Title

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Journal

Journal of Traumatic Stress, 35(2)

ISSN

0894-9867

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Publication Date

2022-04-01

DOI

10.1002/jts.22762

Peer reviewed

HHS Public Access

Author manuscript

J Trauma Stress. Author manuscript; available in PMC 2023 April 01.

Published in final edited form as:

J Trauma Stress. 2022 April ; 35(2): 496–507. doi:10.1002/jts.22762.

Change in PTSD-related Thoughts with PTSD Treatment: Do Thoughts Drive Change When Pills Are Involved?

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Preliminary results previously presented at the 54th Annual Meeting of the Association for Behavioral and Cognitive Therapy, Washington, DC (11/15/18- 11/18/18)

ClinicalTrials.gov: NCT01524133

Abstract

Posttraumatic negative thoughts about the self and the world are related to PTSD symptom severity and change in cognitive behavioral treatment (CBT), but little is known about this relationship when CBT is delivered with medication. The current study presents a planned comparison of change in negative posttraumatic negative thoughts during (1) Prolonged Exposure (PE) plus pill placebo [PE+PLB], (2) sertraline plus enhanced medication management [SERT+EMM], and (3) PE plus sertraline [PE+SERT] (N = 176 veterans) as part of a randomized clinical trial. Lagged regression modeling revealed that change in posttraumatic negative thoughts was associated with PTSD symptom change in the conditions where participants were receiving sertraline (e.g., d=.20 (p=.003) for the lagged effect of Negative Thoughts About Self on symptoms in SERT+EMM). However, contrary to previous research, both the models starting with thought change and those starting with symptom change were statistically significant (d=.23 (p<.001) for the lagged effect of symptom on Negative Thoughts about Self), indicating a bidirectional relationship between such thoughts and PTSD symptoms except for the PE plus placebo condition, which showed no significant relationship between posttraumatic thoughts and PTSD symptoms in either direction. These results suggest that the previously demonstrated role of change in posttraumatic thoughts leading to PTSD symptom reduction in PE may be altered when combined with pill administration (either active or placebo).

Keywords

randomized controlled trial; posttraumatic stress disorder; cognition; treatment; exposure; mechanisms

Posttraumatic negative thoughts about the self and the world are key factors that contribute to both development and maintenance of posttraumatic stress disorder (PTSD) symptoms over time (Foa & Rauch, 2004; Rauch, Abelson, et al., 2015). Negative thoughts about the self include an individual's perceived ability to handle negative affect and stressful situations. Both inhibitory learning and emotional processing theory predict that increased sense of self-competence leads to reduction in avoidance and other symptoms characterizing PTSD and anxiety disorders (Craske et al., 2014; Rauch & Foa, 2006). Prolonged exposure (PE) provides a therapeutic context for approaching trauma related stimuli to allow for extinction and experiential learning that increases an individual's perceived ability to effectively deal with negative affect.

Reductions in negative thoughts about the self, the world, and self-blame, as measured by the Posttraumatic Cognitions Inventory (Foa et al.), are significantly related to treatment reductions in PTSD symptoms in multiple studies (Foa & Rauch, 2004; Kumpula et al., 2017; Rauch, King, et al., 2015; Zalta et al., 2014). Of importance, these negative thoughts and symptom changes are robust and are not augmented when specific cognitive restructuring is added to PE, suggesting that the treatment's core components (i.e., exposure) lead to changes in posttraumatic negative thoughts about the self, the world, and self-blame (Foa et al., 2005; Foa & Rauch, 2004). Several PE studies have used lagged regression modeling to determine whether change in posttraumatic thoughts is driving change in symptoms or vice versa. Consistently, these studies show that change in thoughts occurs

prior to changes in PTSD symptoms in PE (Kumpula et al., 2017; Zalta et al., 2014). Similarly, in a study examining both PE and sertraline, changes in negative posttraumatic thoughts about self preceded and predicted changes in PTSD symptoms, as well as depression, though to a lesser extent (Cooper et al., 2017). However, the magnitude of this relationship was considerably smaller in participants who received sertraline compared to PE. While preliminary, this suggests that the relationship between changes in posttraumatic negative thoughts and PTSD symptoms may exist across different treatment modalities (medication and therapy), but the strength of this relationship may be attenuated in medication compared to therapy.

Research on mechanisms of change in depression has shown differential brain biomarker 'paths to response' for psychotherapy and medication (McGrath et al., 2013), and one might expect the same for PTSD. Specific examination of brain mechanisms related to change in PTSD treatment has not revealed differential predictors thus far (Duval et al., 2020; Joshi et al., 2020; Rauch et al., 2020) though such studies are typically underpowered to detect conditional difference for medication and psychotherapy.

