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Long-Term Outcome of Early Interventions to Prevent Posttraumatic Stress Disorder

Arieh Y. Shalev, MD[a,b,*]; Yael Ankri, MA[b]; Moran Gilad, MA[b]; Yossi Israeli-Shalev, MA[b]; Rhonda Adessky, PhD[b]; Meng Qian, PhD[a]; and Sara Freedman, PhD[b,c]

ABSTRACT

Background: Failing to prevent posttraumatic stress disorder (PTSD) has major clinical and public health consequences. This work evaluates the 3-year outcome of offering early interventions to survivors with acute PTSD.

Methods: Adults admitted consecutively to the hospital with acute *DSM-IV* PTSD were randomized, between June 2003 and October 2007, to 12 weeks of prolonged exposure (n = 63) or cognitive therapy (n = 40) or concealed SSRI (escitalopram; n = 23) versus placebo (n = 23). Eighty-two participants who declined treatment were followed as well. Treatment started 1 month after the traumatic event, and participants were reassessed 5 and 36 months later. Assessors were blinded to treatment allocation and acceptance. The Clinician-Administered PTSD Scale (CAPS) evaluated PTSD and PTSD symptoms. Self-reported symptoms, general functioning, and employment status were secondary outcomes. Participants lost to follow-up were missing completely at random.

Results: Prolonged exposure and cognitive therapy significantly reduced PTSD and PTSD symptoms between 1 and 5 months (mean CAPS total scores [95% CI] at 1 month: prolonged exposure = 73.59 [68.21–78.96] and cognitive therapy = 71.78 [66.92–78.93]; mean CAPS total scores [95% CI] at 5 months: prolonged exposure = 28.59 [21.89–35.29] and cognitive therapy = 29.48 [21.32–37.95], $P < .001$), and their results remained stable. At 3 years, however, the study groups had similar levels of PTSD symptoms (mean CAPS total scores [95% CI]: prolonged exposure = 31.51 [20.25–42.78]; cognitive therapy = 32.08 [20.74–43.42]; SSRI = 34.31 [16.54–52.07]; placebo = 32.13 [20.15–44.12]; and no intervention = 30.59 [19.40–41.78]), similar prevalence of PTSD (28.6%–46.2%), and similar secondary outcomes.

Conclusion: Early prolonged exposure and cognitive therapy accelerated the recovery from acute PTSD. Their effect remained stable, however, without reducing the 3-year prevalence of the disorder. The lingering prevalence of PTSD, despite efficient interventions, illustrates a nonremitting, treatment-refractory subset of survivors and outlines a major clinical and public health challenge.

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[a]Department of Psychiatry, New York University Langone Medical Center, New York

[b]Center for Traumatic Stress Studies, Department of Psychiatry, Hadassah University Hospital, Jerusalem, Israel

[c]Department of Social Work, Bar Ilan University, Ramat Gan, Israel

**Corresponding author:* Arieh Y. Shalev, MD, Department of Psychiatry, NYU Langone Medical Center, One Park Ave, 8-221, New York, NY 10016 (Arieh.shalev@nyumc.org).

A significant proportion of trauma survivors develop posttraumatic stress disorder (PTSD).[1–3] Chronic PTSD is tenacious and disabling,[4,5] hence the desirability of prevention by early interventions. Despite extensive research, preventing PTSD remains a major challenge.[6] Illustrating that challenge, the prevalence of PTSD following recent US military engagements does not differ from that observed after the 1965–1974 Vietnam war: 9.1% of Vietnam combat veterans[7] versus 12.9% following combat duty in Iraq,[3] or 7.3% among active duty and 11.2% in National Guard veterans following combat in Iraq.[8] Similarly, the reported prevalence of PTSD among civilians remained stable across 2 waves of the US National Comorbidity Study (NCS): 5.0% in men and 10.4% in women in 1990–1992[1] and 3.6% in men and 9.7% in women in 2001–2003.[9]

Addressing the challenge of early prevention, controlled studies, systematic reviews,[10] and meta-analyses[11,12] established the efficacy of trauma-focused cognitive-behavioral therapy (CBT) in reducing the prevalence of PTSD. Table 1 summarizes 11 controlled studies of secondary prevention of PTSD with CBT.[13–23] Intriguingly, 2 studies[20,21] failed to show a difference between CBT and control conditions, and, of the 3 studies that followed survivors for more than 12 months, 1 reported no differential effect,[22] another[13] found similar prevalence of PTSD but lower levels of PTSD symptoms 13 months after trauma exposure, and a third study[23] documented a better outcome of CBT with only 2 CBT and 4 control PTSD participants at end point.

Early intervention studies have been limited by evaluating individuals who agreed to engage in treatment. However, numerous studies have documented barriers to receiving early care in military personnel[3,4] and civilians[24–26] with PTSD symptoms. Without evaluating those who decline treatment, the effectiveness of early interventions remains unknown.

