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Augmentation of Sertraline With Prolonged Exposure in the Treatment of Posttraumatic Stress Disorder

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The present study was designed to determine whether augmenting sertraline with prolonged exposure (PE) would result in greater improvement than continuation with sertraline alone. Outpatient men and women with chronic PTSD completed 10 weeks of open label sertraline and then were randomly assigned to five additional weeks of sertraline alone (n = 31) or sertraline plus 10 sessions of twice-weekly PE (n = 34). Results indicated that sertraline led to a significant reduction in PTSD severity after 10 weeks but was associated with no further reductions after five more weeks. Participants who received PE showed further reduction in PTSD severity. This augmentation effect was observed only for participants who showed a partial response to medication.

At present there is robust empirical evidence showing that two different treatment approaches for posttraumatic stress disorder (PTSD) are both effective. There is more evidence from well-controlled efficacy studies regarding the efficacy of prolonged exposure (PE) than any other treatment for PTSD (Foa, Rothbaum, & Furr, 2003; Treatment Guidelines Task Force, 2000). Similarly, four multisite randomized clinical trials comparing selective serotonin reuptake inhibitors (SSRIs) with placebo have resulted in formal Federal Drug Administration (FDA) approval in the United States for two selective serotonin reuptake inhibitors (SSRIs), sertraline (Brady et al., 2000; Davidson,

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Rothbaum, van der Kolk, Sikes, & Farfel, 2001) and paroxetine (Marshall, Beebe, Oldham, & Zaninelli, 2001; Tucker et al., 2001), as indicated treatments for PTSD. However, the recent National Institute of Clinical Evidence (NICE) Guidelines from England and Wales did not find a statistically significant positive effect for sertraline (National Collaborating Centre for Mental Health [NCCMH], 2005). In the medication studies, the response rates ranged from 53% to 60% for active medication and 32% to 38% for placebo. Thus, at least 40% of participants on active medication failed to respond. Londborg et al. (2001) studied the effects of open label continuation of sertraline for an additional 24 weeks in the treatment of PTSD in 126 participants from the acute studies, all of whom had received active sertraline. Nonresponders of the 12-week phase obtained greater benefit from medication continuation, with 54% of the acute-phase nonresponders converting to responders, half of whom did so within the first 6 weeks of continuation treatment.

Regarding psychotherapy, the literature favors cognitive–behavioral therapy (CBT) approaches, and of the CBT approaches, PE has received the most evidence supporting its efficacy (Treatment Guidelines Task Force, 2000). Five well-controlled studies (Foa, Rothbaum, Riggs, & Murdock, 1991; Foa et al., 1999; Foa et al., 2005; Resick, Nishith, Weaver, Astin, & Feuer, 2002; Rothbaum, Astin, & Marsteller, 2005) investigated the efficacy of PE finding, in general, 60% to 95% of participants who received PE no longer met PTSD criteria following treatment. Despite these important advances, the current PTSD treatment literature consists entirely of research on monotherapy—either pharmacotherapy alone or psychotherapy alone. Although both medication and CBT have been found consistently effective for anxiety disorders, including PTSD, many patients remain somewhat symptomatic and some do not benefit from either treatment alone. The above discussion of the PTSD treatment outcome literature indicates that both medication and PE are helpful in treating PTSD. Both treatments appear to help many, but certainly not all, sufferers of PTSD, but only produce remission in a minority of patients. Thus, there is potentially a role for augmentation treatment and a need to study it systematically. The aims of the present study are directly informed by the extant empirical literature described above. The present study was conducted to determine whether augmenting sertraline with PE would result in greater improvement than sertraline alone.

METHOD

Participants

This study was conducted at three sites: Emory University in Atlanta, Georgia; University of Pennsylvania in Philadelphia, Pennsylvania; and Duke University in Durham, North Carolina. The study was approved by the institutional review boards at each institution and participants gave written informed consent. Eligible participants were men and women (age ≥ 18) in general good health with a primary psychiatric diagnosis of chronic PTSD (minimum duration of 3 months) as determined by administration of the SCID. Major exclusion criteria included: history of a psychotic or bipolar disorder, prior failure of an adequate trial of sertraline for PTSD, current administration of psychiatric medication, and any medical contraindication to taking sertraline. Participants were recruited through advertisements and referrals from professionals and received modest compensation for their participation in the study.

Figure 1 summarizes the flow of participants from the point of initial contact through completion of Phase II. The overall dropout rate of those entering treatment was 30%. A total of 139 individuals were screened for participation in this study, 95 of whom were eligible (68% of those screened) and 88 (63% of those screened, 93% of those meeting study criteria) of whom began medication at Week 0. Of the 88 participants who began medication, 19 (22%) did not complete Phase I, all of whom were lost to follow-up. Four of the 69 participants (6%) who completed Phase I did not advance to Phase II because they were nonresponders ($n = 3$) or for some other clinical reason ($n = 1$). Of the 65 participants entering Phase II, 31 were randomly assigned to receive