Of importance to patient care, attributions of change during psychotherapy may be moderated if/when a patient is also taking a medication that is identified as a PTSD treatment. In addition to attribution of change, patients may have different expectations for change related to pill versus therapy that can also influence response when combined. Two studies examining these processes in substance use disorder and panic disorder treatments found moderation of outcomes by attribution (Biondi & Picardi, 2003; Schaumberg et al., 2013). Specifically, those who thought they had received placebo reported greater confidence that they could maintain reductions in substance use and panic symptoms without medication compared to those who thought they received naltrexone (Schaumberg et al., 2013). Similarly, when examining patient attribution of why they believe they have social anxiety disorder (SAD), those who attributed their SAD to genetic, biological, and early life experiences had the more rapid response to paroxetine than those who had more psychosocially focused attributions (Cohen et al., 2015). In a depression clinical trial comparing supportive-expressive psychotherapy (SET), clinical management combined with pharmacotherapy (CM+MED), or clinical management with placebo pill (CM+PBO), all conditions were related to changes in attribution with no differences between conditions (Zilcha-Mano et al., 2016) supporting that even pill placebo can have an active impact on therapeutic change. Overall response to therapy or medication may be either increased or reduced when two possible change agents are introduced, based on whether the patient can notice the effects of each contributor, or whether each may mask the impact of the other. That is, in cases where patients may attribute change not to their internal capacity, but at least partially to the pill, such an attribution may interfere with therapy related change.

Despite evidence that changes in specific thoughts and symptoms are linked in PE and sertraline, no study has examined this relationship across these two treatments while also including a pill placebo control of a medication's 'active' mechanism of improvement. The current study sought to examine the patterns of change in negative thoughts about the self, negative thoughts about the world, and self-blame in a large PTSD randomized clinical trial examining PE plus placebo (PE+PLB), sertraline plus enhanced medication management

(SERT+EMM), and PE plus sertraline (PE+ SERT) using time lagged regression modeling. Because previous research using the PTCI subscales has more consistently supported negative thoughts about the self and negative thoughts about the world subscales as related to PTSD treatment symptoms reduction (Foa & Rauch, 2004; Kumpula et al., 2017; Rauch, King, et al., 2015) and in order to reduce the number of tests run, we hypothesized that change in self-perception regarding one's ability to handle PTSD symptoms (negativenegative thoughts about the self and negative thoughts about the world subscales) would occur prior to change in PTSD symptoms, and that change in these thoughts would be related to outcomes across all conditions.

Method

Participants and Procedure

The current study presents planned mechanistic analyses examining thoughts about the self and the world in a treatment outcomes and mechanisms clinical trial. The PROlonGed ExpoSure and Sertraline Trial (PROGrESS) is a randomized controlled trial (RCT) approved by all site IRBs. Participants were combat veterans (see inclusion/exclusion below) randomized to receive 24 weeks of either PE plus placebo (PE+PLB), sertraline plus enhanced medication management (SERT+EMM), or PE plus sertraline (PE+SERT). Participants and providers were blind to pill condition through the end of treatment at week 24. Independent evaluators were blind to treatment assignments for the study duration. Follow-up assessments were conducted through week 52. Readers are referred to the previously published methods paper (Rauch et al., 2018) and the primary outcomes paper for details (Rauch et al., 2019). The three conditions did not show significant differences in PTSD severity at posttreatment or follow-up (Rauch et al., 2019).

Four sites recruited 223 patients between 2011 and 2016 who completed the Posttraumatic Cognitions Inventory (Foa et al., 1999) and other measures as noted below. Inclusion criteria were service members or veterans of Iraq/Afghanistan wars with combat-related PTSD and significant impairment (Clinicians Administered PTSD Scale (CAPS) ≥50) of at least three months duration. Exclusion criteria included: 1) current imminent risk of suicide, 2) active psychosis, 3) alcohol or substance dependence (past 8 weeks), 4) inability to attend weekly appointments for the treatment period, 5) prior intolerance or failure of adequate trial of PE or SERT, 6) medical illness likely to result in imminent hospitalization or contraindication to study treatments, 7) serious cognitive impairment (e.g., confusion, inability to track discussion), and 8) concurrent antidepressants or antipsychotics, benzodiazepines, prazosin, and sleep agents (e.g., zolpidem) were allowed if the dose was stable for 2 weeks by baseline. Mild traumatic brain injury was not exclusionary.

Veterans and service members were recruited, consented, and completed diagnostic assessments and rating scales prior to randomization. Self-report and clinician administered measures occurred at weeks 0 (intake), 6, 12, 24, 36, and 52. After completion of week 24 outcome measures, patients and providers were unblinded and participants were offered open PE and/or sertraline or treatment outside of the study while completing the follow-up assessments.

For PE treatment, participants received up to 13 standard, 90-minute PE sessions weekly with allowance to complete by week 24. PE sessions included recording sessions and *in-vivo* exposure homework (Foa et al., 2007). All study therapists were trained with a VA PE four-day workshop and demonstrated fidelity on at least two supervised cases. PE fidelity was assured via structured weekly supervision calls and independent audio-recording of a random 20% of sessions (381 sessions) with 94% fidelity across sites and sessions (Rauch et al., 2019).

