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A personalized index to inform selection of a trauma-focused or non-trauma-focused treatment for PTSD☆

Shannon Wiltsey Stirman [a,*], Zachary D. Cohen [b], Carole A. Lunney [c], Robert J. DeRubeis [d], Joshua F. Wiley [e], Paula P. Schnurr [f]

[a] National Center for PTSD and Stanford University, United States
[b] National Center for PTSD and University of California, Los Angeles, United States
[c] National Center for PTSD, United States
[d] University of Pennsylvania, United States
[e] School of Psychological Sciences and Monash Institute of Cognitive and Clinical Neurosciences, Monash University, Melbourne, Victoria, Australia
[f] National Center for PTSD and Geisel School of Medicine at Dartmouth, United States

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ABSTRACT

PTSD treatment guidelines recommend several treatments with extensive empirical support, including Prolonged Exposure (PE), a trauma-focused treatment and Present-Centered Therapy (PCT), a non-trauma-focused therapy. Research to inform treatment selection has yielded inconsistent findings with single prognostic variables that are difficult to integrate into clinical decision-making. We examined whether a combination of prognostic factors can predict different benefits in a trauma-focused vs. a non-trauma-focused psychotherapy. We applied a multimethod variable selection procedure and developed a prognostic index (PI) with a sample of 267 female veterans and active-duty service members (mean age 45; $SD = 9.37$; 53% White) with current PTSD who began treatment in a randomized clinical trial comparing PE and PCT. We conducted linear regressions predicting outcomes (Clinician-Administered PTSD Scale score) with treatment condition, the PI, and the interaction between the PI and treatment condition. The interaction between treatment type and PI moderated treatment response, moderated post-treatment symptom severity, $b = 0.30$, $SE_b = 0.15$ [95% CI: 0.01, 0.60], $p = .049$. For the 64% of participants with the best prognoses, PE resulted in better post-treatment outcomes; for the remainder, there was no difference. Use of a PI may lead to optimized patient outcomes and greater confidence when selecting trauma-focused treatments.

Current PTSD treatment guidelines recommend delivery of several treatments with extensive empirical support, one of which is Prolonged Exposure (PE; Foa, Hembree, & Rothbaum, 2007). Present-Centered Therapy (PCT; Schnurr et al., 2005) is a non-trauma-focused therapy that has been shown to be effective for treating PTSD in a number of randomized controlled trials. To date, in most direct comparisons to trauma-focused treatments, the trauma-focused treatments produce somewhat larger effects (Belsher et al., 2019). Therefore, the Department of Veterans Affairs/Department of Defense guideline (VA/DOD, 2017) International Society for Traumatic Stress Studies (ISTSS, 2018) and American Psychological Association (2017) gave strong recommendations for trauma-focused therapies and ISTSS and VA/DOD gave a moderate recommendation for PCT. Although these guidelines are intended to inform clinical decision-making, thus far they have not focused on the question of which treatment should be recommended for an individual patient, based on characteristics that can be

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* Corresponding author.
E-mail address: sws1@stanford.edu (S.W. Stirman).

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ascertained at intake. In routine care, however, this is a question clinicians answer every day, with little or no guidance from the research literature (Raza & Holohan, 2015).

In efforts to inform these decisions, researchers have used data from clinical trials to investigate patient factors that may predict outcomes in trauma-focused evidence-based psychotherapies (TF-EBPs). In a study of PE and another guideline-recommended treatment, Cognitive Processing Therapy (CPT) for female sexual assault survivors (Rizvi, Vogt, & Resick, 2009), greater PTSD symptom improvement was associated with higher levels of pre-treatment depression and guilt. A secondary outcome, treatment dropout, was predicted by each of three baseline variables (younger age, lower intelligence, and less education).

Rather than pointing to prescriptive features (moderators) that could guide decisions about which might be the better treatment choice for a given individual, these observed relations would be considered prognostic across the two treatments, because the associations with symptom change and dropout (respectively) did not differ between the two treatments. One of the variables that was prognostic for dropout – age – did indeed act as a moderator in the differential prediction of symptom reduction. The best outcomes were experienced by younger women who received CPT and older women who received PE. Another variable – anger – moderated dropout risk such that individuals with higher levels of anger had a higher likelihood of dropout in PE (Rizvi et al., 2009). Anger has been examined as a predictor in three other studies of exposure for PTSD. In two of them, higher anger was associated with poorer prognosis (Foa et al., 2005; Pitman et al., 1991), but in a third study, after controlling for pretreatment PTSD severity, failed to find an association (Cahill, Rauch, Hembree, & Foa, 2003). Anger did not moderate outcome in any of these studies.

