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

Patricia T. Spangler1,2, James C. West1,2, Brian Andrews-Shigaki2, Kyle Possemato3, Shannon McKenzie3, Maegan Paxton1, and David M. Benedek1,2

1Center for the Study of Traumatic Stress; 2Uniformed Services University of the Health Sciences; 3Syracuse VA Medical Center

Introduction

Current pharmacological treatment for PTSD, particularly combat-related PTSD1,2, is suboptimal, leaving an urgent need to develop novel treatments that rapidly and robustly improve symptoms. Increased concentrations of glutamate in the brain have been linked to cognitive effects that are correlated with PTSD symptoms3. 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 (e.g., amygdala and anterior cingulate cortex), potentially improving the symptoms of PTSD, as well as mild traumatic brain injury (mTBI). Riluzole is a glutamatergic modulator that is FDA approved for treating amyotrophic lateral sclerosis (ALS) and has been found to have antidepressant4 and anxiolytic5 properties. It may enhance the effect of PTSD medications and help reduce traumatic stress symptoms. The current study is a randomized controlled trial evaluating the efficacy of acute riluzole treatment for combat-related PTSD in service members and veterans, with or without mTBI, who have responded suboptimally to other pharmacotherapeutic methods.

Methods

Up to 100 DoD/DEA/OND veterans aged 18 to 65 are being recruited at Walter Reed National Military Medical Center (WRNMMC) and Syracuse VA Medical Center for a randomized, double-blind, placebo-controlled, parallel trial. Participants must currently be taking an SSRI or SNRI for PTSD and have a current CAPS score ≥ 40. The study is being conducted in two phases: eligibility screening with a 2- to 4-week stabilization period and an 8-week acute treatment phase.

During the acute phase participants are randomized (1:1) to 8-week treatment with riluzole or placebo. Participants are assessed weekly from Visit 1 through Visit 9. Dosage begins at 100mg/day and is increased to 200 mg/day if a participant’s PTSD symptoms improve. Participants randomized to riluzole will have significant improvement in depression, anxiety, and global functioning compared to those given placebo. In addition, a subgroup of eligible participants from WRNMMC is undergoing magnetic resonance spectroscopy pre- and post-treatment to evaluate changes in N-acetyl aspartate (NAA) absolute concentration assessed at pre-, mid-, and post-treatment. In addition, a subgroup of eligible participants will be undergoing proton MR spectroscopy of the amygdala (AMYG) and anterior cingulate cortex (ACC).

Methods (cont.)

Proton magnetic resonance spectroscopy (1H MRS) is an in vivo technique that provides direct neurochemical information about regions of interest in the brain (Fig. 1). NAA levels serve as a surrogate marker for neuronal integrity and reflect extent of neuronal loss or injury. Reduced NAA/CR ratios in the ACC and hippocampus have been reported in combat veterans9 and PTSD patients10. The current study will evaluate pre-to-post-treatment changes in absolute NAA concentrations in the ACC and amygdala. Hypotheses: (1) Participants randomized to riluzole will have superior improvement in PTSD symptoms compared to subjects given placebo. (2) Participants randomized to riluzole will have significant improvement in depression, anxiety, and global functioning compared to those given placebo. (3) NAA concentrations in the amygdala and anterior cingulate, measured using 1H MRS, will increase after 8-week treatment with riluzole.

Discussion

The current study is the first known RCT of the glutamatergic modulator, riluzole, for combat-related PTSD symptoms following suboptimal response to pharmacotherapeutic treatment. Because the researchers remain blinded at this point, current findings do not include a comparison of riluzole and placebo outcomes. Preliminary test results indicate PTSD and depression symptomatology are homogeneous across active duty and non-active-duty participants. The current sample is comparable to prior post-SSRI samples on total CAPS scores. For our sample, all of whom were on a minimum 8-week SSRI/SSRI trial, mean CAPS score = 69.07, which is within range of CAPS scores (59.0 to 72.5) in prior post-SSRI studies in veterans10. Additionally, 1H MRS pre-treatment data from 17 participants and post-treatment data from 9 participants has been collected, with n ≥ 47 the target for pre-to-post-treatment analysis. By investigating symptom change and neurochemical changes in brain regions implicated in PTSD symptomatology, the current study will help determine the therapeutic benefit of riluzole while elucidating its neuroprotective effects in regions of interest.

Table 1. Comparison of Active Duty and Non-Active Duty Symptom Cluster Means

<table>
<thead>
<tr>
<th>Symptom Cluster</th>
<th>Active Duty Mean (SD)</th>
<th>Non-Active Duty Mean (SD)</th>
<th>t</th>
<th>df</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N.A.</td>
<td>23.14 (9.76)</td>
<td>22.79 (10.88)</td>
<td>-0.21</td>
<td>26</td>
<td>0.834</td>
</tr>
<tr>
<td>D.D.</td>
<td>24.57 (12.14)</td>
<td>24.15 (11.12)</td>
<td>0.22</td>
<td>26</td>
<td>0.827</td>
</tr>
</tbody>
</table>

**Fig. 1.** Transverse images of voxel location and spectrograph for amygdala (left) and anterior cingulate cortex (right). The dominating peaks of NAA, creatine and choline (Cho) are labeled. Concentration levels of NAA will be compared pre-to-post-treatment.

**Table 1.** Comparison of Active Duty and Non-Active Duty Symptom Cluster Means

**Preliminary Findings**

Twenty-eight participants have screened-in to date, with a mean age of 35.71 years (SD = 8.35). The sample is 85.7% male, 78.6% White, 57% married, and 85% with a current/highest rank of E4-E9. All participants were exposed to combat or aftermath, 96.4% had been in a transportation accident, 89.3% had been in a fire or explosion, 67% had a history of mTBI, and 21.4% had attempted suicide (Fig. 2). Mean CAPS score was 69.07 (SD = 15.74), re-experiencing = 18.86 (SD = 5.75); avoidance = 27.75 (SD = 8.38); and hyperarousal = 22.82 (SD = 6.78). Mean depression (MADRS) = 21.93 (SD = 10.51). Independent-samples t-test results (Table 1) indicate no significant differences between active-duty and non-active-duty participants on total PTSD, re-experiencing, avoidance, hyperarousal, sleep disturbance, guilt, dissociation, or depression symptoms. To date, 18 participants have completed the trial.

References and Acknowledgments

12. Acknowledgements: We thank Tung Tu and Krista Engle, Center for the Study of Traumatic Stress; Gail Kohls, MR technologist at WRNMMC, and Jason Schroeder, neuroradiologist at USUHS and WRNMMC, for their hard work and dedication to this project.