For pharmacotherapy, SERT doses were flexibly adjusted between 50 and 200 mg/day, with last dose increase at week 10 to ensure stable dosing by week 12. Medication was continued until week 24. Medication management (SERT or PLB) was manualized to standardize pharmacotherapy delivery as brief (approximately 15 minute) medication management (MM) when administered alongside PE, or as enhanced medication management (EMM). EMM was approximately 30 minutes for those randomized to SERT alone to balance time, psychoeducation, and provider support compared with PE conditions (Rauch et al., 2018). Prior to participation, pharmacotherapists were trained and certified on the manual and study procedures and participated in cross-site monthly supervision. EMM and MM sessions were taped, and fidelity and avoidance of proscribed PE elements were rated in a randomly selected 20% with 97% fidelity across sites and sessions (Rauch et al., 2019).

Measures

The self-report Posttraumatic Cognitions Inventory (PTCI; (Foa et al., 1999) is a measure of trauma-related thoughts and beliefs. It was developed by adopting emotional processing theory suggesting that PTSD is a consequence of disruptions in the normal processes of recovery (Foa and Kozak, 1986) based on the idea that two basic dysfunctional cognitions mediate the development of PTSD: the world is completely dangerous and one's self is totally incompetent (Foa and Riggs, 1993). PTCI has three subscales: negative thoughts about the self (21 items), the world (7 items), and self-blame (5 items). Each item is assessed using a 7-point agreement scale, and each subscale score is an average of the item scores corresponding to each subscale and can range from 1 to 7 with higher scores corresponding to greater negative thoughts. Although the number of the items differ across the three subscales, excellent internal consistency, good test-retest reliabilities, and convergent validity have been reported for all three subscales (Foa, Ehlers, et al., 1999). Using only the baseline data, Cronbach's alphas were 0.95 for the Self subscale, 0.89 for the World subscale, and 0.82 for the Self-blame subscale. Because previous research using the PTCI has more consistently supported negative thoughts about the self and negative thoughts about the world subscales as related to PTSD treatment symptoms reduction (Foa & Rauch, 2004; M. J. Kumpula et al., 2017; Rauch, King, et al., 2015) and in order to reduce the number of tests run, we focused on the Self and the World subscales in this study.

PTSD symptoms were assessed by evaluators who were blind to treatment condition using the Clinician Administered PTSD Scale (CAPS; (Blake et al., 1995). The CAPS is a semi-structured interview that assesses PTSD severity in relation to the target most distressing war-zone trauma. It has been widely used in both clinical and research settings. The CAPS has excellent psychometric properties including strong test-retest reliability and internal

consistency of 0.94 for all 17 items (Blake et al., 1995). Past month symptoms total score was used for this study. Higher total scores correspond to greater PTSD severity, and of note, PROGrESS had an inclusion criterion of significant impairment defined as a CAPS score 50 or higher. Since the study started well before the introduction of the DSM-5, DSM IV-TR criteria were used. Of note, the issue of symptom overlap between these cognitive constructs and PTSD symptoms is not an issue since DSM IV-TR did not include the D2 and D3 criteria.

Data Analyses

Assessments were completed during the 24-week treatment period up to 4 times at baseline and weeks 6, 12 and 24. To examine potential mechanistic association between thoughts and PTSD symptoms during the treatment period, a series of time-lagged mixed-effects regression analyses was conducted using the longitudinally assessed data (Granger, 1969; Zalta et al., 2014). Specifically, we tested the hypotheses that change in posttraumatic negative thoughts generates successive PTSD symptom changes and examined the time-lagged effects of each PTCI subscale during treatment period on subsequent PTSD symptoms separately. We ran separate mixed-effects models with CAPS scores at follow-up times as the response variable and each PTCI subscale scores as time-lagged predictors. Each model also included time-lagged values of CAPS scores to account for autocorrelation, time slope for changes in symptoms, and random intercepts. Time slope was included as log-transformed (weeks + 1) to reflect the decreasing rate of symptom decrease during follow-up time. To test the reverse directional hypotheses where change in PTSD symptom generates successive changes in thoughts, we conducted three additional mixed-effects models with each PTCI subscale scores during follow-up as response variables and CAPS scores as a time-lagged predictor. These models also included time-lagged values of CAPS scores as well as time slope and time-lagged values of each response variable for autocorrelation. If the time-lagged effect of thoughts on symptom is present, but the reverse is not, it would support our hypothesis that change in these thoughts would occur prior to change in PTSD symptoms. Analyses were conducted separately by treatment arms to examine mechanisms during each treatment, specifically to see if change in these thoughts would be associated to outcomes. For the fit of each model, we calculated R^2 values as the squared value of the correlation coefficient between the predicted and the observed outcome values. All analyses were done using Stata 15.0 (College Station, Texas). The smallest and largest analytic cohort sample sizes were 51 in PE+PLB arm and 67 in SERT+EMM arm, and the study has 80% statistical power to detect with 0.05 level tests minimum standardized slope of 0.40 and 0.36, respectively, reflecting the relationships between a time-lagged PTCI subscale and subsequent PTSD symptoms or vice versa. With longitudinal data and covariate adjustments, the study is likely to have adequate power to detect smaller slopes.