Dissociation has been examined as a predictor of symptom change in three separate investigations, using two different assessments of the construct. Cohen, Wiltsey Stirman et al., (2019) reported that higher levels of dissociation, as assessed by the Trauma Symptoms Inventory (TSI; Briere, Elliott, Harris, & Cotman, 1995) were associated with lower levels of symptom change in PE. Higher reported levels of dissociation on the TSI predicted a smaller magnitude of symptom change in PE, although individuals with dissociative symptoms still experienced substantial improvement (Wolf, Lunney, & Schnurr, 2016). However, Hagenaars, van Minnen, and Hoogduin (2010) had not found a prognostic relation between dissociation, as assessed by the Dissociative Experiences Scale (Van IJzendoorn & Schuengel, 1996), and symptom change.

Similarly, inconsistent findings have emerged from investigations of the predictive power of experiences of abuse. Current partner conflict was identified as a predictor of dropout (Keefe et al., 2018) as well as treatment outcome in PE; women who experienced greater relationship conflict experienced worse treatment outcomes than those who did not (Cohen, Wiltsey Stirman et al., 2019). The wisdom of providing trauma-focused treatments and cognitive behavioral therapies for individuals with a large amount of cumulative trauma exposure has been questioned (Suliman et al., 2009) in light of research suggesting that factors such as childhood abuse, anger, and dissociative symptoms are associated with poorer outcomes in Cognitive Behavioral Therapies (Lonergan, 2014). However, in secondary analyses from a clinical trial comparing CPT and PE, Resick, Suvak, and Wells (2014) found that childhood abuse did not moderate outcomes.

In recent explications of the goals of clinical prediction, several authors have reasoned that a single variable will rarely capture enough of the relevant variance to support clinical decision-making in mental health contexts (Cohen & DeRubeis, 2018; Gillan & Whelan, 2017; Kessler, 2018; Simon & Perlis, 2010). When multiple relatively independent patient characteristics each account for some of the variance in outcome, an integration of the relevant factors, rather than a focus on each of them one at a time, will yield the most powerful predictions. Importantly, recent research suggests that multivariable prediction models can outperform unguided clinical prediction (Kautzky et al., 2017, 2018), which is the pragmatic standard that ultimately any clinical decision tool must exceed. Identifying prediction models to better inform treatment selection can reduce burdens placed on the patient and the healthcare system by trial-and-error approaches. In fact, many individuals may not stay in treatment long enough to pursue a change in treatment plan if they perceive their initial treatment to be ineffective.

There are several distinct but related approaches to the use of information obtained from patients prior to treatment, that have been applied to data from randomized clinical trials (RCTs) (Cloitre, Bryant, & Schnyder, 2015; Cohen, Wiltsey Stirman et al., 2019; Kraemer, 2013). Cloitre et al. (2015) have suggested the development of a profile comprising moderators that capture key patient-level, diagnostic, historical, and behavioral factors that, in combination, can predict outcomes (Cloitre et al., 2015; Cloitre, Petkova, Su, & Weiss, 2016). Kraemer (2013) created a weighted combination of the selected individual moderators to identify individuals for whom psychotherapy may be more appropriate than medications for depression. DeRubeis et al. (2014) developed an approach for the case in which two (or more) treatments yield similar average levels of improvement via different mechanisms. The proposed approach, the Personalized Advantage Index (PAI), uses pre-treatment information and outcome data to develop context-specific algorithms that are then used to generate an index for any given patient. The sign of the PAI indicates which of two treatments can be expected to lead to a better outcome, and the absolute magnitude indicates the expected magnitude of the advantage (Cohen, Kim, Van, Dekker, & Driessen, 2019; Deisenhofer et al., 2018; Huibers et al., 2015; Keefe et al., 2018; Vittengl, Clark, Thase, & Jarrett, 2017; Zilcha-Mano et al., 2016). The PAI approach has been applied in a trial that compared PE with CPT for PTSD (Resick, Nishith, Weaver, Astin, & Feuer, 2002) to predict differential likelihood of dropout (Keefe et al., 2018) and benefit (Cohen, Wiltsey Stirman et al., 2019).

When two treatments in an RCT are not equivalently effective, it becomes less plausible that the treatments tap into different change mechanisms. In these cases, the question is not: "Which works for whom?" but rather "For whom is the more effective treatment likely to be particularly advantageous?" In this context, constructing a single prognostic model is likely to yield the most powerful, generalizable differential predictions (VanderWeele, Luedtke, van der Laan, & Kessler, 2019). Model estimates derive from a larger sample, since data from both conditions are used, and interaction terms are not estimated, thus conferring an advantage in regard to the power and generalizability of the resulting index.

