Predictors of response to cognitive-behavioral therapy in patients with posttraumatic stress disorder: a systematic review

Predictores de resposta à terapia cognitivo-comportamental em pacientes com transtorno de estresse pós-traumático: uma revisão sistemática

RESUMO

Objetivo: O transtorno de estresse pós-traumático (TEPT) é um transtorno altamente prevalente e incapacitante. Mesmo quando tratado com uma intervenção de primeira linha, terapia cognitivo-comportamental (TCC), 45% dos pacientes continuam sofrendo desse transtorno. Portanto, conhecer os fatores que podem prever quem responderá à TCC seria de grande valor no tratamento desses pacientes. Por esse motivo, revisamos sistematicamente a literatura para identificar as variáveis que poderiam predizer a resposta à TCC em pacientes que sofrem de TEPT. Métodos: Seguindo as diretrizes do PRISMA 2020, pesquisamos em banco de dados eletrônico como ISI Web of Science, Scopus, PsycINFO, MEDLINE e PTSDpubs até novembro de 2021. Dois autores conduziram independentemente a seleção do estudo e a extração de dados. Estudos que examinaram possíveis preditores de resposta à terapia, com amostra de adultos (18-65 anos) de ambos os sexos, com e sem comorbidades, foram considerados elegíveis. As características dos estudos foram sintetizadas em uma tabela. O risco de viés foi avaliado pela ferramenta de avaliação de qualidade de risco de viés da Cochrane. Resultados: Vinte e oito estudos envolvendo 15 variáveis foram selecionados. Desses, oito mostraram baixo risco de viés, 19 mostraram algumas preocupações e um mostrou alto risco potencial de viés. A relação terapêutica foi a única variável considerada um preditor de boa resposta à terapia. Todas as outras variáveis apresentaram resultados conflitantes. Conclusões: A variável mais promissora, embora muito fraca cientificamente, é a relação terapêutica. Ensaios clínicos randomizados adicionais devem ser conduzidos para esclarecer o papel dessa variável como um preditor de resposta da TCC em pacientes com TEPT.

PALAVRAS-CHAVE
Terapia cognitivo-comportamental, TCC, transtorno de estresse pós-traumático, TEPT, preditor de resposta, revisão sistemática.

ABSTRACT

Objective: Posttraumatic stress disorder (PTSD) is a highly prevalent and disabling disorder. Even when treated with the first-line intervention, cognitive-behavioral therapy (CBT), 45% of the patients continue suffering from this disorder. Therefore, knowing the factors that could foresee who will respond to CBT would be of great value to the treatment of these patients. Thus, we have systematically reviewed the literature to identify the variables that could predict response to CBT in patients suffering from PTSD. Methods: Following the PRISMA 2020 guidelines, we searched the electronic databases ISI Web of Science, Scopus, PsycINFO, MEDLINE, and PTSDpubs until November 2021. Two authors have independently conducted study selection and data extraction. Studies that examined possible predictors of response to therapy on a sample of adults (18-65 years), both genders, with and without comorbidities were considered eligible. The characteristics of the studies were synthesized in a table. The risk of bias was assessed by the Cochrane risk of bias quality assessment tool. Results: Twenty-eight studies comprising 15 variables were selected. Among those, eight showed a low risk of bias, 19 showed some concerns, and one showed a high potential risk of bias. The therapeutic relationship was the only variable considered to be a predictor of a good response to therapy. All other variables showed conflicting results. Conclusions: The most promising variable, although scientifically weak, is the therapeutic relationship. Additional randomized clinical trials should be conducted to clarify the role of this variable as a predictor of response to CBT in patients with PTSD.

KEYWORDS
INTRODUCTION

Posttraumatic stress disorder (PTSD) is a prevalent and debilitating disorder caused by exposure to a traumatic event, such as exposure to actual death or threat of death, serious injury, or sexual violation. In the general population, the diagnosis of PTSD increases by 13 times the rate of death by suicide when compared with people without PTSD. Although severe, PTSD is quite frequent in the general population worldwide, with a 12 monthly prevalence achieving 3.8% in some European countries, and 5% in South American countries. Despite already being highly prevalent, PTSD rates have been increasing among the general population in the last 15 years.

The first-line intervention to treat people with PTSD is cognitive-behavioral therapy (CBT). CBT is effective for treating PTSD symptoms caused by diverse types of trauma and also comorbid disorders frequently associated with PTSD. The basic components of CBT for PTSD include psycho-education, exposure techniques, cognitive restructuring, and anxiety management. Exposure therapy has sufficient evidence to support its efficacy in treating PTSD showing an important clinical benefit. This treatment involves confronting their fears — either in imaginary or in vivo forms —, varying duration, and the arousal level during exposure.