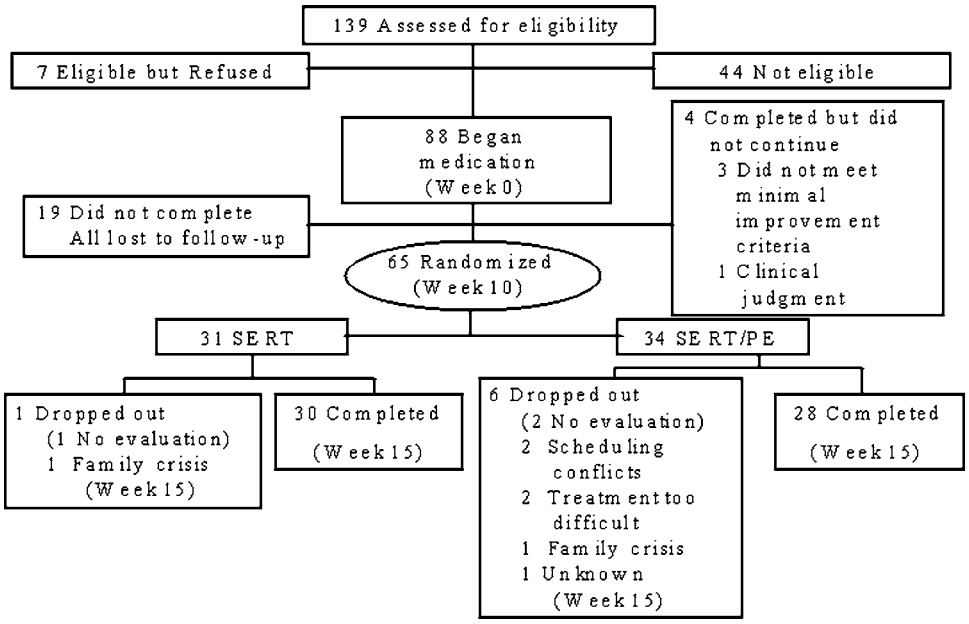

Figure 1. Summary of participant flow through the phases of the study from initial screen through completion of Phase II.

continuation with sertraline alone and 34 were assigned to receive augmentation with PE. Seven participants dropped out of Phase II (11% of those randomized), 6 of whom were in the PE augmentation condition. Thus, dropout during Phase II was 3% in the medication only condition and 18% in the PE augmentation condition (Fisher's exact test, *ns*). In the PE augmentation condition, the number of therapy sessions received prior to dropping out ranged between 0 to 7 ($mdn = 2$, mode = 2). Of the seven Phase II dropouts, 4-returned for a postdropout assessment, all of whom had been assigned to receive PE. For the remaining 3 participants who were lost to follow-up, data from their Week 10 assessment were carried forward for purpose of statistical analysis. Two participants, both assigned to receive PE, were not able to consistently keep scheduled PE sessions (2-hour sessions, twice per week) due to scheduling conflicts; 2 participants, one of whom was assigned to receive PE, dropped out following family crises; 2 participants, both assigned to receive PE, dropped out because they found the therapy too difficult; and the reason for dropout for one person is unknown.

Participant demographics, trauma characteristics, Week 0 outcome measures, and comorbidity for participants who entered Phase II compared with those who did not enter Phase II are presented in Table 1. Participants who entered Phase II were not different from those who did not enter Phase II on any of these variables. The average age of participants entering Phase II was 39.3 years. The majority of these participants were women (65%) and 80% were White (all but one of the non-White participants was African American) and 78% completed at least some college education. A minority of participants were living with a partner (40%), working fulltime (46%), with another 12% working part-time; 5% were students. However, 37% were disabled or unemployed and 35% reported an annual household income of less then $30,000. The most common index traumas were sexual assault, including childhood sexual abuse (37%); nonsexual assault, including childhood physical abuse (25%); and the death (not combat-related) of another person (22%), usually someone of significance to the participant (i.e., child, parent, sibling, spouse or romantic partner). The circumstances

Table 1. Participant Demographics, Trauma Characteristics, and Week 0 Outcome Measures

	Entered Phase II ($n = 65$)		Did not enter Phase II ($n = 23$)		Completed Phase II ($n = 58$)		Did not complete Phase II ($n = 7$)	
Variable	*n*	%	*n*	%	*n*	%	*n*	%
Gender (female)	42	64.6	13	56.5	36	62.1	6	85.7
Index trauma								
Sexual assault	24	36.9	5	21.7	22	37.9	2	28.6
Non-sexual assault	16	24.6	6	26.1	15	25.9	1	14.3
Death of another	14	21.5	5	21.7	13	22.4	1	14.3
Motor vehicle accident	6	9.2	4	17.4	4	6.9	2	28.6
Other	5	7.7	3	13.0	4	6.9	1	14.3
Ethnicity								
White	52	80.0	15	65.2	46	79.3	6	85.7
African American	12	18.5	7	30.4	11	19.0	1	14.3
Other	1	1.5	1	4.3	1	1.7	0	0
Relationship status								
With partner	26	40.0	7	30.4	24	41.4	2	28.6
Employment status			($n = 22$)					
Fulltime	30	46.2	11	50.0	27	46.6	3	42.9
Part-time	8	12.3	4	18.2	8	13.8	0	0
Student	3	4.6	1	4.5	2	3.4	1	14.3
Unemployed/disabled	24	36.9	6	27.3	21	36.2	3	42.9
Education	($n = 64$)				($n = 57$)			
High school graduate or less	14	21.9	5	21.7	12	21.1	2	28.6
Some college	23	35.9	7	30.4	19	33.3	4	57.1
Bachelor's degree or higher	27	42.2	11	47.8	26	45.6	1	14.3
Income	($n = 64$)		($n = 22$)		($n = 57$)			
< in $10,000	5	7.8	2	9.1	4	7.0	1	14.3
$10,001–$30,000	17	26.6	6	27.3	16	28.1	1	14.3
> $30,000	42	65.6	14	63.6	37	64.9	5	74.4
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
Age in years	39.3	10.69	39.9	9.85	39.7	10.62	35.4	11.33
Years since index trauma	($n = 43$)	($n = 43$)	($n = 13$)	($n = 13$)	($n = 38$)	($n = 38$)	($n = 5$)	($n = 5$)
	8.1	11.77	8.1	10.20	8.6	12.31	8.1	4.62
Week 0 outcome measures								
SIP	35.9	8.98	34.7	10.64	6.1	9.35	34.9	5.24
BDI	($n = 64$)	($n = 64$)	($n = 19$)	($n = 19$)	($n = 57$)	($n = 57$)		
	21.5	10.07	22.7	7.27	21.1	10.37	25.1	6.67
STAI-S	($n = 64$)	($n = 64$)	($n = 18$)	($n = 18$)	($n = 57$)	($n = 57$)		
	54.7	2.45	8.38	8.38	53.7	12.45	63.1	9.37

