“If I ever feel better, remind me to spend some good time with you. You can give me your number, when it’s all over I’ll let you know.”

Phoenix, lyrics from ‘If I Ever Feel Better’
CHAPTER 6

Predicting trauma-focused treatment outcome in psychosis

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ABSTRACT

OBJECTIVE
Although trauma-focused 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 trauma-focused 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 trauma-focused treatments. Also, we speculate that patients with psychosis and severe baseline PTSD might derive more benefit if given more than eight sessions.
INTRODUCTION

Childhood adversities and comorbid posttraumatic stress disorder (PTSD) are common in psychosis, but are often underdiagnosed and undertreated. A recent randomized controlled trial (RCT) found trauma-focused treatments, prolonged exposure (PE) and eye movement desensitization and reprocessing (EMDR) therapy to be effective and safe in patients with long-standing psychotic disorders. Similarly, cognitive restructuring was found to be effective in two controlled trials with patients suffering from severe mental illnesses of which a subgroup had a psychotic disorder. Interestingly, despite the presence of a severe psychiatric disorder, the outcomes and dropout rates in these trauma-focused treatment studies were similar to studies with general PTSD samples. Based on the above results, it seems that meeting the criteria for a psychotic disorder does not necessarily predict poor trauma-focused treatment outcome. However, it remains unclear which factors influence trauma-focused 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 trauma-focused treatments in psychosis. This information may also elucidate whether it’s necessary to adapt trauma-focused treatment protocols in this patient group to improve effects and reduce the likelihood of dropout.

Of the many studies examining the potential predictors of trauma-focused 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 trauma-focused 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. Interestingly, greater baseline PTSD severity was also found to be associated with greater improvements by some, although this was not found by others. 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 trauma-focused 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
trauma-focused treatment outcome or dropout. Because researchers and clinicians tend to exclude patients with psychotic disorders from effective trauma-focused treatments, 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 trauma-focused 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. In contrast with these beliefs, in the parent trial of the current study, trauma-focused treatment was found to reduce symptom exacerbation and adversities, such as self-harm or psychiatric hospitalization. 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 trauma-focused treatment, i.e. working memory difficulties, and antipsychotic medication. Working memory problems are common in patients with psychosis and the presence of cognitive functioning problems is one of the reasons why clinicians tend to exclude patients from trauma-focused treatment. We selected this specific cognitive factor, since working memory capacity is also associated with trauma-focused treatment effects. The majority of patients with psychotic disorders use antipsychotic medications, which are associated with many side-effects, e.g. sedation, emotional numbing, and reduced speed of processing. These side-effects may undermine the possibility of patients to benefit from trauma-focused treatment, e.g. by interfering with the ability to follow treatment procedures, or difficulty to activate the 'fear structure'. Indeed, the use of psychotropic medication in a sample of veterans was found to be associated with less PTSD symptom reduction during trauma-focused treatment. 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 trauma-focused 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.

EXPERIMENTAL MATERIALS AND METHODS

Participants
Participants were 108 patients with a psychotic disorder and PTSD who were allocated to trauma-focused treatment (PE or EMDR therapy) in a recently published multicenter single-blind RCT investigating trauma-focused PTSD treatments in psychosis. The participants were characterized by long-standing psychotic disorders (mean duration = 18.5, SD = 12.5 years). The MINI-International Neuropsychiatric Interview-Plus 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. All participants met the full criteria for chronic PTSD on the Clinician-Administered PTSD Scale (CAPS). Complete details of the study procedure are available elsewhere.

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. 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).

Treatment
Trauma-focused treatment consisted of eight weekly 90-min sessions of either PE or EMDR therapy. The first session comprised psycho-education about PTSD and the development of a hierarchy of the most intrusive trauma memories. The active trauma-focused 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.

**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.\(^46\) Outcome was measured with the CAPS,\(^45\) 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.\(^5\)

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),\(^49\) 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.\(^50\) 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.\(^51\) 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).\(^52\) 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.\(^46\) In that way higher scores reflect less working memory capacity. There were 9 missings 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.

**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 trauma-focused treatments, 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. 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. 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, 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. In logistic regression analysis, similar rules of thumb have been suggested, e.g. 10 subjects in the smallest group per predictor. 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. 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. With eight comparisons (baseline PTSD symptom severity was also included as a potential predictor of dropout) 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 = .006.

RESULTS

Baseline PTSD symptom severity
Higher baseline PTSD symptom severity score was significantly associated with higher posttreatment PTSD severity score ($P < .001$), explaining 11.4% of the variance. Also, greater baseline PTSD severity was related to greater net reductions in PTSD symptoms at posttreatment ($P = .015$), explaining 6.5% of the variance.

