Schizophrenia Research 176 (2016) 239–244

Contents lists available at ScienceDirect

Schizophrenia Research

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

Predicting trauma-focused treatment outcome in psychosis

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ARTICLE INFO

Article history:
Received 31 March 2016
Received in revised form 8 June 2016
Accepted 17 July 2016
Available online 21 July 2016

Keywords:
PTSD
Prolonged exposure
Eye movement desensitization and reprocessing
Prediction

ABSTRACT

Objective: Although TF treatments are effective in patients with psychosis, it is unknown whether specific psychosis-related obstacles limit the effects, and what determines good outcome.
Methods: Baseline posttraumatic stress disorder (PTSD) symptom severity and seven psychosis-specific variables were tested as predictors in patients with a psychotic disorder *and* PTSD ($n = 108$), who received eight sessions of TF treatment (Prolonged Exposure, or Eye Movement Desensitization and Reprocessing therapy) in a single-blind randomized controlled trial. Multiple regression analyses were performed.
Results: Baseline PTSD symptom severity was significantly associated with posttreatment PTSD symptom severity, explaining 11.4% of the variance. Additionally, more severe PTSD at baseline was also significantly associated with greater PTSD symptom improvement during treatment. After correction for baseline PTSD symptom severity, the model with the seven baseline variables did not significantly explain the variance in posttreatment PTSD outcome. Within this non-significant model, the presence of auditory verbal hallucinations contributed uniquely to posttreatment outcome but explained little variance (5.4%). Treatment completers and dropouts showed no significant difference on any of the psychosis-related variables.
Conclusions: Given the low predictive utility of baseline psychosis-related factors, we conclude that there is no evidence-based reason to exclude patients with psychotic disorders from TF treatments. Also, we speculate that patients with psychosis and severe baseline PTSD might derive more benefit if given more than eight sessions.
Trial registration current controlled-trials.com | Identifier: ISRCTN79584912 | http://www.isrctn.com/ISRCTN79584912

1. Introduction

Childhood adversities and comorbid posttraumatic stress disorder (PTSD) are common in psychosis (Achim et al., 2011; de Bont et al., 2015; Matheson et al., 2013), but are often underdiagnosed and undertreated (de Bont et al., 2015; Lommen and Restifo, 2009). A recent randomized controlled trial (RCT) found TF treatments, prolonged exposure (PE) and eye movement desensitization and reprocessing (EMDR) therapy to be effective and safe in patients with long-standing psychotic disorders (van den Berg et al., 2015). Similarly, cognitive restructuring was found to be effective in two controlled trials with

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http://dx.doi.org/10.1016/j.schres.2016.07.016
0920-9964/

patients suffering from severe mental illnesses of which a subgroup had a psychotic disorder (Mueser et al., 2015; Mueser et al., 2008). Interestingly, despite the presence of a severe psychiatric disorder, the outcomes and dropout rates in these TF treatment studies were similar to studies with general PTSD samples (Bradley et al., 2005; Hembree et al., 2003).

Based on the above results, it seems that meeting the criteria for a psychotic disorder does not necessarily predict poor TF treatment outcome. However, it remains unclear which factors influence TF treatment outcome in this subgroup of individuals with psychosis and whether specific obstacles need to be taken into account when initiating treatment. It is important to identify these factors in order to disseminate effective TF treatments in psychosis. This information may also elucidate whether it's necessary to adapt TF treatment protocols in this patient group to improve effects and reduce the likelihood of dropout.

Of the many studies examining the potential predictors of TF treatment outcome, most focused on PE, cognitive reprocessing, or other cognitive behavioral therapies. However, the results have not been consistent, e.g. some predictors were found in one study but not others, and vice versa. Consequently, despite the large number of studies on this topic, no robust predictors of TF treatment outcome have been detected, with the exception of baseline severity of PTSD symptoms. Greater baseline PTSD symptom severity has repeatedly predicted greater posttreatment PTSD symptom severity (Blanchard et al., 2003; Hembree et al., 2004; Moser et al., 2010; Popiel and Zawadzki, 2013; Taylor, 2003; van Emmerik et al., 2011; van Minnen et al., 2002). Interestingly, greater baseline PTSD severity was also found to be associated with greater improvements by some (Elliott et al., 2005; Foa et al., 1995; Forbes et al., 2003; Karatzias et al., 2007; Rizvi et al., 2009; Thrasher et al., 2010), although this was not found by others (de Kleine et al., 2014; Speckens et al., 2006). Part of the larger improvements may be explained by regression to the mean. Nevertheless, the broader picture appears to be that patients with high baseline PTSD symptom severity do benefit (perhaps even more than patients with lower scores) from TF treatment with regard to symptom reduction, but their posttreatment end state is still relatively high compared to patients with lower baseline scores.

The present study aimed to determine the predictive value of several baseline factors that characterize patients with a psychotic disorder, that could be expected to influence TF treatment outcome or dropout. Because researchers and clinicians tend to exclude patients with psychotic disorders from effective TF treatments (Becker et al., 2004; Meyer et al., 2014; Ronconi et al., 2014), it is important to test the validity of this assumption. Because the common denominator for excluding patients from treatment is the presence of psychotic symptoms, we included the most important symptom clusters of psychosis, i.e. *paranoia, auditory verbal hallucinations,* and *negative symptoms* as potential predictor variables.