To explore the effect of nonparticipation, we previously reported that declining early care, 1 month after a traumatic event, was associated with limited recovery at 9 months, that is, shortly after treatment termination.[26] A 9-month end point may not be sufficient, however. Two nationally representative epidemiological studies have outlined longer time to asymptomatic remission: the National Comorbidity Survey (NCS)[1] found a median time to remission of 36 months in respondents who sought professional treatment and 64 months in those who had not; the Australian National Survey of Mental Health and Wellbeing study[27] reported a median time to remission of 14 years, with 37.9% remission by 5 years. Admittedly, the NCS and the Australian National Survey of Mental Health and Wellbeing studies retrospectively evaluated time to remission, and their results have not been corroborated by prospective studies. They, nonetheless, provide a tentative time

Clinical Points

- Preventing posttraumatic stress disorder (PTSD) is highly desirable, but information about the long-term effect of early intervention is missing.
- For patients presenting with acute PTSD 1 month after trauma exposure, cognitive-behavioral therapy reduces early symptoms, and the resulting remission is stable.
- About a third of all trauma survivors with acute PTSD may develop intractable, treatment-refractory disorder and should receive special clinical attention.

frame for assuming time to asymptomatic remission in this work.

The results of the NCS further suggested that seeking professional treatment accelerated the recovery from acute PTSD without reducing the disorder's long-term prevalence. Conversely, CBT has been equated with fear extinction,[28] and, as such, its immediate effect might be subject to renewal, reinstatement, or recovery,[29] expressed as progressive return of symptoms.

This work used a 36-month (3-year) time frame to addresses the following questions: (1) Is the immediate effect of CBT maintained over time? and (2) Does the long-term outcome of CBT differ from that of receiving initially inefficient interventions or declining treatment? To perform this work, we continued to follow treatment-eligible participants of our previously published study of early prevention of PTSD[14]; interviewers who performed follow-up evaluations were blinded to treatment acceptance, allocation, or adherence.

METHODS

The study's recruitment, assessment, randomization, and treatment approach have been described in previous

Table 1. Studies of Early Clinical Interventions (in chronological order)

Study	N	Trauma Type	Baseline Assessment	Intervention	Treatment Duration	Follow-Up Period	Instruments	Results
Bryant et al, 1998[16]	24	MVA, industrial accidents	< 2 wk	Exposure-based CBT (n = 12) SC (n = 12)	5 wk	2 and 6 mo	CIDI, IES, BDI, STAI	Fewer PTSD cases. Greater reductions of intrusive, avoidance, and depressive symptoms in CBT.
Bryant et al, 1999[17]	45	MVA, nonsexual assault	< 2 wk	PE (n = 14) PE and anxiety management (n = 15) SC (n = 16)	5 wk	2 and 6 mo	CAPS-2, IES, BDI, STAI	Fewer patients with PTSD in PE and PE + anxiety management participants.
Bryant et al, 2003[18]	80	MVA, assault	< 2 wk	CBT (n = 50) SC (n = 30)	5 wk	4 y	CAPS-2	Fewer PTSD cases with CBT (n = 2; 8% vs n = 4; 24%).
Bisson et al, 2004[13]	152	Physical injury	< 3 wk	Exposure-based CBT (n = 76) Standard care (n = 76)	4 sessions	12 wk and 13 mo	CAPS, IES	Fewer PTSD symptoms. Similar number of PTSD cases.
Bryant et al, 2006[23]	87	MVA, nonsexual assault	< 2 wk	Exposure-based CBT (n = 33) CBT plus hypnosis (n = 30) SC (n = 24)	6 wk	2 and 6 mo and 2 y	CAPS, IES, BDI, STAI	Fewer PTSD cases in CBT and CBT + hypnosis compared with SC.
Foa et al, 2006[20]	90	Assault (females)	21 d	Brief CBT (n = 31) Assessment alone (n = 30) SC (n = 29)	4 wk	3 and 9 mo	SCID, PSS, BDI, BAI, SAI	Greater decreases in PTSD severity following CBT after treatment and at 3 months. No group difference at 9 months.
Sijbrandij et al, 2007[21]	143	Miscellaneous trauma	Up to 3 mo	Brief CBT (n = 79) Waitlist control (n = 64)	4 wk	1 wk and 4 mo	SCID	Accelerated recovery in the CBT group; no difference in long-term outcome.
Bryant et al, 2008[15]	90	MVA, nonsexual assault	< 1 mo	Exposure-based CBT (n = 30) Cognitive restructuring (n = 30) Waitlist (n = 30)	5 wk	2 and 6 mo	CAPS, BDI, BAI, PTCI	Fewer PTSD in exposure-based CBT, not in cognitive restructuring.
Freyth et al, 2010[22]	40	Miscellaneous trauma	1 mo	PE vs SC (3 sessions)	3 wk	3 and 52 mo	ASDI, ADIS, IES	No difference between groups at follow-up.
Irvine et al, 2011[19]	193	Surgery and defibrillator	< 2 mo	CBT (n = 96) Usual care (n = 97)	8 wk	6 and 12 mo	None	Significant improvements in PTSD symptoms at 6 and 12 months.
Shalev et al, 2012[14]	298	MVA, terror, work, other incidents	< 1 mo	PE (n = 63) CT (n = 40) Escitalopram (n = 23) Placebo (n = 23) WL/delayed PE (n = 93)	12 wk	5 and 9 mo	CAPS, PSS, BDI	Lower 5-month prevalence of PTSD in PE and CT relative to SSRI, placebo, and WL/delayed PE. No 9-month difference between early and delayed PE.

