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Prevention of Posttraumatic Stress Disorder by Early Treatment

Results From the Jerusalem Trauma Outreach and Prevention Study

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Context: Preventing posttraumatic stress disorder (PTSD) is a pressing public health need.

Objectives: To compare early and delayed exposure-based, cognitive, and pharmacological interventions for preventing PTSD.

Design: Equipoise-stratified randomized controlled study.

Setting: Hadassah Hospital unselectively receives trauma survivors from Jerusalem and vicinity.

Participants: Consecutively admitted survivors of traumatic events were assessed by use of structured telephone interviews a mean (SD) 9.61 (3.91) days after the traumatic event. Survivors with symptoms of acute stress disorder were referred for clinical assessment. Survivors who met PTSD symptom criteria during the clinical assessment were invited to receive treatment.

Interventions: Twelve weekly sessions of prolonged exposure (PE; n=63), or cognitive therapy (CT; n=40), or double blind treatment with 2 daily tablets of either escitalopram (10 mg) or placebo (selective serotonin reuptake inhibitor/placebo; n=46), or 12 weeks in a waiting list group (n=93). Treatment started a mean (SD) 29.8 (5.7) days after the traumatic event. Waiting list participants with PTSD after 12 weeks received PE a mean (SD) 151.8 (42.4) days after the traumatic event (delayed PE).

Main Outcome Measure: Proportion of participants with PTSD after treatment, as determined by the use of the Clinician-Administered PTSD Scale (CAPS) 5 and 9 months after the traumatic event. Treatment assignment and attendance were concealed from the clinicians who used the CAPS.

Results: At 5 months, 21.6% of participants who received PE and 57.1% of comparable participants on the waiting list had PTSD (odds ratio [OR], 0.21 [95% CI, 0.09-0.46]). At 5 months, 20.0% of participants who received CT and 58.7% of comparable participants on the waiting list had PTSD (OR, 0.18 [CI, 0.06-0.48]). The PE group did not differ from the CT group with regard to PTSD outcome (OR, 0.87 [95% CI, 0.29-2.62]). The PTSD prevalence rates did not differ between the escitalopram and placebo subgroups (61.9% vs 55.6%; OR, 0.77 [95% CI, 0.21-2.77]). At 9 months, 20.8% of participants who received PE and 21.4% of participants on the waiting list had PTSD (OR, 1.04 [95% CI, 0.40-2.67]). Participants with partial PTSD before treatment onset did similarly well with and without treatment.

Conclusions: Prolonged exposure, CT, and delayed PE effectively prevent chronic PTSD in recent survivors. The lack of improvement from treatment with escitalopram requires further evaluation. Trauma-focused clinical interventions have no added benefit to survivors with subthreshold PTSD symptoms.

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SIGNIFICANT NUMBERS OF INDIviduals who have experienced traumatic events develop posttraumatic stress disorder (PTSD).[1-3] Chronic PTSD is tenacious and disabling.[4,5] Short-term interventions without prior assessment or diagnosis have failed to prevent PTSD.[6] Barriers to care limit the effectiveness of clinical interventions.[3] Developing interventions to prevent PTSD is a pressing public health need.[7]

Controlled studies, systematic reviews, and meta-analyses have established the efficacy of trauma-focused, exposure-based, cognitive behavioral therapy in preventing chronic PTSD.[8-12] Some studies[11,12] have further suggested that the preventive effect of these interventions is confined to individuals who meet *DSM-IV* diagnostic criteria for acute stress disorder (ASD) or PTSD. The preventive effects of cognitive therapy[10] and pharma-

cotherapy[13-17] have not been established. To our knowledge, the proper timing of early interventions, relative to the traumatic event, and the long-term effect of refusing care have not been explored in controlled studies.

Clarifying the above issues is critical: Cognitive therapy (CT) involves less potentially distressing exposure to traumatic recollections. Pharmacological interventions can be provided to a large number of survivors of trauma who are at risk in war-torn and disaster-prone areas. Comparing early and delayed interventions can inform service-delivery decisions and mitigate the rush to intervene as soon as possible. Delineating a threshold for treatment requirement can lead to a better use of often-scarce resources.

To explore these issues, we compared early and delayed interventions in adult trauma survivors consecutively admitted to a general hospital emergency department. Participants were reached for and screened by structured telephone interviews. Those who exhibited qualifying symptoms (defined below) were promptly referred for structured clinical evaluations, and those who exhibited qualifying PTSD symptoms in these evaluations were invited to receive treatment. Equipoise-stratified randomization was used to allocate eligible and consenting survivors to 1 of 4 intervention arms: prolonged exposure (PE), CT, a double-blind comparison of treatment with a selective serotonin reuptake inhibitor (SSRI [ie, escitalopram]) vs placebo, and a waiting list (WL) control group. The WL participants who met PTSD diagnostic criteria at 5 months received PE at that time (hereafter referred to as delayed PE). Participants were repeatedly clinically assessed by clinicians who were blind to their treatment allocation and attendance.

The methodological and service-delivery aspects (feasibility, acceptance, and cost) of the Jerusalem Trauma Outreach and Prevention study have been reported elsewhere.[18] This publication addresses the efficacy of these interventions. Additionally, we report the effects of the different types of treatments on the survivors with partial PTSD and the long-term effect of declining treatment.

METHOD

PARTICIPANTS

The candidates for our study were adult (age range, 18-70 years) survivors of traumatic events who were admitted to Hadassah University Hospital's emergency services between June 2003 and October 2007. Potential participants were included if they resided within a 1-hour drive from Jerusalem (and could attend treatment). Participants were not included if they sustained an injury that required more than 7 days of hospital stay, were unconscious on admission to emergency services, had medical or surgical conditions that interfered with their ability to participate or provide informed consent, or were not fluent enough in Hebrew, Arabic, or English to answer questions and/or interact during clinical assessments.

Hadassah University Hospital's institutional review board approved and monitored our study. Participants provided oral consent for telephone interviews and written informed consent for clinical assessments, randomization, and treatment.

INSTRUMENTS

Telephone-Based Assessments

The PTSD Symptom Scale–Interviewer Version (PSS-I)[19] and the ASD Scale (ASDS)[20] are structured diagnostic interviews for PTSD and ASD, respectively. The instruments' items replicate the 2 disorders' *DSM-IV* symptom criteria. We used the PSS-I and the ASDS to establish a baseline for subsequent follow-up of the entire cohort, regardless of the participant's clinical assessment or treatment. To enable the administration of these interviews by telephone, these items were dichotomized to provide a present/absent statement about each symptom. Tentative diagnoses were made when a participant endorsed qualifying *DSM-IV* diagnostic criteria. Symptom severity scores were obtained by summing up all items.

The telephone interviewers were graduate medical and psychology students. They were trained to be proficient at administering the study's instruments (a 1-day workshop followed by observing 5 interviews administered by experienced interviewers and then conducting 5 supervised interviews), at using good clinical practice, and at conducting 10 supervised interviews.