Note: SIP = Structured Interview for PTSD, BDI = Beck Depression Inventory, STAI-S = state-anxiety portion of the State-Trait Anxiety Inventory. Statistical tests for differences between participants who entered versus those who did not enter Phase II, and between participants who completed II versus those who did complete Phase II not were not significant at $p < .05$.

of these deaths in the latter category varied considerably, such as a parent's death to cancer or after a fall, the suicide of a sibling, and the death of a friend or spouse in a motor-vehicle accident. Another 9% reported being in a motor-vehicle accident as the index trauma. The remaining traumas coded as *other* were one case each of the following: combat exposure, house fire, airplane crash, discovering a parent after a nonfatal overdose, and a police officer who felt he came very close to shooting an unarmed suspect. The average time since the index trauma was 8.1 years.

Exposure to events that would meet the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition's* (*DSM-IV*; American Psychiatric Association [APA], 1994) A1 (objective) criterion for trauma, in addition to the index trauma, and psychiatric comorbidity were both highly prevalent. Fifty-one percent of participants entering Phase II reported at least an additional traumatic event; 63% of Phase II entrants met criteria for current major depression, dysthymia, or both; and 52% met criteria for one or more comorbid anxiety disorders. Altogether, 75% of Phase II entrants met criteria for at least one concurrent mood or anxiety disorder.

Table 1 also presents demographic variables, outcome measures at Week 0, and comorbidity for participants who completed Phase II compared to those who dropped out of Phase II. Participants who completed Phase II were not different from those who dropped out of Phase II on any of these variables, although there was a trend for Phase II dropouts to have higher Week 0 State-Trait Anxiety Inventory-State Anxiety Scale (STAI-S; Spielberger, Gorsuch, Lushene, & Press, 1970) scores, $t(62) = 1.9$, *ns.*

Comparisons were also conducted between participants who completed Phase II and participants who did not complete Phase II on the Structured Interview for PTSD (SIP; Davidson, Malik, & Travers, 1997; $M = 15.5$, $SD = 11.45$ vs. $M = 14.0$, $SD = 7.72$, respectively), the Beck Depression Inventory (BDI; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961; $M = 10.4$, $SD = 8.12$ vs. $M = 9.4$, $SD = 10.33$, respectively), STAI-S ($M = 40.6$, $SD = 13.47$ vs. $M = 45.8$, $SD = 13.68$, respectively). No significant differences were obtained, all three t values < 1, *ns.*

Measures

Structured Clinical Interview for DSM–Patient Edition With Psychotic Screen. Developed by First, Spitzer, Gibbon, and Williams (1996), the Structured Clinical Interview for DSM–Patient Edition with Psychotic Screen (SCID; Version 2.0) is a semistructured interview designed to assess major Axis I disorders according to *DSM-IV* criteria. In the present study, it was used to assess study eligibility and comorbid disorders.

Standardized Trauma Interview. The Standardized Trauma Interview (STI) is a modification of the Standardized Assault Interview (SAI; Rothbaum, Foa, Riggs, Murdock, & Walsh, 1992) designed to be appropriate for use with a full range of traumatic events and not restricted to physical or sexual assault. The STI is a 94-item semistructured interview that gathers information regarding demographic variables, and characteristics of the index trauma such as injury and life threat, and interactions with the legal system. It also collects information on up to two additional traumas, one prior to the index trauma and one subsequent to the index trauma. An earlier version of the SAI reported an interrater reliability of 0.90.

Structured Interview for PTSD (SIP). The SIP (Davidson, Malik, & Travers, 1997) is a 17-item semistructured interview assessing the combined frequency and severity of each PTSD symptom on a 0.4 scale, yielding a total severity score ranging between 0-68. Psychometric validation data come from participants enrolled in a randomized placebo-controlled study of pharmacotherapy for PTSD (Davidson, Malik, & Travers, 1997). The scale has good internal consistency (Cronbach's alpha = .80), four-week test-retest reliability ($r = .89$), and interrater reliability ($r = .90$). The SIP is significantly correlated with the Davidson Trauma Scale (Davidson, Brook et al., 1997) ($r = .67$) and the Impact of Event Scale (Horowitz, Wilner, & Alvarez, 1979) ($r = .49$). At the end of treatment, participants meeting DSM-IV symptom criteria for PTSD according to the SCID (Spitzer, Williams, & Gibbon, 1988) had an average SIP score of

30.5 ($SD = 9.6$), while participants who no longer met criteria for PTSD had an average SIP score of 8.0 ($SD = 5.7$). Internal consistency at Week 0 for the present sample of the 88 participants that began medication was high (Cronbach's alpha = .81) and similar to that found by Davidson, Malik, & Travers (1997).

Beck Depression Inventory. The Beck Depression Inventory (BDI; Beck et al., 1961) is a 21-item measure of cognitive and vegetative symptoms of depression that is widely used in a variety of populations. The inventory has a split half reliability of .93. Correlations with clinician ratings of depression range from .62 to .65. Internal consistency at Week 0 for the present sample of the 77 participants with complete BDI data that began medication was high (Cronbach's $\alpha = .85$).

