Study:
Riluzole for PTSD: Efficacy of a Glutamatergic Modulator as Augmentation Treatment for Posttraumatic Stress Disorder

NCT02155829

Date:
04/30/2019

EIRB Protocol Template (Version 1.13)

1.0 General Information

***Please enter the full title of your study:**

Riluzole for PTSD: Efficacy of a Glutamatergic Modulator as Augmentation Treatment for Posttraumatic Stress Disorder

***Please enter the Protocol Number you would like to use to reference the protocol:**

380797
* This field allows you to enter an abbreviated version of the Protocol Title to quickly identify this protocol.

Is this a multi-site study (i.e. Each site has their own Principal Investigator)?

No

Does this protocol involve the use of animals?

○ Yes ◉ No

2.0 Add Site(s)

2.1 List sites associated with this study:

Primary Dept?	Department Name
○	**P and R** - Walter Reed National Military Medical Center (WRNMMC)

3.0 Assign project personnel access to the project

3.1 *Please add a Principal Investigator for the study:

Benedek, David Manfred MD, MD

Select if applicable

☐ Student ☐ Site Chair
☐ Resident ☐ Fellow

3.2 If applicable, please select the Research Staff personnel:

A) Additional Investigators

Dempsey, Catherine L, PhD
Associate Investigator
Paxton, Megan Marie

Associate Investigator
Spangler, Patricia Tschirhart, PhD
Associate Investigator
Strother, Natara
Associate Investigator
WEST, JAMES C, M.D. CAPT
Associate Investigator

B) Research Support Staff

Aliaga, Pablo Alfredo
Statistician
Asabre, Eva Y, MPH
Research Coordinator
Morganstein, Joshua CHAIM
Monitor
ROY, MICHAEL JOSEPH
Monitor
Schuler, Keke, PHD
Statistician

3.3 *Please add a Protocol Contact:

Asabre, Eva Y, MPH
Benedek, David Manfred MD, MD

The Protocol Contact(s) will receive all important system notifications along with the Principal Investigator. (i.e. The protocol contact(s) are typically either the Protocol Coordinator or the Principal Investigator themselves).

3.4 If applicable, please select the Designated Site Approval(s):

Waits, Wendi Michelle, MD COL
Department Chair

Add the name of the individual authorized to approve and sign off on this protocol from your Site (e.g. the Site Chair).

4.0 Project Information

4.1 Is this a research study?

(•) Yes ( ) No

4.2 What type of research is this?

- [x] Biomedical Research
- [x] Clinical trial (FDA regulated)
- [x] Behavioral Research
- [ ] Educational Research
- [x] Psychosocial Research
- [ ] Oral History

☐ Other

4.4 Is this human subjects research (Activities that include both a systematic investigation designed to develop or contribute to generalizable knowledge AND involve a living individual about whom an investigator conducting research obtains data through intervention or interaction with the individual or identifiable private information. Activities covered by 32 CFR 219.101(a) (including exempt research involving human subjects) and DoDI 3216.02)?

◉ Yes ○ No

4.5 Do you believe this human subjects research is exempt from IRB review?

○ Yes ◉ No

5.0 Personnel Details

5.1 Will you have a Research Monitor for this study?

◉ Yes
○ No
○ N/A

Research Monitor Role:

Research Monitor will be responsible to promptly report any observations and findings to the Institutional Review Board (IRB), the Human Protections Administrator (HPA), or the Institutional Official. The research monitor will review the study monitoring plans, review Adverse Events and determine their relatedness to the protocol, review Unanticipated Problems Involving Risks to Subjects of Others, make recommendations on changes to the informed consent process based on the review of study events, and review and sign the continuing review report. The monitor will notify the IRB or HPA if you will not be able to fulfill your duties due to reassignment, retirement, deployment, or change of responsibilities. A replacement Research Monitor will need to be assigned and approved.

If applicable, you may nominate an individual to serve as the Research Monitor:

	Selected Users
☐	Joshua CHAIM Morganstein
☐	MICHAEL JOSEPH ROY

6.0 Data/Specimens

6.1 Does the study involve the use of existing data or specimens only (no interaction with human subjects)?

○ Yes ◉ No

7.0 Funding and Disclosures

7.1 Source of Funding:

Funding Source	Funding Type	Amount
Congressionally Directed Medical Research Program (CDMRP) DOD - MRMC	Research Development Testing and Evaluation (RDT&E) funds	1948488

Total amount of funding:

1948488

7.2 Do you or any other Investigator(s) have a disclosure of a personal interest or financial nature significant with sponsor(s), product(s), instrument(s) and/or company(ies) involved in this study?

○ Yes ◉ No

8.0 Study Locations

8.1 List any Research Team members without EIRB access that are not previously entered in the protocol:

Name: (Last, First, M.I.)	Phone Number:	Email Address:	Associated Institution:
Lin, Alexander Role on Protocol: Collaborator	617-525-5081	APLIN@bwh.harvard.edu	Brigham and Women's Hospital / Harvard Medical School
Irvine, John Role on Protocol: Collaborator		jirvine@draper.com	Charles Stark Draper Laboratory, Inc.

8.2 Has another IRB reviewed this study?

◉ Yes ○ No

IRB Name	Review Date	Determination
USUHS IRB #1 If other, please define:	04/22/2016	Approved via expedited procedures Other Determination: Secondary Concurrence of CR

8.3 Is this a collaborative or multi-site study? (e.g., are there any other institutions involved?)

(•) Yes ( ) No

8.4 Study Facilities and Locations:

	Institution	Site Name	Site Role	FWA or DoD Assurance Number	Assurance Expiration Date	Is there an agreement?	IRB Reviewing for Site

Other:

	Other Institution Site	Site Role	FWA or DoD Assurance Number	FWA or DoD Expiration Date	Is there an agreement?	IRB Reviewing for Site
	Central New York Research Corporation	Performance site			: MOU	: Other

8.5 Are there international sites?

Attach international approval documents, if applicable, when prompted. Note: Ensure local research context has been considered

( ) Yes (•) No

8.6 Is this an OCONUS (Outside Continental United States) study?

( ) Yes (•) No

Select the area of responsibility:

Have you obtained permission from that area of responsibility? (This is a requirement prior to study approval)

( ) Yes ( ) No

9.0 Study Details

9.1 Abstract/ Summary:

Summarize the proposed study in 500 words or less, to include the purpose, the subject population, the study's design type, and procedures

Riluzole is a glutamatergic modulator that inhibits glutamate release and enhances AMPA trafficking and clearance of excessive synaptic glutamate resulting in neuroprotective properties. Riluzole is FDA-approved for the treatment of amyotrophic lateral sclerosis (ALS) and has been found to have antidepressant and anxiolytic properties in animals and in humans (Zarate et al., 2004). Posttraumatic stress disorder (PTSD) is a chronic and seriously debilitating anxiety disorder that develops following exposure to severe trauma, such as combat exposure. Structural magnetic resonance imaging has been used to measure the volume of crucial structures implicated in the pathophysiology of PTSD, with several morphometric studies confirming smaller hippocampal volume in PTSD patients. Current

pharmacological treatment for PTSD, and particularly combat-related PTSD, is suboptimal. Drugs that alter neuronal survival pathways through reduction of glutamate activity may play a role in reversing the loss of neuronal integrity and possible focal atrophy in regions of the brain implicated in the pathophysiology of PTSD, potentially improving the symptoms of PTSD, as well as TBI.

This study will evaluate the efficacy of acute riluzole treatment in active duty and Operation Iraqi Freedom (OIF), Operation Enduring Freedom (OEF), and Operation New Dawn (OND) veterans with PTSD, with or without mild TBI (mTBI), who are sub-optimally responsive to other medication treatments. A total of 158 active duty and OIF, OEF and OND veterans, aged 18 to 65 will be enrolled from WRNMMC and the Syracuse VA Medical Center to participate in this 8-week randomized, double-blind, placebo-controlled, parallel study. Patients who are suboptimal responders to their current psychotropic drugs will continue these at stable dosage for at least 2 weeks prior to randomization during the screening period. We hypothesize that those subjects with PTSD, with or without mTBI, who are only partially responsive to initial therapy and are subsequently randomized to augmentation therapy with Riluzole (100-200mg/day) will have a superior response rate compared to those subjects randomized to placebo.

9.2 Key Words:

Provide up to 5 key words that identify the broad topic(s) of your study

9.3 Background and Significance:

Include a literature review that describes in detail the rationale for conducting the study. Include descriptions of any preliminary studies and findings that led to the development of the protocol. The background section should clearly support the choice of study variables and explain the basis for the research questions and/or study hypotheses. This section establishes the relevance of the study and explains the applicability of its findings

An over-simplification of the Research Proposal:

A service member experiences a physical and or emotional stressor during combat. The release of glutamate (from stress or brain injury) along with higher levels of glucocorticoids (endogenous cortisol) is toxic to the hippocampus causing a constellation of symptoms defined as PTSD. The neurotoxic effects on the hippocampus are part of the picture; the effects of glutamate on the ability to extinguish fear memory is really what we are concerned about as failure to extinguish fear memory (that is failure to learn to forget) seems to be the process responsible for the intrusive recollections and excessive over-generalized response to new stimuli we observe in PTSD. The challenge is that increased concentrations of glutamate in the brain have been linked to a variety of cognitive effects included over-excitation, neurodegeneration and impaired neuronal plasticity, and many of the associated symptoms such as impaired memory, depression and chronic stress are also correlated with PTSD. Whether PTSD is solely a direct result of changes in glutamate concentration is an open question.

Posttraumatic stress disorder (PTSD)

PTSD is a chronic anxiety disorder that develops in approximately one fifth of individuals exposed to severe trauma (Kessler et al., 1995; Breslau et al., 1998). Rates of PTSD in returning OIF and OEF active duty soldiers are between 6 and 19% (Hoge et al., 2004; Hoge et al., 2007; Friedman, 2007; Erbes et al., 2007). Over 20% of those injured in Iraq have suffered head/brain injuries that require lifetime continual care and rates of TBI have been estimated as high as 30%. The presence of PTSD in patients with TBI can be difficult to identify and treat. Although TBI and PTSD are among the most common disorders as a result of the OIF and OEF missions, currently available treatments are not targeted towards this group. A recent Institute of Medicine (IOM) review found insufficient evidence to support the efficacy of any single pharmacologic agent for PTSD (IOM, 2007). While the American Psychiatric Association's 2009 Practice Guideline Watch and the most recent DoD-VA practice guideline suggestthat there is growing evidence for the efficacy of certain pharmacologic treatments, studies suggest these treatments may not be effective for combat-related PTSD (DoD-VA Practice Guideline for the Management of Posttraumatic Stress, 2010)).

Medication Treatments for PTSD

Selective serotonin re-uptake inhibitors (SSRIs) are currently the only class of FDA-approved medications available for the treatment of PTSD. Although studies demonstrating the efficacy of SSRIs in PTSD use well-designed, double-blind strategies, the results are inconsistent, producing low to

moderate effect sizes (0.3 to 0.5) (Van der Kolk et al., 1994; Conner et al., 1999; Marternyi et al., 2002; Brady et al., 2000; Davidson et al., 2002; Marshall et al., 2001; Tucker et al., 2007), or no significant effect at all (Friedman et al., 2007; Zohar et al., 2002; Martenyi et al., 2007; Van der Kolk et al., 2007), compared to placebo (Pitman et al., 2002). Prazosin, a centrally active alpha-1 adrenoreceptor antagonist, reduced nightmares associated with PTSD in addition to overall PTSD symptoms when used as an adjunct to other psychotropic medications in PTSD (Raskind et al., 2007; Peskind et al., 2003). Other novel pharmacological strategies, including low dose cortisol (Aerni et al., 2004) have provided limited reduction in PTSD symptoms, but need further investigation.

