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Is Exposure Necessary? A Randomized Clinical Trial of Interpersonal Psychotherapy for PTSD

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Abstract

Background—Exposure to trauma reminders has been considered imperative in psychotherapy for posttraumatic stress disorder (PTSD). No treatment benefits all patients, however. We tested Interpersonal Psychotherapy, which has demonstrated antidepressant efficacy and showed promise in pilot PTSD research, as a non-exposure-based, non-cognitive behavioral PTSD treatment.

Methods—A randomized, fourteen-week trial compared Interpersonal Psychotherapy; Prolonged Exposure, an exposure-based exemplar; and Relaxation Therapy, an active control psychotherapy. Subjects were 110 unmedicated patients having DSM-IV chronic PTSD and Clinician-Administered PTSD Scale (CAPS) score >50. Randomization stratified for comorbid major depression. We hypothesized Interpersonal Psychotherapy would be no more than minimally inferior (CAPS difference <12.5 points) to Prolonged Exposure.

Results—All therapies had large within-group pre/post effect sizes (d=1.32–1.88). Response rates (>30% CAPS improvement) were: Interpersonal Psychotherapy 63%, Prolonged Exposure 47%, Relaxation Therapy 38% (n.s.). Interpersonal psychotherapy and Prolonged Exposure CAPS outcome differed by 5.5 points (n.s.); the null hypothesis of more than minimal Interpersonal Psychotherapy inferiority was rejected (p=0.035). Patients with comorbid major depression dropped out from Prolonged Exposure nine times more than non-depressed Prolonged Exposure patients. Interpersonal Psychotherapy and Prolonged Exposure improved quality of life and social functioning more than Relaxation Therapy.

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Conclusions—This first controlled study of individual Interpersonal Psychotherapy for PTSD demonstrated non-inferiority to the "gold standard" PTSD treatment. Interpersonal Psychotherapy had (non-significantly) lower attrition and higher response rates than Prolonged Exposure. Contradicting a widespread clinical belief, PTSD treatment may not require cognitive behavioral exposure to trauma reminders. Moreover, as differential therapeutics, patients with comorbid major depression may fare better in Interpersonal Psychotherapy than Prolonged Exposure.

Posttraumatic stress disorder (PTSD) is a widespread (1) and debilitating (2) disorder. Its annual prevalence of 3.5% (1), lifetime prevalence of 6.8% (3), and suicidal risk (4) constitute a public health problem. Cognitive behavioral therapies dominate the moderately effective available treatments (5,6). The central technique of most empirically-validated psychotherapies for PTSD exposes patients to objectively safe reminders of their trauma, including reviewing traumatic memories, aiming to habituate and extinguish patients' learned fear responses (7). Validated cognitive behavioral therapies – Prolonged Exposure, Cognitive Processing Therapy, Eye Movement Desensitization and Reprocessing – rely largely on exposure modalities (8–10), albeit Cognitive Processing Therapy has demonstrated efficacy without its exposure component (11). Expert consensus and treatment guidelines emphasize: "The shared element of controlled exposure may be the critical intervention" (8). The Institute of Medicine in 2008 endorsed exposure therapy as the sole adequately empirically supported trauma treatment, finding too little evidence to support other psychosocial techniques and psychopharmacology (9). The mechanism of exposure-based treatment meshes with animal models of fear activation (12); imaging studies link it to prefrontal cortical suppression of amygdalar fear responses to trauma reminders (13).

Like most psychiatric interventions, exposure-based treatments also have known limits. Not all patients respond; most do not remit (14,15). Exposure-based treatments can feel grueling for patients and therapists (16). Moreover, PTSD's complex picture contains a powerful interpersonal theme. Interpersonal traumas more often trigger PTSD (10,17), causing more severe distress than events without human agency such as natural disasters. Many PTSD symptoms reflect interpersonal difficulties (17), such as emotional withdrawal from relationships. Mistrusting their interpersonal environments, traumatized individuals develop "interpersonal hypervigilance" (18). Social support protects against developing PTSD and fosters recovery (10,18).

We therefore adapted Interpersonal Psychotherapy (19), a time-limited, diagnosis-targeted psychotherapy efficacious for depression (20) and eating disorders (19), as a *non*-exposure-based, non-cognitive behavioral PTSD treatment. Patients focus on current interpersonal encounters rather than past trauma (10,18). Interpersonal Psychotherapists, monitored by adherence raters checking session tapes, may neither evoke nor encourage exposure to trauma reminders.

Interpersonal Psychotherapy's antidepressant effect intimated added benefit: roughly half of individuals with PTSD have comorbid major depression disorder (21), and exposure-based treatments focus on PTSD rather than mood disorders. Nonetheless, we doubted Interpersonal Psychotherapy effects on PTSD would be circumscribed to depressive

symptoms. Interpersonal Psychotherapy demonstrably helps patients master social interactions and mobilize social supports, crucial PTSD issues (18).

