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Randomized Controlled Trial of Riluzole Augmentation for Posttraumatic Stress Disorder: Efficacy of a Glutamatergic Modulator for Antidepressant-Resistant Symptoms

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Abstract

Objective: Current pharmacologic treatments for posttraumatic stress disorder (PTSD) have shown limited efficacy, prompting a call to investigate new classes of medications. The current

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study investigated the efficacy of glutamate modulation with riluzole augmentation for SSRI/SNRI-resistant, combat-related PTSD symptoms.

Methods: A randomized, double-blind, placebo-controlled, parallel trial was conducted at Walter Reed National Military Medical Center and Syracuse VA Medical Center between December 2013 and November 2017. Veterans and active duty service members with combat-related PTSD who were not responsive to SSRI or SNRI pharmacotherapy were randomized to 8-week augmentation with a starting dose of 100 mg/day of riluzole ($n = 36$) or placebo ($n = 38$) and assessed weekly for symptoms of PTSD, anxiety, depression, disability, and side effects.

Results: Intent-to-treat analyses ($N = 74$) of the primary outcome (CAPS for DSM-IV) showed no significant between-group difference in change in overall PTSD symptoms ($F=0.64$, $P = .422$), with a small effect size ($d = .25$). There was clinically significant within-group improvement in overall PTSD symptoms in both groups, with a greater mean decrease in the riluzole group (-21.1 , $SD = 18.9$) than in the placebo group (-16.7 , $SD = 17.2$). Exploratory analyses of PTSD symptom clusters showed significantly greater improvement on hyperarousal symptoms in the riluzole group as measured by the PTSD Checklist-Specific-Subscale D ($d = 0.48$) and near-significant findings on the CAPS-Subscale D. Riluzole augmentation was not superior to placebo on change in depression, anxiety, or disability severity.

Conclusions: Although preliminary, the exploratory findings of this study offer some evidence that riluzole augmentation of an SSRI or SNRI may selectively improve PTSD hyperarousal symptoms without changes in overall PTSD symptoms, depression, anxiety, or disability. Additional investigation of the mechanism of riluzole's efficacy for hyperarousal symptoms is warranted.

Keywords

posttraumatic stress disorder; riluzole; randomized controlled trial; glutamate

Posttraumatic stress disorder (PTSD) is a trauma- and stressor-related disorder characterized by intrusive symptoms, avoidance of stimuli, negative alterations in mood and thought, and increased arousal and reactivity. Current pharmacologic treatments are suboptimal, leaving many patients with refractory symptoms.^{1–3} Selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) are the only pharmacologic treatments recommended for PTSD and, with variable efficacy and low to moderate effect sizes,^{4–6} are considered second-line treatments.⁷ SSRI-augmentation trials of anticonvulsants,^{8,9} antipsychotics,^{10–12} and cholinesterase inhibitors¹³ have not consistently demonstrated efficacy. Hence, investigating novel pharmacologic approaches to treating PTSD remains a priority.

One potential approach is through modulation of the glutamatergic system. A recent review summarized findings that implicated glutamate dysregulation in the pathophysiology of PTSD.¹⁴ Glutamate excitotoxicity is believed to lead to overactivation of NMDA receptors, which is detrimental over time. Plasticity is believed to be mediated by AMPA and metabotropic receptors on both neurons and glial cells.¹⁵ Chronic stress leads to dysregulation of glutamatergic neurons with subsequent hyperinflammatory states and impaired synaptic plasticity.¹⁴ Drugs that regulate glutamate brain concentrations may be an

effective treatment strategy for PTSD. One initially promising drug, ketamine, is an NMDA receptor antagonist that has been found to improve PTSD symptoms.^{16,17} However, subanesthetic antidepressant doses of ketamine have been associated with psychotomimetic side effects and abuse liability. Another glutamate modulator, D-cycloserine (DCA), a partial NMDA agonist, has shown limited efficacy. A recent systematic review found that prior studies did not support the use of DCA as adjunctive treatment.¹⁸ Finally, N-acetylcysteine (NAC), a glutamate modulator that has been investigated as a treatment for substance use disorders, was recently tested in a randomized clinical pilot trial for comorbid PTSD and substance use disorders.¹⁹ Results indicated a greater decrease in PTSD symptoms in the NAC group than in placebo, however between-group difference was not significant. Taken together, results of these investigations indicate a need for further research on the role that glutamatergic modulators may play in treating PTSD.

Riluzole, a glutamatergic modulator approved for treating amyotrophic lateral sclerosis, has been suggested as a novel PTSD treatment approach.¹⁴ Riluzole exerts a neuroprotective effect by increasing neuronal and glial reuptake of glutamate, decreasing presynaptic release, and modulating postsynaptic voltage-gated sodium channels.²⁰ Upregulation of glial reuptake results in decreased extrasynaptic glutamate concentrations and release from tonic inhibition of these neurons by activating presynaptic mGluR 2/3 receptors.^{21,22} These findings may offer an explanation of how riluzole induces trophic factors, including brain-derived neurotrophic factor.^{23,24} In addition, preclinical evidence suggests that riluzole facilitates fear extinction in rats,^{25,26} and a recent preliminary meta-analysis of clinical trials showed that riluzole had small positive effects on depression and obsessive compulsive disorder symptoms,²⁷ which have some commonality with PTSD symptoms. These findings suggest that riluzole may be an effective pharmacologic agent in the treatment of PTSD.

The primary objective of the current study was to test the efficacy of riluzole augmentation in Iraq and Afghanistan combat veterans with PTSD symptoms resistant to SSRI or SNRI monotherapy. We hypothesized that participants who were randomized to riluzole would have significantly greater baseline-to-posttreatment improvement in PTSD symptoms compared to those randomized to placebo. Our secondary hypothesis was that those who received riluzole would have significantly greater baseline-to-posttreatment improvement in depression, anxiety, and disability than those who received placebo.

METHODS

Design

This study was a two-phase, randomized (1:1), double-blind, placebo-controlled, parallel trial conducted at Walter Reed National Military Medical Center (WRNMMC; Bethesda, MD) and Syracuse Veterans Administration Medical Center (SVAMC; Syracuse, NY). Institutional review board approval was obtained from Uniformed Services University, WRNMMC, and SVAMC. The study was registered at [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02155829) (identifier: [NCT02155829](https://clinicaltrials.gov/ct2/show/study/NCT02155829)).