In summary, for patients with PTSD, existing medication treatment options are suboptimal. Therefore, there is an urgent need for the development of novel interventions for PTSD that rapidly and robustly improves PTSD symptoms with minimal side effects.

The Role of Glutamate in acute and chronic stress: Pre-clinical models

Glutamate is an excitatory amino acid that has been implicated in the pathophysiology of major depression, TBI, Huntington's disease, and Alzheimer's disease (Hynd et al., 2004; Benn et al., 2007). Glutamate plays a crucial role in acute and chronic neurodegeneration, as well as neural plasticity (Einat & Manji, 2006; Parsons et al., 2007; Du et al., 2004). The stress-related effects of glucocorticoids and the excitatory effect of glutamate on the hippocampus make this brain region susceptible to damage following the experience of a stressor. For example, corticosterone has been found to prolong NMDA receptor-mediated calcium activation (Sato et al., 2004) and reduce plasticity of the hippocampus, also via NMDA receptors (McEwen et al., 2000). It appears that stress increases levels of glutamate which may be neurotoxic, particularly to the hippocampus; whereas drugs that reduce glutamatergic neurotransmission are neuroprotective and improve symptoms in preclinical models of chronic stress and depression. While there have not been studies of the direct effects of cortisol administration on PTSD, drugs that more tightly regulate glutamate brain concentrations by either decreasing glutamate release or activity or enhance its uptake could provide a novel strategy to reduce symptoms of PTSD and alleviate distress in this chronic stress disorder.

Is PTSD associated with impairment of neural plasticity and cellular resilience?

Yes, a very rough outline of this connection is based on increased glutamate levels triggering prolonged LTP causing stressful or highly emotional memories to become associated with non-stressful events. This results in someone displaying heightened stress responses to otherwise mundane situations, a hallmark symptom of PTSD.

Structural magnetic resonance imaging has been used to measure the volume of crucial structures implicated in the pathophysiology of PTSD. Several (Carrion et al., 2007; Pavic et al., 2007; Bremner et al., 2005; Vythilingam et al., 2005), but not all (Jatzko et al., 2006; Woodward et al., 2006; Pederson et al., 2004), morphometric studies have confirmed smaller hippocampal volume in PTSD patients, compared to controls. A recent meta-analysis of valid structural MRI studies in PTSD also confirmed a smaller hippocampal volume in this disorder (Karl et al., 2006). Volumetric reduction in the anterior cingulate appears to be a consistent finding in PTSD, as well (Kasai et al., 2007; Kim et al., 2007; Rauch et al., 2003). The only postmortem study in PTSD confirmed neuronal loss in the locus coeruleus (LC) in combat veterans, compared to controls (Bracha et al., 2005).

Proton magnetic resonance spectroscopy (^{1}H MRS), an in vivo imaging technique, provides direct neurochemical information in the brain. NAA levels that were measured using ^{1}H MRS served as a surrogate marker for neuronal integrity and reflected the extent of neuronal loss or injury (Sager et al., 2001; Ebisu et al., 1994). Reduced levels of NAA/Cr ratio in the hippocampus and anterior cingulate have been reported in patients with PTSD due to mixed traumas (Mahmutyazicioglu, 2005), in fire survivors (Li, 2006) and in combat veterans (trend) (Villarreal et al., 2002). Reduced NAA/Cr ratio was also reported in the anterior cingulate of maltreated children (De Bellis, 2000) and in the basal ganglia of adolescent fire survivors with PTSD (Lim et al., 2003). Studies that attempted to differentiate traumatized subjects with and without PTSD using NAA/Cr ratio reported no differences; however, small sample sizes may have been a limitation (Seedat et al., 2005; Kimbrell et al., 2005).

Patients with ALS demonstrated a significant increase in NAA/Cr ratio in the motor cortex following 3-week treatment with 100mg of riluzole daily (Kalra et al., 1998). Riluzole may result in rapid improvement of neuronal integrity, as an increase in the NAA/Cr ratio was found as early as 1 day following treatment with riluzole in ALS patients (Kalra et al., 2006). Patients with Generalized anxiety disorder (GAD) who responded to 8 weeks of riluzole treatment (9 of 14, 64%) demonstrated a significant increase in hippocampal NAA using ^{1}H MRS in contrast to a decrease in NAA levels in non-responders (Mathew et al., 2008). The effects of riluzole treatment on hippocampal and anterior cingulate NAA levels in PTSD have not yet been assessed.

Structural MRI studies of the pathophysiology of PTSD have not established a correlation between LC neuronal loss and volumetric loss for the hippocampus and the ACC, possibly due to methodologies with

study sampling and design. While several of these studies investigated mixed traumas, these were in exclusively in civilian settings. Few studies have considered the subset of combat-trauma exposure, which we believe is an entirely unique presentation. The 2005 Bracha et al. finding of postmortem LC neuronal loss in combat veterans could indicate such a correlation, hence the decision to pursue structural MRI analysis in this trial.

Taken together, current data suggest the loss of neuronal integrity and possible focal atrophy in regions of the brain are implicated in the pathophysiology of PTSD. Drugs that alter neuronal survival pathways through reduction of glutamate activity may play a role in reversing these effects and improving symptoms of PTSD, as well as TBI. Given that the neuropsychiatric community continues to refine clinically significant diagnostic points of departure for co-morbidity, it remains challenging to distinguish clearly PTSD and TBI with regard to symptomology and clinical outcomes. Nowhere is this more clearly evident than in the overlapping associated symptoms of PTSD and Persistent Post-concussive Syndrome (TBI), which include depression, anxiety, insomnia, irritability/anger, poor concentration, fatigue, hyper-arousal, and avoidance. As research into this field continues, characterization of the neurological change from each diagnosis may become more likely.

TBI is frequently diagnosed in comorbidity with PTSD and, as a result, it is nearly impossible to find a sufficient sample of PTSD patients in combat veteran populations. Because the goal of this study is to provide an empirical assessment of whether riluzole is an effective treatment in real world, combat veteran PTSD populations, the effect of riluzole on TBI symptoms is not one of our objectives. This is why we are concerned only in the efficacy of treating PTSD in patients regardless of their TBI history. However, there is ample evidence within the field that brain injury is associated with increased glutamate concentrations in the brain. Chamoun et al (2010) provides strong evidence that increased levels of glutamate following a traumatic brain injury are strongly predictive of poorer outcomes.

Riluzole (Rilutek®)

Riluzole, a neuroprotective agent with anticonvulsant properties, is a member of the benzothiazole class. Chemically, riluzole is 2-amino-6-(trifluoromethoxy) benzothiazole. Riluzole is the only drug currently approved (by the FDA in US, CPMP in Europe and MHW in Japan) for the treatment of ALS. Riluzole is an antagonist at a subset of Glu receptors (Benavides 1985), functional antagonist at NMDA and kainate receptors (Debono, 1993), and noncompetitive antagonist of AMPA receptors in the rat spinal cord (Albo, 2004) and cortex (Zona, 2002). Riluzole also inhibits the release of Glu in vivo (Cheramy, 1992) and in vitro (Doble, 1992; Martin, 1993; Jehle, 2000). Riluzole interacts with a large number of ion channels (voltage-activated sodium channels) (Benoit, 1993; Hebert, 1994; Zona, 1998; Urbani, 2000), voltage-gated calcium channels (VGCCs) (Huang et al., 1997; Stefani et al., 1997), and voltage-gated potassium channels (Zona, 1998; Duprat, 2000; Xu, 2001; Ahn, 2005; Ahn, 2006) that may contribute to a reduction in Glu release (Chéramy et al., 1992) and its neuroprotective effects. It enhances AMPA trafficking and increases glial uptake of glutamate (Azbill, 2000; Dunlop, 2003). Upregulation of glial Glu reuptake results in decreased extrasynaptic Glu concentrations and a release from the tonic inhibition of these neurons by activation of the presynaptic mGluR 2/3 receptors. This finding could offer an explanation for how riluzole induces trophic factors, including BDNF (Mizuta, 2001; Katoh-Semba, 2002). The interaction of BDNF with other trophic factors is a matter is scientific debate in the published literature and is beyond the scope of a clinical trial. Elucidation of BDNF biochemistry would be more appropriate in a cell culture or rodent model investigation. As such, a more descriptive presentation would neither strengthen the protocol nor provide necessary information for the participant in their process of granting informed consent. Further, any attempt would be beyond the reading comprehension level implicit and necessary in the Consent Form. While we consider it a fair point for the Reviewer to raise, we respectfully submit that it is beyond the scope of this trial.

In summary, preclinical and clinical data suggest that dysfunction in glutamatergic neurotransmission is a prime candidate in the pathophysiology of PTSD. The antiglutamatergic agent riluzole appears to have significant neuroprotective effects and the potential to be a novel agent in the treatment of PTSD. This study will permit us to determine the therapeutic benefit of reducing glutamate activity in subjects with PTSD.

Scientific Justification.

Scientific justification for the proposed research, as well as rationale for the research hypotheses, is detailed in the preceding Section.

Human Subjects Justification.

For patients with PTSD, existing medication treatment options are suboptimal. Current research suggests that the loss of neuronal integrity and possible focal atrophy in regions of the brain are implicated in the pathophysiology of PTSD, and drugs that alter neuronal survival pathways through the reduction of glutamate activity may play a role in reversing these effects and improving symptoms of PTSD, as well as TBI. Riluzole is an FDA-approved drug for the treatment of ALS, and research indicates

that it may result in rapid improvement of neuronal integrity, as an increase in the NAA/Cr ratio was found as early as 1 day following treatment with riluzole in ALS patients (Kalra et al., 2006). However, the effects of riluzole treatment on hippocampal and anterior cingulate NAA levels in PTSD have not yet been assessed, despite the drug appearing to have significant neuroprotective effects and the potential to be a novel agent in the treatment of PTSD. This study will permit us to determine the therapeutic benefit of reducing glutamate activity in subjects with PTSD with minimal side effects.

9.4 Objectives/Specific Aims/Research Questions:

Describe the purpose and objective(s) of the study, specific aims, and/or research questions/hypotheses

Objective: To evaluate the efficacy of acute riluzole treatment (100-200mg/day) in 158 active duty and returning OIF, OEF, and OND veterans, aged 18 to 65 with a diagnosis of PTSD, with or without mTBI, who are sub-optimally responsive to their current medication treatment (8 weeks).

Hypothesis 1: *Subjects with PTSD, with or without mTBI, who are only partially responsive to initial therapy (e.g., CAPS score greater than or = 40 at the completion of an adequate trial of medication therapy) who are subsequently randomized to augmentation therapy with riluzole will have a superior response rate compared to subjects randomized to placebo.*

Hypothesis 2: *PTSD patients randomized to augmentation with riluzole therapy will have significant improvement in depression, anxiety and global functioning compared to those who receive placebo in addition to their pre-study PTSD medication.*

Hypothesis 3: *The N-acetyl aspartate to creatine ratio (NAA/Cr) in the hippocampus and anterior cingulate, measured using magnetic resonance spectroscopy (^{1}H MRS), will increase after 8-week treatment with riluzole.*

In addition to indicating simple change in severity, the change in CAPS total score will be the primary outcome variable at the end of Phase II (Visit 10). We believe this study is powered to detect a 9 point or greater difference in CAPS total score from baseline between riluzole and placebo augmentation (after Phase I) to the last measured value of Phase II.

