Change in Posttraumatic Stress Disorder–Related Thoughts During Treatment: Do Thoughts Drive Change When Pills Are Involved?

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/jts.22762.

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Author Note

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; W81XWH-11-1-0073; PI: Sheila A. M. Rauch) and the National Center for Advancing Translational Sciences of the National Institutes of Health (UL1TR000433). This material is the result of work supported with resources and the use of facilities at Massachusetts General Hospital, the Veterans Affairs (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 authors 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. Sheila A.M. Rauch receives support from the Wounded Warrior Project (WWP), VA, National Institute of Health (NIH), Woodruff Foundation, and Department of Defense (DoD) as well as royalties from American Psychological Association Press and Oxford University Press. Katherine Porter receives funding from the VA. Sonya Norman has no competing interests in relation to the manuscript content. In the past 12 months, Sonya Norman reports research support from the Department of Defense, Patient Centered Outcomes Research

Institute (PCORI), NIH; in addition, she receives royalties from Elsevier Press. Naomi M. 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, and NIH; in addition, she reports consulting for Axovant Sciences, Springworks, Praxis Therapeutics, Aptinyx, Genomind, Wolters Kluwer (royalty), and spousal equity in G1 Therapeutics. Barbara O. Rothbaum reports funding from WWP, Department of Defense, National Institute of Mental Health (NMIH), and McCormick Foundation and receives royalties from Oxford University Press, Guilford, American Psychiatric Association Publishing, and Emory University; in addition, she has served on recent advisory boards for Aptinyx, Sandoz, Neuronetics, and Nobilis and owns equity in Virtually Better, Inc., which 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. Peter W. Tuerk receives compensation for educational consultation services from the Cohen Veterans Network, Psych Congress Network, and Virtually Better Inc. He is the principal investigator on an NIMH-funded award (5R42MH111277-03) and receives royalties from Springer International. Eric Bui received grants from the NIH, the Department of Defense, Osher Center for Integrative Medicine, Patient-Centered Outcomes Research Institute, and Elizabeth Dole Foundation, as well as royalties from Springer Nature and Wolters Kluwer. Erin R. Smith receives funding from the VA. Elizbeth Goetter receives royalties from New Harbinger Publications. The rest of the authors report no competing interests or disclosures.

Preliminary results of the present study were previously presented at the 54th Annual Meeting of the Association for Behavioral and Cognitive Therapy, Washington, DC, November 15–18, 2018. ClinicalTrials.gov: NCT01524133

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Abstract

Posttraumatic negative thoughts about one's self and the world are related to posttraumatic stress disorder (PTSD) symptom severity and change in cognitive behavioral treatment (CBT), but little is known about this association when CBT is delivered with medication. The current study presents a planned comparison of changes in negative posttraumatic thoughts during (a) prolonged exposure (PE) plus pill placebo (PE+PLB), (b) sertraline plus enhanced medication management (SERT+EMM), and (c) PE plus sertraline (PE+SERT) as part of a randomized clinical trial in a sample of 176 veterans. Lagged regression modeling revealed that change in posttraumatic negative thoughts was associated with PTSD symptom change in the conditions in which participants received sertraline, *d*s = 0.14–0.20, *p*s = 0.04–.003). However, contrary to previous research, the models that started with symptom change were also statistically significant, $d = 0.23$, $p < .001$, for the lagged effect of symptoms on negative thoughts about self in the SERT+EMM condition, indicating a bidirectional association between such thoughts and PTSD symptoms. In the PE+PLB condition, no significant association between posttraumatic thoughts and PTSD symptoms emerged 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.

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Posttraumatic negative thoughts about one's self and the world are key factors that contribute to both the development and maintenance of posttraumatic stress disorder (PTSD) symptoms over time (Foa & Rauch, 2004; Rauch, Abelson, et al., 2015). Negative thoughts about self include an individual's perceived ability to handle negative affect and stressful situations. Both inhibitory learning and emotional processing theory posit that an increased sense of self-competence leads to reductions in avoidance and other symptoms that characterize 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, which increase an individual's perceived ability to effectively deal with negative affect.

