Predictors of Response to Prolonged Exposure, Sertraline, and Their Combination for the Treatment of Military PTSD

Sheila A. M. Rauch, PhD[a,b,*]; H. Myra Kim, ScD[c]; Seth Lederman, MD[d]; Gregory Sullivan, MD[d]; Ron Acierno, PhD[e,f]; Peter W. Tuerk, PhD[g]; Naomi M. Simon, MD[h,i]; Margaret R. Venners, MPH, MSW[j,k]; Sonya B. Norman, PhD[l,m,n]; Carolyn B. Allard, PhD[o,p]; Katherine E. Porter, PhD[q,r]; Brian Martis, MD[m,s]; Eric Bui, MD[i,t]; and Amanda W. Baker, PhD[i,u]; for the PROGrESS Team

ABSTRACT

Objective: The current study is an analysis of predictors of posttraumatic stress disorder (PTSD) treatment response in a clinical trial comparing (1) prolonged exposure plus placebo (PE + PLB), (2) PE + sertraline (PE + SERT), and (3) sertraline + enhanced medication management (SERT + EMM) with predictors including time since trauma (TST), self-report of pain, alcohol use, baseline symptoms, and demographics.

Methods: Participants (N = 196) were veterans with combat-related PTSD (*DSM-IV-TR*) of at least 3 months' duration recruited between 2012 and 2016 from 4 sites in the 24-week PROlonGed ExpoSure and Sertraline (PROGrESS) clinical trial (assessments at weeks 0 [intake], 6, 12, 24, 36, and 52).

Results: Across treatment conditions, (1) longer TST was predictive of greater week 24 PTSD symptom improvement (β = 1.72, *P* = .01) after adjusting for baseline, (2) higher baseline pain severity was predictive of smaller symptom improvement (β = –2.96, *P* = .003), and (3) Hispanic patients showed greater improvement than non-Hispanic patients (β = 12.33, *P* = .03). No other baseline characteristics, including alcohol consumption, were significantly predictive of week 24 improvement. Comparison of TST by treatment condition revealed a significant relationship only in those randomized to the PE + SERT condition (β = 2.53, *P* = .03). Longitudinal analyses showed similar results.

Conclusions: The finding that longer TST shows larger symptom reductions is promising for PTSD patients who might not seek help for years following trauma. Higher baseline pain severity robustly predicted attenuated and slower response to all treatment conditions, suggesting a common neuropathologic substrate. Finally, in the current study, alcohol use did not impede the effectiveness of pharmacotherapy for PTSD.

Trial Registration: ClinicalTrials.gov identifier: NCT01524133

J Clin Psychiatry 2021;82(4):20m13752

To cite: Rauch SAM, Kim HM, Lederman S, et al. Predictors of response to prolonged exposure, sertraline, and their combination for the treatment of military PTSD. *J Clin Psychiatry*. 2021;82(4):20m13752.

To share: https://doi.org/10.4088/JCP.20m13752

[a]Mental Health Service Line, VA Atlanta Healthcare System, Decatur, Georgia
[b]Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, Georgia
[c]Consulting for Statistics, Computing and Analytics Research, University of Michigan, Ann Arbor, Michigan
[d]Tonix Pharmaceuticals Inc, New York, New York
[e]Mental Health Service Line, Ralph H. Johnson VA Medical Center, Charleston, South Carolina
[f]Department of Psychiatry & Behavioral Sciences, McGovern Medical School, University of Texas Health Sciences, Houston, Texas
[g]Department of Human Services, University of Virginia, Charlottesville, Virginia
[h]Department of Psychiatry, New York University Grossman School of Medicine, New York, New York
[i]Department of Psychiatry, Massachusetts General Hospital, Boston, Massachusetts
[j]National Center for PTSD, VA Palo Alto Medical Center, Menlo Park, California
[k]Research Service Line, VA Ann Arbor Healthcare System, Ann Arbor, Michigan
[l]National Center for PTSD, White River Junction VA Medical Center, White River Junction, Vermont
[m]Department of Psychiatry, University of California, San Diego, School of Medicine, La Jolla, California
[n]VA Center of Excellence for Stress and Mental Health, San Diego, California
[o]PhD Program, California School of Professional Psychology, Alliant International University, San Diego, California
[p]Research Service, VA San Diego Healthcare System, San Diego, California
[q]Department of Psychiatry, University of Michigan, Ann Arbor, Michigan
[r]Mental Health Service Line, VA Ann Arbor Healthcare System, Ann Arbor, Michigan
[s]Mental Health Care Line, VA San Diego Healthcare System, San Diego, California
[t]Department of Psychiatry, University of Caen Normandy & Caen University Hospital, Caen, France
[u]Department of Psychiatry, Harvard Medical School, Boston, Massachusetts
**Corresponding author:* Sheila A. M. Rauch, PhD, Emory University School of Medicine, 12 Executive Park, 3rd Floor, Atlanta, GA 30329 (sheila.a.m.rauch@emory.edu).

Clinical practice guidelines support both psychotherapy and certain medications as effective for posttraumatic stress disorder (PTSD).[1,2] Among psychotherapies, prolonged exposure therapy (PE)[3] has demonstrated efficacy across a wide range of patient presentations. Among pharmacotherapies, the US Food and Drug Administration has approved sertraline and paroxetine for treating PTSD; however, pharmacotherapy generally produces weaker outcomes than psychotherapies,[4] and some guideline groups (ie, US Office of Veterans Affairs/Department of Defense [VA/DoD]) consider evidence in support of their use insufficient or suggest that the aforementioned psychotherapies should be considered before these pharmacotherapies.[1]

The PROlonGed ExpoSure and Sertraline (PROGrESS) study[5] examined the comparative effectiveness of PE and sertraline for the treatment of PTSD among combat veterans and found all 3 conditions—prolonged exposure therapy plus placebo, prolonged exposure therapy plus sertraline, and sertraline plus enhanced medication management—produced significant and large reductions

Clinical Points

- Understanding patient level factors that predict response to posttraumatic stress disorder treatments (medication and psychotherapy) is critical to clinical decision-making, but few studies have examined this issue.
- Patients showed large treatment benefits across the conditions and baseline characteristics examined. Longer time since trauma and Hispanic ethnicity predicted better response, and higher reported pain at baseline predicted less response across conditions.

in PTSD over 6 months with no significant differences between conditions. Despite overall equivalence in outcomes, variability in response is apparent and examination of whether certain baseline variables may predict greater response overall or greater response within a treatment condition is warranted.

