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The influence of posttraumatic stress disorder treatment on anxiety sensitivity: Impact of prolonged exposure, sertraline, and their combination

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Abstract

Trauma-informed beliefs often decrease during posttraumatic stress disorder (PTSD) treatment. This may also extend to anxiety sensitivity (AS), defined as a fear of anxiety-related sensations and beliefs that anxiety is dangerous and/or intolerable. However, little is known about how AS changes during exposure-based and psychopharmacological PTSD treatments. Further, high AS may be a risk factor for diminished PTSD symptom improvement and increased treatment

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OPEN PRACTICES STATEMENT

This trial was preregistered at ClinicalTrials.gov (number: NCT01524133). Neither data nor the materials have been made available on a permanent third-party archive. Requests for data used in this manuscript should be sent to the principal investigator of the study at sheila.a.m.rauch@emory.edu.

dropout. To better understand how AS impacts and is impacted by PTSD treatment, we conducted a secondary analysis of a randomized clinical trial with a sample of 223 veterans (87.0% male, 57.5% White) with PTSD from four U.S. sites. Veterans were randomized to receive prolonged exposure (PE) plus placebo (n = 74), sertraline plus enhanced medication management (n = 74), or PE plus sertraline (n = 75). Veterans answered questions about PTSD symptoms and AS at baseline and 6-, 12-, 24-, 36-, and 52-week follow-ups. High baseline AS was related to high levels of PTSD severity at 24 weeks across all conditions, β = .244, p = .013, but did not predict dropout from exposure-based, β = .077, p = .374, or psychopharmacological therapy, β = .009, p = .893. AS also significantly decreased across all three treatment arms, with no between-group differences; these reductions were maintained at the 52-week follow-up. These findings suggest that high AS is a risk factor for attenuated PTSD treatment response but also provide evidence that AS can be improved by both PE and an enhanced psychopharmacological intervention for PTSD.

Anxiety sensitivity (AS) is defined as a fear of anxiety-related sensations and the belief that anxiety is dangerous or intolerable. AS often compounds functional impairment in anxiety-spectrum disorders as part of a negative feedback loop wherein maladaptive cognitions about anxiety and fearful interpretations of anxiety beget more anxiety (Reiss et al., 1986). Although AS is most often discussed in relation to mental health conditions such as panic and generalized anxiety disorders (Naragon-Gainey, 2010), research also suggests that AS and posttraumatic stress disorder (PTSD) are strongly correlated in a reciprocal association (Marshall et al., 2010). This may be because AS causes individuals to avoid anxiety-provoking situations, such as trauma cues, thereby impeding trauma processing and reinforcing beliefs about the dangerousness of anxiety symptoms. Indeed, AS may lead to avoidance, which may ultimately diminish the effectiveness of treatment and increase PTSD symptom severity (Naifeh et al., 2012). Given these associations, understanding the role that AS plays in PTSD-focused treatment could provide valuable clinical information such that clinicians might tailor treatment recommendations based on pretreatment AS.

Existing psychotherapies for PTSD may incidentally reduce AS. Gutner and colleagues (2013) found that AS decreased from pre- to posttreatment after each of three trauma-focused treatments, including standard cognitive processing therapy (CPT; Resick et al., 2016), CPT with only cognitive components, and written trauma accounts only. This may be because confronting trauma-related memories in psychotherapy causes patients to experience previously avoided symptoms of anxiety and ultimately teaches them that these anxiety experiences are safer and more tolerable than they once believed (i.e., a change in fear cognitions). Interestingly, participants who were randomized to write trauma accounts experienced the largest decrease in AS among all three groups (Gutner et al., 2013). This finding suggests that exposure-based approaches are especially effective in decreasing AS, which may lead to downstream effects on PTSD. This supposition is supported by studies of interoceptive exposure for PTSD, which includes exercises aimed at simulating distressing physical sensations for patients. One such study randomized patients to either an interoceptive exposure condition or a health education control group (Allen et al., 2015). Individuals in the interoceptive exposure condition had larger reductions in PTSD symptoms than those in the control group, and this treatment effect was mediated through reductions in global and social AS concerns. Short and colleagues (2017) reported observed results,

finding that cognitive AS concerns mediated the association between interoceptive exposure and PTSD symptoms. Thus, exposure-based techniques can be effective in reducing AS, which, in turn, can lead to reductions in PTSD symptoms.