Exclusion of patients with psychotic disorders from TF treatments is likely to be influenced by the fear that these treatments will destabilize patients or exacerbate symptoms and induce suicidal tendencies or other adverse events (Becker et al., 2004; Foa et al., 2013; Gairns et al., 2015). In contrast with these beliefs, in the parent trial of the current study, TF treatment was found to reduce symptom exacerbation and adversities, such as self-harm or psychiatric hospitalization (van den Berg et al., 2016). However, because it remains unclear to what extent the presence of markers of instability at baseline, such as *suicide risk* or *the presence of recent adversities*, affect treatment outcome, we included these potential predictor variables.

Besides symptoms of psychosis and instability factors that are associated with this patient group, we selected two additional factors that are highly prevalent in these patients and are expected to interfere with the ability to benefit from TF treatment, i.e. working memory difficulties, and antipsychotic medication. Working memory problems are common in patients with psychosis (Forbes et al., 2009; Lee and Park, 2005) and the presence of cognitive functioning problems is one of the reasons why clinicians tend to exclude patients from TF treatment (Salyers et al., 2004). We selected this specific cognitive factor, since *working memory capacity* is also associated with TF treatment effects (Gunter and Bodner, 2008; van den Hout et al., 2010; van den Hout et al., 2011). The majority of patients with psychotic disorders use antipsychotic medications, which are associated with many side-effects, e.g. (Young et al., 2015). Moreover, some of these side-effects, e.g. sedation, emotional numbing, and reduced speed of processing (Faber et al., 2012; Moncrieff et al., 2009; Moritz et al., 2013; Saeedi et al., 2006), may undermine the possibility of patients to benefit from TF treatment, e.g. by interfering with the ability to follow treatment procedures, or difficulty to activate the 'fear structure' (Rauch and Foa, 2006). Indeed, the use of psychotropic medication in a sample of veterans was found to be associated with less PTSD symptom reduction during TF treatment (Goodson et al., 2013). Therefore, we included *chlorpromazine hydrochloride dose equivalents* as a potential predictor.

In the present sample of patients, with both psychotic disorder and posttraumatic stress disorder, we first tested the hypothesis that, also in the current sample, baseline posttraumatic stress disorder severity would significantly predict TF treatment outcome. Secondly, we tested the hypothesis that psychosis-specific baseline factors (paranoia, auditory verbal hallucinations, negative symptoms, suicide risk, recent adversities, working memory, and antipsychotic medication) would add unique variance beyond that already explained by baseline posttraumatic stress disorder severity. We also tested the hypothesis that treatment completers and dropouts would differ on these variables at baseline.

2. Experimental materials and methods

2.1. Participants

Participants were 108 patients with a psychotic disorder and PTSD who were allocated to TF treatment (PE or EMDR therapy) in a recently published multicenter single-blind RCT investigating TF treatments in psychosis (van den Berg et al., 2015). The participants were characterized by long-standing psychotic disorders (mean duration = 18.5, SD = 12.5 years). The MINI-International Neuropsychiatric Interview-Plus (Sheehan et al., 1997) DSM-IV-TR diagnoses for the sample were: 60.2% schizophrenia, 29.6% schizoaffective disorder, 3.7% bipolar disorder with psychotic features, 3.7% psychotic disorder not otherwise specified, and 2.8% depression with psychotic features. The mean age of the current sample was 41.5 (10.8) years and 44.4% was male. Most participants had experienced repeated and severe childhood trauma (van den Berg et al., 2015). All participants met the full criteria for chronic PTSD on the Clinician-Administered PTSD Scale (CAPS) (Blake et al., 1995). Complete details of the study procedure are available elsewhere (de Bont et al., 2013; van den Berg et al., 2015).

2.2. Procedure

Both PTSD symptom severity and the other potential predictor variables were assessed at baseline. PTSD symptom severity was also assessed posttreatment. There were 24 treatment dropouts: 9 never started and 15 dropped-out during treatment (van den Berg et al., 2015). The prediction of posttreatment outcome was performed on the intention-to-treat sample of participants with posttreatment data ($n = 91$). Analyses regarding dropout were performed on the total sample ($n = 108$). The study design was approved by the Medical Ethics Committee of the VU University Medical Center (NL:36,649.029.12).

2.3. Treatment

TF treatment consisted of eight weekly 90-min sessions of either PE or EMDR therapy (Foa et al., 2007; Shapiro, 2001). The first session comprised psycho-education about PTSD and the development of a hierarchy of the most intrusive trauma memories. The active TF treatment

started in the second session. No psychotherapeutic stabilization or skills training was applied, and standard PE and EMDR therapy protocols were used. Participants received treatment as usual for psychosis, delivered by multidisciplinary assertive outreach teams.

2.4. Assessments

Baseline values for the potential predictor variables are presented in Table 1. More specific details of the psychometric properties of the tests applied are described elsewhere (de Bont et al., 2013). Outcome was measured with the CAPS (Blake et al., 1995), which provides a symptom severity score based on frequency (0–4) and intensity ratings (0–4) of each of the 17 DSM-IV-TR PTSD criteria, resulting in a total score (range 0–136) with higher scores reflecting more severe symptoms. The CAPS was administered at baseline and at posttreatment. Each participant that terminated therapy, while not meeting criteria for early completion, was considered to be a dropout (van den Berg et al., 2015).

