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Research Article

PRIMUM NON NOCERE (FIRST DO NO HARM): SYMPTOM WORSENING AND IMPROVEMENT IN FEMALE ASSAULT VICTIMS AFTER PROLONGED EXPOSURE FOR PTSD

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Background: *Prolonged Exposure (PE) therapy is an efficacious treatment for PTSD; despite this, many clinicians do not utilize it due to concerns it could cause patient decompensation.* **Method:** *Data were pooled from four published well-controlled studies of female assault survivors with chronic PTSD (n = 361) who were randomly assigned to PE, waitlist (WL), or another psychotherapy, including cognitive processing therapy (CPT), Eye Movement and Desensitization Reprocessing (EMDR), or the combination of PE plus stress inoculation training (SIT) or PE plus cognitive restructuring. PTSD and depression severity scores were converted to categorical outcomes to evaluate the proportion of participants who showed reliable symptom change (both reliable worsening and reliable improvement).* **Results:** *The majority of participants completing one of the active treatments showed reliable improvement on both PTSD and depression compared to WL. Among treatment participants in general, as well as those who received PE, reliable PTSD worsening was nonexistent and the rate of*

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reliable worsening of depression was low. There were no differences on any outcome measures among treatments. By comparison, participants in WL had higher rates of reliable symptom worsening for both PTSD and depression. Potential alternative explanations were also evaluated. **Conclusions:** ***PE and a number of other empirically supported therapies are efficacious and safe treatments for PTSD, reducing the frequency of which symptom worsening occurs in the absence of treatment. Depression and Anxiety 31:412–419, 2014.***

Key words: ***Anxiety; Cognitive Behavioral Therapy; Depression; Exposure Therapy; PTSD; Trauma; Treatment Outcome***

Exposure therapy for posttraumatic stress disorder (PTSD) typically includes imaginal exposure to the trauma memory and in vivo exposure to safe but feared or avoided trauma reminders. Exposure therapy has received substantial empirical support for its efficacy,[1,2] but despite this, many clinicians do not utilize it, frequently due to insufficient training and concerns it could cause patient decompensation.[3,4]

Empirical support for concerns about the safety of exposure therapy for PTSD is limited. Based on six Vietnam veterans unsuccessfully treated with imaginal exposure, Pitman et al.[5] suggested it is not suitable for patients displaying negative emotions other than anxiety (e.g. anger) and that cognitive approaches may be more beneficial for such patients. Tarrier et al.[6] compared imaginal exposure with cognitive therapy and found that on average both treatments were similarly effective at decreasing PTSD symptoms. The authors reported that a significantly greater number of patients receiving imaginal exposure worsened over treatment (31 vs. 9.1%), with symptom worsening defined as an increase of one or more points on the Clinician Administered PTSD Scale (CAPS). At the 6-month follow-up assessment, however, no significant differences between groups emerged.

Devilly and Foa[7] noted a number of methodological problems that complicate interpretation of the Tarrier et al.[6] findings. First, they questioned the exclusive reliance on a single outcome measure (i.e. the CAPS) for defining symptom worsening when the study included other relevant measures (e.g. the Impact of Events Scale; the Penn Inventory for PTSD) on which no differential rates of worsening emerged. Second, given the measurement error associated with the CAPS, they questioned whether participants showing minimal increases in CAPS scores can be viewed as having experienced symptom worsening. To address these problems, Devilly and Foa[7] proposed an alternative operational definition of symptom change, termed "reliable change," that is based on the standard error of the differences between two administrations of the instrument (test–retest), so to assess for random fluctuations due to measurement error. Therefore, "reliable worsening" would be a pre-to posttreatment increase in symptoms larger than the standard error of the difference between two measurements. Third, as with Pitman et al.,[4] the absence of a waitlist (WL) condition hampers interpretation of the Tarrier et al.[6] results, because the percentage of patients who would experience symptom worsening without treatment is unknown.

In the present study, we examined whether prolonged exposure (PE), a specific exposure therapy protocol that combines imaginal and in vivo exposure, leads to PTSD symptom worsening using methodology that overcomes the limitations of previous studies. We accomplished this by pooling data from four published, well-controlled clinical trials. Each of the four trials compared PE to WL and at least one other psychotherapy with demonstrable efficacy for PTSD that include an element of exposure: cognitive processing therapy (CPT), Eye Movement and Desensitization Reprocessing (EMDR), and combination treatments of PE plus stress inoculation training (PE/SIT) or cognitive restructuring (PE/CR). Participants in all these studies were female assault victims; we deliberately limited the focus of our study to this particular population so that the data were homogenous in terms of sampled population. The Devilly and Foa[7] definition (termed here "reliable change") were used to compare the percentage of participants receiving PE who showed reliable symptom worsening versus WL and other treatments. Because withholding treatment may also cause harm by preventing possible improvement, we also compared the percentage of participants who showed reliable improvement in response to treatment with PE, other active treatments, and WL.