All Clinical Assessments

The Clinicians-Administered PTSD Scale (CAPS)[21] was used to confer a diagnosis of PTSD and a continuous measure of PTSD symptoms. As per previous recommendations,[22] a symptom criterion was rated as "present" when its frequency score was 1 or greater and its intensity score was 2 or greater. A diagnosis of PTSD required *DSM-IV* diagnostic criteria A through F, save the 1-month duration (criterion E) in the first clinical interview. It also required a CAPS total score of at least 40.[22]

The Structured Clinical Interview for *DSM-IV*[23] was used to evaluate current and lifetime *DSM-IV* Axis I disorders. The PTSD Symptom Scale–Self-Report (PSS-SR)[24] was used to evaluate participant-reported PTSD symptoms; participants graded their symptoms using a 3-point severity scale for each symptom.

The clinical assessments were made by clinical psychology interns. They were trained to be proficient at administering the study's instruments, at using good clinical practice, and at conducting 10 supervised interviews. They remained blind to treatment attendance and adherence. The treating clinicians administered the PSS-SR biweekly, before starting the interventions.

PROCEDURE

Outreach, Screening, and Inclusion

Computerized records of all trauma admissions to emergency services were manually screened, within 24 hours of admission, for inclusion and exclusion criteria. Eligible survivors (n=5286) were called by telephone, and 5053 (95.6%) were reached within 21 days of admission to emergency services (mean [SD], 9.61 [3.91] days).

Of the 5053 eligible survivors reached, 310 (6.1%) declined to be interviewed. The participants who declined were older ($t=3.09$, $P<.05$) than those who agreed (n=4743). The 2 groups had a similar sex distribution and experienced similar traumatic events.

Of the 4743 participants who agreed to be interviewed, 519 (10.9%) met the study's exclusion criteria. Of the remaining 4224 participants, 2228 (52.7%) did not meet *DSM-IV* PTSD criterion A (a traumatic event), mainly because most of the participants (n=2014 [90.4%]) did not report intense fear, help-

lessness, or horror (PTSD criterion A2). The prevalence of reported *DSM-IV* traumatic events was higher in women than in men (54.2% vs 42.5%; $\chi^2_1=56.1$, $P<.005$) and was higher in survivors of terrorist attacks (93.8%) and survivors of motor vehicle accidents (52.1%) than in survivors of work (20.4%) and other incidents (14.2%) ($\chi^2_3=465.2$, $P<.005$). Survivors without a qualifying traumatic event were thanked, and their interviews were stopped.

Survivors with a qualifying traumatic event (n=1998) continued to take the full structured interview. Telephone interviewees who met *DSM-IV* ASD diagnostic criteria or who had ASD without either the dissociation criterion or the avoidance criterion were invited to undergo a clinical assessment. Participants without dissociation symptoms were included because PTSD most often develops without initial ASD,[25-27] mainly for lack of dissociation symptoms.[27] Avoidance often develops at a distance from trauma,[28] and its use to restrict treatment access would have improperly excluded survivors at risk.

In order not to exclude survivors who might have failed to communicate the extent of their distress by telephone, participants who wished to see a clinician, and those for whom the interviewer felt that further assessment was needed, were also invited to undergo clinical assessments.

Ultimately, 1502 participants were invited to undergo clinical assessments, but only 756 (50.3%) did. Of the 746 participants who did not receive a clinical assessment, 306 (41.0%) declined during their telephone interviews, 194 (26.0%) did not show up despite 3 reminders, 97 (13.0%) felt better, 89 (11.9%) could not attend for technical reasons, 37 (5.0%) had physical problems related to their injury, and 23 (3.1%) started treatment elsewhere.

Participants who underwent the clinical assessments had higher levels of PTSD symptoms than those who did not (mean [SD] total PSS-I score, 10.98 [3.06] vs 10.19 [3.11]; $t=4.98$, $P<.001$). The groups had a similar sex distribution and experienced similar traumatic events.

Initial Clinical Assessment

The first clinical assessment (CA-1) of 756 survivors took place a mean (SD) 19.8 (5.2) days after the traumatic event. These CA-1 participants were invited to receive treatment if they met *DSM-IV* PTSD diagnostic criteria save the 1-month duration criterion.

The CA-1 participants were not invited if they had current or past psychosis or bipolar disorder, a current substance abuse problem, other conditions requiring urgent attention (eg, suicidal ideations or acute grief), or chronic PTSD or if they started treatment elsewhere.

To ensure a comprehensive coverage of survivors at risk, clinically distressed participants who met 2 of 3 PTSD symptom criteria (B, C, and D) were also invited to receive treatment. We refer to these participants as having had "partial PTSD." Their data were analyzed separately. However, secondary analyses evaluated the potential bias generated by excluding them.

Participants with full PTSD and those with partial PTSD were similar with respect to age (mean [SD], 38.59 [11.84] vs 37.94 [12.03] years), sex (55.8% vs 53.7% males; $\chi^2<1$), and trauma type (83.1% vs 81.5% road traffic accidents, 17.7% vs 11.1% terrorist attacks, and 5.4% vs 7.4% other incidents; $\chi^2=1.00$, $P=.82$). The CA-1 participants who met the treatment inclusion criteria (n=397) received an explanation about the study and were invited for treatment. Of these, 296 (74.6%) accepted the invitation, including 242 with full PTSD and 54 with partial PTSD, and 101 (25.4%) declined (**Figure 1**).

Randomization

The equipoise-stratified randomization is a method for randomly allocating participants to interventions in treatment studies that include more than 2 arms.[29,30] It allows potential participants to decline treatment options that they do not desire and to be randomly assigned to the remaining arms. By making that choice, each participant assigns himself or herself to a "stratum," which consists of all the options that he or she finds equally acceptable. Nonstratified comparisons across several groups are reported in **Table 1**.[30] Group comparisons within strata are reported in **Table 2** and in the abstract.

The equipoise-stratified randomization prevents a rigid exclusion of participants and thereby allows the greatest number of potential participants to contribute data to as many comparisons as possible.[29] Participants' choices additionally reflect the relative desirability of treatment options.

In our study, participants who agreed to start treatment (n=296) were informed about the 4 treatment options (PE, CT, treatment with SSRI vs placebo, and WL and subsequent delayed PE), could decline up to 2 treatment options (including the WL for delayed PE), and were randomly assigned to the remaining treatment options. Of 242 consenting participants with full PTSD symptoms, 103 (42.6%) declined the SSRI vs placebo treatment option, 12 (5.0%) declined to be on the WL (including 6 who also declined medication), 8 (3.3%) declined CT (including 5 who declined medication), and 3 (1.2%) declined PE (including 2 who declined medication).

Participants with full PTSD symptoms who declined any treatment modality (n=113) did not differ from those who accepted all treatment modalities (n=129) in CA-1 CAPS total scores (mean [SD] score, 72.61 [16.35] vs 72.18 [16.93]; $F=0.02$). To protect against the expected attrition due to natural recovery and leave enough participants with PTSD at 5 months for delayed PE, we used a randomization ratio of 1:1:1:2, favoring the WL group.