The primary analytic cohort included 71 participants in the SERT+EMM arm, 67 in the PE+PLB arm, and 69 in the PE+SERT arm as summarized in Table 1. Each time-lagged mixed model analyses (Tables 2 to 4) included only data collected during follow-up time as the response variable and also required non-missing time-lagged values of the predictor. For example, for the model with CAPS as the response variable, a patient can contribute data to the analytic model only if at least one set of data are non-missing simultaneously including

current CAPS, prior cognition, and prior CAPS (for autocorrelation). The analytic cohort therefore is smaller, but considering what is needed for the analysis, the reduction in analytic cohort size for the time-lagged model due to missingness was not substantial. Specifically, percentage of patients included in the CAPS analyses were 94% (67/71) in SERT+EMM arm, 79% (53/67) in PE+PLB arm and 81% (56/69) in PE+SERT arm. The analytic cohort sizes for each model are provided in Tables 2 to 4.

Results

Of the 223 randomized patients, 16 did not initiate pills (either sertraline or placebo) and thus were excluded from analysis. Among the 207 participants included in analyses were 71 in the SERT+EMM arm, 67 in the PE+PLB arm, and 69 in the PE+SERT arm. As reported in the primary outcome paper, participant demographic data were as follows: mean age 34.6 (SD = 8.3), 87% were male, 58% were white, 30% were Black, and 15% reported Hispanic ethnicity. Unadjusted summary statistics of CAPS scores and each of the three PTCI subscale scores at each assessment time during the treatment period by treatment arm are reported in Table 1. In all three treatment arms, mixed-effects models with longitudinally assessed CAPS scores as response variables showed significant decrease in symptoms with significant log-transformed time effects (p<0.001 in all three arms). Similarly, Negative Thoughts about Self and about the World subscales showed significant decreases during treatment in all three arms, but Self-Blame subscale showed significant decrease only in SERT+EMM (p<.001) and PE+PLB arms (p<.001) and did not show significant decrease over the treatment period in PE+SERT (p=0.16 for log-time coefficient).

In SERT+EMM arm, each of the time-lagged Negative Thoughts About Self and time-lagged Negative Thoughts About the World were predictive of the subsequent symptom scores indicating that change in thoughts is related to change in PTSD symptoms (Table 2). Models of the time-lagged PTSD symptom effect on cognitive changes also showed significance indicating that change in PTSD symptoms was related to change in thoughts. In addition, the lagged effect of PTSD symptom on Negative Thoughts about Self had a larger standardized slope (d = 0.23) than the lagged effect of Negative Thoughts About Self on symptoms (d = 0.20). The results indicated a bidirectional relationship between negative thoughts about self and negative thoughts about the world and PTSD symptoms in SERT+EMM condition.

In PE+SERT arm, the effect of time-lagged Negative Thoughts About the World was predictive of the symptom scores (d = 0.14), but we did not find the effect of time-lagged Negative Thoughts About Self on symptoms (Table 3). We also found significant time-lagged PTSD symptom effect on negative thoughts about the world (d = .29). Importantly, this indicates a bidirectional relationship for negative thoughts about the world and PTSD symptoms change in PE+SERT where each is impacting the other but a different pattern for negative thoughts about the self where overall PTSD symptom change is occurring prior to change in negative thoughts about the self in the PE+SERT condition.

In PE+PLB arm (Table 4), the relationship between posttraumatic thoughts and PTSD symptoms were not significant in either direction, except that time-lagged PTSD symptoms

were predictive of Negative Thoughts About the World (p=0.01). Thus, a differential pattern was observed for the PE+PLB condition where negative thoughts about the self and negative thoughts about the world were not related to symptom change but PTSD symptom change was related to change in negative thoughts about the world.