METHOD

STUDIES AND PARTICIPANTS

We pooled data from four studies conducted by three of the current authors (E.B.F., P.A.R, and B.O.R [8–11]). All four studies randomly assigned adult female participants with chronic PTSD to at least nine sessions of PE, WL, and at least one other active empirically supported psychotherapeutic intervention that includes some degree of exposure. One of the studies included SIT as a treatment condition,[8] but these individuals were excluded from the current analyses as SIT does not include an exposure element. All studies utilized a reliable and valid measure of PTSD administered by an independent evaluator blind to participants' study condition, as well as a self-report measure of depression. Finally, all studies took standard steps to insure high treatment fidelity for all conditions. Inclusion criteria for all the studies included

TABLE 1. Summary of studies included in current analyses

Study	Condition	*N* Completers	Sample and Target Trauma	*N* Dropouts (%)	Sessions (#, duration, frequency)	Measures	
						PTSD	Depression
Foa et al. (1999)	PE	23	Female survivors of rape and nonsexual assault after age 16	2 (8%)	9 sessions 90–120 min 2×/week	PSS-I	BDI
	PE/SIT	22		8 (27%)			
	WL	15		0 (0%)			
Foa et al. (2005)	PE	52	Female survivors of sexual and nonsexual assault after age 16 and childhood sexual abuse	27 (34%)	9 –12 sessions 90–120 min 1×/week	PSS-I	BDI
	PE/CR	44		30 (41%)			
	WL	25		1 (4%)			
Resick et al. (2002)	PE	40	Female survivors of rape	15 (27%)	PE: 9 sessions 90–120 min, 2×/week	CAPS	BDI
	CPT	41		15 (27%)			
	WL	40		7 (15%)	CPT: 12 sessions 60 min, 2×/week		
Rothbaum et al. (2005)	PE	20	Female survivors of rape	3 (13%)	9 sessions 90–120 min 2×/week	CAPS	BDI
	EMDR	20		5 (20%)			
	WL	20		4 (17%)			

Note: Foa et al. (2005) reported 25 waitlist completers, but posttreatment PSSI data was not available for one of them; accordingly, only the 24 participants with complete data were included in the present analyses. Measures of PTSD were the PTSD Symptom Scale Interview (PSS-I) Clinician Administered PTSD Scale (CAPS), the measure of depression was the Beck Depression Inventory (BDI: all four studies). The treatments were prolonged exposure (PE), stress inoculation training (SIT), prolonged exposure combined with stress inoculation training (PE/SIT), prolonged exposure combined with cognitive restructuring (PE/CR), eye movement desensitization and reprocessing (EMDR), and cognitive processing therapy (CPT); the control condition was waitlist (WL).

a primary diagnosis of PTSD and being a female survivor of assault. Two studies[8,9] included victims of both sexual and nonsexual assault. The other two studies[10,11] included only victims of sexual assault. For all studies, exclusion criteria included current schizophrenia, psychosis or bipolar disorder; organic mental disorder, alcohol or drug dependency, and severe suicidal ideation/intent. Illiteracy in English was an exclusion criteria in three studies,[9–11] being in an abusive relationship in two studies,[9,10] and self-injurious behavior in two studies.[9,11] The following were exclusion criteria in a single study: current relationship with assailant,[8] developmental disabilities,[10] being less than six months since the end of a relationship where martial rape took place,[10] blindness or history of eye disease,[11] use of cocaine within 60 days of receiving treatment,[11] and being in a current threatening situation.[11] A summary of these four studies is provided in Table 1; for further details see the published research reports.

Because the goal of this study was to determine if individuals who received a therapeutic course of PE experienced symptom worsening, our analyses focused on treatment completers. Moreover, few participants who dropped out of treatment returned for a postdropout evaluation, limiting our ability to evaluate symptom status with a clinical interview for PTSD symptoms.[1] Accordingly, participants were 361 female assault survivors that completed participation in the four studies mentioned above. Participants were distributed as follows: PE alone, $N = 135$;[8–11] PE/SIT, $N = 22$;[8] PE/CR, $N = 44$;[9] CPT, $N = 41$;[10] EMDR, $N = 20$;[11] and WL, $N = 99$.[8–11] Pre- and posttreatment PTSD data were available for 100% of participants and BDI data were available for 339 (93.9%) of participants.

