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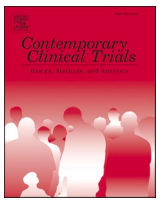

A comparison of prolonged exposure therapy, pharmacotherapy, and their combination for PTSD: What works best and for whom; study protocol for a randomized trial

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ABSTRACT

Background: Several efficacious psychological and pharmacological treatments for posttraumatic stress disorder (PTSD) are available; however, the comparative effectiveness of these treatments represents a major gap in the literature. The proposed study will compare the effectiveness of two leading PTSD treatments – Prolonged Exposure (PE) therapy and pharmacotherapy with paroxetine or venlafaxine extended release – as well as the combination of PE and medication.

Methods: In a randomized clinical trial, veterans with PTSD (N = 450) recruited across six Veterans Affairs Medical Centers will complete assessments at baseline, mid-treatment (Week 7), post-treatment (Week 14), and follow-up (Weeks 27 and 40). The primary outcome will be change in (both clinician-rated and self-reported) PTSD severity. Depression symptoms, quality of life, and functioning will also be measured and examined as secondary outcomes. Baseline demographic and clinical data will be used to develop "personalized advantage indices" (PAIs), with the goal of identifying who is most likely to benefit from which treatment.

Conclusions: This planned trial will yield findings to directly inform clinical practice guidelines for PTSD, by providing comparative effectiveness data to support recommendations about what can be considered the "first-line" treatment option(s) for PTSD. Further, findings from this trial have the potential to guide treatment

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planning for individual patients, through implementation of PAIs developed from study data, in service of "personalized medicine."
Trial registration: https://clinicaltrials.gov/ct2/show/NCT04961190

1. Introduction

Posttraumatic stress disorder (PTSD) is a debilitating mental health problem that affects over 8% of the general population [1] and is estimated to be twice as common among US military veterans [2]. PTSD in veterans is associated with increased medical disease burden [3,4] and diminished social functioning and life satisfaction [5,6,7]. Effective psychological and pharmacological treatments exist for PTSD [8], and found to be effective among veterans [9,10,11]; however, there is insufficient evidence about the comparative effectiveness of these treatment options to guide shared decision-making [8,10].

A recent systematic review of 193 PTSD treatment trials indicated that Prolonged Exposure therapy (PE) had the highest strength of evidence among psychological intervention protocols for PTSD ([8]; see also [12,10] for evidence supporting PE among veterans).[1] Likewise, paroxetine and venlafaxine were identified as the best-established pharmacotherapies for PTSD ([13,14,8,15,16]; see [17]). Paroxetine is a selective serotonin reuptake inhibitor (SSRI) that has been FDA approved for the treatment of depression since 1992 and for the treatment of PTSD since 2000. Venlafaxine extended release (XR) is a serotonin-norepinephrine reuptake inhibitor (SNRI) that has been FDA approved since 1997 for the treatment of depression and anxiety disorders.

People seeking treatment for PTSD must decide whether to pursue psychotherapy, pharmacotherapy, or both. Some practice guidelines for PTSD (e.g., US Department of Veterans Affairs & Department of Defense, 2017) suggest that trauma-focused psychotherapy is the first-choice treatment, while pharmacotherapy is offered as a secondary treatment option. Nevertheless, VA treatment utilization data indicate that more people receive pharmacotherapy than trauma-focused psychotherapy [18]. To understand the comparative effectiveness of psychotherapy and pharmacotherapy and to inform shared decision-making with patients, randomized clinical trials (RCTs) directly comparing PTSD treatments are needed [8,19,10]. Moreover, trials that test the effectiveness of treatments under "real world" conditions are needed to ensure direct relevance to clinical practice. Few RCTs have directly compared the efficacy of psychotherapies with pharmacotherapies for PTSD [20,21,22,23] and none have addressed comparative effectiveness of "best evidence" psychotherapy and pharmacotherapy options. One trial [20] compared PE and paroxetine, and found some evidence for better outcomes in those who received PE. However, the sample population (motor vehicle accident survivors) and high treatment refusal rates limit confidence in generalizability. In brief, there is insufficient evidence to draw conclusions about the comparative effectiveness of psychotherapy and pharmacotherapy for PTSD [8,19].[2]

