Received: 20 October 2020 | Revised: 13 July 2021 | Accepted: 15 July 2021

DOI: 10.1002/jts.22744

ISTSS International Society for Traumatic Stress Studies WILEY

RESEARCH ARTICLE

The effect of perceived life stress on posttraumatic stress disorder treatment outcome

Mark S. Burton[1] | **Elizabeth H. Marks**[2] | **Michele A. Bedard-Gilligan**[2] | **Norah C. Feeny**[1] | **Lori A. Zoellner**[2]

[1] Department of Psychological Sciences, Case Western Reserve University, Cleveland, Ohio, USA

[2] Department of Psychology, University of Washington, Seattle, Washington, USA

Correspondence
Mark Burton, Department of Psychiatry, Emory University School of Medicine, 12 Executive Park, 3rd Floor, Atlanta GA 30329.
E-mail: msburto@emory.edu

[#]Mark Burton is now at the Department of Psychiatry, Emory University (Atlanta, GA).

Funding information
National Institute of Mental Health, Grant/Award Numbers: R01MH066347, R01MH066348; William T. Dahms, M.D. Clinical Research Unit, funded under the Cleveland Clinical and Translational Science Award, Grant/Award Number: UL1 RR024989

Abstract

Life stress following trauma exposure is a consistent predictor of the development of posttraumatic stress disorder (PTSD). However, there is a dearth of research on the effect of life stress on PTSD treatment outcomes. The current study examined the effects of pretreatment levels of perceived life stress on treatment outcome in a sample of 200 individuals with PTSD who were randomized to receive either prolonged exposure (PE) therapy or sertraline as part of a clinical trial. Life stress over the year prior to treatment significantly interacted with treatment type to predict higher residual PTSD symptom severity, as assessed using the PTSD Symptom Scale–Interview, among participants who received sertraline but not those who received PE, $\beta = .24$, $p = .017$, $\Delta R^2 = .03$. These findings were similar for self-reported depression severity, $\beta = .27$, $p = .008$, $\Delta R^2 = .04$. Adherence to either PE homework or sertraline compliance did not mediate this association nor did life stress predict treatment retention for either treatment arm. Higher levels of perceived life stress may serve as a prescriptive predictor of PTSD treatment outcome, with PE remaining efficacious regardless of heightened pretreatment life stress. These findings encourage clinician confidence when providing PE to individuals with higher levels of life stress. Future researchers should examine the impact of PTSD treatment on perceived and objective measures of life stress to improve treatment for individuals who experience chronic stress.

There are several effective treatments for posttraumatic stress disorder (PTSD), including psychotropic medications and psychotherapy (Watts et al., 2013). Treatment guidelines consistently recommend exposure-based cognitive behavioral therapies, such as prolonged exposure (PE), as first-line treatment for PTSD, whereas pharmacological intervention with selective serotonin reuptake inhibitors is typically recommended as a secondary treatment (e.g., American Psychological Association [APA], 2017). Understanding factors related to the effectiveness of these evidence-based treatments is essential for improving outcomes for individuals suffering from PTSD. Environmental conditions following trauma exposure, such as perceived life stress, are consistent predictors of PTSD symptom severity (Brewin et al., 2000; Ozer et al., 2003). However, it remains unclear whether life stress influences PTSD treatment response, retention, and adherence.

There is strong support for perceived life stress as an etiological factor in the development of numerous psychological disorders (see Cohen, et al., 2007; Marin et al., 2011). Multiple theories have been developed to explain the association between life stress and psychopathology, including diathesis-stress models (Monroe & Simons, 1991), the conservation of resource models (Hobfoll, 2002), the

kindling hypothesis (Post, 1992), the theory of allostatic load (Juster et al., 2010), and the stress generation hypothesis (Hammen, 2006), as well as more recent theories that examine the association between stress and neurobiological systems related to reward (Pizzagalli, 2014), immune system inflammation (Slavich & Irwin, 2014), and corticosteroids (McEwen et al., 2016). The type of life stress (i.e., interpersonal loss) an individual experiences and the timing of stress (i.e., more recent) have been shown to be related to an increased risk of depression onset and severity (McGonagle & Kessler, 1990; Muscatell et al., 2009; Paykel, 2003).