State-Trait Anxiety Inventory. The State-Trait Anxiety Inventory (STAI; Spielberger et al., 1970) contains 20 items for state anxiety and 20 items for trait anxiety. Test-retest reliability for the state-anxiety scale is .40 and for the trait-anxiety scale is .81. Internal consistency ranges from .83 to .92. Only data from the state-anxiety scale (STAI-S) were used in the present study. Internal consistency at Week 0 for the present sample of the 77 participants with complete STAI data that began medication was high (Cronbach's $\alpha = .93$).

Treatment

Sertraline was administered in open-label fashion according to a flexible dosing schedule. Participants met with the study physician once per week for the first 4 weeks and then every other week for the next 6 weeks. Dosing began at 25 mg/day and was gradually increased to 200 mg/day or the maximum tolerated dose by Week 6. Small adjustments in dosing were permitted between Weeks 6–10, but no further adjustments were permitted between Weeks 10–15. The average dose of sertraline among participants entering Phase II was 173.1 mg/day ($SD = 44.26$) at Week 10 and 173.5 mg/day ($SD = 42.82$) at Week 15 or the last known dose for dropouts (endpoint).

Compliance was determined by recording date, amount dispensed and dosing instructions when the medication was dispensed. This information was recorded at every visit beginning with the first medication visit. At the next visit, all unused medication was returned, counted, and the date, number returned, and the number of days since the last visit was recorded. The number of tablets taken was then divided by the number of tablets that should have been taken and the resulting number multiplied by 100%. Compliance data for Week 10 and Week-15 endpoint were available on 51 of the 64 Phase II entrants. Average compliance was 97.1% ($SD = 7.99$) at Week 10 and 97.1% ($SD = 5.86$) at Week-15 endpoint.

Prolonged exposure. Prolonged exposure treatment consisted of psychoeducation about common reactions to trauma, breathing retraining, in vivo exposure, prolonged imaginal exposure, and homework (e.g., Foa & Rothbaum, 1998). Prolonged imaginal exposure consisted of reliving the traumatic event in imagination and recounting the memory in the present tense for 45–60 minutes per session. Imaginal exposure was tape-recorded and participants were instructed to listen to the tapes daily at home. Additional homework included in vivo exposure to objectively safe situations that provoke trauma-related anxiety and avoidance. Participants received 10 twice-weekly sessions, each lasting 90–120 minutes.

Independent evaluators and therapists. Independent evaluators were trained in the study measures and all had at least a masters degree in psychology or were an experienced registered nurse, with several having their doctorates in psychology.

Therapists at all three sites had at least a masters degree but several had doctorates in clinical psychology and were trained in the use of PE by one of three recognized experts in PE: Edna B. Foa and Barbara O. Rothbaum, two coauthors of this article, and Elizabeth A. Hembree, Department of Psychiatry, University of Pennsylvania, Philadelphia, PA. Preliminary analyses indicated no difference in response to PE across the three sites.

Procedure

Assessment for eligibility was conducted during an intake evaluation that included administration of the SCID and STI and a clinical assessment that included a medical and psychiatric history. Individuals meeting all eligibility criteria and deciding to enter Phase I of the study were scheduled to return for the Week 0 assessment with an independent evaluator and to begin treatment with open-label sertraline. Participants met with the study physician once per week for the first 4 weeks and then every other week for the next 6 weeks. A second assessment with an independent evaluator was conducted after Week 10 to determine eligibility for continuation into Phase II and, for those entering Phase II, at a third assessment at Week 15 or at the point of dropout. At each of the Week 0, Week 10, and Week 15 assessments, the independent evaluators assessed PTSD severity with SIP and participants completed the BDI and STAI-S. The independent evaluators were not otherwise involved in participants' treatment and were kept blind to the treatment condition of those participants who entered Phase II.

All participants with a minimum reduction in PTSD severity of 20% were eligible to advance to Phase II in which they were randomly assigned to one of two treatment conditions. All participants continued on medication for 5 additional weeks and met with the physician at Weeks 12 and 15. Participants assigned to receive sertraline plus PE also received a course of 10 PE sessions administered two sessions per week by a separate therapist. Participants who did not achieve at least a 20% reduction in PTSD severity in Phase I (Phase I nonresponders) were removed from the study and provided additional treatment or referrals as deemed appropriate. At the time this study was designed, the results of the Londborg et al. (2001) study of medication continuation, in which it was found that 54% of nonresponders after 12 weeks of blinded administration of sertraline became responders with continued treatment (up to 24 weeks, although most had achieved their gains within 6 weeks), had not been published. Therefore it was deemed clinically inappropriate to subject Phase I nonresponders to random assignment to either continuation of sertraline alone or augmentation with PE.

Randomization and Statistical Analysis

Randomization was conducted separately at each site after completion of Phase I and determination of eligibility to enter Phase II in a manner designed to insure that each participant had a 50% chance of receiving either treatment. For the main outcome analyses, SIP, BDI, and STAI-S scores from all participants entering Phase II (i.e., all randomized participants) were submitted to separate treatment (sertraline, sertraline + PE) by assessment (Week 0, Week 10, Week-15 endpoint) mixed factorial analyses of variance (ANOVAs) in which type of treatment was the between group factor and time of assessment was the repeated factor. Week 10 scores were carried forward to Week 15 for participants who dropped out after Week 10 and did not return for a final evaluation ($n = 2$). Treatment response curves frequently are not linear, but rather show greater improvement during earlier sessions than in later sessions. Accordingly, the treatment by assessment ANOVAs evaluated both linear and quadratic main effects for time of assessment as well as linear and quadratic interactions involving Treatment × Time of Assessment. The presence of a linear main effect for time of assessment would indicate the slope of the best-fitting straight line is significantly different from zero. The presence of a quadratic main effect would indicate the rate of change between Weeks 0–10 differs from the rate of change between Weeks 10–15. A significant linear treatment by time of assessment interaction would indicate that the slope of the best-fitting straight line differs across treatment groups and a significant quadratic interaction would indicate that the best fitting quadratic function differs across treatment groups. Significant main effects and interactions were followed by the investigation of simple main effects using t tests for independent samples or paired samples as appropriate.