Early Interventions

In administering PE, we followed the protocol in Hembree et al.[31] Prolonged exposure includes psychoeducation, training in breathing control, prolonged imaginal exposure to traumatic memories, and in vivo exposure to avoided situations. Clinical psychologists with previous experience in the treatment of PTSD administered 12 weekly 1.5-hour sessions. Delayed PE followed the same protocol.

In administering CT, we followed the protocol in Marks et al.[32] Cognitive therapy includes identifying and challenging negative automatic thoughts and modifying underlying cognitive schemas. Clinical psychologists with previous experience in the treatment of PTSD administered 12 weekly 1.5-hour sessions.

Certified supervisors with extensive teaching experience in CT and PE (Drs Adessky and Freedman) provided training and weekly supervision for therapists. The PE therapists had extensive training in PE. One was a certified PE supervisor. The cognitive therapists had extensive training in CT. One was a CT supervisor.

SSRI vs Placebo

To separate the pharmacological effect of an SSRI from that of receiving medication and psychiatric care, this blinded group includes both the active agent and placebo. Concealed tablets of either 10 mg of escitalopram or placebo were prepared and coded by Lundbeck Pharmaceuticals (Copenhagen, Denmark) and were supplied to clinicians by a research associate.

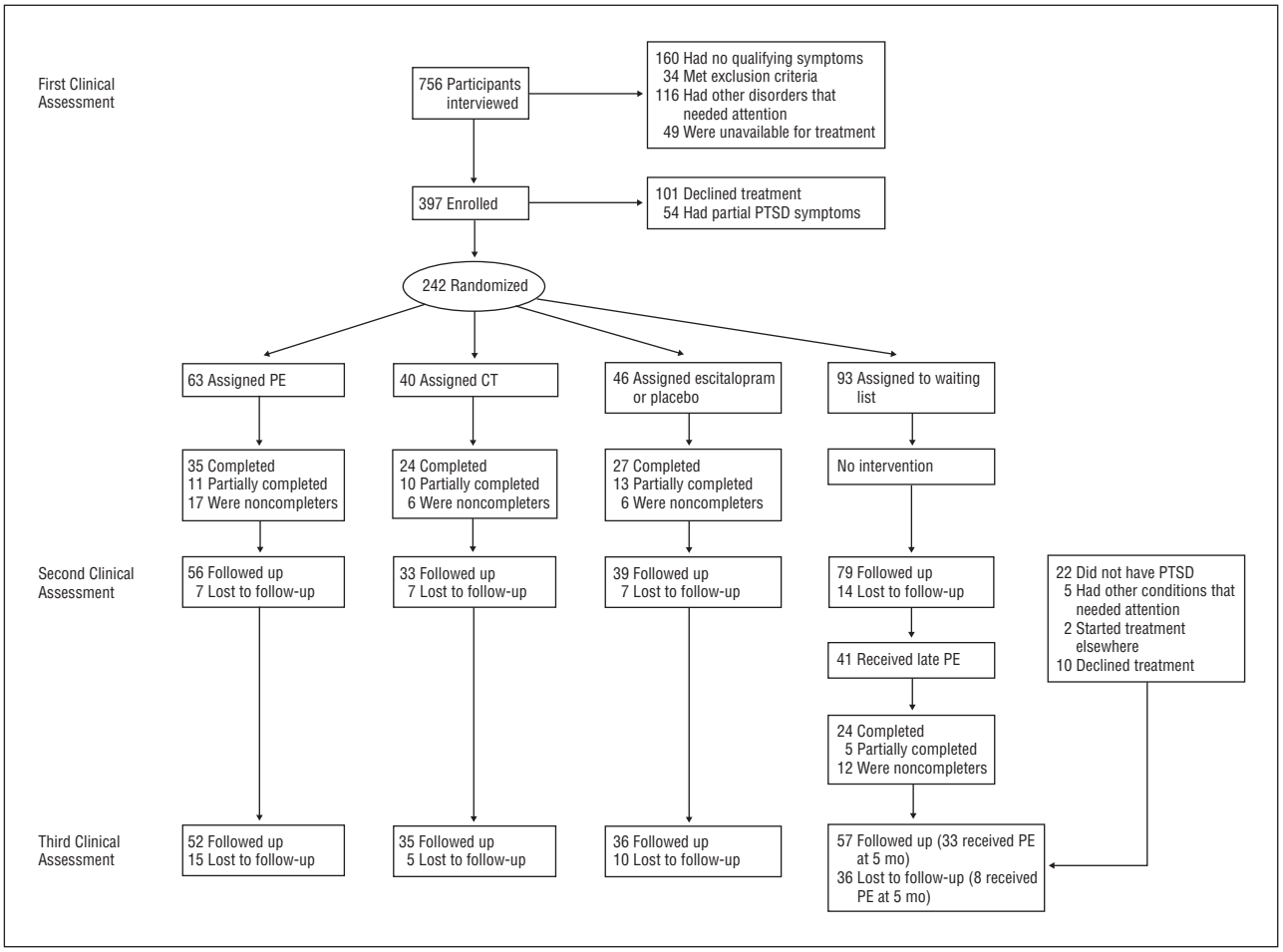

Figure 1. Patient flowchart of survivors of trauma for study comparing early and delayed exposure-based, cognitive, and pharmacological interventions for preventing posttraumatic stress disorder (PTSD). The first clinical assessment of 756 survivors took place a mean (SD) 19.8 (5.2) days after the traumatic event. The second clinical assessment (at 5 months) took place a mean (SD) 144.1 (35.2) days after the traumatic event and after the completion of early interventions. The third clinical assessment (at 9 months) took place a mean (SD) 279.0 (62.0) days after the traumatic event and following the completion of delayed prolonged exposure (PE). CT indicates cognitive therapy. For specifics of the equipoise stratified randomization, please refer to the text.

An initial dose of 1 tablet daily was increased to 2 tablets after 2 weeks of treatment. Trained psychiatrists provided 4 weekly sessions (weeks 1-4) followed by 4 biweekly sessions (weeks 6-12). The concealment was broken and added to the study's data file at the end of the study. At the end of our study, 8 participants with PTSD who received placebo were invited to receive PE, which was accepted by 5 of them.

Waiting List

A telephone interviewer briefly contacted participants on the WL every 2 weeks to inquire about emerging needs or possible emergencies. These calls did not contain elements of PE or CT.

Five Months' Clinical Assessment

The second clinical assessment (CA-2) took place a mean (SD) 144.1 (35.2) days after the traumatic event and after the completion of early interventions. During the CA-2, all CA-1 participants who could be contacted were evaluated. Of 756 CA-1 participants, 604 (79.9%) were reached, including 254 of 296 participants (85.8%) who started treatment, 79 of 101 participants (78.2%) who declined treatment, and 271 of 359 participants (75.5%) who had not been referred to treatment. Among treatment participants, 207 of 242 (85.5%) had full initial (CA-1) PTSD symptoms, and 47 of 54 (87.0%) had partial PTSD. The CA-2 guided the referral of 79 WL participants to delayed PE (Figure 1). The delayed PE followed the early PE's protocol.