Studies that have specifically examined PTSD have demonstrated that life stress interacts with a history of childhood adversity (McLaughlin et al., 2010) and cognitive vulnerabilities (Elwood et al., 2009) to predict depression and PTSD symptoms. Other studies suggest that individuals with PTSD report higher levels of life stress and show increased physiological indicators of allostatic load (Glover et al., 2006). These findings complement translational research suggesting that individuals with PTSD demonstrate a reduced capacity to attenuate their physiological reaction to stressful stimuli (Fani et al., 2012; Jovanovic et al., 2010), possibly explaining why life stress following a traumatic event is a consistent predictor of PTSD symptom severity (e.g., Brewin et al., 2000).

Theories of resilience suggest that treatment for chronic PTSD can and should address environmental factors beyond symptoms to ensure substantial and long-lasting change (see Burton et al., 2015). If life stress helps to maintain PTSD symptoms, treatments that do not address life stress may be less effective. However, the literature on the impact of life stress on treatment outcomes is outdated, sparse, and the findings are mixed. For example, some studies have shown that life stress experienced before and during treatment that combines psychotherapy and psychotropic medications for depression predicts higher posttreatment depression symptom severity and a lower likelihood of remission (McQuaid et al., 2000; Monroe et al., 1992). However, in a study of fluoxetine for depression, life stress prior to treatment did not predict treatment outcomes (Otto et al., 1997). In the anxiety literature, retrospective self-report (i.e., 3–5 years posttreatment) of experiencing chronic life stress pretreatment predicted poorer outcomes for individuals with agoraphobia with panic attacks (Wade et al., 1993). It remains unclear whether life stress exacerbates symptoms, leading to poor response, or if it impacts adherence to treatment and, thus, a reduction in the efficacy of a given intervention. In the HIV literature, for example, life stress has been shown to reduce adherence to antiviral drug regimens, leading to poorer outcomes (Leserman et al., 2008; Mellins et al., 2003). However, no previous research has explored the associations between life stress and psychotherapy or psychotropic adherence.

The present study examined the effects of perceived life stress on treatment outcome, retention, and adherence among a sample of individuals who were receiving either pharmacotherapy (i.e., sertraline) or psychotherapy (i.e., PE) as part of a large clinical trial for the treatment of chronic PTSD. We hypothesized that the perceived negative impact of stressful life events during the year before treatment would be related to more severe PTSD and depression symptoms at baseline and posttreatment, as well as higher dropout rates for individuals who received both types of treatments. We also posited that adherence to the treatment protocols would mediate the association between baseline levels of life stress and treatment outcome.

METHOD

Participants

This was a secondary analysis of a published clinical trial comparing PE to sertraline for the treatment of chronic PTSD in 200 men and women between 18 and 65 years of age (NCT:00127673; Zoellner et al., 2019). Participants were recruited through community referrals, flyers, and advertisements. The inclusion criteria included being 18 to 65 years of age and having a diagnosis of primary, chronic PTSD, according to the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., text rev; *DSM-IV-TR*; APA, 2000). The exclusion criteria were a current diagnosis of schizophrenia or another psychotic disorder; medically unstable bipolar disorder; depression with psychotic features or depression severe enough to require immediate psychiatric treatment; substance dependence within the past 3 months; severe self-injurious behavior or attempted suicide within the past 3 months; or, for assault cases, an ongoing intimate relationship with the perpetrator.