Although CBT is recommended as the first-line intervention for treating PTSD by most guidelines, many patients continue suffering from the disorder after treatment. Even when treated with prolonged exposure (PE), one of the most effective interventions, not everyone will benefit up to 45% continue to meet the diagnostic criteria for PTSD immediately after therapy, and 44% after 3.5 months of follow-up. Although there is little scientific evidence about the predictors of response to CBT, some studies indicated patient factors as responsible for up to 87% of outcome divergence. Previous studies on response predictors have been conducted. However, exclusively investigated biomarkers as possible predictors of response to CBT in the treatment of PTSD, or addressed several different psychotherapies, or did not perform a systematic review.

Therefore, it is necessary to systematically review the literature for randomized controlled trials investigating possible predictors of response to CBT for PTSD. Finding these predictors, the mental health assistants could deliver more refined treatment procedures, optimizing the efficacy of PTSD treatment. To fulfill this knowledge gap, we have conducted a systematic review of the literature aiming to investigate the clinical and social variables that could predict the response to CBT in patients with PTSD. We hypothesize that patient factors would be the strongest predictors of CBT outcome for the treatment of PTSD.

METHODS

Search strategy

We have conducted a systematic review of the literature, following the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines. This study was registered with the International Prospective Register of Systematic Reviews – PROSPERO (CRD42019109653).

On November 10th, 2021, we systematically searched five electronic databases, namely ISI Web of Science, Scopus, PsycINFO, MEDLINE, and PTSDB (formerly PILOTS), for studies reporting on the predictors of response to CBT in patients with PTSD. No time or language restrictions were applied. Using Boolean search, the following terms were sought in the field “title, abstract and keywords” or it is equivalent: (“Cognitive training” OR “trauma-focused CBT” OR “trauma-focused therap*” OR “exposure therap*” OR “cognitive behav* therap*” OR CBT OR “cognitive-behav*” OR “behav* therap*” OR EMDR OR “Eye Movement Desensitization and Reprocessing” OR “Cognitive Processing Therap*” OR “Prolonged Exposure”) AND (PTSD OR “posttraumatic stress” OR “post-traumatic stress” OR “post traumatic stress”) AND (“predictor* of response” OR “predictor* of outcome” OR “response predictor*” OR Moderator* OR “outcome predictor*”). The asterisks mean that all terms beginning with these roots were searched.

Then, two authors (J.P. and M.M.) independently screened the abstracts of all studies identified and applied the inclusion and exclusion criteria, using a predefined form. In a second screening, the same two authors scrutinized the full text of the remaining studies, extracted study characteristics, and assessed the risk of bias. Disagreements were resolved by a senior researcher (WB). Some authors were contacted to access the full text of their studies when needed, but not all have responded.

The main characteristics of selected studies were synthesized in a table. The risk of bias assessment was performed according to the Cochrane RoB 2.0 tool and categorized as high risk, some concerns, or low risk for the following domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in the measurement of the outcome and bias in the selection of the reported result. Two authors (JP and MM) assessed the risk of bias, and the senior researcher (WB) resolved all doubts.

We scrutinized any independent variable that could predict the response to CBT on PTSD patients. We classified the variables as patient-related (e.g., civil or military, sample size, and mean age), clinical characteristics (e.g., baseline PTSD severity and type of trauma), and treatment characteristics (e.g., type of intervention, comparison, and the number of sessions). The outcome variable was the reduction of mean PTSD symptoms.
Inclusion criteria were: (1) randomized clinical trials (RCTs), (2) providing data on the predictors of response to CBT (cognitive restructuring, behavioral therapy, mainly exposure therapy, or the combination of both techniques) for the treatment of PTSD, (3) using adult samples (18 to 65 years), (4) with or without comorbidities. Exclusion criteria were: (1) studies published in non-peer-reviewed journals and gray literature, (2) other systematic reviews and meta-analysis, (3) papers do not mention possible variables that may predict response to CBT, (4) inpatient samples, and (5) studies that do not provide PTSD data alone (composite sample of a variety of anxiety disorders), (6) variables that were investigated in less than three RCTs due to the low level of evidence. We also reviewed the reference lists of all selected papers and reviews excluded for additional relevant studies.

RESULTS

We identified a total of 422 different RCTs. After applying inclusion and exclusion criteria, 28 RCTs were selected (Tables 1 and 2), comprising 2,652 participants (Figure 1). We found 15 discrete variables supposed to predict CBT response in patients with PTSD, including patient-related factors as well as clinical and treatment characteristics (Table 3).