MEASURES

PTSD was assessed with PTSD Symptom Scale – Interview (PSS-I[12]) in the two studies by Foa et al.,[8,9] on which scores range between 0 and 51. The Clinician Administered PTSD Scale (CAPS[13]) was utilized in the studies by Resick et al.[10] and Rothbaum et al.,[11] on which scores range between 0 and 136. There is a strong correspondence between the two instruments.[14] Depression was assessed with the Beck Depression Inventory (BDI).[15]

STUDY CONDITIONS

All treatments included basic education in the nature of PTSD and a rationale for the specific interventions that would be used. In addition to patient education, each treatment contained other specific elements.

Prolonged Exposure. PE comprised training in controlled breathing (one session), imaginal exposure (IE) to the trauma memory followed by a discussion of the experience (called processing), and in vivo exposure to safe but feared or avoided trauma reminders. PE was administered in either nine, twice weekly 90-min sessions[8,10,11] or 9–12 weekly 90-min sessions, with the number of sessions determined by the participants' response to treatment.[9] Homework assignments consisted of practicing controlled breathing, and both imaginal and in vivo exposure exercises. Foa, Hembree, and Rothbaum[16] provide a detailed description of the PE protocol.

[1]We examined PTSD symptoms for the PSS-SR (12), the self-report version of the PSS-I, among participants who dropped out of treatment (PE and PE/CR) in the study with the largest dropout rate (i.e., 32.4%; [11]). The PSS-SR was administered at the pre-treatment assessment, at each even numbered therapy session, and at post-treatment. Of 57 participants who dropped out of treatment, 49 had a pre-treatment PSS-SR plus at least one additional PSS-SR obtained during treatment or at post-treatment. Reliable change for the PSS-SR, obtained from Foa et al. [22], was +/− 6.15 points. Among treatment dropouts, 59% showed reliable improvement, 16% showed numerical worsening, and 6% showed reliable worsening. These rates are similar to what we found for the WL condition in this study, for which the corresponding rates were 52%, 24%, and 5%. Thus, rates of symptom improvement were lower among treatment dropouts than among treatment completers, and rates of reliable symptom worsening were greater for treatment dropouts than for treatment completers. However, these rates for treatment dropouts are similar to those obtained for WL participants.

PE/SIT and PE/CR. PE/SIT followed the nine-session, twice-weekly format and included education, training in SIT skills, imaginal exposure, and *in vivo* exposure. The SIT skills were adapted from the program developed by Veronen and Kilpatrick,[17] consisting of teaching coping skills to manage assault-related anxiety and postassault problems. Skills included deep muscle relaxation, cue-controlled and differential relaxation, thought stopping, cognitive restructuring, guided self-dialogue, covert modeling, and role-playing. PE/CR was identical to PE as administered in the Foa et al.[9] study with two exceptions. First, Session 3 focused on CR, thereby delaying the introduction of imaginal exposure until session 4. Second, all subsequent sessions included both imaginal exposure and CR. PE/CR entailed the same amount of exposure homework as those in PE, plus daily practice of CR using a daily diary form. See Foa et al.[9] for more details.

Cognitive Processing Therapy. CPT included two sessions of written narrative accounts, although it is primarily a trauma-focused cognitive therapy in which participants are taught to challenge distorted beliefs about the causes and consequences of their traumatic experience(s). CPT was administered according to the Resick and Schnicke[18] manual and comprised 12, twice weekly 60-min sessions. Sessions 7–12 focused on the specific topics of safety, trust, power-control, esteem, and intimacy. Homework consisted of writing exercises about the nature and meaning of the participant's traumatic experience and practice challenging trauma-related cognitions with a sequential series of worksheets and practice assignments.

Eye Movement and Desensitization Reprocessing. The manual distributed at EMDR training workshops served as the study treatment manual. EMDR involved having the participant imagine a scene that represented the worst part of the trauma while focusing on bodily sensations of distress and rehearsing negative thoughts that match the picture. When distress over the memory substantially decreased, new, preferred beliefs are rehearsed until they feel true to the patient. This whole process was conducted while the patient tracked the therapist's fingers moving back and forth in front of her. EMDR also utilizes a form of cognitive therapy referred to as the cognitive interweave.[19] EMDR was administered in nine, twice weekly 90-min sessions. Homework assignments were not given.

Waitlist. Participants in the WL conditions were informed they would receive treatment after a 4–9 week waiting period, depending on the specific study in which they were participants.