The findings from multiple studies have demonstrated that reductions in negative thoughts about one's self, negative thoughts about the world, and self-blame, as measured by the Posttraumatic Cognitions Inventory (PTCI; Foa et al., 1999), are significantly related to treatment reductions in PTSD symptoms (Foa & Rauch, 2004; Kumpula et al., 2017; Rauch, King, et al., 2015; Zalta et al., 2014). It is important to note that these negative thoughts and symptom changes are robust and have not been shown to be augmented when specific cognitive restructuring is added to PE, suggesting that the treatment's core components (i.e., in vivo and imaginal exposure, and psychoeducation) lead to changes in posttraumatic negative thoughts about self, the world, and self-blame (Foa et al., 2005; Foa & Rauch, 2004). Several PE studies have used lagged regression modeling to determine whether changes in posttraumatic thoughts drive symptom change or vice versa. Consistently, these studies have shown that in PE, changes in thoughts occur prior to changes in PTSD symptoms (Kumpula et al., 2017; Zalta et al., 2014). Similarly, in a study that examined both PE and sertraline, changes in negative posttraumatic thoughts about the self preceded and predicted changes in PTSD symptoms and, to a lesser extent, changes in depressive

symptoms (Cooper et al., 2017). However, the magnitude of this association was considerably smaller among participants who received sertraline compared to PE. Although preliminary, this suggests that the relation between changes in posttraumatic negative thoughts and PTSD symptoms may exist across different treatment modalities (i.e., medication and therapy), but the strength of this association may be attenuated in medication compared with therapy.

Research on the mechanisms of change in depression has shown differential brain biomarker "paths to response" for psychotherapy and medication (McGrath et al., 2013), and the same might be expected for PTSD. Specific examinations of brain mechanisms related to change in PTSD treatment have not revealed differential predictors thus far (Duval et al., 2020; Joshi et al., 2020; Rauch et al., 2020), although such studies are typically underpowered to detect conditional differences in medication and psychotherapy.

Of importance to patient care, attributions of change during psychotherapy may be moderated if or when a patient is also taking a medication that has been 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. The findings of two studies examining these processes in substance use disorder and panic disorder treatments demonstrated moderation of outcomes by attribution (Biondi & Picardi, 2003; Schaumberg et al., 2013). Specifically, participants who thought they had received a placebo reported more confidence that they could maintain reductions in substance use and panic symptoms without medication compared with those who thought they received naltrexone (Schaumberg et al., 2013). Similarly, when examining patients' perceptions of the reasons for their social anxiety disorder (SAD), those who attributed their SAD to genetic, biological, and early-life experiences had a more rapid response to paroxetine than those who reported more psychosocially focused attributions (Cohen et al., 2015). In a depression

clinical trial comparing supportive–expressive psychotherapy (SET), clinical management (CM) combined with pharmacotherapy, and CM combined with a placebo pill, changes in attribution emerged in all conditions, with no differences between conditions (Zilcha-Mano et al., 2016), supporting the idea that even a placebo pill can have an active impact on therapeutic change. The 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 recognize the effects of each contributor or each masks the impact of the other. That is, for cases in which patients may attribute change not to their internal capacity but, at least partially, to a pill, such attribution may interfere with therapy-related change.

Despite evidence that changes in specific thoughts and symptoms are linked in treatment with PE and treatment with sertraline, no study of which we are aware has examined this association across each of these treatments while also including a pill placebo control condition. The current study sought to examine the patterns of change in negative thoughts about 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 (EMM; i.e., SERT+EMM), and PE plus sertraline (PE+ SERT) using time-lagged regression modeling. Because previous research using the PTCI subscales has more consistently supported associations between scores on the Negative Thoughts About Self (PTCI Self) and Negative Thoughts About the World (PTCI World) subscales and treatment-related reductions in PTSD symptoms (Foa & Rauch, 2004; Kumpula et al., 2017; Rauch, King, et al., 2015), and to reduce the number of tests run, we hypothesized that change in self-perception regarding one's ability to handle PTSD symptoms (i.e., PTCI Self and PTCI 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 paper presents the findings from 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 VA Ann Arbor Healthcare System IRB, University of Michigan IRB, Ralph H. Johnson VA Medical Center/Medical University of South Carolina IRB, VA San Diego Healthcare System/University of California San Diego IRB, Massachusetts General Hospital IRB and the U.S. Army Medical Research and Materiel Command, Office of Research Protections, Human Research Protection Office. Participants were combat veterans randomized to one of three conditions (i.e., PE+PLB, SERT+EMM, or PE+SERT) for 24 weeks of treatment. 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. Detailed information regarding the study methods and primary outcomes is published elsewhere (Rauch et al., 2018, 2019). Briefly, the outcomes analyses demonstrated no significant differences in PTSD symptom severity between the three conditions at posttreatment or follow-up (Rauch et al., 2019).