One of the most empirically supported exposure-based treatments for PTSD is prolonged exposure (PE). PE helps patients extinguish fear responses and challenges their maladaptive beliefs through in vivo and imaginal exposures (Foa et al., 2019; Hamblen et al., 2019; Powers et al., 2010). Little is known about how an individual's perception of anxiety symptoms may change throughout PE; however, facing anxiety-provoking experiences and seeing that the resulting symptoms are safe and tolerable may allow patients to extinguish AS responses and learn that anxiety is less consequential than they previously believed.

Selective serotonin reuptake inhibitors (SSRIs), such as sertraline, have also been shown to effectively reduce symptoms of PTSD (Brady et al., 2000; Davidson et al., 2001; Brady & Clary, 2003). Additional studies suggest that AS may also be improved by both anxiolytics and antidepressants. For example, Simon and colleagues (2004) found that AS decreased similarly over three pharmacotherapies for panic disorder, including paroxetine, paroxetine plus sustained clonazepam, and paroxetine plus brief clonazepam. Although sertraline is effective in reducing symptoms of PTSD, and although similar SSRIs have been shown to reduce AS for patients with other mental health disorders, it is still unclear if sertraline may influence AS among those with PTSD.

Given the established efficacy of PE and sertraline in the treatment of PTSD, it is not unreasonable to hypothesize that there may be an additive effect of combining PE with sertraline. For example, Rothbaum and colleagues (2006) found that individuals who received both sertraline and PE had larger reductions in PTSD symptoms than those who received sertraline alone. However, Rauch and colleagues (2019) found that there were no differences in the rate of improvement for PTSD severity between individuals randomized to PE plus placebo, PE plus sertraline, and sertraline plus enhanced medication management (EMM). Thus, mixed findings on sertraline and PE warrant a deeper examination into other possible outcomes of interest, such as AS.

Although PE, sertraline, and/or their combination may theoretically decrease AS over the course of treatment, high AS may also be a risk factor for attenuated PE treatment outcomes by interfering with effective engagement in exposure-based elements of treatment. Prior research suggests that AS is a risk factor for slower PTSD improvement, poorer PTSD outcomes (Zandberg et al., 2016), and higher PE treatment dropout (Bealleau, 2017). Additionally, higher AS is associated with lower positive beliefs about the efficacy of PE (Zoellner et al., 2009), which may lead patients to engage less with treatment and respond more poorly to the intervention (Taylor, 2003).

High AS may also be a risk factor for attenuated treatment outcomes in pharmacotherapies. Olatunji and colleagues (2007) found that anxiety symptoms decreased after a 6-week open trial of fluoxetine in a small group of patients with generalized anxiety disorder and that there was a trend wherein baseline physical and social AS concerns were associated with slower improvement in anxiety during treatment.

The current study examined the impact of AS on three treatment approaches for PTSD: PE plus placebo, sertraline plus EMM, and PE plus sertraline. We hypothesized that high AS at baseline would predict high posttreatment PTSD symptom severity and treatment dropout. We also hypothesized that AS would decrease in all conditions over the course of treatment and at each follow-up assessment. Given evidence that both sertraline and PE are associated with reductions in PTSD symptoms and anxiety, we hypothesized that the largest reductions in AS would be observed in the PE plus sertraline condition.

METHOD

Participants

Participant demographic characteristics can be found in Table 1 and are summarized in greater detail in the primary outcome publication from this project (Rauch et al., 2019). Veterans (N = 223) were recruited from four sites across the United States (i.e., Ann Arbor, Michigan; Boston, Massachusetts; Charleston, South Carolina; and San Diego, California). The average participant age was 34.2 years (SD = 8.2). All veterans served in support of recent conflicts in Iraq and Afghanistan. Additional inclusion criteria were based on the PTSD criteria outlined in the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; *DSM-IV*; American Psychiatric Association, 1994) and included a Clinician-Administered PTSD Scale for *DSM-IV* (CAPS-IV; Weathers et al., 1994) score of 50 or higher and exposure to a combat-related Criterion A traumatic event. Participants were excluded if they endorsed imminent risk of suicide, active psychosis, substance dependence over the past 8 weeks, a medical illness that would result in imminent hospitalization, concurrent use of antidepressants or antipsychotics, and/or serious cognitive impairment. In total, 223 veterans were randomized to receive either sertraline plus EMM (n = 74), PE plus placebo (n = 74), or PE plus sertraline (n = 75).