The following seven independent (potential predictor) variables were included: 1) Severity of paranoid ideation was measured with the Green et al. Paranoid Thought Scales (GPTS, range 32–160) (Green et al., 2008), with higher score representing more severe paranoid ideation. 2) Presence of auditory verbal hallucinations at least once per week was assessed with the Auditory Hallucination Rating Scale (Haddock et al., 1999). This variable was dichotomized after failure to normalize it through transformation (due to an excess of zeros). 3) Presence of negative symptoms of psychosis was defined as at least two scores of 3 (at least mildly present) or one score of 4 (present at a clinical level) on one of the three negative symptom items (blunted affect, passive social withdrawal, lack of spontaneity) in the Structured Clinical Interview for Symptoms of Remission for the PANSS (Andreasen et al., 2005). This dichotomization was performed since it is not a continuous scale. 4) Presence of moderate to high suicide risk was determined with the 8-item suicidal ideation section of the MINI-International Neuropsychiatric Interview-Plus (MINI-Plus) (Sheehan et al., 1998). 5) Presence of recent adversities (defined as at least 1 adversity in the preceding month) was assessed by self-report into seven types of adversities: self-harm, suicide attempt, aggressive behavior, problematic alcohol use, problematic drug use, crisis contact with mental healthcare, and psychiatric hospitalization. 6) The working memory capacity index was defined as the deceleration in reaction time in the distraction condition on the computerized auditory Random Interval Repetition task compared to the no-distraction condition (de Bont et al., 2013). In that way higher scores reflect less working memory capacity. There were 9 missing in this variable (the 9 participants that never started treatment) which were replaced with the median score. The working memory capacity index was positively skewed, which was successfully corrected with square root transformation. 7) In this sample 91 participants (84.3%) were receiving antipsychotic medication. Chlorpromazine hydrochloride dose equivalents were based on the dosages of antipsychotic medications reported in the patient files. This variable also exhibited positive skew and could successfully be corrected with square root transformation.

2.5. Statistical analysis

All analyses were performed with SPSS 23 (IBM SPSS) and according to the intention-to-treat principle. In order to create a sample size in which prediction is feasible, we pooled the data from the participants allocated to PE and to EMDR therapy. This was done because no significant differences in treatment outcome and dropout were found between these two TF treatments (van den Berg et al., 2015), and because there are no theoretical reasons to assume that the potential effects of the selected baseline variables would differ between PE and EMDR therapy.

To test whether severity of baseline PTSD symptoms was associated with outcome in the current sample, we regressed baseline CAPS scores on posttreatment CAPS scores and, secondly, on the net PTSD symptom change scores.

Residual gain score was used as criterion variable to test the predictive value of the other seven independent baseline variables over and above baseline PTSD severity (Steketee and Chambless, 1992). Residual gain score is the post-assessment score minus the expected gain on the basis of the regression of the baseline score on the posttreatment score. Therefore, residual gain score reflects change in symptoms over treatment, adjusted for the information that is linearly predicted from the baseline score (DuBois, 1957). In this way, a higher residual gain score reflects less reduction of PTSD symptoms than expected on the basis of the baseline score.

Because overfitting regression models negatively influences the generalizability of study results (Babyak, 2004), several rules of thumb for the number of cases per predictor in regression analyses have been suggested to safeguard against overfitting. The most commonly used rule is to include at least 10 subjects per predictor (Austin and Steyerberg, 2015; Harrell, 2001). In logistic regression analysis, similar rules of thumb have been suggested, e.g. 10 subjects in the smallest group per predictor (Peduzzi et al., 1996; Vittinghoff and McCulloch, 2007). Therefore, in predicting outcome, we minimized the number of potential predictors to seven (resulting in a ratio of 1/13) and used a standard linear multiple regression model (Babyak, 2004). In this model all seven independent variables were included in one model to predict the residual gain score for posttreatment. This allows to test the predictive value of the independent variables combined, and the unique contribution for each of the potential predictor variables. To ensure generalizability of our results, we reported the adjusted R^2. The residual gain scores (baseline to posttreatment) were normally distributed and all other assumptions for linear regression analysis were met.

Since there were only 24 dropouts we could not perform multiple logistic regression analyses with more than two independent variables to predict dropout. Consequently, we used independent samples t-tests and Chi-square tests to determine whether treatment completers and dropouts significantly differed on any of the baseline variables. Correcting for multiple testing should depend on the relative chance and importance of type I and type II error for that specific situation (Cabin and Mitchell, 2000). With eight comparisons (baseline PTSD symptom severity was also included as a potential predictor of dropout)

Table 1
Baseline values[a] for the independent variables.