Both epidemiologic and treatment literature suggest the likelihood of recovery or treatment response in PTSD may depend in part on the elapsed time since trauma (TST). McFarlane and colleagues[6] recently highlighted how chronic PTSD has a neurobiology that should be differentiated from that of acute disorder. The National Comorbidity Survey[7] indicated any mental health treatment was associated with an increased rate of recovery in the first 6 years compared to no treatment, but thereafter more than a third of persons failed to remit regardless of any reported treatment. A similar rate of PTSD persistence at 6-year follow-up was reported in the Millennium Cohort Study.[8]

While some psychotherapy trials found longer TST related to needing more sessions for response,[9,10] a meta-analysis of PE trials[11] failed to find an association between TST and outcomes. In Canadian combat veterans receiving outpatient care with psychotherapy and/or medication, Richardson et al[12] found no significant association between symptom chronicity/TST and poorer treatment response. A study of paroxetine for PTSD[13] reported a significant treatment-by-TST interaction such that those with TST greater than 5 years exhibited greater improvement with paroxetine. However, the authors cautioned that interpretation of the interaction was problematic due to a confounding high discontinuation rate in those with TST less than 5 years of 52% (5–19 years, 33%; 20 years, 27%). Previous studies with sertraline[14,15] did not report on the impact of TST on outcome, and as such the PROGrESS sample provides a unique opportunity.

With respect to additional predictors of PTSD treatment response, an association between pretreatment pain severity and intensity and posttreatment PTSD outcomes is emerging. Greater pain intensity predicted attenuated PTSD treatment response in a national sample of veterans (N = 2,715) receiving inpatient treatment at VA residential programs,[16] with similar findings among veterans receiving trauma-focused treatment.[17] Notably, greater pain interference, not pain intensity, predicted poorer PTSD treatment outcomes among refugees.[18] Accordingly, though pretreatment pain appears to be related to posttreatment PTSD outcomes, the experience of pain is nuanced and its relationship with PTSD may depend on pain context and the behavioral consequences of pain. Finally, pain has not been examined as a predictor of response in pharmacotherapy trials to date.

Studies related to the simultaneous treatment of PTSD and alcohol use disorder have indicated that PTSD symptoms predict attenuated substance use response, whereas the reverse has not been found, as alcohol use has not predicted PTSD treatment response.[19] The finding that alcohol use disorder is not predictive of PTSD treatment outcomes in trauma-focused therapy is often replicated in the literature for both integrated and PTSD-only treatment modalities.[20,21] Earlier evidence suggesting that alcohol use during treatment is associated with dropout[22] has not been broadly replicated, and a recent high-quality study[23] found that pretreatment number of days drinking did not predict dropout. Finally, alcohol and substance use have not been examined as predictors of response in pharmacotherapy studies to date.

Additional predictors that have been studied include psychosocial variables. Phelps et al[24] studied 2,686 Australian veterans and found that higher guilt and depression at baseline were associated with poorer outcomes, a finding replicated in a refugee population with PTSD.[25] Demographic predictors have shown mixed results. Lower age was associated with better SSRI response in a study of veterans,[26] though other studies show that lower age is related to higher dropout rates for psychotherapy.[27] Race and ethnicity have not been closely examined in pharmacotherapy studies, but McClendon et al[28] concluded that race and/or ethnicity does not appear to impact magnitude of symptom change in psychotherapy for PTSD but may impact initiation and retention, such that Black patients with PTSD are less likely to start and less likely to complete PTSD treatment. Previous studies[29,30] have not found gender differences in response to psychotherapy, though additional examination is warranted.

On the basis of this research, the current study aimed to examine these potentially predictive factors in an analysis of a large clinical trial focused on treatment of military/veteran PTSD. The primary aims of the analysis were to examine factors that may relate to overall treatment response both within and across treatment conditions. Primary hypotheses were (1) TST affects treatment response in those treated with sertraline (longer TST related to less PTSD reduction), but not in those treated with PE, whether PE is provided in combination with sertraline or with placebo; and (2) higher baseline levels of guilt, depression, pain intensity, and alcohol use will reduce magnitude of treatment response.

METHODS

Design

PROGrESS was a randomized controlled trial approved by site institutional review boards and DoD Human Research Protection Office (HRPO) and registered at ClinicalTrials.gov (NCT01524133). Participants provided informed consent. Participants and providers were blind to pill condition through week 24, and independent evaluators were blind

to treatment assignments for study duration (for detailed methods, see previously published articles[5,31]). The current study was an analysis of this large clinical trial examining predictors of PTSD treatment response in (1) prolonged exposure plus placebo (PE + PLB), (2) PE + sertraline (PE + SERT), and (3) sertraline + enhanced medication management (SERT + EMM), including TST, self-report of pain, alcohol use, and other demographics.

Participants

Participants were recruited between 2012 and 2016 from 4 sites: Veterans Affairs Ann Arbor Healthcare System, VA San Diego Healthcare System, Ralph H. Johnson VA Medical Center, and Massachusetts General Hospital (MGH). Inclusion criteria were being a service member or veteran of Iraq/Afghanistan wars with combat-related PTSD (*DSM-IV-TR*)[32] and significant impairment (Clinician Administered PTSD Scale [CAPS][33] score ≥ 50) of at least 3 months' duration. Exclusion criteria were (1) current, imminent risk of suicide; (2) active psychosis; (3) alcohol or substance dependence, but not abuse (past 8 weeks, as determined at intake that included medical record review and diagnostic assessment); (4) inability to attend weekly appointments for the treatment period; (5) prior intolerance or failure of adequate trial of PE or sertraline; (6) medical condition likely to result in imminent hospitalization or contraindication to study treatments; (7) serious cognitive impairment (eg, confusion, inability to track discussion); and (8) pregnancy. Concurrent antidepressants or antipsychotics, benzodiazepines, prazosin, and sleep agents (eg, zolpidem) were allowed if the dose was stable for 2 weeks by baseline,. For this study, the primary predictor was TST, and the analytic cohort included 196 patients with valid TST data.

Procedures

Full details of study methods, participant selection, randomization, blinding, and outcome assessments are published elsewhere.[5,31] Participants were unblinded after the week 24 assessment and offered continued treatment as needed.

Measures

Self-report and clinician-administered clinical measures occurred at weeks 0 (intake), 6, 12, 24, 36, and 52. The primary outcome was past-month PTSD symptom severity per the Clinician Administered PTSD Scale (CAPS) for *DSM-IV-TR*,[32] a clinician interview assessing symptom severity and diagnostic status. Current PTSD severity was assessed in relation to the target most distressing war-zone trauma. Patients also completed self-report assessments of PTSD symptoms (PTSD Symptom Checklist Specific Stressor Version [PCL-S][34]), level of alcohol use (number of alcoholic drinks per day), pain severity and intensity (Brief Pain Inventory [BPI][35]), depression (Beck Depression Inventory–Second Edition [BDI-II]), somatic symptom severity (15-symptom Patient Health Questionnaire [PHQ-15][36]), and guilt cognitions (Trauma Related Guilt Inventory [TRGI][37]). The primary predictor, TST, was calculated as number of years elapsed between the most stressful event identified at baseline in the PCL-S to the study enrollment date. For this study, target trauma was required to be a post–September 11, 2001, combat trauma. Additional biological measures were assessed and are reported elsewhere.[38–41]

Treatment

Active treatment started at week 0 and continued through week 24. Sertraline was titrated through week 10 and maintained through week 24. For those assigned to PE, participants were scheduled to complete 13 standard, 90-minute PE sessions by week 12 and allowed to complete by week 24, and expected to complete between-session assignments per standard PE protocol. For pharmacotherapy, sertraline and placebo doses were flexibly adjusted between 50 and 200 mg/d, with the last dose increase at week 10 to ensure stable dosing by week 12 and continued to week 24. EMM was approximately 30 minutes for those randomized to sertraline alone to balance time, psychoeducation, and provider support compared with PE conditions,[31] adding 15 minutes of psychoeducation and/or active listening to the 15-minute routine medical management.