Studies testing whether combinations of psychotherapy and pharmacotherapy for PTSD yield better outcomes than either treatment alone have failed to establish combined treatment as the standard of care. One small RCT found a significant benefit from combining PE and paroxetine, compared to PE plus placebo [24]. However, two other trials failed to show a reliable benefit for combining PE with sertraline [21] or paroxetine [20], compared to monotherapy. As such, the potential combined effects of PE and front-line medications require further testing. In addition to symptom reduction, the potential impact of combined treatment on engagement/adherence warrants consideration and investigation (e.g., see [25]).

Comparative effectiveness trials provide critical information about the treatments that work best on average, but not necessarily for individual patients [26]. Research aimed at predicting who will respond to a given treatment by prescriptively matching participants to treatments based on theoretically relevant variables has generally proven unfruitful [27,28]. An emerging alternate approach, "Personalized Advantage Indices" (PAIs), uses machine learning methods to identify individual participant characteristics that can be used in algorithms for predicting outcomes within and across treatment conditions [29,30]. A strength of the PAI methodology is that results provide concrete recommendations about the optimal treatment plan for individual patients. This approach is expected to be particularly useful when impact of individual patient variables is small, as the goal is to systematically explore of range of potentially relevant variables in order to optimize outcome prediction, and has shown significant promise in treatment research on depression [29].

Only two studies have used these methods to develop PAIs in treatment trials for PTSD [31,32], and a third study used PTSD treatment trial data to develop "prognostic indices" (using a very similar methodology focused on identifying predictors across treatment conditions; [33]). All of these studies compared two psychotherapy protocols, and only one [33] examined PTSD as the primary outcome being predicted in their analyses. No studies have developed PAIs to predict who will respond best to front-line forms of psychotherapy, pharmacotherapy, or their combination for PTSD, which we propose would be particularly fruitful (since treatments may work through different mechanisms) and clinically informative (given the salience of this decision for patients and providers). The current study aims to address this gap.

In sum, there are important gaps in the current PTSD literature, including: 1) lack of comparative effectiveness studies to inform treatment decisions about psychotherapy and pharmacotherapy, and 2) insufficient evidence about which treatments are most effective for which patients. To address these gaps, we propose a RCT of veterans with PTSD to compare the effectiveness of best-proven treatments – PE and pharmacotherapy with either paroxetine or venlafaxine XR – both alone and in combination. We chose to include both medications in our pharmacotherapy conditions to better mirror current clinical practice, and permit patients who have had previous unsuccessful trials or

[1] Of note, Forman-Hoffman et al. [8] concluded that "CBT-mixed" (involving both exposure- and non-exposure-based psychotherapy techniques) also had high strength of evidence for treating PTSD in adults. However, this category did not include one specific PTSD treatment protocol, but rather combined data from studies that used different CBT protocols. Also of note, Cognitive Processing Theory (a form of psychotherapy that, like PE, has been widely used throughout the VA Healthcare System) was deemed to have moderate strength of evidence in this review (for recent results from a large-scale comparison of PE and Cognitive Processing Therapy, see [12]).