**TABLE 1** · Baseline Values* for the Independent Variables

<table>
<thead>
<tr>
<th>Baseline variable</th>
<th>Total sample (n=108)</th>
<th>Treatment completers (n=84)</th>
<th>Treatment dropouts (n=24)</th>
<th>P-valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTSD symptom severity, mean (SD)</td>
<td>70.8 (16.3)</td>
<td>70.7 (15.5)</td>
<td>71.5 (19.3)</td>
<td>.833</td>
</tr>
<tr>
<td>Severity of paranoid ideation, mean (SD)</td>
<td>85.7 (33.6)</td>
<td>81.4 (32.1)</td>
<td>100.4 (35.0)</td>
<td>.014</td>
</tr>
<tr>
<td>Presence of auditory verbal hallucinations, No. (%)</td>
<td>45 (41.7)</td>
<td>36 (42.9)</td>
<td>9 (37.5)</td>
<td>.814</td>
</tr>
<tr>
<td>Presence of negative symptoms, No. (%)</td>
<td>55 (50.9)</td>
<td>39 (46.4)</td>
<td>16 (66.7)</td>
<td>.129</td>
</tr>
<tr>
<td>Presence of moderate to high suicide risk, No. (%)</td>
<td>50 (46.3)</td>
<td>36 (42.9)</td>
<td>14 (58.3)</td>
<td>.267</td>
</tr>
<tr>
<td>Presence of recent adversities, No. (%)</td>
<td>34 (31.5)</td>
<td>25 (29.8)</td>
<td>9 (37.5)</td>
<td>.638</td>
</tr>
<tr>
<td>Working memory capacity index, mean (SD)</td>
<td>86.5 (71.4)</td>
<td>85.3 (75.6)</td>
<td>90.9 (55.3)</td>
<td>.516</td>
</tr>
<tr>
<td>Chlorpromazine hydrochloride dose equivalent, mean (SD)</td>
<td>240.4 (221.3)</td>
<td>253.8 (224.1)</td>
<td>193.9 (208.9)</td>
<td>.117</td>
</tr>
</tbody>
</table>

* Observed untransformed values.

b P-values for the independent samples t-tests and Chi-square tests for completers versus dropouts. Alpha = .006 after Bonferroni adjustment for multiple testing.
Predicting posttreatment outcome
The multiple regression model with all 7 independent variables was not significant \( F [7, 83] = 1.89, P = .080 \), 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 = .25, \( P = .025 \)) contributed uniquely to the variability in residual gain score, explaining 5.4% of the variance (TABLE 2).

Baseline differences between treatment completers and treatment dropouts
Treatment completers and dropouts did not differ significantly on any of the baseline variables (TABLE 1).

**TABLE 2** · Results of Standard Multiple Regression Analyses Predicting Treatment Outcome (n = 91)

<table>
<thead>
<tr>
<th>Baseline variable</th>
<th>Beta</th>
<th>P-Value</th>
<th>Part</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severity of paranoid ideation, mean (SD)</td>
<td>0.047</td>
<td>.680</td>
<td>0.042</td>
</tr>
<tr>
<td>Presence of auditory verbal hallucinations, No. (%)</td>
<td>0.250</td>
<td>.025</td>
<td>0.233</td>
</tr>
<tr>
<td>Presence of negative symptoms, No. (%)</td>
<td>0.194</td>
<td>.076</td>
<td>0.183</td>
</tr>
<tr>
<td>Presence of moderate to high suicide risk, No. (%)</td>
<td>0.018</td>
<td>.875</td>
<td>0.016</td>
</tr>
<tr>
<td>Presence of recent adversities, No. (%)</td>
<td>0.006</td>
<td>.952</td>
<td>0.006</td>
</tr>
<tr>
<td>Working memory capacity index, mean (SD)</td>
<td>0.099</td>
<td>.342</td>
<td>0.097</td>
</tr>
<tr>
<td>Chlorpromazine hydrochloride dose equivalent, mean (SD)</td>
<td>0.037</td>
<td>.729</td>
<td>0.035</td>
</tr>
</tbody>
</table>

* Dependent variable: Residual gain score
\(^b\) Standardized coefficients
\(^c\) Semipartial correlation coefficients

**DISCUSSION**

We tested whether baseline PTSD severity and several psychosis-specific variables would predict trauma-focused 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,\(^9\) 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 trauma-focused 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.\textsuperscript{61} Therefore, future studies should test the beneficial effects of a greater number of treatment sessions for this often severely traumatized population.

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 trauma-focused treatment was, on average, still effective in participants with auditory verbal hallucinations. However, when trauma-focused treatment remains insufficiently effective in voice hearers (also after adding extra sessions), trauma-focused treatment may be combined with cognitive behavioral therapy for auditory verbal hallucinations.\textsuperscript{62}

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 trauma-focused 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.\textsuperscript{63} 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.\textsuperscript{64} 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 trauma-focused 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.\textsuperscript{65}
In patients with psychosis, baseline markers of instability (suicidal ideation and recent adversities) do not appear to influence trauma-focused treatment outcome or dropout. This is at odds with the custom to exclude patients with psychotic disorders from trauma-focused treatments, 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). This is emphasized by the observation that trauma-focused treatment appeared to have a stabilizing effect on the patients with psychosis in the parent trial of this study, in that the application of trauma-focused treatment was associated with less adversities and less symptom exacerbation among participants.

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 trauma-focused treatment. Conversely, since PTSD is also associated with working memory problems, 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. The experience of childhood trauma and other distressing life events were also found to be associated with less response to medications. Therefore, also here, the effect may be reversed. Effective trauma-focused 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 trauma-focused 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 trauma-focused 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 trauma-focused 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 trauma-focused 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.

REFERENCES