Discussion

The current study examined the relationship between changes in trauma-related beliefs and PTSD symptoms across three treatment conditions (SERT+EMM, PE+SERT, and PE+PBO) in a large, randomized trial. There are several key findings. First, the study replicated the finding that PE and sertraline are associated with reductions in negative thoughts about the self, world, and self-blame and extended these findings to veterans. However, contrary to results from past studies, how these changes relate to each other varies by both treatment and type of posttraumatic negative thought, showing that the addition of a pill impacts treatment process. The SERT+ EMM condition revealed a bidirectional relationship between changes in negative thoughts about the self and world and changes in PTSD symptoms. That is, PTSD symptom reductions preceded reductions in negative self- and world- thoughts *and* reductions in these negative thoughts also preceded PTSD symptom reductions. In the SERT+PE condition, there was a bidirectional relationship between change in negative thoughts about the world and PTSD symptom change, but a unidirectional relationship such that PTSD symptom changes preceded change in negative thoughts about the self. Finally, in the PE+PLB condition there was a unidirectional association such that reductions in PTSD symptoms preceded change in negative thoughts about the self and negative thoughts about the world, but not vice versa. In both PE conditions, regardless of whether the patient was taking sertraline or placebo, PTSD changes preceded reductions in negative self-referential trauma thoughts, but this was not the case when patients were taking sertraline without PE (in which there was a bidirectional relationship between PTSD symptom change and reductions in negative thoughts about the self). These differential patterns suggest that one potential driver of PTSD change found in many previous PE studies (change in negative thoughts about the self; i.e., Foa & Rauch, 2004; Kumpula et al, 2017) may be altered when a pill is initiated at the same time as therapy. Importantly, despite possible differences in how symptom reduction is occurring across the conditions, the veterans still demonstrated a robust and stable response in PTSD symptoms and negative thoughts about the self and world to all the conditions.

Of importance, the current results have implications regarding the potential impact of simultaneous medication and psychotherapy initiation on an important potential mechanism of change: change in negative thoughts about the self. Emotional processing theory suggests that as negative thoughts about the self improve through treatment, patients feel more competent to handle negative affect, which in turn leads to less avoidance, better functioning, and reduction in PTSD symptoms (Craske et al., 2014; Rauch & Foa, 2006). In PE, through confrontation of previously avoided memories and situations, patients can learn that they are more competent than their PTSD had led them to believe. It is possible that starting medication at the same time as PE undercuts this opportunity for learning about the specific self-attribution of change in that patients may attribute their successes to the medication instead of to their own competence. This may be why our results do not

wholly replicate previous findings with PE from trials of psychotherapy without medication (Kumpula et al., 2017). Specifically, veterans who attribute change in PTSD symptoms to themselves will show reductions in negative thoughts about the self while those who attribute change to taking a pill may be less likely to report changes on this scale. Finding the same pattern of results for PE with sertraline and PE with placebo further supports that our findings were not a function of the medication but rather the expectancy of what the medication would do. However, alternative explanations are also possible and additional research is needed to replicate and examine attribution in combination treatment more closely. These results highlight the importance of collaborative treatment planning and support a common practice in many clinical care settings to base the timing of the administration of psychotherapy and medication on a staged process that includes shared decision making between patients and providers.

In addition, as mentioned in the primary outcome paper, the lack of additive efficacy of combination treatment for either PTSD symptoms or (as shown in the current study) cognitive changes suggests that a preferred strategy may be to stage the treatments, first initiating the patient's and provider's preferred treatment before augmenting with another medication, therapy, or strategy. For instance, previous research suggests potential time points for adding interventions for partial response to therapy (Simon et al., 2008; Sripada et al., 2019) that may ensure that patients get the benefit of one treatment prior to adding another intervention. Despite this, while some studies have examined sequencing care for PTSD between medication and psychotherapy (Rothbaum et al., 2006; Simon et al., 2008), additional research is warranted to understand more precisely what and when to add medication. Of note, in some settings, including many clinics in the VA and many primary care clinics, the standard practice results in most patients being started on medication even before discussing therapy options. Thus, many patients may not have the choice between starting with therapy alone. Educating systems and providers about the current study's findings and the need for shared decision making prior to starting a patient on medication for PTSD to allow the best chance for treatment choice and response is warranted.

These results must be interpreted in the context of the study limitations. Specifically, there was no PE alone condition to see how negative posttraumatic thoughts and PTSD symptom change varied when no pill was present. In order to partially examine whether the pill placebo impacted symptom change or changes in thoughts over time, we examined the pre to post within condition effect size for PE+PLB in our study (d = 1.45; (Rauch et al., 2019)) with the comparable 24-week within treatment effect size reported for PE from the Kline et al (2018) meta-analysis (d = 2.32; (Kline et al., 2018). Indeed, both are large but the current study effect size is smaller than the previous meta-analysis. While meta-analyses examining shorter duration outcomes (12 weeks) have shown smaller effect sizes in Veterans, Kline and colleagues did not find such a difference when examining 24-week outcomes (Kline et al., 2018). A related limitation is that veterans had to be willing to take a pill and accept the possibility that they might not also receive a CBT as part of their participation in this study. Only veterans who were willing to be randomized to medication vs. therapy and who were not currently on an SSRI or other exclusionary medication could be included in the current study. This means that patients who are not amenable to medication are not represented and those amenable to medication who are already on one are not represented either. This is

an important limitation in the context of our findings: expectancy about the impact of pill taking is likely different for those who prefer to take medication for PTSD. Finally, previous studies that have examined change in negative thoughts as they relate to PTSD symptoms change in treatment have modeled more timepoints during active treatment. Other studies typically examined measures every other week for 10 to 12 weeks while we examined patients less frequently to week 24). This may account for the difference in the models and the current study's differential findings regarding sequencing of change in negative posttraumatic thoughts and change in PTSD symptoms.