Procedure

Institutional review board approval was obtained from each recruiting site. Veterans were primarily assessed for eligibility via the CAPS-IV (Blake et al., 1995) and the Mini International Neuropsychiatric Interview for *DSM-IV* (MINI; Sheehan et al., 1998). Eligible veterans were randomized by site to one of the three treatment conditions. Randomization was stratified by site using varying block sizes within each site. Trained study assessors were blinded to treatment condition and medication, and sessions were checked for fidelity throughout the course of the study. Participants were compensated at a rate of $50 (USD) per assessment, which occurred at baseline and 6-, 12-, 24-, and 52-week follow-up appointments. Additional details about the study design and procedures have been published elsewhere (Rauch et al., 2018). This study was preregistered at ClinicalTrials.gov, although the specific set of secondary analyses presented in this manuscript was not included in the preregistration.

In the PE plus placebo condition, veterans were scheduled for 13 sessions of PE, each lasting 90 min. Sessions were led by a VA-trained PE therapist (i.e., master's level or above) and involved all manualized components, including psychoeducation, imaginal exposures, in vivo exposures, and processing traumatic memories. All sessions were expected to

be completed within 24 weeks. Participants who were randomized to receive PE and medication management were also prescribed a placebo medication that was encapsulated to blind participants and providers. In addition, veterans in this condition received brief medication management that lasted roughly 15 min in length for eight nonconsecutive weeks.

In the sertraline plus EMM condition, veterans were prescribed a sertraline dosage that gradually increased from 50 to 200 mg per day, with the last dosage increase at Week 10. Medication continued until week 24, which was considered the end of treatment. All participants were blinded to the medication condition, and all medication was encapsulated to ensure blinding. EMM lasted roughly 30 min for eight nonconsecutive weeks. The extended time in EMM for individuals randomized to sertraline plus EMM helped balance the contact time when compared to PE and included additional psychoeducation and active listening.

Veterans randomized to the PE plus sertraline condition received all components of PE along with the same sertraline dosage as previously described. Individuals in this condition also received brief medication management, similar to the PE plus placebo condition.

Measures

Anxiety sensitivity—The Anxiety Sensitivity Index (ASI-16; Reiss et al., 1986) is a 16-item questionnaire that is used to assess concerns respondents have about their anxiety symptoms (e.g., “It scares me when my heart beats rapidly”). Respondents answer questions using a scale between 0 (*very little*) and 4 (*very much*). A total score is computed by adding all 16 responses, resulting in a range of 0 to 64, with higher scores indicating higher AS. Psychometric research on the ASI-16 suggests that it has strong reliability and validity (Reiss et al., 1986). In the present sample, Cronbach’s alpha for the total ASI-16 scale was .93 at baseline.

PTSD symptoms and diagnosis—The CAPS-IV (Blake et al., 1995; Weathers et al., 1994) was used to assess PTSD severity and diagnosis. Trained interviewers assess symptom frequency and intensity over the last 30 days indexed to a specific event that is considered the “worst or currently most distressing” by the patient. Frequency and intensity scores were used to create an overall PTSD severity score and determine diagnostic status. The CAPS-IV has demonstrated strong interrater reliability and convergent validity (Weathers et al., 2001). For this study, the CAPS-IV was used as both a screening measure and an outcome measure. In the present sample, Cronbach’s alpha for the CAPS-IV total severity score was .92 at baseline.

Treatment dropout—Two dichotomous variables were calculated to assess treatment dropout. The first assessed dropout from PE among participants who were scheduled for either the PE plus sertraline or PE plus placebo condition. A second variable assessed dropout from the medication portion of all three conditions after the first session was scheduled (i.e., representing dropout from sertraline or placebo).

Data analysis

All variables were checked for skewness and kurtosis using recommendations by Tabachnick and Fidell (2013). Outliers were addressed by changing *z* scores greater than 3 to one value larger than the next, nonoutlying score. All analyses were performed using SPSS (Version 23).

To determine if high baseline AS was a risk factor for attenuated PTSD outcomes, we conducted a hierarchical multiple regression with baseline AS as the independent variable and 24-week CAPS-IV score as the outcome. In the first block, we controlled for baseline CAPS-IV score, and two dummy-coded variables for treatment arm (PE plus sertraline vs. other arms; PE plus placebo vs. other arms) were included in the second block. Due to significant missing data on the 24-week CAPS-IV variable, all analyses using this variable were imputed using five iterations. Two logistic regression analyses were also used to determine if baseline AS was associated with treatment dropout for medication and exposure-based treatments.