DEFINITIONS

Reliable worsening was defined as a pre- to posttreatment increase larger than the standard error of the difference between two measurements,[7,20] given as $SED = \mathrm{SQRT}[2(SEM^2)]$, where $SEM = SD^*\mathrm{SQRT}(1\text{-}r)$, *SD* is the standard deviation of a reference sample, and *r* is the instrument's test-retest reliability. *Reliable improvement* was defined as a pre- to post-treatment decrease larger than one SED. All other values reflected changes too small to be considered reliable.

For the PSS-I, a *SD* of 11.1 was calculated from a large sample ($N = 196$) of female assault survivors assessed approximately 10-weeks posttrauma, 39.3% of whom met full symptom criteria for PTSD. A 1-month test–retest reliability coefficient of .77 was computed on a subsample of the women ($n = 184$) who completed the measure again 4 weeks later. Thus, reliable change on the PSS-I was a change greater than +/− 7.53 points. For the CAPS, McDevitt-Murphy et al.[21] obtained a 1-week test–retest reliability of .89 in a group of 55 women exposed to range of potentially traumatic events, 25% of whom met full symptom criteria for PTSD. Separate *SD*s were reported for the PTSD (13.1) and no PTSD (14.9) groups, from which we computed an overall *SD* of 24.2. Thus, reliable change on the CAPS was a change greater than +/− 11.35, similar to the 10-point change Schnurr et al.[22,23] used to reflect statistically and clinically meaningful change. Based on Foa et al.,[20] we adopted a change greater than +/− 4.53 to indicate reliable change on the BDI.

ANALYTIC STRATEGY

Nonparametric tests (chi-square, *Fisher's Exact Test* when one or more cells had an expected frequency less than five) were conducted to analyze the study data using SPSS (version 16.0) and SAS (version 9.2). Confidence intervals for nonparametric tests were calculated by first computing the upper and lower limits of the noncentrality parameter using NDC.EXE, a freeware available at http://www.statpower.net/Software.html, and then converting those values into Cohen's *w*.[24]

We investigated reliable symptom change by submitting PTSD and depression data to separate 2 Group (active treatment, WL) × 3 Outcome (reliable improvement, no reliable change, reliable worsening) analyses. Active treatment comprised the pooled results for all treatments. Significant effects were followed by separate 2 × 2 analyses to compare active treatment with WL on relative proportion of reliable improvement and reliable worsening and PE alone with WL. Next, separate 2 Type of Treatment (PE alone, combination treatment) × 3 Outcome (reliable improvement, no reliable change, reliable worsening) analyses were conducted. The combination treatment condition pooled results from PE/SIT, PE/CR, CPT, and EMDR.

RESULTS

RELIABLE SYMPTOM CHANGE

Table 2 presents the number (percentage) of participants showing reliable improvement, no reliable change, and reliable worsening comparing active treatment with WL for PTSD (top panel) and depression (bottom panel), along with the results of the initial 2 Group × 3 Outcome analyses. *Fisher's Exact Tests* indicated significant differences between treatment and WL conditions for both PTSD and depression. The follow-up 2 × 2 analyses indicated that, compared to WL, active treatment was associated with a greater proportion of participants achieving reliable improvement for both PTSD (91.6 vs. 36.4%; χ^2 (1, $N = 361$) = 121.8, $P < .001$, $\eta^2 = .58$, 95% CI [.48, .68]) and depression (83.1 vs. 36.9%; [χ^2 (1, $N = 339$) = 66.5, $p < .001$, $\eta^2 = .44$, 95% CI [.34, .55]). In addition, compared with WL, active treatment was associated with a smaller proportion of participants displaying reliable worsening for both PTSD (0 vs. 8.1%; *Fisher's Exact Test*, $P < .001$, $N = 361$) and depression (1.9 vs. 10.1%; *Fisher's Exact Test*, $P < .001$, $N = 339$).