Abbreviations: ADIS = Anxiety Disorder Interview Schedule for *DSM-IV*, ASDI = Acute Stress Disorder Interview, BAI = Beck Anxiety Inventory, BDI = Beck Depression Inventory, CAPS = Clinician-Administered PTSD Scale, CBT = cognitive-behavioral therapy, CGI = Clinical Global Impressions scale, CIDI = Composite International Diagnostic Interview, CT = cognitive therapy, IES = Impact of Events Scale, MVA = motor vehicle accident, NR = not reported, PCL = PTSD Checklist, PE = prolonged exposure, PSS = PTSD Symptom Scale, PTCI = Posttraumatic Cognitions Inventory, PTSD = posttraumatic stress disorder, SAI = Standardized Assault Interview, SC = supportive counseling, SCID = Structured Clinical Interview for *DSM-IV*, SSRI = selective serotonin reuptake inhibitor, STAI = State-Trait Anxiety Inventory, WL/delayed PE = waiting list with delayed PE.

Table 2. Comparison of PTSD Symptoms (CAPS total scores) Between Participants Retained in the Study and Those Lost to Follow-Up

	Lost to Follow-Up		Retained		
Intervention Group	N	CAPS Total Scores, Mean (SD)	N	CAPS Total Scores, Mean (SD)	Wilcoxon Test *P* Value
Initial assessment					
PE	28	69.79 (18.99)	35	76.63 (22.87)	.22
CT	15	70.87 (14.03)	25	72.32 (16.08)	.81
WL/delayed PE	56	72.25 (16.59)	37	70.76 (13.04)	.76
SSRI	8	79.50 (14.07)	15	80.08 (17.26)	.93
Placebo	10	68.50 (14.25)	13	78.33 (14.20)	.16
No intervention	50	71.50 (13.61)	32	67.91 (16.37)	.23
5-Month assessment					
PE	21	25.71 (26.09)	35	30.75 (24.39)	.30
CT	8	25.08 (19.97)	25	32.00 (24.71)	.51
WL/delayed PE	42	56.44 (28.43)	37	42.36 (24.28)	.03
SSRI	6	48.13 (27.34)	15	49.07 (32.07)	.88
Placebo	5	50.17 (25.93)	13	45.58 (17.68)	.45
No intervention	32	43.31 (27.77)	32	41.68 (27.63)	.74

Abbreviations: CAPS = Clinician-Administered PTSD Scale, CT = cognitive therapy, PE = prolonged exposure, PTSD = posttraumatic stress disorder, SSRI = selective serotonin reuptake inhibitor (escitalopram), WL/delayed PE = waiting list with delayed PE.

publications.[14,25] Here we summarize dimensions of relevance for this report.

Participants

Candidates for the study were adult survivors of traumatic events (18–70 years old) consecutively admitted to the emergency department of Hadassah University Hospital, Jerusalem, Israel, between June 2003 and October 2007. Potential participants were excluded from the study if they sustained an injury that required more than 7 days of hospital stay, were unconscious at emergency department admission, or had medical or surgical conditions that could interfere with their ability to participate or provide informed consent. Participants provided oral consent for telephone screening interviews and written informed consent for clinical assessments, randomization, and treatment. Hadassah University Hospital's Institutional Review Board approved and monitored the study. The study was registered at ClinicalTrials.gov (identifier: NCT00146900).

Instruments

Main outcome measure. The Clinician-Administered PTSD Scale (CAPS)[30] for *DSM-IV* provided continuous measure of PTSD symptoms and *DSM-IV*–based diagnosis of PTSD.

Secondary outcome measures. The Structured Clinical Interview for *DSM-IV* (SCID-IV)[31] evaluated current and lifetime *DSM-IV* Axis I disorders other than PTSD and provided a Global Assessment of Functioning (GAF) score.

The revised PTSD Symptom Scale–Self-Report (PSS-SR)[32] recorded participants' self-reported PTSD symptoms using a 0- to 3-point severity score for each *DSM-IV* symptom criterion (total score range, 0 to 51).

The Beck Depression Inventory (BDI)[33] evaluated symptoms of depression at all time points.

Additionally, we recorded participants' employment status (employed vs unemployed), traumatic events that occurred during the study, and additional treatment received during follow-up.

The assessors were psychology interns with experience in diagnosis and management of PTSD. Their training included proficiency in the study's instruments, good clinical practice, and 10 supervised interviews. They remained blinded to treatment allocation, attendance, and adherence.

Interventions

The interventions consisted of twelve 1.5-hour weekly sessions of prolonged exposure[34] or cognitive therapy,[35] 12 weeks of double-blind allocation to either 20 mg of escitalopram (selective serotonin reuptake inhibitor [SSRI] group) or placebo (placebo group), or a waiting list condition group, whose participants received delayed prolonged exposure 5 months after the traumatic event. Protocol adherence was very good across treatment conditions.[14] We used equipoise-stratified randomization[36] to allocate participants to treatment groups, allowing every participant to decline up to 2 treatment modalities and be randomized to the remaining and acceptable arms.