Based on promising pilot data (18,22,23) that Interpersonal Psychotherapy might benefit PTSD, including our own small open trial (N=14; 69% response rate [18]), we conducted a 14-week randomized trial comparing Interpersonal Psychotherapy; Prolonged Exposure (24), as standard, reference treatment; and Relaxation Therapy (25), an active control condition, treating unmedicated patients with chronic (>3 month) DSM-IV PTSD. Previous research had shown Prolonged Exposure superior to Relaxation Therapy (26,27). We hypothesized Interpersonal Psychotherapy would demonstrate no more than minimal inferiority to Prolonged Exposure (<12.5 points on the Clinician-Administered PTSD Scale [CAPS; 28]), with both Prolonged Exposure and Interpersonal Psychotherapy superior to Relaxation Therapy. We secondarily hypothesized comparable response and remission rates for Prolonged Exposure and Interpersonal Psychotherapy, exceeding those of Relaxation Therapy; and improvements in social functioning and quality of life echoing this pattern. Because Interpersonal Psychotherapy has had low attrition (18,22) and takes a more supportive, less confrontational stance, we anticipated lower attrition than for Prolonged Exposure, which has historical dropout rates >20% (29). We further investigated the effect of comorbid depression on PTSD outcome.

Methods

IRB-approved advertisements appeared on the internet, in print media, and as hospital billboard flyers. Potential subjects telephoned research assistants for brief, semi-structured phone screens (30). Screen-eligible individuals attended clinical interviews with research psychiatrists. Signing informed consent for intake, individuals were interviewed to determine DSM-IV-defined trauma, PTSD as primary diagnosis, and exclusion criteria. They received physical examinations and appropriate laboratory studies. Ph.D. psychologist independent evaluators interviewed subjects using CAPS (28), Structured Clinical Interview for DSM-IV, Patient Version (31), and SCID-II to establish current and lifetime diagnoses.

Eligible subjects signing IRB-approved informed consent for the treatment study were randomly assigned to Prolonged Exposure, Interpersonal Psychotherapy, or Relaxation Therapy in 4:4:3 ratio. Randomization followed a computer-generated program designed by the statistician, who had no patient contact. Randomization was stratified by major depressive disorder (Structured Clinical Interview for DSM-IV diagnosis, with 24-item Hamilton Depression Rating Scale [Ham-D; 32] score ≥20) and implemented in blocks of random sizes (11 or 22).

Patients

Patients, 18–65 years old, had primary DSM-IV diagnosis of chronic PTSD and CAPS score ≥50 (at least moderate PTSD severity). Exclusion criteria comprised psychotic disorders, bipolar disorder, unstable medical condition, substance dependence, active suicidal ideation; antisocial, schizotypal, or schizoid personality disorder; prior non-response to ≥8 weeks of study therapy; and ongoing psychiatric treatment including pharmacotherapy.

Treatments

The three manualized psychotherapies differ markedly. In Prolonged Exposure patients narrate an increasingly detailed trauma narrative (imaginal exposure) and confront trauma reminders (*in vivo* exposure) to extinguish fear responses. Relaxation Therapy, highly scripted, induces progressive muscle and mental relaxation. These treatments require listening to session or relaxation tapes as homework. Interpersonal Psychotherapy addresses not trauma but its interpersonal aftermath, and assigns no homework. The first half of Interpersonal Psychotherapy emphasized affective attunement, recognizing, naming, and expressing one's feelings in non-trauma-related interpersonal situations; the remainder addressed typical Interpersonal Psychotherapy problem areas (e.g., role disputes, transitions) (19).

Interpersonal Psychotherapy had been tested as 14 weekly 50-minute sessions (700 minutes) (18); Prolonged Exposure had been delivered in ten weekly 90-minute sessions (900 minutes), and Relaxation Therapy in nine weekly 90-minute and a final 30 minute session (840 minutes). NIMH reviewers recommended stretching the latter therapies across 14 weeks to equalize treatment duration. Prolonged Exposure and Relaxation Therapy expert supervisors were comfortable scheduling seven consecutive weekly sessions and dispersing the remaining three sessions over seven weeks.

Therapists

Study therapists, psychologists or psychiatrists, treated a minimum of two pilot cases to ensure expertise, were audiotaped, monitored for adherence, and supervised by experts to ensure adherence and competence. Dr. Hembree supervised two Prolonged Exposure therapists, experienced from previous PTSD research (15). The principal investigator trained and supervised four Interpersonal Psychotherapy therapists. Dr. Lovell trained and supervised four Relaxation Therapy therapists. Therapists reported primary allegiance to their study therapy (33). Therapy teams did not significantly differ in mean age (Prolonged Exposure= 47.5 (sd=10.6), Interpersonal Psychotherapy= 41 (9.1), Relaxation Therapy= 34.8 (5.1); $F_{(2,7)}$ =1.80, p=0.23) or years of modality-specific psychotherapy experience (Prolonged Exposure= 7.5 (0.7), Interpersonal Psychotherapy= 9.0 (8.4), Relaxation Therapy= 3.8 (4.4); $F_{(2,7)}$ =0.74, p=0.51). Patients could choose male or female therapists.

Assessments

Independent evaluators were blinded to treatment condition. Patients were reminded not to identify therapy or therapist during evaluations. Major evaluations occurred at baseline, week 7, and week 14.

The trial employed established instruments. The widely used 30-item CAPS assessed PTSD using 0–4 Likert-style item symptom frequency and intensity scales. Subscales describe intrusion, avoidance, and hyperarousal symptom clusters, and associated affective features. Interrater reliability for frequency and severity is excellent for intrusion, hyperarousal, and avoidance subscales (r>.92). Each subscale has good internal consistency (α= .87) (28,34). A CAPS score ≥50 defines at least moderate PTSD; 60, severe PTSD; 80, extreme; scores <20 indicate remission (35). Experienced independent evaluators achieved excellent

interrater reliability on CAPS (primary outcome measure; Shrout-Fleiss interclass reliability coefficient= 0.93), Ham-D (0.89), and other instruments, meeting regularly to compare taped interview ratings.

