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Efficacy of Prolonged Exposure Therapy, Sertraline Hydrochloride, and Their Combination Among Combat Veterans With Posttraumatic Stress Disorder
A Randomized Clinical Trial

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IMPORTANCE Meta-analyses of treatments for posttraumatic stress disorder (PTSD) suggest that trauma-focused psychotherapies produce greater benefits than antidepressant medications alone.

OBJECTIVE To determine the relative efficacy of prolonged exposure therapy plus placebo, prolonged exposure therapy plus sertraline hydrochloride, and sertraline plus enhanced medication management in the treatment of PTSD.

DESIGN, SETTING, AND PARTICIPANTS The Prolonged Exposure and Sertraline Trial was a randomized, multisite, 24-week clinical trial conducted at the Veterans Affairs Ann Arbor Healthcare System, Veterans Affairs San Diego Healthcare System, Ralph H. Johnson Veterans Affairs Medical Center, and Massachusetts General Hospital Home Base Veterans Program between January 26, 2012, and May 9, 2016. Participants and clinicians were blinded to pill condition, and outcome evaluators were blinded to assignment. Participants completed assessments at weeks 0 (intake), 6, 12, 24, and 52 (follow-up). Participants (N = 223) were service members or veterans of the Iraq and/or Afghanistan wars with combat-related PTSD and significant impairment (Clinician-Administered PTSD Scale score, ≥50) of at least 3 months' duration. Analyses were on an intent-to-treat basis.

INTERVENTION Participants completed up to thirteen 90-minute sessions of prolonged exposure therapy by week 24. Sertraline dosage was titrated during a 10-week period and continued until week 24; medication management was manualized.

MAIN OUTCOMES AND MEASURES The primary outcome was symptom severity of PTSD in the past month as assessed by the Clinician-Administered PTSD Scale score at week 24.

RESULTS Of 223 randomized participants, 149 completed the study at 24 weeks, and 207 (180 men and 27 women; mean [SD] age, 34.5 [8.3 years]) were included in the intent-to-treat analysis. Modified intent-to-treat analysis using a mixed model of repeated measures showed that PTSD symptoms decreased significantly during the 24 weeks (sertraline plus enhanced medication management, 33.8 points; prolonged exposure therapy plus sertraline, 32.7 points; and prolonged exposure therapy plus placebo, 29.4 points; β, −9.39; 95% CI, −11.62 to −7.16; P < .001); however, slopes did not differ by treatment group (prolonged exposure therapy plus placebo group, −9.39; sertraline plus enhanced medication management group, −10.37; and prolonged exposure therapy plus sertraline group, −9.99; P = .81).

CONCLUSIONS AND RELEVANCE No difference in change in PTSD symptoms or symptom severity at 24 weeks was found between sertraline plus enhanced medication management, prolonged exposure therapy plus placebo, and prolonged exposure therapy plus sertraline.

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clinical practice guidelines for posttraumatic stress disorder (PTSD) have presented both trauma-focused psychotherapies and selective serotonin reuptake inhibitors (SSRIs) as effective, strongly recommended treatments.1-3 The American Psychological Association4 and the Veterans Affairs (VA) and Department of Defense recommended trauma-focused psychotherapy vs medication for the treatment of PTSD1 based on meta-analyses comparing effect sizes across studies that rarely involved direct head-to-head comparisons of psychotherapy vs medication.5,6 Without direct comparisons, effect sizes across studies may not accurately reflect efficacy, owing to differences in study designs and comparators. Furthermore, although combined medication and psychotherapy is the most common treatment practice for veterans with PTSD,7 current guidelines are unable to make specific recommendations.8 The few extant comparisons of trauma-focused psychotherapy vs SSRIs or combined treatment have significant limitations in design or generalizability or have focused on refractory conditions or augmentation strategies.9-14