Procedure

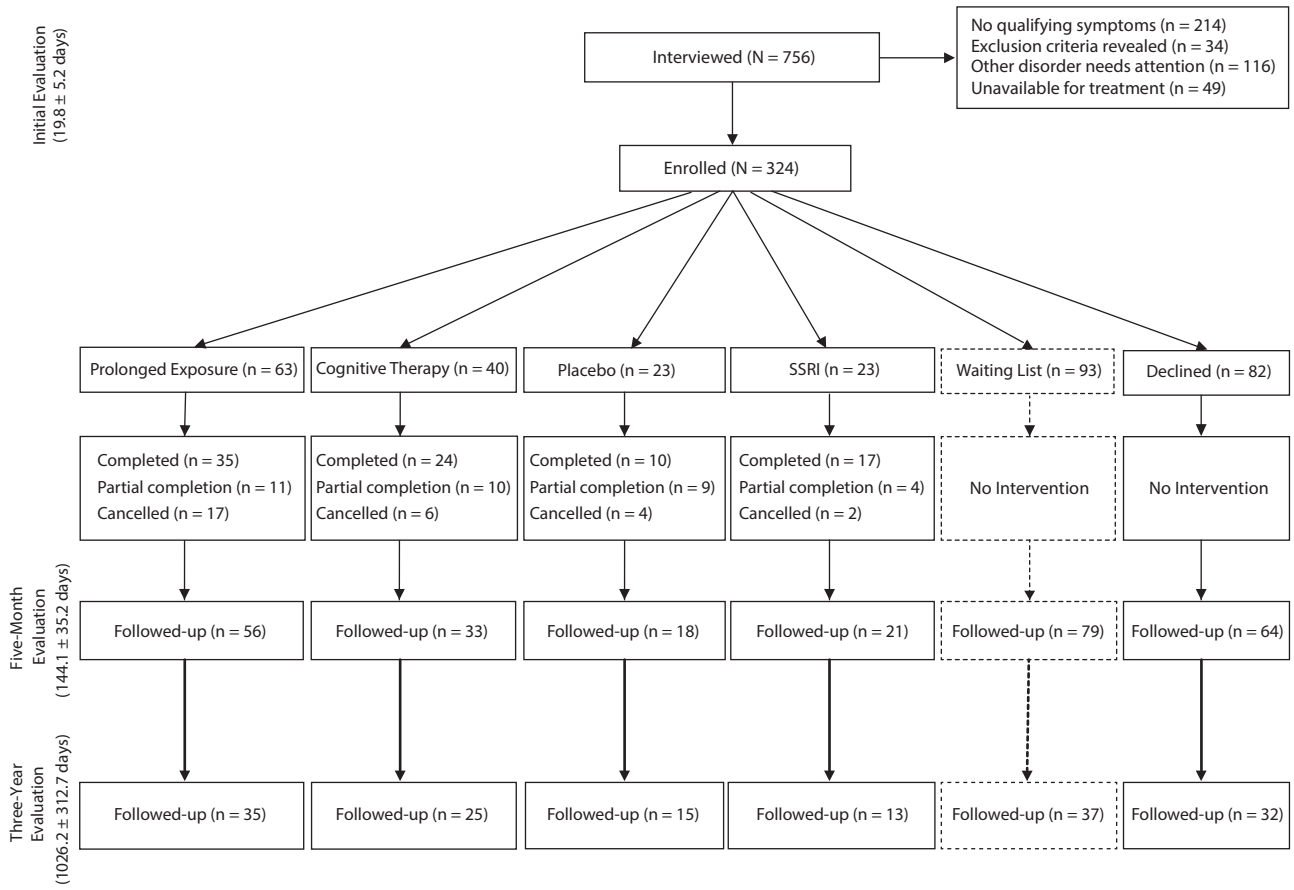
Computerized records of emergency department trauma admissions were screened for inclusion and exclusion criteria. Participants with a confirmed traumatic event received structured telephone screening assessments 9.61 ± 3.91 (mean ± SD) days after the traumatic event. Those with qualifying acute stress disorder symptoms were invited for clinical interviews, which took place 19.80 ± 5.17 (mean ± SD) days after the traumatic event (initial assessment). Participants who met *DSM-IV* diagnostic criteria of acute PTSD (save the 1-month duration; n = 324) received information about the study and were invited to participate. Eighty-two participants (25.3%) declined treatment (a no-intervention group). Those who agreed (n = 242) started treatment 29.83 ± 5.72 days after the traumatic event.

Participants in the initial assessment were reevaluated 145.79 ± 30.17 days (5-month assessment) and 1,026.22 ± 312.74 days (3-year assessment) after the traumatic event. A 9-month (279.45 ± 62.02 days) assessment did not include the participants who declined and was omitted from this report.

Missing Observation

To evaluate the nature of missing observations, we compared, within each intervention group, participants who were retained at 3 years with those lost to follow-up on the study's main outcome variable (CAPS total scores). Participants retained and those lost to follow-up had similar CAPS scores at the initial assessment (Table 2). At 5 months, however, retained waiting list participants had significantly lower CAPS scores than those lost to follow-up. This group (waiting list; presented by dotted lines in Figure 1) was

Figure 1. Study Flowchart



Abbreviation: SSRI = selective serotonin reuptake inhibitor (escitalopram).

subsequently removed from data analyses for this study. However, statistical analysis, available upon request, shows that including the waiting list participants does not change the study's results.

Statistical Analyses

We used 1-way analysis of variance (ANOVA) for cross-section group comparisons of continuous variables and Pearson χ^2 tests for cross-sectional comparisons of categorical variables.