Four sites [VA Ann Arbor Healthcare System, Ralph H. Johnson VA Medical Center, Massachusetts General Hospital, VA San Diego Healthcare System] recruited 223 patients between 2011 and 2016. Individuals completed the PTCI (Foa et al., 1999) and other measures (see Measures section for details). The inclusion criteria were (a) service member or veteran previously deployed in support of recent combat operations in Iraq and Afghanistan, (b) combat-related PTSD, and (c) significant impairment (i.e., a Clinicians Administered PTSD Scale [CAPS] of 50 or higher) of at least 3 months duration. Exclusion criteria were (a) current imminent risk of suicide, (b) active psychosis, (c) alcohol or

substance dependence (i.e., past 8 weeks), (d) inability to attend weekly appointments for the treatment period, (e) prior intolerance or failure of an adequate trial of PE or sertraline, (f) medical illness likely to result in imminent hospitalization or contraindication to study treatments, and (g) serious cognitive impairment (e.g., confusion, inability to track discussion). 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, provided consent, and completed diagnostic assessments and rating scales prior to randomization. Self-report and clinician-administered measures occurred at Weeks 0 (i.e., intake), 6, 12, 24, 36, and 52. After the 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 they completed the follow-up assessments.

For PE treatment, participants received up to 13 standard, 90-min 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 Veterans Affairs (VA) PE 4-day workshop and demonstrated fidelity during at least two supervised cases. PE fidelity was assured via structured weekly supervision calls and independent audio-recording of a random 20% of sessions (n = 381 sessions), with 94% fidelity across sites and sessions (Rauch et al., 2019).

For pharmacotherapy, sertraline doses were flexibly adjusted between 50 and 200 mg/day, with a final dose increase at Week 10 to ensure stable dosing by Week 12. Medication was continued until Week 24. Medication management (i.e., sertraline or placebo) was manualized to standardize pharmacotherapy delivery as brief (i.e., approximately 15-min) medication management (MM) when administered alongside PE or as

EMM, which was approximately 30 min for participants randomized to sertraline 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

Posttraumatic Thoughts

The self-report PTCI (Foa et al., 1999) is a measure of trauma-related thoughts and beliefs. It was developed by adopting emotional processing theory that suggests PTSD is a consequence of disruptions in the normal processes of recovery 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, Hembree, & Rothbaum, 2007). The PTCI has three subscales: PTCI Self (21 items), PTCI World (seven items), and Self-Blame (five items). Each item is rated on a 7-point agreement scale, and each subscale score is calculated as an average of the item scores corresponding to each subscale (range: 1–7), with higher scores corresponding with more negative thoughts. Although the number of the items differs across the three subscales, excellent internal consistency, good test–retest reliabilities, and convergent validity have been reported for all three subscales (Foa et al., 1999). Using only the baseline data, Cronbach's alpha values were .95 for the PTCI Self subscale, .89 for the PTCI World subscale, and .82 for the Self-Blame subscale. Because previous research using the PTCI has more consistently supported the PTCI Self and PTCI World subscales as being related to treatment-related PTSD symptom reduction (Foa & Rauch, 2004; Kumpula et al., 2017; Rauch, King, et al., 2015) and to reduce the number of tests run, we focused on the Self and World subscales in this study