[2] A few published reviews have compared outcomes from trials of psychotherapies and pharmacotherapies for PTSD (e.g., [67,68]), in an effort to draw conclusions about comparative effectiveness. However, we agree with critical commentaries that combining data from different treatments and/or different study samples may be misleading, and ultimately does not rigorously address questions about the comparative effectiveness of specific treatments [19,69,70,71]. Rather, randomized trials that directly compare PTSD treatments with the strongest evidentiary support offer the most rigorous test of comparative effectiveness.

contraindications for one of the medications to enroll.[3] Using outcome data from this trial, we will identify prognostic and prescriptive variables that can be used for developing "Personalized Advantage Indices" for veterans with PTSD.[4]

2. Material and methods

2.1. Study design

This study will be a three-armed randomized comparative effectiveness trial. Participants will be randomly assigned to receive: (a) PE therapy; (b) pharmacotherapy with paroxetine or venlafaxine XR; or c) both PE and pharmacotherapy. Treatment will be delivered by existing VA providers through existing outpatient treatment clinics. Participants will complete assessments at 7, 14, 27, and 40 weeks after randomization, with self-report questionnaires also completed biweekly during treatment. The primary outcome will be change in PTSD severity. Secondary outcomes include depression, quality of life, and functioning/disability ratings.

2.2. Study sites

Study sites are six Veterans Affairs Medical Centers (VAMCs) in Philadelphia and Coatesville, PA; Milwaukee, WI; Dallas, TX; and Palo Alto and San Diego, CA. These sites are geographically diverse and were selected based on previous successful research collaborations, patient volume and flow, and diversity of veterans served. Each site includes a psychologist and a psychiatrist among its investigators. The study protocol has been approved (and will be monitored) by the VA Central Institutional Review Board.

2.3. Study participants and randomization

Participants ($N = 450$) will be veterans ages 18–75 with a current (past month) DSM-5 diagnosis of PTSD (diagnosed by Independent Evaluator [IE]; see below) seeking PTSD treatment at a participating study site. Participants must be fluent in English, willing to participate in PE, pharmacotherapy, or both, and able to provide informed consent. Exclusion criteria include a history of mania, active psychosis, recent (past month) suicidal ideation with intent or plan, or recent suicidal behavior (suicide attempts, interrupted or aborted attempts, or preparatory behavior), and medical conditions or treatments contraindicating paroxetine or venlafaxine XR (e.g., MAO inhibitors, other SSRI or SNRI medications). Additionally, individuals who have not responded to an adequate trial of PE ($\geq$ 8 sessions) and/or have not responded to an adequate trial of both paroxetine and venlafaxine XR (therapeutic dose for $\geq$6 weeks) are ineligible. Recruitment strategies to increase sample diversity include the selection of performance sites from diverse areas/regions, lack of exclusions or restrictions related to index traumas, recruitment strategies with a expected to have a broad reach (e.g., telephone-based trauma screening initiatives), and selective recruitment strategies targeting women and/or minorities (e.g., advertising, screening in women's clinics/programs).

The study biostatistician will create the randomization schedule prior to beginning enrollment using variable-sized permuted block randomization (block sizes will be 3 or 6 to ensure equal distribution between treatments throughout the study). The sample will be stratified by two potential predictors of treatment response/prognosis: a) gender, and b) concurrent benzodiazepine use.[5]

2.4. Measures

Assessments were scheduled to maximize measurement precision and statistical power while minimizing participant burden (see Table 1 for a list of the measures and the assessment schedule). To minimize effects of attrition, there are 5 major assessment points: baseline, 7 weeks (mid-treatment), 14 weeks (post-treatment), 27 weeks, and 40 weeks. Fourteen weeks was selected as optimal timing for post-treatment assessments to capture acute treatment effects based on the anticipated duration of our study treatments (completing PE sessions and/or stabilizing on medication dosage), whereas 40 weeks was selected as a final follow-up to balance feasibility and the goal of testing durability of treatment effects. Midpoint assessments (7 weeks and 27 weeks) were included to minimize the effects of attrition and missing data to maximize statistical power (see below for additional details). A range of demographic and clinical variables will be collected at baseline and used in PAI analyses. The post-baseline assessments (7, 14, 27, and 40 weeks) include primary and secondary trial outcomes – PTSD symptoms, depressive symptoms, and functioning. Administration of the adherence measures weekly and the PCL-5 and PHQ-9 biweekly during treatment will also inform clinical care. Adverse events and reasons for dropout will be monitored.