The present study was designed to address these critical gaps in guidance for clinicians, especially those who serve military service members and veterans. The study provides a comparison of 2 effective treatments for PTSD—prolonged exposure therapy and sertraline hydrochloride—and whether their combination enhances either treatment alone. Prolonged exposure therapy was selected owing to the abundance of research supporting its efficacy.1,15 Of the 2 SSRIs approved by the US Food and Drug Administration for the treatment of PTSD,1 sertraline is generally tolerated better than paroxetine hydrochloride and has more robust data on long-term efficacy.5,6 To control for placebo effects and nonspecific effects of therapy (eg, therapist alliance or consistency of administration), prolonged exposure therapy was combined with pill placebo or sertraline (double-blinded), and sertraline was administered using a manualized enhanced medication management protocol.17 In this context, sertraline and prolonged exposure therapy plus sertraline were administered under matched conditions, with psychotherapists and pharmacotherapists administering treatment modalities according to manualized protocols, under expert supervision. We examined the relative efficacy of prolonged exposure therapy plus placebo, prolonged exposure therapy plus sertraline, and sertraline plus enhanced medication management among 223 veterans with combat-related PTSD on our primary outcome of PTSD severity as assessed by blinded clinicians18 and on our secondary outcomes of clinically meaningful change, remission, response, and self-reported PTSD.19

Based on previous studies,20 we hypothesized that larger reductions in symptom severity would be achieved with prolonged exposure therapy plus sertraline than with prolonged exposure therapy plus placebo and that larger reductions in symptom severity would be achieved with prolonged exposure therapy plus placebo than with sertraline plus enhanced medication management. Finally, based on concerns that sertraline might interfere with learning and reducing symptom severity using prolonged exposure therapy, we hypothesized that treatment dropout in the group treated with prolonged exposure therapy plus sertraline would be greater than in either the group treated with sertraline plus enhanced medication management or the group treated with prolonged exposure therapy plus placebo.

**Methods**

**Design**

The Prolonged Exposure and Sertraline Trial (PROGrESS) is a randomized clinical trial approved by the institutional review boards at the Veterans Affairs Ann Arbor Healthcare System, the Veterans Affairs San Diego Healthcare System, the Ralph H. Johnson Veterans Affairs Medical Center, and the Massachusetts General Hospital Home Base Veterans Program and the Department of Defense Human Research Protection Office. The study is registered at ClinicalTrials.gov, and the trial protocol is available in Supplement 1. A data safety and monitoring board reviewed the conduct of the study. Participants provided written informed consent before enrollment. Participants and clinicians were blinded to pill condition through week 24, and independent evaluators were blinded to treatment assignments for the duration of the study.

**Participants**

Participants were recruited from the following 4 sites: the Veterans Affairs Ann Arbor Healthcare System, the Veterans Affairs San Diego Healthcare System, the Ralph H. Johnson Veterans Affairs Medical Center, and the Massachusetts General Hospital Home Base Veterans Program. Inclusion criteria were service members or veterans of the Iraq or Afghanistan wars with combat-related PTSD and significant impairment (Clinicians-Administered PTSD Scale [CAPS] score, ≥50) of at least 3 months’ duration. Exclusion criteria were the following: (1) current, imminent risk of suicide; (2) active psychosis; (3) alcohol or substance dependence (in the past 8 weeks); (4) inability to attend weekly appointments for the treatment period; (5) prior intolerance to or failure of adequate trial of prolonged exposure therapy or sertraline; (6) medical illness likely to result in imminent hospitalization or contraindication to study treatments; (7) serious cognitive impairment.
meaningful change was defined as a reduction of 20 points or more in the CAPS score or a CAPS score of 35 or less, response was defined as a reduction of 50% or more in CAPS score, and remission was defined as a CAPS score of 35 or less; all definitions are based on week 24 or last observed CAPS score up to week 24.

Procedures
Full details of the study methods, selection of participants, randomization, blinding, and outcome assessments are published elsewhere. Key procedures are reviewed here. Veterans and service members recruited between January 26, 2012, and May 9, 2016, were assessed with a review of their medical records, CAPS, and the Mini International Neuropsychiatric Interview. Once eligibility was determined, randomization (with masked allocation) occurred using a secure centralized interactive web-based application (Treatment Assignment Tool; University of Michigan). Randomization was stratified by site with treatment assignments randomly permuted in varying block sizes within the site.