PTSD symptoms

PTSD symptoms were assessed by evaluators who were blind to treatment condition using the CAPS (Blake et al., 1995). The CAPS is a semistructured interview that is used to assess PTSD severity in relation to a respondent's self-identified most distressing traumatic experience; for the present study, participants were asked to respond relative to their most distressing war zone event. The CAPS has been widely used in both clinical and research settings and has demonstrated excellent psychometric properties, including strong test–retest reliability and excellent internal consistency (Cronbach's $\alpha = .94$) for all 17 items (Blake et al., 1995). The present study used the total score for past-month symptoms. Higher total scores indicate more severe PTSD symptoms, and, of note, the PROGrESS trial had an inclusion criterion of significant impairment, defined as a CAPS score of 50 or higher. Because the study started well before the introduction of the most recent fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5*), PTSD criteria from the fourth edition, text revision of the *DSM* (*DSM-IV-TR*) were used. Of note, the issue of symptom overlap between posttraumatic cognitions and PTSD symptoms was not an issue, as the *DSM IV-TR* criteria did not include what is encompassed by *DSM-5* Criterion D2 and Criterion D3 (i.e., persistent negative beliefs about oneself, others, and the world; distorted cognitions about the event that cause self-blame).

Data analysis

Assessments were completed during the 24-week treatment period up to four times at baseline and at Weeks 6, 12, and 24. To examine the potential mechanistic association between posttraumatic thoughts and PTSD symptoms during the treatment period, a series of time-lagged mixed-effects regression analyses were conducted using the longitudinally assessed data (Granger, 1969; Zalta et al., 2014). Specifically, we tested the hypothesis that change in posttraumatic negative thoughts would generate successive PTSD symptom

changes and examined the time-lagged effects of each PTCI subscale during the treatment period on subsequent PTSD symptoms separately. We ran separate mixed-effects models with follow-up assessment CAPS scores as the response variables and each PTCI subscale score as the 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 the follow-up period. To test the reverse directional hypotheses whereby PTSD symptom change generates successive changes in thoughts, we conducted three additional mixed-effects models, with each PTCI subscale score during the follow-up period as response variables and CAPS scores entered as time-lagged predictors. These models also included time slope and time-lagged values for each response variable for autocorrelation. If the time-lagged effect of thoughts on PTSD symptoms was present but the reverse was not, it would support our hypothesis that change in these thoughts would occur before changes in PTSD symptoms. Analyses were conducted separately by treatment condition to examine mechanisms during each treatment, specifically to see if changes in these thoughts would be associated with outcomes. For model fit, we calculated R^2 values as the squared value of the correlation coefficient between the predicted and the observed outcome values. All analyses were conducted using Stata (Version 15.0).

The smallest and largest analytic cohort sample sizes were 51 in the PE+PLB condition and 67 in the SERT+EMM condition. The study had 80% statistical power, with an alpha level of .05, to detect tests' minimum standardized slopes of 0.40 in the smallest cohort and 0.36 in the largest cohort where the slopes reflect the associations between a time-lagged PTCI subscale and subsequent PTSD symptoms or vice versa. With longitudinal data and covariate adjustments, the study was likely to have adequate power to detect smaller slopes.

The primary cohort included 71 participants in the SERT+EMM condition, 67 in the PE+PLB condition, and 69 in the PE+SERT condition (see Table 1). Each time-lagged mixed-model analysis (Tables 2–4) included only data collected during the follow-up period as the response variable and required nonmissing time-lagged values of the predictor. For example, for the model with CAPS as the response variable, a patient could contribute data to the analytic model only if at least one set of data were nonmissing simultaneously, including current CAPS score, prior PTCI scores, and prior CAPS score (for autocorrelation). The analytic cohort, therefore, is smaller, but considering what was needed for the analysis, the reduction in analytic cohort size for the time-lagged model due to missingness was not substantial. Specifically, the percentage of patients included in the CAPS analyses was 94.4% (i.e., $n = 67$ out of $N = 71$) in the SERT+EMM condition, 79.1% (i.e., $n = 53$ out of $N = 67$) in the PE+PLB condition, and 81.2% (i.e., $n = 56$ of $N = 69$) in the PE+SERT condition. The analytic cohort sizes for each model are provided in Tables 2–4.