For exploratory analyses, participants were divided into two groups, excellent responders (Ex/R) and partial responders (PR), based on their SIP score at Week 10 to

investigate whether the response to sertraline in Phase I moderated response to treatment in Phase II. An excellent response was defined as a Week 10 SIP score no more than one standard deviation greater than the posttreatment mean for participants who did not meet criteria for PTSD in the Davidson, Malek et al. (1997) validation sample. Accordingly, Ex/Rs ($N = 32$; 16 in sertraline alone) were defined as those participants whose Week 10 SIP score was less than 14 and PRs ($N = 33$; 15 in sertraline alone) were defined as those participants whose Week 10 SIP score was 14 or greater. The SIP, BDI, and STAI-S scores for all participants entering Phase II were submitted to a treatment (sertraline, sertraline/PE) by response (Ex/R, PR) by assessment (Week 0, Week 10, Week-15 endpoint) mixed factorial ANOVA. Treatment and response were between group factors and assessment was the repeated factor. This analysis investigated both linear and quadratic main effects for time of assessment as well as linear and quadratic interactions involving time of assessment. Significant interactions were followed by investigation of simple main effects using *t* tests for independent samples or paired samples as appropriate.

RESULTS

Main Outcome

There was a trend for participants randomly assigned to the sertraline/PE condition ($M = 37.1$, $SD = 10.88$) to be younger than those assigned to sertraline alone ($M = 41.6$, $SD = 10.13$), $t(63) = 1.72$, *ns.* The two groups did not differ on any other demographic or trauma variables listed in Table 1 (data not shown) nor did they differ on medication dose or compliance at either Week 10 or Week-15 endpoint, largest *t* value $(49) = 1.17$, *ns, df* adjusted because of unequal variances. Table 2 presents descriptive statistics (*M, SD, n*) for the SIP, BDI, and STAI-S for each group and the two groups combined at each assessment.

The ANOVA results for the SIP revealed no main effect for type of treatment, $F(1, 63) < 1$, *ns,* but significant linear, $F(1, 63) = 227.8$, $p < .001$, and quadratic, $F(1, 63) = 100.4$, $p < .001$, main effects for repeated assessment, and a significant quadratic treatment by assessment interaction, $F(1, 63) = 4.8$, $p < .05$, but not linear interaction, $F(1, 63) = 2.2$, *ns.* Comparisons between treatment groups indicated no differences at Week 0, $t(63) < 1$, *ns*; Week 10, $t(63) < 1$, *ns*; or Week 15, $t(47.1) = 1.5$, *ns, df* adjusted because of unequal variances. The effect size (Cohen's *d*) at Week 15 was small (0.38). Comparisons within each group revealed a significant reduction from Week 0 to Week 10 for both sertraline, $t(30) = 10.6$, $p < .001$, and sertraline/PE groups, $t(33) = 10.7$, $p < .001$. At Week 10, the average reduction from Week 0 in SIP scores for the sertraline and sertraline/PE groups were 21.4 ($SD = 11.27$) and 19.8 points ($SD = 10.79$), respectively. From Week 10 to Week 15, there was no further change in the sertraline group ($M = -0.3$, $SD = 7.60$), $t(30) < 1$, *ns,* while there was further reduction in the sertraline/PE group ($M = 5.9$, $SD = 7.82$), $t(33) = 4.4$, $p < .001$. At Week 15, the average reduction in SIP scores from Week 0 for the sertraline and sertraline/PE groups were 21.1 ($SD = 13.79$) and 25.7 points ($SD = 11.17$), respectively.

The ANOVA results for the BDI revealed significant linear, $F(1, 62) = 99.4$, $p < .001$, and quadratic, $F(1, 62) = 25.5$, $p < .001$, main effects for assessment. There was no main effect for treatment, $F(1, 62) < 1$, *ns,* and no linear, $F(1, 62) < 1$, *ns,* or quadratic, $F(1, 62) = 2.8$, *ns,* treatment by assessment interactions. Combined across groups, there was a significant reduction from Week 0 to Week 10 ($M = 11.1$, $SD = 10.76$), $t(63) = 8.3$, $p < .001$, but no further reduction from Week 10 to Week 15 ($M = 1.6$; $SD = 7.52$), $t(62) = 1.7$, *ns.* The average change in BDI scores from Week 0 to Week 15 was 12.7 points ($SD = 10.10$).

The same pattern was obtained for the STAI-S: Significant linear, $F(1, 62) = 76.6$, $p < .001$, and quadratic, $F(1, 62) = 26.4$, $p < .001$, main effects for assessment, no main effect of treatment, $F(1, 62) < 1$, *ns,* and no linear, $F(1, 62) < 1$, *ns,* or quadratic, $F(1, 62) = 2.2$, *ns,* treatment by assessment interactions. Combined across groups, there was a significant reduction from Week 0 to Week 10 ($M = 13.5$, $SD = 12.49$), $t(63) = 8.6$, $p < .001$, but no further reduction from Week 10 to Week 15

Table 2. Outcome Variables (*M*, *SD*, *n*) for Participants Entering Phase II

		Assessment week					
		Week 0		Week 10		Week 15	
Measure	Treatment	*M*	*SD*	*M*	*SD*	*M*	*SD*
SIP	Sertraline ($n = 31$)	36.0	8.64	14.5	11.65	14.9	15.27
	Sertraline/PE ($n = 34$)	35.9	9.41	16.1	10.64	10.2	8.83
	Combined ($n = 65$)	35.9	8.98	15.3	11.07	12.4	12.45
BDI	Sertraline ($n = 30$)	22.1	11.69	9.5	7.57	9.8	9.74
	Sertraline/PE ($n = 34$)	21.0	8.55	11.2	8.94	8.0	8.33
	Combined ($n = 64$)	21.5	10.07	10.4	8.31	8.8	8.99
STAI-S	Sertraline ($n = 30$)	54.2	13.57	39.2	13.90	39.2	17.84
	Sertraline/PE ($n = 34$)	55.2	11.56	43.0	13.21	39.1	14.48
	Combined ($n = 64$)	54.7	12.45	41.2	13.56	39.2	16.01

Note: SIP = Structured Interview for PTSD, PE = prolonged exposure, BDI = Beck Depression Inventory, STAI-S = state-anxiety portion of the State-Trait Anxiety Inventory.

