Original Investigation

Prolonged Exposure vs Eye Movement Desensitization and Reprocessing vs Waiting List for Posttraumatic Stress Disorder in Patients With a Psychotic Disorder
A Randomized Clinical Trial

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IMPORTANCE The efficacy of posttraumatic stress disorder (PTSD) treatments in psychosis has not been examined in a randomized clinical trial to our knowledge. Psychosis is an exclusion criterion in most PTSD trials.

OBJECTIVE To examine the efficacy and safety of prolonged exposure (PE) therapy and eye movement desensitization and reprocessing (EMDR) therapy in patients with psychotic disorders and comorbid PTSD.

DESIGN, SETTING, AND PARTICIPANTS A single-blind randomized clinical trial with 3 arms (N = 155), including PE therapy, EMDR therapy, and waiting list (WL) of 13 outpatient mental health services among patients with a lifetime psychotic disorder and current chronic PTSD. Baseline, posttreatment, and 6-month follow-up assessments were made.

INTERVENTIONS Participants were randomized to receive 8 weekly 90-minute sessions of PE (n = 53), EMDR (n = 55), or WL (n = 47). Standard protocols were used, and treatment was not preceded by stabilizing psychotherapeutic interventions.

MAIN OUTCOMES AND MEASURES Clinician-rated severity of PTSD symptoms, PTSD diagnosis, and full remission (on the Clinician-Administered PTSD Scale) were primary outcomes. Self-reported PTSD symptoms and posttraumatic cognitions were secondary outcomes.

RESULTS Data were analyzed as intent to treat with linear mixed models and generalized estimating equations. Participants in the PE and EMDR conditions showed a greater reduction of PTSD symptoms than those in the WL condition. Between-group effect sizes were 0.78 ($P < .001$) in PE and 0.65 ($P = .001$) in EMDR. Participants in the PE condition (56.6%; odds ratio [OR], 3.41; $P = .006$) or the EMDR condition (60.0%; OR, 3.92; $P < .001$) were significantly more likely to achieve loss of diagnosis during treatment than those in the WL condition (27.7%). Participants in the PE condition (28.3%; OR, 5.79; $P = .01$), but not those in the EMDR condition (16.4%; OR, 2.87; $P = .10$), were more likely to gain full remission than those in the WL condition (6.4%). Treatment effects were maintained at the 6-month follow-up in PE and EMDR. Similar results were obtained regarding secondary outcomes. There were no differences in severe adverse events between conditions (2 in PE, 1 in EMDR, and 4 in WL). The PE therapy and EMDR therapy showed no difference in any of the outcomes and no difference in participant dropout (24.5% in PE and 20.0% in EMDR, $P = .57$).

CONCLUSIONS AND RELEVANCE Standard PE and EMDR protocols are effective, safe, and feasible in patients with PTSD and severe psychotic disorders, including current symptoms. A priori exclusion of individuals with psychosis from evidence-based PTSD treatments may not be justifiable.

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In a meta-analysis[1] with 20 studies, the prevalence of posttraumatic stress disorder (PTSD) in psychosis was estimated to be 12.4% (95% CI, 4.0%-20.8%). The presence of comorbid PTSD is associated with poorer social functioning and more severe psychiatric symptoms.[2-4] There is strong empirical support for the efficacy of prolonged exposure (PE) therapy and eye movement desensitization and reprocessing (EMDR) therapy in treating PTSD.[5,6] These treatments are recommended as first-choice therapy in PTSD guidelines worldwide.[7,8] However, clinicians seem reluctant to treat PTSD in individuals with psychosis.[9,10] Patients with psychotic disorders have been excluded from randomized clinical trials,[11-13] and psychosis is the most frequently applied exclusion criterion.[14] Nevertheless, evidence suggests that trauma-focused treatments can be effective in this patient population. A randomized clinical trial tested an evidence-based intervention for PTSD (cognitive restructuring)[15] in patients with severe mental illness and found modest results.[16] However, only 16% of the participants had schizophrenia or schizoaffective disorder. Two small open pilot studies (in PE[17] and EMDR[18]) and a controlled case series study[19] (PE and EMDR) found large effects on PTSD and no adverse events. Overall, robust evidence for the efficacy and safety of PE and EMDR in patients with psychosis is lacking.

This study aimed to examine the efficacy and safety of PE and EMDR in reducing PTSD compared with a waiting list (WL) condition in individuals with psychotic disorders receiving treatment as usual for psychosis. To enhance clinical relevance, the trial was designed with features that mimic clinical practice.[20] A representative sample was acquired by applying a minimum of exclusion criteria. The study was conducted in 13 outpatient mental health services and used basic treatment protocols delivered by therapists with different levels of expertise in the target treatments. During the trial, non-trauma-focused cotherapies were allowed. We hypothesized that PE and EMDR compared with WL would both be effective and safe. In comparing PE and EMDR head-to-head, we expected no statistical differences due to insufficient statistical power to detect small effect sizes.

Methods

Design

The trial design was approved by the medical ethics committee of the VU University Medical Center and was registered at isrctn.com (ISRCTN79584912). Participants gave written informed consent before enrollment. Full details of the study methods and selection of participants are published elsewhere.[21] This study is a single-blind randomized clinical trial with 3 arms, including PE therapy, EMDR therapy, and WL. With a medium effect size between conditions, a power of 0.80, and an α level of .05, we needed 159 participants.

Participants

The participants were recruited in 13 Dutch comparable outpatient services for patients with severe mental illnesses. Inclusion criteria were (1) age 18 to 65 years, (2) a lifetime diagnosis of a psychotic disorder or mood disorder with psychotic features according to the Mini-International Neuropsychiatric Interview-Plus,[22,23] and (3) satisfaction of the full *DSM-IV-TR*[24] diagnostic criteria for chronic PTSD on the Clinician-Administered PTSD Scale (CAPS).[25,26] The PTSD severity was rated over the last week, and symptoms were considered present when they occurred at least once a week (frequency ≥2).