The following scales are proposed for primary and secondary outcome measures:

i. Primary Outcomes Assessment: Clinician-Administered PTSD Scale (CAPS), Clinical Global Impression of Severity (CGI-Severity), Clinical Global Impression of Improvement (CGI-Improvement).
ii. Secondary Outcomes Assessment: Montgomery-Asberg Depression Rating Scale (MADRS), Hamilton Anxiety Rating Scale (HAM-A), Sheehan Disability Scale (SDS), PTSD Checklist (PLC-C), UKU Side Effect Rating Scale, Self-rating version.
iii. Additional secondary outcome measure: Changes in NAA levels in the hippocampus and anterior cingulate cortex following riluzole or placebo administration measured using ^{1}H MRS.

Further, these scales are proposed as **Additional Measurement Instruments**: Liebowitz Social Anxiety Scale (LSAS), Pittsburgh Sleep Quality Index (PSQI), Dissociative Experience Scale (DES), World Health Organization Quality of Life (WHOQOL-BREF), Connor-Davidson Resilience Scale (CD-RISC), Childhood Trauma Questionnaire, Short Form (CTQ-SF), Symptom Checklist, 90 items, Revised (SCL-90-R), Peri Traumatic Distress Inventory (PDI).

9.5 Study Design:

Describe study design in one to two sentences (e.g., prospective, use of existing records/data /specimens, observational, cross-sectional, interventional, randomized, placebo-controlled, cohort, etc.). Specify the phase – Phase I, II, III, or IV – for FDA-regulated investigational drug research

The study design is a 1:1 randomized, double-blind, placebo-controlled, parallel trial. The ongoing assessment and monitoring of subjects enrolled in the study will be conducted by a Masters-level Clinical Research Psychologist under the supervision of a credentialed provider within the WRNMMV Behavioral

Health Clinic. Blinded study medication will be manufactured by the WRNMMC Investigational & Research Pharmacy and will be identical and indistinguishable. The WRNMMC Investigational and Research Pharmacy will administer, blind, and distribute all study medications, including secondary distribution to the Syracuse VA Medical Center Pharmacy and maintain the list indicating whether a participant is receiving placebo or study drug in a locked cabinet within the research pharmacy.

All members of the research team and treatment staff will be blinded. Randomization into the treatment and placebo arms will be determined by the Research Pharmacy and is outlined in their Memorandum of Support. Stratification by center will be performed prior to a 1:1 randomization. As explained by the staff of the Research Pharmacy, randomization may be by computer generated random number or random table assignment, and volunteers for the post-treatment magnetic resonance spectroscopy portion of the study will be allotted 1:1 for treatment comparison. Blinded subjects will be asked post-treatment to guess their treatment assignment and the responses statistically analyzed to evaluate the success of the study blinding. Additionally, subjects and providers will be asked at week 2 to guess treatment assignments to assess the similarity of the drug and placebo in appearance, taste and composition.

9.6 Target Population:

Describe the population to whom the study findings will be generalized

See Legacy Protocol

9.7 Benefit to the DoD:

State how this study will impact or be of benefit to the Department of Defense

See Legacy Protocol

10.0 Study Procedures and Data management

10.1 Study Procedures:

Describe step-by-step how the study will be conducted from beginning to end

The clinical component of this study is 10 weeks (although there is an option for subjects to enter a 3 month open label continuation phase, detailed in Section 2.3). The anticipated duration of study including regulatory review and approval, participant recruitment and enrollment, and data analysis, report writing, and dissemination is 36 months.

The **Schedule of Events** lists the clinical assessments conducted at baseline and those carried out at various points during Screening and Study Phases I and II.

Study Period/Phase I			**Study Period/Phase II** [b]									
Screening for all Subjects and Washout for Subjects on Medication			**Randomized, Double-Blind, Placebo Controlled Clinical Trial**									
S1**Description of Data**	Scr	Stabil	V1	V2	V3	V4	V5	V6	V7	V8	V9[a]	SOC
Week	-2		0	1	2	3	4	5	6	7	8	
Informed consent	X											
Demographics/ Hollingshead	X											
Vital signs - body temperature, pulse rate, blood pressure, and respiration rate	X		X	X	X	X	X	X	X	X	X	Yes

Weight/ Height	X		X								X	Yes
Psychiatric examination	X										X	Yes
Physical examination	X										X	Yes
Chemistry panel and CBC w/dif	X										X	Yes
Thyroid function, HIV, HCG, hepatitis screen and urine drug screen	X										X	Yes
Liver function panel	X		X	X	X	X	X	X	X	X	X	Yes
Menstrual history (women)	X											Yes
Family History Screen	X											Yes
SCID-IV-TR	X											
Placebo lead-in												
Study drug/ Placebo			X	X	X	X	X	X	X	X	X	
Efficacy Measures												
CAPS	X		X				X				X	
CGI,	X		X	X	X	X	X	X	X	X	X	
MADRS	X		X	X	X	X	X	X	X	X	X	
HAM-A			X				X				X	
SDS			X				X				X	
PCL-C			X	X	X	X	X	X	X	X	X	
UKU-SERS-Pat	X		X	X	X	X	X	X	X	X	X	
LSAS			X				X				X	
PSQI, DES			X				X				X	
WHOQOL BREF, CD-RISC			X				X				X	
CTQ			X									
SCL-90			X				X				X	
PDI	X											

Description of Data	Scr	Stabil	V1	V2	V3	V4	V5	V6	V7	V8	V9[a]	SOC
Week			0	1	2	3	4	5	6	7	8	
Safety Measures												
Adverse events	X	X	X	X	X	X	X	X	X	X	X	
MRS			X							X		

Abbreviations: Sc = Screening Visit; Sta = Stabilization Visit; CAPS = Clinician-Administered PTSD scale; CD-RISC = Connor-Davidson Resilience Scale; CGI = clinical global impression scale; CTQ = Childhood Trauma Questionnaire; DES = Dissociative Experience Scale; F/U = Follow-up visit; HAM-A = Hamilton Anxiety Rating Scale; HCG = blood pregnancy test; Hollingshead = Hollingshead 4 Factors of Social Status Scale; LSAS = Liebowitz Social Anxiety Scale; MADRS = Montgomery Depression Rating Scale;; PLC-C = PTSD Checklist; UKU-SERS-Pat = UKU Side Effect Rating Scale, Self rating version; PDI = Peri Traumatic Distress Inventory; PSQI = Pittsburgh Sleep Quality Index; SCID-IV-TR = Structure Clinical Interview for DSM-IV; SCR = screen; SCL-90 = Symptom Checklist, 90 items; SDS = Sheehan Disability Scale; WHOQOL BREF = World Health Organization Quality of Life WO = washout phase.

[a]Exit visit to be performed at Visit 9 or sooner if the patient is discontinued from the study.
WO = washout phase. May vary depending on drug but in general is 51/2 lives. If the subject is medication free, they may proceed to Study Period I.

[b]Visits during Study Period II may happen within 2 days of the scheduled visit. SCO = Standard of Care activity – Affirmative notation; Default notation is left blank indicating an activity that is research-related.

The 10-week clinical study will be conducted in two phases, a minimum of 2-weeks and maximum of 4-weeks screening and stabilization phase (Phase I) and an 8-week double-blind placebo controlled treatment (Phase II).

In Phase I, indicated as the "Screening Period" **in Figure 1 Riluzole Augmentation for PTSD**, patients who are suboptimal responders (see inclusion/exclusion criteria) to other psychotropic drugs will continue these at stable dosage for at least 2 weeks prior to study randomization (dose stabilization). Use of antidepressant and sedative/hypnotic drugs at stable dose is permitted. Subjects will be contacted by phone after 1 week to assure that no medication changes were made and to schedule the first Phase II visit.

Subjects will also complete the screening visit where they will be evaluated for study entry and enrollment. Psychiatric history and diagnosis will be administered by study staff at each site using the SCID-P (First et al., 1995) and the DSM-IV Diagnostic Criteria (American Psychiatric Association, 1994). Patients who meet DSM-IV criteria for PTSD must have a Clinician Administered PTSD Scale (CAPS) of 40 at Visits 1 and 2 to be included in the study. Those entering the study at the completion of a referring INTRuST or other medication trial for PTSD will also receive a CGI assessment, and must have a score indicating "NOT improved" or "NOT very much improved" on the CGI scale at the completion of their medication trial to be eligible. The screening visit will include the screening tests, patient history, and psychiatric and physical examinations, as well as menstrual history in females. Subjects will undergo a physical exam, supine and standing vital signs, complete blood cell counts (CBC) with differential, electrolytes, thyroid function test, liver function tests, fasting blood sugar, hematology profile, urinalysis (including screens for substances of abuse), hepatitis screen, SCID, and CAPS. Women of childbearing capacity will have a baseline serum ß-HCG. A positive ß-HCG will exclude them from participating in the study. Subjects must also have a negative Human Immunodeficiency Virus (HIV) test. Results of these tests will identify patients who should be excluded because of active medical problems or substance abuse that might affect the clinical phenomenology or treatment response and to identify conditions that might make randomization into one of the treatment arms less safe. The CGI will be used to collect information on overall improvement, and the UKU side effect rating scale will be used to collect information on side effects. Finally, eligible subjects who consent to participate in the baseline ^{1}H MRS portion of the study will undergo the scan during the screening visit.

The time commitment for the telephone confirmation is estimated to be 10 minutes. The screening visit will take 4 hours. The time commitment for the baseline ^{1}H MRS scan is estimated to be 60-90 minutes.

Phase II, indicated as the "Acute Double-Blind Period", in **Figure 1 Riluzole Augmentation for PTSD**, begins after the completion of the stabilization phase, where subjects will be randomized at a ratio of 1:1 to receive an 8-week double-blind treatment of either riluzole or placebo. Riluzole or placebo will be administered in two divided doses (two tablets twice a day). During the clinical trial, all blinded study medication will be manufactured to identical appearance. All members of the research team and treatment staff will be blinded. Subjects will be assessed weekly from Visit 1 through Visit 9 (see Schedule of Events, **Section 5.5.8 Study Time Line**). Riluzole therapy will be initiated at a dose of 50mg twice daily, as will matching placebo for those subjects randomized to placebo. Riluzole may be increased to 200 mg/day thereafter if the subject's weekly case history (subject self-reported symptomatology and CAPS score and/or additional psychological clinical battery diagnostics) indicate that the increased dose may have therapeutic benefit. The maximal allowable dose of riluzole permitted is 200 mg/day. The minimal allowable dose of riluzole permitted is 100 mg/day. Those subjects unable to tolerate the lowest allowable dose will be discontinued from the study. Eligible subjects who consented to participate in the baseline 1H MRS portion of the study will undergo a post-treatment scan between visits 8 and 9.

The time commitment for the weekly scheduled visit is estimated to be 2-4 hours. The time commitment for the post-treatment ^{1}H MRS scan is estimated to be 60 to 90 minutes.

10.2 Data Collection:

Describe all the data variables, information to be collected, the source of the data, how the data will be operationally measured, and approvals needed for use of information from DoD databases

a. Method of Collection from Study Participants.

Primary Outcomes Assessment – All study assessment materials are in the public domain and will not be altered. Each measure includes a minimum of one citation attesting to the reliability and validity of

the questionnaire based on the consensus of researchers published in the field of behavioral science. In general, each measure has a minimum assessment level of 'adequate', with the majority assessed at a level of 'good' or higher.

Instruments selected are well established neuropsychological questionnaires with extensive clinical and research validation and are structured to ensure the highest levels of clarity and ease of administration. Participants will have no difficulty in reliably completing these instruments in a clinical setting. This instrument battery is currently in use in several WRNMMC-approved research projects conducted by the Investigator in both the inpatient ward and outpatient clinics at WRNMMC. Further, this instrument battery is in use by the INTRuST Clinical Consortium, which is a multi-site research collaboration on PTSD and TBI, which will allow de-identified data from this study to be compared across a nationally-representative dataset. Assessments not directly related to the primary outcome are being made to allow for comparability with these other ongoing trials in this population, and all questionnaires were selected and rigorously reviewed to ensure that content overlap was minimized in the interest of participant welfare. As such, no unnecessary measures are included, and all data collected will be analyzed and results reported and disseminated.