Procedure

All procedures were approved by the Institutional Review Boards of Case Western Reserve University and the University of Washington. After initial telephone contact, participants completed an in-person intake evaluation conducted by trained intake evaluators (IEs), who were masked to the eventual treatment arm, to determine trial eligibility. At the randomization visit, participants completed a battery of self-report questionnaires, including the LES and BDI. Participants were initially randomized to a choice or no choice of their treatment group. Those randomized to

the choice group chose their treatment, whereas those randomized to the no-choice group were randomly assigned. Treatment consisted of 10 weeks of PE or sertraline treatment. A posttreatment assessment was conducted by IEs.

Psychotherapy

PE (Foa et al., 2007) is a 10-week intervention, with weekly sessions, each of which is 90–120 min in duration. Session content includes psychoeducation involving common reactions to trauma exposure, breathing retraining, in vivo exposure homework exercises, and imaginal exposure and processing during sessions. Trained outside raters reviewed 10% of videotaped sessions. PE therapists completed 90% of essential components, and there were no protocol violations observed.

Pharmacotherapy

The pharmacotherapy condition consisted of 10 weeks of sertraline, with weekly meetings with a study psychiatrist, each of which lasted 30–45 min. Sertraline dosage was adjusted based on a standardized titration algorithm (Marshall et al., 2001), starting at 25 mg/day and proceeding up to 200 mg/day, if indicated. The mean dosage at the end of treatment was 115 mg/day (SD = 78.00). Board-certified psychiatrists monitored side effects, adjusted sertraline dosage, and provided general encouragement and support. Trained raters reviewed 10% of videotaped sessions. Pharmacotherapists completed 96% of essential components, and there were no protocol violations observed.

Measures

Interview measures

PTSD symptoms

The PTSD Symptom Scale–Interview (PSS-I; Foa et al., 1993) was used to measure PTSD symptom severity at pre and posttreatment. The PSS-I is a 17-item, semistructured clinical interview that is used to assess the severity and frequency of PTSD symptoms based on *DSM-IV* symptom criteria. In the present study, the PSS-I was used to diagnose PTSD as well as to determine symptom severity. The PSS-I has demonstrated good convergent validity and interrater reliability (i.e., *r*s = .93–.95; Foa et al., 1997; Foa & Tolin, 2000). In the present study, Cronbach's alpha was .65, and interrater reliability was high for a subset (i.e., 10%) of randomly drawn rerated PSS-I assessments, intraclass correlation coefficient (ICC) = .95.

Depression

The Structured Clinical Interview for DSM-IV (SCID-IV; First et al., 1997) was used to determine trial eligibility and assess comorbid major depressive disorder for the present analyses. The SCID-IV is a semistructured interview that is used to assess the presence of psychological disorders based on *DSM-IV* symptom criteria (APA, 2000). The measure has demonstrated good interrater reliability (Lobbestael et al., 2011). In the present study, interrater reliability was acceptable for a subset (i.e., 10%) of randomly rerated SCID assessments, $\kappa = .80$.

Self-report measures

Perceived life stress

The Life Experiences Survey (LES; Sarason et al., 1978) was used to assess perceived life stress during the year prior to the start of treatment. The LES is a 60-item measure, with 10 items relevant to students only. Items consist of descriptions of life events that can be endorsed as having occurred in the past 6 months or 1 year, with a corresponding impact rating system for each event. Participants were asked to rate the impact of each endorsed event as either positive or negative, with the magnitude of impact (i.e., positive or negative) scored on a scale of 0 (*no impact*) to 3 (*extreme impact*). Total impact scores were derived from summing all items, with separate scores calculated for past-year positive impact, negative impact, and overall impact. Original psychometric analyses have indicated good test–retest reliability for the Negative Impact score ($r = .88$) but poor-to-questionable test–retest reliability for the Positive Impact ($r = .53$) and Overall Impact scores ($r = .64$), as well as a lack of a correlation between Positive Impact scores and measures of depression and trait anxiety (Sarason et al., 1978). Therefore, in the present study, only Negative Impact scores were utilized as a measure of perceived life stress, a method in line with those used by previous researchers who have employed this measure (e.g., Constantino et al., 2000; Young et al., 2000)