A linear mixed-effects model was used to compare changes in PTSD symptoms between the initial and the 3-year assessments. Covariates in this model included follow-up time, treatment group, age, gender, initial BDI score, initial PSS-SR score, trauma type, and the interaction between the follow-up time and the treatment group. Random intercept and slope for the follow-up time were assumed to explain within-subject correlation among repeated measurements and between-subject heterogeneity.

To additionally include the earlier effect of treatment, we used a piecewise mixed-effects model with a common knot at 5 months. All available data at different time points were used in the analysis, which neither removed participants for missing data nor relied on imputation techniques. Statistical analyses were conducted using SAS (version 9.2; SAS Institute).

RESULTS

Cross-Sectional Comparisons

Initial evaluation. The study groups had similar age, trauma type, time lag between events and initial assessment, initial CAPS scores, and initial rates of comorbid major depression (Table 3). The groups differed in gender distribution and initial PSS-SR, BDI, and SCID GAF scores.[31] The latter (range, 56.26–61.65) reflected "moderate difficulty in social, occupational, or school functioning."

Five-month assessment. Immediately after receiving treatment, the prolonged exposure and cognitive therapy groups showed lower levels of symptoms and lower prevalence of PTSD (21.4% and 18.2%, respectively) than the SSRI, placebo, and no-intervention groups (61.9%, 55.6%, and 43.8%, respectively), with analogous group differences seen in rates of major depression and PSS-SR, BDI, and SCID GAF scores (Table 3).

Three-year assessment. Unexpectedly, the study groups had similar levels of PTSD symptoms at 3 years, similar prevalence of PTSD and major depression, and similar

Table 3. Group Comparisons on Core Study Variables

Study Groups/Variable	PE (n = 63)	CT (n = 40)	SSRI (n = 23)	Placebo[a] (n = 23)	No Intervention[b] (n = 82)	Total (N = 231)	ANOVA/ χ^2	*df*	*P*
Age, mean (SD), y	40.32 (12.24)	40.75 (12.92)	39.83 (11.75)	36.26 (12.39)	37.99 (11.64)	39.11 (12.10)	0.85	4,226	.49
Gender, n (%) males	35 (55.6)	10 (25.0)	13 (56.5)	10 (43.5)	38 (46.3)	106 (45.9)	10.51	4	.04
Trauma type, % MVA/WA/TER/OTH	72/3/25/0	85/2/13/0	87/4/9/0	92/4/0/4	74/5/17/4	78/4/16/2	15.12	12	.23
Initial assessment[c]	**PE (n = 63)**	**CT (n = 40)**	**SSRI (n = 23)**	**Placebo (n = 23)**	**No Intervention (n = 82)**	**Total (N = 231)**			
Time from trauma, mean (SD), d	18.33 (4.53)	19.68 (4.56)	19.22 (4.81)	19.78 (4.84)	20.32 (5.66)	19.50 (5.04)	1.44	4,226	.22
CAPS total score, mean (SD) [95% CI]	73.59 (21.34) [68.21–78.96]	71.78 (15.17) [66.92–78.93]	79.83 (16.61) [73.08–86.57]	74.91 (14.69) [68.56–81.27]	70.10 (14.75) [66.86–74.34]	72.79 (17.05) [70.58–75.00]	1.66	4,227	.2
PSS-SR total score, mean (SD)	30.88 (8.48)	30.58 (8.34)	34.57 (6.55)	36.55 (7.91)	29.10 (8.56)	31.17 (8.52)	4.42	4,213	.002
BDI score, mean (SD)	20.85 (9.43)	20.82 (6.43)	28.30 (10.00)	24.19 (9.47)	19.96 (10.71)	21.67 (9.76)	3.95	4,211	.004
Major depression, n (%)	34 (54.0)	25 (62.5)	18 (78.3)	12 (52.2)	44 (53.3)	133 (57.6)	6.67	4	.15
SCID GAF score, mean (SD)	60.22 (6.51)	58.63 (5.71)	56.26 (5.31)	59.57 (5.33)	61.65 (6.63)	59.99 (6.37)	4.06	4,226	.003
5-Month assessment	**PE (n = 56)**	**CT (n = 33)**	**SSRI (n = 21)**	**Placebo (n = 18)**	**No Intervention (n = 64)**	**Total (N = 192)**			
Time from trauma, mean (SD)	140.98 (26.74)	149.75 (27.69)	131.71 (14.85)	143.39 (28.45)	151.80 (34.38)	145.79 (30.17)	2.70	4,187	.04
CAPS total score, mean (SD) [95% CI]	28.59 (25.02) [21.89–35.29]	29.48 (23.03) [21.32–37.95]	48.71 (29.63) [35.23–62.2]	47.11 (20.13) [37.1–57.12]	42.59 (27.50) [35.72–49.46]	37.35 (26.69) [33.55–41.15]	4.74	4,187	.001
Prevalence of PTSD, n (%)	12 (21.4)	6 (18.2)	13 (61.9)	10 (55.6)	28 (43.8)	69 (35.9)	20.50	4	.001
PSS-SR total score, mean (SD)	11.02 (11.19)	11.56 (10.47)	22.52 (14.20)	22.22 (11.86)	18.90 (13.81)	16.06 (13.14)	6.60	4, 185	.001
BDI score, mean (SD)	9.54 (9.88)	8.66 (9.70)	18.14 (12.62)	15.44 (10.38)	14.08 (11.07)	12.42 (11.00)	6.60	4,184	.003
Major depression, n (%)	10 (17.9)	7 (9.1)	7 (30.4)	4 (22.2)	21 (32.8)	45 (22.92)	11.07	4	.03
SCID GAF score, mean (SD)	72.05 (19.82)	74.21 (10.17)	66.14 (12.27)	63.72 (8.98)	68.67 (11.12)	69.87 (11.18)	4.16	4,187	.003
3-Year assessment	**PE (n = 35)**	**CT (n = 25)**	**SSRI (n = 13)**	**Placebo (n = 15)**	**No Intervention (n = 32)**	**Total (N = 120)**			
Time from trauma, mean (SD)	1034.3 (288.2)	1015.7 (275.3)	924.4 (212.6)	878.1 (354.0)	1071.5 (377.7)	1008.9 (315.7)	1.26	4,115	.29
CAPS total score, mean (SD) [95% CI]	31.51 (32.79) [20.25–42.78]	32.08 (27.47) [20.74–43.42]	34.31 (29.39) [16.54–52.07]	32.13 (21.64) [20.15–44.12]	30.59 (31.04) [19.40–41.78]	31.77 (29.22) [26.49–37.05]	0.04	4,115	.99
Prevalence of PTSD, n (%)	10 (28.6)	10 (40.0)	6 (46.2)	6 (40.0)	10 (31.2)	42 (35.0)	1.98	4	.74
PSS-SR total score, mean (SD)	11.82 (13.72)	14.28 (13.68)	12.75 (12.93)	16.20 (11.93)	14.00 (14.92)	13.58 (13.60)	0.31	4,116	.87
BDI score, mean (SD)	10.56 (12.23)	11.20 (11.39)	10.08 (9.71)	14.80 (12.33)	11.97 (12.87)	11.56 (11.88)	0.39	4,115	.81
Major depression, n (%)	7 (20.0)	6 (24.0)	3 (23.1)	5 (33.0)	6 (18.8)	27 (22.5)	1.33	4	.56
SCID GAF score, mean (SD)	72.79 (13.52)	70.38 (12.03)	71.33 (11.56)	70.27 (10.46)	70.33 (12.63)	71.17 (12.26)	0.22	4,114	.93