To determine changes in AS over six time points (i.e., baseline and 6-, 12-, 24-, 36-, and 52-week follow-up) and between three treatment arms (PE plus placebo vs. sertraline plus EMM vs. PE plus sertraline), we conducted a mixed-models repeated-measures analysis in SPSS. To this end, we used an autoregressive covariance structure for estimating the variation across repeated measures using a maximum likelihood estimate. Pairwise comparisons were based on estimated marginal means. All analyses used an alpha of .05.

This trial was originally powered to detect differences in PTSD severity between the three treatment arms. However, an a priori power analysis was conducted using AS data from a sample of Cambodian refugees with PTSD who received either sertraline alone or sertraline plus cognitive behavioral therapy that included exposure-based elements (Otto et al., 2003; the results suggest that the current analysis may have been adequately powered to detect differences on AS.

RESULTS

PTSD symptom change, treatment dropout, and AS

High baseline AS was related to 24-week PTSD severity, pooled $\beta = .244$, $p = .013$, after accounting for treatment arm and baseline PTSD severity. Baseline PTSD severity contributed significant variance in the model, pooled $\beta = .369$, $p < .001$, although treatment arm did not, pooled $\beta = .001$, $p = .669$. The model explained 19.5% of the total variance, $F(4, 218) = 13.25$, $p < .001$. In contrast to the stated hypotheses, baseline AS was not related to treatment dropout for veterans receiving medication, $\beta = .009$, $p = .893$, or exposure-based treatments, $\beta = .077$, $p = .374$, in the logistic regression models.

Change in AS over the course of treatment

Estimated marginal means for AS scores, stratified by assessment point and treatment arm, are presented in Table 2. Data on AS for each treatment arm are also displayed in Figure 1. A Type III test for fixed effects indicated a main effect for time, $F(5, 459.52) = 18.97$, $p <$

.001, suggesting that all groups had a reduction in AS over the course of treatment. There was no main effect for treatment arm, $F(2, 223.12) = 1.39$, $p = .252$, and the interaction between time and treatment arm was not significant, $F(10, 458.93) = 1.28$, $p = .240$, suggesting that all treatments resulted in a similar decrease in AS.

In the sertraline plus EMM condition, pairwise comparisons revealed significant decreases in AS starting at 6 weeks (baseline to 6 weeks: $\Delta M = 3.61$), $p = .017$, with improvements present at 52 weeks (baseline to 52 weeks: $\Delta M = 10.13$), $p < .001$. In the PE plus placebo condition, significant decreases in AS started at Week 12 (baseline to 12 weeks: $\Delta M = 5.73$), $p = .002$, with improvements present at 52 weeks (baseline to 52 weeks: $\Delta M = 6.37$), $p = .002$. In the PE plus sertraline condition, significant decreases in AS started at 12 weeks (baseline to 12 weeks: $\Delta M = 4.33$) $p = .030$, with improvements present at 52 weeks (baseline to 52 weeks: $\Delta M = 5.92$), $p = .002$.

DISCUSSION

The findings demonstrate a positive association between baseline AS and posttreatment PTSD severity, supporting the hypothesis that baseline AS is a risk factor for attenuated PTSD treatment response to PE, sertraline, and their combination. These findings mirror those reported by Zandberg and colleagues (2016), who observed that AS was a risk factor for poor PE response among a sample of adults with PTSD and concurrent substance dependence, and run somewhat counter to Bluiett and colleagues (2013), who found individuals with higher baseline AS were slightly more likely to have a reliable change in distress during imaginal exposure. We extend these findings by also showing that treatment type did not contribute meaningful variance in this association. Thus, AS also appears to be a risk factor for attenuated treatment outcomes in treatments involving sertraline with EMM as well as the combination of PE and sertraline.

For participants who received PE, unstudied mediating variables may be responsible for this association. For example, individuals with higher AS may be more reluctant to engage in PE assignments, which would ultimately have downstream effects on PTSD symptom improvement. Some aspect of AS also appears to negatively impact the effectiveness of medication on posttreatment PTSD severity. One logical explanation may be that higher AS inhibits the likelihood of incidental exposure to feared stimuli as anxiety levels decrease in response to medication to a relatively larger extent compared with lower AS.

In addition to assessing posttreatment PTSD severity, we also examined how baseline AS may impact treatment dropout. Contrary to our hypotheses, the findings revealed that AS was not associated with dropout from either the medication components of treatment or PE. This finding is promising for clinicians who may be hesitant to initiate PE with a client who has a strong fear of experiencing anxiety and suggests that both PE and medication can be tolerated by patients with varying degrees of anxiety-related fear.