Baseline variable	Total sample ($n = 108$)	Treatment completers ($n = 84$)	Treatment dropouts ($n = 24$)	p-Value[b]
PTSD symptom severity, mean (SD)	70.8 (16.3)	70.7 (15.5)	71.5 (19.3)	0.833
Severity of paranoid ideation, mean (SD)	85.7 (33.6)	81.4 (32.1)	100.4 (35.0)	0.014
Presence of auditory verbal hallucinations, No. (%)	45 (41.7)	36 (42.9)	9 (37.5)	0.814
Presence of negative symptoms, No. (%)	55 (50.9)	39 (46.4)	16 (66.7)	0.129
Presence of moderate to high suicide risk, No. (%)	50 (46.3)	36 (42.9)	14 (58.3)	0.267
Presence of recent adversities, No. (%)	34 (31.5)	25 (29.8)	9 (37.5)	0.638
Working memory capacity index, mean (SD)	86.5 (71.4)	85.3 (75.6)	90.9 (55.3)	0.516
Chlorpromazine hydrochloride dose equivalent, mean (SD)	240.4 (221.3)	253.8 (224.1)	193.9 (208.9)	0.117

[a] Observed untransformed values.
[b] p-Values for the independent samples t-tests and Chi-square tests for completers versus dropouts. Alpha = 0.006 after Bonferroni adjustment for multiple testing.

and one group with only 24 subjects, we considered it necessary to perform a Bonferroni adjustment for multiple testing to reduce type I error, resulting in an alpha = 0.006.

3. Results

3.1. Baseline PTSD symptom severity

Higher baseline PTSD symptom severity score was significantly associated with higher posttreatment PTSD severity score ($p < 0.001$), explaining 11.4% of the variance. Also, greater baseline PTSD severity was related to greater net reductions in PTSD symptoms at posttreatment ($p = 0.015$), explaining 6.5% of the variance.

3.2. Predicting posttreatment outcome

The multiple regression model with all 7 independent variables was not significant ($F[7, 83] = 1.89$, $p = 0.080$), indicating that these baseline factors did not explain variance in posttreatment PTSD outcome. Within this non-significant model, only the presence of auditory verbal hallucinations (beta = 0.25, $p = 0.025$) contributed uniquely to the variability in residual gain score, explaining 5.4% of the variance (Table 2).

3.3. Baseline differences between treatment completers and treatment dropouts

Treatment completers and dropouts did not differ significantly on any of the baseline variables (Table 1).

4. Discussion

We tested whether baseline PTSD severity and several psychosis-specific variables would predict TF treatment outcome in patients with both psychotic disorder and PTSD. In this sample, baseline PTSD symptom severity was found to predict a small proportion in treatment outcome. This is in line with the fact that, until now, baseline PTSD severity is the most robust predictor of posttreatment PTSD severity. Specifically, and similar to an earlier report (Elliott et al., 2005), the results of the current sample show that participants with more severe PTSD symptoms at baseline exhibited higher posttreatment PTSD symptom severity end state, but also showed a greater reduction in PTSD symptoms; however, the latter may have been influenced by regression to the mean. Taken together, these findings suggest that a significant proportion of the severely traumatized participants in our sample with high baseline PTSD severity responded well, but derived insufficient benefit from only eight sessions of TF treatment (i.e. the maximum treatment dosage in this study). Others found that adding extra treatment sessions enhanced treatment outcomes for patients who did not improve (sufficiently) after a standard dosage (Foa et al., 2005). Therefore, future studies should test the beneficial effects of a greater number of treatment sessions for this often severely traumatized population.

Table 2
Results of standard multiple regression analyses predicting treatment outcome ($n = 91$)[a].

Baseline variable	Beta[b]	*p*-Value	Part[c]
Severity of paranoid ideation, mean (SD)	0.047	0.680	0.042
Presence of auditory verbal hallucinations, no. (%)	0.250	0.025	0.233
Presence of negative symptoms, no. (%)	0.194	0.076	0.183
Presence of moderate to high suicide risk, no. (%)	0.018	0.875	0.016
Presence of recent adversities, no. (%)	0.006	0.952	0.006
Working memory capacity index, mean (SD)	0.099	0.342	0.097
Chlorpromazine hydrochloride dose equivalent, mean (SD)	0.037	0.729	0.035

[a] Dependent variable: Residual gain score.
[b] Standardized coefficients.
[c] Semipartial correlation coefficients.

Besides the modest predictive value of baseline PTSD severity, we found few associations. After correction for baseline PTSD severity, the seven psychosis-specific baseline variables did not explain variance in posttreatment PTSD outcome. Within this non-significant model, only the presence of auditory verbal hallucinations contributed uniquely to posttreatment outcome over and above baseline PTSD symptom severity; however, this factor has limited prognostic value as it explained only 5.4% of the variance in PTSD symptom severity change. This finding indicates that TF treatment was, on average, still effective in participants with auditory verbal hallucinations. However, when TF treatment remains insufficiently effective in voice hearers (also after adding extra sessions), TF treatment may be combined with cognitive behavioral therapy for auditory verbal hallucinations (van der Gaag et al., 2014).

No significant baseline differences were found between treatment completers and dropouts. We corrected for multiple testing to prevent type I error, which may have increased chance of type II error. However, without Bonferroni adjustment, the treatment completers and dropouts differed only in baseline paranoid ideations, with higher mean paranoia scores for the dropouts. Therefore, future studies could test whether or not paranoid ideations influence the odds of dropping out of TF treatment. However, it is reported that delusion conviction and positive psychotic symptoms do not predict dropout in cognitive behavior therapy for psychosis, whereas lack of insight does (Lincoln et al., 2014). In our opinion, lack of insight appears to be less of an issue in PTSD. All participants in the current study appeared to recognize that they had been traumatized and that, as a result, they were suffering from PTSD. However, more severe paranoid ideation may influence the therapeutic alliance and, hence, commitment to therapy (Wittorf et al., 2009). In case of severe paranoid ideation the therapeutic alliance may therefore receive extra attention; however, it is good to note that also highly paranoid patients can apparently benefit from TF treatment. Future studies may test the influence of lack of insight on outcome. These may also test the influence of the duration of (untreated) symptoms, since this factor has been found to influence long term outcome in psychosis (Penttilä et al., 2014).