A modified Posttraumatic Stress Scale-Self Report Version (36) evaluated subjective PTSD symptoms. Other instruments measured social adjustment and functioning (37), quality of life (38), and interpersonal functioning (39). Lacking an instrument to measure self-exposure, we developed the novel, untested Self-Initiated In Vivo Exposure Scale, based on Foa et al.'s Subjective Units of Distress (24) scale, to assess patients' self-exposure to trauma reminders. This scale developed a hierarchy of patients' fear intensity in response to trauma reminders and assessed how often patients were avoiding these feared reminders (*frequency of avoidance*).

All treatment sessions were audiotaped, encrypted, and transmitted to supervisors. Master's level psychologist adherence raters randomly sampled one early session and one late therapy audiotape, rating with Hollon's Collaborative Study Psychotherapy Rating Scale (40) and a briefer quality-of-therapy measure to ensure therapist fidelity. Twenty sessions rated by multiple raters showed perfect agreement on the latter form. Raters found the three disparate therapies easily distinguishable and therapists adherent, correctly identifying rated sessions (N=92), although they did not succeed in rating two tapes for every treatment dyad.

Statistical analysis

Analyses followed the intention-to-treat principle. Some subjects who discontinued treatment were subsequently assessed at the specified assessment times, whereas some treatment completers missed mid-treatment assessment. We compared subjects with missing post-randomization data to those without missing data with respect to baseline characteristics. No comparisons between subjects with and without post-randomization assessment overall, or within treatment groups, approached statistical significance, and no differences neared clinically meaningful magnitude. Efficacy of the three treatments with respect to symptom severity was estimated based on longitudinal mixed effects models (41) using multiple imputations for the missing values (42). For each variable (CAPS, Posttraumatic Stress Scale-Self Report, Ham-D, Social Adjustment Scale, Quality of Life, and Inventory of Interpersonal Problems), we used Markov chain Monte Carlo technique to obtain a monotone missing data pattern. We then applied a predictive mean matching regression method separately for the three treatment groups (43); to increase the likelihood that the missing at random assumption is valid, in addition to the previous values of the variable being imputed, we used all other symptoms variables and baseline major depression status as predictors in predictive mean matching regression. Fifty imputed data sets were generated.

We modeled the post-randomization values as functions of treatment, time, and their interaction, controlling for baseline values of the outcome and major depression status. If the time-by-treatment interaction (a 2 degrees of freedom test) was statistically significant, differences between treatments were estimated separately at mid-treatment (week 7) and treatment end (week 14); otherwise the model was re-fit with only main effects for treatment

and time, and the differences were assessed from a model postulating similar relationships between the treatments at all times.

Response and remission rates were estimated based on the observed data using prespecified criteria for response (>30% decrease from baseline CAPS) and remission (CAPS <20) (28,34,35), assuming subjects without data were non-responders and non-remitters. Statistical significance was judged throughout at level α=0.05, two-sided. *P*-values are reported without adjustment for multiple testing, as the reported results pertain to pre-specified hypotheses and tests. All analyses used SAS/STAT software (44).

Projected enrollment of N=165 subjects (Interpersonal Psychotherapy n=60, Prolonged Exposure n=60, Relaxation Therapy n=45) allowed at least 80% power of two-sided tests based on longitudinal mixed effects models with significance level α=0.05 (a) to establish superiority of both Interpersonal Psychotherapy and Prolonged Exposure compared to Relaxation Therapy (i.e., to reject the null hypothesis of comparability against the alternative that a difference of ≥15 CAPS points favors Interpersonal Psychotherapy or Prolonged Exposure versus Relaxation Therapy) and (b) to establish not more than minimal inferiority of Interpersonal Psychotherapy compared to Prolonged Exposure (i.e., to reject the null hypothesis that the difference is ≥12.5 CAPS points in favor of Prolonged Exposure against the alternative that the difference is 0). The planned sample size provided sufficient power (≥80%) to detect a ≥20% difference between Prolonged Exposure or Interpersonal Psychotherapy versus Relaxation Therapy with respect to response and remission.

The rationale for requiring sufficient power for a difference of 15 CAPS points for efficacy and for declaring a difference of less than 12.5 CAPS points as not more than minimal inferiority is as follows. The CAPS manual suggests a 15 point CAPS difference is clinically significant (45). Regarding minimal inferiority, there is no consensus on the largest difference in efficacy (measured by CAPS) that would render one treatment only minimally inferior to another. Any number lower than 15 is considered not clinically meaningful. We chose the 12.5 CAPS point boundary for minimal inferiority in communication with the NIH reviewers of our application. We thus marked the interval between 10 (including) and 15 (not including) CAPS points difference, *[10, 15)*, the range wherein Interpersonal Psychotherapy would be considered inferior to Prolonged Exposure, but Prolonged Exposure not be considered superior to Interpersonal Psychotherapy, as the logic of non-inferiority trials requires. We split this interval: a difference between 10 (including) and 12.5 (not including) CAPS points *[10, 12.5)* would make Interpersonal Psychotherapy inferior, but only minimally so, to Prolonged Exposure. A difference of 12.5 (including) to 15 (not including) CAPS points, *[12.5, 15)*, would make it more than minimally inferior. NIMH grant reviewers judged this postulation of the primary hypothesis appropriate.