Statistical Analyses

Primary outcome was treatment response at week 24 measured as CAPS score change, and to understand the long-term impact, analysis was repeated with all posttreatment follow-up CAPS scores assessed at weeks 24, 36, and 52 as the outcomes. The primary predictor was TST, and other potential baseline predictors were demographic variables (age, race, ethnicity, sex), alcohol use (number of alcoholic drinks per day), pain severity, pain intensity, depression, somatic symptom severity, and guilt cognitions.

As TST could be a proxy for mental and physical health symptom severity, we first assessed correlations between TST and baseline psychopathology measures. We also graphed the relationship between week 24 CAPS score and TST and other baseline psychopathology measures by treatment conditions to assess for functional relationships between the predictors and treatment responses and to see if the relationships differ by treatment condition. To examine predictors of week 24 treatment response, we used a multiple regression model with change in CAPS score as the response variable and adjusted for study site (stratification factor), treatment arms, and baseline CAPS values.

We assessed if the relationship between TST and treatment response varied by treatment condition using the interactions of TST by treatment condition indicators. Other predictors included age, race/ethnicity, and baseline psychopathology measures. For the analysis of long-term posttreatment follow-up symptoms, we used a mixed model with CAPS score changes at weeks 24, 36, and 52 as the response variables and accounted for within-person correlation of repeatedly assessed data using random intercepts. In addition to baseline predictors, the mixed model included time (weeks) since enrollment to account for trends in symptoms over time, and

Table 1. Baseline Characteristics of the Study Cohort, by Treatment Conditions and Overall (N = 196)

Variable	SERT + EMM[a] (n = 68)	PE + PLB[a] (n = 65)	PE + SERT[a] (n = 63)	Total[a] (n = 196)	*P* Value[b]
Age, y	33.7 (8.2)	34.8 (8.3)	34.7 (8.5)	34.4 (8.4)	.43
Male, n (%)	63 (92.6)	58 (89.2)	52 (82.5)	173 (88.3)	.47
Race, n (%)					.88
White	41 (60.3)	36 (55.4)	37 (58.7)	114 (58.2)	
Black	19 (27.9)	18 (27.7)	19 (30.2)	56 (28.6)	
Other	8 (11.8)	11 (16.9)	7 (11.1)	26 (13.3)	
Hispanic or Latino ethnicity, n (%)	14 (20.6)	7 (10.8)	10 (15.9)	31 (15.8)	.10
Marital status,[c] n (%)					.10
Married	40 (59.7)	35 (53.8)	27 (42.9)	99 (50.8)	
Never married	18 (26.9)	11 (16.9)	14 (22.2)	43 (22.1)	
Divorced	8 (11.9)	14 (21.5)	15 (23.8)	37 (19.0)	
Separated	1 (1.5)	5 (7.7)	7 (11.1)	13 (6.7)	
Education, n (%)					.12
High school (or equivalent)	31 (45.6)	22 (33.8)	19 (30.2)	72 (36.7)	
Some college (13–15 y)	29 (42.6)	26 (40.0)	33 (52.4)	88 (44.9)	
Bachelor's or above (16+ y)	8 (11.8)	17 (26.2)	11 (17.5)	36 (18.4)	
Work status, n (%)					.89
Full time	34 (50.0)	33 (50.8)	32 (50.8)	99 (50.5)	
Part time	6 (8.8)	9 (13.8)	8 (12.7)	23 (11.7)	
Not working	28 (41.2)	23 (35.4)	23 (36.5)	74 (37.8)	
Time since trauma, y	7.2 (2.5)	7.3 (3.4)	6.9 (3.0)	7.2 (3.0)	.83
Clinician-observed symptoms (CAPS score)	74.4 (14.1)	80.5 (13.3)	76.1 (14.6)	77.0 (14.2)	.01
Self-reported PTSD symptoms (PCL-S score)	56.0 (10.2)	59.8 (9.6)	56.9 (11.5)	57.5 (10.5)	.03
Depression (BDI-II score)	22.9 (9.9)	27.2 (11.2)	23.6 (10.8)	24.6 (10.8)	.02
Somatic symptoms (PHQ_{15} score)[c]	12.3 (5.7)	13.2 (4.8)	13.1 (5.0)	12.8 (5.2)	.34
Pain severity (BPI score)[c]	4.1 (2.4)	4.9 (2.0)	4.7 (2.2)	4.6 (2.2)	.03
Guilt cognition (TRGI score)[c]	0.9 (0.7)	1.1 (0.8)	0.8 (0.6)	1.0 (0.7)	.06
No. of drinks per day[c]	2.9 (4.2)	2.6 (3.6)	2.7 (3.2)	2.7 (3.7)	.56

[a]Cell values are mean (SD) unless otherwise noted.
[b]*P* values are from comparing across the 3 treatment arms, stratified by site.
[c]One unknown marital status; 6 missing PHQ_{15} score, 8 missing BPI score, 10 missing TRGI score, 4 missing drinking data.
Abbreviations: BDI-II = Beck Depression Inventory–-Second Edition; BPI = Brief Pain Inventory; CAPS = Clinician-Administered PTSD Scale, total score from 17 items for the past month; EMM = enhanced medication management, PCL-S = PTSD Checklist Specific Stressor Version; PE = prolonged exposure; PLB = placebo; PHQ_{15} = 15-symptom Patient Health Questionnaire; PTSD = posttraumatic stress disorder; SERT = sertraline; TRGI = Trauma Related Guilt Inventory.

similar to the analysis of week 24 treatment response, we further assessed if the relationship between TST and long-term treatment response varied by treatment condition using interactions.

Based on 134 patients with non-missing week 24 CAPS data, a conservative power analysis of this study yields 80% power to detect with a .05 level test an increase in R^2 value of 0.049 or larger, given 0.13 as the R^2 value in the reduced model that includes control variables of study site, treatment arms, and baseline CAPS values.

RESULTS

A total of 207 patients were randomized to 3 treatment conditions and dispensed medication. This study included 196 patients (95%) whose TST could be calculated properly. The range of TST was as recent as 0.5 years to as distant as 14.9 years, with both mean and median of 7.2 years (Table 1). Patient demographics were generally balanced across treatment conditions, but psychopathology measures showed that the PE + PLB condition patients had somewhat greater baseline symptoms, including PTSD symptoms, depression, and pain. Completion of week 24 CAPS did not differ significantly by treatment condition ($P = .10$).[5] In baseline analyses, we did not find TST to be associated with any psychopathology measures visually or statistically, including baseline CAPS score ($r = -0.005$, $P = .94$), except with a slight increase in pain ($r = 0.19$, $P = .008$) and in self-rated PTSD symptoms based on PCL-S ($r = 0.16$, $P = .02$) with increasing TST. All models were adjusted for baseline PCL-S values because of their association with TST.