Participants

Potential participants were contacted through face-to-face recruiting at WRNMMC and targeted mailings and provider referral at SVAMC. Informed consent was obtained after participants were fully apprised of study procedures, risks, and potential benefits. Inclusion criteria required participants to be active duty military service members or veterans 18 to 65 years old with trauma sustained during combat in Afghanistan or Iraq, as assessed with the Life Events Checklist.²⁸ Participants had to have a diagnosis of PTSD by clinical history and sustained symptom severity as confirmed by a Clinician Administered PTSD Scale (CAPS)²⁹ score ≥ 40 despite a minimum of 8 weeks treatment with a stable minimum therapeutic dose of an SSRI or SNRI. In order to capture a sample that was partially responsive to SSRI/SNRI treatment, participants did not have to meet DSM-IV criteria for PTSD diagnosis at baseline. Minimum therapeutic dose was based on study psychiatrist clinical judgment. Exclusion criteria assessed with the MINI International Neuropsychiatric Interview for DSM-IV, version 5.0,³⁰ included bipolar disorder, psychotic disorder, recent (past 90 days) alcohol or substance use disorder, and suicide ideation with planning. In addition, participants could not be taking benzodiazepines, MAOIs, tricyclic antidepressants, mood stabilizers (including lamotrigine), or antipsychotic medications; have serious unstable medical illness; have liver enzymes greater than three times the upper limit of normal (ULN) range; be pregnant or breastfeeding; or be in current evidence-based psychotherapy for PTSD. Participants received compensation for completing study visits.

Randomization and Blinding

Randomization was stratified by site, with each site's research pharmacy using the randomization generator, <http://www.jerrydallal.com/RANDOM/assign.htm>, to allocate participants 1:1 to riluzole or placebo. The research pharmacists maintained allocation records; participants, assessors, and study physicians were blinded to allocation. Participants could request their randomization status after completing all study visits.

Intervention

During phase 1 of the trial, participants continued on their current SSRI or SNRI for an additional 2 to 4 weeks to ensure blood level stabilization and that no other changes were made to medications prior to randomization. In phase 2, participants continued on their SSRI/SNRI and were randomized to riluzole or placebo for 8 weeks. Study drug was administered via identical capsules. Dosage was initiated at 50 mg twice daily and increased to 100 mg twice daily at two weeks unless participants' PCL-S score decreased by 10 or more. Dosing was based on prior studies using doses from 50 mg to 100 mg twice daily.^{31–36} Participants could be kept at 100 mg/day based on study psychiatrists' consideration of self-reported side effects and liver function test results. Treatment adherence was monitored with a daily self-report medication tracker.

Outcome Measures

The primary outcome variable, baseline-to-posttreatment change in PTSD symptom severity, was assessed with the CAPS, which was administered at screening, baseline, midtreatment, and posttreatment. Secondary outcome measures included the PTSD Checklist-Specific

(PCL-S)³⁷ and Montgomery-Asberg Depression Rating Scale (MADRS),³⁸ which were given weekly, and the Hamilton Anxiety Rating Scale (HAM-A)³⁹ and Sheehan Disability Scale (SDS),⁴⁰ which were completed at baseline, midtreatment, and posttreatment.

Safety Measures

Given the increased risk of hepatotoxicity with riluzole,^{1,31–36} safety measures included weekly monitoring of vital signs and serum aminotransferases (AST and ALT). To maintain assessor blinding, blood draws for liver function testing were taken after psychometric assessment, and results were monitored and reported to study psychiatrists. If serum aminotransferases exceeded three times the upper limit of normal (ULN) range, participants were retested. If confirmatory test results remained greater than three times ULN, participants were either reduced to low dose or removed from the study.

Side effects were assessed weekly with the UKU Side Effects Rating Scale-Patient Version (UKU-SERS-Pat).⁴¹ If participants endorsed a side effect on the UKU-SERS-Pat, assessors followed up to determine severity, potential relationship to study drug, and interference with daily functioning.

Statistical Analysis

In order to detect a 9-point change in CAPS score (a difference previously used to indicate minimally clinically significant change¹¹) in subjects receiving riluzole augmentation versus placebo, assuming a two-tailed test, $\alpha = 0.05$, and standard deviation of 15, power analyses indicated that $n = 50$ per treatment group would yield a power of 0.844.^{11,42–46} Blinded interim analyses showed a mean CAPS reduction of 15 points for the first 27 participants, and the required sample size was decreased from 50 per group to 35 per group.

Missing data was addressed with multiple imputation using the Markov Chain Monte Carlo (MCMC) algorithm in the PROC MI procedure in SAS for all of the study outcomes. Each variable with missing data was individually imputed, and the imputed variable was then used as a predictor for the next variable using treatment group, study site, age, education, and baseline scores as predictors. Five imputed datasets were created for each of the study outcomes. The average of the point estimates were computed for each of the imputed outcomes, and the results were combined in a MERGE statement in SAS.

Participant characteristics were analyzed using independent sample *t*-tests for continuous variables and chi-square for categorical variables. All outcome analyses were intent-to-treat (ITT). The primary outcome, between-group difference in baseline-to-posttreatment change in CAPS, was analyzed using one-way ANCOVA, with site as a covariate. ANCOVA was also used for the planned secondary analyses: baseline-to-posttreatment change in depression (MADRS), anxiety (HAM-A), disability (SDS), and self-reported PTSD (PCL-S). Exploratory analyses included ANCOVA of baseline-to-posttreatment change in PTSD symptom clusters (CAPS and PCL-S subscales). Given that the subscale analyses were exploratory, no correction for multiple analyses was applied.⁴⁷ A factorial ANOVA comparing the main effects of treatment group and dose level and the interaction effect between treatment group and dose level on change in PCL from Week 2 and posttreatment. Independent sample *t*-tests were used to test between-group differences in change in mean

side effect intensity and change in AST and ALT levels. All statistical tests were two-sided with a significance level of 0.05. Analyses were carried out using SAS version 9.4.⁴⁸