Maintenance of the blinding was prioritized. All pills were encapsulated to protect the blinding. All evaluators were blinded to both medication and therapy assignments. Only 19 unblinding incidents occurred, with an alternate evaluator assigned for those cases. Independent evaluators completed training and achieved 90% or more agreement on CAPS prior to conducting assessments. Interrater reliability was conducted throughout the study period on 20% of randomly selected taped CAPS and Mini International Neuropsychiatric Interview assessments. Correlations on the CAPS ranged from 0.98 to 0.99, and the percentage agreement for Mini International Neuropsychiatric Interview diagnostic outcomes was 85% to 100%, with a \( \kappa \) coefficient of 0.86 for major depressive episode and 0.85 for generalized anxiety disorder. All raters attended fidelity calls to ensure consistency of rating across sites and over time. Calls occurred bimonthly for CAPS and annually for the Mini International Neuropsychiatric Interview. After completion of week 24 outcome measures, patients and clinicians were unblinded, and participants were offered open prolonged exposure therapy and/or sertraline or treatment outside of the study. Participants received $50 per assessment for weeks 0 (intake), 6, 12, 24, and 52.

Measures
Self-report and clinician-administered clinical measures occurred at weeks 0 (intake), 6, 12, 24, 36, and 52. Blinding was broken at week 24.

The primary outcome was severity of PTSD symptoms in the past month measured by the CAPS, a clinician interview assessing symptom severity and diagnostic status. Current severity of PTSD symptoms was assessed in relation to targeting the most distressing war zone trauma. The DSM IV-TR CAPS version was used, as the DSM-5 was not available at study initiation.

The secondary outcome was self-reported symptoms of PTSD (PTSD Checklist [PCL] Specific Stressor Version), clinically meaningful change, response, and remission. Clinically

Pharmacotherapy
Medication doses were flexibly adjusted between 50 and 200 mg/d, with the last dosage increase at week 10 to ensure stable dosing by week 12. Medication was continued until week 24. Medication management (sertraline or placebo) was fully manualized to standardize pharmacotherapy delivery as brief (approximately 15 minutes) medication management, when administered alongside prolonged exposure therapy, or as enhanced medication management. Enhanced medication management was approximately 30 minutes for those randomized to receive sertraline alone to balance time, psychoeducation, and clinician support compared with prolonged exposure therapy conditions. Thus, enhanced medication management added 15 minutes of psychoeducation and/or active listening to the 15-minute routine medical manage-
ment. Both medication management and enhanced medication management included clear instructions to not talk about the trauma details, included elements of exposure, or gave guidance on addressing certain PTSD-specific symptoms, such as avoidance. Prior to participation, pharmacotherapists were trained and certified on the manual and study procedures, and they participated in cross-site monthly supervision. Enhanced medication management and medication management sessions were recorded, and a randomly selected 20% were rated for fidelity and avoidance of proscribed elements of prolonged exposure therapy. Overall adherence across conditions was 96.7%.

**Statistical Analysis**

The primary analytic cohort is a modified intent-to-treat cohort, excluding veterans who consented but who were not dispensed any medication or placebo. The study design had 82% power to detect a 0.48 standardized effect size (corresponding to a mean [SD] difference of 11.4 [24.0] points in CAPS score) between prolonged exposure therapy plus sertraline and sertraline plus enhanced medication management, and between prolonged exposure therapy plus placebo and sertraline plus enhanced exposure therapy plus sertraline at 24 weeks (primary end point) based on 2-sided .025-level tests using a longitudinal data model.15 The α was chosen at .025 to account for 2 comparisons of interest.