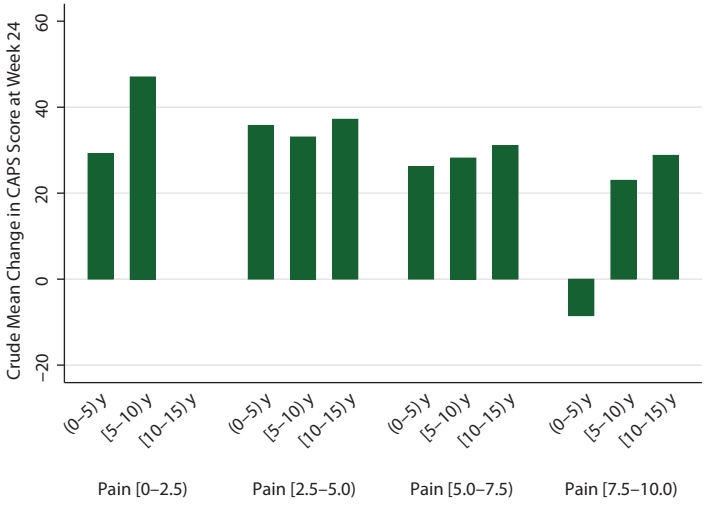
Overall across treatment conditions, longer TST was predictive of greater week 24 PTSD symptom improvement ($\beta = 1.72$, $P = .01$; Table 2) after adjusting for baseline demographic variables and psychopathology measures; the slope can be interpreted as 1.72-point greater improvement in CAPS score at week 24 with each additional year of TST while holding other covariates constant. Baseline pain severity was also predictive of overall treatment response. Symptom improvement was lower by −2.96 points ($P = .003$) with incremental 1-unit increase in baseline pain severity, which can range from 0 to 10. Overall, Hispanic patients also showed greater improvement than non-Hispanic patients by 12.33 points on the CAPS at week 24 ($P = .03$). No other baseline characteristics examined, including alcohol consumption, were significantly predictive of week 24 symptom improvement. We refit the model without adjusting for PCL-S score and found the results to be consistent for TST ($\beta = 1.65$, $P = .02$), pain severity (−3.17, $P = .001$), and Hispanic ethnicity (11.98, $P = .03$). To illustrate

Table 2. Multiple Regression Model of Symptom Improvement at Week 24, Calculated as CAPS Score at Baseline Minus CAPS Score at Week 24 (n = 134)[a]

Week 24 CAPS Score Change[b]	β	SE	*T*	*P* value	95% CI
Baseline CAPS score	**0.49**	**0.18**	**2.75**	**.007**	**0.14 to 0.84**
PE + placebo (reference: SERT)	−2.50	4.63	−0.54	.59	−11.67 to 6.67
PE + SERT (reference: SERT)	−0.22	4.34	−0.05	.96	−8.82 to 8.38
Time since trauma, y	**1.72**	**0.68**	**2.52**	**.01**	**0.37 to 0.06**
Black (reference: White)	−3.68	5.35	−0.69	.49	−14.28 to 6.93
Other or unknown race (reference: White)	−8.90	6.93	−1.28	.20	−22.63 to 4.83
Hispanic	**12.33**	**5.43**	**2.27**	**.03**	**1.58 to 23.09**
Age (y) at randomization	−0.16	0.25	−0.64	.52	−0.65 to 0.33
Self-reported PTSD symptoms (PCL-S score)	−0.42	0.28	−1.48	.14	−0.98 to 0.14
Depression (BDI-II total score)	0.25	0.24	1.04	.30	−0.23 to 0.74
Somatic symptom (PHQ_{15} score)	−0.24	0.46	−0.52	.60	−1.16 to 0.67
Pain severity (BPI score)	**−2.96**	**0.98**	**−3.03**	**.003**	**−4.89 to −1.02**
Guilt cognition (TRGI score)	−3.74	2.92	−1.28	.20	−9.53 to 2.05
No. of drinking days	−0.50	0.33	−1.50	.14	−1.16 to 0.16
Intercept	**31.21**	**15.74**	**1.98**	**.05**	**0.03 to 62.40**

[a]Boldface indicates statistical significance.
[b]The model was also adjusted for study site (stratification factor).
Abbreviations: BDI-II = Beck Depression Inventory–Second Edition; BPI = Brief Pain Inventory; CAPS = Clinician-Administered PTSD Scale, total score from 17 items for the past month; PE = prolonged exposure; PCL-S = PTSD Checklist Specific Stressor Version; PHQ_{15} = 15-symptom Patient Health Questionnaire; PTSD = posttraumatic stress disorder; SE = standard error; SERT = sertraline; TRGI = Trauma Related Guilt Inventory.

Figure 1. Unadjusted Mean Change in CAPS Score at Week 24 by BPI Pain Severity Score Categories and by Time Since Trauma Categories[a]



[a]No person with 10–15 years since trauma had pain severity scores between 0 and 2.5.
Abbreviations: BPI = Brief Pain Inventory, CAPS = Clinician Administered PTSD Scale.

the effect of TST and baseline pain severity on week 24 symptom improvement seen in the regression model, Figure 1 shows means of week 24 CAPS change over 5 baseline BPI pain severity categories—[0–2.5), [2.5–5.0), [5.0–7.5), or [7.5–10.0)—and 3 TST categories—(0–5) years, [5–10) years, or [10–15) years since trauma). Supplementary Figure 1 also shows the predicted adjusted changes in CAPS score based on the model in the 4 subgroups of those with recent trauma with less severe pain (mean = 33.83; 95% CI, 26.65–41.00), recent trauma with severe pain (mean = 18.91; 95% CI, 8.99–28.83), distant trauma with less severe pain (mean = 42.55; 95% CI, 34.05–51.05), and distant trauma with severe pain (mean = 27.63; 95% CI, 16.60–38.66) in otherwise average study participants.

Effects in Treatment Conditions

When we assessed relationships between TST and symptom improvement by treatment condition, we found TST to be a significant predictor of symptom improvement in those randomized to the PE + SERT condition (β = 2.53, *P* = .03). The TST slopes were not significant in the PE + PLB condition (β = 1.54) and SERT + EMM condition (β = 0.94), although the directions of the relationship remained positive (see Supplementary Table 1).