Exclusion criteria were (1) an extremely high acute suicide risk, operationalized as meeting all 3 of the following criteria (current high suicidality score on the Mini-International Neuropsychiatric Interview-Plus, a serious suicide attempt within the past 6 months, and a depression score of ≥35 on the Beck Depression Inventory-II[27,28]); (2) changes in antipsychotic or antidepressant medication regimen within 2 months before the assessment (to control for medication effects on PTSD symptoms); (3) insufficient competence in the Dutch language; (4) severe intellectual impairment, defined as an estimated IQ of 70 or less (mental retardation); (5) not being able to travel (or be accompanied) to the outpatient service; and (6) current involuntary admission in a closed ward. The presence of current psychotic symptoms was not an exclusion criterion.

Measures

Assessors were blinded to treatment allocation. The 2-way mixed single-measures (consistency) intraclass correlation coefficient for CAPS severity among all assessors over 20 randomly selected cases was 0.81.

Assessors and therapists emphasized the importance of blinding to the participants and repeatedly reminded them not to reveal the randomized treatment condition. Assessors avoided contact with the therapists and other caregivers. With these procedures, 27 incidents of unblinding occurred (11 in PE, 11 in EMDR, and 5 in WL). In case of unblinding, another assessor repeated the entire measurement.

The primary outcome measure was the CAPS,[25] which provides a symptom severity score and assesses the presence of a PTSD diagnosis. Full remission (CAPS total score, <20)[26] was also evaluated. The CAPS was administered once over a maximum of 3 index traumas that were most strongly related to PTSD symptom severity. Traumatic psychotic experiences (eg, being physically secluded or restrained in a psychiatric hospital) were accepted as criterion A traumas when these events met *DSM-IV-TR* A1 and A2 criteria.

Secondary outcome measures were the Posttraumatic Stress Symptom Scale Self-Report (PSS-SR),[29] which assesses self-reported frequency of PTSD symptoms, and the Posttraumatic Cognitions Inventory (PTCI),[30] which measures trauma-related cognitive distortions. All outcome measures were assessed at baseline, posttreatment, and the 6-month follow-up. Demographic characteristics were recorded at baseline.

Procedure

Recruitment took place from September 2011 through April 2013 and involved a 3-stage process (**Figure 1**). First, patients were screened for PTSD with the Trauma Screening Questionnaire.[21,31] Patients demonstrating a high risk of PTSD

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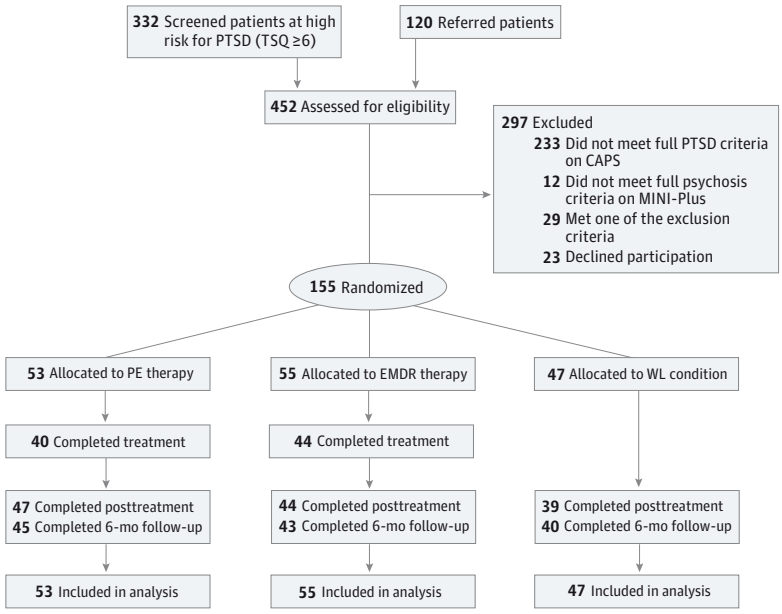
Figure 1. Flow of Participants Through the Trial



CAPS indicates Clinician-Administered PTSD Scale; EMDR, eye movement desensitization and reprocessing; MINI-Plus, Mini-International Neuropsychiatric Interview–Plus; PE, prolonged exposure; PTSD, posttraumatic stress disorder; TSQ, Trauma Screening Questionnaire; and WL, waiting list.

(Trauma Screening Questionnaire score ≥6) were invited for an inclusion interview. Second, patients were assessed using the CAPS, Mini-International Neuropsychiatric Interview-Plus, and Beck Depression Inventory-II to determine inclusion criteria. Third, eligible patients signed informed consent and completed the baseline assessment.

Patients could also be referred for an inclusion interview (stage 2). An independent randomization bureau randomized the treatment condition using stratified randomization blocks per therapist with equal strata sizes. Therapists confirmed the treatment assignment in writing. Data were stored at the study coordination center.

Early completion was allowed when the PSS-SR scores were 10 or less on 2 consecutive occasions and the Subjective Units of Distress Scale score of all memories in the treatment plan was zero. To this end, the PSS-SR was administered before every session in the PE and EMDR conditions. After the 6-month follow-up assessment, participants in the WL condition were offered their treatment of choice. All participants received a financial compensation of €25 (US $31) for each assessment.

Treatment

All participants in the trial received comparable treatment as usual for psychosis delivered by multidisciplinary assertive outreach teams, with care usually consisting of antipsychotic medication and treatment and/or supportive counseling by psychologists, caseworkers, nurses, or psychiatrists. In the WL condition, participants were seen once by a study therapist and informed about the PTSD diagnosis and further course of the study. Also, an appointment was made for the start of their treatment of choice after the 6-month follow-up period.