Nine Months' Clinical Assessment

The third clinical assessment (CA-3) took place a mean (SD) 279.0 (62.0) days after the traumatic event and following the completion of delayed PE. During the CA-3, all retrievable treatment referrals were evaluated, as were 10% (n=30) of randomly selected participants who had not been referred to treatment. Two hundred fifteen treatment participants were reached, including 180 of 242 participants with full PTSD (74.4%) at CA-1 and 35 of 54 participants with partial PTSD (64.8%).

PROTOCOL ADHERENCE

Only the treatment sessions of consenting participants (93%) who underwent PE or CT were recorded. A randomly selected 10% of the sessions (70 PE sessions and 33 CT sessions; 12 participants) were sent to 2 independent cognitive behavior therapy experts who used an integrity checklist (available upon request) to quantify (1) the competency of the therapist (on a scale of 1 to 7, with 1 being unacceptable and 7 being very good);

Table 1. Nonstratified Group Comparisons of Survivors of Trauma at Hadassah University Hospital, Jerusalem, Israel

Demographic and Clinical Characteristics	PE Group (n = 63)	CT Group (n = 40)	SSRI Subgroup (n = 23)	Placebo Subgroup (n = 23)	WL Group (n = 93)	Test[a]	*P* Value	Post Hoc LSD Analysis
Sex, No. (%)								
Male	35 (55.6)	10 (25.0)	10 (43.5)	13 (56.5)	39 (41.9)			
Female	28 (44.4)	30 (75)	13 (56.5)	10 (43.5)	45 (58.1)	$\chi^2_4 = 10.886$	.03	
Age, mean (SD), y	40.1 (12.02)	39.54 (12.22)	39.83 (11.74)	36.26 (12.39)	37.28 (11.91)	$F_{4,237} = 1.023$	.40	
Trauma type, No. (%)								
Motor vehicle accident	45 (71.4)	34 (85.0)	21 (91.3)	20 (87.0)	81 (87.1)			
Terrorist attack	16 (25.4)	5 (12.5)	0 (0)	2 (7.7)	3 (3.2)			
Other	2 (3.2)	1 (2.5)	2 (13.3)	1 (4.3)	9 (9.7)			
Time to first treatment session,[b] mean (SD) d	30.37 (5.7)	29.78 (6.22)	29.35 (4.91)	28.91 (5.71)	140.36 (16.95)	$F_{3,145} = 0.43$	.73	
First clinical assessment	**(n = 63)**	**(n = 40)**	**(n = 23)**	**(n = 23)**	**(n = 93)**			
CAPS, mean (SD)								
Total score	73.59 (21.34)	71.78 (15.18)	79.83 (15.60)	74.91 (14.69)	71.66 (15.22)	$F_{4,237} = 1.199$	.31	
Reexperiencing	21.21 (8.27)	19.95 (6.54)	21.22 (6.76)	19.78 (7.75)	19.59 (8.88)	$F_{4,237} = 0.603$	.66	
Avoidance	29.90 (9.02)	30.23 (6.68)	33.87 (6.47)	31.17 (6.65)	29.30 (7.19)	$F_{4,237} = 1.817$	.13	
Hyperarousal	22.48 (7.34)	21.60 (6.08)	24.74 (5.61)	23.96 (6.03)	22.76 (5.69)	$F_{4,237} = 1.164$	.33	
PSS-SR score, mean (SD)	30.88 (8.48)	30.58 (8.34)	36.55 (7.91)	34.57 (6.55)	31.13 (8.31)	$F_{4,227} = 3.009$	.02	SSRI > WL, PE, CT
PTSD, No. (%)	63 (100)	40 (100)	23 (100)	23 (100)	93 (100)			
Concurrent major depression, No. (%)	34 (54.0)	25 (62.5)	18 (78.3)	12 (52.2)	54 (58.1)	$\chi^2_4 = 4.87$	.33	
Second clinical assessment	**(n = 56)**	**(n = 33)**	**(n = 21)**	**(n = 18)**	**(n = 79)**			
CAPS score, mean (SD)								
Total score	28.59 (25.02)	29.48 (23.03)	48.71 (29.63)	47.11 (20.13)	50.56 (27.51)	$F_{4,202} = 8.285$	.001	SSRI, placebo, WL > PE, CT
Reexperiencing	7.32 (7.44)	6.85 (5.71)	11.19 (8.55)	11.56 (6.30)	11.75 (8.26)	$F_{4,202} = 4.483$	.002	SSRI, placebo, WL > PE, CT
Avoidance	11.36 (11.27)	12.12 (10.39)	21.62 (12.92)	18.56 (8.90)	22.29 (12.75)	$F_{4,202} = 9.538$	.001	SSRI, placebo, WL > PE, CT
Hyperarousal	9.91 (8.65)	10.52 (9.26)	15.90 (9.78)	17.00 (8.57)	16.52 (9.11)	$F_{4,202} = 6.323$	.001	SSRI, placebo, WL > PE, CT
PSS-SR score, mean (SD)	11.02 (11.19)	11.56 (10.47)	22.52 (14.20)	22.22 (11.86)	22.14 (13.09)	$F_{4,197} = 10.002$	.001	SSRI, placebo, WL > PE, CT
PTSD, No. (%)	12 (21.4)	6 (18.2)	13 (61.9)	10 (55.6)	46 (58.2)	$\chi^2_4 = 30.721$	.001	
Third clinical assessment	**(n = 52)**	**(n = 35)**	**(n = 19)**	**(n = 17)**	**(n = 57)**		***P* Value**[c]	**Post Hoc Analysis**
CAPS, mean (SD)								
Total score	27.52 (26.91)	27.89 (25.64)	47.16 (26.71)	45.71 (26.14)	31.11 (25.07)	$F_{4,175} = 3.401$	.01	SSRI, placebo > PE, CT, WL
Reexperiencing	6.67 (7.66)	5.57 (5.63)	9.68 (7.91)	9.65 (8.49)	7.39 (7.34)	$F_{4,175} = 1.528$	.20	
Avoidance	11.21 (11.93)	12.97 (12.66)	21.58 (11.42)	18.18 (11.28)	13.51 (10.80)	$F_{4,175} = 3.415$	.01	SSRI, placebo > PE, CT, WL
Hyperarousal	9.63 (9.46)	9.34 (9.60)	15.89 (9.72)	17.88 (9.88)	10.21 (9.46)	$F_{4,175} = 4.063$	.004	SSRI, placebo > PE, CT, WL
PSS-SR score, mean (SD)	10.35 (11.85)	9.56 (10.60)	21.63 (2.96)	19.35 (12.53)	13.11 (12.33)	$F_{4,170} = 4.996$	.001	SSRI, placebo > PE, CT, WL
PTSD, No. (%)	11 (21.2)	8 (22.9)	8 (42.1)	8 (47.1)	13 (22.8)	$\chi^2_1 = 7.28$	.01[d]	

Abbreviations: CAPS, Clinician-Administered PTSD Scale; CT, cognitive therapy; LSD, least significant difference; PE, prolonged exposure; PSS-SR, PTSD Symptom Scale–Self-Report; PTSD, posttraumatic stress disorder; SSRI, selective serotonin reuptake inhibitor (escitalopram); WL, waiting list.