Results

Cohort

One hundred ten unmedicated patients were recruited over the course of the five year trial. Figure 1 illustrates study flow of the 110 recruited patients with chronic PTSD and CAPS score ≥50. Table 1 presents baseline demographics and clinical characteristics, indicating a

highly traumatized, chronically ill sample. At mean age 40.1 (s.d.=11.57), only 15.5% of these racially and ethnically diverse patients were married or cohabitating; only 36.4% held full-time employment (10.9% were students). Ninety-three percent reported interpersonal trauma. More than half (58.2%) reported chronic traumata (mean duration since primary trauma= 14.1 [14.4] years), including sexual (35%) and physical (61%) abuse. Thirty-six percent reported trauma in childhood or adolescence. Three-quarters of patients had received prior psychotherapy and almost half had had pharmacotherapy for PTSD.

Table 2 illustrates patients' psychiatric debility: half had current comorbid major depression; a third, multiple depressive episodes. Nearly half described personality disorders, particularly paranoid, obsessive-compulsive, and avoidant.

Patients attended 8.3 (s.d.=3.1) Prolonged Exposure sessions (mean 748 (277) minutes), 12.6 (3.4) Interpersonal Psychotherapy sessions (630 (69) minutes), and 7.8 (3.5) Relaxation Therapy sessions (667 (290) minutes), or 83%, 90%, and 78% of prescribed sessions, respectively.

Outcome

CAPS scores showed substantial symptomatic improvement in each therapy over the 14 week course of treatment (see Table 3), with large within-group pre/post effect sizes: Prolonged Exposure Cohen's d=1.88, Interpersonal Psychotherapy d=1.69, and Relaxation Therapy d=1.32. The time by treatment interaction was not significant. Compared to Relaxation Therapy, Prolonged Exposure showed a significant advantage (p= 0.010), Interpersonal Psychotherapy only trend level superiority (p= 0.097). The difference between Prolonged Exposure and Interpersonal Psychotherapy CAPS change scores was 5.5 points, less than the *a priori* 12.5 point minimal inferiority threshold. The null hypothesis of more than minimal inferiority of Interpersonal Psychotherapy was rejected (p= 0.035).

Attrition was: Interpersonal Psychotherapy 15%, Prolonged Exposure 29%, and Relaxation Therapy 34% (n.s.) Two patients quit each condition post-randomization but before beginning therapy. Response rates (>30% CAPS improvement) were: Interpersonal Psychotherapy 63%, Prolonged Exposure 47%, and Relaxation Therapy 38%. Interpersonal Psychotherapy had a significantly higher response rate than Relaxation Therapy (χ^2= 4.45, p= 0.03). Treatment remission rates did not differ: Prolonged Exposure 26%, Interpersonal Psychotherapy 23%, Relaxation Therapy 22%.

Prolonged Exposure (p< 0.001) and Interpersonal Psychotherapy (p= 0.008) showed statistically significant PTSD symptom improvement over Relaxation Therapy on the Posttraumatic Stress Scale-Self Report. Prolonged Exposure improved faster than and showed trend level advantage over Interpersonal Psychotherapy at week 14 (p= 0.053) (Table 3). Prolonged Exposure and Interpersonal Psychotherapy each yielded improvement statistically superior to Relaxation Therapy on Ham-D, quality of life, and social functioning, and the Inventory of Interpersonal Problems (37), without differing from one another.

Mediators and moderators of treatment effect will be addressed elsewhere. We examined two key variables, however. To ensure that IPT therapists were not conducting unintentional exposure therapy, mediation analyses assessed early change (between baseline and week 5) in *frequency of avoidance* of the three highest ranked Self-Initiated In Vivo Exposure Scale trauma items as predictor of week 14 CAPS. Early frequency of avoidance change directly (and expectedly) predicted CAPS outcome for Prolonged Exposure and Relaxation Therapy, but not for Interpersonal Psychotherapy (supplemental Figure 2). This finding supports Prolonged Exposure and Interpersonal Psychotherapy treatment theories.

Comorbid major depressive disorder, a diagnosis half the sample carried, proved a striking moderator of treatment effects. As the study was not powered to detect interaction terms, and to avoid omitting potentially important effects due to low power, interactions between treatment and major depressive disorder status with *p*-values ≤0.15 were followed up with pairwise comparisons. The omnibus test assessing whether dropout depended on the interaction between depression status and treatment showed $p = 0.15$. Half of patients with comorbid depression randomized to Prolonged Exposure dropped out: the odds ratio of Prolonged Exposure attrition with (50%) and without (5.6%) major depression was 17:1 (Table 4). Dropout among depressed patients treated with Prolonged Exposure tended to be higher than among depressed patients treated with Interpersonal Psychotherapy (p=0.086), and higher than dropout of non-depressed Prolonged Exposure patients (p=0.006). Dropout of non-depressed patients treated with Relaxation Therapy tended to be higher than dropout of non-depressed patients receiving either Interpersonal Psychotherapy or Prolonged Exposure (p=0.068 and p=0.065 respectively). The effect of the interaction between major depression status and treatment response was $p=0.058$.

Patients without major depression had higher response rates in Interpersonal Psychotherapy ($p = 0.008$) and Prolonged Exposure ($p = 0.032$) than Relaxation Therapy. Within Prolonged Exposure, non-depressed patients had a higher response rate than depressed patients. No evidence emerged for a moderating effect of major depressive status on treatment effects with respect to longitudinal CAPS severity or remission status.