Both the PE and EMDR therapy were delivered in 8 weekly 90-minute sessions within a 10-week time frame. We did not aim to provide full therapy but rather to test an effective dosage of therapy that falls within the ranges in which PE and EMDR have been found to be effective,[32,33] also in this population.[18] In both conditions, the therapist and participant developed a standardized case conceptualization in the first session, which consisted of a hierarchy of relevant traumatic experiences. The PE therapy was conducted based on the protocol by Foa et al,[34] and imaginal exposure was used in sessions 2 through 8. Each session was audio recorded. Participants listened to these recordings 5 times per week. In sessions 3 through 8, in vivo exposure (based on a list of avoided trauma-related stimuli) was added. The EMDR was conducted according to the standard 8-phase protocol by Shapiro[35] using the Dutch translation of the EMDR protocol.[36] Eye movements were applied as the dual-attention stimulus. In sessions 2 through 8, memories were processed.[35]

The therapists were 19 clinical psychologists and 1 psychiatrist. Of these, 2 were already trained (a minimum of 4 days) in PE and 4 in EMDR. All other therapists received 4-day training in both PE and EMDR and treated at least 2 supervised cases per treatment during training. All therapists delivered both treatments.

Non-trauma-focused therapies were allowed. However, participants and caregivers were instructed not to start any other form of trauma-focused treatment (eg, PE, EMDR, cognitive therapy, or imagery rescripting), to keep medications unchanged, and to report any adverse events or deviations from standard care. After treatment and at the 6-month follow-up, patient files were reviewed to check whether trauma-focused treatments had taken place and if there had been any changes in the prescribed medications, as well as for any deviations from standard care.

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Supervision and Fidelity Monitoring

Four hours of group supervision (group size, 6-8) were provided each month by experts in the target treatments (2 hours by A.Van M. in PE and 2 hours by C.de R. or A.de J. in EMDR). Additional supervision by telephone or e-mail was provided on request. All treatment sessions were videotaped; of these sessions, 10% were randomly selected and rated by trained raters who were blinded to treatment outcome. Raters determined therapist competence and adherence to the treatment protocols. Adherence to protocols was rated as good or excellent in 91.2% of PE sessions and 97.1% of EMDR sessions. In PE, no essential elements of EMDR were detected and vice versa. Almost all (96.9%) of the performances of the therapists were rated as competent. Treatment alliance of therapists to PE and EMDR did not differ (t_{18} = 0.000, P > .99). In PE, participants completed 84.4% of the imaginal exposure and 85.6% of the in vivo exposure homework assignments.

Statistical Analysis

Analyses were conducted with statistical software (SPSS 20; IBM SPSS). The 2 treatment conditions were compared with WL (PE vs WL and EMDR vs WL) and head-to-head (PE vs EMDR) on all outcomes. Continuous variables were analyzed on an intent-to-treat basis with linear mixed models (LMMs). Baseline scores were included as covariates, time as a categorical variable, and treatment condition as a fixed effect. The intercept was treated as a random effect.

Dichotomous outcomes were analyzed with logistic generalized estimating equation analyses with exchangeable correlation structure. A generalized estimating equation analysis is reported to be a significantly better estimator of effects in dichotomous outcomes than a LMM.[37] Effects were computed for posttreatment and 6-month follow-up using interaction effects. Analyses of completers and intent-to-treat analyses with last observation carried forward (with missing data on loss of diagnosis conservatively replaced with a negative value [ie, no loss of diagnosis]) were performed to test the robustness of the findings. Between-group effect sizes (PE vs WL and EMDR vs WL) were computed according to Cohen d[38] using estimated data from the LMM procedure. Baseline differences in demographic and clinical characteristics were analyzed using χ^2 test, t test, and analysis of variance. The number needed to treat was calculated to determine the number of participants who needed to be treated to make one more patient lose diagnosis or achieve full remission compared with the control condition.[39]

Results

Figure 1 shows the participant flow through the study. In total, 440 inclusion interviews were conducted, and 155 participants were randomized. **Table 1** lists the baseline demographic and clinical characteristics. The participants are characterized by severe posttraumatic, psychotic, and depressive symptoms and represent a group with chronic severe mental illness. Most participants experienced multiple childhood traumas: 38.1% had multiple incidents of childhood sexual abuse (at age, ≤12 years). Only 5.2% experienced a single trauma type in adulthood. At baseline, there were no significant differences between the groups in any of the demographic or clinical characteristics.

Intent-to-Treat Analyses

Observed mean CAPS total scores are shown in **Figure 2**. **Table 2** lists estimated marginal means produced by the LMM procedure, pre-post effect sizes, and LMM outcomes. There were significant effects on the mean CAPS total scores for both treatments compared with WL at posttreatment and 6-month follow-up. There were no significant differences between PE and EMDR.

Outcomes on loss of PTSD diagnosis and full remission of PTSD are listed in **Table 3**. According to the logistic generalized estimating equation analyses, participants in both the PE and EMDR conditions were more likely to achieve and maintain loss of PTSD diagnosis than participants in the WL condition. Participants in the PE condition, but not those in the EMDR condition, were more likely to achieve full remission of PTSD than participants in the WL condition. The PE and EMDR did not significantly differ in loss of PTSD diagnosis and full remission.

Self-reported PTSD symptoms (on the PSS-SR) and posttraumatic cognitions (on the PTCI) yielded results that were similar to the CAPS findings (Figure 2 and Table 2). The PSS-SR and PTCI scores were lower for both treatment conditions compared with the WL condition at posttreatment and 6-month follow-up. There were no significant differences between the PE and EMDR.

There was no difference in dropout between the PE (13 participants [24.5%]) and EMDR (11 participants [20.0%]) (P = .57). There were 8 early completers in PE (15.1%) and 2 in EMDR (3.6%); this difference was not statistically significant (P = .09). The mean number of treatment sessions attended by treatment completers was 7.1 in PE and 7.8 in EMDR (P = .007). All severe adverse events were reported to the medical ethics committee. There were 2 severe adverse events in PE, 1 in EMDR, and 4 in WL. However, none of the severe adverse events were judged to have been induced by the study.