Longitudinal Analyses at 1 Year

In longitudinal data analysis of symptom changes at all posttreatment assessment times, we found similar results showing greater posttreatment symptom improvement

Table 3. Longitudinal Data Mixed Model of Symptom Improvement at Weeks 24, 36, and 52, Calculated as CAPS Score at Baseline Minus CAPS Score at Follow-Up Weeks (n = 142)[a]

CAPS Score Change[b]	β	SE	*T*	*P* Value	95% CI
Time,[c] wk	0.07	0.05	1.23	.22	−0.04 to 0.18
Baseline CAPS score	0.40	0.16	2.56	.01	0.09 to.71
PE + placebo (reference: SERT)	1.53	4.11	0.37	.71	−6.53 to 9.58
PE + SERT (reference: SERT)	4.99	3.87	1.29	.20	−2.60 to 12.58
Time since trauma, y	**1.56**	**0.59**	**2.62**	**.009**	**0.39 to 2.72**
Black (reference: White)	−3.56	4.56	−0.78	.44	−12.48 to 5.37
Other or unknown race (reference: White)	−3.96	6.04	−0.66	.51	−15.79 to 7.88
Hispanic	**11.12**	**4.77**	**2.33**	**.02**	**1.76 to 20.48**
Age (y) at randomization	−0.29	0.21	−1.36	.17	−0.71 to 0.13
Self-reported PTSD symptoms (PCL-S score)	−0.18	0.25	−0.71	.48	−0.66 to 0.31
Depression (BDI-II total score)	0.04	0.22	0.19	.85	−0.39 to 0.47
Somatic symptom (PHQ_{15} score)	−0.34	0.42	−0.83	.41	−1.16 to 0.47
Pain severity (BPI score)	**-2.41**	**0.86**	**-2.82**	**.005**	**−4.09 to −0.73**
Guilt cognition (TRGI score)	−3.16	2.64	−1.19	.23	−8.33 to 2.02
No. of drinking days	−0.35	0.28	−1.22	.22	−0.90 to 0.21
Intercept	28.30	13.95	2.03	.04	0.95 to 55.62

[a]Boldface indicates statistical significance.
[b]The model was adjusted also for study site (stratification factor).
[c]Time since randomization, centered at week 24, ie, the value corresponds to 0 for week 24.
Abbreviations: BDI-II = Beck Depression Inventory–Second Edition; BPI = Brief Pain Inventory; PCL-S = PTSD Checklist Specific Stressor Version; PE = prolonged exposure; PTSD = posttraumatic stress disorder; SE = standard error; SERT = sertraline; PHQ_{15} = 15-symptom Patient Health Questionnaire; TRGI = Trauma Related Guilt Inventory.

associated with longer TST (Table 3). Specifically, the slope of TST was 1.56 ($P = .009$), indicating that a 1.56-point greater CAPS score drop was expected with each year increase in TST across posttreatment follow-up time and treatment condition and holding other baseline characteristics constant. Of note, and as expected since this is a follow-up maintenance phase, neither time nor treatment condition was significant. Results in terms of other predictors were also similar to the findings from the analysis of the primary outcome of week 24 CAPS score. Baseline pain severity remained significantly predictive of posttreatment symptoms; symptom improvement was lower with increasing baseline pain severity ($\beta = -2.41$, $P = .005$). Hispanic patients had 11.12 points' ($P = .02$) greater improvement in CAPS score than did non-Hispanic patients, and alcohol consumption (number of drinking days) was not significant. As the analytic sample is reduced by the model requiring follow-up CAPS data, to ensure consistent findings from a model that includes a larger analytic sample, we also conducted an alternate analysis by fitting a model with not only follow-up, but also baseline CAPS scores as response variables, and the findings were consistent (Supplementary Table 2).

When we further assessed for relationships between TST and posttreatment symptom improvement by treatment condition, we found somewhat different results from those of the primary outcome. We found TST slopes to be nearly identical for the two PE conditions; slopes were 1.82 in the PE + PLB condition and 1.86 in the PE + SERT condition ($P = .97$ for test of slope difference). In further analysis, when the model was fit with the two PE conditions combined, TST slope was significant (slope = 1.84, $P = .008$) in the combined PE conditions, but not in the SERT + EMM condition (slope = 0.77, $P = .51$; $P = .44$ for slope difference). This finding somewhat contrasts with the differential relationship seen with the primary outcome, in which the association between TST and week 24 symptom improvement was greatest in the PE + SERT condition.

DISCUSSION

In the current study examining predictors of comparative effectiveness of PE, sertraline, and their combination, longer TST was associated with larger PTSD symptom reduction in treatment. This effect was stronger in the combined PE + SERT condition and remained consistent during follow-up. These results are promising for PTSD patients, as most do not seek treatment until 5 to 6 years posttrauma.[7] Similarly, an unpublished clinical trial of sublingual cyclobenzaprine in military-related PTSD sample (ClinicalTrials.gov identifier: NCT03062540; 80% with combat PTSD) failed to demonstrate a significant effect on change in score on the CAPS for *DSM-5* (CAPS-5) across 12 weeks, but post hoc analyses showed the subgroup with TST less than 9 years showed substantial and clinically meaningful improvement over placebo on the CAPS-5. Thus, certain medications may show differential efficacy based on TST. Replication and clarification of mechanisms are warranted.

Baseline pain severity predicted attenuated response to all treatment conditions. Of note, patients reporting even high levels of baseline pain severity still responded to all treatment conditions, but the response was not as large over the course of care and 1-year follow-up. Neurobiological correlates of treatment response suggest that allopregnanolone and related neurosterioids may play a role in both perception of pain and extinction learning that is critical to PTSD treatment response.[42] Additional research is needed to determine why this association occurs and whether addressing chronic pain

simultaneously with PTSD may reverse this disparity.

As described in our analytic plan, we first assessed correlations between TST and baseline psychopathology measures to determine whether TST could be a proxy for mental and physical health symptom severity, as would be indicated if TST had high correlations across these other physical and mental health measures. Because most of these correlations were nonsignificant, and only baseline pain severity and self-reported PTSD severity were related to TST, we concluded that there is something more specific than a general distress relationship. Specifically, it appears that as time since trauma lengthens, reported pain and PTSD increase.

In addition, Hispanic patients showed larger response across all conditions, while other demographics did not influence treatment response. Previous studies have not consistently examined ethnicity and other demographics to determine predictive effects, and those that have examined them have often found contradictory results.[28,43] Replication is necessary.

We did not find alcohol use at baseline to be associated with response. This finding is consistent previous PTSD treatment studies,[19] and this study is the first to our knowledge to also show that level of alcohol use does not impede the effectiveness of evidence-based pharmacotherapy for PTSD. While our sample did not include the most severe levels of alcohol use disorder, which were excluded from entry, within the wide range of use represented, our study provides evidence that alcohol use below the level of dependence should not hinder patients with PTSD from receiving their preferred evidence-based PTSD treatment. Of note, our focus was symptom change over treatment duration, and as such we did not examine the impact of baseline alcohol use on attrition.

Limitations are also apparent. The current study required recruitment of patients willing to engage in PE and/or sertraline who were not already taking medication. Replication in a clinical care sample to ensure the findings translate to standard care is warranted. In addition, replication in a larger sample to examine the multifactorial effects of these predictors is needed.

Submitted: November 5, 2020; accepted January 11, 2021.

Published online: June 15, 2021.