Among the patient-related, clinical, and treatment characteristics variables, the most studied was the presence of depression (eight studies); followed by age (seven studies); gender, depression severity, PTSD severity; type of trauma (six studies each); anger (five studies); multiple traumatic events (four studies); and anxiety, alcohol use, comorbid personality disorders, dissociative symptoms, level of education, race or ethnicity and therapeutic alliance (three studies).

Patient-related factors

Younger age predicted a better response to cognitive processing therapy (CPT) in only one study and was non-significant to CBT, PE, and CPT in six studies.

The female gender predicted a better response to cognitive therapy and imaginal exposure in only one RCT, while it was non-significant to CBT, eye movement desensitization and reprocessing (EMDR), exposure therapy, and (or) cognitive restructuring, CPT in five studies.

The level of education was non-significant to CBT, PE, and CPT in all three studies.
Table 1. Description of RCTs Investigating Patient-Related Factors as Possible Predictors of Response to CBT

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Population, sample size</th>
<th>Mean Age (SD)</th>
<th>Diagnostic criterion for PTSD</th>
<th>Type of trauma</th>
<th>Type of intervention</th>
<th>Comparison (active/passive)</th>
<th>Treatment</th>
<th>Independent variables evaluated (instrument)</th>
<th>Influence on CBT response (Effect size)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beck et al., 2021</td>
<td>Military, n = 175</td>
<td>CBT: 54.9 (11.54); Present centered therapy: 57.7 (12.10)</td>
<td>CAPS-5</td>
<td>Combat trauma</td>
<td>CBT</td>
<td>Present centered therapy</td>
<td>16 weeks and 14 sessions (1) Age (pretreatment assessment)</td>
<td>(1) None (NR)</td>
<td></td>
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<tr>
<td>Karatzias et al., 2007</td>
<td>Civilian, n = 48</td>
<td>40.6 (11.4)</td>
<td>DSM-IV</td>
<td>Accident, crime, other</td>
<td>EMDR</td>
<td>Imaginal exposure + cognitive restructuring (Active)</td>
<td>12 weeks and sessions (1) Gender (SDQ)</td>
<td>(1) None (NR)</td>
<td></td>
</tr>
<tr>
<td>Rauch et al., 2021</td>
<td>Military, n = 196</td>
<td>34.4 (8.4)</td>
<td>DSM-IV-TR</td>
<td>Combat related PTSD</td>
<td>PE plus placebo</td>
<td>PE + sertraline + enhanced medication management</td>
<td>12 weeks, and 3 sessions (1) Age (NR)</td>
<td>(1) None (NR)</td>
<td></td>
</tr>
<tr>
<td>Resick et al., 2020</td>
<td>Military, n = 165</td>
<td>34.2 (7.3)</td>
<td>DSM-IV</td>
<td>Combat-related, death (noncombat), sexual assault, physical assault, and accident</td>
<td>Individual CPT</td>
<td>Group CPT (Active)</td>
<td>12 sessions, and 6 weeks (1) Younger age (Form developed by the research group)</td>
<td>(1) Positive (NR)</td>
<td></td>
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<tr>
<td>Rizvi et al., 2009</td>
<td>Civilian, n = 145</td>
<td>31.7 (9.8)</td>
<td>CAPS</td>
<td>Discrete incident of completed rape in childhood or adulthood</td>
<td>PE</td>
<td>CPT (Active)</td>
<td>12 weeks and sessions PE: 9 weeks and sessions (1) Age (Standardized trauma interview)</td>
<td>(1) None (d=0.41) (2) None (d=0.02)</td>
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</tr>
<tr>
<td>Ruglass &amp; Yali, 2019</td>
<td>Civilian, n = 107</td>
<td>Black/African American: 45.49 (8.77); White/Caucasian: 44.00 (9.07); Hispanic/Latino: 41.86 (11.10)</td>
<td>SCID-I</td>
<td>Physical assault, sexual assault, accident or disaster, sudden injury or death of other, other</td>
<td>Concurrent Treatment with PE</td>
<td>Relapse Prevention Therapy (Active)</td>
<td>12 weeks (1) Race/ethnicity (baseline interview)</td>
<td>(1) None (NR)</td>
<td></td>
</tr>
<tr>
<td>Tarrier et al., 2000</td>
<td>Civilian, n = 62</td>
<td>36.82 (11.60)</td>
<td>DSM-III-R</td>
<td>Crime, accident and other</td>
<td>Cognitive therapy</td>
<td>Imaginal exposure (Active)</td>
<td>16 weeks and sessions (1) Gender (NR)</td>
<td>(1) Positive (NR)</td>
<td></td>
</tr>
<tr>
<td>Thrasher et al., 2010</td>
<td>Civilian, n = 77</td>
<td>Active treatment: 38.85 (9.92); Relaxation 35.60 (10.00)</td>
<td>DSM-III-R</td>
<td>Injury, death, disability, and disfigurement</td>
<td>Exposure therapy and/or cognitive restructuring</td>
<td>Relaxation Groups (Active)</td>
<td>10 weeks and sessions (1) Gender (2) Age (CI)</td>
<td>(1) None (NR) (2) None (NR)</td>
<td></td>
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<tr>
<td>Zandberg et al., 2016</td>
<td>Civilian and military, n = 165</td>
<td>42.78 (9.76)</td>
<td>DSM-IV</td>
<td>Sexual assault, combat, physical assault, other trauma</td>
<td>Placebo and PE</td>
<td>Naltrexone and PE (Active)</td>
<td>24 weeks, 18 sessions (1) Level of education (NR)</td>
<td>(1) None (NR)</td>
<td></td>
</tr>
<tr>
<td>Zang et al., 2019</td>
<td>Civilian, n = 96</td>
<td>32.20 (9.94)</td>
<td>PSS-I</td>
<td>Childhood sexual abuse or adulthood sexual or physical assault</td>
<td>PE with cognitive restructuring</td>
<td>PE with cognitive restructuring and waitlist (Passive)</td>
<td>8 sessions (1) Age (SAI)</td>
<td>(1) None (OR=0.98)</td>
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</tbody>
</table>