Clinical interviews will be conducted by IEs who are blind to treatment condition. IEs will be trained by completing standardized online trainings (e.g., interactive CAPS trainings prepared by the National Center for PTSD), followed by didactic training meetings with the study PIs (Bredemeier and Thase). Each IE will conduct a mock interview for each measure and receive feedback from the PIs prior to conducting study assessments independently, and will be required to attend weekly calibration meetings throughout the course of the trial. IE assessments will be audio recorded and a random subset of 10% from each site will be assessed for reliability (i.e., independent secondary ratings will be used to compute inter-rater reliability). Selected clinical interviews and self-report measures have been found reliable, valid, and acceptable to participants in previous research [41,38,40,37,49,34,36,35]. Benchmarks from Marx et al. [50] will be used to guide interpretation of change scores from the CAPS-5 and PCL-5.

2.5. Study intervention

Three treatment conditions will be compared. Participants will have the option to complete treatment sessions in person or via telehealth (i.e. VA Video Connect), based on mounting evidence for equivalent outcomes in PTSD treatments (including PE) across these modalities [51,52,53,54]. The active treatment phase (PE and/or medication titration) will take place within 14 weeks of the start of treatment.

2.5.1. Prolonged exposure therapy

PE will involve up to 14 60- to 90-min sessions (minimum = 8) during the active treatment phase, following the protocol outlined by Foa, Hembree, Rothbaum, and Rausch [55]. In brief, the PE protocol involves imaginal exposure (I.e., revisiting the trauma memory) followed by processing of this experiences, as well as psychoeducation about the effects of trauma, breathing retraining, and in vivo exposures to trauma-related reminders/triggers in between sessions (for homework). If the participant has completed at least 8 sessions and scores $\leq$30 on the PCL-5 for two consecutive administrations, then the therapist can

[3] Sertraline was not selected for inclusion/study because this medication was deemed to have low strength of evidence in the systematic review by Forman-Hoffman et al. [8] that guided our proposal.

[4] The PAI method was selected over other (atheoretical) multivariate prediction methods (e.g., clustering methods, prognostic indices) because this method is most suitable to address our aim to optimize treatment outcome prediction to inform treatment selection efforts.

[5] Consistent with the effectiveness nature of the study, individuals taking benzodiazepines on a standing or "as needed" basis are eligible to enroll in the study, though providers are discouraged from starting them during the active treatment phase.

Table 1
Assessment schedule.

Measures	Baseline	Weekly	Biweekly	Mid-treatment Assessment (week 7)	Post-treatment Assessment (week 14)	Wk 27 Follow-up	Wk 40 Follow-up	Type of Assessment: Independent Evaluator Rated (IE), Self-Report (SR), or Other (O)
Diagnostic Interview for Anxiety, Mood, and Obsessive-Compulsive and Related Neuropsychiatric Disorders (DIAMOND; [34])*	X							IE
Clinician Administered PTSD Scale for DSM-5 (CAPS-5; [35])*	X			X	X	X	X	IE
Quick Inventory of Depressive Symptoms, Clinician Rating (QIDS; [36])*	X			X	X	X	X	IE
Social and Occupational Functioning Assessment Scale (SOFAS; [37])*	X			X	X	X	X	IE
Posttraumatic Checklist for DSM-5 (PCL-5; [38])	X		X	X	X	X	X	SR
Patient Health Questionnaire depression module (PHQ-9; [39])	X		X	X	X	X	X	SR
The Veterans RAND 12-item Health Survey (VR-12; [40])	X			X	X	X	X	SR
Client Satisfaction Questionnaire-8 (CSQ-8; [41])					X			SR
Demographic variables (e.g., age, gender identity, sex at birth, service branch and era)	X							SR
Life Events Checklist (LEC-5; [42])	X							SR
Childhood Trauma Questionnaire (CTQ; [43])	X							SR
Connor-Davidson Resilience Scale (CD-RISC; [44])	X							SR
Body weight, blood pressure	X							O
California Verbal Learning Test, 2nd edition – Short Form (CVTL-II; [45])	X							O
Psychological arousal/reactivity (eSense) during Standardized Trauma Interview [46]	X							O
Patient Engagement and Adherence Scale (PEAS; [47]) [adapted] – PE condition only (rated by PE therapist)		X						O
Utility of Techniques Inventory (UTI; [48]) – PE condition only		X						SR
Medication Tracking Log (pharmacotherapy condition only – validated by pill count)		X	X					SR