RESULTS

Participants were enrolled at WRNMMC and SVAMC between December 2013 and November 2017. Initial contact (N=764) yielded 150 in-person screening assessments (see Figure 1). Of the 150 screened, 75 were excluded (66 ineligible, 8 declined, and 1 moved prior to randomization), and 75 were randomized. One participant who met inclusion criteria at screening returned at baseline with a CAPS score of 26, which was below the minimum 40 points required for inclusion. The participant's failure to meet inclusion criteria was discovered at study completion, and a determination was made to exclude this data from analysis. Seventy-four participants were included in ITT analyses (riluzole: $n = 36$, placebo: $n = 38$). Fifty (67.5%) participants met criteria for PTSD diagnosis (riluzole: $n = 26$, placebo: $n = 24$). The between-group difference in diagnosable participants was not significant, $\chi^2(1, N = 74) = .693, P = .405$. Five participants (13.9%) dropped out of treatment in the riluzole group and three participants (7.9%) dropped out of the placebo group. The between-group difference in dropouts was not significant, $\chi^2(1, N = 74) = .689, P = .407$. Dropout was associated with younger age, lower education, and less than full-time employment. Study dropouts did not differ from completers on any other outcome measures.

Participant Characteristics

The majority of participants were male (85%), White/Caucasian (64%), married (68%), employed full-time (64%), enlisted (current or veteran) (85%), active duty (52%), and had completed from 13 to 16 years of education (55%). The mean age for the sample was 37.8 ($SD = 8.5$). Treatment groups were not significantly different on any demographic variable.

Primary Outcome

ITT analysis ($N = 74$) of the primary outcome (CAPS) showed no significant between-group difference in change in overall PTSD symptoms ($F = 0.64, P = .422$), with a small effect size ($d = .25$). There was clinically significant within-group improvement in overall PTSD symptoms in both groups, with a greater mean decrease in the riluzole group ($-21.1, SD = 18.9$) than in the placebo group ($-16.7, SD = 17.2$).

Secondary Outcomes

ITT analysis of change in self-reported PTSD symptoms as measured on the PCL-S indicated no significant difference between treatment groups ($F = .00, P = .994$). Mean baseline-to-posttreatment change on the PCL-S was $-15.4 (SD = 13.5)$ for the riluzole group and $-14.5 (SD = 11.4)$ for the placebo group (Table 2), with large effect sizes in both, $d = 1.01$ (riluzole) and $d = 1.14$ (placebo).

As shown in Table 2, the riluzole and placebo treatment groups did not differ significantly on change in depression ($F = .17, P = .684$), anxiety ($F = .01, P = .913$), or disability ($F = .10, P = .746$). Mean baseline-to-posttreatment change in depression (MADRS) was $-7.9 (SD = 7.6; d = 0.88)$ for the riluzole group and $-8.2 (SD = 9.6; d = 0.95)$ for the placebo

group. Mean change in anxiety (HAM-A) was -7.8 ($SD = 7.4$; $d = 0.98$) for the riluzole group and -6.7 ($SD = 6.9$; $d = 0.95$) for the placebo group. Finally, the mean change in disability (SDS) was -6.3 ($SD = 6.8$; $d = 0.83$) for the riluzole group and -5.7 ($SD = 5.9$; $d = 0.78$) for the placebo group.

PTSD Subscales

As an exploratory analysis, ANCOVA results for baseline-to-posttreatment change in PTSD subscales (Table 2) indicated the riluzole group had significantly greater improvement than placebo on the PCL-S D subscale ($F = 3.88$, $P = .050$) and near-significant greater improvement on the CAPS D subscale ($F = 3.65$, $P = .057$). The mean decrease in PCL-D from baseline to posttreatment was -5.9 ($SD = 5.6$) for riluzole and -3.4 ($SD = 4.9$) for placebo, with a small between-group effect size ($d = 0.48$). The mean decrease in CAPS D was -6.8 ($SD = 8.2$) for riluzole and -3.7 ($SD = 7.3$) for placebo, also a small between-group effect size ($d = 0.40$).

Medication Dose

The mean dose of study medication was 125.65 mg/day ($SD = 37.01$) in the riluzole group and 133.50 mg/day ($SD = 39.39$) in the placebo group. Two-way ANOVA results showed no significant main effects for the influence of treatment group or dose level on change in PCL and no significant interaction of these two factors on PCL change, indicating that dose level, regardless of treatment group, did not affect change in PTSD symptoms. Results for the main effect for treatment group on change in PCL were ($F(1, 69) = 2.53$, $P = 0.12$) and for the main effect for dose level on change in PCL were ($F(1, 69) = 3.90$, $P = 0.052$). Result for the interaction effect of treatment group and dose increase on change in PCL was $F(2, 69) = 0.37$, $P = 0.54$.

Side Effects and Adverse Events

Table 3 shows significant group differences in mean change in side effect intensity as assessed on the UKU-SERS-Pat across all study visits. Out of 43 possible side effects for men and 45 for women, 1 side effect was significantly different between treatment groups, such that participants in the riluzole group reported significantly greater increase in difficulty concentrating ($P = 0.034$). In addition, there were near-significant differences for greater fatigue ($P = 0.064$) and sleepiness ($P = 0.084$).

Pre- to post-treatment changes in transaminase levels were significantly different between treatment groups, such that the riluzole group had increases and the placebo group had decreases in ALT and AST. Mean change in ALT values for the riluzole group was 10.03 U/L ($SD = 30.12$) and -4.91 U/L ($SD = 13.55$) for placebo, $P = .009$. Mean change in AST for the riluzole group was 7.34 U/L ($SD = 17.80$) and -1.63 U/L ($SD = 2.06$) for placebo, $P = .016$. In addition, 19 of 36 participants (52.8%) in the riluzole group and 14 of 38 participants (36.8%) in the placebo group had ALT values that exceeded ULN (41 U/L) at any point in the study. Fifteen participants (41.7%) in the riluzole group and 8 participants (21.1%) in the placebo group had AST values that exceeded ULN (40 U/L) at any point.

Two adverse events were reported that may have been study related. One participant reported gastrointestinal symptoms and was put on a lower dose of study drug, and one participant reported gastrointestinal symptoms that required emergency medical care. Both of these participants were on active drug. In addition, one participant in the active drug group had LFTs greater than 3 times ULN in the seventh week of phase 2. On retest, the values were less than 3 times ULN, and the participant was retained and completed the study. No patients exhibited symptoms of hepatic toxicity.