A recent example of this approach is provided by Lorenzo-Luaces, DeRubeis, van Straten, and Tiemens (2017). They generated a single prognostic predictive model in a sample of depressed patients, some of whom received higher-intensity treatment (Cognitive Therapy), some of whom received lower-intensity treatments (Brief Therapy or Treatment-As-Usual). The prognostic index, which was built to predict patients' outcomes regardless of which treatment they received, was able to identify a subgroup of individuals who experienced (on average) superior outcomes in the stronger versus the weaker treatments, and another group for whom (on average) no difference in outcomes was observed between the stronger and weaker treatments. Prognostic indexes have shown promise in predicting differential response between stronger and weaker treatments in other contexts (e.g., Delgadillo, Huey, Bennett, & McMillan, 2017; Delgadillo, Moreea, & Lutz, 2016). Therefore, we examined the utility of a prognostic index to predict treatment outcome in a trial that found PE was superior to PCT in a sample of female veterans and soldiers with PTSD (Schnurr et al., 2007). We examined whether that index could predict the extent to which a participant was likely to experience greater benefit from PE, a trauma-focused treatment, or PCT, a non-trauma-focused alternative.

1. Method

Details about the original clinical trial have been published

elsewhere (Schnurr et al., 2005, 2007). An institutional review board at each site approved the research protocol. Participants provided written informed consent after they had been given a complete description of the study. Data were collected between August 2002 and October 2005.

1.1. Participants

Participants were female veterans and active-duty service members with current PTSD who enrolled and began treatment in a multi-site randomized clinical trial of PE and PCT. Inclusion criteria were: current DSM-IV PTSD according to the "1/2" rule and minimum severity ≥45 on the Clinician-Administered PTSD Scale (CAPS; Weathers, Keane, & Davidson, 2001); 3 or more months since experiencing trauma; a clear memory of the trauma that caused PTSD; agreement to not receive other psychotherapy for PTSD during study treatment; and, for those on psychoactive medication, a stable regimen for the prior 2 months. Exclusion criteria were current psychotic symptoms, mania, or bipolar disorder; current substance dependence; prominent current suicidal or homicidal ideation; cognitive impairment; current involvement in a violent relationship; and self-mutilation within the past 6 months. Participant characteristics are included in Table 1. Seventeen of the 284 participants in the trial were randomized but never started treatment and thus were excluded from the sample for the current study. These participants did not differ significantly from those who were randomized ($N = 267$) on any of the pretreatment characteristics described in Table 1.

Table 1
Baseline participant characteristics by treatment assignment.

Variable	Present-Centered Therapy ($n = 132$)		Prolonged Exposure ($n = 135$)		t/χ2 (1)
	M/%	*SD*/*n*	*M*/%	*SD*/*n*	
Clinician-rated PTSD symptom severity	78.01	16.75	78.26	16.92	−0.12
Self-reported PTSD symptom severity					
Re-experiencing	16.44	4.60	16.42	4.86	0.03
Avoidance	7.37	2.19	7.60	2.03	−0.88
Numbing	15.79	4.35	16.01	4.51	−0.42
Hyperarousal	17.53	4.20	18.45	3.92	−1.85
Time since trauma (years)	23.25	12.72	23.31	14.33	−0.04
Sexual index trauma	70.5%	93	66.7%	90	0.44
Military sexual trauma	77.3%	102	70.4%	95	1.64
Military stress exposure	26.69	7.57	26.65	6.71	0.04
Number of trauma types	9.38	3.16	9.76	3.02	−1.02
Age	45.42	9.32	44.74	9.42	0.59
White race	51.5%	68	55.6%	75	0.44
College education	28.8%	38	26.7%	36	0.15
Married/living as married	29.6%	39	30.4%	41	0.02
Working full- or part-time	43.9%	58	37.0%	50	1.32
Current mood disorder	65.2%	86	61.5%	83	0.39
Current anxiety disorder (other than PTSD)	45.5%	60	48.9%	66	0.32
Borderline personality disorder	21.2%	28	25.9%	35	0.82
Other personality disorder	51.5%	68	48.9%	66	0.18
Depression symptoms	24.10	9.40	25.50	9.54	−1.20
Anxiety symptoms	52.73	13.43	52.47	13.23	0.16
Dissociative symptoms	12.94	5.95	13.11	5.62	−0.24
Anger symptoms	1.93	0.92	1.97	0.90	−0.38
Physical functioning	39.43	13.15	38.40	11.63	0.68
Mental functioning	30.64	12.06	29.98	9.94	0.49
Self-reported quality of life	0.05	2.10	0.05	1.80	−0.01
Treatment credibility	6.05	1.32	5.94	1.52	0.60
Psychoactive medication use at screening	73.5%	97	76.3%	103	0.28
Benzodiazepine use at screening	18.9%	25	20.7%	28	0.14

Note. $N = 267$. *M*/% = mean/percentage; *SD*/*n* = standard deviation/sample size.