Adverse events

We withdrew five patients who by therapist report and on independent evaluator assessment developed worsening depression (Relaxation Therapy, n=2), manifested bipolar disorder (Interpersonal Psychotherapy, n=1), severely abused substances (Interpersonal Psychotherapy, n=1), or violated protocol by obtaining outside treatment (n=1, Prolonged Exposure).

Discussion

The primary study goal involved testing not more than minimal inferiority of Interpersonal Psychotherapy, a non-exposure treatment, to Prolonged Exposure for patients with severe, chronic PTSD. As Interpersonal Psychotherapy emerged no more than minimally inferior to Prolonged Exposure on the primary outcome measure, had a non-statistically significant but clinically meaningful higher response rate, and a lower dropout rate for patients with comorbid major depression, the treatments appeared roughly equipotent. These findings

contradict the widespread clinical belief in PTSD therapeutics that patients require cognitive behavioral therapy or exposure to trauma reminders. This news may relieve many patients who refuse to face their trauma-related fears, cannot tolerate systematic exposure, or do not benefit from it.

Prolonged Exposure did take faster effect, had a slight (non-significant) CAPS edge, and a trend level advantage over Interpersonal Psychotherapy on the self-report PTSD measure.

Many severely traumatized patients who had reported ineffective community treatment responded to each 14-week treatment modality. In a trial that achieved less than planned enrollment, Relaxation Therapy, an active control, statistically differed only marginally from Interpersonal Psychotherapy on CAPS. A larger sample size might have yielded statistical significance. No ideal psychotherapy control exists comparable to pill placebo in pharmacotherapy trials. A study strength is that Prolonged Exposure and Interpersonal Psychotherapy, competing against a robust, active control condition, still showed differential symptom and social functioning benefits. This trial potentially adds a novel, very differently focused, non-cognitive behavioral treatment to the PTSD armamentarium.

Two other critical findings arose. First, comorbid major depressive disorder strongly predicted dropout in Prolonged Exposure but not Interpersonal Psychotherapy or Relaxation Therapy. Prolonged Exposure was developed to target anxiety; although it often reduces depressive symptoms (14,46), it may treat major depressive disorder less effectively. Alternatively, comorbid major depression may have rendered tolerating Prolonged Exposure more difficult. Interpersonal Psychotherapy was originally developed to treat major depression, however, and did so even while focusing on PTSD. The outcomes suggest differential therapeutics: Interpersonal Psychotherapy may have preferential advantages over Prolonged Exposure for patients with comorbid PTSD and major depression. (Alternatively, patients might benefit from concomitant antidepressant pharmacotherapy [15].) Although few studies have even examined PTSD remission rates, and none to our knowledge this subsample, the extremely low remission rates across treatments for patients with PTSD and comorbid major depression (10–15%; Table 4) suggest this group might benefit from combined treatment with medication (14). Prolonged Exposure may produce greater CAPS improvement in patients without major depression.

Second, a key mediator suggests treatment mechanisms differed. Unsurprisingly for therapy encouraging patients to confront traumatic reminders, patients who faced their traumas early in Prolonged Exposure (and Relaxation Therapy) had better PTSD outcomes, whereas patients whose avoidance increased early had worse final scores than those who did not. Early avoidance had no predictive value in Interpersonal Psychotherapy, which deliberately ignores exposure to trauma reminders. Interpersonal Psychotherapy may work through alternative, attachment mechanisms involving emotional understanding, social support, and learning to cope with current life (18,24,47) rather than confronting past traumas. Yet in order to remit from PTSD, patients must eventually face their fears. As previously reported (18), patients who improved in Interpersonal Psychotherapy seemed to gain confidence in daily social interactions, gathered social support, and then spontaneously – without therapist encouragement – exposed themselves to trauma reminders.

We found what many have suspected: exposure therapy is valuable, but no *sine qua non*. Interpersonal Psychotherapy and Cognitive Behavioral Therapy both relieve major depression and bulimia. Psychotherapy and psychopharmacotherapy each ameliorate syndromes, presumably via different mechanisms. So why expect only one royal road (48) to PTSD response?

Some study findings echo results from other trials. Interpersonal Psychotherapy, which initially focused on affective attunement and only later in treatment encouraged PTSD patients to change their interpersonal interactions in current relationships, yielded somewhat slower symptom improvement than Prolonged Exposure, but caught up. This pattern resembles some eating disorder comparative trials, in which Interpersonal Psychotherapy therapists, barred from discussing bingeing and body image in bulimia, focused on interpersonal relationships. In those studies, Interpersonal Psychotherapy yielded slower improvement than Cognitive Behavioral Therapy but eventually pulled even (19). The Interpersonal Psychotherapy approach to affective attunement also evokes Cloitre et al.'s PTSD treatment study, wherein initial affective attunement and social skills training (based on Dialectal Behavioral Therapy principles rather than Interpersonal Psychotherapy) preceding exposure therapy benefitted patients more than exposure therapy alone (49).

Researcher allegiance can influence study outcomes (33,50). This study's principal investigator has Interpersonal Psychotherapy links; study patients might have entered seeking Interpersonal Psychotherapy. This seems unlikely, however, given their evident lack of psychotherapeutic knowledge at study entry, and our PTSD clinic's historic specialization in Prolonged Exposure treatment (15). The PI encouraged friendly rivalry (33) among the expert-supervised therapy teams. In a prior, Prolonged Exposure-allegiant PTSD trial (15), the study Prolonged Exposure therapists had achieved comparable results: 45% response vs. 44% by identical criteria (Schneier, personal communication, 10/2013); 29% dropout vs. 28%. Our study findings of Prolonged Exposure superiority over Relaxation Therapy confirm assay sensitivity.