1.Clinician-Administered PTSD Scale (CAPS): The CAPS (Blake et al 1995; Blake et al., 1990) is a lengthy structured interview based on the DSM-IV that assesses the presence and severity of PTSD and associated symptoms. Changes from baseline to endpoint in the CAPS total score will serve as the primary efficacy measure for the double blind phase. The CAPS is widely accepted as the Gold Standard for establishing PTSD diagnosis with excellent reliability and validity (Blake et al., 1990; 1995), (Weathers et al., 1999).

2.Clinical Global Impression of Severity (CGI-Severity): The CGI-Severity scale (Guy, 1976) will be administered to assess the clinician's global impression of the severity of the patient's PTSD at each visit over the course of treatment. It is a 7-point scale in which 1 = normal and 7 = extremely severe case of PTSD. The CGI is a core metric for psychiatric research and has demonstrated adequate psychometric properties (Berk et al., 2008).

3. Clinical Global Impression of Improvement (CGI-Improvement): The CGI-Improvement scale (Guy, 1976) will be administered to assess the clinician's global impression of the improvement of the patient's PTSD over the course of treatment. It is a 7-point scale in which 1 = very much improved, 4= no change, and 7 = very much worse. A pre-entry score (e.g., for those subjects entering this protocol from other research studies will be obtained during the screening phase. Those subjects who, at the completion of the previous research study receive scores of 1, 2, or 3 will be excluded from this study.

For this study, treatment response will be defined as those who are very much improved (score of 1), or much improved (score of 2), or improved (score of 3) on the Clinical Global Impressions, improvement item and have a $\geq$ 9 point decrease in CAPS score.

Secondary Outcomes Assessment

1.Montgomery-Asberg Depression Rating Scale (MADRS): The MADRS (Montgomery & Asberg, 1979) is a clinician-rated instrument that measures the presence and severity of depression. The MADRS has demonstrated very good reliability and validity in clinical applications (Cusin et al., 2009). This instrument consists of a 10-symptom scale. Each symptom is rated on a defined step scale (0 to 6). A high numeric rating reflects a greater degree of symptom severity. This outcome will be assessed by the mean change from baseline MADRS score.

2.Hamilton Anxiety Rating Scale (HAM-A): The HAM-A is a clinician-rated instrument that measures the presence and severity of anxiety. The HAMA-A has demonstrated adequate psychometric properties (Riskind et al., 1987). This instrument consists of a 14-symptom scale. Each symptom is rated on a defined step scale (0 to 4). A high numeric rating reflects a greater degree of symptom severity. This outcome will be assessed by the mean change from baseline HAM-A score.

3.Sheehan Disability Scale (SDS): The Sheehan Disability Scale (SDS) (Sheehan, 1983) is a patient-rated instrument designed to assess the impact of perceived problems on work productivity, social/leisure activities, and family life/home responsibilities. The SDS has demonstrated adequate psychometric properties (Frischholz et al., 1990). The Sheehan Disability Scale consists of 3 questions rated on a visual analog scale (0 to 10). Higher scores represent greater impairment of activity. This outcome will be assessed by the mean change from baseline SDS score

4.PTSD Checklist (PLC-C): The PCL-C (civilian) is a 17-item self-report measure of the 17 DSM-IV symptoms of PTSD used for screening individuals for PTSD, diagnosing PTSD, and monitoring symptom change during and after treatment. It asks about symptoms in relation to "stressful experiences" and can be used with any population and has demonstrated adequate psychometric properties (Weathers et al 1994).

5.UKU Side Effect Rating Scale, Self-rating version: The UKU side effect rating scale, self-rating version (UKU-SERS-Pat) (Lingjaerde et al., 1987), a patient-rated scale, is a valid and reliable comprehensive measure to evaluate side effects of psychotropic medications (Lindstrom et al., 2001). Adverse events in the psychic, neurologic, autonomic, dermatological, and sexual domains will be assessed. For symptoms endorsed as present, a clinician will further assess their severity, potential causal relationship with the medications, and interference with daily performance.

6.Additional secondary outcome measures: These will include evaluating changes in N-acetyl asparate (NAA) levels in the hippocampus and anterior cingulate cortex following riluzole or placebo administration measured using magnetic resonance spectroscopy (^{1}H MRS) among a sub-sample of WRNMMC participants.

Acute Trial Assessments

As shown in **Section 5.5.8 Study Time Line**, subjects participating in this study will be rated weekly during the double-blind phase for severity of PTSD using the same scales as were obtained at Visit 2. Week 8 or Visit 9 ratings will be used to determine whether patients meet criteria for response. Side effects will be assessed using the UKU side effect rating scale, self-rating version (Lindstrom et al., 2001).

Additional Measurement Instruments

1.Liebowitz Social Anxiety Scale (LSAS): A 24-item scale providing separate scores for fear and avoidance in social and performance situations over the past week (approx. 8 minutes to complete) (Liebowitz, 1987). This measure has demonstrated adequate psychometric properties (Fresco et al. 2001).

2.Pittsburgh Sleep Quality Index (PSQI): A 19-item instrument to assesses sleep quality and disturbances over a 1-month time interval (approx. 5 to 7 minutes to complete) (Buysse et al. 1989). The PSQI had demonstrated acceptable psychometric properties (Carpenter & Andrykowski, 1998).

3.Dissociative Experience Scale (DES): A 28-item questionnaire used to screen for dissociative symptoms (approx. 8 minutes to complete) (Bernstein et al. 1986). The DES has demonstrated excellent reliability and validity (Frischholz et al., 1990).

4.World Health Organization Quality of Life (WHOQOL-BREF): is a self-report measure of quality of life, life satisfaction and personal well-being (Murphy et al., 2000). 26-items assess the board domains of physical health, psychological health, social relationships and environmental factors (e.g., finances, safety). This measure has strong psychometric properties (Skevington et al., 2004) and will be administered at each time point. The overall QOL score will be used as the QOL outcome measure.

5.Connor-Davidson Resilience Scale (CD-RISC): A 25-item scale of ability to recovery after a traumatic event (approx. 8 minutes to complete) (Connor & Davidson, 2003). The CD-RISC has demonstrated good psychometric properties (Windle et al., 2011).

6.Childhood Trauma Questionnaire, Short Form (CTQ-SF): A 28-item measure of childhood physical, sexual and emotional abuse and physical and emotional neglect (approx. 8 minutes to complete). The CTQ-SF has demonstrated good reliability and validity (Bernstein et al 2003).

7.Symptom Checklist, 90 items, Revised (SCL-90-R): A 90-item instrument to evaluate a broad range of psychological problems and symptoms of psychopathology. The instrument is also useful in measuring patient progress or treatment outcomes (approx. 12-15 minutes to complete) (Derogatis, 1999). The SCL-90-R has demonstrated adequate psychometric properties (Hardt et al., 2000).

8.Peri Traumatic Distress Inventory (PDI): A 13-item self-report measure to obtain a quantitative measure of the level of distress experienced during and immediately after a traumatic event (approx. 5 minutes to complete). The PDI has also demonstrated good reliability and validity (Brunet et al 2001).

10.3 At any point in the study, will you request, use, or access PII from the Military Health System (MHS)?

○ Yes ◉ No

10.4 Have you consulted with an MHS data expert to determine the data elements to be extracted or the information system(s) to access?

Consulting with a data expert often saves time later in the compliance process because the data expert can advise on the data available in the numerous MHS information systems, the quality of that data and the methods for encrypting and collapsing data. To schedule a consult with an MHS data expert, send an email to: (**dha.ncr.pcl.mbx.privacyboard@mail.mil**)

○ Yes, then complete the questions below according to the data consult
◉ No, then complete the questions below according to the best of your knowledge (NOTE: It is highly recommended that you work with an MHS data expert)

10.5 Indicate whether you plan to receive a data extract from the MHS or plan to access an information system directly to create a data set:

A data extract is when the MHS or a contractor provides the data set directly to the researcher. When receiving a data set through data extract, the researcher may indicate whether the data elements should be provided as is, encrypted or collapsed. In contrast to a data extract, access to an information system means that the researcher may directly access an MHS information system and create a data set for the research study

☐ Data Extract
☑ Access

10.6 Do you intend to use only de-identified data from the MHS in your research study?

There are different two methods for de-identifying data pursuant to HIPAA:
1) Safe Harbor Method: Removing all of the identifiers listed in Table 1 below, provided that the researcher does not have actual knowledge that the remaining data can be used alone or in combination with other information to identify the individual who is the subject of the information
2) Statistical Method: An expert, with appropriate knowledge of and experience with generally accepted statistical and scientific principles and methods for rendering information not individually identifiable, determines that the data is not individually identifiable

○ Yes ◉ No

10.7 If your research study requires access to an MHS information system, please indicate the system to obtain data:

If you do not know which system(s) contain the data elements you need, refer to the Guide for DoD Researchers on Using MHS Data or seek guidance from an MHS data expert:

PHI Systems:

MHS Information System	Requesting Data
: AHLTA	: Yes
: CHCS	: Yes

PII-Only Systems:

MHS Information System	Requesting Data

No records have been added

De-Identified Data & Other Systems:

Information System	Requesting Data
Expense Assignment System	
List other system(s):	
List other system(s):	

10.8 Do you intend to merge or otherwise associate the requested data with data from any sources outside of the MHS, including other DoD systems that are not part of the MHS?

- ○ Yes, will merge data
- ◉ No, will not merge data

10.9 Indicate the categories of data that you will request from MHS systems or MHS health care providers about research participants or relatives, employers, or household members of the research participants.

Data Element(s)	MHS	Non-MHS Systems
1. Names	☐	☑
2. Postal address with only town, city, state and zip code	☐	☐
3. Postal address with all geographic subdivisions smaller than a state, including street address, city, county, precinct, zip code and their equivalent geocodes, except for the initial three digits of a zip code if, according to the current publicly available data from the Bureau of Census: 1) the geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people; and 2) the initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000	☐	☑
4. Dates including all elements (except year) directly related to an individual, including birth date, admission date, discharge date, and date of death	☐	☑
5. Ages over 89 and all elements of dates (including year) indicative of such age,	☐	☐

unless you will only request a single category of "age 90 or older"		
6. Telephone numbers	☐	☑
7. Fax numbers	☐	☐
8. Electronic mail addresses	☐	☑
9. Social Security numbers (SSNs)	☐	☑
10. Medical record numbers	☐	☐
11. Health plan beneficiary numbers	☐	☐
12. Account numbers	☐	☐
13. Certificate/license numbers	☐	☐
14. Vehicle identifiers and serial numbers, including license plate numbers	☐	☐
15. Device identifiers and serial numbers	☐	☐
16. Web Universal Resource Locators (URLs)	☐	☐
17. Internet Protocol (IP) address numbers	☐	☐
18. Biometric identifiers, including finger and voice prints	☐	☐
19. Full-face photographic images and any comparable images	☐	☐
20. Any other unique identifying number, characteristic, or code (DEERs ID, EDIPN, Rank)	☐	☐

If you are obtaining SSNs, provide a justification as to why and explain why a substitute cannot be used

Collecting the SSN of participants allows investigators to order required lab tests in CHCS; also required for subject payment thru Henry Jackson Foundation.

10.10 Is it possible that the data will become identifiable because of triangulation, a small cell size, or any unique data element(s)?