[a] One-way analysis of variance was used for continuous variables, and the χ^2 test was used for frequencies.

[b] The WL group is not included in this analysis.

[c] Statistically significant.

[d] Computed for a comparison of 36 participants from the SSRI and placebo subgroups and 144 participants from the PE, CT, and WL groups.

(2) adherence to a session's core treatment components, as per the treatment manuals; and (3) infractions of protocol (for PE: using anxiety management, challenging cognitions, exploring relationships, recommending medication, and solving nontrauma issues, other variations, or irregularities; for CT: using anxiety management, using exposure, exploring relationships, recommending medication, solving nontrauma problems, other variations, or irregularities).

The mean (SD) PE competency rating was 6.22 (1.03). Eight instances of nonadherence (1.6% of 490 PE adherence items) occurred in 6 of the 70 PE sessions (8.6%). There were no infractions to the protocol. The mean (SD) CT competency rat-

Table 2. Stratified Pairwise Group Comparison of Survivors of Trauma at Hadassah University Hospital, Jerusalem, Israel

Group Comparison	CA-1 CAPS Total Score, Mean (SD) [95% CI]	End-Point Assessment (CA-2 or CA-3)			Repeated-Measures ANOVA						Effect Size (95% CI)
					Treat		Time		Interaction		
		CAPS Total Score, Mean (SD) [95% CI]	Prevalence of PTSD, %	OR (85% CI)	*F* Value	*P* Value	*F* Value	*P* Value	*F* Value	*P* Value	
PE vs WL				CA-2							
PE (n = 51)	72.18 (21.59) [67.32-77.04]	27.55 (25.87) [20.29-34.81]	21.60	0.21 (0.09-0.46)	$F_{1,126}$ = 9.2	.003	$F_{1,126}$ = 231.4	.001	$F_{1,126}$ = 27.14	.001	0.93 (0.45-1.19)
WL (n = 77)	71.04 (14.26) [67.08-74.99]	49.18 (26.40) [43.28-55.09]	57.10								
CT vs WL				CA-2							
CT (n = 30)	69.23 (13.50) [63.88-74.58]	29.43 (24.06) [19.63-39.27]	20.00	0.18 (0.06-0.48)	$F_{1,103}$ = 9.67	.002	$F_{1,103}$ = 134.3	.001	$F_{1,103}$ = 11.05	.001	0.80 (0.46-1.13)
WL (n = 75)	72.44 (15.25) [69.05-75.82]	50.39 (28.17) [44.19-56.57]	58.70								
SSRI vs placebo				CA-2							
SSRI (n = 18)	80.33 (15.70) [73.45-87.21]	48.71 (29.63) [37.35-60.01]	55.60	0.77 (0.21-2.77)	$F_{1,37}$ = 0.337	.57	$F_{1,37}$ = 58.72	.001	$F_{1,37}$ = 0.18	.67	0.07 (–0.56 to 0.69)
Placebo (n = 21)	75.44 (15.39) [68.02-82.87]	47.11 (20.13) [34.84-59.39]	61.90								
PE vs CT				CA-2							
PE (n = 54)	73.89 (21.11) [68.84-78.93]	27.43 (24.67) [20.91-33.94]	21.60	0.87 (0.29-2.62)	$F_{1,85}$ = 0.048	.83	$F_{1,85}$ = 276.24	.001	$F_{1,85}$ = 1.25	.27	0.01 (–0.44 to 0.43)
CT (n = 33)	70.0 (13.60) [63.64-76.45]	29.48 (23.03) [21.15-37.81]	20.00								
PE vs delayed PE				CA-3							
PE (n = 48)	73.96 (21.73) [68.85-79.06]	26.88 (27.53) [19.59-34.16]	20.80	1.04 (0.40-2.67)	$F_{1,102}$ = 0	.99	$F_{1,102}$ = 389.43	.001	$F_{1,102}$ = 1.8	.18	0.12 (–0.52 to 0.28)
WL (n = 56)	70.96 (13.65) [66.24-75.69]	29.88 (23.50) [23.13-36.61]	21.40								

Abbreviations: ANOVA, analysis of variance; CAPS, Clinician-Administered PTSD Scale; CA-1, first clinical assessment; CA-2, second clinical assessment; CA-3, third clinical assessment; CT, cognitive therapy; PE, prolonged exposure; PTSD, posttraumatic stress disorder; SSRI, selective serotonin reuptake inhibitor (escitalopram); WL, waiting list.

ing was 5.86 (0.77). Six instances of nonadherence (2.6% of 231 CT adherence items) were recorded in 6 of the 33 CT sessions (18.2%). There was 1 infraction to the protocol.

TREATMENT COMPLETION

We refer to participants who attended all treatment sessions as treatment completers, we refer to those who attended at least 3 sessions and who complied with homework or medication intake as partial completers, and we refer to those who attended less than 3 sessions as noncompleters.

STATISTICAL ANALYSES

Our study's main outcome measure is the proportion of survivors with CAPS-determined PTSD 5 months (CA-2) and 9 months (CA-3) after the traumatic event. Because those who conducted the CA-2 and CA-3 were blinded to treatment attendance and adherence, the resulting comparisons include completers, partial completers, and noncompleters and thereby represent the total yield of participants randomly assigned to an intervention. Continuous measures of PTSD symptoms (CAPS and PSS-SR total scores) were used to buttress group comparisons, evaluate within-subject effects, and calculate effect sizes.

To account for missing observations and the groups' heterogeneities, we used a linear mixed model with covariance for significant initial group differences and for the time lag between the traumatic event of each participant and subsequent assessments. We derived the Cohen *d* effect size by comparing the mean difference between treatment conditions and dividing this by the pooled standard deviation. We used Hedges *g* effect sizes to correct for variations due to small sample sizes.

RESULTS

GROUP ALLOCATION, ADHERENCE, AND RETENTION

Following randomization, 63 participants started PE, 40 started CT, 93 were allocated to the WL, and 46 were in the SSRI and placebo subgroups (23 in each subgroup, as revealed after our study was completed). The study groups were similar with respect to age, traumatic events, and time to first treatment session (Table 1). There were more female participants in the CT group than in the other groups ($P < .03$), and there were higher PSS-SR scores in the SSRI group than in the other groups ($P < .02$).