DISCUSSION

This is the first randomized controlled trial investigating the efficacy of riluzole augmentation for antidepressant-resistant symptoms in military personnel and veterans with combat-related PTSD. Although the results are preliminary and should be interpreted cautiously, our finding of superior improvement in hyperarousal symptoms is supported by its significance on the PCL-S and near significance on the CAPS. Previous studies have demonstrated the prominent role that persistent hyperarousal plays in PTSD illness trajectory.^{49–52} A recent review suggested that treatments effectively targeting hyperarousal may significantly alter illness trajectory and reduce disease morbidity.⁵³

In addition, the findings in the current study may be an indicator of how specific PTSD symptom profiles may relate to variable response to pharmacologic treatments, which may have implications both for treatment strategies and future research. Prior trials have shown, for example, that risperidone adjunctive treatment had no significant effect on overall PTSD symptoms but was associated with improvements in re-experiencing and hyperarousal symptoms.¹¹ In their post hoc, subscale analysis, which showed modest decrease in intrusive and hyperarousal (but not avoidance) subscales, Krystal and colleagues postulated that these potential benefits were mediated through 5HT_{2A} and alpha-one adrenergic blockade, citing the widespread use of trazodone (and alpha one adrenergic blocker) for sleep disturbance in PTSD as anecdotal evidence of potential efficacy through such a mechanism. Riluzole modulates glutamatergic transmission. As glutamate is the most ubiquitous excitatory neurotransmitter in the brain, it seems reasonable that reduction of excitatory signaling in the amygdala might reduce the subsequent brainstem re-activation thought to be responsible for hyperarousal in PTSD.¹⁴

Other studies found significant treatment effects for topiramate augmentation on re-experiencing symptoms but not on avoidance or hyperarousal symptoms⁸ and rivastigmine augmentation on re-experiencing and avoidance but not hyperarousal.¹³ Thus, some symptom clusters may be differentially responsive to SSRI/SNRI augmentation.

Both treatment groups in the current study had clinically significant improvement on overall PTSD symptoms, and, although there was a small between-group effect size ($d = 0.246$) for change in CAPS, the between-group difference was not significant. Similarly, the riluzole group showed a greater decrease in self-reported PTSD, anxiety, and disability, but the differences were not significant. One factor contributing to these negative findings may be that the sample exclusively comprised combat veterans; results of two meta-analyses indicate that pharmacotherapy may be less effective for military-related PTSD.^{54,55} Another

factor may have been higher symptom severity in the riluzole group. A prior study showed that higher symptom severity, particularly re-experiencing and avoidance, was related to nonresponse to SSRI/SNRI-augmentation in a sample of military veterans.⁵⁶

Our dose-increase criterion was implemented in order to determine optimal dose level while minimizing side effects. The results indicating no significant influence of treatment group, dose increase, or the interaction of these factors on change in PCL scores were contrary to our supposition that participants on high-dose riluzole would have greater symptom improvement. These results are consistent with two prior controlled trials of riluzole for depression,^{57,35} which found no effect of dose level on response. In addition, our nonsignificant findings may be partially explained by inconsistent implementation of dose-increase criterion. Ten participants (13.5%) who met criteria for dose increase after two weeks did not receive high dose based on study psychiatrists' assessment of elevated liver enzymes at enrollment, increase in liver enzymes during the study, and participant-reported side effects. In future studies, adherence to high-dose levels might be controlled for by excluding individuals whose liver enzymes are even slightly elevated at baseline.

Treatment with riluzole was generally well-tolerated and did not appear to cause any clinically meaningful harm. Asymptomatic elevations in liver enzymes occurred more frequently in participants treated with riluzole, but no participants had to be removed from the study due to elevations above the 3x ULN range, which was a comparatively conservative criterion. Prior psychiatric trials of riluzole have used the FDA's criterion of up to 5x ULN.^{35,37} On side effects reported on the UKU-SERS-Pat (43 items for men and 45 items for women), participants in the riluzole group reported significantly greater change in intensity on just one—difficulty concentrating, which has been previously reported for riluzole. Participants in the riluzole group also reported increased intensity in fatigue and sleepiness. Although these two side effects were not significantly different between groups, they may have been due to the effects of riluzole, which would be consistent with prior studies investigating riluzole for psychiatric use and with adverse effects listed in the manufacturer's package insert.^{35,58}

The current study had several limitations. Symptom improvement in both groups may have been due in part to continued effects of their SSRI/SNRI beyond their start of their study treatment. Prior studies have shown continued improvement in PTSD symptoms beyond 10 weeks.⁵⁹ Participants entering the study on drugs such as citalopram, that have been shown to be less effective for PTSD,⁵⁵ may have included participants who were not truly treatment resistant but rather were on an ineffective treatment.

Another possible limitation was variability in assessments. All assessors were trained in CAPS administration, but their experience level ranged from novice assessors to certified assessors with hundreds of hours of experience. This potentially introduced variability in the primary outcome measure. Reducing the sample size from 50 per group to 35 per group after interim analyses showed a mean CAPS reduction of 15 points in the first 27 participants likely reduced power to detect a between-group difference. In addition, the clinically significant improvement in both groups may have been due to increased attention given to participants during assessments. Finally, the current study focused exclusively on combat-

related PTSD in active-duty and veteran populations, and results may not generalize to other populations or trauma types.

CONCLUSIONS

The results of this first published randomized controlled trial of riluzole augmentation for antidepressant-resistant PTSD provides evidence that may help further understanding of heterogeneity of treatment response. While these findings should be interpreted with caution, they indicate that riluzole may reduce hyperarousal symptoms in combat veterans whose PTSD symptoms did not remit with SSRI/SNRI monotherapy. Despite the limitations of the current study, its results suggest that riluzole may have the potential to play such a role in treating combat-related PTSD. Further study of riluzole (and other glutamatergic modulators) will help clarify the role for such agents in treating PTSD unrelated to military combat.