Depression

The Beck Depression Inventory (BDI; Beck et al., 1961) was used to assess depression at baseline and posttreatment. The BDI is a 21-item, self-report measure that is used to assess symptoms of depression the respondent has experienced during the past 2 weeks. Items are scored on a 4-point Likert scale ranging from 0 to 3, with total summed scores calculated to represent depression severity and higher scores indicating more severe depressive symptoms. The BDI has demonstrated good internal consistency (i.e., across studies: *M* Cronbach's $\alpha = .86$) and high convergent validity with the Revised Hamilton Rating Scale for

Depression (across studies: $M\ r = .69$; Beck et al., 1988). In the current sample, Cronbach's alpha was .87.

Treatment adherence

To measure overall participant adherence across treatments, standardized scores (i.e., *z* scores) were calculated for adherence measures in each condition. In the PE condition, adherence to homework was measured using the Utility of Treatment Inventory (UTI; Foa et al., 2002), which is used to measure adherence and helpfulness related to homework exercises in PE. In the present study, we used the average score for the adherence items endorsed each week. In the sertraline condition, adherence was measured using the self-reported total number of days the participant took sertraline over the previous week. These indices were averaged across weekly sessions, then converted to a *z* score to provide a single measure of treatment adherence for the entire sample.

Data analysis

In total, 31 individuals had erroneous or missing LES data: 19 participants endorsed every event, seven participants gave no responses, and five participants scored higher than 2 standard deviations above the mean, indicating a misunderstanding of the measure. As a group, these individuals ($n = 31$) did not differ on baseline PTSD or depression symptoms from the rest of the sample, but those with missing or erroneous data were more likely to be assigned to sertraline. The reason for this trend is unclear given that raw LES average scores, including all the erroneous scores, did not differ between treatment groups. Thus, instead of deleting these cases listwise, cases with erroneous data were included as missing, and the entire intent-to-treat (ITT) sample was analyzed assuming data were missing at random (MAR), with the inclusion of the conditional treatment variable and treatment interaction variable in all models. As a check on this analytic approach, analyses were rerun with these cases deleted listwise ($n = 169$), and coefficients were highly similar compared to the full ITT sample. Therefore, coefficients for the ITT sample are reported in the current manuscript.

Linear regression was conducted using M*plus* (Version 7) statistical software (Muthén & Muthén, 2015) to identify the effect of life stress on PTSD and depression outcomes (i.e., posttreatment symptom severity after controlling for pretreatment symptom severity), controlling for the moderating effect of treatment type. The overall model included effects for life stress, treatment assignment, and a Treatment x Life Stress interaction term predicting treatment outcome. Path analyses were conducted, also using M*plus*, to examine the mediating effects of adherence and depression on the direct effect of life stress on PTSD outcome. We examined moderation of treatment type for these mediation models by comparing a constrained model, which held regression coefficients across treatments equal, to an unconstrained model that allowed coefficients to differ across treatments. Significantly lower chi-square tests of model fit and lower Bayesian information criterion (BIC) values are indicative of a better fit to the data. Maximum likelihood estimation procedures were used to identify the regression coefficients. This method allows for the analysis of the entire ITT sample, assuming MAR, and is preferred over other methods (e.g., ordinary least squares regression) for handling missing longitudinal data.