RESULTS

Of the 223 randomized patients, 16 did not initiate pills (either sertraline or placebo) and, thus, were excluded from the present analysis. Among the 207 participants included in the study 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, the mean participant age was 34.6 years ($SD = 8.3$), 87.0% of participants were male, 57.5% were White, 30.0% were Black, and 15.0% 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 condition, are reported in Table 1. In all three treatment arms, mixed-effects models with longitudinally assessed CAPS scores as response variables showed significant decreases in symptoms, with significant log-transformed time effects, ps $< .001$. Similarly, scores on the PTCI Self and World subscales showed significant decreases during treatment in all three

treatment conditions; PTCI Self-Blame scores showed significant decreases among participants in the SERT+EMM and PE+PLB conditions only, *p*s < .001, and did not show a significant decrease over the treatment period in the PE+SERT arm, $p = .157$ (log-time coefficient).

In the SERT+EMM arm, each time-lagged PTCI Self and PTCI World score was predictive of subsequent symptom scores, indicating that change in thoughts was 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 symptoms on PTCI Self score had a larger standardized slope, $d = 0.23$, than the lagged effect of PTCI Self on PTSD symptoms, $d = 0.20$. The results indicate a bidirectional association between negative thoughts about self and negative thoughts about the world and PTSD symptoms among participants in the SERT+EMM condition.

In the PE+SERT arm, the effect of time-lagged PTCI World score was predictive of PTSD symptom scores, $d = 0.14$, but we did not find an effect of time-lagged PTCI Self score on PTSD symptoms (Table 3). We also found a significant time-lagged PTSD symptom effect on negative thoughts about the world, $d = 0.29$. Importantly, this indicates a bidirectional association between negative thoughts about the world and PTSD symptom change among PE+SERT participants where each variable impacted the other. A different pattern, however, emerged for negative thoughts about self whereby overall PTSD symptom change occurred prior to changes in negative thoughts about the self.

In the PE+PLB arm (Table 4), the association between posttraumatic thoughts and PTSD symptoms was not significant in either direction except that time-lagged PTSD symptoms were predictive of PTCI World scores, $p = .012$. Thus, we observed a differential pattern for the PE+PLB condition whereby negative thoughts about self and negative

thoughts about the world were not related to PTSD symptom change, but PTSD symptom change was related to changes in PTCI World score.

DISCUSSION

The current study examined the association between changes in trauma-related beliefs and PTSD symptoms across three treatment conditions (i.e., SERT+EMM, PE+SERT, and PE+PBO) in a large randomized trial. Several key findings emerged. First, the study replicated the previous finding that treatment with PE and treatment with SERT were each associated with reductions in negative thoughts about self, world, and self-blame and extended these findings to veterans. However, contrary to results from past studies, how these changes related to each other varied by both treatment and type of posttraumatic negative thought, showing that the addition of a pill impacted the treatment process. Among participants in the SERT+ EMM condition, we observed a bidirectional association between changes in negative thoughts about self and world and changes in PTSD symptoms. That is, PTSD symptom reductions preceded reductions in negative cognitions about oneself and the world, and reductions in these negative thoughts also preceded reductions in PTSD symptom severity. In the SERT+PE condition, there was a bidirectional association between changes in negative thoughts about the world and PTSD symptom changes but a unidirectional association such that PTSD symptom changes preceded changes in negative thoughts about self. Finally, in the PE+PLB condition, a unidirectional association emerged such that reductions in PTSD symptom severity preceded changes in negative thoughts about self and the world; however, the reverse was not true. In both PE conditions, regardless of whether the patient was taking sertraline or a placebo, changes in PTSD symptom severity preceded reductions in negative self-referential trauma-related thoughts, but this was not the case when patients took sertraline without PE, in which there was a bidirectional association between PTSD symptom change and reductions in negative thoughts about self. These differential

patterns suggest that one potential driver of PTSD change found in many previous PE studies—change in negative thoughts about 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 reductions occurred across conditions, veterans randomized to all conditions still demonstrated a robust and stable response with regard to PTSD symptoms and negative thoughts about self and world.