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REFERENCES

1. Jonas DE, Cusack K, Forneris CA, Wilkins TM, Sonis J, Middleton JC, Feltner C, Meredith D, Cavanaugh J, Brownley KA, Olmsted KR, Greenblatt A, Weil A, Gaynes BN. Psychological and pharmacological treatments for adults with posttraumatic stress disorder (PTSD). Rockville, MD: Agency for Healthcare Research and Quality 2013 4; Report No: 13-EHC011-EF.
2. Forman-Hoffman V, Middleton JC, Feltner C, Gaynes BN, Weber RP, Bann C, Viswanathan M, Lohr KN, Baker C, Green J. Psychological and pharmacological treatments for adults with posttraumatic stress disorder: a systematic review update. Rockville, MD: Agency for Healthcare Research and Quality 2018 5; Report No:18-EHC011-EF.
3. Koek RJ, Schwartz HN, Scully S, Langevin JP, Spangler S, Korotinsky A, Jou K, Leuchter A. Treatment-refractory posttraumatic stress disorder (TRPTSD): a review and framework for the future. *Prog Neuropsychopharmacol Biol Psychiatry*. 2016;70:170–218. [PubMed: 26854815]
4. Hoskins M, Pearce J, Bethell A, Dankova L, Barbui C, Tol WA, van Ommeren M, de Jong J, Seedat S, Chen H, Bisson JI. Pharmacotherapy for post-traumatic stress disorder: systematic review and meta-analysis. *Br J Psychiatry*. 2015;206(2):93–100. [PubMed: 25644881]
5. Lee DJ, Schnitzlein CW, Wolf JP, Vythilingam M, Rasmusson AM, Hoge CW. Psychotherapy versus pharmacotherapy for posttraumatic stress disorder: systematic review and meta-analyses to determine first-line treatments. *Depress Anxiety*. 2016;9;33(9):792–806. [PubMed: 27126398]
6. Shiner B, Westgate CL, Gui J, Maguen S, Youn-Xu Y, Schnurr PP, Watts BV. A Retrospective Comparative Effectiveness Study of Medications for Posttraumatic Stress Disorder in Routine Practice. *J Clin Psychiatry*. 2018;79(5). pii: 18m12145. doi: 10.4088/JCP.18m12145.
7. The Management of Post-Traumatic Stress Working Group. (2017). VA/DoD clinical practice guidelines for management of posttraumatic stress disorder and acute stress disorder. Retrieved 7/19/2019 from <https://www.healthquality.va.gov/guidelines/MH/ptsd/VADoDPTSDCPGFinal012418.pdf>

8. Lindley SE, Carlson EB, Hill K. A randomized, double-blind, placebo-controlled trial of augmentation topiramate for chronic combat-related posttraumatic stress disorder. *J Clin Psychopharmacol*. 2007;27, 677–681. [PubMed: 18004136]
9. Shiner B, Westgate CL, Bernardy NC, Schurr PP, Watts BV. Anticonvulsant medication use in veterans with posttraumatic stress disorder. *J Clin Psychiatry*. 2017 5; 78(5):e545–e552. 10.4088/JCP.16m11031 [PubMed: 28570793]
10. Stein MB, Kline NA, Matloff JL. Adjunctive olanzapine for SSRI-resistant combat-related PTSD: a double-blind, placebo-controlled study. *Am J Psychiatry*. 2002;159(10):1777–9. [PubMed: 12359687]
11. Krystal JH, Rosenheck RA, Cramer JA, Vessicchio JC, Jones KM, Vertrees JE, Horney RA, Huang GD, Stock C; Veterans Affairs Cooperative Study No. 504 Group. Adjunctive risperidone treatment for antidepressant-resistant symptoms of chronic military service-related PTSD: a randomized trial. *JAMA*. 2011;306(5):493–502. [PubMed: 21813427]
12. Hamner MB, Hernandez-Tejada MA, Zuschlag ZD, Agbor-Tabi D, Huber M, Wang Z. Ziprasidone Augmentation of SSRI Antidepressants in Posttraumatic Stress Disorder: A Randomized, Placebo-Controlled Pilot Study of Augmentation Therapy. *J Clin Psychopharmacol* 2019;39(2):153–157. [PubMed: 30640209]
13. Rezaei Ardani A, Hosseini G, Fayyazi Bordbar MR, Talaei A, Mostafavi Toroghi H. Effect of rivastigmine augmentation in treatment of male patients with combat-related chronic posttraumatic stress disorder: a randomized controlled trial. *J Clin Psychopharmacol* 2017;37(1):54–60. [PubMed: 27930500]
14. Averill LA, Purohit P, Averill CL, Boesl MA, Krystal JH, Abdallah CG. Glutamate dysregulation and glutamatergic therapeutics for PTSD: evidence from human studies. *Neurosci Lett* 2017;649:147–155. doi:10.1016/j.neurolet.2016.11.064. [PubMed: 27916636]
15. Vose LR, Stanton PK. Synaptic plasticity, metaplasticity and depression. *Curr Neuropharmacol*. 2017;15:71–86. [PubMed: 26830964]
16. Feder A, Parides MK, Murrough JW, Perez AM, Morgan JE, Saxena S, Kirkwood K, Aan Het Rot M, Lapidus KA, Wan LB, Iosifescu D, Charney DS. Efficacy of intravenous ketamine for treatment of chronic posttraumatic stress disorder: a randomized clinical trial. *JAMA Psychiatry*. 2014 6;71(6):681–8. doi: 10.1001/jamapsychiatry.2014.62. [PubMed: 24740528]
17. Albott CS, Lim KO, Forbes MK, Erbes C, Tye SJ, Grabowski JG, Thuras P, Batres-Y-Carr TM, Wels J, Shiroma PR. Efficacy, Safety, and Durability of Repeated Ketamine Infusions for Comorbid Posttraumatic Stress Disorder and Treatment-Resistant Depression. *J Clin Psychiatry*. 2018 May-Jun;79(3). pii: 17m11634. doi: 10.4088/JCP.17m11634.
18. Baker JF, Cates ME, Luthin DR. D-cycloserine in the treatment of posttraumatic stress disorder. *Ment Health Clin* 2018;7(2):88–94. doi: 10.9740/mhc.2017.03.088 [PubMed: 29955504]
19. Back SE, McCauley JL, Korte KJ, Gros DF, Leavitt V, Gray KM, et al. A double-blind randomized controlled pilot trial of N-acetylcysteine in veterans with PTSD and substance use disorders. *J Clin Psychiatry* 2016; 77(11): e1439–e1466.doi:10.4088/JCP.15m10239. [PubMed: 27736051]
20. Cifra A, Mazzone GL, Nistri A. Riluzole: what it does to spinal and brainstem neurons and how it does it. *The Neurosci* 2012; 19(2):137–144.
21. Azbill RD, Mu X, Springer JE. Riluzole increases high-affinity glutamate uptake in rat spinal cord synaptosomes. *Brain Res* 2000; 871:175–180. [PubMed: 10899284]
22. Zarate C Riluzole in psychiatry: a systematic review of the literature. *Expert Opin Drug Metab Toxicol* 2008;4(9):1223–1234. doi:10.1517/17425255.4.9.1223. [PubMed: 18721116]
23. Mizuta I, Ohta M, Ohta K, Nishimura M, Mizuta E, Kuno S. Riluzole stimulates nerve growth factor, brain-derived neurotrophic factor and glial cell line-derived neurotrophic factor synthesis in cultured mouse astrocytes. *Neurosci Lett* 2001;310:117–120. [PubMed: 11585581]
24. Katoh-Semba R, Asano T, Ueda H, Morishita R, Takeuchi IK, Inaguma Y, Kato K. Riluzole enhances expression of brain-derived neurotrophic factor with consequent proliferation of granule precursor cells in the rat hippocampus. *FASEB J. Off. Publ. Fed. Am Soc Exp Biol* 2002;16,1328–1330.