The study groups had similar adherence rates (PE: 35 treatment completers [55.6%], 11 partial completers [17.5%], and 17 noncompleters [27.0%]; CT: 24 completers [60.0%], 10 partial completers [25.0%], and 6 noncompleters [15.0%]; SSRI vs placebo: 27 completers [58.7%] comprising 17 of 23 participants who received SSRI [79.9%] and 10 of 23 participants who received placebo [43.5%], 13 partial completers [28.3%] comprising 4 participants who received SSRI [17.4%] and 9 who received placebo [39.1%], and 6 noncompleters [13.0%]

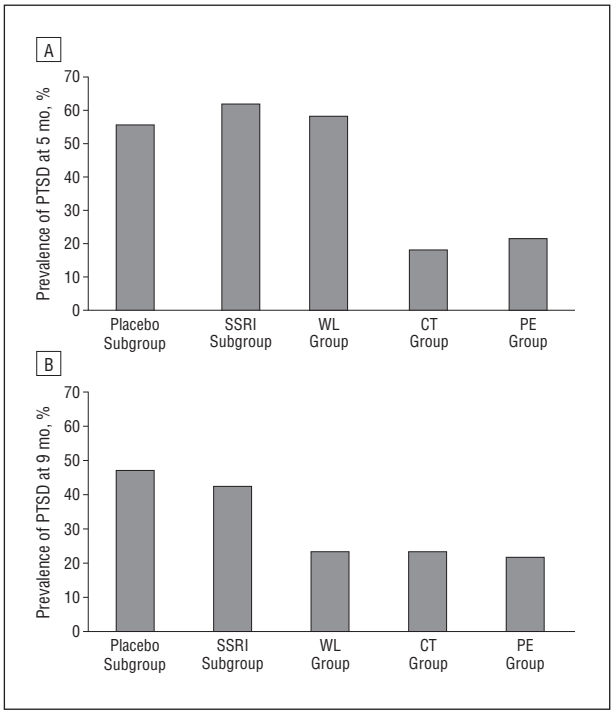

Figure 2. Prevalence of posttraumatic stress disorder (PTSD) at 5 and 9 months, by study group. CT indicates cognitive therapy; PE, prolonged exposure; SSRI, selective serotonin reuptake inhibitor; WL, waiting list (participants received delayed PE).

comprising 2 participants who received SSRI [8.7%] SSRI and 4 who received placebo [17.4%]; χ^2_6=6.45, P=.15).

The study groups had similar retention rates between CA-1 and CA-2: 56 of 63 participants who received PE (88.9%), comprising all 35 completers (100%), 10 of 11 partial completers (90.9%), and 11 of 17 noncompleters (64.7%); 33 of 40 participants who received CT (82.5%), comprising 23 of 24 completers (95.8%), 5 of 10 partial completers (50.0%), and 5 of 6 noncompleters (83.3%); 39 of 46 participants who received either SSRI or placebo (84.8%), comprising 26 of 27 completers (96.3%; all 17 who received SSRI [100.0%] and 9 of 10 who received placebo [90.0%]), 8 of 13 partial completers (61.5%; 3 of 4 who received SSRI [75.0%] and 5 of 9 who received placebo [55.5%]), and 5 of 6 noncompleters (83.3%); 1 of 2 who received SSRI [50.0%] and all 4 who received placebo [100.0%]); and 79 WL participants (84.9%).

Fifty-seven WL participants had PTSD at their CA-2 and were eligible for delayed PE. Of these 57 WL participants, 5 (8.8%) had other conditions requiring clinical attention, 10 (17.5%) declined delayed PE, 1 (1.8%) started treatment elsewhere, and 41 (71.9%) started delayed PE a mean (SD) 151.8 (42.4) days after the traumatic event.

Fewer WL participants (57 of 93 [61.3%]) than participants who received PE (52 of 63 [82.5%]), CT (35 of 40 [87.5%]), and SSRI or placebo (36 of 46 [78.3%]) were reached for a CA-3 (χ^2=14.54, P<.003). However, the lower retention rate mainly involves participants who did not attend delayed PE (25 of 52 [48.1%]), whereas the retention rate of those who attended (33 of 41 [80.5%]) resembles that of other treatment groups.

FIVE MONTHS' OUTCOME FOR ALL STUDY GROUPS (NONSTRATIFIED)

Prevalence of PTSD

At 5 months (CA-2), the prevalences of PTSD in the PE and CT groups (21.4% and 18.2%, respectively) were significantly lower than the prevalences of PTSD in the WL, SSRI, and placebo groups (58.2%, 61.9%, and 55.6%, respectively; χ^2_4=30.72, P<.001). The SSRI, placebo, and WL groups had similar prevalences of PTSD (χ^2_2=0.167, P=.92; **Figure 2**A).

PTSD Symptoms

One-way analysis of variance (ANOVA) showed significant group differences in both the mean CAPS and mean PSS-SR scores at 5 months, with post hoc comparisons showing fewer PTSD symptoms in the PE and CT groups compared with the WL, SSRI, and placebo groups (Table 1).

Effect of Treatment Completion

Two-way ANOVA using treatment completion status (full completion, partial completion, and noncompletion), the study groups (ie, PE, CT, SSRI, and placebo) as grouping factors, and CA-2 CAPS total scores as the dependent variable showed a nonsignificant main effect of completion status ($F_{11,2}$=0.12, P=.98), a significant main effect of groups ($F_{11,3}$=2.97, P<.05), and a nonsignificant completion × group interaction.

Longitudinal Comparison

Linear mixed model analysis for patients with initial PTSD (n=242), using CAPS total scores as the dependent variable, the study groups (PE, CT, WL, SSRI, and placebo) and successive measurements (CA-1 and CA-2) as fixed factors, and age, sex, and time lag between the traumatic event and subsequent assessments as covariates, showed a significant group effect ($F_{4,338}$=6.56, P<.001), a significant time effect ($F_{1,338}$=187.0, P<.001), and a significant group × time interaction ($F_{4,339}$=6.167, P<.001). Post hoc comparisons showed statistically significant differences between the PE and WL groups (P<.001) and between the CT and WL groups (P<.001), but not between the placebo and WL groups (P=.41), the SSRI and WL groups (P=.98), the SSRI and placebo groups (P=.53), or the PE and CT groups (P=.89). Similar results were obtained when participants with partial PTSD were included (group × time interaction: $F_{4,462}$=4.50, P<.001).

PROGRESSION DURING TREATMENT

Figure 3 illustrates the successive PSS-SR scores during treatment. It shows that there was a similar progression in the CT and PE groups. Repeated-measures ANOVA showed significant main effects of time (P<.001) and group (P<.001) and a significant group × time interaction (P<.005).