Author contributions: Drs Kim and Powell had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Potential conflicts of interest: **Dr Rauch** receives support from Wounded Warrior Project (WWP), Department of Veterans Affairs (VA), National Institutes of Health (NIH), McCormick Foundation, Tonix Pharmaceuticals, Woodruff Foundation, and US Department of Defense (DoD), and receives royalties from Oxford University Press and American Psychological Association Press. **Drs Lederman** and **Sullivan** are both employees of Tonix Pharmaceuticals and own stock in the company. **Dr Simon** has received funding from the American Foundation for Suicide Prevention, DoD, Highland Street Foundation, NIH, and Janssen and has been a speaker for MGH Psychiatry Academy, Axovant Sciences, and Springworks Therapeutics, and her spouse has an equity stake in G1 Therapeutics. **Dr Norman** received support from VA, DoD, NIH, and Patient Centered Outcomes Research Institute and royalties from Elsevier. **Dr Allard** receives royalties from Elsevier. **Dr Bui** received grant support from DoD, NIH, and Patient Centered Outcomes Research Institute and royalties from Springer and Wolters Kluwer. **Drs Kim**, **Acierno**, **Tuerk**, **Porter**, **Martis**, and **Baker** and **Ms Venners** have nothing to disclose.

Funding/support: This work was supported by the DoD through the US 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: Dr Rauch); the National Center for Advancing Translational Sciences of the NIH (Award #UL1TR000433); and Tonix Pharmaceuticals. 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.

Role of the sponsor: The DoD had a role in design in that they wanted the study to include only OEF/OIF/OND service members with combat-related PTSD. The DoD had no role in the conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. National Center for Advancing Translational Sciences of the NIH had no role in the conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. Tonix Pharmaceuticals collaborated on the analysis and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: 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 US Government, or the official views of the National Institutes of Health.

Supplementary material: Available at PSYCHIATRIST.COM.

REFERENCES

1. VA/DOD Clinical Practice Guideline for Management of Posttraumatic Stress Disorder and Acute Stress Disorder. US Department of Veterans Affairs. 2017. https://www.healthquality.va.gov/guidelines/MH/ptsd/VADoDPTSDCPGFinal.pdf
2. Clinical Practice Guideline for the Treatment of PTSD. American Psychological Association. 2017. https://www.apa.org/ptsd-guideline/ptsd.pdf
3. Foa EB, Rothbaum AO, Hembree EA, et al. In: Barlow DH, ed. *Prolonged Exposure Therapy for PTSD: Emotional Processing of Traumatic Experiences*. 2nd ed. New York, NY: Oxford University Press; 2019.
4. Lee DJ, Schnitzlein CW, Wolf JP, et al. Psychotherapy versus pharmacotherapy for PTSD: systemic review and meta-analyses to determine first-line treatments. *Depress Anxiety*. 2016;33:792–806.
5. Rauch SAM, Kim HM, Powell C, 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.
6. McFarlane AC, Lawrence-Wood E, Van Hooff M, et al. The need to take a staging approach to the biological mechanisms of PTSD and its treatment. *Curr Psychiatry Rep*. 2017;19(2):10.
7. Kessler RC, Sonnega A, Bromet E, et al. Posttraumatic stress disorder in the National Comorbidity Survey. *Arch Gen Psychiatry*. 1995;52(12):1048–1060.
8. Armenta RF, Rush T, LeardMann CA, et al; Millennium Cohort Study team. Factors associated with persistent posttraumatic stress disorder among US military service members and veterans. *BMC Psychiatry*. 2018;18(1):48.
9. Chard KM, Schumm JA, Owens GP, et al. A comparison of OEF and OIF veterans and Vietnam veterans receiving cognitive processing therapy. *J Trauma Stress*. 2010;23(1):25–32.
10. Galovski TE, Blain LM, Mott JM, et al. Manualized therapy for PTSD: flexing the structure of cognitive processing therapy. *J Consult Clin Psychol*. 2012;80(6):968–981.
11. Powers MB, Halpern JM, Ferenschak MP, et al. A meta-analytic review of prolonged exposure for posttraumatic stress disorder. *Clin Psychol Rev*. 2010;30(6):635–641.
12. Richardson JD, Elhai JD, Sarreen J. Predictors of treatment response in Canadian combat and peacekeeping veterans with military-related posttraumatic stress disorder. *J Nerv Ment Dis*. 2011;199(9):639–645.
13. Tucker P, Zaninelli R, Yehuda R, et al. Paroxetine in the treatment of chronic posttraumatic stress disorder: results of a placebo-controlled, flexible-dosage trial. *J Clin Psychiatry*. 2001;62(11):860–868.
14. Friedman MJ, Marmar CR, Baker DG, et al. Randomized, double-blind comparison of sertraline and placebo for posttraumatic stress disorder in a Department of Veterans Affairs setting. *J Clin Psychiatry*. 2007;68(5):711–720.
15. Davidson J, Pearlstein T, Londborg P, et al. Efficacy of sertraline in preventing relapse of posttraumatic stress disorder: results of a 28-week double-blind, placebo-controlled study.