25. Akagi K, Yamada M, Saito A, Oka JI, Yamada M. Post-reexposure administration of riluzole attenuates the reconsolidation of conditioned fear memory in rats. *Neuropharmacol* 2018; 131:1–10.
26. Sugiyama A, Yamada M, Akiyoshi S, Oka JI, Yamada M. Administration of riluzole to the basolateral amygdala facilitates fear extinction in rats. *Behav Brain Res* 2018;336:8–14. [PubMed: 28843863]
27. de Boer JN, Vingerhoets C, Hirdes M, McAlonan GM, Amelsvoort TV, Zinkstok JR. Efficacy and tolerability of riluzole in psychiatric disorders. *Psychiatry Res* 2019;278:294–302. [PubMed: 31254879]
28. Gray MJ, Litz BT, Hsu JL, Lombard TWI. Psychometric properties of the life events checklist. *Assessment* 2004;11:330–341. doi: 10.1177/1073191104269954 [PubMed: 15486169]
29. Blake DD, Weathers FW, Nagy LM et al. The development of a Clinician-Administered PTSD Scale. *J Trauma Stress*. 1995;8(1):75–90. [PubMed: 7712061]
30. Sheehan DV, Lecrubier Y, Harnett-Sheehan K, Amorim P, Janavs J, Weiller E Hergueta T, Baker R, Dunbar G. The MINI International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview. *J Clin Psychiatry* 1998;59(suppl 20):22–33.
31. Zarate CA, Quiroz JA, Singh JB, Denicoff KD, De Jesus G, Luckenbaugh DA, Charney DS, Manji HK. An open-label trial of the glutamate-modulating agent riluzole in combination with lithium for the treatment of bipolar depression. *Biol Psychiatry*. 2005;57:430–432. [PubMed: 15705360]
32. Grant PJ, Joseph LA, Farmer CA, Luckenbough DA, Lougee LC, Zarate CAJ, Swedo SE. 12-week, placebo-controlled trial of add-on riluzole in the treatment of childhood-onset obsessive-compulsive disorder. *Neuropsychopharmacol* 2014; 39(6):1453–1459.
33. Pittenger C, Bloch MH, Wasylink S, Billingslea E, Simpson R, Jakubowski E, Kelmendi B, Sanacora G, Coric V. Riluzole augmentation in treatment-refractory obsessive-compulsive disorder: a pilot randomized placebo-controlled trial. *J Clin Psychiatry* 2015;76:1075–1084. [PubMed: 26214725]
34. Coric V, Taskiran S, Pittinger C, Wasylink S, Mathalon DH, Valentine G, Saksa J, Wu YT, Gueorguieva R, Sanacora G, Malison RT, Krystal JH. Riluzole augmentation in treatment-resistant obsessive-compulsive disorder: an open-label trial. *Biol Psychiatry* 2005;58:424–428. [PubMed: 15993857]
35. Grant P, Lougee L, Hirschtritt M, Swedo SE. An open-label trial of riluzole, a glutamate antagonist, in children with treatment-resistant obsessive-compulsive disorder. *J Child Adolescent Psychopharm* 2007;17(6):761–767.
36. Pittenger C, Kelmendi B Wasylink S, Bloch M, Coric V. Riluzole augmentation in treatment-refractory obsessive-compulsive disorder. *J Clin Psychopharm* 2008;28(3):363–367
37. Weathers FW, Litz BT, Huska JA, Keane TM. (1994). PTSD Checklist. Boston, MA: National Center for PTSD.
38. Montgomery SA and Asberg M. (1979). A new depression scale designed to be sensitive to change. *Brit J Psychiatry* 1979;134:382–389. [PubMed: 444788]
39. Hamilton M The assessment of anxiety states by rating. *Br J Med Psychol* 1959;32:50–5 [PubMed: 13638508]
40. Sheehan DV. (1983). *The Anxiety Disease*. New York: Scribner.
41. Lindstrom E, Lewander T, Malm U, Malt UF, Lublin H, Ahlfors UG. Patient-rated versus clinician-rated side effects of drug treatment in schizophrenia Clinical validation of a self-rating version of the UKU Side Effect Rating Scale (UKU-SERS-Pat). *Nord J Psychiatry* 2001;55(Suppl):5–69.
42. Stefanovics EA, Rosenheck RA, Jones KM, Huang G, Krystal JH. Minimally clinically important differences (MCID) in assessing outcomes of post-traumatic stress disorder. *Psychiatry Q* 2018;89:141–155.
43. Halvorsen JØ. Defining clinically significant change. *Br J Psychiatry* 2016 7;209(1):85
44. Steenkamp MM, Litz BT, Hoge CW, Marmar CR. Psychotherapy for military-related PTSD: a review of randomized clinical trials. *JAMA*. 2015;314(5):489–500. [PubMed: 26241600]
45. Weathers FW, Kean TM, Davidson JRT. Clinician-Administered PTSD Scale: A review of the first ten years of research. *Depression and Anxiety*. 2001;13:132–156. [PubMed: 11387733]