is permitted to discuss the possibility of ending treatment with the participant. This flexible-length treatment mirrors clinical practice and has been utilized in multiple trials of trauma-focused psychotherapy [56,53,57]. The benchmark of 30 on the PCL-5 is based was selected based on recommended clinical cutoff scores for this measure (e.g., [38]; see https://www.ptsd.va.gov/professional/assessment/adult-sr/ptsd-checklist.asp). PE therapists will be required to have formal PE training including post-training experience and consultation. Training in the study protocol and monitoring to support fidelity will be overseen by PE developer Dr. Edna Foa and the Center for the Treatment and Study of Anxiety. Therapy sessions will be recorded and a subset of 10% will be randomly selected and rated for treatment fidelity (using the Treatment Integrity Checklist; [58]).

2.5.2. Pharmacotherapy

The initial pharmacotherapy session will be a 60-min evaluation to assess symptoms, gather history, and select the study medication (paroxetine or venlafaxine XR) that will be prescribed for the duration of the study (i.e., switching medications will not be permitted). Starting dose of paroxetine will be 20 mg daily and starting dose of venlafaxine XR will be 75 mg daily. Over the 14-week treatment phase, the selected medication will be titrated based on response to potential maximum dose of paroxetine 60 mg or venlafaxine XR 300 mg. During the initial six weeks of dose titration, follow-up visits will be every two weeks (or sooner, if clinically indicated) to assess symptoms, adherence, tolerance, and side effects. If dosage is stabilized over the first six weeks, follow-up visits may be scheduled every four weeks. Thus, each participant in this condition will have between six and fourteen medication visits during the 14-week active treatment phase. Post-treatment, participants will be instructed to remain on the same dosage through week 40. Throughout treatment, participants will be encouraged to contact clinic staff if any issues arise (e.g., symptom exacerbation, concerning side effects). Training and monitoring to support fidelity to the study protocol will be overseen by Dr. Michael Thase and the Mood and Anxiety Disorders Treatment and Research Program. Pharmacotherapy sessions will also be recorded and a subset (10%) will be randomly selected and rated for treatment fidelity.

2.5.3. PE + pharmacotherapy

Treatment in the combined treatment condition will be provided following the aforementioned treatment protocols. Therapy and medication visits will be conducted by different providers. Providers will be asked to communicate regularly about plans and progress, to coordinate care and minimize patient burden (e.g., scheduling sessions on the same day).

2.6. Statistical analysis

2.6.1. Aim 1: comparing effectiveness of treatment conditions

We will use multilevel modeling, which includes the intent-to-treat

sample (i.e., all randomized participants regardless of missing data) and is recommended for longitudinal psychiatric data [59].