1.2. Measures

PTSD symptom severity. PTSD symptom severity was assessed using the CAPS (Weathers et al., 2001). A master's- or doctoral-level assessor who was blinded to treatment assignment rated the frequency and intensity of each of the 17 PTSD symptoms defined in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV; American Psychiatric Association, 1994). Participants also rated how much each of the DSM-IV PTSD symptoms bothered them in the past month on a 5-point scale from 1 (*not at all*) to 5 (*extremely*) using the PTSD Checklist (PCL; Weathers, Litz, Herman, Huska, & Keane, 1993). Symptom cluster scores were computed for reexperiencing, avoidance, numbing, and hyperarousal using the PCL. The C cluster was separated into avoidance (C1, C2) and numbing (C3–C7), based on evidence that they form separate symptom clusters (King, Leskin, King, & Weathers, 1998).

Trauma history and demographic characteristics. Index trauma type and time since the index trauma were measured as part of the CAPS. Military sexual trauma and military stress exposure were assessed using the Military Stress Inventory for Women (Fontana & Rosenheck, 1998), a 14-item questionnaire where participants rate the frequency of stressful experiences in the military. The Life Events Checklist (Weathers et al., 2001) was used to assess direct exposure to 17 types of traumatic events. The number of trauma types was computed by counting the number of events that the participant experienced directly or witnessed. Prior to treatment, demographic characteristics including age, race (non-White race/White Race), college education (less than a college degree/college degree or higher), marital status (not married/-married or living as married), and work status (not working/working full- or part-time) were collected.

Psychological diagnoses and symptoms. Current mood disorder, current anxiety disorder (other than PTSD), borderline personality disorder, and personality disorder other than borderline personality disorder were assessed using the Structured Clinical Interview for DSM-IV-Patient Version (SCID-P; First, Spitzer, Williams, & Gibbon, 1995). Self-reported symptoms of depression and anxiety were measured using the Beck Depression Inventory (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) and Spielberger State Anxiety Inventory (Spielberger, Jacobs, Russell, & Crane, 1983). Subscales of the Trauma Symptom Inventory (TSI; Briere et al., 1995), a self-report questionnaire that assesses PTSD symptoms and associated features experienced over the past 6 months on a scale from 0 to 3 (never to often), was used to assess dissociative (mean of 9 items) and anger symptoms (mean of 2 items: starting arguments or picking fights to get your anger out; yelling or telling people off when you felt you shouldn't have).

Functioning and quality of life. The Physical Component Summary Scale (PCS) and Mental Component Summary Scale (MCS) were calculated from responses to the 36-item Short Form Health Survey (SF-36; Ware & Sherbourne, 1992). Higher scores on the PCS and MCS indicate better functioning. Subjective quality of life was measured using the 16-item Quality of Life Inventory (QOLI; Frisch, 1994). Weighted satisfaction scores on the QOLI range from −6 (most negative) to +6 (most positive).

Treatment credibility. Participants rated treatment credibility at the first treatment session. Four questions about how logical the treatment seems, how successful the treatment will be in reducing trauma-related symptoms and other personal problems, and confidence in recommending the treatment to a friend were adapted from the Credibility/Expectancy Questionnaire (CEQ; Devilly & Borkovec, 2000).

Medication use. Participants reported information about current psychoactive medications during screening for the study. Two predictors were generated from the medication assessment form: whether the participant used any form of psychotropic medication at intake, and whether the participant was currently taking any form of benzodiazepine at intake.

1.3. Procedure

Participants were randomly assigned to receive 10 weekly, 90-min sessions of either PE or PCT. PE included education about common reactions to trauma; breathing retraining; prolonged, in-session imaginal exposure of trauma memories; homework (listening to a recording of the recounting made during the session and repeated in vivo exposure to safe situations the patient avoids due to trauma-related fear); and discussion of thoughts and feelings related to exposure exercises. PCT focuses on current life problems as manifestations of PTSD. Participants were provided with a rationale for the present focus of treatment. PCT included psychoeducation about responses to trauma, normalizing these responses, and increasing insight into their influence on current problems. Therapists could use a range of supportive and insight-oriented interventions that did not focus on participants' traumatic experiences. If a participant discussed her trauma, therapists acknowledged and validated the experience and its consequences and gently redirected her to discuss the consequences in present terms.