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 self. Emotional processing theory suggests that as negative thoughts about oneself improve through treatment, patients feel they are more capable of handling negative affect, which, in turn, leads to less avoidance, better functioning, and reductions in PTSD symptoms (Craske et al., 2014; Rauch & Foa, 2006). In PE, through the confrontation of previously avoided memories and situations, patients can learn that they are more competent than their PTSD has 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 such that patients may attribute their successes to the medication instead of to their own competence. This may be why the present results do not wholly replicate previous findings associated with PE from trials of psychotherapy without medication (Kumpula et al., 2017). Specifically, veterans who attribute changes in PTSD symptoms to themselves have been shown to demonstrate reductions in negative thoughts about self, whereas those who attribute changes to taking a pill may be less likely to see score reductions on the PTCI Self subscale. 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. The present 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, changes in posttraumatic cognitions, suggests that a preferred strategy may be to stage the treatments, first initiating the patient's and provider's preferred treatment before augmenting treatment with another medication, therapy, or strategy. For instance, previous researchers have suggested 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 before another intervention is added. Although 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 when to add medication and what medication should be added. Of note, in some settings, including many clinics within the VA as well as many primary care clinics, standard practice results in most patients starting medication even before discussing therapy options. Thus, many patients may not have a choice between starting with therapy alone. Educating health care systems and individual providers about the current study's findings and the need for shared decision-making before starting a patient on medication for PTSD is warranted to allow the best chance for treatment choice and response.

These present results must be interpreted in the context of the study limitations. Specifically, there was no standalone PE condition, the addition of which would have allowed us to see how negative posttraumatic thoughts and PTSD symptom change varied

when no pill was present. To partially examine whether the placebo pill impacted symptom change or changes in thoughts over time, we examined the pre- to posttreatment within-condition effect sizes 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 by Kline et al. (2018) in their meta-analysis (d = 2.32). Indeed, both effect sizes were large, but the effect size for the current study is smaller than that reported by Kline and colleagues. Although meta-analyses examining shorter-duration outcomes (i.e., 12 weeks) have shown smaller effect sizes in veterans, Kline et al. (2018) did not find such a difference when examining 24-week outcomes. A related limitation is that veterans enrolled in the present study had to be willing to take a pill and accept the possibility that they might not also receive a cognitive behavioral treatment as part of their participation. Only veterans who were willing to be randomized to medication versus therapy and were not currently taking a selective serotonin reuptake inhibitor or other exclusionary medication could be included in the current study. This means that patients who were not amenable to medication, as well as those who were amenable to pharmacotherapy but were already taking certain medications, were not represented in the present sample. This is an important limitation in the context of the present findings: The expectations regarding the impact of taking a pill are likely different for individuals who prefer to take medication for PTSD compared with those who do not. Finally, previous studies that have examined changes in negative thoughts as they relate to treatment-related PTSD symptom change have modeled more time points during active treatment. Other studies have typically administered measures every other week for 10–12 weeks, whereas we examined patients less frequently over 24 weeks. This may account for the difference in the models and the current study's differential findings regarding the sequencing of changes in negative posttraumatic thoughts and PTSD symptom change.

In conclusion, the present 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: reductions 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), does 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, choose the first treatment together, and then provide additional treatment if needed (i.e., medication or psychotherapy) only after an adequate first trial of monotherapy.

Open Practices Statement

The primary outcomes of this study were formally preregistered on ClinicalTrials.gov. Neither data nor the materials have been made available on a permanent third-party archive; requests for the data or materials can be sent via email to the lead author at sheila.a.m.rauch@emory.edu.

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TABLE 1

Unadjusted summary statistics of Clinician-Administered Posttraumatic Stress Disorder (PTSD) Scale (CAPS) scores and Posttraumatic Cognition Inventory (PTCI) subscales over the treatment period, by condition

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

Note. PTCI Self = PTCI Negative Cognitions About Self subscale; PTCI World = PTCI Negative Cognitions About the World subscale; PTCI Self-Blame = PTCI Self-Blame subscale; SERT = sertraline; EMM = enhanced medication management; PE = prolonged exposure; PLB = placebo.