[a]The placebo arm of the blinded SSRI/placebo condition.
[b]No intervention represents participants with acute PTSD who declined to start early treatment.
[c]The prevalence of acute PTSD (save the 1-month duration) is 100% among all groups at the initial assessment.
Abbreviations: ANOVA = analysis of variance, CAPS = Clinician-Administered PTSD Scale, CI = confidence interval, CT = cognitive therapy, MVA = motor vehicle accidents, OTH = other incidents, PE = prolonged exposure, PSS-SR = Posttraumatic Symptom Scale–Self-Report–revised, SCID GAF = Structured Clinical Interview for *DSM-IV* Global Assessment of Functioning, SSRI = selective serotonin reuptake inhibitor (escitalopram up to 20 mg daily), TER = terrorist attacks, WA = work accidents.

PSS-SR, BDI, and SCID GAF scores. The latter (range, 70.27–72.29) reflected "no more than slight impairment in social, occupational, or school functioning."

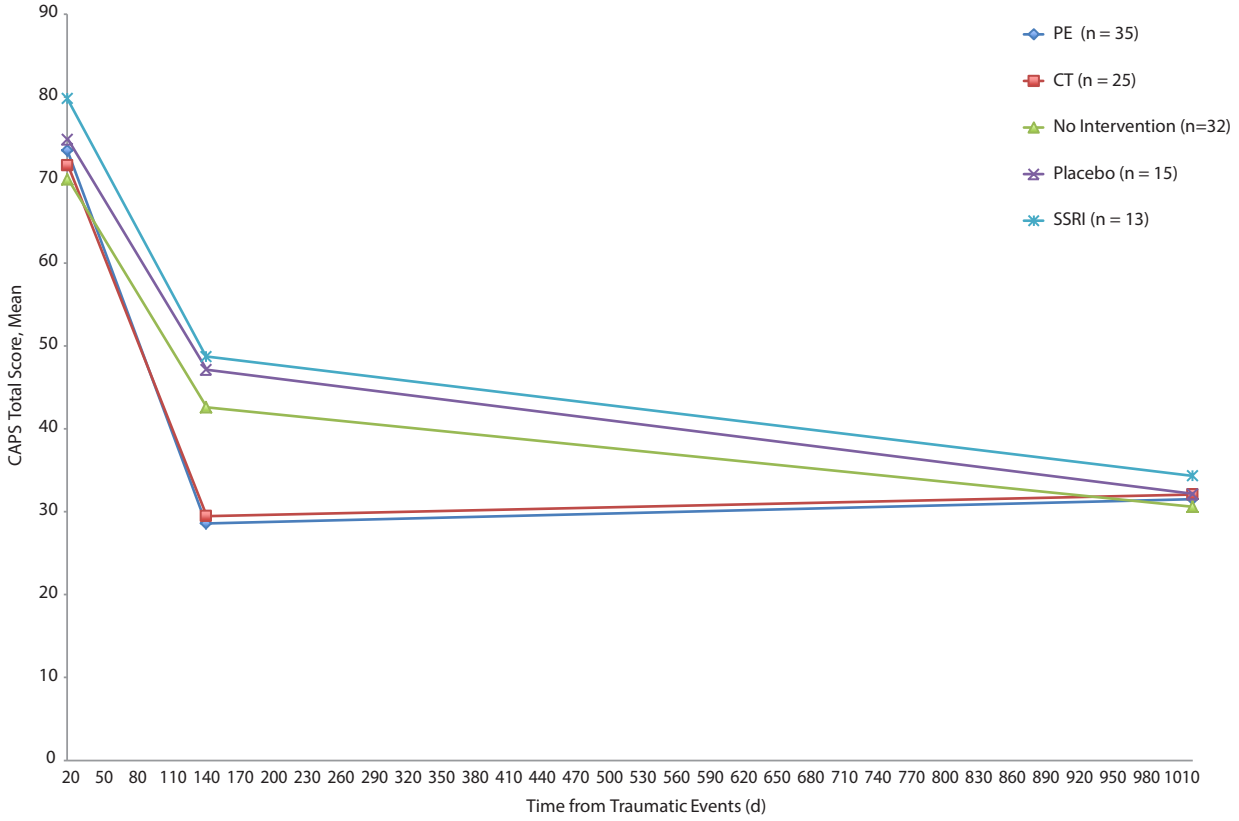
Effect of treatment completion. Six prolonged exposure participants (17.1%), 6 cognitive therapy participants (24.0%), and 2 SSRI participants (15.4%) left before protocol completion. Partial completers (n = 14) did not differ from all others (n = 59) in 3-year mean CAPS total scores (36.79 ± 29.02; 95% CI, 20.03–53.54 vs 31.12 ± 30.46; 95% CI, 23.18–39.05; ANOVA $F < 1$).