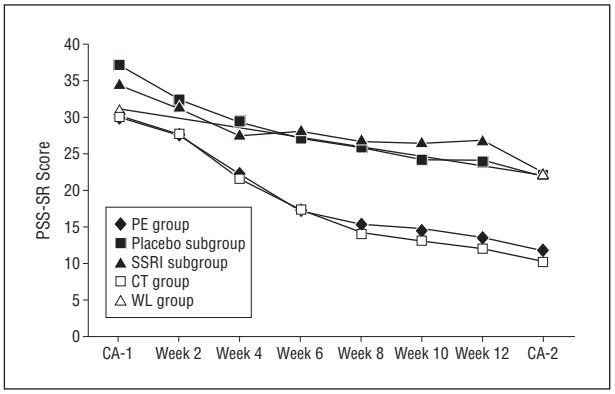

Figure 3. Progression of symptoms of posttraumatic stress disorder (PTSD) during early treatment. Because the waiting list (WL) group of participants did not have therapy sessions (they eventually received delayed prolonged exposure [PE]), only the first and second clinical assessment (CA-1 and CA-2, respectively) PTSD Symptom Scale–Self-Report (PSS-SR) scores are recorded for that group. CT indicates cognitive therapy; and SSRI, selective serotonin reuptake inhibitor.

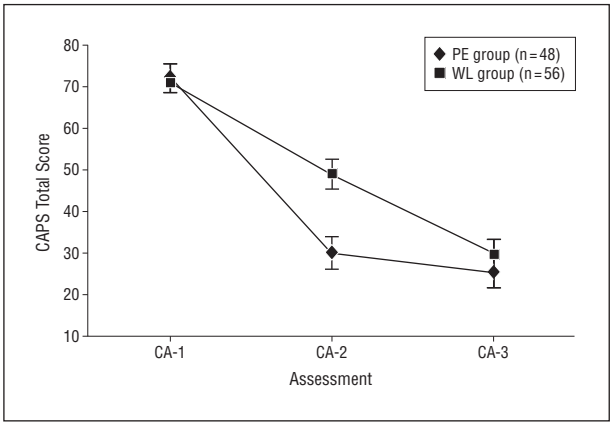

Figure 4. Symptoms of posttraumatic stress disorder (PTSD) determined by use of the Clinicians-Administered PTSD Scale (CAPS) total scores. A comparison is shown between participants who received prolonged exposure (PE) and participants on the waiting list (WL), including those who received delayed PE and those who recovered spontaneously. CA-1, indicates the first clinical assessment; CA-2, second clinical assessment; CA-3, third clinical assessment.

Last observation carried forward analyses for within-treatment PSS-SR scores showed significant differences between the study groups ($F_{3,126}$=5.47, $P<.001$), with post hoc least significant difference analysis showing a nonsignificant difference between the PE and CT groups (mean difference, –1.73 [95% CI, –3.72 to 1.19]) and between the SSRI and placebo subgroups (mean difference, 2.29 [95% CI, –0.57 to 10.27]) and a significant difference between the PE and SSRI groups (mean difference, –7.86 [95% CI, –14.11 to –1.62]), between the PE and placebo groups (mean difference, –10.16 [95% CI, –17.13 to –3.19]), between the CT and SSRI groups (mean difference, –9.60 [95% CI, –16.30 to –2.90]), and between the CT and placebo groups (mean difference, –11.89 [95% CI, –19.27 to –4.52]).

NINE MONTHS' OUTCOME FOR ALL STUDY GROUPS (NONSTRATIFIED)

Prevalence of PTSD

At 9 months (CA-3), the prevalences of PTSD in the PE, CT, and WL groups were (21.2%, 22.8%, and 22.9%, respectively). The prevalences of PTSD in the SSRI and placebo subgroups (42.1% and 47.1%, respectively) remained higher than the prevalences of PTSD in the PE, CT, and WL groups (Figure 2B).

PTSD Symptoms

One-way ANOVA showed significant group differences in both the mean CAPS and mean PSS-SR scores at 9 months, with post hoc group comparisons showing fewer PTSD symptoms in the PE, CT, and WL groups compared with the SSRI and placebo subgroups (Table 1).

Longitudinal Comparison

Linear mixed model analysis using CAPS total scores as the dependent variable, the study groups (PE, CT, WL, SSRI, and placebo) and successive measurements (CA-1, CA-2, and CA-3) as fixed factor, and age, sex, and time lag between the traumatic event and subsequent assessments as covariates showed a significant group effect ($F_{8,488}$=8.42, $P<.001$), a significant time effect ($F_{2,363}$=166.61, $P<.001$), and a significant group × time interaction ($F_{8,361}$=3.628, $P<.001$). Post hoc comparisons showed statistically significant differences between the PE and WL groups ($P<.001$), between the CT and WL groups ($P<.003$), between the SSRI and WL groups ($P<.05$), and between the placebo and WL groups ($P<.003$), but not between the SSRI and placebo subgroups ($P=.46$).

Omitting CA-2 from the model yielded nonsignificant pairwise differences between the PE and WL groups (mean difference, 0.83 [95% CI, –6.44 to 4.79]) and between the CT and WL groups (mean difference, 1.55 [95% CI, –4.79 to 7.89]), suggesting that the 3-point difference reflects different recovery trajectories between the PE and WL groups (**Figure 4**). Omitting CA-2 did not change the significant group difference between the SSRI and WL groups (mean difference, 8.93 [95% CI, 0.86-17.0]) or between the placebo and WL groups (mean difference, 12.11 [95% CI, 4.29-19.9]).

COMPARISONS WITHIN STRATA

Table 2 presents pairwise group comparisons within strata, including the odds ratios (ORs) for dichotomous PTSD outcomes and the effect size estimates of CAPS total scores. The groups are composed of completers, partial completers, and noncompleters.

At 5 months (CA-2), fewer participants who received PE had PTSD compared with participants on the WL (OR, 0.21 [95% CI, 0.09-0.46]), and fewer participants who received CT had PTSD compared with participants on the WL (OR, 0.18 [95% CI, 0.06-0.48]). Participants who received PE did not differ from participants who received CT with regard to PTSD outcome (OR, 0.87 [95% CI, 0.29-2.62]), and participants who received SSRI did not differ from participants who received placebo with regard to PTSD outcome (OR, 0.77 [95% CI, 0.21-

2.77]). At 9 months (CA-3), with regard to PTSD outcome, participants who received PE did not differ from participants on the WL (OR, 1.04 [95% CI, 0.40-2.67]) or from participants who received CT (OR, 0.92 [95% CI, 0.33-2.45]), and participants who received SSRI did not differ from participants who received placebo (OR, 0.82 [95% CI, 0.22-3.06]).

Repeated-measures ANOVA using CA-1 and CA-2 CAPS total scores as within-subjects variables showed significant group × time interactions for the comparisons between the PE group and the WL group and between the CT group and the WL group, and nonsignificant group × time interactions for the comparison between the SSRI subgroup and the placebo subgroup and between the PE group and the CT group. The observed group × time interactions remained unchanged after controlling for age, sex, and initial PSS-SR scores.