Therapists were 52 female masters or doctoral-level clinicians who were randomized to deliver one of the two treatments. All received specialized training in their assigned treatment. Sessions were videotaped and reviewed by an expert supervisor, who provided telephone supervision. Therapist adherence and competence, rated by an independent fidelity monitor, were excellent and equivalent across treatments (Schnurr et al., 2007).

1.4. Analytic strategy

Data processing. Dichotomous variables were effect-coded (as −0.5/0.5) and continuous predictors were standardized. Missing values were imputed using a non-parametric random forest method (R package "missForest"; Stekhoven & Buhlmann, 2012). Out-of-the-bag error estimates for the imputations were as follows: CAPS post treatment score: (N = 36 missing [13.5%]); RMSE = **14.96447**; QOLI: (N = 1 missing [0.37%]) RMSE = **1.619698**; PCS: (N = 1 missing [0.37%]) RMSE = **11.01657**; MCS: (N = 1 missing [0.37%]) RMSE = **7.984888**.

Variable selection. To select which variables to include in the final model, we used a two-step procedure. First, we employed Elastic Net Regularization (ENR; glmnet package; Friedman, Hastie, & Tibshirani, 2010) to identify potential prognostic predictors of treatment response. ENR is suitable for large numbers of potential predictors and can overcome issues of high correlation between baseline variables (Garge, Bobashev, & Eggleston, 2013). ENR combines the L1 and L2 penalizations to allow for the selection of a parsimonious set of variables that predict outcome (Hastie, Tibshirani, & Friedman, 2009), providing a hybrid of the least absolute shrinkage and selection operator (LASSO) and Ridge regression approaches. The alpha parameter, which in ENR determines the ratio of L1/L2 penalization, was set to 0.75 (alpha = 1 corresponds with pure LASSO regularization, and alpha = 0 corresponds with pure ridge regression). Tuning of the lambda parameter, which determines the degree of penalization (with larger lambda values corresponding to heavier shrinkage of regression coefficients) was optimized using 10-fold cross-validation. We performed 5 iterations of ENR (with different randomization seeds resulting in different permutations of the 10-fold cross-validation) and retained only those variables that were selected across all 5 runs. Those variables were then subjected to stepwise AIC-penalized bootstrapped variable selection (Austin & Tu, 2004) via the BootStepAIC package (Rizopoulos, 2009). Using this approach, 10,000 bootstrapped samples were drawn. Each sample was the same size as the full dataset, with $^{2}/_{3}$ of the unique original cases represented, with the remaining $^{1}/_{3}$ resampled. Within each sample, the BootStepAIC algorithm uses backwards elimination (with $\alpha = 0.05$) to select variables that independently contribute to predicting outcome. Following the recommendations of Austin and Tu (2004), variables that were selected by BootStepAIC in at least 60% of the bootstrapped replicates were retained for the final model. This approach increases the likelihood that the variables selected will function properly and consistently, and that the final model will replicate in future samples drawn from the same population.

Generation of prognostic index through 10-fold cross-validation (CV). Each patient's prognostic index (PI) was constructed similarly to the approach demonstrated by Lorenzo-Luaces et al. (2017). Ten-fold CV was used when generating PIs to protect against over-fitting during the model weight-setting process (Kuhn & Johnson, 2013). The data were split into 10 folds. Predictions for each of the held out 1/10 of the sample were generated by regression models, whose weights were set using the other 9/10 of the data. Within each held-out sample, each patient's predicted outcome is estimated by entering their baseline values on the relevant variables into the model. This estimate of each patient's value on the PI is generated without his or her data. The 10-fold CV procedure was repeated multiple times ($N = 1000$) to ensure stable results (Kuhn & Johnson, 2013), and the findings presented below summarize results from the 1000 runs. Point estimates for regression weights and other associated statistics presented are the means across the 1000 runs, and the associated variances were estimated using the between-run and within-run variances. Supplemental Tables 1-2 include more detailed results from this process, including regression weights and number of ENR iterations that each variable was selected.

Treatment response. We conducted linear regressions predicting outcomes at follow-up with variables representing treatment condition, the PI (controlling for baseline symptoms by its inclusion in the model from which the PI is derived), and the interaction between the PI and treatment condition. If the test associated with the coefficient for the interaction between the PI and treatment is statistically significant, it is an indication that outcomes vary between the treatments across different values of the PI (Lorenzo-Luaces et al., 2017). We used the Johnson-Neyman technique (Johnson & Neyman, 1936) to determine the cut-point on the PI at which the difference between PE and PCT became significant, using a modified version of the MODPROBE macro (Hayes & Matthes, 2009).