Information about employment status was available for 116 of 120 3-year participants, of whom 88 (75.9%) were employed, including 27 of 34 in the prolonged exposure group (79.4%), 16 of 24 in the cognitive therapy group (66.7%), 10 of 12 in the SSRI group (83.3%), 12 of 15 in the placebo group (80.0%), and 23 of 31 in the no-intervention group (74.2%) (all groups: $\chi^2 = 1.89$, $P = .75$). Data informing eventual changes in employment status between 5 months and 3 years were available for 100 of 120 participants (83.3%). Of those, 71 (71.0%) were employed at 5 months, 76 (76.0%) were employed at 3 years, and 63 (63.0%) were employed at both time points. Eight participants lost their job between 5 months and 3 years (11.3% of n = 71), and 13 participants (44.8% of n = 29) were newly employed.

Thirty-seven participants (30.8%) reported new traumatic events during the study period. The study groups did not differ in the number of new traumatic events: (prolonged exposure: n = 10, 28.6%; cognitive therapy: n = 9, 36.0%; SSRI: n = 5, 38.5%; placebo: n = 4, 26.7%; and no-intervention: n = 9, 28.1%; $\chi^2_4 = 1.31$, $P = .86$). Subjects reexposed to a new traumatic event (n = 37) did not differ from those who were not exposed (n = 83) in 3-year total CAPS scores (30.59 ± 28.02 vs 32.29 ± 29.89, respectively; ANOVA $F_{1,118} < 1$).

Twenty-three (19.3%) of 120 participants received trauma-focused interventions between 5 months and 3 years: 7 (20%) of the prolonged exposure group, 5 (20%) of the cognitive therapy group, 3 (23.1%) of the SSRI group, 5 (33%) of the placebo group, and 3 (9.4%) of the no-intervention group. The difference is not statistically significant.

Figure 2. PTSD (CAPS total) Symptom Progression From Initial Assessment to 3 Years



Abbreviations: CAPS = Clinician-Administered PTSD Scale, CT = cognitive therapy, PE = prolonged exposure, PTSD = posttraumatic stress disorder, SSRI = selective serotonin reuptake inhibitor (escitalopram).

To document eventual differences in the severity of PTSD between 5 months and 3 years, we compared the mean CAPS and PSS-SR scores of those who met *DSM-IV* diagnostic criteria for PTSD at 5 months (n = 69) with those having PTSD at 3 years (n = 42). Respectively, for 5 months and 3 years, the mean ± SD total CAPS scores of participants with PTSD were 66.16 ± 16.04 and 64.98 ± 19.35, and the total PSS-SR scores were 29.18 ± 9.95 and 28.75 ± 9.81.

Longitudinal Analysis

From initial assessment to 3 years. A linear mixed-effects analysis found significant main effect of time ($F_{1,201} = 143.5$, $P < .001$), significant treatment effect ($F_{4,106} = 13.18$, $P < .02$), and nonsignificant time-by-treatment interaction ($F_{4,106} = 0.76$), suggesting that the change in CAPS total scores is similar among groups (Figure 2). The 3-years mean CAPS score for all study participants (31.77 ± 29.22) was significantly lower than that observed at 5 months (37.35 ± 26.69; paired-sample $t_{106} = 2.89$, $P < .005$).

From initial assessment via 5 months to 3 years. A piecewise mixed-effects model with a common knot at 5 months showed significant time-by-treatment effect for the initial to 5-month comparison ($F_{4,229} = 5.62$, $P < .001$) and significant time-by-treatment interaction for the 5-month to 3-year comparison ($F_{4,112} = 5.83$, $P < .001$).