The primary outcomes are CAPS-5 assessed at post-treatment and follow-ups. Secondary outcomes are the PCL-5, QIDS, PHQ-9, VR-12, and SOFAS. The PCL-5 and PHQ-9 will be administered more frequently (biweekly) during the active treatment phase (baseline through post-treatment), consistent with VA measurement-based care guidelines. Because change in clinical outcomes is unlikely to be linear, we will examine non-linear growth curve models (e.g., quadratic, logarithmic, piecewise) and select the best fitting model (based on Akaike information criterion [AIC] and Bayesian information criterion [BIC] criteria). Treatment condition will be modeled using level-2 dummy variables, coded to assess the comparisons of interest. Time will be coded as weeks from baseline and centered at either week 14 (post) or week 40 (final follow-up) to compare treatment effects at these end-points, with the primary end-point being post-treatment. Planned comparisons will be made between PE and pharmacotherapy, and between each of these and PE + Pharmacotherapy. The Benjamini-Hochberg correction for multiple tests will be used to avoid inflation of Type 1 error.

Sensitivity analyses will account for the effect of time-varying confounds affected by treatment. As PE duration is dependent on reductions on the PCL-5, it is a potential time-varying confound. Likewise, medication dosage may be a time-varying confound in the pharmacotherapy conditions. To account for these time-varying confounds, we will use inverse-probability-of-treatment weighting [60], and robust variance estimators to provide accurate confidence intervals [61] for the regression coefficients in these weighted analyses. Treatment adherence will also be examined in sensitivity analyses with this approach, operationalized as the number of days the participant engages in therapy homework (in PE) or takes medications (in pharmacotherapy). Further, medication adherence will be combined with PE homework adherence to create a composite 'days adherent with treatment' variable to examine in sensitivity analyses involving all three treatment conditions.[6] Finally, sensitivity analyses will examine in-person vs. telehealth approaches (with therapy mode dummy-coded at the session level).

2.6.2. Aim 2: personalized advantage indices

To generate PAIs, we will apply machine learning to generate models to predict CAPS-5 PTSD severity ratings at post treatment (Week 14). Specifically, we will tune a random forest algorithm using cross-validation. This cross-validation process will generate three final tuned predictive models for each of the three treatment conditions (PE, pharmacotherapy, and combined). These models will be applied to create predictions of patient outcome in each of the three treatment conditions. A PAI will then be calculated by subtracting the difference between predicted outcomes, where greater symptom improvement in one treatment over the other conditions will help us determine which treatment a patient is expected to benefit from most.

2.6.3. Sample size and power

Based on documented effect sizes for PE ($d > 1.0$) and paroxetine/venlafaxine XR ($d < 0.5$; [8]) as well as data from the one published comparison of PE and paroxetine [20], we hypothesize that participants who receive PE will show better outcomes relative to those who only receive pharmacotherapy, with a predicted between group effect size of Cohen's $d = 0.5$ (medium size effect). We plan to recruit $N = 150$ per arm and expect 33% attrition across conditions, based on study attrition rates in the most comparable trial ([21]; note that [12] reported slightly lower attrition in a very large PTSD psychotherapy trial with veterans, supporting this estimate).

Monte Carlo studies calculated the smallest effect size detectable with power > 0.80 and $p < .01$, given our sample size and attrition rates, for Aim 1 (comparative effectiveness; Aim 2 is focused on the development of PAIs, and thus is not hypothesis driven). We tested various potential effect sizes, each using 1000 replications. The Monte Carlo studies indicated that, for the outcome measures with 5 assessments (interview measures), we will have power > 0.80 to detect treatment condition differences at the 40-week follow-up as small as $d = 0.29$. Power is >0.80 to detect $d = 0.28$ for the outcome measures with 10 assessments (self-report measures). Using a higher estimated rate of attrition (50%), Monte Carlo studies found that we would still have >0.80 power to detect effects as small as $d = 0.32$ for the outcomes with five assessments, and as small as $d = 0.30$ for the outcomes with 10 assessments.

2.6.4. Missing data

We will use pattern mixture modeling to assess the effect of missing data. We will rerun analyses coding for various missing data patterns to determine: 1) if missingness impacts our findings; and 2) how differences between treatment arms depend on the missing data pattern. To maximize participant retention, electronic medical records and personal contacts will be utilized whenever feasible.