46. Lunney CA, Schnurr PP. Domains of quality of life and symptoms in male veterans treated for posttraumatic stress disorder. *J Traum Stress*. 2007;20:955–964.
47. Proschan MA, Waclawiw MA. Practical guidelines for multiplicity adjustment in clinical trials. *Controlled Clinical Trials*. 2000;21:527–539. [PubMed: 11146147]
48. SAS version 9.4. Copyright [2017]. SAS Institute, Cary, NC.
49. Thompson KE, Vasterling JJ, Benotsch EG, et al. Early symptom predictors of chronic distress in Gulf War veterans. *J Nerv Ment Dis* 2004;192:146–152. [PubMed: 14770059]
50. Schell TL, Marshall GN, Jaycox LH. All symptoms are not created equal: the prominent role of hyperarousal in the natural course of posttraumatic psychological distress. *J Abnorm Psychol* 2004;113(2):189–197. [PubMed: 15122939]
51. Solomon Z, Horesh D, Ein-Dor T. The longitudinal course of posttraumatic stress disorder symptom clusters among war veterans. *J Clin Psychiatry* 2009;70(6):837–843. [PubMed: 19573481]
52. Doron-LaMarca S, Niles BL, King DK, King LA, Kaiser AP, Lyons MJ. Temporal associations among chronic PTSD symptoms in U.S. combat veterans. *J Trauma Stress*. 2015;28:410–417. [PubMed: 26367017]
53. Able ML, Benedek DM. Severity and Symptom Trajectory in Combat-Related PTSD: A Review of the Literature. *Curr Psych Rep*. 2019 6 6;21(7):58.
54. Stein DJ, Ipser JC, Seedat S. Pharmacotherapy for post traumatic stress disorder (PTSD). *Cochrane Database Syst Rev* 2006;25(1):CD002795.
55. Watts BV, Schnurr PP, May I, et al. Meta-analysis of the efficacy of treatments for posttraumatic stress disorder. *J Clin Psychiatry* 2013;74(6):e541–e550. [PubMed: 23842024]
56. Byrne SP, Krystal JH, Rosenheck RA, Vessicchio J, Pietrzak RH, Veterans Affairs Cooperative Study No. 504 Group. Correlates of nonimprovement to pharmacotherapy for chronic, antidepressant-resistant, military service-related posttraumatic stress disorder. *J Clin Psychopharmacology*. 2017;37(6):717–721.
57. Ibrahim L, Diazgranados N, Franco-Chaves J, Brutsche N, Henter ID, Kronstein P, Moaddel R, Wainer I, Luckenbaugh DA, Manji HK, Zarate CAJ. Course of improvement in depressive symptoms to a single intravenous infusion of ketamine vs Add-on riluzole: results from a 4-week, double-blind, placebo-controlled study. *Neuropsychopharmacology*. 2012;37(6):1526–1533. [PubMed: 22298121]
58. Rilutek [package insert]. Laval, Quebec: Sanofi-Aventis Canada;2010.
59. Rauch SAM, Kim HM, Powell C, Tuerk PW, Simon NM, Alcierno R et al. Efficacy of prolonged exposure therapy, sertraline hydrochloride, and their combination among combat veterans with posttraumatic stress disorder: a randomized clinical trial. *JAMA Psychiatry*. 2019;76(2):117–126. doi:10.1001/jamapsychiatry.2018.3412 [PubMed: 30516797]

Figure 1. Riluzole CONSORT Diagram

^a Psychiatric diagnosis/symptoms included substance use disorder or suicidality/homicidality within 90 days, schizophrenia, schizoaffective disorder, bipolar disorder, dementia, or psychotic symptoms.

^b Logistical reasons for ineligibility included moving out of the area, scheduling, and work conflicts.

Table 1.

Participant Characteristics by Group

	<u>All (n = 74)</u>	<u>Riluzole (n = 36)</u>	<u>Placebo (n = 38)</u>	<u>Group Difference</u>	
	<u>n (%)</u>	<u>n (%)</u>	<u>n (%)</u>	<u>Statistic</u>	<u>P</u>
Age (years)					
M (SD)	37.8 (8.5)	37.4 (8.9)	38.1 (8.2)	0.31 ^a	0.761
Sex					
Male	63 (85.01)	31 (86.1)	32 (84.2)	0.05	0.818
Female	11 (14.9)	5 (13.9)	6 (15.8)		
Race					
White	47 (63.5)	22 (61.1)	25 (65.8)	0.17	0.676
Non-White	27 (36.5)	14 (38.9)	13 (34.2)		
Education (years)					
12	18 (26.1)	11 (35.5)	7 (18.4)	2.58	0.275
13 – 16	38 (55.1)	15 (48.4)	23 (60.5)		
> 16	13 (18.8)	5 (16.1)	8 (21.1)		
Employment Status					
Full-time	47 (63.5)	23 (63.9)	24 (63.2)	0.00	0.948
Others	27 (36.5)	13 (36.1)	14 (36.8)		
Marital Status					
Currently married	50 (67.6)	25 (69.4)	25 (65.8)	0.11	0.737
Not currently married	24 (32.4)	11 (30.6)	13 (34.2)		
Pay Grade (rank)					
Enlisted	63 (85.1)	30 (83.3)	33 (86.8)	0.18	0.672
Officer	11 (14.9)	6 (16.7)	5 (13.2)		
Active Duty (Current)					
Yes	38 (52.1)	19 (54.3)	19 (50.0)	0.13	0.714
No	35 (48.0)	16 (45.7)	19 (50.0)		
Baseline CAPS^c score		70.6 (19.8) ^d	62.4 (16.9) ^d	−1.92 ^a	0.058
DSM-IV Diagnosis	50 (67.5)	26 (72.2)	24 (63.2)	0.693	0.405

^a t-test was used to test group differences on continuous variables.

^b Chi-square was used to test group differences on categorical variables.