In patients with psychosis, baseline markers of instability (suicidal ideation and recent adversities) do not appear to influence TF treatment outcome or dropout. This is at odds with the custom to exclude patients with psychotic disorders from TF treatments (Becker et al., 2004; Meyer et al., 2014; Ronconi et al., 2014), and also with the belief that stabilization is a prerequisite in patients who experienced severe childhood trauma (as did the majority of participants in the present sample) (Cloitre et al., 2012; De Jongh et al., 2016). This is emphasized by the observation that TF treatment appeared to have a stabilizing effect on the patients with psychosis in the parent trial of this study, in that the application of TF treatment was associated with less adversities and less symptom exacerbation among participants (van den Berg et al., 2016).

In the present sample, both working memory capacity and chlorpromazine hydrochloride dose equivalents were unrelated to treatment outcome and dropout. Apparently these factors do not influence the ability of patients with psychosis to undergo and endure TF treatment. Conversely, since PTSD is also associated with working memory problems (Polak et al., 2012; Schweizer and Dalgleish, 2011), effectively treating PTSD may improve this executive function in patients with both a psychotic disorder and PTSD; future studies should test this hypothesis. Similarly, it was found that patients with severe mental illness who experienced childhood trauma use more psychotropic medication than those without these experiences (Schneeberger et al., 2014). The experience of childhood trauma and other distressing life events were also found to be associated with less response to medications (Hassan and De Luca, 2015). Therefore, also here, the effect may be reversed. Effective TF treatment may reduce the need for high dosages of medication on the long term, but this idea also needs testing in future studies.

The present study has several limitations. As in most prediction studies, our sample size was limited thereby forcing us to restrict the number of potential predictor variables to be tested. Secondly, because

we pooled the data from patients receiving two different TF treatments (PE and EMDR therapy) we cannot rule out that there may be subtle differences in predictors for the two treatments separately. The strength of this study is that, to our knowledge, it is the first to examine baseline predictors of TF treatment outcome and dropout in patients with psychosis. Moreover, we reduced the risk of type I error, which lowers the chance of finding sample-specific predictors that have no prognostic value in other samples. However, replication of these findings is warranted. Future studies could also focus on identifying possible mediators of treatment outcome.

We conclude that, in patients with long-standing psychotic disorders, baseline psychosis-specific factors have little value in predicting treatment outcome and dropout in TF treatment. The current data support the notion that it is not justified to use pretreatment characteristics to exclude patients with psychotic disorders and comorbid PTSD from evidence-based TF treatment. Also, it appears that eight sessions are too few for many patients with very high baseline PTSD symptom severity. Offering more sessions to these patients may be a sensible first step in both clinical practice and in planning new intervention trials.

Conflict of interest

Mark van der Gaag, David van den Berg, and Anton Staring receive income for published books on psychotic disorders, and for the training of postdoctoral professionals in the treatment of psychotic disorders. Ad de Jongh receives income for published books on EMDR therapy and for the training of postdoctoral professionals in this method. Agnes van Minnen receives income for published book chapters on PTSD and for the training of postdoctoral professionals in Prolonged Exposure. Carlijn de Roos receives income for the training of postdoctoral professionals in EMDR therapy. The other authors declare that they have nothing to disclose.

Contributors

De Bont, Van der Vleugel, De Roos, De Jongh, Van Minnen, Van der Gaag, & Van den Berg designed the study and wrote the protocol. All authors were involved in the acquisition of data and management of the study. Van den Berg and Van Minnen conducted the literature search. Van den Berg conducted the statistical analyses and interpreted these with De Jongh, Van Minnen, & Van der Gaag. Van den Berg wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Funding

The study was funded by the Dutch Support Foundation (sub0211) 'Stichting tot Steun VCVGZ', P.O. Box 9219, 6800 HZ Arnhem, +31(26) 38 98,900, E-mail: info@stichtingtotsteunVCVGZ.nl (awarded to Dr. M. van der Gaag). Stichting tot Steun VCVGZ had no part in the design and conduct of the study or decisions about this report.

Acknowledgment

The authors thank all participants, therapists, research assistants, local researchers, independent specialists, advisors, involved mental health workers, the participating mental health institutions, and all others who contributed to this study. Special thanks go to Marion Bruns, BSc, and Daniëlle Tilburgs, MSc, Parnassia Psychiatric Institute, for their role in the organization and management of the data collection and data entry.

References

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

Andreasen, N.C., Carpenter, W.T., Kane, J.M., Lasser, R.A., Marder, S.R., Weinberger, D.R., 2005. Remission in schizophrenia: proposed criteria and rationale for consensus. Am. J. Psychiatry 162 (3), 441–449.

Austin, P.C., Steyerberg, E.W., 2015. The number of subjects per variable required in linear regression analyses. J. Clin. Epidemiol. 68 (6), 627–636.