3. Discussion

Despite some treatment guidelines supporting trauma-focused psychotherapy as the preferred "first-line" approach, few trials have directly compared the effectiveness of psychotherapy and pharmacotherapy for PTSD. Further, existing comparative trials have been limited in scope (e.g., small sample size, single trauma type) and/or studied treatments that have lower strength-of-evidence [20,21,24,22,23]. The current trial addresses these gaps by testing treatments with high strength-of-evidence and including a large and diverse sample in terms of trauma types, real world clinical settings, and a geographically diverse patient population. The trial also advances this work by exploring individual characteristics as treatment outcome predictors and moderators using advanced statistical methods. The trial is designed and powered to test comparative effectiveness in real-world conditions, to facilitate more rapid translation to clinical practice.

Ease of translation to clinical practice guided several design considerations. We considered targeting civilians, but ultimately selected a veteran population so that study findings could be quickly translated into VA through clinical practice guidelines. Focusing on VA-enrolled veterans is expected to enhance recruitment feasibility, given the prevalence of PTSD within VA. In addition, the existing system infrastructure supports the use of evidence-based treatments, allowing for a true effectiveness trial.

We also considered the specific treatments to study and the duration of treatment. PE was chosen because of its strong evidentiary support [8], and because it is formally "rolled-out" within VA. In terms of the duration of psychotherapy, we chose a flexible number of sessions to mirror real world clinical practice. Data from previous work on PE effectiveness with veterans (in which the number of sessions is flexible) suggests that the average number of sessions is 10 to 12 [62,63,47,64,65,66] and few will show further clinical benefit from >14 sessions. Fewer than 14 sessions will also be permitted, with the number being determined by individual clinical response. In determining which pharmacotherapy to include, we considered which treatments with strong evidence were already in clinical use at VAMCs. Both paroxetine and venlafaxine XR currently have moderate strength-of-evidence supporting their use for PTSD [8] without clear evidence for superiority of one over the other. Rather than select only one, we chose to allow pharmacotherapy providers to select from these two options to better mirror clinical practice where providers choose among pharmacotherapy options with different mechanisms of action and side effect profiles that impact their appropriateness for a given individual.

[6] In the combined treatment condition, this variable will be operationalized based on the numbers of days that the participant both completed PE homework and took their medication as prescribed, so that the maximum value on this variable is consistent across treatment arms.

Inclusion of both medications has the additional advantage of allowing veterans to enroll who have a contraindication or have not benefited from a previous trial of one of the study medications.

Design features routinely used in medication efficacy trials, such as the use of placebo controls and enhanced medication management protocols, have not been proposed here given that the efficacy of these medications has been established – the goal of this study is to compare the effectiveness of pharmacotherapy with PE. Therefore, the current study will more closely match standard VA practice and will have greater potential for generalizability to routine VA clinical practice. Offering treatment via telehealth in addition to in-person sessions will also permit diversification of the sample and rapid translation of our findings into clinical practice, given the widespread use of telehealth in VA that has further increased due to the COVID-19 pandemic. Finally, our use of PAIs will also allow for the translation of findings into clinical practice, by helping to identify which patients may be most likely to benefit from which treatment options—a decision that is key for veterans beginning PTSD treatment, and providers who help them make those decisions. PAIs generated from this trial can be used to directly test whether following personalized treatment recommendations based on this methodology leads to improved outcomes for veterans with PTSD, using results from the present study to inform necessary sample size estimation.

In summary, this study was designed to maximize the ability to compare two treatments, along with their combination, in conditions that closely mirror real-world settings. We expect that this study will also contribute to our ability to identify what treatment(s) will work for whom. In addition to dissemination through http://ClinicalTrials.gov and scientific conferences and publications, we intend to share our results directly with participants, VA clinicians and VA policy-making units at the end of the study with the hope of accelerating the application of knowledge to clinical practice. Results will therefore shape policy and clinical practice, within the VA and beyond.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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