There were no differences between groups in additional support provided by caregivers. Groups did not differ in the percentage of participants receiving additional non-trauma-focused psychotherapy during treatment (17.0% in PE, 20.8% in EMDR, and 21.3% in WL) and follow-up (24.5% in PE, 18.9% in EMDR, and 25.5% in WL). No participants received other or additional trauma-focused treatments during the study period. There were no significant group differences in changes in prescribed antipsychotics, sedatives or anxiolytics, antidepressants, or mood stabilizers during treatment or the follow-up period. Most changes concerned antipsychotics. The dosage of prescribed antipsychotic medication was decreased in 7 participants and increased in 12 participants during treatment and was decreased in 10 participants and increased in 15 participants during follow-up.

Sensitivity Analyses

Completer analyses were performed (n = 113), among which no baseline differences were observed between groups in any

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Table 1. Baseline Demographic and Clinical Characteristics

Characteristic	PE (n = 53)	EMDR (n = 55)	WL (n = 47)	Total Sample (N = 155)
Age, mean (SD), y	42.6 (10.3)	40.4 (11.3)	40.3 (9.7)	41.2 (10.5)
Sex, No.				
Male	23	25	23	**71**
Female	30	30	24	**84**
Cultural background, No. (%)				
Dutch	36 (67.9)	34 (61.8)	27 (57.4)	**97** (62.6)
Non-Western	12 (22.6)	17 (30.9)	19 (40.4)	**48** (31.0)
Western, non-Dutch	5 (9.4)	4 (7.3)	1 (2.1)	**10** (6.5)
Post-high school education, No. (%)[a]				
High	7 (13.2)	4 (7.3)	3 (6.4)	**14** (9.0)
Middle	23 (43.4)	21 (38.2)	18 (38.3)	**62** (40.0)
Low	23 (43.4)	30 (54.5)	26 (55.3)	**79** (51.0)
Employed, No. (%)	8 (15.1)	4 (7.3)	6 (12.8)	**18** (11.6)
Living condition, No. (%)				
Married or cohabitating	11 (20.8)	12 (21.8)	10 (21.3)	**33** (21.3)
With parents, other relatives, or friends	8 (15.1)	7 (12.7)	7 (14.9)	**22** (14.2)
Alone	26 (49.1)	24 (43.6)	27 (57.4)	**77** (49.7)
Sheltered housing	8 (15.1)	12 (21.8)	3 (6.4)	**23** (14.8)
DSM-IV-TR A1 and A2 trauma categories, single or multiple, No. (%)				
Sexual abuse	38 (71.7)	28 (50.9)	28 (59.6)	**94** (60.6)
Multiple childhood sexual abuse at age ≤12 y	26 (49.1)	20 (36.4)	13 (27.7)	**59** (38.1)
Physical abuse	29 (54.7)	30 (54.5)	23 (48.9)	**82** (52.9)
Traumatic psychosis	9 (17.0)	6 (10.9)	13 (27.7)	**28** (18.1)
Emotional abuse in childhood	4 (7.5)	3 (5.5)	3 (6.4)	**10** (6.5)
Other traumatic event such as accident, disaster, war	27 (50.9)	33 (60.0)	24 (51.1)	**84** (54.2)
Lifetime MINI-Plus diagnosis, No. (%)				
Schizophrenia	31 (58.5)	34 (61.8)	30 (63.8)	**95** (61.3)
Schizoaffective disorder	17 (32.1)	15 (27.3)	13 (27.7)	**45** (29.0)
Brief psychotic disorder	0	0	1 (2.1)	**1** (0.6)
Psychotic disorder not otherwise specified	1 (1.9)	3 (5.5)	0	**4** (2.6)
Bipolar disorder with psychotic features	2 (3.8)	2 (3.6)	3 (6.4)	**7** (4.5)
Depression with psychotic features	2 (3.8)	1 (1.8)	0	**3** (1.9)
Suicide attempt ever, No. (%)	33 (62.3)	33 (60.0)	28 (59.6)	**94** (60.6)
Current medium or high suicide risk on MINI-Plus, No. (%)	27 (50.9)	23 (41.8)	20 (42.6)	**70** (45.2)
Current delusions on DRS, No. (%)[b]	34 (64.2)	32 (58.2)	30 (63.8)	**96** (61.9)
Current auditory verbal hallucinations on AHRS, No. (%)	21 (39.6)	24 (43.6)	17 (36.2)	**62** (40.0)
CAPS total score, mean (SD)	69.6 (14.9)	72.1 (17.6)	68.1 (15.9)	69.9 (16.2)
PSS-SR score, mean (SD)	28.5 (8.0)	30.3 (7.8)	27.7 (8.9)	28.9 (8.2)
PTCI score, mean (SD)	153.1 (35.8)	147.6 (32.6)	144.9 (28.7)	148.6 (32.6)
BDI-II score, mean (SD)	30.9 (11.4)	28.2 (11.6)	29.7 (12.4)	29.6 (11.7)
Chlorpromazine hydrochloride dose equivalent, mean (SD)[c]	227.3 (187.9)	253.2 (250.5)	250.7 (232.8)	243.6 (224.2)
Duration of psychosis, mean (SD), y	18.9 (12.8)	18.2 (11.7)	15.7 (10.5)	17.7 (11.8)
Duration of PTSD, mean (SD), y	22.8 (13.6)	21.1 (13.9)	18.95 (12.9)	21.0 (13.5)

Abbreviations: AHRS, Auditory Hallucination Rating Scale[40]; BDI-II, Beck Depression Inventory–II; CAPS, Clinician-Administered PTSD Scale; DRS, Delusion Rating Scale[40]; EMDR, eye movement desensitization and reprocessing; MINI-Plus, Mini-International Neuropsychiatric Interview–Plus; PE, prolonged exposure; PSS-SR, Posttraumatic Stress Symptom Scale Self-Report; PTCI, Posttraumatic Cognitions Inventory; PTSD, posttraumatic stress disorder; WL, waiting list.

[a] Lower indicates primary education or lower general secondary education; middle, intermediate vocational education or higher high school level; and high, higher vocational education or university.