^c CAPS = Clinician Administered PTSD Scale

^d Mean (Standard Deviation)

Table 2.
Treatment Efficacy Outcomes for PTSD, Depression, Anxiety, Disability, and PTSD Subscales

	Risperidone (n = 36)				Placebo (n = 38)				Group Differences ^b		
	Mean (SD)	(95% CI, Mean)	Within-Group ES, <i>d</i>	Mean (SD)	(95% CI, Mean)	Within-Group ES, <i>d</i>	<i>F</i>	<i>P</i>	Between-Group ES, <i>d</i>	(95% CI, Between-Group)	
Primary Outcome											
CAPS											
Baseline	70.6 (19.8)	(64.2 to 77.1)	--	62.4 (16.9)	(56.8 to 68.0)	--	--	--	--		
Change ^a	-21.1 (18.9)	(-28.1 to -14.2)	1.09	-16.7 (17.2)	(-22.8, -10.6)	0.979	0.64	0.422	-0.246	(-0.684 to 0.193)	
Secondary Outcomes											
PCL-S											
Baseline	55.9 (14.3)	(51.3 to 60.6)	--	51.2 (12.3)	(47.1 to 55.2)	--	--	--	--		
Change	-15.4 (13.5)	(-20.4 to -10.4)	1.01	-14.5 (11.4)	(-18.4 to 10.6)	1.14	0.00	0.994	-0.071	(-0.519 to 0.378)	
MADRS											
Baseline	22.4 (7.3)	(20.1 to 24.8)	--	21.8 (9.1)	(18.8 to 24.8)	--	--	--	--		
Change	-7.9 (7.6)	(-10.9 to -4.8)	1.01	-8.2 (9.6)	(-11.6 to -4.8)	0.951	0.17	0.684	0.042	(-0.413 to 0.498)	
HAM-A											
Baseline	23.0 (8.0)	(20.4 to 25.6)	--	22.3 (7.7)	(19.7 to 24.8)	--	--	--	--		
Change	-7.8 (7.4)	(-10.4 to -5.1)	0.975	-6.7 (6.9)	(-9.1 to -4.3)	0.954	0.012	0.913	-0.148	(-0.592 to 0.296)	
SDS											
Baseline	18.9 (6.9)	(16.6 to 21.1)	--	17.5 (7.5)	(15.0 to 20.0)	--	--	--	--		
Change	-6.3 (6.8)	(-8.7 to -4.0)	0.825	-5.7 (5.9)	(-7.7 to -3.7)	0.781	0.102	0.746	-0.099	(-0.546 to 0.349)	
Exploratory Outcomes											
PTSD Re-experiencing											
CAPS-B											
Baseline	18.8 (8.8)	(15.9 to 21.6)	--	15.7 (7.5)	(13.2 to 18.2)	--	--	--	--		
Change	-4.4 (7.1)	(-7.4 to -1.3)	0.478	-3.6 (8.6)	(-6.6 to -0.5)	0.455	0.10	0.755	-0.101	(-0.555 to 0.352)	
PCL-B											

Riluzole (n = 36)				Placebo (n = 38)				Group Differences ^b	
Mean (SD)	(95% CI, Mean)	Within-Group ES, <i>d</i>	Mean (SD)	(95% CI, Mean)	Within-Group ES, <i>d</i>	<i>F</i>	<i>P</i>	Between-Group ES, <i>d</i>	(95% CI, Between-Group)
Baseline	16.1 (6.4)	--	14.3 (4.2)	(12.9 to 15.7)	--	--	--	--	
Change	-4.1 (5.4)	0.692	-4.3 (3.8)	(-5.6 to -3.0)	1.01	0.04	0.844	0.054	(-0.408 to 0.517)
PTSD Avoidance									
CAPS-C									
Baseline	27.5 (8.3)	--	23.6 (9.5)	(20.5 to 26.7)	--	--	--	--	
Change	-9.2 (10.1)	0.853	-8.9 (9.6)	(-12.2 to -5.6)	0.848	0.01	0.932	-0.029	(-0.486 to 0.429)
PCL-C									
Baseline	22.7 (6.3)	--	20.5 (6.4)	(18.4 to 22.6)	--	--	--	--	
Change	-6.3 (5.9)	0.862	-6.8 (4.8)	(-8.6 to -5.0)	1.05	0.12	0.730	0.097	(-0.368 to 0.561)
PTSD Hyperarousal									
CAPS-D									
Baseline	24.3 (6.6)	--	23.1 (5.8)	(21.2 to 25.0)	--	--	--	--	
Change	-6.8 (8.2)	0.861	-3.7 (7.3)	(-6.6 to -0.7)	0.515	3.648	0.057	-0.400	(-0.835 to 0.036)
PCL-D									
Baseline	18.2 (6.1)	--	16.6 (3.9)	(15.3 to 17.8)	--	--	--	--	
Change	-5.9 (5.6)	1.001	-3.4 (4.9)	(-5.1 to -1.7)	0.731	3.881	0.0496	-0.477	(-0.908 to -0.046)

^aChange is the difference between baseline and post-treatment (8 weeks).

^bANCOVA covariates included site.

Abbreviations: ES, *d*=Effect size, Cohen's *d*; CAPS = Clinician Administered PTSD Scale; PCL-S = PTSD Checklist-Specific; MADRS = Montgomery-Asberg Depression Scale; HAM-A = Hamilton Anxiety Rating Scale; SDS = Sheehan Disability Scale; CAPS-B, CAPS-C, and CAPS-D = CAPS Criterion B, Criterion C, and Criterion D, respectively; PCL-B, PCL-C, and PCL-D = PCL Re-experiencing, Avoidance, and Hyperarousal Subscales, respectively.

Table 3.

Significant and Nearly Significant Between-Group Differences in Change in Mean Intensity of UKU-SERS-Pat Side Effects from Week 1 to Week 8^a

Adverse Event	Riluzole (n = 36)			Placebo (n = 38)			Group Differences		
	Mean	(95% CI)	SD	Mean	(95% CI)	SD	ES, <i>d</i>	<i>t</i>	<i>p</i>
Difficulty Concentrating	0.222	(−0.035 to 0.479)	0.760	−0.158	(−0.406 to 0.09)	0.754	0.502	−2.16	0.034
Fatigue	0.306	(−0.045 to 0.656)	1.037	−0.132	(−0.448 to 0.185)	0.963	0.437	−1.88	0.064
Sleepiness	0.250	(−0.087 to 0.587)	0.996	−0.132	(−0.419 to 0.156)	0.875	0.407	−1.75	0.084

^aMultiple imputation was used to impute missing side effects data across all treatment weeks.

Abbreviations: UKU-SERS-Pat = UKU Side Effects Rating Scale-Patient Version; ES, *d* = Effect size, Cohen's *d*