TABLE 1 Demographic and trauma characteristics

Variable	*M*	*SD*
Age (years)	37.41	11.30
	n	%
Gender		
Female	151	76.0
Male	49	24.0
Educational attainment		
College-educated	60	30.0
Not college-educated	140	70.0
Ethnicity		
Caucasian	131	65.5
African American	43	21.5
Other	26	13.0
Primary trauma type		
Adult sexual assault	62	31.0
Adult non-sexual assault	45	22.5
Childhood sexual assault	35	17.5
Childhood nonsexual assault	13	6.5
Motor vehicle or other accident	25	12.5
Natural disaster	2	1.0
Combat/war	5	2.5
Death/suicide of loved one	13	6.5

RESULTS

Demographic characteristics, psychopathology, and trauma type information for the sample are reported in Tables 1 and 2. The treatment conditions did not differ between demographic variables (i.e., age, gender, race, and income), PTSD symptom severity, depression symptom severity, or negative life stress scores. PTSD and depression

TABLE 2 Mean scores for psychological variables, by treatment arm

Variable	PE (n = 116)		Sertraline (n = 84)	
Psychological assessments	***M***	***SD***	***M***	***SD***
Baseline PTSD severity (PSS-I)	29.41	6.87	29.78	6.38
Posttreatment PTSD severity (PSS-I)	10.67	10.63	12.97	10.74
Baseline depression severity (BDI)	24.40	9.65	25.90	9.84
Posttreatment depression severity (BDI)	9.30	10.04	12.98	11.69
Baseline negative life stress (LES-N)	17.97	15.18	22.22	19.85
Adherence				
Mean adherence to PE homework (UTI)	3.52	0.73	–	–
Mean medication adherence[a]	–	–	2.45	1.18

Note: Means and standard deviations for posttreatment measures of pathology and adherence were estimated based on statistical modeling of the intent-to-treat (ITT) sample in the current study. PTSD = posttraumatic stress disorder; PSS-I = PTSD Symptom Scale–Interview; BDI = Beck Depression Inventory; LES-N = Life Events Checklist–Negative; PE = prolonged exposure; UTI = Utility of Treatment Inventory.

[a]Reflects the number of days medication was taken over the week, averaged across all weeks of treatment, recorded on the medication adherence form.

symptom severity were both correlated with life stress at baseline, $r = .20$ and $r = .22$, respectively.

Direct effect of life stress on PTSD outcomes

The overall model that included effects for life stress, treatment assignment, and a Treatment x Life Stress interaction term on PTSD outcome demonstrated a significantly better fit over the baseline model, $\chi^2(4, N = 196) = 21.02$ $p < .001$, $R^2 = .13$, with a significant interaction term, $\beta = .24$, $p = .017$, $\Delta R^2 = .03$, indicating that higher pretreatment levels of life stress predicted poorer PTSD outcomes more so for participants receiving sertraline compared to those receiving PE. Similarly, higher pretreatment ratings of life stress predicted a poorer depression outcome for individuals receiving sertraline compared to those receiving PE, $\chi^2(4, N = 196) = 35.98$ $p < .001$, $R^2 = .20$, $\beta = .27$, $p = .008$, $\Delta R^2 = .04$. Figure 1 and Figure 2 depict the moderation effect of treatment on the association between life stress and PTSD and depression outcomes, respectively. Importantly, life stress did not predict either PTSD or depression outcome when treatment was not included in the model or when the individual treatment groups were examined as separate samples, indicating a small general effect for life stress. Life stress was not a predictor of treatment dropout for the overall sample or within either treatment group.

Mediating effects of adherence and depression

The z score measure of general adherence to imaginal exposure homework in the PE condition and medication compliance in the sertraline condition did not mediate the