We also hypothesized that AS would decrease over time and across the three treatment conditions, with the largest decreases occurring in the PE plus sertraline condition. The results from this analysis partially support this hypothesis. Although we observed reductions

in AS over the course of treatment in all three conditions, there were no differences across treatment conditions. These findings align with previous research showing decreases in AS across three CPT-based PTSD treatment approaches (Gutner et al., 2013). This suggests that both exposure-based psychotherapy, when combined with a pill, and sertraline, when combined with 30-min medication management, may similarly improve beliefs about the dangerousness of anxiety symptoms. It may also suggest that PE and sertraline reduce approach fear either by homework directive or reduced anxiety, thus facilitating incidental exposure. For PE, it is likely that having veterans spend time in anxiety-provoking situations teaches them that anxiety can be tolerated. For sertraline, an antidepressant with ant-anxiety properties, it may be that a decrease in anxiety or depression-related negative thinking is responsible for decreases in AS. This is in line with previous research on anxiety and depression showing that symptoms of both are associated with AS (Taylor et al., 1996).

Interestingly, veterans randomized to receive sertraline plus EMM had a quicker reduction in AS, with significant changes occurring as early as 6 weeks, compared with those in either of the two PE conditions, where significant changes in AS were not noted until the 12-week assessment. This may imply that combined treatment may impede change over monotherapy. As there was no standalone PE condition, it is unclear if concurrent exposure therapy may temporarily impact the effect of sertraline on AS or whether adding a placebo to PE reduced the effect size of PE (Rauch et al., 2022). Additional research on this topic is needed to better understand this finding.

Because AS was associated with attenuated PTSD outcomes across treatments but also improved during PTSD treatments, it may be beneficial for therapists to consider addressing AS behaviors and beliefs early in therapy and within effective protocols. To achieve this, clinicians may wish to assess AS prior to therapy and directly target AS with psychoeducation. This may include brief interventions to reduce AS, which have been shown to be effective in alleviating AS from pre- to posttreatment (Fitzgerald et al., 2021) and may help patients benefit more from PTSD treatment, during which further decreases in AS can occur. Additionally, interoceptive exposure may be integrated throughout PE as part of the in vivo exposure hierarchy as an effective strategy for reducing anxiety sensitivity. Interoceptive exposure integrated into PE may be especially effective because both approaches utilize similar principles. Integrating components of these interventions directly into PE as opposed to prefacing treatment with brief interventions should be considered so as not to delay the benefits of PE (Wiedeman et al., 2020). More research is needed to understand who might benefit from such an integrated AS intervention. Until then, clinicians can consider using ASI-16 scores greater than 20, or ASI-3 scores greater than 23, as potential intervention screeners (Allan et al., 2014; Smits et al., 2016).

The study had a number of strengths. First, we included measurements of AS at multiple time points from baseline to 52 weeks (i.e., 28 weeks posttreatment), which allowed us to take a more fine-grained analytic approach. Second, the use of multiple sites increases the external validity of the study. However, several limitations should also be noted. For example, our study did not include a standalone PE, standalone placebo, or waitlist-only condition; thus, it is not possible to know if reductions in AS are the result of time or an intervention effect. Additionally, this study did not use the more recent version of the CAPS

(Weathers et al., 2018) or the ASI (Taylor et al., 2007). Finally, our use of EMM to balance contact time is not generalizable to other sertraline or placebo studies.

The results of this study suggest that although AS may be a risk factor for attenuated PTSD treatment response, it can also be improved over the course of exposure-based psychotherapy and SSRI-based pharmacotherapy for PTSD. Our novel examination of AS in PE is especially important because clinicians may hold inaccurate beliefs about using PE to treat PTSD despite evidence demonstrating its efficacy (Meyer et al., 2014). For example, clinicians may wrongfully assume that individuals with high levels of AS may be unable to benefit from exposure-based treatment approaches or that exposure will lead to dropout among those with high AS (Deacon et al., 2013). This study suggests that neither is true. Prescribers may also benefit from knowing that sertraline can be effective in reducing AS, a question that has not received any attention in the literature to our knowledge.

Future research should examine how PE may reduce AS when compared to a control group to increase confidence in the present findings. Additionally, further analyses should examine ASI subscales to understand which beliefs are driving the effects we observed. Finally, researchers should test whether integrating content on AS within evidence-based treatment protocols for PTSD adds additional benefit to the effects seen here.