DISCUSSION

This is the first follow-up study of early interventions for PTSD that, using a blinded design, compares survivors who received initially efficient treatment (CBT) with those who received initially inefficient interventions (SSRI, placebo) or declined treatment. The study shows an impressive conservation of the effects of early CBT, thereby suggesting that providing CBT effectively reduces the duration of suffering and dysfunction. The study also shows that the differential effect of early CBT disappeared at 3 years, at which time members of all groups, including those who declined treatment, showed similar prevalence of PTSD and major depression and similar PTSD and depression symptoms, global functioning, and employment status. The reduction in the PTSD symptom severity of the whole sample between 5 months and 3 years is entirely due to changes in the SSRI, placebo, and no-intervention groups (Table 2 and Figure 2), whereas the early CBT groups (prolonged exposure and cognitive therapy) conserved their 5-month scores.

The 3-year prevalence of PTSD across groups (35.0%) is in line with the NCS finding that more than one third of people with an index episode of PTSD fail to recover even after many years.[1] The rates exceed the recovery rates reported in the Australian National Survey of Mental Health

and Wellbeing study.[27] The failure of initially efficient CBT to affect the 3-year outcome is also in line with some,[1,22] but not all[23] previous observations. These findings outline the occurrence of persistent, treatment-refractory PTSD in a subset of survivors and position the nonremitting course of PTSD as a major clinical and public health challenge.

Nonremitting PTSD symptom trajectories and nonextinction of fear conditioning in subsets of exposed individuals have been subjects of recent studies.[37–39] Using latent growth mixture modeling (LGMM),[38] we recently described 3 classes of PTSD symptom trajectories during the 15 months that follow trauma exposure: rapid remitting, slow remitting, and nonremitting. The latter (17% of n = 957) were not responsive to early CBT. DeRoon-Cassini et al[39] similarly described persistent PTSD symptoms in 22% of recently traumatized survivors identified upon hospital admission for injury. An analogous analysis of threat-conditioned responses in male Sprague-Dawley rats[40] similarly found a nonextinction trajectory in 10% of the animals, suggesting a putative biological underpinning of persistent fear responses.

Because our results may have significant clinical, public health, and heuristic implications, their generalizability must be carefully examined. At a first level, this work examined survivors of single traumatic events, mostly road traffic accidents, occurring to previously healthy individuals, whose community remained stable and resourceful and who had limited (30.8%) reexposure to new traumatic events during the years that followed the index trauma. Survivors of repeated exposures (such as wars or domestic abuse) or those belonging to shattered, resource-depleted communities (eg, following major disasters or relocation) may have different response trajectories and treatment responses. Given the relatively favorable recovery environments in this study, the 3-year prevalence of PTSD (35.0%) is particularly striking.

The dose of treatment received might have similarly affected our results. Participants of this study were offered 12 weeks of treatment with no "booster," retraining sessions, or prolongation of care for those who did not respond to early CBT. It is possible, therefore, that additional care could have further reduced the rate of PTSD among those who did not respond to early intervention. Studies of second- and third-line intervention for survivors who fail to respond to an early intervention are missing. This work illustrates the need for such studies.

Finally, participants of the study's treatment groups (prolonged exposure, cognitive therapy, SSRI, and placebo) were randomized, whereas those who declined treatment had chosen not to participate. While this could introduce a sampling error, the similar 3-year outcome of the randomly assigned placebo group does not differ from that of the no-intervention group.

The results of this work reflect a core feature of early PTSD, namely its intractable chronic course in a subset of survivors.[37,39,40] Nonremitting survivors might be those who ultimately populate PTSD clinics and, as such, account for some of the tenacity of chronic PTSD. Recent studies[40,41] have shown that survivors' membership in a nonremitting class is highly predictable from information obtained shortly after trauma exposure. Low urinary cortisol excretion in an emergency department setting contributes to the likelihood of nonremitting PTSD in survivors with history of childhood trauma (I. R. Galatzer-Levy, PhD; A. Y. Statnikov, MD; S. Ma, PhD; unpublished data, 2001–2003). A recent prospective study[42] has shown that combined genetic variants predict those most at risk for developing PTSD following trauma. Together, these and future findings may help to identify survivors at high risk and inform better-targeted interventions (eg, cortisol to those with childhood trauma). Future studies may benefit from exploring the distinct pathogenesis of nonremitting posttraumatic psychopathology, its predictors, course modulators, and dedicated therapies.

CONCLUSIONS

This work is limited by sampling from civilian survivors of single, salient, and short events and including only emergency department referrals and, thus, a degree of physical injury and significant attrition rate. The following conclusions are nonetheless warranted: (1) early CBT effectively shortens the duration of PTSD episodes in recent trauma survivors; (2) the effect of early CBT is maintained for 3 years; (3) following single, salient traumatic event, survivors who do not receive CBT recover more slowly but to the same extent; and (4) studies of nonremitting PTSD may improve our understanding of the lingering, decades-long prevalence of this disorder. The finding that CBT efficiently reduces PTSD symptoms without modifying the disorder's 3-year prevalence illustrates the discrepancy between the availability of efficient therapies and the lingering prevalence of PTSD.

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