2. Results

2.1. Variable selection

Table 2 contains a summary of variable selection results for all variables that were considered for inclusion in the model. ENR was applied to the full set of 29 potential baseline predictors. The 10 potential predictors that were selected across all 5 runs of ENR were then submitted to a final variable selection stage with BootStepAIC. Bold text indicates the variables selected in at least 60% of 10,000 bootstrapped replicates by BootStepAIC and thus included in the final model.

Table 3 contains the results of the final regression model. Higher baseline PTSD symptoms and experience of military sexual trauma were associated with higher posttreatment PTSD symptoms. Better physical and mental functioning and higher perception of treatment credibility were associated with lower post-treatment CAPS.

2.2. Outcomes for those with good versus poor prognoses

The mean PI across all 1000 reps was 58.22 ($sd = 16.50$ min = 10.44 max = 111.54). Linear regressions predicting post-treatment symptom severity from treatment type, the PI, and the interaction between the two variables (PI and treatment) across all 1000 repetitions accounted for approximately 39% of the variance in posttreatment symptom severity (mean $R^2 = 0.39$ [95% CI: 0.38587, 0.38789], mean root MSE = 20.28 [95% CI: 20.27, 20.28]), and indicated that in addition to treatment type and prognistic index, their interaction moderated post-treatment symptom severity, $b = 0.30$, $SE_b = 0.15$ [95% CI: 0.01, 0.60], $p = .049$, with a mean increase $R^2 = 0.0091$ [95% CI: 0.0090, 0.0091]; See Table 4 for the full model. Fig. 1 depicts the observed advantage of PE over PCT for participants with different prognoses. For

Table 2
Summary of variable selection process.

Variable	Step 1: Retained by Elastic Net? (# of times retained out of 5 runs)	Step 2: Decision Based on Elastic Net: Included in BootStep AIC?	Result: Final Decision: Selected by Bootstep AIC?
Clinician-rated PTSD symptom severity (baseline)	5/5	Yes	Yes
Re-experiencing	1/5	No	
Avoidance	2/5	No	
Numbing	0/5	No	
Hyperarousal	1/5	No	
Time since trauma	5/5	Yes	No
Sexual index trauma	5/5	Yes	No
Military sexual trauma	5/5	Yes	Yes
Military stress exposure	2/5	No	
Number of trauma types	4/5	No	
Age	3/5	No	
White race	4/5	No	
College Education	1/5	No	
Married/living as married	4/5	No	
Working full- or part-time	0/5	No	
Current mood disorder	5/5	Yes	No
Current anxiety disorder	0/5	No	
Borderline personality disorder	0/5	No	
Other personality disorder	0/5	No	
Depression symptoms	3/5	No	
Anxiety symptoms	0/5	No	
Dissociative symptoms	5/5	Yes	No
Anger symptoms	5/5	Yes	No
Physical Functioning	5/5	Yes	Yes
Mental Functioning	5/5	Yes	Yes
Self-reported quality of life	0/5	No	
Treatment credibility	5/5	Yes	Yes
Psychoactive medication use at screening	1/5	No	
Benzodiazepine use at screening	0/5	No	

Note. Variables selected to be in the final model are in boldface. PTSD = post-traumatic stress disorder.

Table 3
Regression model predicting posttreatment posttraumatic stress symptoms from predictors chosen by variable selection process.

Predictor	Estimate	*SE*	*Standardized Estimate*
Intercept	56.51	1.41	
Baseline PTSD severity	11.87	1.37	0.46
Treatment credibility	−4.48	1.24	−0.17
Mental functioning	−4.39	1.41	−0.17
Physical functioning	−5.95	1.29	−0.23
Military sexual trauma	7.20	2.86	0.12

Note. $N = 267$. *SE* = standard error; *CI* = 95% confidence interval; PTSD = posttraumatic stress disorder. Posttraumatic stress symptom severity at baseline and posttreatment were measured using the Clinician-Administered PTSD Scale. Model $R^2 = 0.39$, root mean squared error = 20.01.

the subset of patients with the best prognoses, a large advantage of PE over PCT was observed: the average post-treatment CAPS score for individuals who received PE was over 20 points lower than for individuals who received PCT among those with the very best prognoses (mean Cohen's d = 1.84 across 1000 repetitions), and at least 10 points lower for individuals who were within approximately the top 60th percentile of prognoses.

The average point of transition between significance and non-significance across 1000 repetitions was 63.45 on the PI [95% CI: 63.43, 63.47], meaning there was a significant advantage of PE over PCT for PI scores below the cutpoint, which corresponded to roughly the 64th percentile of prognoses. In other words, for the 64% of patients with the best prognoses, PE resulted in statistically significantly better post-treatment outcomes, while among the patients with the worst prognoses, outcomes in the two treatment groups were not statistically different. Treatment with PCT was not associated with statistically significantly better post-treatment scores at any point on the continuum.