Study strengths include matched rival teams of dedicated, allegiant psychotherapists. Few previous PTSD trials have defined response or remission *a priori*. The proscription of pharmacotherapy in the treatment sample eliminated the confounds of undocumented pharmacotherapy dosage changes and of potential psychotherapy/pharmacotherapy interactions. On the other hand, proscribing pharmacotherapy contributed to the study limitation in sample size, doubtless constrained by excluding patients who were receiving psychopharmacotherapy. We felt it inappropriate to stop patients' antidepressant medications which, even if ineffective for PTSD, might benefit depressive or anxiety symptoms. A larger sample would have increased statistical power to test between-treatment differences. Unmedicated status might also limit generalizability of this patient sample. A further limitation is our failure to complete two session adherence ratings on every treatment dyad, though all we rated were adherent.

The hypothesized *a priori* not more than minimal inferiority margin of 12.5 CAPS points between Prolonged Exposure and Interpersonal Psychotherapy derived from a literature review (e.g., 34) and statistical estimation based on our pilot data (18). Our empirical CAPS

data suggest a much narrower (5.5 point) clinical difference between the two treatments. The effect of the smaller than intended sample size on testing this hypothesis is that it increased the probability of Type II error, i.e., of not rejecting the null hypothesis when the null is false. Here it means there was higher than 20% chance to fail to reject the null hypothesis "Interpersonal Psychotherapy is more than minimally inferior to Prolonged Exposure," when in fact Interpersonal Psychotherapy was not more than minimally inferior. The smaller sample size might also be responsible for failing to find differences between Interpersonal Psychotherapy or Prolonged Exposure against Relaxation Therapy with respect to some outcomes. Finally, although even the planned sample size did not allow sufficient power to detect clinically meaningful treatment effect moderators, the smaller than intended sample size further reduces power for moderation hypotheses.

Findings of this comparative trial require replication in combat veterans (only two of our 110 subjects were veterans) and other PTSD populations, and at other treatment centers with differing allegiances. Treatment mechanisms require further exploration. Yet having another potentially efficacious treatment benefits patients with PTSD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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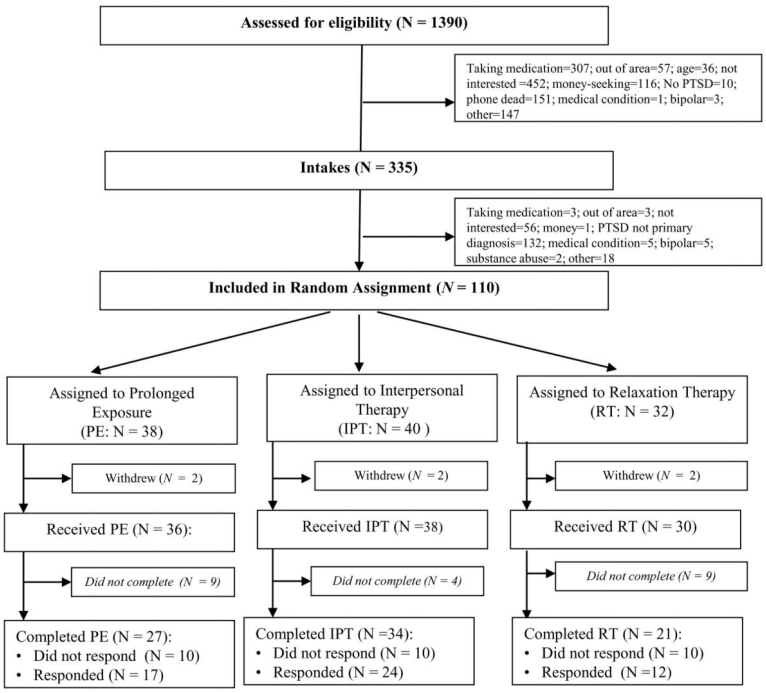