Table 3 presents the number (percentage) of participants showing reliable improvement, no reliable change, and reliable worsening comparing PE and WL for PTSD (top panel) and depression (bottom panel), along with the results of the 2 Group × 3 Outcome analyses. *Fisher's Exact Tests* indicated significant differences between PE and WL conditions for both PTSD and depression. The follow-up 2 × 2 analyses indicated that, compared to WL, PE was associated with a greater proportion of participants achieving reliable improvement for both PTSD (77.6 vs. 22.4%; χ^2 (1, $N = 234$) = 84.31, $P < .001$, $\eta^2 = .6$, 95% CI [.47, .73]) and depression (78.2 vs. 21.8%; [χ^2 (1, $N = 217$) = 49.33, $P < .001$,

TABLE 2. Frequency (percentage) of reliable improvement and reliable worsening for active treatment and WL conditions

Outcome variable	Active treatment	WL	Statistic	*P*
PTSD				
Reliable improvement	240 (91.6%)	36 (36.4%)	*Fisher's Exact*	< .000
No reliable change	22 (8.4%)	55 (55.6%)	$N = 361$	
Reliable worsening	0	8 (8.1%)		
N	281	99		
Depression				
Reliable improvement	212 (83.14%)	31 (36.9%)	*Fisher's Exact*	< .000
No reliable change	38 (14.9%)	43 (51.2%)	$N = 339$	
Reliable worsening	5 (2%)	10 (11.9%)		
N	274	84		

Note: Measures of PTSD were the PTSD Symptom Scale Interview (PSS-I) and Clinician Administered PTSD Scale (CAPS), the measure of depression was the Beck Depression Inventory (BDI). The treatments were prolonged exposure (PE), prolonged exposure combined with stress inoculation training (PE/SIT), prolonged exposure combined with cognitive restructuring (PE/CR), eye movement desensitization and reprocessing (EMDR), and cognitive processing therapy (CPT). The control condition was waitlist (WL). See text for the definitions of reliable change.

TABLE 3. Frequency (percentage) of reliable improvement and reliable worsening for PE and WL condition

Outcome variable	PE	Waitlist	Statistic	*P*
PTSD				
Reliable improvement	125 (92.6%)	36 (36.4%)	*Fisher's*	<.001
No reliable change	10 (7.4%)	55 (55.6%)	*Exact*	
Reliable worsening	0	8 (8.1%)	$N = 234$	
N	135	99		
Depression				
Reliable improvement	111 (83.5%)	31 (36.9%)	*Fisher's*	<.001
No reliable change	20 (15.0%)	43 (51.2%)	*Exact*	
Reliable worsening	2 (1.5%)	10 (11.9%)	$N = 217$	
N	133	84		

Note: Measures of PTSD were the PTSD Symptom Scale Interview (PSS-I) and Clinician Administered PTSD Scale (CAPS), the measure of depression was the Beck Depression Inventory (BDI). PE = prolonged exposure. See text for the definitions of reliable change.

$\eta^2 = .48$, 95% CI [.34, .61]]). In addition, compared with WL, PE was associated with a smaller proportion of participants displaying reliable worsening for both PTSD (0 vs. 8.1%; *Fisher's Exact Test*, $P < .01$, $N = 234$) and depression (1.5 vs. 11.9%; *Fisher's Exact Test*, $P < .01$, $N = 217$).

Table 4 presents the number (percentage) of participants showing reliable improvement, no reliable change, and reliable worsening comparing PE and combination treatment for PTSD (top panel) and depression (bottom panel), along with the results of the 2 Group × 3 Outcome analyses. *Fisher's Exact Tests* found no significant differences across treatments for either PTSD or depression.

ALTERNATIVE EXPLANATIONS

We investigated two methodological variables that may provide alternative explanations for the above findings. The first variable we investigated was whether results differed as function of who conducted the study. Specifically, we compared whether studies conducted by Foa et al.[8,9] were different from studies conducted by other researchers.[10,11] Second, we investigated whether results were different in studies with high rates of dropout compared to studies with low rates of dropout. As there were no cases of reliable worsening of PTSD symptoms, the outcome variable in these analyses was reliable worsening of depression symptoms.

Comparison Between Foa et al. Studies and the Other Two Studies. Because two of the four studies included here were done by Foa et al.,[8,9] the present results could reflect differences unique to Foa's site, with fewer participants in her studies showing symptom worsening than participants in the other two studies. To investigate this possibility, we examined whether the rates of reliable worsening on depression were lower in the combined studies by Foa et al. compared the combined studies by Resick et al. and Rothbaum et al. for the PE and WL conditions (all four studies had both conditions, thus there is no confounding of treatment condition with site). There were no differences between the studies of Foa et al. compared to studies by Resick et al. and Rothbaum et al. on reliable depression symptom worsening (3.7 vs. 7.4%, χ^2 (1, $N = 217$) = 1.45, $P = 0.23$, *ns*, $\eta^2 = .08$, 95% CI [0, .21]).