Repeated-measures ANOVA using CA-1, CA-2, and CA-3 CAPS total scores for the PE-to-WL contrast showed a nonsignificant linear group × time interaction ($F_{1,99}$=1.839, P=.18) and a significant quadratic interaction ($F_{1,99}$=21.05, P<.001). The latter reflects different recovery trajectories, with the WL group improving only upon receiving delayed PE (Figure 4).

PARTICIPANTS WITH PARTIAL PTSD

Of 54 survivors with partial PTSD, 9 (16.7%) were randomly assigned to receive PE, 12 (22.2%) received CT, 6 (11.1%) eventually received either SSRI or placebo, and 27 (50.0%) were randomly assigned to the WL. Of the 54 survivors with partial PTSD, 47 (87.0%) were assessed at the CA-2. Those assessed comprise 6 of 9 who received PE (66.7%), all 12 who received CT (100.0%), 5 of 6 who were in the SSRI/placebo group (83.3%), and 24 of 27 who were on the WL (88.9%). Of the 47 participants with partial PTSD who received a CA-2, only 5 (10.6%) had PTSD (none from the PE group, 1 from the CT group, 3 from the WL group, and 1 from the SSRI/placebo group).

To evaluate the effect of interventions, we compared participants assigned to "effective therapies" (ie, PE and CT; n=18) with those on the WL (n=24). The 2 groups had similar initial (CA-1) CAPS scores (mean [SD], 43.92 [2.66] vs 38.39 [12.29]; $F_{1,41}$=2.01, P=.17) and similar 5-month (CA-2) CAPS scores (mean [SD], 20.54 [15.3] vs 19.22 [16.30]; $F_{1,41}$=0.08). Repeated-measures ANOVA yielded a nonsignificant main effect of group ($F_{1,40}$=0.36), a significant main effect of time ($F_{1,40}$=76.26, P<.001), and a nonsignificant group × time interaction ($F_{1,40}$=0.74).

EFFECT OF DECLINING TREATMENT

Participants who declined treatment (n=82, of whom 79 were reached at CA-2) did not differ from the WL participants in CA-1 CAPS scores (mean SD, 70.10 [14.65] vs 71.66 [15.21]; $F_{1,173}$=0.47) or CA-2 CAPS scores (mean [SD], 42.59 [27.5] vs 50.56 [27.51]; $F_{1,142}$=2.96) (P=.09). Repeated-measures ANOVA comparing participants who declined treatment with participants on the WL showed a nonsignificant group effect ($F_{1,141}$=2.53, P=.12), a significant time effect ($F_{1,141}$=1424.3, P<.001), and a nonsignificant group × time interaction ($F_{1,141}$=2.16, P=.15). Compared with participants who received effective treatment (PE or CT; n=89), those who declined treatment had significantly higher CA-2 scores (mean [SD], 42.59 [27.6] vs 28.92 [24.74]; P<.001). Repeated-measures ANOVA showed a significant ($F_{1,166}$=11.60, P<.001) group × time interaction.

COMMENT

The results of our study show that there are significant and similar preventive effects of PE and CT. Delaying PE did not affect the 9-month outcome. The escitalopram subgroup did not differ from the placebo subgroup or the WL group at 5 months; however, the escitalopram subgroup fared worse than all the other groups at 9 months. Participants with partial PTSD fared similarly well with or without treatment. The use of equipoise-stratified randomization allowed us to include participants who declined 1 or 2 treatment options and to additionally explore survivors' preferences regarding treatment.

To our knowledge, this is the first comparative study of early and delayed cognitive behavioral interventions for PTSD. Our finding suggests that delaying the intervention does not increase the risk of chronic PTSD. Delaying treatment somewhat reduced the number of treatment candidates: about a third of those with initial PTSD recovered by 5 months. For those who did not experience spontaneous recovery, however, delaying treatment prolonged the duration of symptoms.[1] Thus, a delayed intervention is an acceptable option when early clinical interventions cannot be provided (eg, during wars, disasters, or continuous hostilities).

To our knowledge, this work is the first randomized controlled trial that used an SSRI to prevent PTSD. Participants who received escitalopram did not differ from those who received placebo (absolute risk reduction, 6.3% [95% CI, –24.6% to 37.3%]) or those on the WL at 5 months; however, participants who received escitalopram fared worse than other groups of participants at 9 months. This finding joins several other disappointing findings in studies on the pharmacological prevention of PTSD (eg, by propranolol hydrochloride, gabapentin, and benzodiazepines).[13-15,33,34] Cortisol[17] and, more recently, opiates[35] had some beneficial effect in severely injured survivors, but their clinical use for noninjured survivors requires extension and replications. The high refusal rate for SSRI or placebo (42.6%) in the equipoise-stratified randomization has lead to small group sizes for both SSRI and placebo. Therefore, although clearly reflecting participants' preference, the sample size of the SSRI and placebo subgroups in our study does not yield enough statistical power to refute a potential preventive effect. This finding and the limited (20-mg) daily dose of escitalopram leave ample space for replications.

Our finding of the similar effects of PE and CT differs from the finding of Bryant et al[8] of a better efficacy of PE relative to cognitive restructuring. The difference might be explained by the shorter interventions (5 sessions) in Bryant et al, by their more severe patients (full ASD), or by their addressing other traumatic events (about 70%

assault survivors). Added to previous studies, our work extends the array of cognitive behavioral interventions for acute PTSD beyond exposure-based therapies.

The lack of an added beneficial effect of cognitive behavioral interventions on survivors with partial PTSD is in line with previous observations.[11,12] This finding buttresses the need to reserve clinical interventions for PTSD to carefully diagnosed survivors.

Several studies have challenged the rationale for using individual resource-demanding clinical interventions to prevent PTSD. Norris et al[36] argued that individual therapies inappropriately exhaust the already depleted community resources following major disasters. Zatzick et al[37,38] suggested that need-focused interventions, collaboratively administered by relevant professionals and helpers, may have a larger population impact than clinical interventions. The documented barriers to mental health care[10] further reduce the efficiency of clinical services.

Our study similarly illustrates the difficulty of bringing survivors to clinical interventions. However, the negative consequences of refusing care and the consistently documented efficacy of trauma-focused cognitive behavioral interventions, which our study supports, are compelling arguments for providing these clinical interventions. Future studies should evaluate simplified and more readily acceptable cognitive behavioral techniques (and the novel technologies to dispense them).

Our study is limited by the sample of civilian survivors of single, short traumatic events. Additionally, our sample includes referrals from emergency services and thus a number of participants who had a physical injury. Furthermore, our study group sizes did not allow us to further explore the factors underlying the heterogeneity of treatment responses or the effect of treatment completion. Nonetheless, the following conclusions are warranted: (1) Distressed trauma survivors should have their symptoms carefully diagnosed before starting clinical treatment. (2) Survivors with persistent PTSD symptoms should be encouraged to engage in early, trauma-focused cognitive behavioral therapies. (3) Under service-delivery constraints, health care providers can safely delay the onset of interventions until resources become available. (4) Future studies should further evaluate the timing and efficacy of the early use of pharmacotherapy for the prevention of PTSD.

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