Figure 1.
CONSORT diagram

Table 1

Demographics by Treatment

Variable	PE n=38	IPT n=40	RT n=32	Total N=110
Age (mean, s.d.)	41.76 (11.99)	38.12 (11.21)	40.62 (11.48)	40.10 (11.57)
Gender female (%)	21(55%)	28 (70%)	28 (88%)	77 (70%)
Race				
White	22(58%)	31(78%)	19(59%)	72(65%)
African-American	9(24%)	4(10%)	6(19%)	19(17%)
Asian/Pacific Islander	2(5%)	3(8%)	4(13%)	9(8%)
Other	5(13%)	2(5%)	3(9%)	10(9%)
Ethnicity				
Hispanic	12(32%)	8 (20%)	11 (34%)	31 (28%)
Marital Status				
Single	26(68%)	28 (70%)	19 (59%)	73 (66%)
Married/cohabitating	5(13%)	6 (15%)	6 (19%)	17 (15%)
Divorced	7(18%)	6 (15%)	7 (22%)	20 (18%)
Religion				
Declined to answer	1(3%)	0 (0%)	0 (0%)	1 (1%)
Protestant	6(16%)	3 (8%)	6 (19%)	15 (14%)
Catholic	12(32%)	10 (25%)	8 (25%)	30 (27%)
Jewish	2(5%)	3 (8%)	6 (19%)	11 (10%)
Muslim	0(0%)	2 (5%)	1 (3%)	3 (3%)
Other	17(45%)	22 (55%)	11 (34%)	50 (45%)
Education in years (mean, s.d.)	15.39	15.78	16.25	15.78
Employment				
Full time	14(37%)	12 (30%)	14 (44%)	40 (36%)
Part time	4(11%)	5 (13%)	6 (19%)	15 (14%)
Homemaker	0(0%)	1 (3%)	0 (0%)	1 (1%)
Student	5(13%)	4 (10%)	4 (13%)	13 (12%)
Unemployed <6 mo	3(8%)	4 (10%)	3 (9%)	10(9%)
Unemployed >6 mo	8(21%)	10 (25%)	4 (13%)	22 (20%)
Retired	0(0%)	1 (3%)	0 (0%)	1 (1%)
Disabled	2(5%)	0 (0%)	0 (0%)	2 (2%)
Other	2(5%)	3 (8%)	1 (3%)	6 (5%)
Trauma number				
Mean (s.d.)	2.95(1.96)	2.63(1.79)	2.84(1.67)	2.80(1.81)
Range	1–7	1–7	1–7	1–7

Variable	PE n=38	IPT n=40	RT n=32	Total N=110
Trauma type (primary)				
Interpersonal	34(89%)	37(93%)	31(97%)	102(93%)
Acute	20(53%)	16(40%)	10(31%)	46 (42%)
Chronic	18(47%)	24 (60%)	22 (69%)	64 (58%)
Sexual abuse	11(29%)	17 (43%)	11 (34%)	39 (35%)
Physical abuse	25(66%)	22 (55%)	21 (66%)	68 (62%)
Trauma Onset				
Early (age<13)	6(15.8%)	10(25.0%)	6(18.8%)	22(20.0%)
Adolescent (14–20)	4 (10.5%)	7 (17.5%)	6 (18.8%)	17 (15.5%)
Adult (>=21)	28(73.7%)	23(57.5%)	18(56.3%)	69 (62.7%)
Missing	0 (0.00%)	0 (0.0%)	2 (1.8%)	2 (1.8%)
Age at Primary Trauma: mean (s.d)	27.7 (13.60)	24.2 (13.7)	26.9 (15.8)	26.2 (14.2)
Prior treatment				
Psychotherapy	27(71%)	27(68%)	28(88%)	82(75%)
Pharmacotherapy	18(47%)	19(48%)	15(47%)	52(47%)

Table 2

Clinical Variables by Treatment

Variable	IPT n=40	PE n=38	RT n=32	Total n=110
Current MDD(n, %)	20 (50%)	20 (53%)	15 (47%)	55 (50%)
Recurrent MDD(n, %)	14 (35%)	12 (32%)	11 (34%)	37 (34%)
Comorbid Generalized Anxiety Disorder (n, %)	3 (8%)	8(21%)	3 (9%)	14 (13%)
Axis II disorders				
Paranoid	11 (28%)	6 (16%)	11 (34%)	28 (25%)
Narcissistic	7 (18%)	3 (8%)	5 (16%)	15 (14%)
Borderline	2 (5%)	2 (5%)	1 (6%)	5 (5%)
Avoidant	8 (20%)	7 (18%)	8 (25%)	23 (21%)
Dependent	1 (3%)	2 (5%)	0 (0%)	3 (3%)
Obsessive-Compulsive	11 (28%)	10 (26%)	6 (22%)	27 (25%)
Depressive	9 (23%)	6 (16%)	12 (38%)	27 (25%)
Passive-Aggressive	7 (18%)	4 (11%)	5 (16%)	16 (15%)
Any Axis II diagnosis	17 (43%)	18 (47%)	19 (59%)	54 (49%)
Lifetime substance abuse	5 (13%)	3 (8%)	4 (13%)	12 (11%)
Lifetime alcohol abuse	11 (28%)	7 (18%)	4 (13%)	22 (20%)