($M = 2.0$, $SD = 10.40$), $t(63) = 1.6$, *ns.* The average change in STAI-S scores from Week 0 to Week 15 was 15.4 points ($SD = 14.05$).

Exploratory Analysis

The Ex/Rs and PRs did not differ on any of the demographic or trauma variables listed in Table 1 (data not shown), nor did they differ on medication dose or compliance at Week 10 and Week-15 endpoint, largest $t(36.1) = 1.5$, *ns, df* adjusted because of unequal variances. The ANOVA results for the exploratory analyses on the SIP, BDI, and STAI-S revealed the same pattern of significance and nonsignificance as the main outcome analyses for the main effects of type of treatment and assessment, as well as the treatment by assessment interaction. Therefore, these findings will not be repeated here. New findings on the SIP were a significant main effect for response, $F(1, 61) = 58.5$, $p < .001$, and significant linear, $F(1, 61) = 19.6$, $p < .001$, and quadratic, $F(1, 61) = 32.6$, $p < .001$, response by assessment interactions. The three-way linear interaction was also significant, $F(1, 61) = 7.5$, $p < .01$, but not the quadratic interaction, $F(1, 61) = 1.5$, *ns.*

The three-way interaction is illustrated in Figure 2. For the Ex/Rs (left-hand panel), there were no differences between treatment groups at any assessment, all three t values $(30) < 1$. The effect size (Cohen's d) at Week 15 was small (−0.18). There was a significant reduction from Week 0 to Week 10 for both the sertraline, $t(15) = 14.9$, $p < .001$, and sertraline/PE, $t(15) = 13.5$, $p < .001$, groups. At Week 10, the average reduction from Week 0 in SIP scores for the sertraline and

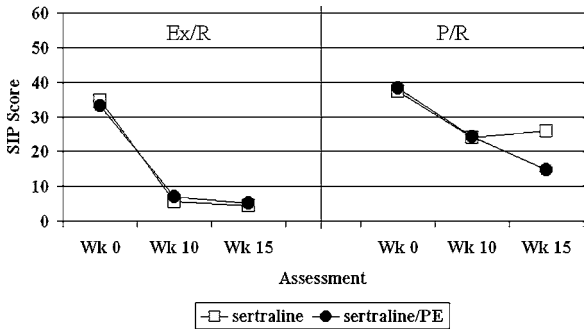

Figure 2. The Structured Interview for PTSD (SIP) scores for excellent responders (Ex/R) and partial responders (PR) at each assessment point in response to sertraline alone (sertraline) or sertraline augmented with prolonged exposure (sertraline/PE). The SIP scores obtained at Week 10 were used to determine responder status. Ex/Rs were defined as participants with Week 10 SIP scores <14 and PRs were defined as participants with Week 10 SIP scores ≥14. Participants were randomly assigned to sertraline or sertraline/PE at Week 10.

Table 3. Outcome Variables (*M*, *SD*, *n*) for Participants Entering Phase II

		Assessment week					
		Week 0		Week 10		Week 15	
Measure	Responder status	*M*	*SD*	*M*	*SD*	*M*	*SD*
BDI	Excellent responders ($n = 31$)	21.2	11.56	4.9	4.16	4.2	6.71
	Partial responders ($n = 33$)	21.9	8.60	15.6	7.92	13.2	8.74
STAI-S	Excellent responders ($n = 31$)	52.7	12.25	33.4	10.15	31.2	11.19
	Partial responders ($n = 33$)	56.6	12.52	48.6	12.25	46.7	16.35

Note. BDI = Beck Depression Inventory, STAI-S = state-anxiety portion of the State-Trait Anxiety Inventory. Structured Interview for PTSD (SIP) scores obtained at Week 10 were used to determine responder status. Excellent responders (Ex/Rs) were defined as participants with Week 10 SIP scores < 14 and partial responders (PRs) were defined as participants with Week 10 SIP scores ≥ 14.