Triangulation means using different data elements that are not themselves identifiable but that when combined can be used to identify an individual. For example, triangulation would be using rank and race together to determine the identity of an individual with a particular health condition
Small cell size means that there are only a small number of eligible individuals that satisfy the category description. Guidance for acceptable cell size is available from the Centers for Medicare and Medicaid Services. For example, the rank category of four star generals with a particular diagnosis may be less than 30 so the rank category may need to be expanded to include lower ranks
A unique data element includes any unique features that are not explicitly enumerated in the categories of data in rows 1 – 19 of Table 1 above, but that could be used to identify an individual. Examples of unique data elements include: 1) a unique number, such as a medical record number or EDIPN; 2) a unique code, such as a diagnosis code or a bar code on an electronic health record; and 3) any unique characteristic, such as the rank of general or admiral, or a race or gender combined with another unique characteristic

- ○ Yes, there is a reasonable possibility the data will become identifiable
- ◉ No, there is no reasonable possibility the data will become identifiable

10.11 HIPAA Privacy Rule and Use of Protected Health Information in Research:

- ○ N/A – will not use or disclose protected health information (PHI)
- ◉ HIPAA Authorization will be obtained
- ○ Use of a limited data set where a data use agreement will be obtained
- ○ Waiver/alteration of HIPAA Authorization is being requested

10.12 Managing Data (Data Management and/or Sharing Plan) and/or Human Biological Specimens for this Study:

Include in this section the plan for acquiring data (both electronic and hard copy), access during the study, data/specimen storage and length of time stored, shipment/transmission, and the plan for storage and final disposition at the conclusion of the study. Describe any data agreements in place for accessing data within and/or outside of your institution (e.g., Data Sharing Agreement, Data Use Agreement, Business Agreements, etc.)

See Legacy Protocol

10.13 Managing Data (Data Management and/or Sharing Plan) and/or Human Biological Specimens for Future Research:

If the study involves collecting, storing, or banking human specimens, data, or documents (either by the Investigator or through an established repository) for FUTURE research, address. How the specimens /data will be used, where and how data/specimens will be stored (including shipping procedures, storage plan, etc.), whether and how consent will be obtained, procedures that will fulfill subjects' request as stated in the consent, whether subjects may withdraw their data/specimens from storage, whether and how subjects may be recontacted for future research and given the option to decline, whether there will be genetic testing on the specimens, who will have access to the data/specimens, and the linkage, the length of time that data/specimens will be stored and conditions under which data/specimens will be destroyed

See Legacy Protocol

11.0 Statistical/Data Analysis Plan

11.1 Statistical Considerations:

List the statistical methods to be used to address the primary and secondary objectives, specific aims, and/or research hypotheses. Explain how missing data and outliers will be handled in the analysis. The analysis plan should be consistent with the study objectives. Include any sub-group analyses (e.g., gender or age group). Specify statistical methods and variables for each analysis. Describe how confounding variables will be controlled in the data analysis

5.7.1 Data Analysis Table

Independent Variable / Predictor	Dependent Variable/ Outcome	Statistical Test
Riluzole/placebo	PTSD anxiety symptomatology (CAPS total score)	t-test/Mann-Whitney U test
Riluzole/placebo	Clinical Response Rate	Pearson's chi-square test, Fisher's exact test
Riluzole/placebo	Effects of treatment status longitudinally	Regression Analysis
Riluzole/placebo	Origin, gender, age, dose level, illness characteristics	ANOVA, Mantel-Haenszel common odds ratio test, Breslow-Day test
Riluzole/placebo	NAA/Cr ratio	t-test/Mann-Whitney U test
Not Applicable	Not Applicable	Descriptive Statistics

11.2 Sample Size Estimation:

A power analysis confirms the study will be able to detect a 9 point change in CAPS score in subjects receiving riluzole augmentation versus placebo using a sample size of 50, assuming a two-tailed test, an alpha = 0.05, and a standard deviation of 15 (based on the PI's experience in this population seeking treatment at WRNMMC). This yields a power of 0.844. Power increases to 0.909, under the same assumptions, when a single-tailed test is used. The difference value of 9 is considered the minimally clinically significant difference and is supported by recent publications (Krystal et al, 2013; Schnurr et al, 2001; Weathers et al, 2001; Fontana et al, 1997; Norman et al, 2003; Lunney et al, 2007).

The SAS System
The POWER Procedure
Two-Sample t Test for Mean Difference
Fixed Scenario Elements
Distribution Normal
Method Exact
Number of Sides 2
Mean Difference 9
Standard Deviation 15
Group 1 Sample Size 50
Group 2 Sample Size 50
Null Difference 0
Alpha 0.05

Computed Power
Power 0.844

The SAS System
The POWER Procedure
Two-Sample t Test for Mean Difference
Fixed Scenario Elements
Distribution Normal
Method Exact
Number of Sides 1
Mean Difference 9
Standard Deviation 15
Group 1 Sample Size 50
Group 2 Sample Size 50
Null Difference 0
Alpha 0.05

Computed Power
Power 0.909

To allow for ineligibility (30-40%) and the possibility that more participants will be needed from

WRNMMC (~2:1 ratio), a total of up to 158 participants will be consented study-wide, with up to 104 participants recruited at WRNMMC.

11.3 Data Analysis Plan:

Primary Analysis: *(Hypothesis 1) Subjects with PTSD randomized to acute therapy with Riluzole will have a superior response rate acutely compared to subjects randomized to placebo.*

The PI will be primarily responsible for data analysis in this study. He will be assisted by a data analyst or analysts within the Department of Psychiatry at USUHS and this person (or persons) will be added to the protocol as investigators (with IRB approval) prior to any handling of the data. The primary intent of this study is to compare the efficacy of riluzole relative to placebo in the treatment of overall anxiety symptomatology of subjects who have PTSD. This will be analyzed by comparing reductions from baseline scores on the CAPS total score after up to 8-weeks of double-blind therapy to the original score before the start of therapy using t-tests or Mann-Whitney U tests when assumptions for t-tests are not satisfied.

In addition to utilizing the CAPS continuous score, scores will also be dichotomized to examine clinical responders versus non-responders in the treatment and placebo groups. A responder will be defined as any patient who demonstrates a 30% or greater decrease in CAPS total score from baseline (phase I) to the last measured value of Phase II. Response rate analyses will then be performed by comparing the proportion of subjects in each treatment group who met the response criteria. Response rates will be analyzed using Pearson's chi-square test or Fisher's exact test when expected cell sizes are less than 5.

In order to more thoroughly assess the effects of treatment status in a longitudinal setting, random effects regression will also be used to examine the study groups over time in the presence of additional covariates.

In general, variables that are continuous, yet non-normally distributed, will be appropriately transformed or will be analyzed using appropriate non-parametric tests. Variables that are non-continuous (ordinal, nominal) will be analyzed using appropriate non-parametric tests. All tests of hypotheses will be tested at a two-sided a level of 0.05.

Secondary Analyses:

Additional analyses will be performed for origin, gender, age, dose level and certain illness characteristics (if there are at least 10 subjects in each treatment group). All subgroup analyses will be considered secondary analyses. Continuous outcomes will be assessed using ANOVA models. The treatment-by-subgroup interaction will be tested to determine whether treatment differences in the continuous outcomes are the same for each subgroup category. The Mantel-Haenszel common odds ratio and the Breslow-Day test for homogeneity of odds ratio will be used to evaluate differences across the subsets for dichotomous categorical outcomes.

Secondary Outcomes: *(Hypotheses 2 and 3) PTSD patients randomized to augmentation with riluzole therapy will have significant improvement in depression, anxiety and global functioning compared to those who receive placebo in addition to their pre-study PTSD medication. The NAA/Cr ratio in the hippocampus and anterior cingulate, measured using ^{1}H MRS, will increase after 8 week treatment with Riluzole.*

The analysis techniques described above will also be employed with the additional secondary outcomes. Further, post-hoc analysis will be performed by the PI in the comparison of outcomes from this research to other PTSD research being conducted by the PI at WRNMMC, including the INTRuST Clinical Consortium. All comparisons will involve de-identified data.

Collaborators from Draper Lab and Brigham and Women Hospital/ Harvard will be responsible for the ^{1}H MRS data analysis.

12.0 Participant Information

12.1 Subject Population:

The subject population consists of 158 active duty and returning Operation Iraqi Freedom (OIF), Operation Enduring Freedom (OEF), and Operation New Dawn (OND) veterans, aged 18 to 65 with a

diagnosis of PTSD despite adequate trial of medication treatment (8 weeks) (e.g., CAPS score greater than or = 40).

Subjects will be recruited from collaborator- and provider-referrals at WRNMMC and the Syracuse VA Medical Center, as well as from associated community-based outpatient clinics (CBOCs) and other referring research studies.

12.2 Age Range:

- [ ] 0-17
- [x] 18-24
- [x] 25-34
- [x] 35-44
- [x] 45-54
- [x] 55-64
- [ ] 65-74
- [ ] 75+

12.3 Gender:

- [x] Male
- [x] Female

12.4 Special categories:

- [ ] Minors /Children - "You must also consider the requirements of 45 CFR 46 Subpart D and DoDI 3216.02, Enclosure 3, paragraph 7.d."
- [ ] Students
- [ ] Employees - Civilian - "You must also consider the requirements of DoDI 3216.02, paragraph 7.e."
- [ ] Employees - Contractor
- [ ] Resident/trainee
- [ ] Cadets /Midshipmen - "You must also consider the requirements of DoDI 3216.02, Enclosure 3, paragraphs 7.e. and 12."
- [x] Active Duty Military Personnel - "You must also consider the requirements of DoDI 3216.02, Enclosure 3, paragraph 7.e."
- [ ] Wounded Warriors - "Depending on your intended subjects' status, you may also need to consider the requirements of DoDI 3216.02, Enclosure 3, paragraph 7.e."
- [ ] Economically Disadvantaged Persons - "You must also consider the requirements of 32 CFR 219.111 (b)."
- [ ] Educationally Disadvantaged Persons - "You must also consider the requirements of 32 CFR 219.111 (b)."
- [ ] Physically Challenged (Physical challenges include visual and/or auditory impairment)
- [ ] Persons with Impaired Decisional Capacity - "You must also consider the requirements of 10 USC 980."
- [ ] Prisoners - "You must also consider the requirements of 45 CFR 46 Subpart C and DoDI 3216.02, Enclosure 3, paragraphs 7.b. and 7.c."
- [ ] Pregnant Women, Fetuses, and Neonates
- [ ] Non-English Speakers
- [ ] International Research involving Foreign Nationals - Headquarters Review is necessary

12.5 Inclusion Criteria:

Order Number	Criteria

1	a. **Inclusion Criteria –** Male and female subjects, aged 18 to 65 are eligible for inclusion in the study if they satisfy the following criteria: 1.Are an active-duty service member or an Operation Iraqi Freedom (OIF), Operation Enduring Freedom (OEF), or Operation New Dawn (OND) veteran. 2.Are diagnosed with PTSD and have not achieved remission with an adequate trial of medication treatment (8 weeks) as indicated by self-report at referral and confirmed by baseline CAPS score of greater than or = to 40 after informed consent is obtained.