To compare week 24 outcomes and pace of recovery, we used a mixed model of repeated measures with week 0, 6, 12, and 24 assessments as dependent variables, and with indicators for sertraline plus enhanced medication management and for prolonged exposure therapy plus sertraline, In (time), interactions of In (time) by indicators for sertraline plus enhanced medication management and for prolonged exposure therapy plus sertraline and study sites (stratification factor) as predictors. In the CAPS model, log-transformed time was used to model nonlinear slopes of time, and the interaction term of ln (time) by group was used to test for treatment effects on the rate of symptom changes over time. The model included random intercepts and slopes with autoregressive covariance structure, and, based on the model, predicted mean CAPS scores at week 24 were compared between 2 pairs of treatment groups. We examined the extent and pattern of missing data and used logistic regression model to evaluate baseline factors predictive of missing week 24 CAPS score and included them as covariates in sensitivity analysis. For the PCL, polynomial terms of time were included to account for the nonlinearity of PTSD symptom decreases (mean [SD] difference in score, 6.69 [4.77]; P < .001) over 24 weeks in the prolonged exposure therapy plus placebo group; 32.7 points for prolonged exposure therapy plus sertraline (P < .001), and 29.4 points for sertraline plus enhanced medication management group. Prolonged exposure therapy plus placebo group had fewer men and fewer married participants. Completion of week 24 CAPS did not differ significantly across treatment groups (56 of 71 [78.9%] in the sertraline plus enhanced medication management group, 42 of 67 [62.7%] in the prolonged exposure therapy plus placebo group, and 51 of 69 [73.9%] in the sertraline plus prolonged exposure therapy group; P = .10).

Unadjusted descriptive statistics of primary and secondary outcomes are shown in Table 2, and unadjusted mean cross-sectional CAPS scores are shown in Figure 2. Changes in unadjusted CAPS scores showed significant symptom reductions at week 24 (33.8 points for sertraline plus enhanced medication management [P < .001], 32.7 points for prolonged exposure therapy plus sertraline [P < .001], and 29.4 points for prolonged exposure therapy plus placebo [P < .001]). The primary model of longitudinally assessed CAPS scores showed no significant difference at week 24 between prolonged exposure therapy plus placebo and sertraline plus enhanced medication management (mean [SD] difference in score, 9.11 [4.65]; P = .05) or between prolonged exposure therapy plus placebo and prolonged exposure therapy plus sertraline (mean [SD] difference in score, 6.69 [4.77]; P = .16) (Table 3); the predicted mean scores were 41.9 for the sertraline plus enhanced medication management group, 51.0 for the prolonged exposure therapy plus placebo group, and 44.4 for the prolonged exposure therapy plus sertraline group. The symptoms of PTSD decreased significantly (β, −9.39; 95% CI, −11.62 to −7.16; P < .001) over 24 weeks in the prolonged exposure

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**Results**

**Figure 1** shows the CONSORT diagram; 472 participants underwent eligibility assessments after providing informed consent, 223 were randomized, and 207 participants (33, 34, 95, and 45 at each of the 4 sites) were dispensed medication (primary intent-to-treat cohort). After flexible dosage titration to tolerability and response, the mean (SD) week 12 sertraline hydrochloride dosage was 170.7 (46.9) mg/d for the sertraline plus enhanced medication management group, 171.6 (45.0) mg/d for the sertraline plus prolonged exposure therapy group, and 197.4 (11.3) mg/d for the prolonged exposure therapy plus placebo group (P < .001). The week 12 dosage for prolonged exposure therapy plus placebo differed from the 2 sertraline groups combined (P < .001). As previously noted, concurrent treatment with antidepressants or antipsychotics, benzodiazepines, prazosin, or sleep agents (eg, zolpidem) was allowed if the dosage was stable for 2 weeks. At baseline, the difference in concomitant psychiatric medications was significant across groups: allowed psychiatric medications at stable dosages were present in 9 of 71 patients (12.7%) in the sertraline plus enhanced medication management group, 20 of 67 patients (29.9%) in the prolonged exposure therapy plus placebo group, and 16 of 69 patients (23.2%) in the sertraline plus prolonged exposure therapy group (P = .04).