sertraline/PE groups were 29.1 ($SD = 7.80$) and 26.3 points ($SD = 7.77$), respectively. There was no further significant reduction from Week 10 to Week 15 for either sertraline ($M = 1.1$, $SD = 2.94$), $t(15) = 1.5$, *ns,* or sertraline/PE ($M = 1.7$, $SD = 4.27$), $t(15) = 1.6$, *ns.* At Week 15, the average reduction in SIP scores from Week 0 for the sertraline and sertraline/PE groups were 30.2 ($SD = 7.44$) and 28.1 points ($SD = 8.11$), respectively. For the PRs (right-hand panel), there were no differences between treatment groups at either Week 0 or Week 10, both t values $(31) < 1$, *ns.* At Week 15, SIP scores were significantly higher for sertraline alone than sertraline/PE, $t(23.3) = 2.52$, $p < .05$, *df* adjusted because of unequal variances. The effect size (Cohen's *d*) at Week 15 was large (0.90). There was a significant reduction from Week 0 to Week 10 for both sertraline, $t(14) = 6.3$, $p < .001$, and sertraline/PE, $t(17) = 6.0$, $p < .001$, groups. At Week 10, the average reduction from Week 0 in SIP scores for the sertraline and sertraline/PE groups were 13.2 ($SD = 8.17$) and 14.1 points ($SD = 9.88$), respectively. There was no further reduction from Week 10 to Week 15 for sertraline ($M = -1.9$, $SD = 10.42$), $t(14) < 1$, *ns,* while there was further reduction for sertraline/PE ($M = 9.6$, $SD = 8.50$), $t(17) = 4.8$, $p < .001$. At Week 15, the average reduction in SIP scores from Week 0 for the sertraline and sertraline/PE groups were 11.3 ($SD = 12.26$) and 26.61 points ($SD = 13.20$), respectively. At Week 0, there was a trend for Ex/Rs ($M = 33.9$, $SD = 7.62$) to have lower SIP scores than PRs ($M = 37.8$, $SD = 9.86$), $t(63) = 1.8$, $p = .079$. At Week 10, Ex/Rs ($M = 6.2$, $SD = 3.82$) had significantly lower SIP scores than PRs ($M = 24.2$, $SD = 8.21$), $t(45.5) = 11.4$, $p < .001$, *df* adjusted because of unequal variances. At Week 15, Ex/Rs ($M = 4.8$, $SD = 3.86$) had significantly lower SIP scores than PRs in both sertraline ($M = 26.0$, $SD = 14.89$), $t(13.7) = 5.4$, $p < .001$, *df* adjusted because of unequal variances, and sertraline/PE groups ($M = 14.7$, $SD = 9.77$), $t(20.0) = 4.1$, $p < .001$, *df* adjusted because of unequal variances.

New findings for the BDI were a significant main effect for response, $F(1, 60) = 16.7$, $p < .001$, and significant linear, $F(1, 60) = 14.3$, $p < .001$, and quadratic, $F(1, 60) = 9.8$, $p < .01$, response by assessment interactions. Neither the three-way linear, $F(1, 60) = 3.0$, *ns*, nor quadratic, $F(1, 60) < 1$, *ns,* interactions were significant. The top portion of Table 3 presents descriptive statistics (*M, SD, n*) for the BDI for excellent and partial responders combined across treatment groups at each assessment. There was a significant reduction from Week 0 to Week 10 for both Ex/Rs ($M = 16.3$, $SD = 11.14$), $t(30) = 8.2$, $p < .001$, and PRs ($M = 6.3$, $SD = 7.82$), $t(32) = 4.6$, $p < .001$, but no further reduction from Week 10 to Week 15 for either Ex/Rs ($M = 0.7$, $SD = 6.99$), $t(30) < 1$, *ns,* or PRs ($M = 2.4$, $SD = 8.12$), $t(32) = 1.7$, *ns.* At Week 15, the average reduction in BDI scores from Week 0 for the Ex/Rs and PRs were 17.1 ($SD = 9.54$) and 8.7 points ($SD = 8.96$), respectively. There was no difference on the BDI between Ex/Rs and PRs at Week 0, $t(62) < 1$, *ns.* Ex/Rs had significantly lower BDI scores than PRs at

Week 10, $t(49.1) = 6.8$, $p < .001$, *df* adjusted because of unequal variances, and Week 15, $t(59.7) = 4.7$, $p < .001$, *df* adjusted because of unequal variances.

New findings for the STAI-S were a significant main effect for response, $F(1, 60) = 18.0$, $p < .001$, and significant linear, $F(1, 60) = 13.8$, $p < .001$, and quadratic, $F(1, 60) = 5.9$, $p < .05$, response by assessment interactions. Neither the three-way linear, $F(1, 60) = 3.0$, *ns,* nor quadratic, $F(1, 60) < 1$, *ns,* interactions were significant. The bottom portion of Table 3 presents descriptive statistics (*M, SD, n*) for the STAI-S for excellent and partial responders at each assessment. There was a significant reduction from Week 0 to Week 10 for both Ex/Rs ($M = 19.3$, $SD = 10.69$), $t(30) = 10.0$, $p < .001$, and PRs ($M = 8.0$, $SD = 11.70$), $t(32) = 4.0$, $p < .001$, but no further reduction from Week 10 to Week 15 for either Ex/Rs ($M = 2.2$, $SD = 8.65$), $t(30) = 1.4$, *ns,* or PRs ($M = 1.9$, $SD = 12.08$), $t(32) < 1$, *ns.* At Week 15, the average reduction in STAI-S scores from Week 0 for the Ex/Rs and PRs were 19.4 ($SD = 11.68$) and 13.1 points ($SD = 14.58$), respectively. There was no difference on the STAI-S between Ex/Rs and PRs at Week 0, $t(62) = 1.3$, *ns.* Ex/Rs had significantly lower STAI-S scores than PRs at Week 10, $t(62) = 5.4$, $p < .001$, and Week 15, $t(56.8) = 4.4$, $p < .001$, *df* adjusted because of unequal variances.

DISCUSSION

Participants receiving 10 weeks of open-label treatment for PTSD with sertraline showed significant reductions in PTSD severity, depression, and general anxiety. Five additional weeks of treatment with sertraline alone did not result in any further improvement on any of these measures. Augmentation with 10 sessions of twice-weekly prolonged exposure (PE) after the initial 10 weeks of sertraline alone resulted in further reductions in PTSD severity but not in depression or general anxiety. However, differences between groups on PTSD severity at the end of treatment was neither statistically significant nor clinically meaningful. An exploratory analysis revealed the augmentation effect on PTSD severity was evident for partial medication responders but not excellent medication responders. Notably, partial medication responders who received augmentation with PE still had significantly more severe PTSD symptoms after 15 weeks of treatment than did excellent medication responders, regardless of the excellent responders' treatment condition. There was no evidence of an augmentation effect even for medication partial responders on measures of depression and general anxiety.