12.6 Exclusion Criteria:

Order Number	Criteria
	b. **Exclusion Criteria -** Subjects will be excluded from the study for any of the following reasons: 1. Female subjects of childbearing capacity who test positively for ß-HCG, or are either self-reporting as pregnant, planning to become pregnant, or nursing. 2. Presence of psychotic features. 3. Unable to provide informed consent or comply with study procedures. 4. Previous treatment with riluzole. 5. Serious, unstable illnesses including hepatic, renal, gastroenterological, respiratory, cardiovascular (including ischemic heart disease), endocrinologic, neurologic, immunologic, hematologic disease, or HIV. This includes individuals with a history of COPD by diagnosis as well as persons taking inhalers for Asthma or Reactive Airway Disease. 6. Clinically significant abnormal levels (3x ULN or greater) of serum transaminases (ALT/SGPT; AST/SGOT), current or past blood dyscrasia. 7. Subjects with uncorrected hypothyroidism or hyperthyroidism. 8. DSM-IV alcohol or substance abuse or dependence within 90 days of the screening visit. 9. Treatment with a reversible MAOI, guanethidine, or guanadrel within 1 week, or any change in fluoxetine dosing within 8 weeks prior to visit 2. Use of antidepressant and sedative/hypnotic drugs at stable dose is permitted. 10. Documented history of hypersensitivity or intolerance to riluzole. 11. Subjects with a current or past history of other axis I disorders including schizophrenia, schizoaffective disorder, bipolar disorder or dementia. However, those with a co-morbid history of other Axis I disorder like major depression, dysthymia or other anxiety disorders will be included; the justification for this is that approximately 70% of subjects with PTSD have co-morbid depression and or alcohol abuse, and restricting the sample to PTSD patients without depression will not accurately reflect the scope of this disorder. 12. Patients who are currently at high risk for homicide or suicide, as indicated by an affirmative answer to the question: "In the last three months, have you attempted to kill yourself, made specific plans to kill yourself, or had the intention to kill yourself?" 13. Current or planned litigation regarding the traumatic event. 14. Patients who recently started trauma focused cognitive behavioral psychotherapy (Patient's underlying educational or supportive individual or group therapy will be included). 15. Patient's actively enrolled in an evidence based psychotherapy treatment (e.g., Cognitive Processing Therapy or Prolonged Exposure Therapy) will be excluded until that therapy has concluded, but may be re-approached at that time if patient self-report or clinician referral suggests persistent PTSD symptoms upon conclusion of that treatment. 16. Subjects with an artificial cardiac pacemaker or metallic implants within their body will be enrolled at WRNMMC for the placebo-control clinical trial portion of the study only. These individuals, due to their pre-existing medical condition, are medically ineligible to participate in the ^{1}H MRS imaging portion of the study. Further, the Magnetic Resonance (MRI) Screening Form is use at WRNMMC will be used for participant screening prior to any imaging procedures. 17. Use of benzodiazepines. **Rationale and further discussion for General Inclusion and Exclusion criteria**

1

Age criteria: The absence of data demonstrating the efficacy and tolerability of riluzole in children with PTSD makes their inclusion unethical.

Diagnosis: Subjects with other co-morbid Axis I disorders except for major depressive disorder and other anxiety disorders are excluded because patients with this characteristic may constitute a group with a more severe form of illness that requires a different treatment approach. Patients with a co-morbid diagnosis of major depressive disorder will be included because of the frequent co-occurrence of major depression in patients with PTSD.

Severity criteria: Only subjects with a certain severity of PTSD will be included to increase the likelihood of finding the desired results. That is, PTSD must be unremitting and under current treatment on a stable prescriptive dosage for a minimum of 8 weeks on either of the two FDA-approved drugs for PTSD (Paroxetine – Paxil or Sertraline – Zoloft) or any other SSRI/SNRI in off-label prescriptive use for the management of PTSD. A score of 40 or more on CAPs is also required.

Exclusion of recent substance abuse or dependence: We elect to use a narrower exclusion criterion of abuse and dependence than DSM-IV (within the past three months) in order to allow participation by subjects with a history of substance abuse or dependence problems that could be secondary to their mood disorders. Allowing participation by patients with histories of substance abuse/dependence more than three months earlier broadens the inclusion criteria to more closely approximate patients seen in "real world" settings. Study medications are not associated with increased risk of future dependence problems.

To safeguard participants from self-incrimination, two exclusion criteria will be grouped and presented using the following script, which will be read aloud to each potential participant as part of obtaining informed consent for study enrollment:

> "There are two situations that would preclude you from participating in this study. I'm going to read these two to you. If you believe that either of these is relevant to you, you cannot be in this study. You do not need to state what your personal reasons are to me. And I will not record them in any manner. If you can participate in this study, please state, '**YES**' when I ask you if you'd like to be in the study. You do not need to say, '**NO**' if you cannot be in the study. Simply say '**THANK YOU**', and I will understand. I appreciate your time and consideration in participating.
>
> The two situations are:
>
> 1. In the past 90 days, have you struggled with significant alcohol or substance abuse?
> 2. Are you planning to file legal suit or seek litigation regarding your traumatic event?
>
> '**WOULD YOU LIKE TO BE IN THE STUDY?**' "
>
> Referral information for alcohol/substance/sedative use and legal counseling in use at WRNMMC will be maintained in the clinical area where screenings are conducted. These are commonly posted and displayed for any individual to review. In general, these materials are also maintained with other health and welfare referrals so anonymity and privacy is maintained. As the participant leaves, the research clinician will inform the participant that resources are available should they be interested. If the research clinician feels the individual is at personal risk, active intervention will be necessary as detailed in Section 6.3. a.

Exclusion of acute or unstable medical illnesses: This would prevent subjects from tolerating the acute trial target doses of medication. We will include subjects with chronic stable medical illnesses.

Exclusion of women who are pregnant, plan to become pregnant or are breast-feeding: The study medication is a Category C drug, and we cannot be certain that it will not have teratogenic effects and it may be present in breast milk. As such, the Consent Form advises female participants to avoid becoming pregnant for at least one month after last receiving the study drug. Pregnancy within this time after the study drug is given may be a risk to an unborn baby. No evidence of teratogenic effects is found in the literature for males; however, all participants will be advised of the pregnancy category of the drug (C) and be informed that they should avoid attempting to conceive during participation or for at least one month after last receiving the study drug. Female participants will be given a pregnancy test post-treatment.

Because it is unknown whether riluzole can adversely affect human sperm, male participants will be informed of the possible risk to a child conceived while using the study drug and be advised they avoid engaging in sexual activity with the intent to conceive.

13.0

Recruitment and Consent

13.1 Identification and Selection of Subjects:

See Legacy Protocol

13.2 Recruitment Process:

Subjects will be recruited from collaborator- and provider-referrals at WRNMMC and the Syracuse VA Medical Center, as well as from associated community-based outpatient clinics (CBOCs) and other referring research studies drawing from current patients with PTSD, with or without mild TBI, who are sub-optimally responsive to their current medication treatment over a minimum of 8 weeks. We intend to use office space in the WRNMMC Behavioral Health Clinic. Collaborators and providers will identify these potentially eligible patients and discuss with them the possibility of participating in the study.

During the standard of care intake or initial evaluation process, collaborators and providers will give referral patients the contact information to reach the study research staff only if they express interest in contacting the study research staff and learning more information about participating in the study, specifically, the inclusion and exclusion criteria necessary for study participation. Referral interactions with study research staff may occur by telephone, email, text and/or instant messaging, as well as in person at WRNMMC. Patients who then meet inclusion criteria will be scheduled for the Screening Visit once informed consent is obtained. All advertisements and information to be given to potential participants regarding how to contact study staff if interested will be approved by the IRB prior to dissemination. Advertisements will include posters, trifold brochures, and provider handouts, which will be disseminated at Walter Reed National Military Medical Center services and intranet, and posting on clinicaltrials.gov and Facebook. To ensure confidentiality, on the study Facebook page, only study personnel will be permitted to post information; potential participants and providers may privately message and "Like" or "Share" the page. All PI information for participants and enrollees will be maintained in secured files or electronic storage under locked quarters. Only Research Staff will have access to these records. This is further detailed in Section 6.3.c.

All subjects will be evaluated for study entry during the Screening Visit by a Masters-level Clinical Research Psychologist under the supervision of a credentialed provider within the WRNMMV Behavioral Health Clinic using a CAPS assessment; WRNMMC study research staff will recruit, screen, consent and enroll subjects at WRNMMC, while Syracuse VA Medical Center study research staff will recruit, screen, consent and enroll subjects at the Syracuse VA Medical Center, as well as from associated community-based outpatient clinics (CBOCs). CAPS score > or = to 40 will be necessary for study enrollment. Those entering the study at the completion of an INTRuST medication trial will also receive a CGI assessment, and must have an assessment determination of "NOT improved" or "NOT very much improved" on the CGI at the completion of their medication trial to be eligible for study enrollment.

The Screening Visit will include all screening tests, patient and family history, and psychiatric and physical examinations, as well as menstrual history in females. Inclusion and exclusion criteria will be assessed. Subjects will undergo a physical exam, supine and standing vital signs, blood chemistries, liver function tests, hematology profile, urinalysis (including screens for substances of abuse), hepatitis screen, SCID, and CAPS. Women of childbearing capacity will have baseline serum ß-HCG, and a positive ß-HCG will exclude them from participating in the study. Subjects must also have a negative Human Immunodeficiency Virus (HIV) test.

A complete medication list will be compiled prior to dispensing riluzole and verification of the list for change will be done at the weekly clinical visit to assess for compounds that may interact with clearance of the drug.

Participants will be advised to take riluzole 1 hour before or two hours after meals for optimal metabolism of the compound. Education will be provided that the bioavailability of the compound is significantly affected by high fat meals and that charbroiled food may increase the speed of clearance of the compound from their bodies.

13.3 Compensation for Participation:

Compensation is provided for off-duty military personnel participating at WRNMMC and for participants recruited from the Syracuse VA and associated CBOCs. Reimbursement is determined by the number of hours spent completing study assessments and equates generally to a rate of $15 per hour. Reimbursement will be pro-rated for incomplete research sessions. Reimbursement is not

provided for treatment visits. Reimbursement will be issued as a gift card given directly to the participant (WRNMMC) or as a check mailed to the participant's home (Central New York Research Corporation (Syracuse VA and associated CBOCs).

Participant Reimbursement

Visit	Rate	Hours	Reimbursement
Screening	$15	5	$ 75
Visit 1	$15	4	$ 60
Visit 2	$15	2	$ 30
Visit 3	$15	2	$ 30
Visit 4	$15	2	$ 30
Visit 5	$15	4	$ 60
Visit 6	$15	2	$ 30
Visit 7	$15	2	$ 30
Visit 8	$15	2	$ 30
Visit 9	$15	4	$ 60
Bonus for attending all clinical sessions			$ 80
Bonus for completing both ^{1}H MRS imaging scans (pre and post)		5	$ 75
Total Reimbursement per participant			$ 590

13.4 Eligibility Assessment Process:

See Legacy Protocol

13.5 Consent Process:

Are you requesting a waiver or alteration of informed consent?

○ Yes ◉ No

Please explain the consent process:

A. Informed consent will be collected at the start of screening. Participants will only be assigned a study ID number upon randomization after successfully being screened in. Any participant who is found to be ineligible after screening will not be randomized or assigned a study ID number, however their consent and screening data will be stored with the rest of the study data files. The stated recruitment goal of 158 participants approximately refers to consented participants and does include participants who were not randomized because of screen failure or any other ineligibility factor.

Informed consent and HIPAA authorization will be administered by a member of the research team at each site prior to screening and psychological testing and is a process that is initiated prior to the individual's agreeing to participate in the study and continuing throughout the individual's study participation. risks and possible benefits of the study and opportunity to fully review the consent form, and ask questions. The individual will be given sufficient opportunity to discuss the study and process the information in the consent process prior to agreeing to participate. As a part of this process, all subjects are informed that they are not obligated to participate in this study, and the rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care as well as the care to which they are entitled to in their referring research study participation will not be adversely affected or penalized if they decline to participate in this study. If they choose to take part in the study, they will be asked to sign the consent form. This process will be monitored as required at each participating institution and in accordance with all regulatory guidelines. Patients will be informed of their right to withdraw from the study at any time prior to obtaining informed consent and at subsequent scheduled visits. This is anticipated to be a time ccommitment of one hour.