What is the Effect of Differential Dropout?. The overall dropout rate from PE for the four studies included in the current analyses was 25.8% (range 8 – 34%) which was significantly higher than 10.7% dropouts for WL (range 0–17%), χ^2 (1, $N = 293$) = 9.66, $P < .01$, $\eta^2 = .18$, 95% CI [.07, .30]. The dropout rate from the Tarrier et al.[6] study was 17% for imaginal exposure and 11% for cognitive therapy. Accordingly, the higher rates of reliable symptom worsening following WL compared to active treatment across all measures in the present study and the higher rates of PTSD numerical symptom worsening following exposure compared to cognitive therapy in Tarrier et al.[6] may be related

TABLE 4. Frequency (percentage) of reliable improvement and reliable worsening for different classes of treatment (pe and combination treatments)

Outcome variable	PE	Combination Treatment	Statistic	*P*
PTSD				
Reliable improvement	125 (92.6%)	115 (90.6%)	*Fisher's*	= .66
No reliable change	10 (7.4%)	12 (9.4%)	*Exact*	
Reliable worsening	0	0	$N = 262$	
N	135	127		
Depression				
Reliable improvement	111 (83.5%)	101 (82.8%)	*Fisher's*	= .91
No reliable change	20 (15.0%)	18 (14.8%)	*Exact*	
Reliable worsening	2 (1.5%)	3 (2.5%)	$N = 255$	
N	133	122		

Note: Measures of PTSD were the PTSD Symptom Scale Interview (PSS-I) and Clinician Administered PTSD Scale (CAPS), the measure of depression was the Beck Depression Inventory (BDI). PE = prolonged exposure, Combination Treatment = prolonged exposure combined with SIT (PE/SIT) or cognitive restructuring (PE/CR), cognitive processing therapy (CPT), and eye movement desensitization and reprocessing (EMDR). See text for the definitions of reliable change.

to differential dropout across studies and conditions. As can be seen from Table 1, for PE, the Foa et al.[9] and Resick et al.[10] studies had higher dropout rates (34 and 27%, respectively) than the Foa et al.[8] and Rothbaum et al.[11] studies (8 and 13%, respectively). To test the hypothesis that symptom worsening would be lower in studies with higher dropout rates, we combined the two studies with the low dropout rates[8,11] and the two studies with the higher dropout rates.[9,11] Rates of reliable depression worsening following PE were low and similar for the low dropout rate studies and the higher dropout rate studies (0 vs. 2.2%, Fisher's Exact Test, $P = .99$, $N = 133$).

DISCUSSION

In this study, we evaluated pre- to posttreatment symptom worsening for several empirically supported therapies to determine whether PE is harmful compared to WL and compared to other active treatments, specifically SIT, CPT, EMDR, and PE combined with SIT or CR. We utilized data from four published well controlled studies of female assault victims that all included PE and WL conditions, along with at least one other empirically supported psychotherapy and we considered both reliable improvement and reliable worsening. Treatment outcome was evaluated for clinician-administered measures of PTSD (CAPS and PSS-I) and self-reported depression (BDI).

Results revealed a consistent pattern for both PTSD and depression. First, active treatment in general, and PE in particular, resulted in a greater percentage of participants achieving reliable improvement on measures of PTSD and depression than WL. Second, rates of reliable symptom worsening were low for treatment participants, with no cases of reliable worsening of PTSD symptoms; these rates were significantly lower than those found in WL. Third, there were no significant differences among the different treatments on rates of reliable improvement or reliable worsening. The exact pattern of results was observed when we compared PE alone to WL.

We conducted additional analyses to evaluate two alternative explanations for our finding that PE is not associated with higher rates of reliable worsening on depression compared to other treatments. First, we examined if results differed as function of who conducted the study. It is possible that some aspect of the procedures used by Foa and colleagues were responsible for the lower rates of reliable worsening of depression symptoms. As all four studies included the BDI, we were able to evaluate whether the studies by Foa and colleagues showed lower rates of reliable worsening on depression than the other two studies. Inconsistent with the explanation that the studies by Foa and colleagues produced lower rates of reliable symptom worsening than other researchers, our results indicated no differences between the two groups of studies.

We then examined whether rates of reliable worsening on depression were related to rates of dropout. Specifically, it could be hypothesized that participants who experience symptom worsening are more likely to dropout from treatment. It follows that studies with higher dropout rates will exhibit lower rates of symptom worsening. To investigate this possibility, we compared studies with high and low dropout rates. Inconsistent with the dropout explanation, our results indicated that rates of reliable depression symptom worsening following PE were not lower in studies with higher rates of dropout than in studies with lower rates of dropout.