There are several notable results important to the field and to clinicians treating PTSD. The beneficial results of sertraline found in randomized clinical trails were generally replicated in this study as a substantial proportion of participants did appear to respond to sertraline, and there was a beneficial effect of augmenting medication with CBT, in particular PE, among medication partial responders. This latter finding is clinically very relevant, as it lends itself to real-world recommendations for treatment. Medication has the advantage of being widely available, through psychiatrists, other physicians (e.g., primary care physicians, obstetricians/gynecologists), and nurse practitioners in most states. By contrast, the availability of high-quality CBT at present is much more limited to specialty centers. In the short run, medication also requires fewer resources as medication management visits tend to be shorter and scheduled less frequently than therapy sessions, but the costs of continuing medication and pharmacy charges over time can be substantial. It is also notable that we aimed for a full response, with a clinically significant reduction in PTSD and related symptoms.

Unlike the Londborg et al. (2001) study, we did not find a benefit of continued sertraline alone following the acute phase. There are at least three possible reasons for the discrepancy between these results and those of Londborg et al. First, they had a substantially longer continuation phase (24 weeks) than we did (5 weeks). This is not very likely the explanation, however, because Londborg reported that most of the improvement occurred during the first 6 weeks of continuation. Londborg reported that the improvement during continuation came from participants who were nonresponders during the randomized phase and became responders during continuation. Second, their criterion for a responder was a minimum of a 30% reduction

in PTSD. We excluded people who did not get at least a 20% reduction. Therefore, we had very few medication nonresponders (by the Londborg et al. definition) going into our Phase II. Third, the fact that improvement in the Londborg study occurred only in those who were nonresponders during blind administration and became responders within about 6 weeks of entering nonblind continuation raises the possibility that the improvement in Phase II was a placebo effect introduced by breaking the blind. Our participants were never blind, so there would be no enhanced placebo effect in Phase II.

Regarding the choice between medication and CBT, many PTSD sufferers are hesitant to take psychiatric medications and research has documented a strong preference among female victims of assault for CBT over medication (Zoellner, Feeny, Cochran, & Pruitt, 2003). Many medications are associated with side effects and discontinuation effects that some patients find difficult to tolerate. In addition, CBT may be more cost effective in the long run, because the increased risk of relapse upon discontinuation of medication (Davidson, Pearlstein et al., 2001) results in longer duration of medication with the associated long-term costs. However, we recognize that currently PE has limited availability. In addition, there was a higher dropout rate in Phase II for those participants who received the PE augmentation. One possible explanation for this is that participants, after having received some symptomatic relief with medication, may be hesitant to delve into the traumatic memory and reminders. It is certainly a reasonable clinical approach to consider the reverse of what was attempted in this study and treat all patients with CBT first and then only offer medication to those requiring a greater response. It is also true that the response to PE, although statistically better for weaker medication responders than stronger medication responders, may not have been of clinical significance.

Strengths of this study include the use of an FDA-approved medication for PTSD, an empirically supported psychotherapeutic treatment for PTSD, the collaboration of three sites and investigative teams with different areas of expertise, the use of an augmentation design to more closely simulate the real world, randomization to treatment conditions, blind independent raters, manualized treatment, standardized assessment, and clear inclusion requirements based on *DSM-IV* diagnosis. Another strength is that our exclusion criteria were minimal and reflected appropriate clinical considerations only. In particular, epidemiological studies of PTSD indicate that PTSD is highly comorbid with other psychiatric disorders and that exposure to multiple traumas is common. However, many of the published treatment studies on PTSD have not adequately reported on important variables, causing some reviewers to question the generalizability of extant research on treatment of PTSD (e.g., Bradley, Greene, Russ, Dutra, & Westen, 2005). Both exposure to multiple traumas and psychiatric comorbidity were highly represented in our sample. A related concern that has been expressed (again, see Bradley et al., 2005) is the potential biasing effect of attrition during the study on the final sample. Participants who dropped out of either phase of the current study were not different from those who completed treatment across a range of demographic, trauma, and psychopathology variables.

The major limitations of the current design are lack of a placebo control condition in Phase I, a credible control psychotherapy condition (e.g., relaxation or supportive counseling) in Phase II, and a relatively small sample size. Accordingly, we cannot draw any conclusions about the mechanisms responsible for improvement in Phase I or additional improvement in Phase II. However, these were not the questions under consideration. Although both treatments were selected because of their status as empirically supported treatments, other medications (e.g., paroxetine) and other CBT programs have been found effective in treating PTSD. Our findings may not generalize to different combinations of other medications and CBT programs. Here again, the question of the optimal combination of medication and CBT was not a question this study was designed to address. Directly related to the question of augmentation of sertraline by PE, the relatively small sample size in the randomized portion of the study may have limited our statistical power to find clear evidence for an augmentation effect in the full sample and the finding that the augmentation effect was only evident among medication partial responders was the result of an exploratory

analysis. Finally, even among the medication partial responders, the augmentation effect was obtained only for PTSD and not for depression or general anxiety. Accordingly, replication of these results is warranted.

In conclusion, the augmentation effects of PE added to sertraline, and the finding that the augmentation effect was limited to partial medication responders, would probably not have been evident in the typical combination study designs where combined treatments begin simultaneously. Moreover, it is more typical of clinical practice to initiate a single treatment, examine response to it, and then change or augment, rather than to initiate two or more treatments simultaneously. We would argue that future studies of the combined effects of pharmacotherapy and psychotherapy should utilize this real-world design.

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