In conclusion, this study presents a mechanistic analysis from a large randomized clinical trial of two efficacious PTSD treatments with clinically actionable results. Specifically, providers should be aware that simultaneous initiation of PE and medication (or even a pill placebo), particularly among patients who have preferences for pill-taking, may impact a key PE mechanism of change: reduction in negative posttraumatic thoughts about the self. This finding alongside our previously reported finding of a lack of differences in treatment efficacy across combined versus single treatments (Rauch et al., 2019) do not provide support for initiating both treatments simultaneously. Instead, a preferred strategy may be to talk with the patient about their preference for medication or psychotherapy, together choose a first treatment, and then provide additional treatment if needed only after an adequate first trial of monotherapy (medication or psychotherapy).

Disclosures and Acknowledgements

Dr. Rauch receives support from Wounded Warrior Project (WWP), Department of Veterans Affairs (VA), National Institute of Health (NIH), Woodruff Foundation, and Department of Defense (DOD). Dr. Rauch receives royalties from American Psychological Association Press and Oxford University Press. Dr Kim has nothing to disclose. Margaret R. Venners has nothing to disclose. Dr. Porter receives funding from the Department of Veterans Affairs. Dr Norman has no competing interests in relation to the manuscript content. In the past 12 months, Dr. Norman reports research support from the Department of Defense, PCORI, NIH. Dr Norman receives royalties from Elsevier Press. Dr Simon has no competing interests in relation to the manuscript content. In the past 12 months, Dr. Simon reports research support from the Department of Defense, PCORI, NIH. Dr Simon reports consulting for Axovant Sciences, Springworks, Praxis Therapeutics, Aptinyx, Genomind, Wolters Kluwer (royalty) and spousal equity in G1 Therapeutics. Dr. Rothbaum has funding from Wounded Warrior Project, Department of Defense, National Institute of Mental Health, and McCormick Foundation. Dr. Rothbaum receives royalties from Oxford University Press, Guilford, APPI, and Emory University and has served on recent advisory boards for Aptinyx, Sandoz, Neuronetics, and Nobilis. Dr. Rothbaum owns equity in Virtually Better, Inc. that creates virtual reality products. The terms of this arrangement have been reviewed and approved by Emory University in accordance with its conflict of interest policies. Dr. Norman receives funding from the Department of Defense, VA, and NIH. She receives royalties from Elsevier Press. Dr. Tuerk receives compensation for educational consultation services from the Cohen Veterans Network, Psych Congress Network, and Virtually Better Inc. He is PI on an NIMH funded award, 5R42MH111277-03, and receives royalties from Springer International. Dr. Acierno has nothing to disclose.

Dr. Bui received grants from the NIH, the US Department of Defense, Osher Center for Integrative Medicine, Patient-Centered Outcomes Research Institute, and Elizabeth Dole Foundation, and royalties from Springer Nature and Wolters Kluwyer. Dr. Powell has nothing to disclose. Dr. Smith receives funding from the Department of Veterans Affairs. Dr.Goetter receives royalties from New Harbinger Publications. Dr. Mc Sweeney has nothing to disclose.

Funding:

This work was supported by the U.S. Department of Defense through the U.S. Army Medical Research and Materiel Command (MRMC; Randomized Controlled Trial of Sertraline, Prolonged Exposure Therapy, and Their Combination in OEF/OIF Combat Veterans with PTSD; (Award #W81XWH-11-1-0073; PI: Rauch); the National Center for Advancing Translational Sciences of the National Institutes of Health (Award #UL1TR000433). This material is the result of work supported with resources and the use of facilities at Massachusetts General Hospital, the VA Ann Arbor Healthcare System, Ralph H. Johnson VA Medical Center, and VA San Diego Healthcare

System. The views expressed in this article presentation are solely those of the author(s) and do not reflect an endorsement by or the official policy of the Department of Veterans Affairs, Department of Defense, or the U.S. Government, or the official views of the National Institutes of Health.