[b] See de Bont et al[21] for details on the DRS and AHRS.

[c] One hundred milligrams of chlorpromazine hydrochloride is equivalent to 2 mg of haloperidol.

of the demographic or clinical characteristics. In addition, intent-to-treat analyses with last observation carried forward were performed (n = 155). All results for the CAPS, PSS-SR, and PTCI were similar to the results from the intent-to-treat analyses, thereby underlining the robustness of the findings (Table 3).

Discussion

Both PE therapy and EMDR therapy were more effective than the WL condition in reducing trauma symptoms and achieving loss of PTSD diagnosis among participants with

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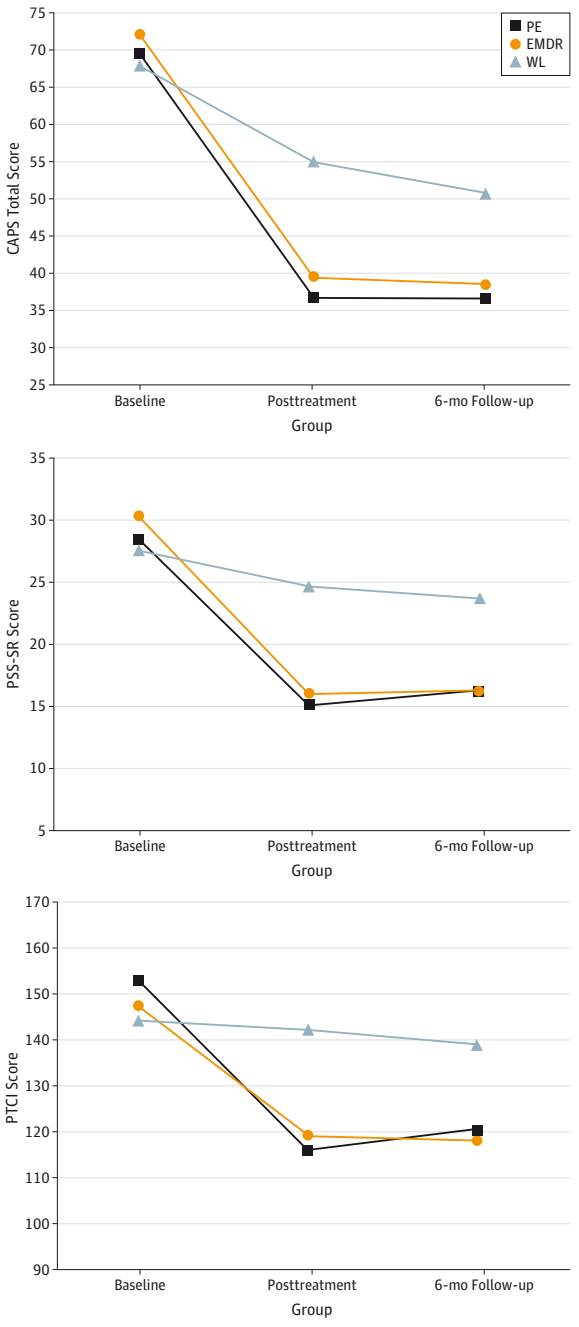
Figure 2. Observed Trajectories of the CAPS, PSS-SR, and PTCI Scores as a Function of Treatment Group in the Intent-to-Treat Sample



The intent-to-treat sample comprised 155 participants at baseline, 130 participants at posttreatment, and 128 participants at the 6-month follow-up. CAPS indicates Clinician-Administered PTSD Scale; EMDR, eye movement desensitization and reprocessing; PE, prolonged exposure; PSS-SR, Posttraumatic Stress Symptom Scale Self-Report; PTCI, Posttraumatic Cognitions Inventory; and WL, waiting list.

severe PTSD and psychotic disorders. Prolonged exposure therapy was more effective than WL in achieving full remission, while EMDR therapy was not. We found no differences in head-to-head comparisons of the 2 active treatments in any of the outcomes.

Similar to most trauma treatment trials, treatment effects were observed directly after treatment and persisted over time.[41] Moreover, in the present sample with comorbid psychotic disorder, change rates in the diagnostic status were comparable to those reported in a meta-analysis[6] of general samples. The dropout rate was low and comparable to that of other trials.[42] Most important, both treatments were found to be safe and did not result in severe adverse events.

Some of the patients in the control condition achieved remission. This might be the result of anticipation of a positive outcome of treatment and setting a date for the first session. Also, exposure to an extensive trauma interview and repeated assessments in the study protocol[21] may have functioned as covert exposure.[43] Last, trauma symptoms appear to fluctuate over time,[44] and long-term remission rates without specific treatment are high in PTSD.[45] Therefore, future studies should include an active non-trauma-focused (eg, befriending) control group to control for factors such as therapy time and attention.

The present results can be generalized to routine clinical practice. We used standard protocols of guideline trauma treatments in a sample of patients with psychotic disorders and severe psychopathology (including current paranoia, auditory verbal hallucinations, depression, and high suicide risk). Psychotherapeutic stabilization was not applied and appears unnecessary; it may even needlessly delay treatment.[13] The dropout rate was comparable to that in the trial by Mueser and colleagues[16] and was lower than that in an open study[17] using stabilizing interventions.

Dissemination of effective trauma treatments to clinical practice appears to be problematic,[9,46-48] and PTSD is missed in most patients with a psychotic disorder.[49,50] These factors decrease the chance that patients with psychosis and PTSD will receive evidence-based trauma treatment. There are multiple reasons for this, but the most important factors seem to be fear of symptom exacerbation, safety issues, and questions about tolerability.[13,46] The fact that professionals are particularly reluctant to treat trauma in psychosis[9,10] is not based on empirical evidence.[47,51] Exclusion of patients with psychotic disorders from effective trauma treatments has been the norm in both clinical practice and research.[14] Even researchers stressing the importance of broadening inclusion criteria for trauma treatment studies indicate that schizophrenia is a reasonable exclusion criterion.[6] The present results are at odds with these prejudices.