**Modified Intent-to-Treat Cohort**

Patient characteristics were comparable across groups, except for sex, marital status, and baseline function (Table 1). The prolonged exposure therapy plus sertraline group had fewer men and fewer married participants. Completion of week 24 PCL, polynomial terms of time were included to account for the nonlinearity of PTSD symptom decreases (mean [SD] difference in score, 6.69 [4.77]; P < .001) over 24 weeks in the prolonged exposure therapy plus placebo group; 32.7 points for prolonged exposure therapy plus sertraline (P < .001), and 29.4 points for prolonged exposure therapy plus placebo (P < .001). The primary model of longitudinally assessed CAPS scores showed no significant difference at week 24 between prolonged exposure therapy plus placebo and sertraline plus enhanced medication management (mean [SD] difference in score, 9.11 [4.65]; P = .05) or between prolonged exposure therapy plus placebo and prolonged exposure therapy plus sertraline (mean [SD] difference in score, 6.69 [4.77]; P = .16) (Table 3); the predicted mean scores were 41.9 for the sertraline plus enhanced medication management group, 51.0 for the prolonged exposure therapy plus placebo group, and 44.4 for the prolonged exposure therapy plus sertraline group. The symptoms of PTSD decreased significantly (β, −9.39; 95% CI, −11.62 to −7.16; P < .001) over 24 weeks in the prolonged exposure
therapy plus placebo group, and the rate of the decrease in the CAPS scores did not differ significantly for the sertraline plus enhanced medication management group (β, -0.98; P = .52) or for the prolonged exposure therapy plus sertraline group (β, -0.60; P = .70) (Table 3; Figure 2).

Secondary outcomes of self-reported symptoms of PTSD (PCL) estimated from a mixed model of repeated measures did not differ significantly across groups (eFigure in Supplement 2). The predicted mean difference in PCL scores at week 24 was 0.01 between the prolonged exposure therapy plus placebo group and the sertraline plus enhanced medication management group (P = .99) and 2.6 between the prolonged exposure therapy plus placebo group and the prolonged exposure therapy plus sertraline group 2.6 (P = .28).

Sensitivity Analysis
Missing data for the week 24 CAPS scores occurred for 15 of 71 participants (21.1%) in the sertraline plus enhanced medication management group, 25 of 67 participants (37.3%) in the prolonged exposure therapy plus placebo group, and 18 of 69...
participants (26.1%) in the prolonged exposure therapy plus sertraline group. Missing data were associated with race/ethnicity and marital status, and the primary model of CAPS, adjusting for marital status and race/ethnicity, did not show a difference in the week 24 outcomes by treatment groups. The dropout rate from the blinded study medication was 26.8% (19 of 71) for the sertraline plus enhanced medication management group, 47.8% (32 of 67) for the prolonged exposure therapy plus placebo group, and 40.6% (28 of 69) for the prolonged exposure therapy plus sertraline group, with a median time of discontinuation of therapy of 12 weeks for the sertraline plus enhanced medication management group, 5 weeks for the prolonged exposure therapy plus placebo group, and 5 weeks for the prolonged exposure therapy plus sertraline group. The dropout rate was 47.8% (32 of 67) in the prolonged exposure therapy plus placebo group and 42.0% (29 of 69) in the prolonged exposure therapy plus sertraline group, with a median time of discontinuation of prolonged exposure therapy of 5 weeks in both groups. Adherence (retention) to the entire treatment condition (ie, both the prolonged exposure therapy and the pill for the prolonged exposure therapy plus placebo group and the prolonged exposure therapy plus sertraline group) differed across groups whether unadjusted or adjusted, with the highest rate of adherence in the sertraline plus enhanced medication management group (52 of 71 [73.2%]), and the lower rates of adherence in the prolonged exposure therapy plus placebo group (31 of 67 [46.3%]) and the prolonged exposure therapy plus sertraline group (37 of 69 [53.6%]) (unadjusted $P = .005$ and adjusted $P = .006$). Similar to the primary modified intent-to-treat analysis, sensitivity analysis examining the adherent subset found no differences in CAPS scores by treatment group.

