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

Patricia T. Spangler[1,2], James C. West[1,2], Brian Andrews-Shigaki[2], Kyle Possemato[3], Shannon McKenzie[3], Maegan Paxton[1], and David M. Benedek[1,2]

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

Introduction

Current pharmacological treatment for PTSD, particularly combat-related PTSD[1,2], 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 symptoms[3]. 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 antidepressant[4] and anxiolytic properties[5]. 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 pharmacologic treatments.

Methods

Up to 100 OIF/OEF/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 be currently 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 Checklist score does not decrease by 10 or more points after 2 weeks of treatment.

Outcome variables include PTSD, depression, anxiety, and global functioning, which are assessed at pre-, mid-, and post-treatment. 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 levels in the amygdala (AMYG) and anterior cingulate cortex (ACC).

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

Symptom Cluster	Active Duty Mean (SD), *n*=14	Non-Active Duty Mean (SD), *n*=14	*t*	*df*	*p*
CAPS Total	70.14 (19.56)	68.00 (15.94)	-0.32	26	.753
Re-experiencing	20.50 (7.49)	17.21 (7.51)	-1.16	26	.257
Avoidance	27.71 (9.63)	27.79 (7.30)	0.02	26	.983
Hypervigilance	23.36 (6.90)	22.29 (6.88)	-0.41	26	.684
Sleep Disturbance[a]	8.50 (4.18)	8.86 (3.39)	0.25	26	.806
Guilt[b]	4.14 (4.66)	3.86 (4.54)	-0.16	26	.871
Dissociation[c]	4.29 (5.17)	3.93 (3.93)	-0.21	26	.839
MADRS (Depression)	22.43 (9.81)	21.43 (11.52)	-0.25	26	.807

Notes: [a]Sleep Disturbance = CAPS distressing dreams + difficulty falling or staying asleep. [b]Guilt = guilt over acts of commission or omission + survivor guilt. [c]Dissociation = reduction in awareness + derealization + depersonalization.

Methods (cont.)

Proton magnetic resonance spectroscopy (^{1}H 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[7,8]. Reduced NAA/CR ratios in the ACC and hippocampus have been reported in combat veterans[9] and PTSD patients[10]. 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 ^{1}H MRS, will increase after 8-week treatment with riluzole.

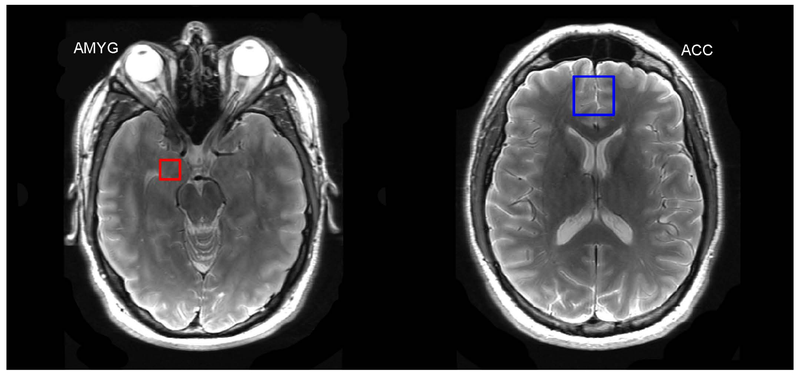
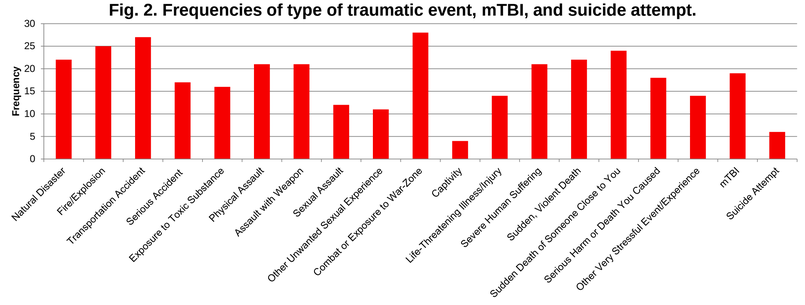


Fig. 1. Transverse images of voxel location and spectrograph for amygdala (left) and anterior cingulate cortex (right). The dominating peaks of NAA, creatine (Cr) and choline (Cho) are labeled. Concentration levels of NAA will be compared pre- to post-treatment.