Babyak, M.A., 2004. What you see may not be what you get: a brief, nontechnical introduction to overfitting in regression-type models. Psychosom. Med. 66 (3), 411–421.

Becker, C.B., Zayfert, C., Anderson, E., 2004. A survey of psychologists' attitudes towards and utilization of exposure therapy for PTSD. Behav. Res. Ther. 42 (3), 277–292.

Blake, D.D., Weathers, F.W., Nagy, L.M., Kaloupek, D.G., Gusman, F.D., Charney, D.S., et al., 1995. The development of a clinician-administered PTSD scale. J. Trauma. Stress. 8 (1), 75–90.

Blanchard, E.B., Hickling, E.J., Malta, L.S., Jaccard, J., Devineni, T., Veazey, C.H., et al., 2003. Prediction of response to psychological treatment among motor vehicle accident survivors with PTSD. Behav. Ther. 34 (3), 351–363.

de Bont, P.A., van den Berg, D.P., van der Vleugel, B.M., de Roos, C., de Jongh, A., van der Gaag, M., et al., 2015. Predictive validity of the trauma screening questionnaire in detecting post-traumatic stress disorder in patients with psychotic disorders. Br. J. Psychiatry 206 (5), 408–416.

de Bont, P.A., van den Berg, D.P., van der Vleugel, B.M., de Roos, C., Mulder, C.L., Becker, E.S., et al., 2013. 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 disorder: study protocol for the randomized controlled trial treating trauma in psychosis. Trials 14, 151.

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

Cabin, R.J., Mitchell, R.J., 2000. To bonferroni or not to bonferroni: when and how are the questions. Bull. Ecol. Soc. Am. 81 (3), 246–248.

Cloitre, M., Courtois, C.A., Ford, J.D., Green, B.L., Alexander, P., Briere, J., et al., 2012. The ISTSS expert consensus treatment guidelines for complex PTSD in adults (Retrieved november).

DuBois, P.H., 1957. Multivariate Correlational Analysis. Harper, New York.

Elliott, P., Biddle, D., Hawthorne, G., Forbes, D., Creamer, M., 2005. Patterns of treatment response in chronic posttraumatic stress disorder: an application of latent growth mixture modeling. J. Trauma. Stress. 18 (4), 303–311.

Faber, G., Smid, H.G., Van Gool, A.R., Wiersma, D., Van Den Bosch, R.J., 2012. The effects of guided discontinuation of antipsychotics on neurocognition in first onset psychosis. Eur. Psychiatry 27 (4), 275–280.

Foa, B., Gillihan, J., Bryant, A., 2013. Challenges and successes in dissemination of evidence-based treatments for posttraumatic stress: lessons learned from prolonged exposure therapy for PTSD. Psychol. Sci. Public Interest 14 (2), 65–111.

Foa, E.B., Hembree, E.A., Cahill, S.P., Rauch, S.A., Riggs, D.S., Feeny, N.C., et al., 2005. Randomized trial of prolonged exposure for posttraumatic stress disorder with and without cognitive restructuring: outcome at academic and community clinics. J. Consult. Clin. Psychol. 73 (5), 953–964.

Foa, E.B., Hembree, E.A., Rothbaum, B.O., 2007. Prolonged Exposure Therapy for PTSD: Emotional Processing of Traumatic Experiences: Therapist Guide. Oxford University Press, Oxford.

Foa, E.B., Riggs, D.S., Massie, E.D., Yarczower, M., 1995. The impact of fear activation and anger on the efficacy of exposure treatment for posttraumatic stress disorder. Behav. Ther. 26 (3), 487–499.

Forbes, D., Creamer, M., Hawthorne, G., Allen, N., McHugh, T., 2003. Comorbidity as a predictor of symptom change after treatment in combat-related posttraumatic stress disorder. J. Nerv. Ment. Dis. 191 (2), 93–99.

Forbes, N.F., Carrick, L.A., McIntosh, A.M., Lawrie, S.M., 2009. Working memory in schizophrenia: a meta-analysis. Psychol. Med. 39 (6), 889–905.

Gairns, S., Alvarez-Jimenez, M., Hulbert, C., McGorry, P., Bendall, S., 2015. Perceptions of clinicians treating young people with first-episode psychosis for post-traumatic stress disorder. Early Interv. Psychiatry 9 (1), 12–20.

Goodson, J.T., Lefkowitz, C.M., Helstrom, A.W., Gawrysiak, M.J., 2013. Outcomes of prolonged exposure therapy for veterans with posttraumatic stress disorder. J. Trauma. Stress. 26 (4), 419–425.

Green, C.E., Freeman, D., Kuipers, E., Bebbington, P., Fowler, D., Dunn, G., et al., 2008. Measuring ideas of persecution and social reference: the Green et al. Paranoid Thought Scales (GPTS). Psychol. Med. 38 (1), 101–111.

Gunter, R.W., Bodner, G.E., 2008. How eye movements affect unpleasant memories: support for a working-memory account. Behav. Res. Ther. 46 (8), 913–931.

Haddock, G., McCarron, J., Tarrier, N., Faragher, E.B., 1999. Scales to measure dimensions of hallucinations and delusions: the psychotic symptom rating scales (PSYRATS). Psychol. Med. 29 (4), 879–889.