Am J Psychiatry. 2001;158(12):1974–1981.
16. Sripada RK, Blow FC, Rauch SAM, et al. Examining the nonresponse phenomenon: Factors associated with treatment response in a national sample of veterans undergoing residential PTSD treatment. *J Anxiety Disord*. 2019;63:18–25.
17. Bartoszek G, Hannan SM, Kamm J, et al. Trauma-related pain, reexperiencing symptoms, and treatment of posttraumatic stress disorder: a longitudinal study of veterans. *J Trauma Stress*. 2017;30(3):288–295.
18. Nordin L, Perrin S. Pain and posttraumatic stress disorder in refugees who survived torture: the role of pain catastrophizing and trauma-related beliefs. *Eur J Pain*. 2019;23(8):1497–1506.
19. Back SE, Brady KT, Sonne SC, et al. Symptom improvement in co-occurring PTSD and alcohol dependence. *J Nerv Ment Dis*. 2006;194(9):690–696.
20. Bedard-Gilligan M, Garcia N, Zoellner LA, et al. Alcohol, cannabis, and other drug use: engagement and outcome in PTSD treatment. *Psychol Addict Behav*. 2018;32(3):277–288.
21. van Minnen A, Harned MS, Zoellner L, et al. Examining potential contraindications for prolonged exposure therapy for PTSD. *Eur J Psychotraumatol*. 2012;3(1):3.
22. van Minnen A, Arntz A, Keijsers GP. Prolonged exposure in patients with chronic PTSD: predictors of treatment outcome and dropout. *Behav Res Ther*. 2002;40(4):439–457.
23. Belleau EL, Chin EG, Wanklyn SG, et al. Pre-treatment predictors of dropout from prolonged exposure therapy in patients with chronic posttraumatic stress disorder and comorbid substance use disorders. *Behav Res Ther*. 2017;91:43–50.
24. Phelps AJ, Steele Z, Cowlishaw S, et al. Treatment outcomes for military veterans with posttraumatic stress disorder: response trajectories by symptom cluster. *J Trauma Stress*. 2018;31(3):401–409.
25. Haagen JFG, Ter Heide FJJ, Mooren TM, et al. Predicting post-traumatic stress disorder treatment response in refugees: multilevel analysis. *Br J Clin Psychol*. 2017;56(1):69–83.
26. Martenyi F, Brown EB, Zhang H, et al. Fluoxetine versus placebo in posttraumatic stress disorder. *J Clin Psychiatry*. 2002;63(3):199–206.
27. Eftekhari A, Crowley JJ, Mackintosh M-A, et al. Predicting treatment dropout among veterans receiving prolonged exposure therapy. *Psychol Trauma*. 2020;12(4):405–412.
28. McClendon J, Dean KE, Galovski T. Addressing diversity in PTSD treatment: disparities in treatment engagement and outcome among patients of color. *Curr Treat Options Psychiatry*. 2020;7(3):275–290.
29. Jaycox LH, Foa EB, Morral AR. Influence of emotional engagement and habituation on exposure therapy for PTSD. *J Consult Clin Psychol*. 1998;66(1):185–192.
30. Marks I, Lovell K, Noshirvani H, et al. Treatment of posttraumatic stress disorder by exposure and/or cognitive restructuring: a controlled study. *Arch Gen Psychiatry*. 1998;55(4):317–325.
31. Rauch SAM, Simon NM, Kim HM, et al. Integrating biological treatment mechanisms into randomized clinical trials: design of PROGrESS (PROlonGed ExpoSure and Sertraline Trial). *Contemp Clin Trials*. 2018;64:128–138.
32. American Psychiatric Association. *Diagnostic and Statistical Manual for Mental Disorders*. Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association; 2000.
33. Blake DD, Weathers FW, Nagy LM, et al. The development of a clinician-administered PTSD scale. *J Trauma Stress*. 1995;8(1):75–90.
34. Wilkins KC, Lang AJ, Norman SB. Synthesis of the psychometric properties of the PTSD checklist (PCL) military, civilian, and specific versions. *Depress Anxiety*. 2011;28(7):596–606.
35. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singapore*. 1994;23(2):129–138.
36. de Vroege L, Hoedeman R, Nuyen J, et al. Validation of the PHQ-15 for somatoform disorder in the occupational health care setting. *J Occup Rehabil*. 2012;22(1):51–58.
37. Kubany ES, Haynes SN, Abueg FR, et al. Development and validation of the Trauma-Related Guilt Inventory (TRGI). *Psychol Assess*. 1996;8(4):428–444.
38. Rauch SAM, King A, Kim HM, et al. Cortisol awakening response in PTSD treatment: predictor or mechanism of change. *Psychoneuroendocrinology*. 2020;118:104714.
39. Joshi SA, Duval ER, Sheynin J, et al. Neural correlates of emotional reactivity and regulation associated with treatment response in a randomized clinical trial for posttraumatic stress disorder. *Psychiatry Res Neuroimaging*. 2020;299:111062.
40. Duval ER, Sheynin J, King AP, et al. Neural function during emotion processing and modulation associated with treatment response in a randomized clinical trial for posttraumatic stress disorder. *Depress Anxiety*. 2020;37(7):670–681.
41. Sheynin J, Duval ER, King AP, et al. Associations between resting-state functional connectivity and treatment response in a randomized clinical trial for posttraumatic stress disorder. *Depress Anxiety*. 2020;37(10):1037–1046.
42. Joksimovic SL, Covey DF, Jevtovic-Todorovic V, et al. Neurosteroids in pain management: a new perspective on an old player. *Front Pharmacol*. 2018;9:1127.
43. Benuto LT, Bennett NM, Casas JB. Minority participation in randomized controlled trials for prolonged exposure therapy: a systematic review of the literature. *J Trauma Stress*. 2020;33(4):420–431.

See supplementary material for this article at PSYCHIATRIST.COM.

THE JOURNAL OF
CLINICAL PSYCHIATRY
THE OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF CLINICAL PSYCHOPHARMACOLOGY

Supplementary Material

Article Title: Predictors of Response to Prolonged Exposure, Sertraline, and Their Combination for the Treatment of Military PTSD

Author(s): Sheila A. M. Rauch, PhD; H. Myra Kim, ScD; Seth Lederman, MD; Gregory Sullivan, MD; Ron Acierno, PhD; Peter W. Tuerk, PhD; Naomi M. Simon, MD; Margaret R. Venners, MPH, MSW; Sonya Norman, PhD; Carolyn B. Allard, PhD; Katherine Porter, PhD; Brian Martis, MD; Eric Bui, MD; and Amanda Baker, PhD; for the PROGrESS Team

DOI Number: https://doi.org/10.4088/JCP.20m13752

List of Supplementary Material for the article

1. Figure 1 — Predicted adjusted mean change in CAPS at week 24 and 95% confidence intervals in average persons if they belong to each of the four subgroups defined by dichotomized time-since-trauma [recent (<9 years) vs. distant (≥9 years)) and baseline pain severity [less than severe (<6) vs. severe (≥6)]

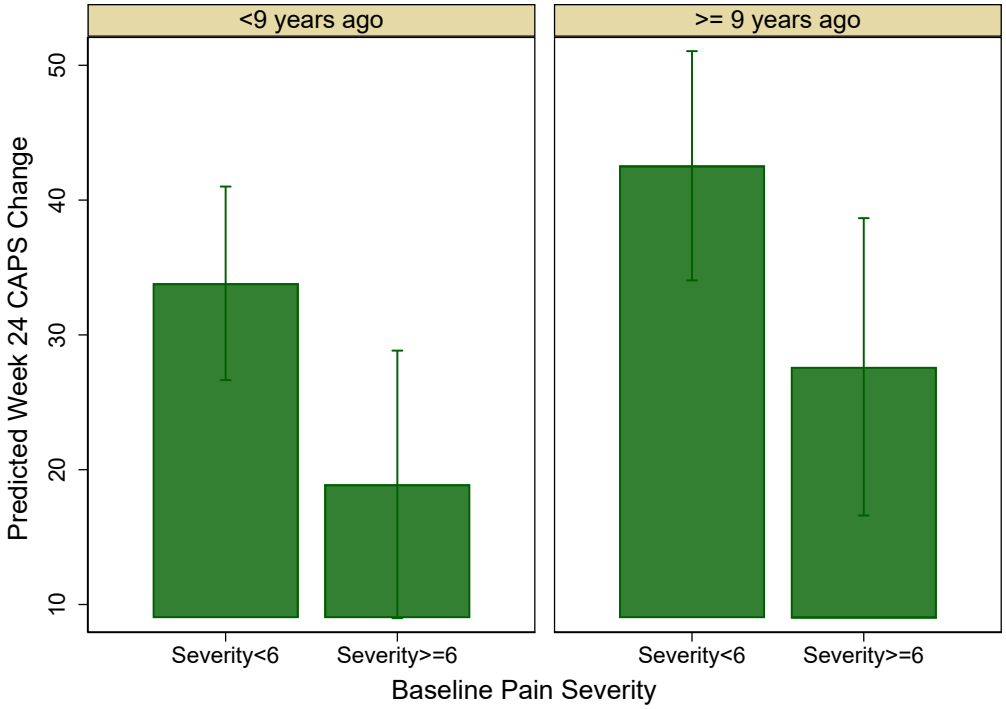
2. Table 1 — Multiple regression model of symptom improvement at week 24, calculated as CAPS at baseline minus CAPS at week 24 assessing differential effect of time-since-trauma on week 24 symptom change by treatment arms (N = 134)