**Clinically Meaningful Change, Response, and Remission Outcomes**

None of the dichotomized response ($\chi^2 = 2.07; P = .36$), clinical response ($\chi^2 = 1.37; P = .50$), and remission ($\chi^2 = 3.43$; $P = .13$) outcomes differed by treatment group.
outcomes differed significantly by treatment group (Table 2) after adjusting for site, baseline CAPS score, and sex.

Discussion

This head-to-head randomized clinical trial comparing sertraline plus enhanced medication management, prolonged exposure therapy plus placebo, and prolonged exposure therapy plus sertraline was initiated to answer fundamental questions about the efficacy of these treatments alone or in combination in a population of veterans. All treatments led to significant reductions in the severity of PTSD symptoms. However, contrary to our hypotheses and findings in meta-analyses, no significant differences were observed across the 3 study groups in severity of PTSD symptoms for either clinician-assessed measures or self-report measures. These results are unlikely to be the result of type II error because the study was well powered for these comparisons. The high rates of clinically meaningful change observed among veterans in this trial (eg, ranging from 52% to 62%) are noteworthy, given the proportion of participants with chronic treatment-resistant PTSD. There were no significant differences in response rates or remission rates across treatment groups.

Although we hypothesized greater effects for combination treatment than for either treatment alone and greater effects for prolonged exposure therapy plus placebo than for sertraline plus enhanced medication management, the results that we observed were not entirely unexpected. A previous randomized clinical trial of eye movement desensitization and reprocessing vs fluoxetine showed no differences 12 weeks after treatment,12 and a study comparing a hybrid trauma-focused exposure-based acceptance and commitment therapy and medical management (sertraline supplemented with a sleep aid), or their combination, showed no significant differences after treatment.9 Finally, prolonged exposure therapy resulted in statistically higher rates of remission of PTSD compared with paroxetine, but the combination of prolonged exposure therapy and paroxetine did not differentiate from either alone.11

Importantly, this study was designed to deliver sertraline and prolonged exposure therapy plus sertraline under matched conditions that included rigorous training and ongoing supervision of psychotherapists and pharmacist. To balance clinical attention and expectations, the group receiving sertraline without prolonged exposure therapy received 30

Table 2. Unadjusted Summary Statistics of Primary Outcome and Secondary Outcomes During 24 Weeks

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Sertraline Hydrochloride Plus EMM (n = 71)</th>
<th>PE Plus Placebo (n = 67)</th>
<th>PE Plus Sertraline (n = 69)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total CAPS score, mean (SD)</td>
<td>75.5 (15.0)</td>
<td>80.9 (13.2)</td>
<td>76.0 (14.2)</td>
</tr>
<tr>
<td>Week 0 (n = 207)</td>
<td>75.5 (15.0)</td>
<td>80.9 (13.2)</td>
<td>76.0 (14.2)</td>
</tr>
<tr>
<td>Week 6 (n = 172)</td>
<td>54.9 (21.9)</td>
<td>66.9 (19.2)</td>
<td>60.6 (20.9)</td>
</tr>
<tr>
<td>Week 12 (n = 159)</td>
<td>47.4 (24.4)</td>
<td>52.9 (24.9)</td>
<td>47.3 (26.4)</td>
</tr>
<tr>
<td>Week 24 (n = 149)</td>
<td>41.7 (25.7)</td>
<td>51.5 (25.3)</td>
<td>43.3 (27.2)</td>
</tr>
<tr>
<td>Total PCL score, mean (SD)</td>
<td>56.2 (10.0)</td>
<td>59.6 (9.6)</td>
<td>56.6 (11.6)</td>
</tr>
<tr>
<td>Week 0 (n = 207)</td>
<td>56.2 (10.0)</td>
<td>59.6 (9.6)</td>
<td>56.6 (11.6)</td>
</tr>
<tr>
<td>Week 6 (n = 168)</td>
<td>48.1 (14.4)</td>
<td>51.5 (13.6)</td>
<td>46.9 (16.2)</td>
</tr>
<tr>
<td>Week 12 (n = 154)</td>
<td>42.8 (15.5)</td>
<td>43.0 (14.7)</td>
<td>40.5 (17.7)</td>
</tr>
<tr>
<td>Week 24 (n = 146)</td>
<td>41.5 (16.6)</td>
<td>42.3 (13.9)</td>
<td>40.5 (19.2)</td>
</tr>
<tr>
<td>Remission*</td>
<td>28</td>
<td>14</td>
<td>26</td>
</tr>
<tr>
<td>% (95% CI)</td>
<td>39.4 (28.0 to 51.7)</td>
<td>20.9 (11.9 to 32.6)</td>
<td>37.7 (26.3 to 50.2)</td>
</tr>
<tr>
<td>Response*</td>
<td>29</td>
<td>18</td>
<td>26</td>
</tr>
<tr>
<td>% (95% CI)</td>
<td>40.8 (29.3 to 53.2)</td>
<td>26.9 (16.8 to 39.2)</td>
<td>37.7 (26.3 to 50.2)</td>
</tr>
<tr>
<td>Clinically meaningful change*</td>
<td>44</td>
<td>35</td>
<td>39</td>
</tr>
<tr>
<td>% (95% CI)</td>
<td>62.0 (49.7 to 73.2)</td>
<td>52.2 (39.7 to 64.6)</td>
<td>56.5 (44.0 to 68.4)</td>
</tr>
</tbody>
</table>