Harrell, F.E., 2001. Regression Modeling Strategies: With Applications to Linear Models, Logistic Regression, and Survival Analysis. Springer-Verslag, New York.

Hassan, A.N., De Luca, V., 2015. The effect of lifetime adversities on resistance to antipsychotic treatment in schizophrenia patients. Schizophr. Res. 161 (2–3), 496–500.

Hembree, E.A., Foa, E.B., Dorfan, N.M., Street, G.P., Kowalski, J., Tu, X., 2003. Do patients drop out prematurely from exposure therapy for PTSD? J. Trauma. Stress. 16 (6), 555–562.

Hembree, E.A., Street, G.P., Riggs, D.S., Foa, E.B., 2004. Do assault-related variables predict response to cognitive behavioral treatment for PTSD? J. Consult. Clin. Psychol. 72 (3), 531–534.

De Jongh, A., Resick, P.A., Zoellner, L.A., van Minnen, A., Lee, C.W., Monson, C.M., et al., 2016. Critical analysis of the current treatment guidelines for complex PTSD in adults. Depress. Anxiety.

Karatzias, A., Power, K., McGoldrick, T., Brown, K., Buchanan, R., Sharp, D., et al., 2007. Predicting treatment outcome on three measures for post-traumatic stress disorder. Eur. Arch. Psychiatry Clin. Neurosci. 257 (1), 40–46.

de Kleine, R.A., Hendriks, G.J., Smits, J.A., Broekman, T.G., van Minnen, A., 2014. Prescriptive variables for D-cycloserine augmentation of exposure therapy for posttraumatic stress disorder. J. Psychiatr. Res. 48 (1), 40–46.

Lee, J., Park, S., 2005. Working memory impairments in schizophrenia: a meta-analysis. J. Abnorm. Psychol. 114 (4), 599.

Lincoln, T.M., Rief, W., Westermann, S., Ziegler, M., Kesting, M.L., Heibach, E., et al., 2014. Who stays, who benefits? Predicting dropout and change in cognitive behaviour therapy for psychosis. Psychiatry Res. 216 (2), 198–205.

Lommen, M.J., Restifo, K., 2009. Trauma and posttraumatic stress disorder (PTSD) in patients with schizophrenia or schizoaffective disorder. Community Ment. Health J. 45 (6), 485–496.

Matheson, S.L., Shepherd, A.M., Pinchbeck, R.M., Laurens, K.R., Carr, V.J., 2013. Childhood adversity in schizophrenia: a systematic meta-analysis. Psychol. Med. 43 (2), 225–238.

Meyer, J.M., Farrell, N.R., Kemp, J.J., Blakey, S.M., Deacon, B.J., 2014. Why do clinicians exclude anxious clients from exposure therapy? Behav. Res. Ther. 54, 49–53.