B. After the subject has been given ample time to read the consent document, the consenter will ask him or her to briefly explain the document. At this time, any questions will be answered. If in the judgment of the consenter the subject does not understand, the subject will be excluded; the consenter will then try to explain the reason for exclusion as best as possible.

C. The subject will verbally list health information to be accessed and released to ensure complete understanding. If, in the judgment of the consenter, the subject is not able to understand the health information to be accessed and possibly released, the subject will be excluded; the consenter will then try to explain the reason for exclusion as best as possible.

D. A HIPPA waiver will not be requested.

13.6 DoDI 3216.02 requires an ombudsman to be present during recruitment briefings when research involves greater than minimal risk and recruitment of Service members occurs in a group setting. If applicable, you may nominate an individual to serve as the ombudsman.

- (•) N/A
- ( ) Propose ombudsman

13.7 Withdrawal from Study Participation:

Explain the process for withdrawal and specify whether or not the subjects will be given the opportunity to withdraw their data their data/specimens in the event they wish to withdraw from the study

See Legacy Protocol

14.0 Risks and Benefits

14.1 Risks of Harm:

Identify all research-related risks of harm to which the subject will be exposed for each research procedure or intervention as a result of participation in this study. Consider the risks of breach of confidentiality, psychological, legal, social, and economic risks as well as physical risks. Do not describe risks from standard care procedures; only describe risks from procedures done for research purposes

General: By agreeing to participate in this study, subjects will be temporarily forgoing the opportunity to receive routine clinical care and psychiatric medication in the community. 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 physicians 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 baseline evaluations are minimal. No discomfort is expected to be associated with the physical examination or the clinical interview. Venipuncture may be associated with the momentary discomfort of the needle stick, as well as a small risk of hematoma (bruise) formation. Subjects will be exposed to the discomfort of asking personal questions that they may find distressing.

Stabilization Period and Treatment Trial: Since it is unknown whether riluzole is effective in the treatment of PTSD, participation in this trial could delay additional potentially effective treatments by 10 weeks. That is, participation in this study would preclude a subject from receiving other potential augmenting medications (although none are FDA approved for PTSD) or additional psychotherapy for his or her refractory PTSD. If the patient is discontinued from the study due to a worsening of their illness, they will receive standard care.

Risks Due to Riluzole Administration: Controlled studies in medically ill patients taking multiple concomitant medications indicate that it is well tolerated. The most frequent dose-related adverse events included nausea, asthenia, and elevated liver enzyme levels. Less frequent dose-related adverse events include exfoliative dermatitis and tremor. Nausea was reported by 12 to 21% of riluzole-treated patients, compared with 12% for placebo. Less than 1% of patients with asthenia discontinued treatment. Dizziness, diarrhea, anorexia, and circumoral paresthesia occurred more frequently with 200-mg/day riluzole. It should be noted that concomitant medications were permitted in the trials that examined riluzole, thus adverse events may be over-reported (approximately 72% took at least one

concomitant medication, the mean number of concomitant medications per patient during this trial period of 6.6). Elevated ALT levels (>5 X ULN) accounted for the majority of treatment discontinuations based on laboratory adverse events. This event represented less than 4% with any treatment group (50 mg, 100 mg, or 200 mg riluzole) (Lacomblez et al 1996).

Another potential side effect of riluzole that has been reported to rarely occur is neutropenia. In ALS trials, three out of 4,000 patients given riluzole developed marked neutropenia, all seen within the first 2 months of riluzole treatment. Because of the risk of an elevation of liver enzymes and neutropenia, we will exclude patients with a history of significant liver disease or neutropenia. Of note, is that in one of these trials, approximately 72% took at least one concomitant medication, the mean number of concomitant medications per patient during this trial period of 6.6. It is possible that other medications, concomitant medical illnesses, etc could account for these cases of neutropenia. In our preliminary studies, approximately 33 subjects with major depression were exposed to riluzole. Overall the drug was well tolerated and no serious adverse events occurred. Another potentially serious but very rare event is pancreatitis.

Our (NIH) experience with riluzole is outlined below:

An 8-week open-label study with riluzole in treatment-resistant DSM-IV bipolar depression (Protocol #03-M-00092) (Zarate et al., 2005). Eight subjects (57%) completed the 8-week trial. The reasons for discontinuation were adverse events (N =3; 2 asymptomatic increase in liver function tests, 1 renal calculi) and lack of improvement (N =3). Patients received riluzole at a mean daily dose of 171.4 + 42.6 mg (79% took a dose of 150 mg/day or more). The most common adverse events during the trial were fatigue (N = 4), decreased salivation (N = 4), reduced sleep (N = 4), nausea (N = 3), diarrhea (N = 3), weight loss (N = 3), decreased sex drive (N = 3), blurred vision (N = 3), and headache (N = 3). No serious adverse events were noted. Two subjects were discontinued from the study because of increased liver function tests (LFTs) that were more than three times the upper normal limit. These subjects were asymptomatic for hepatic dysfunction, and LFTs normalized shortly after discontinuing riluzole. One additional subject was discontinued because of renal calculi. Overall riluzole was well tolerated.

A 6-week open-label study with riluzole in treatment-resistant DSM-IV major (unipolar) depression (Protocol #02-M-0034) (Zarate et al., 2004). Patients received riluzole at a mean daily dose of 168.8 + 27.2 mg (84.2% took a dose of 150 mg/day or more) for a mean duration of 5.4 ± 3.7 weeks. Sixty-eight percent (N=13) of subjects completed the 6-week trial. The reasons for discontinuation were adverse events N=3 (1 increased liver function tests, 1 malaise, 1 nausea/vomiting), non-response N=2, and administrative N=1. The most common adverse events during the trial were headache (58%), gastrointestinal distress (nausea or vomiting) (43%), decreased salivation (47%), constipation (32%), and tension/inner unrest (26%); similar side effects have been observed with riluzole in ALS trials (Bensimon et al., 1994). No serious adverse events were noted. One subject was discontinued from the study because of an increase in liver function tests (LFTs) that was 3 times the upper normal limit. This subject was asymptomatic for hepatic dysfunction, and LFTs normalized shortly after discontinuing riluzole. There was no relationship between dose of riluzole and adverse events or changes in laboratory tests.

A condition called interstitial lung disease has occurred in some patients who have taken riluzole. Participants will be advised of this risk and informed that should they develop a dry cough with shortness of breath or difficulty breathing, they will need to seek medical attention including a chest x-ray assessment and will need to discontinue taking riluzole immediately.

Risks Associated with Magnetic Resonance Spectroscopy: ^{1}H MRS is not associated with any known deleterious biological effects in normal subjects. However, there are risks for subjects who have any metallic implants in their body or who have an artificial cardiac pacemaker. For this reason, they will be screened for the presence of any metallic prostheses or cardiac pacemaker both at the time of recruitment, and just prior to ^{1}H MRS imaging. Subjects will be advised of two potential discomforts. The first is that the procedure requires remaining still while lying on their back for an extended period of time (up to 60 minutes). The second is the MRS machine is a tightly enclosed space, which may be of concern for those with claustrophobia.

14.2 Measures to Minimize Risks of Harm (Precautions, safeguards):

For each research procedure or intervention, describe all measures to minimize and/or eliminate risk of harms to subjects and study personnel

a. Safety Monitoring Plan

Research participants will be continuously monitored throughout the study by the Medical Monitor in conjunction with the Principal and Associate Investigators. During the 8-week treatment period, study staff meets weekly with participants to assess their symptom status and side effects and to administer the research surveys and questionnaires. Based on the anticipated rate of participant recruitment and study enrollment, the Medical Monitor and Investigators will hold a monthly meeting to review the status of enrollment and the overall progression of the study. Records of the meeting will be compiled and maintained by the study coordinator. Meetings of a more frequent interval will be implemented if necessary to account for accelerated rates of study enrollment exceeding the baseline estimate.

The Safety Monitoring Committee will be comprised of the following members:

Chair: COL David Benedek, MD, MC
Medical/Research Monitor: COL (Ret.) Michael Roy, MD MPH
Data Monitor: David Kopp, MPH
Member, at-large: Kyle Possemato, PhD; Larry Lantinga, PhD

The Medical Monitor and Investigators define three event triggers, which will result in the unscheduled review and potential discontinuation of the participant from the study. These triggers are:

1. signs of increasingly severe physiological or psychological symptoms as evidenced by clinical observation during the scheduled weekly visit as well as participant self-report or disclosure;
2. exhibited distress or objection raised during the administration of the research questions;
3. and study-related medical complications experienced while taking the assigned medication as determined by physical examination and supporting laboratory report.

Further, if during the weekly visit, a participant's response to the research battery indicate increasingly severe physiological or psychological symptoms that require an immediate intervention or they express suicidal ideation, intent, or plan, study staff will promptly notify the Principal Investigator for referral and treatment management of the individual. As part of study enrollment, participants will be given the 24-hour emergency contact information for the Investigators and will receive careful instruction on how to reach members of the research team for assistance. Finally, before enrolling in the study, participants will be asked to complete a Treatment Contract. In the Treatment Contract participants will identify a doctor, family member or friend who is aware of their participation in this research study and is willing to be a part of their support system. The Investigator may contact the person(s) who have agreed to act as the participant's support system in the case their symptoms worsen during the study or there is an emergent medical issue that requires immediate contact.

End of treatment/early discontinuation for the trial:

Participants may withdraw at any time or be removed from the study at the discretion of the Investigator, should medical contraindications to the assigned medication develop, if intolerable adverse reactions occur, if mood or anxiety worsens, or if in the clinician's judgment the patient has worsened to such a degree that further participation would put the individual at risk. If a participant begins evidence based psychotherapy (such as CPT or prolonged exposure therapy) or if any of the medications the participant takes for PTSD or other psychiatric conditions are changed after they begin the study, the participant may be withdrawn from the study. Participants are at no risk of losing their right to medical care and some period of observation by the investigators may be recommended for the participants to safely stop taking part in the study because of the study drug.

Continuous monitoring of the participant's health while taking the assigned medication is performed by the Medical Monitor in conjunction with the Principal and Associate Investigators during the scheduled weekly visits. Participants will have clinical biochemistry laboratory blood assays performed to monitor their liver state and function. Liver Function Test (LFTs) will be run first at the Screening Visit and then weekly while taking the assigned medication. In the period between screening and randomization, the participant will be instructed not to begin taking study medication until the Investigator confirms that LFTs are within normal limits. Specifically, their alanine transaminase (ALT), aspartate transaminase (AST), total/direct bilirubin, and alkaline phosphate, will be monitored on a weekly basis during Study Period II to ensure that participants do not have liver function tests elevated over 3x normal ranges. If elevated LFTs are encountered, the test will be repeated, and if levels remain elevated at or above 3x upper limit of normal, the participants on the higher dose will have their dose reduced to 100mg per

day and participants on the low dose will be removed from the study. If a participant's LFTs ever exceed 5x upper limit of normal, the study drug will be discontinued and the subject will be withdrawn from the study.

Elevated LFTs of only 2xs level are not clinically uncommon and are often associated with any number of unrelated medical conditions or complications. A mild elevation in LFTs is quite often temporary in nature, and quickly reversible. Initial studies in riluzole established the 3x level as diagnostic for liver enzyme impairment or disruption to ensure that unrelated medical conditions and complications do not compromise the study while still ensuring the highest safeguarding of the participant.