Table 3

Outcomes Over Time By Treatment Group

Outcomes	Assessment times	Descriptive summary															Model-based Inference[1]			
		Prolonged Exposure					Interpersonal Psychotherapy					Relaxation Therapy					Time*trt $\chi^2(2)$ p-value[4]	Difference[5], (p-value), ES		
		N	Mean	SD	Change from B[2]	ES[3]	n	Mean	SD	Change from B[2]	ES[3]	n	Mean	SD	Change from B[2]	ES[3]		PE-RT	IPT-RT	IPT-PE
CAPS	B	37	72.1	18.2			40	68.9	16.2			30	68.9	16.4			1.07 (.343)			
	W7	29	39.9	21.0	29.0	1.72	37	50.5	22.3	18.0	1.07	23	54.3	30.8	16.9	1.00		−14.93 (.010) ES=−.88	−9.47 (.097) ES=−.56	5.46 [6](.323) ES=.32
	W14	28	37.5	28.8	31.6	1.88	36	39.8	24.3	28.6	1.69	24	46.5	31.0	22.3	1.32				
PSS-SR	B	30	77.7	22.3			32	74.3	20.2			23	83.2	15.3			4.67 (0.010)			
	W7	19	43.0	23.4	28.6	1.44	31	57.6	24.2	15.2	0.76	17	61.9	28.0	20.4	1.02		−16.51 (.053) ES=−.83	2.20 (.769) ES=.11	18.71(.005) ES=.94
	W14	17	34.1	26.4	36.1	1.81	23	41.7	26.1	32.1	1.61	13	64.7	27.4	14.1	0.71		−30.75 (<.001) ES=−1.55	−18.22 (.008) ES=−.92	12.54 (.053) ES=.63
HAM-D	W0	33	20.2	6.7			37	18.3	6.5			28	21.0	7.1			.128 (.880)			
	W7	29	14.0	8.1	5.8	0.86	36	16.3	8.2	2.0	0.30	22	18.2	10.6	4.6	0.68		−4.42 (.034) ES=−.65	−.98 (.642) ES=−.14	3.44 (.065) ES=.51
	W14	28	12.3	8.8	7.3	1.07	35	13.8	8.8	4.2	0.62	23	14.8	9.1	7.0	1.03				
SAS-SR	W0	27	2.7	0.6			33	2.7	0.6			21	2.8	0.4			3.875 (.022)			
	W7	20	2.4	0.5	0.3	0.53	34	2.5	0.5	0.2	0.36	16	2.5	0.6	0.1	0.24		−.15 (.359) ES=−.26	.00 (.989) ES=.00	.14 (.241) ES=.26
	W14	15	2.1	0.5	0.4	0.81	22	2.2	0.5	0.5	0.93	14	2.7	0.6	0.1	0.16		−.57 (<.001) ES=−1.05	−0.46 (.001) ES=−0.83	0.12(.409) ES=0.21
Q-LES-Q	W0	31	43.5	14.7			31	43.9	15.0			21	43.1	8.7			3.561 (.037)			
	W7	21	55.8	15.1	−11.8	−0.88	32	51.9	15.1	−8.9	−0.66	17	52.2	20.0	−5.9	−0.44		4.73 (.285) ES=.35	.88 (.831) ES=.07	−3.85 (.302) ES=−.29
	W14	15	63.5	19.2	−17.9	−1.33	24	54.6	18.3	−11.3	−0.84	14	46.1	19.2	−0.8	−0.06		17.83(<.001) ES=1.33	10.13(.017) ES=0.75	−7.69 (.061) ES=−.57
IIP	W0	30	1.7	0.6			32	1.6	0.6			23	1.5	0.4			3.327 (.029)			
	W7	21	1.4	0.4	0.4	0.69	34	1.5	0.7	0.1	0.15	17	1.7	0.7	−0.1	−0.21		−.27 (.064) ES=−.49	−.13 (.358) ES=−.23	.15 (.251) ES=.26
	W14	16	1.1	0.6	0.7	1.26	23	1.0	0.7	0.5	0.95	14	1.5	0.6	−0.1	−0.19		−.58 (<.001) ES=−1.03	−.53 (<.001) ES=−.95	.05 (.771) ES=.08

Legend: B= baseline; CAPS= Clinician-Administered PTSD Scale; IIP= Inventory of Interpersonal Problems; IPT= Interpersonal Psychotherapy; PE= Prolonged Exposure; PSS-SR= Posttraumatic Stress Scale- Self-Report; Q-LES-Q= Quality of Life Enjoyment and Satisfaction Scale; RT= Relaxation Therapy SAS-SR= Social Adjustment Scale- Self Report; W= study week number

[1]Generalized linear mixed effects models (GLMMs) on the imputed data; outcomes at weeks 7 and 14 are modeled as functions of treatment and time, adjusting for baseline value of the outcome and MD status

[2]Mean change from baseline using inly those subjects with data at week 7 or at week 14

[3]Effect size of the change from baseline

[4]Test for interaction between time and treatment from generalized linear mixed effects models (GLMMs) for the outcomes at weeks 7 and 14, adjusting for baseline (week 0) value of the outcome and MD status: χ^2 test on 2 d.f., p-value in parentheses. If the interaction term is significant differences between treatment groups are estimated at each time point; if the interaction term is not significant, a GLMM is fit without the interaction term and a single contrast between treatments is estimated, valid for both time points

[5]Difference between treatments, p-value of the difference and effect size of the difference

[6]The null hypothesis for inferiority of IPT compared to PE (Difference of 12.5 points on CAPS) is rejected (p=0.035), thus establishing non-inferiority of IPT.

Table 4

Proportion of Dropout, Response and Remission by Treatment and Comorbid Major Depression Status

Comorbid MDD Diagnosis	Outcome % (95% CI)	Treatment		
		IPT, n=40	PE, n=38	RT, n=32
With MDD n=55		n=20	n=20	n=15
	Dropout	20% (5.7, 43.7)	50% (27.2, 72.8)	26.7% (7.8, 55.1)
	Response	50% (27.2,72.8)	30% (11.9, 54.3)	46.7% (21.3, 73.4)
	Remission	10% (1.2, 31.7)	15% (3.2, 37.9)	13.3% (1.7, 40.5)
Without MDD n=55		n=20	n=18	n=17
	Dropout	10% (1.2, 31.7)	5.6% (0.1, 27.3)	35.3% (14.2, 61.7)
	Response	75% (50.9, 91.3)	66.6% (41.0, 86.7)	29.4% (10.3, 56.0)
	Remission	35% (15.4, 59.2)	38.9% (17.3, 64.3)	29.4% (10.3,56.0)

Legend: IPT= Interpersonal Psychotherapy, MDD= Major depressive disorder; PE= Prolonged Exposure;

RT= Relaxation Therapy