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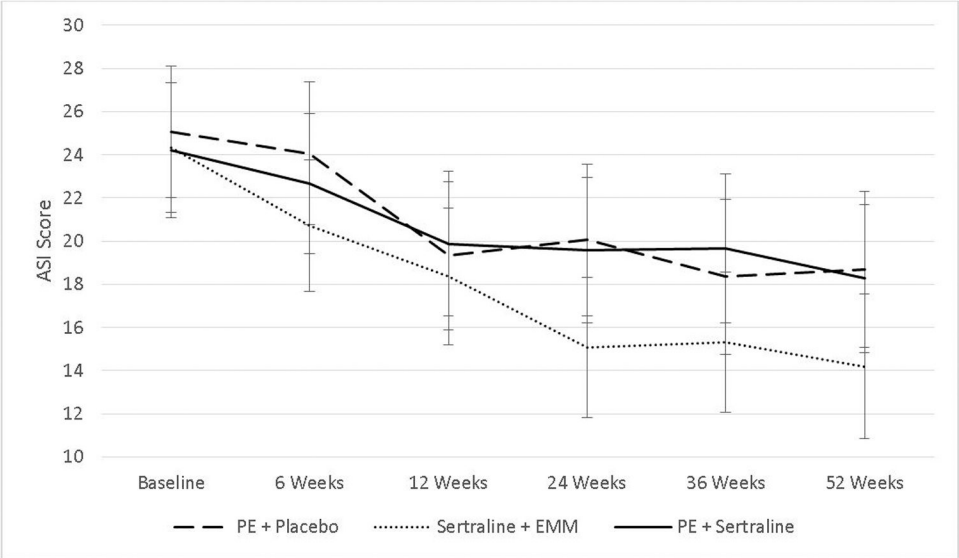

FIGURE 1.

Change in anxiety sensitivity over time and between the three treatment approaches

Note: Data used model-based mean estimates that account for missing data. Error bars represent 95% confidence intervals.

TABLE 1

Sample demographic characteristics, by treatment arm

	All treatment arms (*N* = 223)				PE + placebo (*n* = 74)				Sertraline + EMM (*n* = 74)				PE + sertraline (*n* = 75)			
Variable	***n***	**%**	***M***	***SD***	***n***	**%**	***M***	***SD***	***n***	**%**	***M***	***SD***	***n***	**%**	***M***	***SD***
Male gender	194	87.0			65	87.8			69	93.2			60	80.0		
Race																
White	129	57.8			40	54.1			45	60.8			44	58.7		
Black	65	29.1			22	29.7			20	27.0			23	30.7		
Other	29	13.0			12	16.2			9	12.2			8	10.7		
Hispanic/Latino ethnicity	31	13.9			7	9.5			13	17.6			11	14.7		
Marital status[a]																
Married/remarried	114	51.4			37	50.0			42	57.5			35	46.7		
Separated/divorced	58	26.1			23	31.1			11	15.1			24	32.0		
Never married	50	22.5			14	18.9			20	24.7			16	21.3		
Years of education			13.6	2.3			14.1	2.3			13.0	2.6			13.8	2.0
Number of deployments			2.6	3.0			2.3	1.3			3.1	4.8			2.4	1.6
Baseline CAPS-IV score			74.6	17.8			79.2	16.0			72.1	17.67			72.5	18.8

Note: PE = prolonged exposure; EMM = enhanced medication management; CAPS-IV = Clinician-Administered PTSD Scale for *DSM-IV*.

[a]One veteran in the sertraline + EMM condition had unknown marital status.

TABLE 2

Estimated marginal means and standard errors for anxiety sensitivity

	All Arms		PE + placebo		Sertraline + EMM		PE + sertraline	
Time point	***M***	***SE***	***M***	***SE***	***M***	***SE***	***M***	***SE***
Baseline	24.52	.90	25.05	1.55	24.32	1.53	24.20	1.59
6 weeks	22.48	.95	24.06	1.69	20.71	1.56	22.67	1.66
12 weeks	19.19	.98	19.32	1.75	18.37	1.62	19.88	1.71
24 weeks	18.24	1.00	20.05	1.80	15.08	1.65	19.59	1.72
36 weeks	17.78	1.01	18.35	1.83	15.32	1.66	19.68	1.76
52 weeks	17.05	1.02	18.68	1.84	14.19	1.71	18.28	1.75

Note: PE = prolonged exposure; EMM = enhanced medication management.