Moncrieff, J., Cohen, D., Mason, J.P., 2009. The subjective experience of taking antipsychotic medication: a content analysis of internet data. Acta Psychiatr. Scand. 120 (2), 102–111.
Moritz, S., Andreou, C., Klingberg, S., Thoering, T., Peters, M.J., 2013. Assessment of subjective cognitive and emotional effects of antipsychotic drugs. Effect by defect? Neuropharmacology 72, 179–186.
Moser, J.S., Cahill, S.P., Foa, E.B., 2010. Evidence for poorer outcome in patients with severe negative trauma-related cognitions receiving prolonged exposure plus cognitive restructuring: implications for treatment matching in posttraumatic stress disorder. J. Nerv. Ment. Dis. 198 (1), 72–75.
Mueser, K.T., Gottlieb, J.D., Xie, H., Lu, W., Yanos, P.T., Rosenberg, S.D., et al., 2015. Evaluation of cognitive restructuring for post-traumatic stress disorder in people with severe mental illness. Br. J. Psychiatry http://dx.doi.org/10.1192/bjp.bp.114.147926.
Mueser, K.T., Rosenberg, S.D., Xie, H., Jankowski, M.K., Bolton, E.E., Lu, W., et al., 2008. A randomized controlled trial of cognitive-behavioral treatment for posttraumatic stress disorder in severe mental illness. J. Consult. Clin. Psychol. 76 (2), 259–271.
Peduzzi, P., Concato, J., Kemper, E., Holford, T.R., Feinstein, A.R., 1996. A simulation study of the number of events per variable in logistic regression analysis. J. Clin. Epidemiol. 49 (12), 1373–1379.
Penttilä, M., Jääskeläinen, E., Hirvonen, N., Isohanni, M., Miettunen, J., 2014. Duration of untreated psychosis as predictor of long-term outcome in schizophrenia: systematic review and meta-analysis. Br. J. Psychiatry 205 (2), 88–94.
Polak, A.R., Witteveen, A.B., Reitsma, J.B., Olff, M., 2012. The role of executive function in posttraumatic stress disorder: a systematic review. J. Affect. Disord. 141 (1), 11–21.
Popiel, A., Zawadzki, B., 2013. Temperamental traits as predictors of effectiveness of psychotherapy (prolonged exposure) for PTSD in a group of motor vehicle accident survivors. Curr. Issues Pers. Psychol. 1, 43–50.
Rauch, S., Foa, E., 2006. Emotional processing theory (EPT) and exposure therapy for PTSD. J. Contemp. Psychother. 36 (2), 61–65.
Rizvi, S.L., Vogt, D.S., Resick, P.A., 2009. Cognitive and affective predictors of treatment outcome in cognitive processing therapy and prolonged exposure for posttraumatic stress disorder. Behav. Res. Ther. 47 (9), 737–743.
Ronconi, J.M., Shiner, B., Watts, B.V., 2014. Inclusion and exclusion criteria in randomized controlled trials of psychotherapy for PTSD. J. Psychiatr. Pract. 20 (1), 25–37.
Saeedi, H., Remington, G., Christensen, B.K., 2006. Impact of haloperidol, a dopamine D2 antagonist, on cognition and mood. Schizophr. Res. 85 (1–3), 222–231.
Salyers, M.P., Evans, L.J., Bond, G.R., Meyer, P.S., 2004. 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. 40 (1), 17–31.
Schneeberger, A.R., Muenzenmaier, K., Castille, D., Battaglia, J., Link, B., 2014. Use of psychotropic medication groups in people with severe mental illness and stressful childhood experiences. J Trauma Dissociation 15 (4), 494–511.
Schweizer, S., Dalgleish, T., 2011. Emotional working memory capacity in posttraumatic stress disorder (PTSD). Behav. Res. Ther. 49 (8), 498–504.
Shapiro, F., 2001. Eye Movement Desensitization and Reprocessing (EMDR): Basic Principles, Protocols, and Procedures. Guilford Press, New York.
Sheehan, D.V., Lecrubier, Y., Harnett Sheehan, K., Janavs, J., Weiller, E., Keskiner, A., et al., 1997. The validity of the mini international neuropsychiatric interview (MINI) according to the SCID-P and its reliability. Eur. Psychiatry 12 (5), 232–241.
Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., et al., 1998. 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 59, 22–33.
Speckens, A.E., Ehlers, A., Hackmann, A., Clark, D.M., 2006. Changes in intrusive memories associated with imaginal reliving in posttraumatic stress disorder. J Anxiety Disord. 20 (3), 328–341.
Steketee, G., Chambless, D.L., 1992. Methodological issues in prediction of treatment outcome. Clin. Psychol. Rev. 12 (4), 387–400.
Taylor, S., 2003. Outcome predictors for three PTSD treatments: exposure therapy, EMDR, and relaxation training. J. Cogn. Psychother. 17 (2), 149–162.
Thrasher, S., Power, M., Morant, N., Marks, I., Dalgleish, T., 2010. Social support moderates outcome in a randomized controlled trial of exposure therapy and (or) cognitive restructuring for chronic posttraumatic stress disorder. Can. J. Psychiatr. 55 (3), 187–190.
van den Berg, D.P., de Bont, P.A., van der Vleugel, B.M., de Roos, C., de Jongh, A., Van Minnen, A., et al., 2015. 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. JAMA Psychiatry 72 (3), 259–267.
van den Berg, D.P., de Bont, P.A., van der Vleugel, B.M., de Roos, C., de Jongh, A., van Minnen, A., et al., 2016. Trauma-focused treatment in PTSD patients with psychosis: symptom exacerbation, adverse events, and revictimization. Schizophr. Bull. 42 (3), 693–702.
van den Hout, M.A., Engelhard, I.M., Beetsma, D., Slofstra, C., Hornsveld, H., Houtveen, J., et al., 2011. EMDR and mindfulness. Eye movements and attentional breathing tax working memory and reduce vividness and emotionality of aversive ideation. J. Behav. Ther. Exp. Psychiatry 42 (4), 423–431.
van den Hout, M.A., Engelhard, I.M., Smeets, M.A.M., Hornsveld, H., Hoogeveen, E., de Heer, E., et al., 2010. Counting during recall: taxing of working memory and reduced vividness and emotionality of negative memories. Appl. Cogn. Psychol. 24 (3), 303–311.
van der Gaag, M., Valmaggia, L.R., Smit, F., 2014. The effects of individually tailored formulation-based cognitive behavioural therapy in auditory hallucinations and delusions: a meta-analysis. Schizophr. Res. 156 (1), 30–37.
van Emmerik, A.A., Kamphuis, J.H., Noordhof, A., Emmelkamp, P.M., 2011. Catch me if you can: do the five-factor model personality traits moderate dropout and acute treatment response in post-traumatic stress disorder patients? Psychother. Psychosom. 80 (6), 386–388.
van Minnen, A., Arntz, A., Keijsers, G.P., 2002. Prolonged exposure in patients with chronic PTSD: predictors of treatment outcome and dropout. Behav. Res. Ther. 40 (4), 439–457.
Vittinghoff, E., McCulloch, C.E., 2007. Relaxing the rule of ten events per variable in logistic and cox regression. Am. J. Epidemiol. 165 (6), 710–718.
Wittorf, A., Jakobi, U., Bechdolf, A., Müller, B., Sartory, G., Wagner, M., et al., 2009. The influence of baseline symptoms and insight on the therapeutic alliance early in the treatment of schizophrenia. Eur. Psychiatry 24 (4), 259–267.
Young, S.L., Taylor, M., Lawrie, S.M., 2015. "First do no harm." a systematic review of the prevalence and management of antipsychotic adverse effects. J. Psychopharmacol. 29 (4), 353–362.