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Table 1:

Unadjusted summary statistics of clinician-administered PTSD scale (CAPS) scores and posttraumatic cognition inventory (PTCI) subscales over treatment period by arm

Arm	Sertraline + enhanced med management (SERT+EMM)											
	CAPS			PTCI Self			PTCI World			PTCI Self-Blame		
Weeks	N	mean	SD	N	mean	SD	N	mean	SD	N	Mean	SD
0	71	75.54	14.99	69	3.24	1.31	69	5.16	1.40	69	2.19	1.33
6	65	54.91	21.90	63	2.95	1.33	63	4.84	1.47	63	2.17	1.54
12	60	47.40	24.43	55	2.82	1.36	55	4.66	1.67	55	1.81	1.31
24	56	41.73	25.69	52	2.67	1.46	52	4.55	1.83	52	1.72	1.17
Arm	**Prolonged exposure + placebo (PE+PLB)**											
	CAPS			PTCI Self			PTCI World			PTCI Self-Blame		
Weeks	N	Mean	SD	N	mean	SD	N	mean	SD	N	Mean	SD
0	67	80.88	13.25	65	3.57	1.27	65	5.12	1.16	65	2.49	1.31
6	51	66.86	19.19	46	3.18	1.22	46	4.97	1.36	46	2.02	1.32
12	45	52.89	24.86	43	2.62	1.11	43	4.53	1.44	43	1.81	1.12
24	42	51.45	25.26	38	2.76	1.17	38	4.55	1.44	38	1.99	1.25
Arm	**Prolonged exposure + sertraline (PE+SERT)**											
	CAPS			PTCI Self			PTCI World			PTCI Self-blame		
Weeks	N	mean	SD	N	mean	SD	N	mean	SD	N	mean	SD
0	69	76.01	14.24	66	3.33	1.10	66	4.77	1.28	66	2.01	1.05
6	56	60.57	20.85	53	3.20	1.36	53	4.79	1.47	53	2.00	1.18
12	54	47.33	26.37	51	2.68	1.39	51	4.44	1.61	51	1.69	1.02
24	51	43.33	27.16	48	2.70	1.42	48	4.31	1.66	48	1.98	1.18

Abbreviations: CAPS is clinician-administered PTSD scale; PTCI-Self is posttraumatic cognition inventory negative cognition about self subscale; PTCI-World is posttraumatic cognition inventory negative cognition about world subscale.

Table 2:

Time-lagged mixed-effects regression analyses during treatment period in sertraline plus enhanced medication management arm (SERT+EMM)

	Beta	SE	z	p-value	95% CL		d*
Relationship between CAPS and PTCI-Self							
CAPS as the response variable (N=67, n=169, $R^{2\wedge}$=.60)							
Lagged PTCI-Self	3.63	1.22	2.99	.003	1.25	6.02	0.20
Autocorrelation	0.56	0.08	7.42	<.001	0.41	0.71	0.54
Time, Ln(week+1)	4.75	2.48	1.91	.056	−0.12	9.61	NA
Intercept	−8.42	9.14	−0.92	.357	−26.33	9.49	NA
PTCI-Self as the response variable (N=64, n=160, $R^{2\wedge}$=.40)							
Lagged CAPS	0.01	0.00	3.69	<.001	0.01	0.02	0.23
Autocorrelation	0.73	0.05	13.56	<.001	0.63	0.84	0.72
Time, Ln(week+1)	0.40	0.14	2.99	.003	0.14	0.67	NA
Intercept	−1.25	0.45	−2.74	.006	−2.14	−0.36	NA
Relationship between CAPS and PTCI-World							
CAPS as the response variable (N=67, n=169, $R^{2\wedge}$=.63)							
Lagged PTCI-World	4.11	0.98	4.20	<.001	2.19	6.03	0.25
Autocorrelation	0.64	0.07	9.04	<.001	0.50	0.77	0.62
Time, Ln(week+1)	6.80	2.50	2.72	.007	1.89	11.71	NA
Intercept	−27.21	8.82	−3.09	.002	−44.49	−9.93	NA
PTCI-World as the response variable (N=64, n=160, $R^{2\wedge}$=.50)							
Lagged CAPS	0.02	0.00	3.76	<.001	0.01	0.03	0.27
Autocorrelation	0.67	0.06	10.37	<.001	0.54	0.79	0.62
Time, Ln(week+1)	0.45	0.18	2.47	.014	0.09	0.80	NA
Intercept	−0.77	0.61	−1.27	.203	−1.96	0.42	NA

Abbreviations: CAPS is clinician-administered PTSD scale; PTCI-Self is posttraumatic cognition inventory negative cognition about self subscale; PTCI-World is posttraumatic cognition inventory negative cognition about world subscale; N is number of persons; n is number of observations; NA is not applicable.

$^{\wedge}$Calculated to assess the fit of the models as the squared value of the correlation coefficient of the observed and the predicted of the outcomes.

*Standardized slopes obtained by standardizing all variables in each model to mean=0 and SD=1 except time variable before fitting for ease of interpretation.