Abbreviations: CAPS, Clinician-Administered PTSD Scale; EMM, enhanced medication management; PCL, PTSD checklist; PE, prolonged exposure therapy; PTSD, posttraumatic stress disorder. *Remission is defined as a CAPS score of 35 or less, response is defined as 50% or higher reduction in CAPS score from baseline, and clinically meaningful change is defined as a reduction of 20 points or more in the CAPS score from baseline or a CAPS score of 35 or less. All definitions are based on week 24 CAPS scores or the last observed CAPS scores if week 24 scores are missing, and participants were considered nonremitted, not responsive, and without clinically meaningful change if all follow-up CAPS scores were missing.

Figure 2. Cross-sectional Mean Scores of Clinician-Administered PTSD Scale (CAPS) Showing Change in Posttraumatic Stress Disorder Symptoms During Treatment

PE indicates prolonged exposure therapy; PLB, placebo; PTSD, posttraumatic stress disorder; and SERT, sertraline hydrochloride. Error bars represent 95% CIs.

P = .18) outcomes differed significantly by treatment group (Table 2) after adjusting for site, baseline CAPS score, and sex.
Contrary to our hypotheses, while sertraline plus enhanced medication management performed better than expected, in the purist effectiveness comparison of prolonged exposure therapy plus sertraline vs prolonged exposure therapy plus placebo, there was no evidence for added benefit for active medication. It is possible that participants in both the prolonged exposure therapy plus placebo group and the prolonged exposure therapy plus sertraline group attributed changes to the pill, reducing motivation for exposure components. The combined prolonged exposure therapy treatments had a greater burden for participants owing to the requirement to attend 2 different appointments and more time required per week in addition to homework, which may have contributed to the higher attrition among the participants who received prolonged exposure therapy compared with the participants who received sertraline alone. The present study design allowed for early response, and the prolonged exposure therapy plus sertraline group did show significantly more early responders (13 of 69 [18.8%]) than did the other 2 groups (6 of 67 participants [9.0%] in the prolonged exposure therapy plus placebo group and 4 of 71 participants [5.6%] in the sertraline plus enhanced medication management group were early responders). However, the overall slopes of change and the results of the intent-to-treat analysis did not differ. There were significant differences in rates of adherence, with adherence being lower in both the prolonged exposure therapy plus sertraline group and the prolonged exposure therapy plus placebo group.