The strengths of this study are the sample size, the generalizability to clinical practice owing to the use of standard protocols with patients in routine long-term care, the correction for unblinding, and the limited loss to follow-up. We believe that this study demonstrates the efficacy and safety of trauma treatment in psychosis.

There are several limitations. The first limitation is that treatment consisted of only 8 sessions. Most participants had experienced multiple childhood traumas, and for some par-

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Table 2. Estimated Outcomes as a Function of Treatment Group in the Intent-to-treat Sample[a]

Outcome	Posttreatment			6-mo Follow-up		
	PE (n = 53)	EMDR (n = 55)	WL (n = 47)	PE (n = 53)	EMDR (n = 55)	WL (n = 47)
CAPS total score, mean (95% CI)	37.8 (31.2-44.3)	40.3 (33.6-47.1)	56.5 (49.5-63.6)	36.7 (30.1-43.4)	38.8 (31.9-45.6)	51.9 (44.9-58.9)
Baseline score	69.6	72.1	68.1	NA	NA	NA
Effect size	0.78	0.65	NA	0.63	0.53	NA
LMM	$t_{193} = -3.84$, $P < .001$	$t_{193} = -3.26$, $P = .001$	NA	$t_{194} = -3.10$, $P = .002$	$t_{193} = -2.66$, $P = .009$	NA
PSS-SR score, mean (95% CI)	16.1 (13.1-19.1)	16.1 (12.9-19.2)	25.8 (22.5-28.9)	16.4 (13.4-19.4)	16.2 (13.0-19.3)	24.1 (20.9-27.4)
Baseline score	28.5	30.3	27.7	NA	NA	NA
Effect size	0.88	0.85	NA	0.70	0.70	NA
LMM	$t_{188} = -4.33$, $P < .001$	$t_{187} = -4.26$, $P < .001$	NA	$t_{189} = -3.46$, $P = .001$	$t_{187} = -3.51$, $P = .001$	NA
PTCI score, mean (95% CI)	113.9 (104.4-123.5)	120.4 (110.6-130.3)	146.5 (136.2-156.9)	120.4 (110.7-130.1)	119.8 (109.9-129.7)	140.5 (130.3-150.8)
Baseline score	153.1	147.6	144.9	NA	NA	NA
Effect size	0.93	0.72	NA	0.57	0.57	NA
LMM	$t_{195} = -4.56$, $P < .001$	$t_{196} = -3.61$, $P < .001$	NA	$t_{196} = -2.82$, $P = .005$	$t_{195} = -2.87$, $P = .005$	NA

Abbreviations: CAPS, Clinician-Administered PTSD Scale; EMDR, eye movement desensitization and reprocessing; LMM, linear mixed model; NA, not applicable; PE, prolonged exposure; PSS-SR, Posttraumatic Stress Symptom Scale Self-Report; PTCI, Posttraumatic Cognitions Inventory; WL, waiting list.

[a] The CAPS, PSS-SR, and PTCI scores reflect the estimated marginal mean (95% CI) from the LMM analyses. Between-group effect sizes are Cohen *d* based on estimated data from the LMM procedure. The reported effect sizes concern the differences between the 2 treatment conditions and the WL condition (PE vs WL and EMDR vs WL) at the different time points. Results from the LMM analyses concern the differences at the different time points for PE vs WL and for EMDR vs WL.

Table 3. Observed Outcomes of Loss of Diagnosis and Full Remission on the CAPS by Treatment Group in the Intent-to-treat Sample[a]

Outcome	Posttreatment									6-mo Follow-up								
	PE (n = 53)				EMDR (n = 55)				WL (n = 47)	PE (n = 53)				EMDR (n = 55)				WL (n = 47)
	No. (%)	OR	*P* Value	NNT (95% CI)	No. (%)	OR	*P* Value	NNT (95% CI)	No. (%)	No. (%)	OR	*P* Value	NNT (95% CI)	No. (%)	OR	*P* Value	NNT (95% CI)	No. (%)
Loss of diagnosis[b]	30 (56.6)	3.41	.006	3.5 (2.1 to 9.6)	33 (60.0)	3.92	<.001	3.1 (2.0 to 7.1)	13 (27.7)	31 (58.5)	3.01	.003	3.8 (2.2 to 12.9)	31 (56.4)	2.76	.002	4.1 (2.3 to 17.4)	15 (31.9)
Still PTSD	17 (32.1)	NA	NA	NA	11 (20.0)	NA	NA	NA	26 (55.3)	14 (26.4)	NA	NA	NA	12 (21.8)	NA	NA	NA	25 (53.2)
Lost to follow-up	6 (11.3)	NA	NA	NA	11 (20.0)	NA	NA	NA	8 (17.0)	8 (15.1)	NA	NA	NA	12 (21.8)	NA	NA	NA	7 (14.9)
Full remission[c]	15 (28.3)	5.79	.01	4.6 (2.8 to 12.6)	9 (16.4)	2.87	.10	10.0 (4.5 to −49.8)	3 (6.4)	14 (26.4)	5.26	.01	5.0 (3.0 to 16.0)	8 (14.5)	2.49	.15	12.3 (5.0 to −28.7)	3 (6.4)
No full remission	32 (60.4)	NA	NA	NA	35 (63.6)	NA	NA	NA	36 (76.6)	31 (58.5)	NA	NA	NA	35 (63.6)	NA	NA	NA	37 (78.7)
Lost to follow-up	6 (11.3)	NA	NA	NA	11 (20.0)	NA	NA	NA	8 (17.0)	8 (15.1)	NA	NA	NA	12 (21.8)	NA	NA	NA	7 (14.9)

Abbreviations: CAPS, Clinician-Administered PTSD Scale; EMDR, eye movement desensitization and reprocessing; NA, not applicable; NNT, number needed to treat; OR, odds ratio; PE, prolonged exposure; PTSD, posttraumatic stress disorder; WL, waiting list.