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, 57.1% married, and 85.7% 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, 67.9% had a history of mTBI, and 21.4% had attempted suicide (Fig. 2). Mean CAPS score was 69.07 (*SD* = 17.54), re-experiencing = 18.86 (*SD* = 7.55); avoidance = 27.75 (*SD* = 8.38); and hypervigilance = 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, hypervigilance, sleep disturbance, guilt, dissociation, or depression symptoms. To date, 18 participants have completed the trial.

Fig. 2. Frequencies of type of traumatic event, mTBI, and suicide attempt.



Discussion

The current study is the first known RCT of the glutamatergic modulator, riluzole, for combat-related PTSD symptoms following suboptimal response to pharmacologic treatment. Because the researchers remain blinded at this point, current findings do not include a comparison of riluzole and placebo outcomes. Preliminary *t*-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/SNRI trial, mean CAPS score = 69.07, which is within range of CAPS scores (59.0 to 72.5) in prior post-SSRI studies in veterans[10,11]. Additionally, ^{1}H 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 further elucidating its neuroprotective effects in regions of interest.

References and Acknowledgements

1. DoD-VA Practice Guideline for the Management of Posttraumatic Stress, 2010.
2. van der Kolk BA, Dreyfuss D, Michaels M, Shera D, Berkowitz R, Fisler R, Saxe G. Fluoxetine in posttraumatic stress disorder. J Clin Psychiatry 1994; 55:517-522.
3. Sherin JE, & Nemeroff CB. Post-traumatic stress disorder: the neurobiological impact of psychological trauma. *Dial Clin Neurosci 2011*;*13*(3):263–278.
4. Zarate CA, Jr., Payne JL, Quiroz J et al. An open-label trial of riluzole in patients with treatment-resistant major depression. *Am J Psychiatry* 2004 January;161(1):171-4.
5. Mathew SJ, Price RB, Mao X, Smith EL, Coplan JD, Charney DS, Shungu DC. Hippocampal N-acetylaspartate concentration and response to riluzole in generalized anxiety disorder. *Biol Psychiatry*. 2008 May 1;63(9):891-8.
6. Sager TN, Topp S, Torup L, Hanson LG, Egestad B, Moller A. Evaluation of CA1 damage using single-voxel 1H-MRS and un-biased stereology: Can non-invasive measures of N-acetyl-asparate following global ischemia be used as a reliable measure of neuronal damage? *Brain Res* 2001 February 16;892(1):166-75.
7. Ebisu T, Rooney WD, Graham SH, Weiner MW, Maudsley AA. N-acetylaspartate as an in vivo marker of neuronal viability in kainate-induced status epilepticus: ^{1}H magnetic resonance spectroscopic imaging. *J Cereb Blood Flow Metab* 1994 May;14(3):373-82.
8. Villarreal G, Petropoulos H, Hamilton DA et al. Proton magnetic resonance spectroscopy of the hippocampus and occipital white matter in PTSD: preliminary results. *Can J Psychiatry* 2002 September;47(7):666-70.
9. Mahmutyazicioglu K, Konuk N, Ozdemir H, Atasoy N, Atik L, Gundogdu S. Evaluation of the hippocampus and the anterior cingulate gyrus by proton MR spectroscopy in patients with post-traumatic stress disorder. *Diagn Interv Radiol* 2005 September;11(3):125-9.
10. Friedman MJ, Marmar CR, Baker DG, Sikes CR, Farfel GM. Randomized, double-blind comparison of sertraline and placebo for posttraumatic stress disorder in a Department of Veterans Affairs setting. *J Clin Psychiatry* 2007 May;68(5):711-20.
11. Zohar J, Amital D, Miodownik C et al. Double-blind placebo-controlled pilot study of sertraline in military veterans with posttraumatic stress disorder. *J Clin Psychopharmacol* 2002 April;22(2):190-5.

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.

UNIFORMED SERVICES UNIVERSITY
of the Health Sciences