**Limitations**

Although our results are informative, limitations are apparent. Based on study design, only combat veterans were included, suggesting that an extension to other trauma populations and demographic groups that are not represented is necessary. In addition, only participants who were not currently taking an SSRI and were willing to receive prolonged exposure therapy and/or sertraline could be randomized. This restriction made recruitment challenging because many veterans with PTSD were already receiving an SSRI, and many

### Table 3. Mixed-Effects Model of Primary Outcome (CAPS 17-Item Total Score) Using Follow-up Data at Weeks 6, 12, and 24 and Marginal Mean Scores at Week 24 Estimated Based on the Model*

<table>
<thead>
<tr>
<th>Model arm (with PE plus placebo as reference)</th>
<th>Coefficient (SE)</th>
<th>z Score</th>
<th>P Value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sertraline hydrochloride plus EMM</td>
<td>-5.95 (2.60)</td>
<td>-2.29</td>
<td>.02</td>
<td>-11.04 to -0.87</td>
</tr>
<tr>
<td>PE plus sertraline</td>
<td>-4.74 (2.62)</td>
<td>-1.81</td>
<td>.07</td>
<td>-9.87 to 0.38</td>
</tr>
<tr>
<td>Site 2</td>
<td>0.84 (3.48)</td>
<td>0.24</td>
<td>.81</td>
<td>-5.98 to 7.66</td>
</tr>
<tr>
<td>Site 3</td>
<td>1.19 (2.88)</td>
<td>0.41</td>
<td>.68</td>
<td>-4.46 to 6.83</td>
</tr>
<tr>
<td>Site 4</td>
<td>-0.81 (3.26)</td>
<td>-0.25</td>
<td>.80</td>
<td>-7.21 to 5.58</td>
</tr>
<tr>
<td>In (time + 1) (with PE plus placebo as reference)b</td>
<td>-9.39 (1.14)</td>
<td>-8.25</td>
<td>&lt;.001</td>
<td>-11.62 to -7.16</td>
</tr>
<tr>
<td>In (time + 1) by sertraline plus EMM</td>
<td>-0.98 (1.52)</td>
<td>-0.64</td>
<td>.52</td>
<td>-3.96 to 2.00</td>
</tr>
<tr>
<td>In (time + 1) by PE plus sertraline</td>
<td>-0.60 (1.56)</td>
<td>-0.39</td>
<td>.70</td>
<td>-3.66 to 2.45</td>
</tr>
<tr>
<td>Marginal CAPS mean score at week 24</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PE plus placebo</td>
<td>51.04 (3.49)</td>
<td>14.64</td>
<td>&lt;.001</td>
<td>44.20 to 57.87</td>
</tr>
<tr>
<td>Sertraline plus EMM</td>
<td>41.93 (3.07)</td>
<td>13.66</td>
<td>&lt;.001</td>
<td>35.91 to 47.94</td>
</tr>
<tr>
<td>PE plus sertraline</td>
<td>44.35 (3.26)</td>
<td>13.62</td>
<td>&lt;.001</td>
<td>44.20 to 57.87</td>
</tr>
</tbody>
</table>

**Abbreviations:** CAPS, Clinician-Administered PTSD Scale; EMM, enhanced medication management; PE, prolonged exposure therapy; PTSD, posttraumatic stress disorder.

*The model is based on CAPS scores at weeks 0, 6, 12, and 24 and had random intercepts and slopes with autoregressive covariance structure. The CAPS score was also evaluated using longer-term data by including weeks 36 and 52 and no differences in slope were found across groups (P = .83).

Responses in the text are natural language and not tabular data.
Prolonged Exposure Therapy, Sertraline, and Their Combination Among Combat Veterans With PTSD

Conclusions

In this first direct comparison of 2 of the most commonly administered treatments of PTSD (sertraline and prolonged exposure therapy) and their combination (sertraline plus prolonged exposure therapy) for veterans, we found no significant differences between the 3 treatment groups. These results require additional replication and may suggest changes to future clinical guidelines, particularly when SSRIs are administered under similar conditions to this study.

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Data Sharing Statement: See Supplement 3.

REFERENCES