3. Table 2 — Alternate model of outcomes during post-treatment follow-up period using mixed model with symptom at baseline and weeks 24, 36 and 52 as response variable (N=180)

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary Figure 1: Predicted adjusted mean change in CAPS at week 24 and 95% confidence intervals in average persons if they belong to each of the four subgroups defined by dichotomized time-since-trauma [recent (<9 years) vs. distant (≥9 years)) and baseline pain severity [less than severe (<6) vs. severe (≥6)]. Note that in the sample included in the model, 48.5% had recent trauma with less than severe pain, 15.7% had recent trauma with severe pain, 21.6% had distant trauma with less than severe pain and 14.2% had distant trauma with severe pain.



To illustrate the effect of TST and baseline pain severity on week 24 symptom improvement, we refit the model with the same predictors except using dichotomized TST (≥9 years-since-trauma vs. <9 years-since-trauma) and baseline pain severity (≥6 baseline pain severity vs. <6 baseline pain severity) instead of continuous variables. The model estimated 8.72 (p=0.04) greater improvement in CAPS in those with distant compared with recent trauma and 14.92 (p=0.02) lower improvement in CAPS in those with severe compared with less severe baseline pain after adjusting for all other variables. Figure 1 shows the predicted adjusted changes in CAPS based on the model in the four subgroups of those with recent trauma with less severe pain (mean=33.83; 95% CI=26.65, 41.00), recent trauma with severe pain (18.91; 8.99, 28.83), distant trauma with less severe pain (42.55; 34.05, 51.05), and distant trauma with severe pain (27.63; 16.60, 38.66) in otherwise average study participants.

Supplementary Table 1. Multiple regression model of symptom improvement at week 24, calculated as CAPS at baseline minus CAPS at week 24 assessing differential effect of time-since-trauma on week 24 symptom change by treatment arms (N = 134)

Week 24 CAPS Change[a]	**Beta**	**Std. Err.**	**T**	**p-value**	**95% CI**
Baseline CAPS	0.51	0.18	2.81	0.006	.15, .87
PE+Placebo	-6.91	13.64	-0.51	0.61	-33.93. 20.11
PE+SERT	-12.01	13.46	-0.89	0.37	-38.68, 14.66
Time-since-trauma slope by arms					
SERT	**0.94**	**1.34**	**-0.70**	**0.49**	**-1.71, 3.59**
PE+Placebo	**1.54**	**1.08**	**-1.42**	**0.16**	**-.61, 3.68**
PE+SERT	**2.53**	**1.12**	**-2.26**	**0.03**	**.31, 4.75**
Black (ref: White)	-4.33	5.42	-0.80	0.43	-15.07, 6.41
Other or unknown race (Ref: White)	-8.97	7.03	-1.28	0.21	-22.91, 4.97
Hispanic	**11.99**	**5.49**	**2.19**	**0.03**	**1.12, 22.86**
Age (years) at randomization	-0.20	0.25	-0.80	0.43	-.70, .30
Self-report PTSD symptom (PCL-S)	-0.46	0.29	-1.60	0.11	-1.03, .11
Depression (BDI-II Total)	0.28	0.25	1.11	0.27	-.22, .79
Somatic symptom (PHQ15)	-0.25	0.47	-0.52	0.60	-1.18, .69
Pain severity (BPI)	**-2.84**	**0.99**	**-2.87**	**0.01**	**-4.80, -.88**
Guilt cognition (TRGI)	-4.04	3.11	-1.30	0.20	-10.20, 2.13
Number of drinking days	-0.51	0.33	-1.54	0.13	-1.18, .15
Intercept	38.97	19.35	2.01	0.05	.63, 77.32

[a]The model was adjusted for study site as well (stratification factor). A test of time-since-trauma slope difference across treatment conditions was not significant (F=0.47, p=0.62).

Abbreviations: BDI-II is Beck Depression Inventory- Second Edition; BPI is brief pain inventory; CAPS is Clinician Administered PTSD Scale; PCL-S is PTSD Checklist Specific Stressor Version; PE is prolonged exposure; PHQ15 is 15-symptom Patient Health Questionnaire; PTSD is post traumatic symptom disorder; SERT is sertraline; TRGI is Trauma Related Guilt Inventory.

Supplementary Table 2. Alternate model of outcomes during post-treatment follow-up period using mixed model with symptom at baseline and weeks 24, 36 and 52 as response variable (N=180)

CAPS score[a]	**Beta**	**Std. Err.**	**T**	**p-value**	**95% CI**
Maintenance period[b] (Ref: Baseline)	-32.52	1.56	-20.91	<0.001	-35.57, -29.47
PE+Placebo	.47	2.76	0.17	0.87	-4.95, 5.89
PE+SERT	-3.35	2.70	-1.24	0.21	-8.64, 1.93
Time-since-trauma (years)	**-.89**[c]	**.40**	**-2.21**	**0.03**	**-1.68, -.10**
Black (ref: White)	3.95	3.12	1.27	0.21	-2.16, 10.06
Other or unknown race (Ref: White)	1.44	3.78	0.38	0.70	-5.96, 8.84
Hispanic	**-6.78**	**3.25**	**-2.09**	**0.04**	**-13.15, -.41**
Age (years) at randomization	.19	.15	1.28	0.20	-.10, .48
Self-report PTSD symptom (PCL-S)	.50	.16	3.22	0.001	.20, .81
Depression (BDI-II Total)	.24	.15	1.56	0.12	-.06, .53
Somatic symptom (PHQ15)	.30	.28	1.08	0.28	-.24, .84
Pain severity (BPI)	**1.51**	**.58**	**2.61**	**0.01**	**.38, 2.64**
Guilt cognition (TRGI)	2.67	1.79	1.49	0.14	-.84, 6.18
Number of drinking days	.36	.19	1.92	0.06	-.01, .74
Intercept	29.16	8.54	3.41	0.001	12.41, 45.90

[a]The model was adjusted for study site as well (stratification factor).
[b]Maintenance period is weeks 24, 36 and 52.
[c]The value is negative because CAPS (instead of change in CAPS) values at all follow-up times including baseline are response variables in this model and hence -.89 can be interpreted as 0.89 lower CAPS scores (lower symptoms) associated with each additional year-since-trauma.

Abbreviations: BDI-II is Beck Depression Inventory-Second Edition; BPI is brief pain inventory; PCL-S is PTSD Checklist Specific Stressor Version; PE is prolonged exposure; PHQ15 is 15-symptom Patient Health Questionnaire; ; PTSD is post traumatic symptom disorder; SERT is sertraline; TRGI is Trauma Related Guilt Inventory.