Table 4
Regression model predicting post-treatment symptom severity from treatment type, the PI, and their interaction.

Variable	Estimate	Standard Error	95% Confidence Limits	t	p-value
Treatment	−6.7088	2.4854	−11.580, −1.8375	−2.70	0.0069
Prognostic Index	0.9154	0.0765	0.7654, 1.06547	11.96	<.0001
Interaction	0.2999	0.1526	0.0008, 0.59906	1.97	0.0494

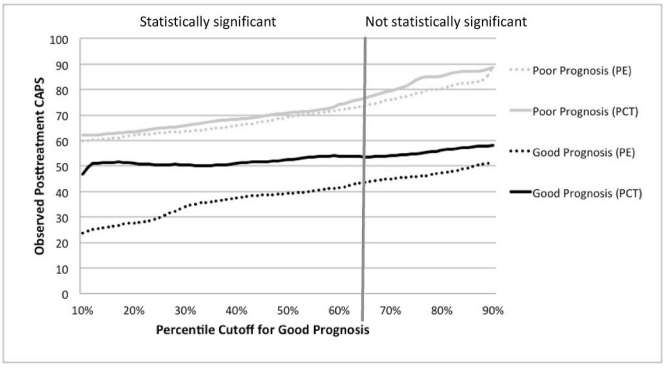

Fig. 1. Observed posttreatment symptom severity for Prolonged Exposure (PE) and Present-Centered Therapy (PCT) for participants with different prognoses. The sample was split into either a "Good Prognosis" or "Poor Prognosis" group using a range of cutoffs, represented along the X-axis. As one moves from left to right, the percentage of the overall sample included in the "Good Prognosis" group grows, and the sample size for the "Poor Prognosis" group shrinks. Within each of these two groups, the average posttreatment Clinician Administered PTSD Scale (CAPS) score for those who received PE (dotted line) and those who received PCT (solid line) was calculated. The four lines represent the average posttreatment CAPS score for each of the two treatments in the "Good Prognosis" and "Poor Prognosis" subgroups.

3. Discussion

Using data from a large practical clinical trial, we demonstrated how multivariable predictive models can generate patient-specific information that could be used to inform treatment decisions. Analyses to identify individual predictive factors indicated that lower perceived treatment credibility and having higher baseline PTSD symptoms, worse physical and mental functioning, and military sexual trauma predicted higher post-treatment PTSD symptoms across treatment groups. We combined these factors to form a single prognostic index that was associated with, for each individual, the expected advantage of PE over PCT. Although the primary study observed a small overall advantage of PE over PCT (Schnurr et al., 2007), we found a substantial advantage for PE in the subset of participants with better overall prognoses. Among this subset, those who received PE experienced lower post-treatment PTSD symptoms than those who received PCT. In contrast, we found no appreciable difference between the two treatments for the individuals with poor prognostic profiles.

Multivariable predictive models improve upon both the accuracy

and clinical utility of past efforts to identify single variables that predict treatment outcomes for the purpose of informing treatment selection (Cohen & DeRubeis, 2018). The variable selection and modeling approach we used stands in contrast to treatment selection modeling efforts that focus more (e.g., DeRubeis et al., 2014) or explicitly on moderators, which predict differential response between two treatments. The prognostic approach used here draws upon work by other groups who have demonstrated the ability of prognostic models to identify individuals who will benefit from stronger versus weaker treatments (e.g., Delgadillo et al., 2017; Lorenzo-Luaces et al., 2017). However, recent work has suggested approaches other than prognostic models might be superior in some circumstances (VanderWeele et al., 2019). Future efforts with larger samples that can accommodate a true-holdout could compare the approaches.