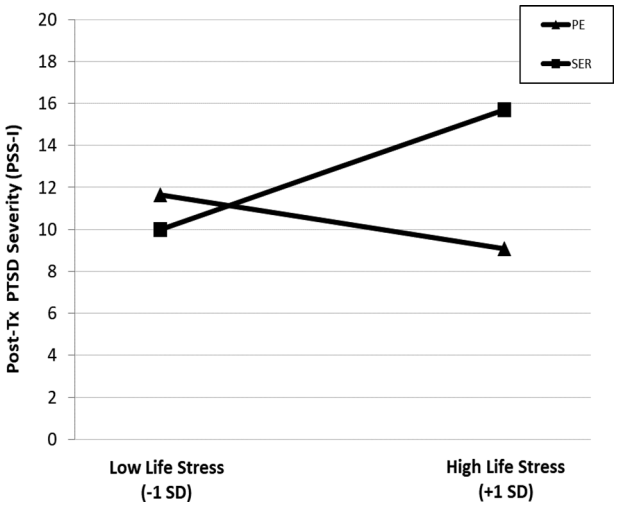

FIGURE 1 Life stress and posttraumatic stress disorder outcome, by treatment group. *Note*: Post-tx = posttreatment; PSSI = PTSD Symptom Scale–Interview

effect of life stress on PTSD outcome regardless of whether the model (a) constrained coefficients across treatment groups to be equal, $\beta = 0.00$, $p = .967$, thereby assuming no difference in adherence between groups, or (b) allowed coefficients to vary across groups, assuming different effects for PE and sertraline, $\beta = -0.00$, $p = .808$ and $\beta = -0.01$, $p = .691$, respectively. Similarly, neither baseline nor posttreatment depression mediated the relation between life stress and treatment outcome for the sample as a whole. However, when we analyzed each treatment arm separately, posttreatment depression severity significantly mediated the effect of life stress on PTSD outcome among participants in the sertraline group, indirect effect: $\beta = 0.18$, $p = .004$, but not the PE group, $\beta = 0.00$, even when controlling for baseline PTSD and depression severity. Table 3 includes the coefficients for each path

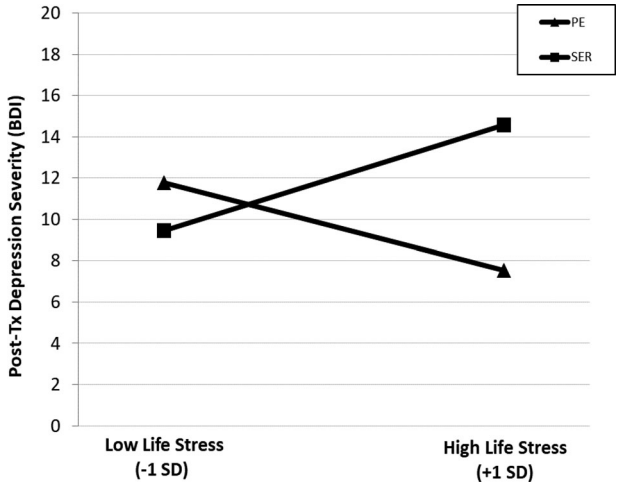

FIGURE 2 Life stress and depression outcome, by treatment group. *Note*: Post-tx = posttreatment; BDI = Beck Depression Inventory

TABLE 3 Mediation model for life stress on the posttraumatic stress disorder (PTSD) symptom scale–interview (PSSI) at posttreatment- among participants receiving sertraline

Effect path	*β*	*p*
BDI-post on LES (Path *a*)	.25	.003
Posttreatment PSSI on posttreatment BDI (Path *b*)	.74	< .001
Posttreatment PSSI on LES (Path *c*)	.04	.39
Indirect effect (Path *c*')	.18	.004

Note: The model controlled for baseline Beck Depression Inventory (BDI) and PSSI scores on posttreatment PSSI score. LES = Life Event Scale.

of the significant mediation model for participants who received sertraline.

DISCUSSION

Counter to our hypothesis that pretreatment life stress would negatively impact PTSD treatment outcomes, both PE and sertraline, but especially PE, were robust against the effects of elevated past-year life stress. Higher levels of stressful life events in the previous year should not deter the prescription of these evidence-based treatments for PTSD. The findings suggest that among individuals who report life stress, PE may be a better treatment match compared to sertraline. The present findings are encouraging given that clinicians are sometimes reluctant to provide exposure-based treatments for PTSD due to worries about decompensation, dropout, and nonadherence (Eftekhari et al., 2006).