Our results suggest that cognitive-behavior therapy, including exposure therapy, as well as EMDR are safe treatments for chronic PTSD among individuals meeting the basic inclusion (i.e. chronic PTSD is the primary disorder) and exclusion criteria (i.e. not psychotic or actively dependent on substances other than nicotine, not actively suicidal and no recent history of self mutilation) used in these studies.

We note several caveats. First, the current study drew its participants from only four randomized controlled trials. Although the number of participants in the current study is quite large, the inclusion of other studies would have allowed us to make more definitive conclusions about the safety of PE. Second, our pooled data set consisted only of females with a history of assault. The focus on female assault survivors has the advantage that it makes the four studies included here comparable; however, it limits the generalizability of our findings to other traumatized populations. Third, the reliable improvement scores for the PSS-I and CAPS varied based on the test-retest reliability (4 weeks for the PSS-I vs. 1 week for the CAPS), resulting in a different rubric used for each measure. It is possible that the estimate of reliable improvement for the CAPS is too conservative. However, as noted earlier, Schnurr et al.[23]'s estimate of reliable change for the CAPS was +/−10 points, similar to the +/−11.35 used in the current analyses.

Fourth, symptom worsening was the sole measure of safety examined. Symptom worsening formed the basis of Tarrier et al.'s[6] concern about PE. However, other potential adverse effects, (i.e. increased alcohol use) were systematically collected in only 1 of the 4 studies examined.[10] However, a long-term follow up evaluation of participants in this study found that patients who received either PE or CPT did not experience significantly more alcohol dependence 5–10 years posttreatment.[25]

Fifth, as each study involved random assignment of participants and each had a PE and WL control group, randomization was maintained when we pooled the PE and WL participants across studies. However, the studies differed in the non-PE treatments that were provided. Thus, randomization is essentially lost when comparing PE or WL with the non-PE treatments.

Sixth, there were substantially more participants in PE and WL than in the other treatments, which could bias results in two opposite ways. On the one hand, given the overall low rates of symptom worsening, the larger the sample the more likely it will contain cases of symptom worsening. On the other hand, even a single case of symptom worsening in a small sample can yield an inflated percentage. For both reasons (randomization and sample size), our conclusions are stronger for comparisons between PE and WL than any other comparisons.

Seventh, our analyses were restricted to study completers. It is possible that rates of symptom worsening are higher for those who dropout than for those who complete treatment. However, when we compared individuals who dropped out from active treatment, those who had dropped out from WL in the study with the largest dropout rate,[9] individuals who dropped out of treatment fared no worse than individuals who completed WL. Clinical experience further indicates that, at least in some cases, participants may drop out from treatment because they have improved and are no longer motivated to remain in the study. Consistent with this possibility, we found nearly 60% of participants who dropped out of treatment in the Foa et al.[9] study showed reliable improvement on self-reported PTSD severity. Similarly, Schnurr et al.[23] found that in their study comparing PE and present-centered therapy, a supportive intervention, in a sample of 277 female veterans, 63.8% of those who dropped out in the PE condition achieved PTSD responder status posttreatment (i.e. a reduction of 10 or more points on the CAPS, similar to the definition of reliable improvement on the CAPS used in the current study, a reduction of 11.35 or more points).

The above caveats notwithstanding, our results suggest that withholding effective treatment for PTSD is harmful in two ways. First, a larger proportion of WL participants showed symptom worsening than participants who received treatment. Second, fewer WL participants showed reliable symptom improvement than participants who received treatment. To date, the discussion around the safety of exposure therapy has focused on concerns about harm caused through acts of commission without balancing concerns about harm caused through acts of omission. Becker-Blease and Freyd[26] have addressed concerns some researchers have expressed about assessing research participants for histories of childhood abuse and discussed both the potential benefits of conducting such assessments and the costs of not conducting them. We encourage researchers and clinicians alike to similarly take into consideration the likelihood of causing harm through withholding treatment (acts of omission) as well as commission (administering a treatment) in the design of future research and selection of treatments.

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REFERENCES

1. Institute of Medicine. Treatment of posttraumatic stress disorder: An assessment of the evidence. Washington, DC: The National Academies Press; 2008.
2. Cahill SP, Rothbaum BO, Resick PA, Follette VM. In: Foa EB, Keane TM, Friedman MJ, Cohen JA, editors. Cognitive-behavioral therapy for adults, in Effective Treatments for PTSD: Practice Guidelines from the International Society For Traumatic Stress Studies. New York, NY: Guilford Press; 2008:139–222.
3. Becker CB, Zayfert C, Anderson E. A survey of psychologists' attitudes towards and utilization of exposure therapy for PTSD. Behav Res Ther 2004;42:277–292.
4. van Minnen A, Hendriks L, Olff M. When do trauma experts choose exposure therapy for PTSD patients? A controlled study of therapist and patient factors. Behav Res Ther 2010;48:312–320.
5. Pitman RK, Altman B, Greenwald E, et al. Psychiatric complications during flooding therapy for post-traumatic stress disorder. J Clin Psychiatry 1991;52:17–20.