Although replication of these results is essential before drawing conclusions about clinical implications, the findings suggest that it may be possible to inform treatment selection by identifying patients with specific prognostic profiles that are associated with better treatment outcomes for TF-EBPs. Hundt, Barrera, Arney, and Stanley (2017) found that clinicians may be reluctant to offer PE, although patients who complete PE have indicated that "it's worth it in the end" (p. 51). By identifying individuals who are likely to experience more substantial benefit from a TF-EBP, clinicians and patients may have greater confidence in the decision to begin PE. In this study, we did not identify patients for whom the non-trauma-focused option could be expected to produce better results. Our findings do suggest that for individuals who are unlikely to benefit substantially more from trauma-focused than non-trauma-focused treatment, factors such as patient preference, provider availability, costs, or availability of other treatment options may be factored more heavily in the treatment decision (VanderWeele et al., 2019). Because there was no appreciable difference in outcomes among the subset with the poorest prognoses, and these patients' symptoms remained elevated, our findings also highlight the importance of identifying the most effective and appropriate treatments for such individuals. Whether another trauma-focused treatment such as CPT may be more effective with this population remains to be explored. Recent findings (Cohen, Wiltsey Stirman et al., 2019; Deisenhofer et al., 2018; Keefe et al., 2018) suggest that model-based treatment selection approaches may be useful in helping individuals make treatment decisions by identifying those for whom one trauma focused treatment may outperform another to a clinically significant extent. Identification, refinement, and development of treatments that will improve outcomes for individuals with poorer prognoses will be an important advance in PTSD treatment.

While this study demonstrates a promising approach to optimizing clinical decision making and improves upon methodologies that test individual moderators, several limitations should be noted. First, although we used 10-fold CV to specify predictive model weights and generate the predictions that were evaluated, we performed variable selection and imputation using the full sample. Without a true hold-out sample for all stages of analysis risks invalid statistical inference (Kriegeskorte, Simmons, Bellgowan, & Baker, 2009), model overfitting and inflated relationships is a possibility (Fiedler, 2011), and can increase risk of overconfidence (Hastie et al., 2009). Simulations by Luedtke, Sadikova, and Kessler (2019) suggest that at least 300 individuals per treatment arm are needed to detect reliable improvements in outcomes related to treatment selection models, but RCTs with these samples are currently unavailable for PTSD. In fact, across medicine and mental health, less than 30% of the clinical prediction models have been externally validated (4–10% in psychiatry, according to a recent review by Salazar de Pablo et al., 2021). Sample sizes from most trials are not sufficient to include a holdout sample, and few replication studies comparing the same interventions make external validation a challenge for psychotherapy research. Findings from our study and others may inform efforts to develop and refine prediction models in settings such as healthcare systems.

The population of patients and therapists should also be considered in conjunction with our findings. The patients were female and were mostly veterans with a high degree of chronicity and diagnostic complexity. Most of the therapists in the study were PE novices who treated relatively few patients over the course of the study. While this maximizes the generalizability of the findings to clinical practice with therapists who are not experts in the treatments, the study was not designed to inform treatment selection using this approach. Further research with greater variability in patient and therapist characteristics will be important to carry this work forward.

Before launching a real-world clinical application of a prognostic index approach, it is essential that the predictive relationships and the prognostic index presented in this study be validated in an independent sample. Even then, this model may not generalize to a population other than the female military and veteran sample from which it was built (Nigatu, Liu, & Wang, 2016). This model may be improved upon if other variables that were not available for this sample (e.g., additional details about the trauma history such as whether childhood sexual abuse occurred) were also included in the selection process. Additionally, future research on this approach should include consideration of outcomes such as quality of life and functioning, and approaches to using a prognostic index to inform treatment decisions in routine care settings. It is reassuring that recently, Bone et al., (in press) identified studies using data from naturalistic settings in which prediction models were used that reported impressive prediction accuracy. Their findings suggest that data from routine care samples may further efforts to develop valid predictive and prognostic models. However, the ability of prediction models to inform treatment selection in new samples has yet to be established, with tests of generalizability yielding mixed results (e.g., Schwartz et al., 2020; van Brunswijk et al., 2020).

Therapists and their patients share the goal of pursuing a treatment that will alleviate PTSD and improve quality of life. Rapid development and integration of clinical decision-making tools that can estimate the benefit of one treatment compared to others can support this goal and reduce uncertainty about which available approach will be most beneficial. Such decision aids may increase confidence in, and uptake of, treatments outlined in the practice guidelines. Efforts to develop, test, and implement predictive and prognostic models that account for the numerous factors that may impact treatment can accelerate the integration of such approaches into everyday clinical care.

Conflicts of interest

The authors have no conflicts of interest to declare.

CRediT authorship contribution statement

Shannon Wiltsey Stirman: Conceptualization, Writing – original draft, Writing – review & editing. **Zachary D. Cohen:** Conceptualization, Methodology, Formal analysis, Writing – review & editing. **Carole A. Lunney:** Formal analysis, Data curation, Visualization, Writing – review & editing. **Robert J. DeRubeis:** Conceptualization, Methodology, Writing – review & editing. **Joshua F. Wiley:** Conceptualization, Methodology, Writing – review & editing. **Paula P. Schnurr:** Funding acquisition, and Investigation in underlying trial, Conceptualization, Writing – review & editing.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brat.2021.103872.

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