Further, higher perceived negative life stress was related to posttreatment depressive symptoms but not treatment adherence, suggesting that life stress may signal a more depressed symptom presentation but not necessarily a less-engaged client. The finding that PE was effective for these participants is in line with evidence that depression symptom severity reduces with PTSD treatment (Ronconi et al., 2015). Individuals with high levels of life stress and PTSD may need treatments that also reduce their depressive symptoms, such as exposure therapy (Zoellner et al., 2019).

The present study did not test hypotheses regarding cognitive processes that potentially drive the association between life stress and treatment outcome; however, the larger stress literature suggests that cognitive functioning may play a role. Specifically, chronic life stress can "overload" cognitive capacity (Juster et al., 2010) and degrade hippocampal connectivity (Gianaros et al., 2006). PE is thought to target cognition and emotional processing through exposure exercises (Foa et al., 2006; Foa & Kozak, 1986) and, thus, may be better suited for individuals with an increased cognitive load due to higher perceived life stress. Future studies should examine this potential process.

A limitation of the present study was the use of a retrospective, self-report measure of perceived life stress, which may not adequately discriminate between the objective impact and subjective appraisal of the stressor, which might be biased by pathology (e.g., Dohrenwend et al., 1984). However, some researchers have argued that it is neither possible nor preferable to remove subjective appraisal from measures of life stress (Harkness & Monroe, 2016; Lazarus et al., 1985). We did not measure life stress during treatment to gauge whether treatment improved perceptions of life stress. Although the original trial design did repeat the life stress measurement at posttreatment, the timeframe of the retrospective measure (i.e., the past year) overlapped considerably with the pretreatment measure and did not, therefore, provide a distinct signal for changes in life stress during treatment; thus, these data were not included in the analyses. However, the present model is informative for clinicians making treatment decisions based on the initial client presentation.

In addition, the onset of the clinical trial began before the publication of the *DSM-5*, which included several changes to the diagnostic algorithm for PTSD relative to the *DSM-IV*, possibly reducing the generalizability of the findings. However, 94.0% (n = 188) of the full sample (N = 200) met the criteria for *DSM-5* PTSD, excluding the assessment of three new symptoms, which were not collected in this study. Moreover, we utilized a well-validated structured interview to measure PTSD, likely reducing the impact of this limitation. Finally, as discussed previously, we were not able to identify drivers of our effects through this study design. Future studies should examine potential cognitive, behavioral, and physiological correlates of life stress and explore how they change during treatment.

Understanding these processes will lead to improved PTSD treatments for highly stressed individuals.

In general, the dearth of research on life stress and PTSD treatment outcome is surprising and unfortunate given the increased rates of PTSD and barriers to care in underserved, potentially highly stressed communities (e.g., Davis et al., 2008). With recent advances in the assessment of life stress (Harkness & Monroe, 2016), there is a renewed opportunity to develop a comprehensive understanding of how environmental stimuli impact psychopathology and treatment response. Future research should replicate these findings using more advanced methods to assess life stress as a prescriptive predictor of treatment outcome.

OPEN PRACTICES STATEMENT

The preregistration for this study can be accessed at https://clinicaltrials.gov/ct2/show/NCT00127673. The data have not been made available on a permanent third-party archive. Queries regarding the data should be sent to msburto@emory.edu.

AUTHOR NOTE

This research was funded by the National Institute of Mental Health (R01 MH066347, PI: Lori A. Zoellner; R01 MH066348, PI: Norah C. Feeny) and the William T. Dahms, MD, Clinical Research Unit, funded under the Cleveland Clinical and Translational Science Award (UL1 RR024989).

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How to cite this article: Burton, M. S., Marks, E. H., Bedard-Gilligan, M. A., Feeny, N. C., & Zoellner, L. A. (2021). The effect of perceived life stress on posttraumatic stress disorder treatment outcome. *Journal of Traumatic Stress. 34*:1219–1227. https://doi.org/10.1002/jts.22744