6. Tarrier N, Pilgrim H, Sommerfield C, et al. A randomized trial of cognitive therapy and imaginal exposure in the treatment of chronic posttraumatic stress disorder. J Consult Clin Psychol 1999;67:13–18.
7. Devilly GJ, Foa E B. The investigation of exposure and cognitive therapy: comment on Tarrier et al. (1999). J Consult Clin Psychol 2001;69:114–116.
8. Foa EB, Dancu CV, Hembree EA, Jaycox LH, Meadows EA, Street GP. A comparison of exposure therapy, stress inoculation training, and their combination for reducing posttraumatic stress disorder in female assault victims. J Consult Clin Psychol 1999;67:194–200.
9. Foa EB, Hembree EA, Cahill SP, et al. Randomized trial of prolonged exposure for PTSD with and without cognitive restructuring: outcome at academic and community clinics. J Consult Clin Psychol 2005;73:953–964.
10. Resick PA, Nishith P, Weaver TL, Astin MC, Feurer CA. A comparison of cognitive-processing therapy with prolonged exposure and a waiting condition for the treatment of chronic posttraumatic stress disorder in female rape victims. J Consult Clin Psychol 2002;70:867–879.
11. Rothbaum BO, Atsin M, Marsteller F. Prolonged exposure versus eye movement desensitization and reprocessing (EMDR) for PTSD rape victims. J Trauma Stress 2005;18:607–616.
12. Foa EB, Riggs DS, Dancu CV, Rothbaum BO. Reliability and validity of a brief instrument for assessing post-traumatic stress disorder. J Trauma Stress 1993;6:459–473.
13. Blake DD, Weathers FW, Nagy LM, et al. The development of a clinician-administered PTSD scale. J Trauma Stress 1995;8:75–90.
14. Foa EB, Tolin DF. A comparison of the PTSD symptom scale-interview version and the clinician administered PTSD scale. J Trauma Stress 2000;13:181–191.
15. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:561–571.
16. Foa EB, Hembree EA, Rothbaum BO. Prolonged exposure therapy for PTSD: emotional processing of traumatic experiences: therapist guide. New York, NY: Oxford University Press; 2007.
17. Veronen LJ, Kilpatrick DG. Stress management for rape victims. In: Meichenbaum D, Jaremko M, editors. Stress Reduction and Prevention. New York, NY: Plenum; 1983:341–374.
18. Resick PA, Schnicke MK. Cognitive processing therapy for rape victims: a treatment manual. Newbury Park, CA: Sage; 1993.
19. Shapiro F. Eye movement desensitization and reprocessing: basic principles, protocols, and procedures. 2nd ed. New York, NY: Guilford Press; 2001.
20. Foa EB, Zoellner LA, Feeny NC, Hembree EA, Alvarez-Conrad J. Does imaginal exposure exacerbate PTSD symptoms? J Consult Clin Psychol 2002;70:1022–1028.
21. McDevitt-Murphy ME, Weathers FW, Adkins JW. Use of the Personality Assessment Inventory in assessment of posttraumatic stress disorder in women. J Psychopathol Behav Assess 2005;27:57–65.
22. Schnurr PP, Friedman MJ, Engel CC, et al. Cognitive behavioral therapy for posttraumatic stress disorder in women: a randomized controlled trial. JAMA 2007;297:820–830.
23. Schnurr PP, Friedman MJ, Foy DW, et al. Randomized trial of trauma-focused group therapy for posttraumatic stress disorder: results from a department of veterans affairs cooperative study. Arch Gen Psychiatry 2003;60:481–489.
24. Odgaard EC, Fowler RL. Confidence intervals for effect sizes: compliance and clinical significance in the Journal of Consulting and Clinical Psychology. J Consult Clin Psychol 2010;78:287–297.
25. Resick PA, Williams LF, Suvak MK, Monson C, Gradus JL. Long-term outcomes of cognitive-behavioral treatments for posttraumatic stress disorder among female rape survivors. J Consult Clin Psychol 2012;80:201–210
26. Becker-Blease KA, Freyd JJ. Research participants telling the truth about their lives: the ethics of asking and not asking about abuse. Am Psychol 2006;61:218–226.