[a] The ORs and NNTs are based on observed CAPS total score differences between the 2 treatment conditions and the WL condition (PE vs WL and EMDR vs WL) at the different time points. *P* values were derived from the logistic generalized estimating equation analyses.

[b] Loss of diagnosis indicates no longer meeting PTSD criteria.[26]

[c] Full remission indicates a total score of less than 20 on the CAPS.[26]

ticipants 8 sessions were probably too few to significantly affect trauma symptoms. The second limitation is the fact that this study was powered to find medium to large effects. Therefore, small effects between conditions may not have been detected. The third limitation is that experts supervised the therapies, whereas similar supervision may not always be available in clinical practice. The fourth limitation is that treatment as usual for psychosis may vary between countries. Most participants in the present trial were treated in assertive outreach teams.

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Conclusions

This study demonstrates that standard PE and EMDR protocols are effective, safe, and feasible in patients with psychosis and comorbid PTSD without using stabilizing psychotherapeutic interventions. One in 8 patients with a psychotic disorder has PTSD.[1] There is no need to exclude these patients from effective trauma treatments.

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REFERENCES

1. Achim AM, Maziade M, Raymond E, Olivier D, Mérette C, Roy MA. How prevalent are anxiety disorders in schizophrenia? a meta-analysis and critical review on a significant association. *Schizophr Bull*. 2011;37(4):811-821.

2. Mueser KT, Lu W, Rosenberg SD, Wolfe R. The trauma of psychosis: posttraumatic stress disorder and recent onset psychosis. *Schizophr Res*. 2010;116 (2-3):217-227.

3. Lysaker PH, Larocco VA. The prevalence and correlates of trauma-related symptoms in schizophrenia spectrum disorder. *Compr Psychiatry*. 2008;49(4):330-334.

4. Sautter FJ, Brailey K, Uddo MM, Hamilton MF, Beard MG, Borges AH. PTSD and comorbid psychotic disorder: comparison with veterans diagnosed with PTSD or psychotic disorder. *J Trauma Stress*. 1999;12(1):73-88.

5. Bisson JI, Roberts NP, Andrew M, Cooper R, Lewis C. Psychological therapies for chronic post-traumatic stress disorder (PTSD) in adults. *Cochrane Database Syst Rev*. 2013;12:CD003388.

6. Bradley R, Greene J, Russ E, Dutra L, Westen D. A multidimensional meta-analysis of psychotherapy for PTSD. *Am J Psychiatry*. 2005;162(2):214-227.

7. Forbes D, Creamer M, Bisson JI, et al. A guide to guidelines for the treatment of PTSD and related conditions. *J Trauma Stress*. 2010;23(5):537-552.

8. World Health Organization. *Guidelines for the Management of Conditions Specifically Related to Stress*. Geneva, Switzerland: World Health Organization; 2013.

9. Becker CB, Zayfert C, Anderson E. A survey of psychologists' attitudes towards and utilization of exposure therapy for PTSD. *Behav Res Ther*. 2004; 42(3):277-292.

10. Meyer JM, Farrell NR, Kemp JJ, Blakey SM, Deacon BJ. Why do clinicians exclude anxious clients from exposure therapy? *Behav Res Ther*. 2014;54:49-53.

11. Olatunji BO, Cisler JM, Tolin DF. A meta-analysis of the influence of comorbidity on treatment outcome in the anxiety disorders. *Clin Psychol Rev*. 2010;30(6):642-654.

12. Spinazzola J, Blaustein M, van der Kolk BA. Posttraumatic stress disorder treatment outcome research: the study of unrepresentative samples? *J Trauma Stress*. 2005;18(5):425-436.

13. van Minnen A, Harned MS, Zoellner L, Mills K. Examining potential contraindications for prolonged exposure therapy for PTSD. *Eur J Psychotraumatol*. 2012:3.

14. Ronconi JM, Shiner B, Watts BV. Inclusion and exclusion criteria in randomized controlled trials of psychotherapy for PTSD. *J Psychiatr Pract*. 2014;20 (1):25-37.

15. Watts BV, Schnurr PP, Mayo L, Young-Xu Y, Weeks WB, Friedman MJ. Meta-analysis of the efficacy of treatments for posttraumatic stress disorder. *J Clin Psychiatry*. 2013;74(6):e541-e550. doi:10.4088/JCP.12r08225.

16. Mueser KT, Rosenberg SD, Xie H, et al. A randomized controlled trial of cognitive-behavioral treatment for posttraumatic stress disorder in severe mental illness. *J Consult Clin Psychol*. 2008;76(2):259-271.

17. Frueh BC, Grubaugh AL, Cusack KJ, Kimble MO, Elhai JD, Knapp RG. Exposure-based cognitive-behavioral treatment of PTSD in adults with schizophrenia or schizoaffective disorder: a pilot study. *J Anxiety Disord*. 2009;23(5):665-675.

18. van den Berg DP, van der Gaag M. Treating trauma in psychosis with EMDR: a pilot study. *J Behav Ther Exp Psychiatry*. 2012;43(1):664-671.

19. de Bont PA, van Minnen A, de Jongh A. Treating PTSD in patients with psychosis: a within-group controlled feasibility study examining the efficacy and safety of evidence-based PE and EMDR protocols. *Behav Ther*. 2013;44(4):717-730.

20. Tunis SR, Stryer DB, Clancy CM. Practical clinical trials: increasing the value of clinical research for decision making in clinical and health policy. *JAMA*. 2003;290(12):1624-1632.

21. de Bont PA, van den Berg DP, van der Vleugel BM, et al. A multi-site single blind clinical study to compare the effects of prolonged exposure, eye movement desensitization and reprocessing and waiting list on patients with a current diagnosis of psychosis and co morbid post traumatic stress

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disorder: study protocol for the randomized controlled trial Treating Trauma in Psychosis. *Trials*. 2013;14:151.

22. Sheehan DV, Lecrubier Y, Harnett Sheehan K, et al. The validity of the Mini International Neuropsychiatric Interview (MINI) according to the SCID-P and its reliability. *Eur Psychiatry*. 1997;12: 232-241.

23. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for *DSM-IV* and *ICD-10*. *J Clin Psychiatry*. 1998;59(suppl 20):22-33.

24. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed, text revision. Washington, DC: American Psychiatric Association; 2000.

25. Blake DD, Weathers FW, Nagy LM, et al. The development of a Clinician-Administered PTSD Scale. *J Trauma Stress*. 1995;8(1):75-90.

26. Weathers FW, Keane TM, Davidson JR. Clinician-Administered PTSD Scale: a review of the first ten years of research. *Depress Anxiety*. 2001;13 (3):132-156.

27. Beck AT, Steer RA, Ball R, Ranieri W. Comparison of Beck Depression inventories –IA and –II in psychiatric outpatients. *J Pers Assess*. 1996; 67(3):588-597.

28. Beck AT, Steer RA, Brown GK. *Manual for the Beck Depression Inventory–II*. San Antonio, TX: Psychological Corporation; 1996.

29. Foa EB, Riggs DS, Dancu CV, Rothbaum BO. Reliability and validity of a brief instrument for assessing post-traumatic stress disorder. *J Trauma Stress*. 1993;6:459-473.

30. Foa EB, Ehlers A, Clark DM, Tolin DF, Orsillo SM. The Posttraumatic Cognitions Inventory (PTCI): development and validation. *Psychol Assess*. 1999; 11(3):303-314.

31. Brewin CR, Rose S, Andrews B, et al. Brief screening instrument for post-traumatic stress disorder. *Br J Psychiatry*. 2002;181:158-162.

32. Nijdam MJ, Gersons BP, Reitsma JB, de Jongh A, Olff M. Brief eclectic psychotherapy v. eye movement desensitisation and reprocessing therapy for post-traumatic stress disorder: randomised controlled trial. *Br J Psychiatry*. 2012; 200(3):224-231.

33. Powers MB, Halpern JM, Ferenschak MP, Gillihan SJ, Foa EB. A meta-analytic review of prolonged exposure for posttraumatic stress disorder. *Clin Psychol Rev*. 2010;30(6):635-641.

34. Foa EB, Hembree EA, Rothbaum BO. *Prolonged Exposure Therapy for PTSD: Emotional Processing of Traumatic Experiences: Therapist Guide*. Oxford, England: Oxford University Press; 2007.

35. Shapiro F. *Eye Movement Desensitization and Reprocessing (EMDR): Basic Principles, Protocols, and Procedures*. New York, NY: Guilford Press; 2001.

36. de Jongh A, ten Broeke E. *Handboek EMDR: Een Geprotocolleerde Behandelmethode Voor de Gevolgen van Psychotrauma [Handbook of EMDR: A Standardized Treatment for the Consequences of Psychotrauma]*. Amsterdam, the Netherlands: Harcourt; 2003.

37. Twisk JW. *Applied Longitudinal Data Analysis for Epidemiology: A Practical Guide*. New York, NY: Cambridge University Press; 2013.

38. Cohen J. A power primer. *Psychol Bull*. 1992;112 (1):155-159.

39. Laupacis A, Sackett DL, Roberts RS. An assessment of clinically useful measures of the consequences of treatment. *N Engl J Med*. 1988;318 (26):1728-1733.

40. Haddock G, McCarron J, Tarrier N, Faragher EB. Scales to measure dimensions of hallucinations and delusions: the Psychotic Symptom Rating Scales (PSYRATS). *Psychol Med*. 1999;29(4):879-889.

41. Schnurr PP, Friedman MJ, Engel CC, et al. Cognitive behavioral therapy for posttraumatic stress disorder in women: a randomized controlled trial. *JAMA*. 2007;297(8):820-830.

42. Hembree EA, Foa EB, Dorfan NM, Street GP, Kowalski J, Tu X. Do patients drop out prematurely from exposure therapy for PTSD? *J Trauma Stress*. 2003;16(6):555-562.

43. Krakow B, Hollifield M, Warner TD. Placebo effect in posttraumatic stress disorders. *JAMA*. 2000;284(5):563-564.

44. McFarlane AC. Posttraumatic stress disorder: a model of the longitudinal course and the role of risk factors. *J Clin Psychiatry*. 2000;61(suppl 5):15-20.

45. Morina N, Wicherts JM, Lobbrecht J, Priebe S. Remission from post-traumatic stress disorder in adults: a systematic review and meta-analysis of long term outcome studies. *Clin Psychol Rev*. 2014; 34(3):249-255.

46. Cahill SP, Foa EB, Hembree EA, Marshall RD, Nacash N. Dissemination of exposure therapy in the treatment of posttraumatic stress disorder. *J Trauma Stress*. 2006;19(5):597-610.

47. Frueh BC, Cusack KJ, Grubaugh AL, Sauvageot JA, Wells C. Clinicians' perspectives on cognitive-behavioral treatment for PTSD among persons with severe mental illness. *Psychiatr Serv*. 2006;57(7):1027-1031.

48. Karlin BE, Ruzek JI, Chard KM, et al. Dissemination of evidence-based psychological treatments for posttraumatic stress disorder in the Veterans Health Administration. *J Trauma Stress*. 2010;23(6):663-673.

49. Mueser KT, Goodman LB, Trumbetta SL, et al. Trauma and posttraumatic stress disorder in severe mental illness. *J Consult Clin Psychol*. 1998;66(3): 493-499.

50. Lommen MJ, Restifo K. Trauma and posttraumatic stress disorder (PTSD) in patients with schizophrenia or schizoaffective disorder. *Community Ment Health J*. 2009;45(6):485-496.

51. Salyers MP, Evans LJ, Bond GR, Meyer PS. Barriers to assessment and treatment of posttraumatic stress disorder and other trauma-related problems in people with severe mental illness: clinician perspectives. *Community Ment Health J*. 2004;40(1):17-31.

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