TABLE 2

Time-lagged mixed-effects regression analyses during treatment period in the sertraline plus enhanced medication management study arm

Response variable	*B*	*SE*	*z*	*p*	95% CI	*d*[a]
Association between CAPS and PTCI-Self						
CAPS (N = 67 participants, N = 169 observations), R^{2b} = .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]	-
Intercept	-8.42	9.14	-0.92	.357	[-26.33, 9.49]	-
PTCI-Self (N = 64 participants, n = 160 observations), R^{2b} = .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
Association between CAPS and PTCI-World						
CAPS (N = 67 participants, n =169 observations), R^{2b} = .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]	-

Intercept	-27.21	8.82	-3.09	.002	[-44.49, -9.93]	-
PTCI-World (N = 64 participants, N = 160 observations), R^{2b} = .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]	-
Intercept	-0.77	0.61	-1.27	.203	[-1.96, 0.42]	-

Note. CAPS = Clinician-Administered Posttraumatic Stress Disorder Scale; PTCI = Posttraumatic Cognitions Inventory; PTCI-Self = PTCI Negative Cognitions About Self subscale; PTCI-World = PTC Negative Cognitions About the World subscale.

[a]For ease of interpretation, standardized slopes were obtained by standardizing all variables, except time, in each model to M = 0, SD = 1. [b]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.

TABLE 3

Time-lagged mixed-effects regression analyses during treatment period in prolonged exposure plus sertraline study arm

Response variable	*B*	*SE*	*z*	*p*	95% CI	*d*[a]
Association between CAPS and PTCI-Self						
CAPS (N = 56 participants, n = 151 observations), R^{2b} = .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]	-
Intercept	31.47	9.89	3.18	< .001	[12.09, 50.84]	-
PTCI-Self (N = 55 participants, n = 145 observations), R^{2b} = .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]	-
Intercept	-0.25	0.53	-0.46	.643	[-1.29, 0.80]	-
Association between CAPS and PTCI-World						
CAPS (N = 56 participants, n = 151 observations), R^{2b} = .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]	-
Intercept	23.80	10.00	2.38	.017	[4.21, 43.39]	-
PTCI-World (N = 55 participants, n = 145 observations), R^{2b} = .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]	-
Intercept	0.03	0.72	0.04	.966	[-1.39, 1.45]	-

Note. CAPS = Clinician-Administered Posttraumatic Stress Disorder Scale; PTCI = Posttraumatic Cognitions Inventory; PTCI-Self = PTCI Negative Cognitions About Self subscale; PTCI-World = PTC Negative Cognitions About the World subscale.

[a]For ease of interpretation, standardized slopes were obtained by standardizing all variables, except time, in each model to M = 0, SD = 1. [b]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.

TABLE 4

Time-lagged mixed-effects regression analyses during treatment period in prolonged-exposure plus pill placebo study arm

Response variable	*B*	*SE*	*z*	*p*	95% CI	*d*[a]
Association between CAPS and PTCI-Self						
CAPS (*N* = 53 participants, *n* =126 observations), R^{2b}=.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]	-
Intercept	-1.56	13.69	-0.11	.909	[-28.38, 25.26]	-
PTCI-Self (*N* = 51 participants, *n* = 116 observations), R^{2b} = .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]	-
Intercept	-0.21	0.63	-0.33	.743	[-1.45, 1.03]	-
Association between CAPS and PTCI-World						
CAPS (*N* = 53 participants, *n* = 126 observations), R^{2b} = .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]	-
Intercept	-6.26	13.63	-0.46	.646	[-32.97, 20.45]	-
PTCI-World (*N* = 51 participants, *n* = 116 observations), R^{2b} =.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]	-

Intercept	-0.31	0.79	-0.39	.697	[-1.85, 1.24]	-

Note. CAPS = Clinician-Administered Posttraumatic Stress Disorder Scale; PTCI = Posttraumatic Cognitions Inventory; PTCI-Self = PTCI Negative Cognitions About Self subscale; PTCI-World = PTC Negative Cognitions About the World subscale.

[a]For ease of interpretation, standardized slopes were obtained by standardizing all variables, except time, in each model to $M = 0$, $SD = 1$. [b]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.