Participants requiring removal from the study will receive immediate medical treatment and follow up care as necessary. As this is an augmentation trial, we will not taper off medications that have been even minimally effective for the participant's current depression or PTSD (as indicated by CGI-Severity/Improvement assessment score at the completion of a previous referring trial or baseline assessment). If participants are outpatients but their deteriorating condition requires hospitalization, they will be admitted to the specific site's appropriate inpatient treatment facility until stable for outpatient care. Participants removed from the study because of a worsening of their illness will have the option to continue care at the study sites as necessary for up to 90 days. Since subjects are either active duty military or veterans and may move during or shortly after the study, continued care will be coordinated at the appropriate military treatment facility or veteran's administration hospital, since this is more convenient as a result of change of duty location or medical separation from service. Should they choose not to receive standard clinical treatment that the study psychiatrist recommends; the participants will be discharged to the care of the primary physician or psychiatrist who followed them prior to enrollment. If they do not have a primary provider we will assist them in finding an appropriate referral in the community for further treatment and follow-up.

b. Safety Analysis Plan

Exposure to dangerous interventions will be minimized by the discontinuation criteria described above, as well as monitoring of laboratory tests by the Medical Monitor in conjunction with the Principal and Associate Investigators to ensure that liver function is not elevated over 3x normal ranges.

14.3
Confidentiality Protections (for research records, data and/or specimens):

Describe in detail the plan to maintain confidentiality of the research data, specimens, and records throughout the study and at its conclusion (e.g., destruction, long term storage, or banking). Explain the plan for securing the data (e.g., use of passwords, encryption, secure servers, firewalls, and other appropriate methods). If data will be shared electronically with other team members/collaborators outside the institution, describe the method of transmission and safeguards to maintain confidentiality. Explain whether this study may collect information that State or Federal law requires to be reported to other officials or ethically requires action, e.g., child or spouse abuse

i. The Principal Investigator at each site maintains adequate and accurate records in order for the conduct of the study to be fully documented and study data subsequently verified. All records pertaining to the identity of the subjects will be kept private and confidential. For documentation containing personal identifying information that is to be retained locally, on-site, it will be maintained in a locked file cabinet. After study closure, Investigators retain all source documents and study-related documents pertinent to protocol compliance. Because the length of time required for retention of records depends upon a number of regulatory and legal factors, Investigators will store documents until they receive notification that documents can be destroyed. In general, study records are retained and securely stored for a minimum of 7 years after the completion of all study activities.

ii. When will you destroy the research source documents, data file, and the master code?

In general, study records are retained and securely stored for a minimum of 7 years after the completion of all study activities.

iii. Will research data including Identifiable Protected Health Information be sent outside of WRNMMC?

_x_ Yes – Please explain assurances you have received from the outside party that they will appropriately follow confidentiality protections, follow the HIPAA requirements, and abide by the provisions of your Authorization.
___ No

Only where necessary, research data may be sent outside of WRNMMC. Principal and Associate Investigators in consultation with the Medical Monitor will review all research data prior to release to ensure that only the minimum amount of necessary information is released. In their review, all records pertaining to the identity of the subjects will be kept private and confidential and the research data will be password protected and encrypted using National Institute of Standards and Technology (NIST)-certified cryptography. Transmission of research data will occur through a secured carrier recognized in the transport of confidential materials with delivery exclusively to a designated individual or agent required. Prior to release, all necessary assurances will be obtained and agreements established and entered into as required by regulation and institutional standard of practice.

14.4 Potential Benefits:

Describe any real and potential benefits of the research to the subject and any potential benefits to a specific community or society

If the individuals in the research are considered experimental subjects (per 10 USC 980), and they cannot provide their own consent, the protocol must describe the intent to directly benefit all subjects

There may be no direct benefits from participating in this study. It is unknown if riluzole will decrease PTSD symptoms. Information obtained from the study of all participating subjects will benefit society in the way of increased knowledge and understanding of PTSD.

14.5 Privacy for Subjects:

Describe the measures to protect subject's privacy during recruitment, the consent process, and all research activities, etc.

See Legacy Protocol

14.6 Incidental or Unexpected Findings:

Describe the plan to address incidental findings and unexpected findings about individuals from screening to the end of the subject's participation in the research. In cases where the subject could possibly benefit medically or otherwise from the information, state whether or not the results of screening, research participation, research tests, etc., will be shared with subjects or their primary care provider. State whether the researcher is obligated or mandated to report results to appropriate military or civilian authorities and explain the potential impact on the subject

See Legacy Protocol

15.0 Study Monitoring

15.1 Data Monitoring Plan:

Describe the plan to monitor the data to verify that data are collected and analyzed as specified in the protocol. Include who will conduct the monitoring, what will be monitored and the frequency of monitoring

See Legacy Protocol

15.2 Safety Monitoring Plan:

Describe the plan to monitor the data to ensure the safety of subjects

See section 14.2 of the protocol application

15.3 Does your study require independent data and safety monitoring?

○ Yes ◉ No

16.0 Reportable Events

16.1 Reportable Events:

Consult with the research office at your institution to ensure requirements are met
• Describe plans for reporting expected adverse events. Identify what the expected adverse events will be for this study, describe the likelihood (frequency, severity, reversibility, short term management and any long term implications of each expected event)
• Describe plans for reporting unexpected adverse events and unanticipated problems. Address how unexpected adverse events will be identified, who will report, how often adverse events and unanticipated problems will be reviewed to determine if any changes to the research protocol or consent form are needed and the scale that will be used to grade the severity of the adverse event

Expected adverse events which are not serious are reported on the Continuing Review (CR) Progress Report is generally performed on a 12-month cycle. More frequent Progress Reports may be required at the discretion of the IRB.

For multi-center studies, a summary of adverse events study-wide or the report of the Data Safety Monitoring Board (DSMB) should be included with the CR.

Serious Adverse Events: The PI, within 24 hours, must report all related or possibly-related AND serious adverse events (SAE) occurring in subjects enrolled at FBCH. This is accomplished by submitting an adverse event report to the IRB via IRBNet. For protocols involving investigational drugs or devices, the investigator must also report a serious adverse event to the sponsor of the IND or IDE immediately (within 24 hours). Serious adverse events must be reported even if the PI believes that the adverse events are unrelated to the protocol.

Unexpected (but not serious) adverse events occurring in subjects enrolled at FBCH which, in the opinion of the PI, are possibly related to participation AND places subjects or others at a greater risk of harm that was previously known or recognized in the protocol must be reported by the PI within 24 hours of discovery by email or phone to the IRB and the Research Monitor. A follow-up written report within 5 business days to the IRB and the Research Monitor through IRBNet is required.

Unanticipated problems involving risks to subjects or others (UPIRTSOs) must be reported to the IRB and Research Monitor via email or telephone within 24 hours of discovery and a written follow up report within 5 business days.

When a deviation occurs, the investigator shall report the occurrence to the IRB. The investigator is required to make the determination whether the deviation meets the criteria for an unanticipated problem involving risks to subjects or others. The IRB Chair or IRB staff member shall also make the determination if the protocol deviation meets the definition of an unanticipated problem involving risks to participants or others. If the IRB Chair or IRB Staff member determines and documents that the deviation is an unanticipated problem involving risks to subjects or others or the deviation resulted from serious or continuing noncompliance, the IRB staff member shall place the deviation on the agenda of the next available IRB meeting for review. If the IRB Chair or IRB Staff member

determines and documents that the deviation is not an unanticipated problem involving risks to subjects or others, the IRB Chair or staff member shall acknowledge the submission and complete the review through an administrative review procedure.

As a reminder, according to DoDI 3216.02 (November 8, 2011), the IRB shall approve an independent research monitor by name for all DoD-conducted research involving human subjects determined by the IRB to involve more than minimal risk to human subjects. Additionally, the research monitor may be identified by an investigator or appointed by an IRB or IO for research involving human subjects determined to involve minimal risk.

The research monitor may perform oversight functions and will report their observations to the IRB or a designated official. The research monitor may discuss the research protocol with the investigators, interview human subjects, and consult with others outside of the study about the research. The research monitor shall have the authority to stop a research protocol in progress, remove individual subjects from a research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can assess the monitor's report. Research monitors shall have the responsibility to promptly report their observations and findings to the IRB or other designated official. The research monitors shall have expertise consonant with the nature of risk(s) identified within the research protocol and they shall be independent of the team conducting the research involving human subjects.

17.0 Equipment/non-FDA Regulated Devices

17.1 Does the study involve the use of any unique non-medical devices/equipment?

○ Yes ◉ No

18.0 FDA-Regulated Products

18.1 Will any drugs , dietary supplements, biologics, or devices be utilized in this study?

☑ Drugs
☐ Dietary Supplements
☐ Biologics
☐ Devices
☐ N/A

18.2 Drug Details:

☐ Are drug(s) in this research being used in accordance to the approved labeling?
☑ Are drug(s) in this research being used in a manner other than its approved labeling?

When adding a drug indicate in the details section of the drug if the use is either used in accordance to the approved labeling or in a manner other than it's approved labeling

View Details	Drug Name	FDA Approved	A new drug or a new use of approved drug:	IND Number
⊟	**Trade Drug Name:** Riluzole **Generic Drug Name:** **Investigational Drug Name:**	Yes	Yes	

Trade Drug Name:	Riluzole

Generic Drug Name:	
Investigational Drug Name:	
Identify the name of the manufacturer or source of investigational drug/biologic:	Rilutek
Is the drug supplied at no cost?	Yes
Is the Drug FDA Approved:	Yes
Is this a new drug or a new use of an already approved drug	Yes
Is an IND necessary	No
IND Number	
Who holds the IND:	N/A
IND details:	
If FDA Approved and an IND is not required, Please provide a rationale for exemption:	
Are you currently using this IND in another research project?	No
If yes, list the IRB Number(s):	
Dose Range:	
Frequency:	
Route of administration:	
Will the investigational pharmacy be dispensing?	Yes
If the source is not a FDA licensed facility, provide details regarding the purity, quality, stability and sterility of the investigational drug/biologic:	
Identify who will be preparing the investigational drug/biologic for administration and describe in detail how it will be prepared:	
Indication(s) under Investigation:	
Where will the drug be stored	
Drug Storage Restrictions (including temperature, etc.):	
Administration Instructions:	
Possible Untoward Effects, Their Symptoms & Treatment:	
Potential or Actual Antidotes for Excessive or Adverse Drug Effect:	
Contraindications and Interactions, If Known:	
Investigators Authorized to Prescribe:	

18.4 Reporting Requirements for FDA-regulated research under IND and IDE:

Describe the process for complying with FDA regulatory requirements for adverse event reporting and adverse device effects reporting to the sponsor

Riluzole (Rilutek®) is FDA-approved (December 1995) for the treatment of amyotrophic lateral sclerosis (ALS). It is taken in oral dosage form (tablets) - 50mg every 12 hours. The Package Insert is provided as an addendum. Because of its anti-glutamatergic effect and its relative safe profile, riluzole has been evaluated for off-label usage in a number of trials for adult psychiatric conditions in which glutamate excess has been proposed as part of the pathologic mechanism. Seven open-label trials of riluzole in adult subjects are reported in a recent review including three in major depressive disorder (MDD), one in bipolar depression one in generalized anxiety disorder (GAD), and two in the treatment of obsessive-compulsive disorder (OCD) (Grant et al, 2010).

18.5 Sponsor (organization/institution/company):

☑ N/A

If applicable, provide sponsor contact information:

19.0 Research Registration Requirements

19.1 ClinicalTrials.gov Registration:

- ◉ Registration is not required
- ○ Registration pending
- ○ Registration complete

19.2 Defense Technical Information Center Registration (Optional):

- ◉ Registration is not required
- ○ Registration pending
- ○ Registration complete

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20.2 Abbreviations and Acronyms: