Psychiatry Research 273 (2019) 567–574

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Clinical efficacy of trauma-focused psychotherapies in treatment-resistant depression (TRD) in-patients: A randomized, controlled pilot-study

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ARTICLE INFO

Keywords:
Treatment resistant depression
Clinical trial
Childhood trauma
EMDR
TF-CBT
Major depressive disorder

ABSTRACT

In major depressive disorder (MDD) patients, life stress events represent a risk factor for a severe, early-onset, treatment-resistant and chronic endophenotype. Treatment-resistant depression (TRD) patients who have experienced traumatic events could benefit from evidence-based trauma-focused psychotherapies. Because this topic has never been investigated, the aim of this pilot trial was to evaluate whether trauma-focused cognitive-behavioural therapy (TF-CBT) and/or eye movement desensitization and reprocessing (EMDR) can help achieve depressive symptom remission in TRD patients. We carried out a single-blind randomized controlled trial with TRD patients and we compared EMDR (N = 12) with TF-CBT (N = 10). Patients received 3 individual sessions per week over a period of 8 weeks. The symptomatological assessments were performed at 4 timepoints: baseline (T0), 4 (T4), 8 (T8) and 12 (T12) weeks. After 24 weeks, a clinical interview was carried out by phone. All TRD patients showed a significant improvement in depressive symptomatology; however, post hoc comparisons showed a significant difference between the two treatment groups, with lower depressive symptom scores in the EMDR than in the TF-CBT group at the follow-up (T12). This effect was partly maintained at 24 weeks. This pilot study suggests that evidence-based trauma-focused psychotherapies, particularly EMDR, can represent effective interventions to treat TRD patients.

1. Introduction

Major depressive disorder (MDD) is a disabling psychiatric condition that is among the top five leading causes of disability and disease burden throughout the world. MDD is associated with gradual and often incomplete recovery and with significant limitations in functioning and well-being. Several studies have shown that approximately two-thirds of patients did not experience full remission after first-choice treatment and that for many patients, achieving remission requires repeated trials of sufficient doses of antidepressant medication (Gaynes et al., 2008; Trivedi et al., 2006). In addition, a high percentage of MDD patients (15–30%) are classified as having treatment-resistant depression (TRD), which is defined as the failure to achieve a response to one or more standard antidepressant treatment trials of adequate dosage and duration (Berlim and Turecki, 2007; Thomas et al., 2013). For TRD patients novel therapeutics and innovative treatments are especially essential (Papakostas and Ionescu, 2015).

Several studies have shown that life stress events (physical and emotional abuses) are relevant psychosocial risk factors for the development of MDD, and they have been associated with a poorer response and remission outcome for commonly prescribed antidepressants, earlier illness onset, greater severity of symptoms, suicidal behaviours, and comorbidity (Bahk et al., 2017; Dias de Mattos Souza et al., 2016; Tunnard et al., 2014; Vitriol et al., 2017; Wiersma et al., 2009; Williams et al., 2016). Childhood abuse has also been found to be related to specific subtypes of MDD, having been associated with the presence of psychotic symptoms (Gaudiano and Zimmerman, 2010). In turn, all these clinical features have been widely demonstrated to be negative clinical predictors of treatment outcome in MDD (Perlis, 2013; Schlaepfer et al., 2012; Williams et al., 2016). All this evidence indicates that childhood trauma is, directly or indirectly, associated with the TRD condition.

Based on the above literature, it is possible to hypothesize that TRD patients who have experienced traumatic events could benefit from a

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https://doi.org/10.1016/j.psychres.2019.01.070
Received 11 December 2018; Received in revised form 23 January 2019; Accepted 23 January 2019
Available online 24 January 2019
0165-1781/

treatment with evidence-based trauma-focused psychotherapies. According to the World Health Organization practice guidelines (WHO, 2013) trauma-focused cognitive-behavioural therapy (TF-CBT) and eye movement desensitization and reprocessing (EMDR) are the only psychotherapies recommended for children, adolescents, and adults with post-traumatic stress disorders (PTSD). Several studies have shown that TF-CBT and EMDR are effective for the psychological treatment of adults with PTSD (Cusack et al., 2016; Lancaster et al., 2016). Moreover, new evidence of the efficacy of these methods is also growing for other mental disorders, such as bipolar disorder, MDD, psychosis and anxiety (Behnammoghadam et al., 2015; de Bont et al., 2016; Hase et al., 2015; Novo et al., 2014), but further data are necessary to achieve robust findings.

To date, no study has investigated the efficacy of trauma-focused psychotherapies in TRD. The aim of this pilot trial was to evaluate whether EMDR and/or TF-CBT can contribute to depressive symptoms remission in TRD patients with traumatic events in their life history.

2. Material and methods

2.1. Sample

Twenty-seven TRD patients were voluntarily enrolled in the study. Their diagnosis of MDD met Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) classification system criteria. All of the patients had been referred to the Villa S. Chiara Psychiatric Hospital in Verona. The diagnostic inclusion criterion was a diagnosis of unipolar depression according to DSM-IV. The exclusion criteria were as follows: (a) mental retardation or cognitive disorder; (b) a lifetime history of schizophrenic, schizoaffective, or bipolar disorder; (c) personality disorder, substance abuse, alcohol abuse or dependency, obsessive compulsive disorder, or post-traumatic stress disorder as the primary diagnosis; and (d) comorbidity with an eating disorder.

All TRD selected have already had several psychiatric hospitalizations where they received several drug medications in augmentation with other inpatient therapy setting such as occupational therapies and psychotherapies not focused on trauma. Many of them (about 60%), previously underwent to somatic therapies such as transcranial direct current stimulation (tDCS) and/or repetitive transcranial magnetic stimulation (rTMS). No one underwent to electroconvulsive therapy (ECT).

Diagnoses were confirmed using the Italian version of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) diagnostic scale and the Millon Clinical Multiaxial Inventory – III (MCMI-III).

Treatment resistance to antidepressants was defined as the failure to respond to two or more adequate trials of two or more different classes of antidepressants and to an adequate trial of a tricyclic antidepressant (TCA) drug; such patients were classified as being at least at stage III according to the Thase and Rush staging method (Thase and Rush, 1997).

All participants needed to have experienced at least three documentable traumatic events over their lifetime. All the subjects were assessed for exposure to childhood traumatic experiences according to the Italian version of the Childhood Experience of Care and Abuse Questionnaire (CECA-Q) (Bifulco et al., 2005). For the evaluation of recent stressful life events that occurred during the 12 months before the assessment, we used the Italian versions of the Paykel Scale of stressful life events and of the Holmes–Rahe Life Stress Inventory (Baratta et al., 1985; Holmes and Rahe, 1967). Moreover, a stressful life events anamnestic schedule was compiled to assess the presence of any lifetime traumatic events taking into account the following types: sexual abuse, physical abuse, emotional abuse, emotional and physical neglect, death of a close family member, divorce, marital separation, personal injury or severe illness, dismissal from work, injury or illness of a close family member, miscarriage, and abortion.

2.2. Study design

The study was designed as a single-blind randomized controlled trial to evaluate the efficacy of EMDR and TF-CBT as an adjunctive to pharmacological treatment in TRD subjects with a history of traumatic events in an inpatient setting.

After the enrolment of TRD in-patients in accordance with the inclusion and exclusion criteria and after obtaining written informed consent, the participants were randomized to one of the trauma-focused psychotherapies with 3 individual sessions per week, lasting 60 min each over a period of 8 weeks, in addition to drug treatment as usual (TAU). The allocation of the patients to EMDR or TF-CBT was performed through a simple randomization with the software https://www.sealedenvelope.com/simple-randomiser/v1/lists by the project manager (AM) that carried out neither the evaluation, nor the therapies. The participants who were assigned to EMDR were allocated to one of the three EMDR therapists, whereas subjects and patients who were assigned to TF-CBT were allocated to one of the three available CBT therapists. Thus, each patient received 24 sessions of EMDR or TF-CBT carried out by highly experienced psychotherapists. We developed an intensive psychotherapy session protocol to offer TRD patients a psychotherapeutic path focused on trauma without any costs to the patients and their families using our maximum allowed hospitalization time, as these patients frequently do not have free access to outpatient therapists.

The investigation was carried out in accordance with the latest version of the Declaration of Helsinki; the study design was approved by the Local Ethics Committees (Ethics Committee for Clinical Trials of the province of Verona and Rovigo N: 234777/11.05.16); and written informed consent of the participants was obtained after the nature of the procedures had been fully explained to and understood by the patients. All participants were also informed that their non-participation or retreat from the protocol would have no direct or indirect influence on or consequence for their usual treatment.

For the EMDR therapy, the standardized eight-phase protocol was used (Shapiro, 2001, 2014), whereas for the TF-CBT therapy, interventions specifically tailored to meet the needs of adults experiencing emotional and psychological difficulties as a result of a trauma were integrated with cognitive behavioural approach for trauma (Kornor et al., 2008; Bisson et al., 2013).

The patients were maintained on the same drug treatment during the entire period of the study. Changes in pharmacological therapy due to clinical needs were noted.

2.3. Assessments

All participants were evaluated by two psychiatrists (MB, EZ) who were not otherwise involved in the study. The symptomatological assessment was carried out at 4 timepoints: baseline (T0), after four weeks of treatment during the hospitalization (T4), after eight weeks of treatment that represented the end of the hospitalization (T8) and four weeks after the end of the treatment when the patients came back to the hospital for the visit (T12). The evaluations were performed using the Montgomery–Åsberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979), the Beck Depression Inventory II (BDI-II) (Beck, 1993), the Beck Anxiety Inventory (BAI) (Beck and Steer, 2013), the Pittsburgh Sleep Quality Index (PSQI) (Curcio et al., 2013) to evaluate the clinical efficacy of the therapy and using the MINI-ICF-APP (Balestrieri et al., 2013) to monitor changes in psychosocial functioning. Twenty-four weeks after the beginning of the protocol (T24), we performed a phone interview for clinical assessment. The EMDR and TF-CBT therapists were blind to the symptomatological evaluations. The assessors were blind to treatment allocation. We claim to be able to exclude researcher allegiance (RA) effect since RA has been defined as a researcher's 'belief in the superiority of a treatment and in the superior validity of the theory of change that is associated

with the treatment (Dragioti et al., 2015). Indeed, the assessors were blind to the group of allocation and the project manager did not perform the psychotherapies and the evaluations. Moreover, both the assessors (MB, EZ) and the project manager (AM) are trained both in CBT and in EMDR and they use these forms of psychotherapies in their clinical practice. Patients were defined as responders if the percentage MADRS reduction (ΔMADRS) at T12 was >50%.

2.4. Statistical analysis

Due to the small sample size of the EMDR and TF-CBT groups, baseline group differences were assessed using non-parametric tests. In particular, to detect differences in demographic and clinical variables, the Mann–Whitney U test was used to compare the two groups for continuous measures, and Fisher's exact test was used for categorical measures. The Pearson coefficient was used to evaluate bivariate correlations.

To evaluate clinical efficacy, the MADRS scores were analysed by a linear mixed-effects model that provides a flexible framework for the analysis of repeated measures. These models treated the outcome score at different times as the dependent variable, the time as the within-subject factor and the treatment group as the between-subjects factor. Moreover, we included as covariate in the analyses the time by treatment interaction term as well as the baseline score to control for potential confounders. An ANOVA analysis has been performed on this model to evaluate the effect of each covariate, in particular to study the role of the variable time. For each time point, the estimated between-groups differences were reported (with 95% confidence intervals). All *p*-values were corrected for multiple comparisons using the false discovery rate (FDR). The analyses of the secondary endpoints, measured by the BDI-II, BAI, PSQI and MINI-ICF-APP scales, were performed for exploratory purposes with the same statistical model. Moreover, as secondary end-points, dominant depression factors were also considered using the three-factor model of the MADRS (Suzuki et al., 2005). This model provides a more detailed description of depression severity because it regroups the symptoms in mood (MADRSF1), cognitive (MADRSF2) and neurovegetative (MADRSF3) dimensions. All analyses were performed with R version 3.1.1 and SPSS version 17.0 (SPSS Inc., Chicago, IL).

3. Results

Twenty-seven TRD patients were screened, of whom 26 fulfilled the inclusion criteria. Four TRD patients have interrupted the psychotherapy (3 EMDR, 1 TF-CBT) for independent causes that led patients to stop the hospitalization at our hospital (1 personal health problems, 2 health problems of relatives, 1 urgent non-deferrable work commitments). Thus, all these patients did not interrupt the psychotherapy for non-adherence reasons. All socio-demographic and clinical characteristics of the TF-CBT and EMDR groups and p-values for the differences are shown in Table 1. The results of the two groups did not diverge for any variables tested except for the administration of SSRIs. Moreover, as shown in Table 2, the two groups were also comparable with respect to symptoms measured with the scales described above, and as shown in Table 3 there were no differences in the results of the traumatic and stressful life events assessment between TRD patients treated with TF-CBT vs. EMDR. In Table 4, the Paykel life event items most frequently reported by TRD patients, as well as the TF-CBT and EMDR subgroups, are shown.

The trauma-focused psychotherapies reduced depression symptomatology as measured with MADRS from baseline to the follow-up visit (T0 = 29.18 ± 7.12; T12 = 11.95 ± 12.32; $F_{3,66} = 40.64$; $p = 5.33\times10^{-15}$), whereas the treatment variable was not statistically significant ($F_{1,22} = 1.91$; $p = 0.18$). The treatment group by timepoint interaction also did not show any significant difference ($F_{3,66} = 1.71$; $p = 0.17$) (Fig. 1). However, MADRS post hoc comparisons showed a significant difference in scores between the two treatment groups ($p_{corrected} = 0.04$; Table 2), with a lower score in the EMDR group than in the TF-CBT group at the follow-up visit (T12: 7.83 ± 10.36 vs. 16.90 ± 13.16).

Considering the MADRS scores using the three-factor model, we obtained that the time variable was statistically significant in all dimensions ($F_{3,66} = 31.78$, $p = 7.89\times10^{-13}$; $F_{3,66} = 37.43$, $p = 3.00\times10^{-14}$; $F_{3,66} = 28.30$, $p = 6.99\times10^{-12}$; respectively). The treatment group did not show any significant difference by timepoint interaction for any dimensions; however, post hoc comparisons revealed a significant difference in scores between the two treatment groups ($p_{corrected} = 0.04$) at T12 for the second factor (Table 2). Indeed, TRD patients treated with EMDR had a decrease of 72.8% in cognitive depressive symptoms, compared to a decrease of 40.9% among the patients treated with TF-CBT. Interestingly, concerning neurovegetative symptoms, we obtained a significant treatment effect ($F_{1,22} = 6.06$; $p = 0.02$), and trend in treatment groups differences in the T12 post hoc comparison ($p_{corrected} = 0.07$) (Fig. 2).

Consistent with the MADRS results, the BDI-II score analysis showed that the trauma-focused interventions reduced depression symptomatology as reported by patients from baseline to the follow-up visit (T0 = 34.50 ± 10.60; T12 = 19.41 ± 15.82; $F_{3,66} = 15.82$; $p = 7.41\times10^{-8}$), whereas the treatment and the treatment group by timepoint interaction were not significant ($F_{1,22} = 2.61$; $p = 0.12$; $F_{3,66} = 2.28$; $p = 0.09$) (Fig. 3). However, BDI-II post hoc comparisons showed a significant difference in scores between the two treatment groups ($p_{corrected} = 0.02$; Table 2), with a lower score in the EMDR group than in the TF-CBT group at the follow-up visit (T12: 26.60 ± 17.30 vs. 13.42 ± 12.13).

In addition, for the other endpoints, the assessed trauma-focused psychotherapies reduced symptomatology from baseline to the follow-up visit, but no other significant effects were obtained. Indeed, the amelioration concerned anxiety symptoms (T0 = 24.50 ± 12.71; T12 = 15.82 ± 13.83; $F_{3,66} = 5.73$; $p = 1.48\times10^{-3}$; 51.3% and 18.9% for the EMDR and TF-CBT groups, respectively), sleep disturbances (T0 = 11.91 ± 3.80; T12 = 8.59 ± 3.62; $F_{3,66} = 7.37$; $p = 2.48\times10^{-4}$; EMDR 33.3% and TF-CBT 21.2%), and social functioning impairment (T0 = 14.91 ± 8.72; T12 = 7.95 ± 6.95; $F_{3,66} = 11.02$; $p = 5.89\times10^{-6}$; EMDR 62.2% and TF-CBT 29.5%).

Comparing the frequencies of the responders and non-responders, the results showed a higher percentage of responders in the EMDR group (83.3% vs. 50%), but this difference was not statistically significant ($z = -1.63$, $p = 0.10$). Instead, when we considered the percentages of symptomatology reduction, a trend effect was observed (ΔMADRS EMDR 71.78% ± 36.20%; ΔMADRS TF-CBT 39.87% ± 43.40%; $z = -1.88$, $p = 0.06$).

Through an unstructured clinical interview, which included questions about admissions in psychiatric hospitals, increases in psychiatric drug therapy, and Likert scale questions, we could identify remission in 50% of patients treated with TF-CBT and 75% of those treated with EMDR. The difference in frequency between the two treatment groups was not significant ($p = 0.22$). The results obtained with a question concerning mood status, which asked the patients to evaluate their mood in that moment on a Likert scale of 0 to 10 where 0 is very bad and 10 is very good, were in agreement with the data regarding remission. Indeed, TRD patients treated with EMDR obtained a higher score than patients treated with TF-CBT, but the difference was not significant (5.67 ± 3.05 vs. 3.40 ± 3.41 respectively; $z = -2.27$, $p = 0.12$).

Correlation analyses on all variables collected showed the following significant effects: a higher BMI in patients who experienced an emotional abuse by father ($p = 0.002$); a positive correlation between the number of life stress events experienced during childhood and the MADRS scores at the baseline ($p = 0.02$), in particular with mood ($p = 0.02$) and neurovegetative symptoms ($p = 0.04$); and a strong negative effect of the presence of psychotic symptoms in MDD episode.

Table 1
Demographic and clinical characteristics of TRD patients treated with TF-CBT and EMDR.

Characteristics	TF-CBT group (N = 10)	EMDR group (N = 12)	p-value
Age (years), mean (SD)	53.3 (6.5)	52.3 (10.7)	0.64[a]
Gender (%F)	60.0	83.3	0.35[b]
Education (years), mean (SD)	13.0 (3.7)	12.7 (3.1)	0.97[a]
% of smokers	50.0	25.0	0.38[b]
Body Mass Index (BMI), mean (SD)	24.9 (2.8)	27.2 (5.4)	0.49[a]
Age of onset (years), mean (SD)	33.8 (15.7)	31.5 (13.2)	0.68[a]
% of presence of psychotic symptoms	30.0	16.7	0.62[b]
% comorbidity with personality disorders	70.0	66.7	1.00[b]
% comorbidity with anxiety disorders	90.0	66.7	0.32[b]
% PTSD	40.0	41.7	1.00[b]
% of psychiatric disorders among the first-degree relatives	100	83.3	0.48[b]
% administration of first-generation antipsychotics	0.0	16.7	0.48[b]
% administration of second-generation antipsychotics	50.0	33.3	0.67[b]
Number of antipsychotics, mean (SD)	0.5 (0.5)	0.5 (0.5)	1.00[a]
% administration of SSRIs	80.0	25.0	**0.03**[b]
% administration of SNRIs	30.0	50.0	0.42[b]
% administration of TCAs	0.0	8.3	1.00[b]
% administration of NaSSAs	50.0	25.0	0.38[b]
% administration of other classes of antidepressants	20.0	25.0	1.00[b]
Number of antidepressants, mean (SD)	1.8 (0.6)	1.4 (0.5)	0.15[a]
% administration of mood stabilizers	50.0	41.7	1.00[b]
Number of mood stabilizers, mean (SD)	0.5 (0.5)	0.5 (0.7)	1.00[a]
% administration of benzodiazepines or hypnotic drugs	100	91.7	1.00[b]
Number of benzodiazepines or hypnotic drugs, mean (SD)	1.8 (0.6)	1.7 (0.9)	0.72[a]

Bold numbers indicate significant p-values (<0.05)
The total number could exceed the number of subjects due to the presence of comorbidities diagnosis and multiple drugs administration
[a] p-values using the Mann–Whitney U test.
[b] p-values using the Fisher's exact two-sided test.

In particular, we found that TRD patients with psychotic symptoms obtained a lower ΔMADRS (p = 0.019) ΔMADRSF1 (p = 0.033), ΔMADRSF2 (p = 0.015), ΔBAI (p = 0.05), Δ MINI-ICF-APP (p = 0.028), and a higher frequency of non-responder (p = 0.02).

4. Discussion

To the best of our knowledge, this study is the first trial of a trauma treatment intervention in patients with TRD. As a primary outcome measure, we found a decrease in depressive symptomatology in TRD patients treated with trauma-focused psychotherapy, with a greater efficacy of EMDR. These findings are in line with data from studies of patients with PTSD showing that both TF-CBT and EMDR are highly efficacious in reducing PTSD symptoms, with comparable effect sizes, but that the benefits of EMDR therapy appear more rapidly (Bradley et al., 2005; Shapiro, 2014).

The association between stressful life events, in particular childhood adversity, and the development of depression has been widely studied. It is also well known that in patients affected by MDD, traumatic experiences represent a risk factor for developing a severe phenotype with a more complex symptomatology and comorbidities that lead to a higher probability of unfavourable pharmacological treatment outcomes (Nelson et al., 2017). Furthermore, many MDD and TRD patients have a PTSD comorbidity, and the problem of underestimated PTSD diagnosis in depression is well documented in the scientific literature (Ashbaugh et al., 2018; Campbell et al., 2007).

Taken together, these results suggest that it is important to assess childhood trauma and stressful life events in the management of depression and to consider alternative or supplemental treatments for patients with a trauma history.

To date, few clinical trials have been carried out to evaluate the efficacy of interventions for traumatic experiences in MDD patients. The efficacy of CBT in the treatment of depression is well documented (Cuijpers et al., 2009, 2013; Minelli et al., 2011; Wiles et al., 2014), but no data are available regarding the specific interventions for traumatic events in depressed patients through TF-CBT. Regarding EMDR, an initial study by Hofmann and collaborators revealed a significant difference in the decrease in depressive symptoms between a group of MDD patients treated with CBT with adjunctive EMDR treatment and another group treated with a similar number of CBT sessions alone. More recently, in two studies of Hase et al.(2015, 2018), MDD patients treated with EMDR in conjunction to TAU showed a greater reduction in

Table 2
Mean (95% CI) differences between TF-CBT and EMDR groups at any timepoints (T0, T4, T8, T12) for all scales and subscales.

	Differences between groups											
	Baseline			4 weeks			8 weeks			12 weeks		
	Coefficient	(CI 95%)	p	Coefficient	(CI 95%)	p	Coefficient	(CI 95%)	p	Coefficient	(CI 95%)	p
MADRS	−1,04	(−7.75, 5.66)	0,97	−2,31	(−9.01, 4.40)	0,97	0,11	(−6.81, 6.60)	0,97	−8,79	(−15.50, -2.09)	**0,04**
BAI	−1,00	(−9.36, 7.35)	0,81	−2,10	(−10.46, 6.25)	0,81	−3,44	(−11.79, 4.92)	0,81	−7,75	(−16.11, 0.60)	0,28
BDI	0,42	(−8.83, 9.66)	0,93	−1,95	(−11.20, 7.30)	0,91	−5,47	(−14.71, 3.78)	0,49	−13,50	(−22.75, -4.25)	**0,02**
MADRSF1	−0,45	(−2.73, 1.83)	0,70	0,52	(−1.76, 2.80)	0,70	1,32	(−0.97, 3.60)	0,51	−1,73	(−4.01, 0.55)	0,51
MADRSF2	0,33	(−2.98, 3.65)	0,84	−1,00	(−4.32, 2.31)	0,84	0,45	(−2.87, 3.76)	0,84	−4,32	(−7.63, -1.00)	**0,04**
MADRSF3	−0,30	(−2.06, 1.46)	0,74	−1,20	(−2.96, 0.56)	0,33	−1,03	(−2.79, 0.73)	0,33	−2,12	(−3.88, -0.36)	0,07
MINI-ICF-APP	−0,88	(−5.54, 3.79)	0,71	−2,94	(−7.61, 1.72)	0,43	−0,96	(−5.63, 3.71)	0,71	−5,19	(−9.86, -0.53)	0,12
PSQI	0,10	(−2.49, 2.68)	0,94	−1,19	(−3.77, 1.40)	0,49	−2,65	(−5.24, −0.07)	0,18	−1,40	(−3.99, 1.18)	0,49

Bold numbers indicate significant p-values (<0.05). All p-values were corrected for multiple comparisons using FDR.

Table 3
Traumatic and event stressful life events assessment results of TRD patients treated with TF-CBT and EMDR.

Characteristics	TF-CBT group (*N* = 10)	EMDR group (*N* = 12)	*p*-value
Trauma CECA-Q: %Mother antipathy (hostility, coldness.)	90.0	66.7	0.32[b]
Trauma CECA-Q: %Father antipathy (hostility, coldness.)	0.0	25.0	0.22[b]
Trauma CECA-Q: %Mother neglect	70.0	50.0	0.41[b]
Trauma CECA-Q: %Father neglect	60.0	75.0	0.65[b]
Trauma CECA-Q: %Physical abuse mother	50.0	25.0	0.38[b]
Trauma CECA-Q: %Physical abuse father	10.0	16.7	1.00[b]
Trauma CECA-Q: %Sexual abuse	40.0	58.3	0.67[b]
N° of childhood stressful life events[c], mean (SD)	3.7 (2.3)	3.5 (1.7)	1.00[a]
N° of adult stressful life events[c], mean (SD)	5.6 (2.0)	4.5 (1.2)	0.13[a]
Normative value of event, Paykel score, means (SD)	56.1 (36.2)	55.5 (29.9)	0.82[a]
Normative value of event, Holmes score, means (SD)	217.9 (131.2)	196.2 (98.3)	0.66[a]

[a] *p*-values using the Mann–Whitney U test.
[b] *p*-values using the Fisher's exact two-sided test.
[c] Stressful life events considerate: Sexual abuse, physical abuse, emotional abuse, emotional and physical neglect, death of a close family member, divorce, marital separation, personal injury or severe illness, dismissal from work, injury or illness of a close family member, miscarriage, abortion.

depressive symptoms than did patients in a control group treated with TAU alone showing that EMDR therapy may provide additional benefit in the treatment of depression. Finally, Ostacoli et al. (2018) performed the first randomized controlled trial to evaluate the efficacy of EMDR in comparison with CBT in MDD patients and reported that both interventions were effective in reducing clinical levels of depression, with a significant difference in favour of EMDR treatment at the end of the intervention phase. However, only our study has tested their efficacy in comparison to the efficacy of TF-CBT, considering that this intervention alone is comparable to EMDR in the treatment of traumatic experiences, as demonstrated by several studies and meta-analyses (Ehring et al., 2014). Furthermore, no study has focused on TRD patients, who, with their long history of depression, unfavourable pharmacological treatment outcomes, severe symptoms and frequent suicidal ideation, represent subjects with a high need for safe and efficacious new interventions.

The most significant result highlighted by our study is that EMDR was shown to be as effective as TF-CBT in reducing depression symptoms in TRD patients during hospitalization; however, at the follow-up visit, only EMDR maintained this amelioration, as measured both with MADRS and with BDI, revealing that there is complete agreement between the clinicians' and patients' perspectives. In addition, the same pattern of results was obtained when we analysed the mood, cognitive and neurovegetative symptoms separately, but interestingly, for neurovegetative symptoms, we obtained a treatment effect in favour of EMDR, which also supports the well-documented effect of EMDR in the reduction of hyperarousal activation among severe TRD patients (Pagani et al., 2017).

With regard to the secondary outcome of the study, both treatments were effective in reducing anxiety symptoms, sleep disturbances and psychosocial functioning impairments. This last result is particularly important because of the increasing awareness that the real goal in the treatment of depression is a full symptomatic and functional recovery (Habert et al., 2016; Oluboka et al., 2018). The achievement of both symptom remission and full functional recovery after trials of antidepressant treatments is even more difficult (Soares et al., 2014), and functional recovery can lag behind symptom remission (Oluboka et al., 2018). This condition is particularly relevant in TRD patients. Therefore, successful management of MDD necessitates the development of a personalized treatment plan that allows individual patients to achieve full functional recovery in the most effective and efficient manner (McIntyre et al., 2015). Thus, our study supports the hypothesis that stressful events, in particular childhood maltreatment, can be promising targets for innovative interventions offered specifically for MDD patients with a trauma history. Indeed, our data showed that trauma-focused psychotherapy, particularly EMDR when a more rapid response is necessary, could represent a new challenge in the clinical practice setting.

Finally, EMDR exceeded CBT in terms of the proportion of patients who could be considered to be responders and in remission after the interventions, but no significant effects were obtained.

Some limitations have to be addressed for the present study. The first is that this study represents a pilot trial, and the small sample size might have influenced the results. Furthermore, the trial should include further follow-up visits with the same assessment scales. Because TRD patients arrive at our hospital from all parts of the national territory, it is difficult to carry out personal visits, and we decided to carry out one visit 24 weeks after the beginning of the protocol and a clinical interview by phone because of the various limitations. Consequently, we recommend that the results be replicated in larger studies and that a longer follow-up should be included to clarify possible long-term effects. A further limitation is represented by the lack of the evaluation at the different time-points of PTSD symptoms. Indeed, our primary outcome measure was depression, however, a significant proportion of participants in this study had a PTSD as comorbid diagnosis. PTSD symptom changes during treatment could add valuable information on possible underlying mechanisms of trauma-focused treatment in TRD, as it is possible that positive changes in depression symptoms in trauma-focused treatment were mediated by decrease of PTSD symptoms. An additional limitation is that the TF-CBT group had more SSRI

Table 4
Paykel life event items most frequently reported by TRD patients, as well as the TF-CBT and EMDR subgroups.

Paykel Scale item	All TRD patients (%)	TF-CBT group (*N* = 10) (%)	EMDR group (*N* = 12) (%)
41, Change in work conditions	45.5	50.0	41.7
26, Increased arguments with family member	40.9	50.0	33.3
54, Minor personal illness	31.8	20.0	41.7
6, Major financial difficulties	27.3	20.0	33.3
31, Argument with non-resident family member	27.3	40.0	16.7
18, Major personal illness	22.7	30.0	16.7
25, Increased arguments with spouse	22.7	20.0	25.0

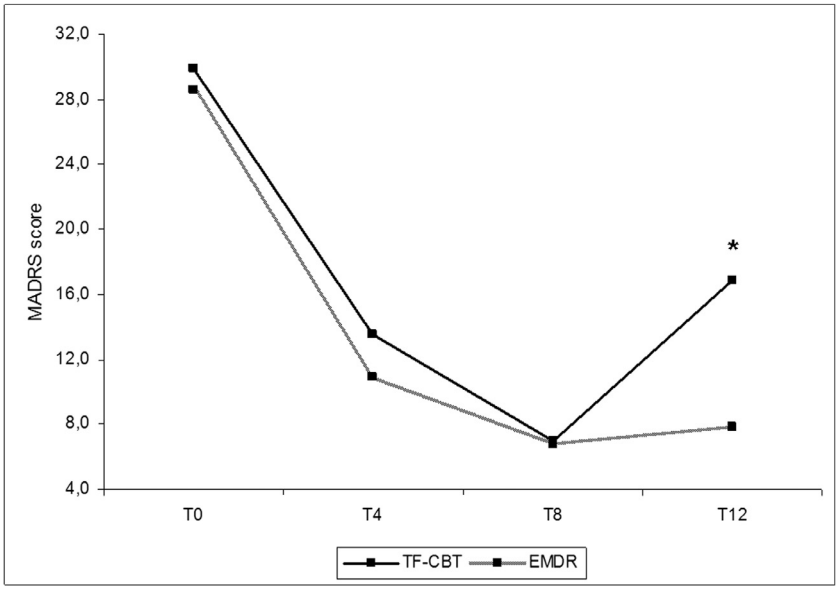

Fig. 1. Evolution of MADRS scores assessed at baseline (T0), at the middle of the interventions (T4), at the end (T8) and at the follow-up visit (T12) for the EMDR and TF-CBT groups.
Legend Fig. 1: Time Effect $F_{3,66} = 40.64$; $p = 5.33 \times 10^{-15}$; Treatment Effect $F_{1,22} = 1.91$; $p = 0.18$; Time x Treatment Effect $F_{3,66} = 1.71$; $p = 0.17$; Asterisk indicates significant post-hoc p-values (< 0.05).

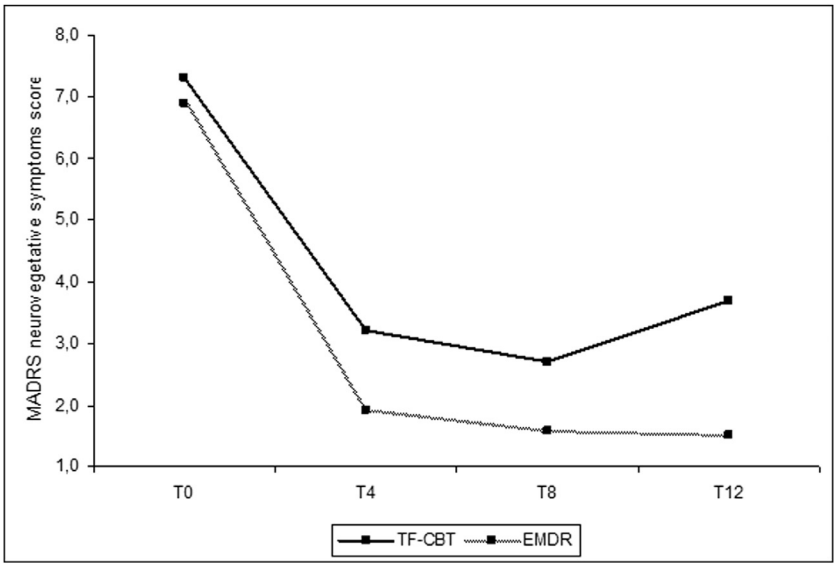

Fig. 2. Evolution of MADRS F3 (neurovegetative symptoms) scores assessed at baseline (T0), at the middle of the interventions (T4), at the end (T8) and at the follow-up visit (T12) for the EMDR and TF-CBT groups.
Legend Fig. 2: Time Effect $F_{3,66} = 28.30$; $p = 6.99 \times 10^{-12}$; Treatment Effect $F_{1,22} = 6.06$; $p = 0.02$; Time x Treatment Effect $F_{3,66} = 0.72$; $p = 0.55$.

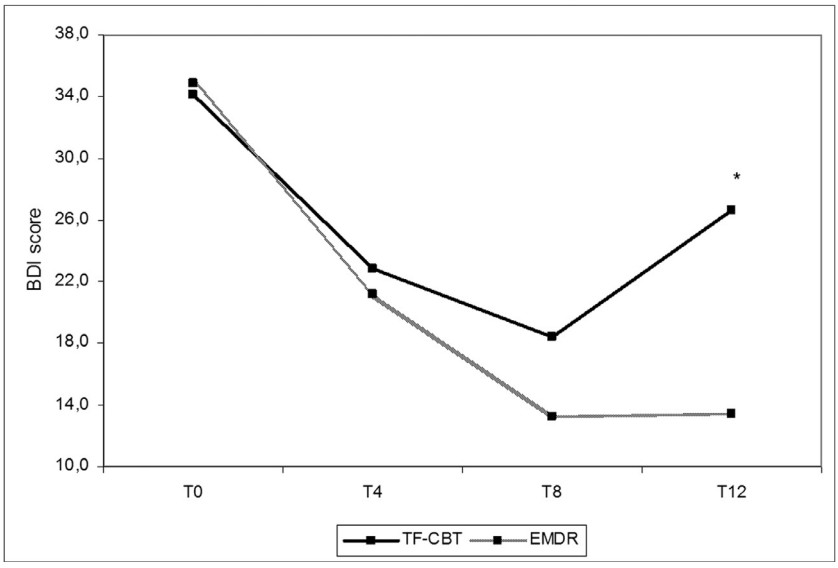

Fig. 3. Evolution of BDI scores assessed at baseline (T0), at the middle of the interventions (T4), at the end (T8) and at the follow-up visit (T12) for the EMDR and TF-CBT groups.
Legend Fig. 3: Time Effect $F_{3,66} = 15.82$; $p = 7.41 \times 10^{-8}$; Treatment Effect $F_{1,22} = 2.61$; $p = 0.12$; Time x Treatment Effect $F_{3,66} = 2.28$; $p = 0.09$; Asterisk indicates significant post-hoc p-values (< 0.05).

use during the trial compared to EMDR subjects, however we can suppose no influence on results since we did not obtain any significant effect in correlation with this variable. Moreover, because of all patients had a complex poly-pharmacological treatment with multiple interactions, it is not possible to identify the effect of single compounds. Furthermore, there is no statistical difference regarding the number of antidepressant drugs between the two groups. Additionally, to date there is no clear evidence regarding how psychiatric drug medications can affect the effectiveness of psychotherapy. The available data on this issue indicate a negative influence only concerning the concomitant use of benzodiazepines or sedative hypnotics, as shown in a recent study that reported a reduction of the efficacy of exposure therapy in PTSD patients (Rosen et al., 2013). This agrees with the well-known negative effect of benzodiazepines that impair the ability to encode new information (Sperling et al., 2002), that is a fundamental process in any kind of psychotherapy. Finally, another limitation is represented by the absence of a control group, however we selected TRD patients with a long history of illness, that have already had several psychiatric hospitalizations where they received several drug medications alone or in augmentation with other inpatient therapy setting such as occupational therapies, psychotherapies not focused on trauma, and/or somatic therapies. Consequently, we need to provide new therapeutic solution.

In conclusion, despite these limitations, this study provides a 'proof of principle' that TRD patients benefit from a treatment with evidence-based trauma-focused psychotherapies, such as EMDR and TF-CBT, with a greater and more persistent amelioration in symptomatology after the EMDR intervention. The DSM-5 states unequivocally that adverse childhood experiences, particularly when there are multiple experiences of diverse types, constitute a set of potent risk factors for MDD, and several studies showed the association to chronic and severe depression. To invest in preventing or reducing adverse experiences particularly during childhood as well as addressing the resulting trauma can help reduce future health service demand and costs.

Conflict of interest

This research was partly funded by a grant from the EMDR Europe Research Foundation; PI of the project was Minelli Alessandra. The EMDR Europe Research Foundation had no involvement in the design or conduct of the trial or in the production of this report. The other authors declare no conflicts of interest.

Acknowledgement

We would like to express our sincere gratitude to all volunteers who participated in the study. We thank all the staff of Santa Chiara Psychiatric hospital.

Role of the founding source

This research was supported by grants from the University of Brescia (Project "REFRACT", Principal Investigator Prof. Massimo Gennarelli). This research was also partly funded by a grant from the EMDR Europe Research Foundation (Project "Eye Movement Desensitization and Reprocessing (EMDR) therapy in Treatment Resistant Depression (TRD) in-patients: clinical and biomarkers efficacy", Principal Investigator Dr. Alessandra Minelli).

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