Table 3:

Time-lagged mixed-effects regression analyses during treatment period in prolonged-exposure plus sertraline arm (PE+SERT)

	Beta	SE	z	p-value	95% CL		d*
Relationship between CAPS and PTCI-Self							
CAPS as the response variable (N=56, n=151, $R^{2\wedge}$=.50)							
Lagged PTCI-Self	1.44	1.56	0.92	.357	−1.62	4.49	0.07
Autocorrelation	0.42	0.09	4.71	<.001	0.24	0.59	0.38
Time, Ln(week+1)	−4.33	2.52	−1.72	.085	−9.26	0.60	NA
Intercept	31.47	9.89	3.18	<.001	12.09	50.84	NA
PTCI-Self as the response variable (N=55, n=145, $R^{2\wedge}$=.35)							
Lagged CAPS	0.01	0.00	1.95	.051	0.00	0.02	0.14
Autocorrelation	0.74	0.07	10.56	<.001	0.60	0.88	0.68
Time, Ln(week+1)	0.12	0.15	0.75	.452	−0.19	0.42	NA
Intercept	−0.25	0.53	−0.46	.643	−1.29	0.80	NA
Relationship between CAPS and PTCI-World							
CAPS as the response variable (N=56, n=151, $R^{2\wedge}$=.53)							
Lagged PTCI-World	2.41	1.16	2.08	.038	0.13	4.69	0.14
Autocorrelation	0.42	0.08	5.22	<.001	0.26	0.58	0.38
Time, Ln(week+1)	−4.17	2.57	−1.62	.104	−9.21	0.86	NA
Intercept	23.80	10.00	2.38	.017	4.21	43.39	NA
PTCI-World as the response variable (N=55, n=145, $R^{2\wedge}$=.45)							
Lagged CAPS	0.02	0.01	3.51	<.001	0.01	0.03	0.29
Autocorrelation	0.55	0.08	6.85	<.001	0.39	0.71	0.50
Time, Ln(week+1)	0.25	0.21	1.21	.226	−0.16	0.67	NA
Intercept	0.03	0.72	0.04	.966	−1.39	1.45	NA

Abbreviations: CAPS is clinician-administered PTSD scale; PTCI-Self is posttraumatic cognition inventory negative cognition about self subscale; PTCI-World is posttraumatic cognition inventory negative cognition about world subscale; N is number of persons; n is number of observations; NA is not applicable.

$^{\wedge}$Calculated to assess the fit of the models as the squared value of the correlation coefficient of the observed and the predicted of the outcomes.

*Standardized slopes obtained by standardizing all variables in each model to mean=0 and SD=1 except time variable before fitting for ease of interpretation.

Table 4:

Time-lagged mixed-effects regression analyses during treatment period in prolonged-exposure plus pill placebo arm (PE+PLB)

	Beta	SE	z	p-value	95% CL		d*
Relationship between CAPS and PTCI-Self							
CAPS as the response variable (N=53, n=126, $R^{2\wedge}$=.43)							
Lagged PTCI-Self	0.09	1.55	0.06	.956	−2.94	3.11	0.004
Autocorrelation	0.75	0.10	7.88	<.001	0.57	0.94	0.68
Time, Ln(week+1)	3.03	3.65	0.83	.406	−4.12	10.17	NA
Intercept	−1.56	13.69	−0.11	.909	−28.38	25.26	NA
PTCI-Self as the response variable (N=51, n=116, $R^{2\wedge}$=.14)							
Lagged CAPS	0.01	0.00	1.53	.126	0.00	0.02	0.12
Autocorrelation	0.71	0.07	9.76	<.001	0.57	0.85	0.72
Time, Ln(week+1)	0.17	0.17	0.98	.327	−0.17	0.50	NA
Intercept	−0.21	0.63	−0.33	.743	−1.45	1.03	NA
Relationship between CAPS and PTCI-World							
CAPS as the response variable (N=53, n=126, $R^{2\wedge}$=.44)							
Lagged PTCI-World	2.45	1.49	1.64	.101	−0.48	5.38	0.13
Autocorrelation	0.68	0.10	6.87	<.001	0.48	0.87	0.61
Time, Ln(week+1)	2.28	3.63	0.63	.530	−4.84	9.40	NA
Intercept	−6.26	13.63	−0.46	.646	−32.97	20.45	NA
PTCI-World as the response variable (N=51, n=116, $R^{2\wedge}$=.26)							
Lagged CAPS	0.01	0.01	2.50	.012	0.00	0.03	0.21
Autocorrelation	0.69	0.08	8.24	<.001	0.53	0.86	0.62
Time, Ln(week+1)	0.26	0.21	1.23	.218	−0.15	0.68	NA
Intercept	−0.31	0.79	−0.39	.697	−1.85	1.24	NA

Abbreviations: CAPS is clinician-administered PTSD scale; PTCI-Self is posttraumatic cognition inventory negative cognition about self subscale; PTCI-World is posttraumatic cognition inventory negative cognition about world subscale; N is number of persons; n is number of observations, NA is not applicable.

$^{\wedge}$Calculated to assess the fit of the models as the squared value of the correlation coefficient of the observed and the predicted of the outcomes.

*Standardized slopes obtained by standardizing all variables in each model to mean=0 and SD=1 except time variable before fitting for ease of interpretation.