b) adverse events occurring with a greater frequency than expected; and c) other unanticipated problems involving risks to subjects or others.

These adverse events or unanticipated problems involving risks to subjects or others will be reported to the IRB within 5 business days of it becoming known to the investigator, using the appropriate forms.

**7. Plan for reporting adverse events to co-investigators on the study, funding and regulatory agencies**

For the current study, the following individuals, funding, and/or regulatory agencies will be notified:

- All Co-Investigators listed on the protocol.

The principal investigator, Chadi Abdallah M.D., will conduct a review of all adverse events upon completion of every study subject. The principal investigator will evaluate the frequency and severity of the adverse events and determine if modifications to the protocol or consent form are required.

**14. Informed consent**: A VA waiver of written informed consent and VA HIPAA authorization is requested for a pre-screening phone interview and medical record review. Following the phone screen, if an individual appears to meet enrollment criteria and is interested in participating, the subject is invited for a face-to-face interview and VA informed consent and HIPAA authorization is obtained by one of the project investigators. A release of information is obtained for review of any available historical and clinical data. A written authorization form is obtained from each subject, permitting the research team to use, create, or disclose the subject's PHI for research purposes. The nature of the project, procedures, relative risks and benefits, and alternatives to participation in the project are discussed with the individual. Following this discussion, the individual is given a copy of the consent form to review at their leisure, and any questions are answered.

If the individual is interested in the project, written informed consent is obtained, and medical and psychiatric screening procedures are undertaken to confirm eligibility. A copy of the consent form is provided to all participants. If the individual decides not to participate in this study, the decision not to participate does not affect eligibility to participate in future studies, to receive treatment at the VACHS or to receive treatment on a private basis from a referring clinician.

**15. Confidentiality:** Reports generated from this study will not contain any identifying information about the participants. Research records are coded only by a number, and are stored in locked cabinets. Research records will be stored with the Clinical Neuroscience Division at the VA. Consent forms, HIPAA forms, enrollment logs and release of information forms will be kept locked in a place separate from subject data collection forms. Subjects will be informed their name and social security number will appear on subject payment vouchers that will be sent to Fiscal Service and the Agent Cashier for approval and reimbursement. Subjects will also be informed that medical evaluations, including physicals, EKGs, and urine/blood tests will be administered through the hospital and will become part of their permanent record. Finally, subjects will be informed that a hard copy of the consent form will be placed in their paper record. An electronic progress note citing subjects' participation in this research study will be entered in their VA electronic medical record upon entry into and exit from, the study.

**16**. **Location of Study**: West Haven VACHS.

**17. Payment to Subjects:** Subjects will be paid $15.00 per hour for their participation in the screening visit (up to $75). During the clinical trial, subjects will be paid $50 per visit. Subjects will also be paid $50 for the one-month follow-up visit. At the discretion of the investigator, subjects may be reimbursed for additional costs including travel, parking, transportation, meals, or other expenses. Participants may receive a possible total of $825.00 if they participate in all aspects of the study.

**18. Sources of Funding:**
National Center for PTSD

**19. Probable duration**: The study will be conducted over 5 years.

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