Note. CAPS = Clinician Administered PTSD Scale; CI = clinical interview; CPT = Cognitive processing therapy; DSM-III-R = Diagnostic and statistical manual of mental disorders, 3rd edition revised; DSM-IV = Diagnostic and statistical manual of mental disorders 4th Ed; EMDR = Eye movement desensitization and reprocessing; NR = Not reported; OR = Odds ratio; PE = Prolonged exposure; PSS-I = PTSD symptom scale interview; SAI = Standardized assault interview; SCID-I = Structured Clinical Interview for DSM-IV for Axis I Disorders; SDQ = Socio-demographic questionnaire.
Table 2. Description of RCTs Investigating Clinical and Treatment Characteristics as Possible Predictors of Response to CBT

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Population, sample size</th>
<th>Mean Age (SD)</th>
<th>Diagnostic criterion for PTSD</th>
<th>Type of trauma</th>
<th>Type of intervention</th>
<th>Comparison (active/passive)</th>
<th>Treatment</th>
<th>Independent variables evaluated (instrument)</th>
<th>Influence on CBT response (Effect size)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assmann et al., 2021</td>
<td>Civilian (155)</td>
<td>38.54 (11.17)</td>
<td>CAPS-5</td>
<td>Childhood trauma</td>
<td>EMDR</td>
<td>Imagery rescripting (Active)</td>
<td>6 weeks, and 12 sessions</td>
<td>(1) Presence of Depression (BDI-II)</td>
<td>(1) None (d=1.22)</td>
</tr>
<tr>
<td>Beck, et al., 2021</td>
<td>Military (175)</td>
<td>CBT: 54.9 (11.54); Present centered therapy: 57.7 (12.10)</td>
<td>CAPS-5</td>
<td>Combat trauma</td>
<td>CBT</td>
<td>Present centered therapy (Active)</td>
<td>16 weeks, and 14 sessions</td>
<td>(1) PTSD severity (CAPS)</td>
<td>(1) Positive (d=1.31)</td>
</tr>
<tr>
<td>Bosch et al., 2020</td>
<td>Civilian and military, n = 126</td>
<td>46.5 (11.9)</td>
<td>CAPS-IV</td>
<td>Neglect, sexual abuse, and physical abuse</td>
<td>CPT via videoteleconferencing</td>
<td>CPT inperson (Active)</td>
<td>12 sessions, once or twice per week</td>
<td>(1) Anger (STAEI)</td>
<td>(1) Negative (NR)</td>
</tr>
<tr>
<td>Cahill et al., 2003</td>
<td>Civilian, n = 67</td>
<td>34.6 (10.5)</td>
<td>DSM-III-R</td>
<td>Female assault victims</td>
<td>PE</td>
<td>SIT (Active) PE and SIT (Active)</td>
<td>5 weeks, 9 sessions</td>
<td>(1) Borderline personality characteristics (SCID-II)</td>
<td>(1) None (NR)</td>
</tr>
<tr>
<td>Cloitre et al., 2017</td>
<td>Civilian, n = 104</td>
<td>36.48 (9.39)</td>
<td>DSM-IV</td>
<td>Childhood sexual and/or physical abuse</td>
<td>STAIR</td>
<td>Narrative therapy (Active)</td>
<td>16 weeks and sessions</td>
<td>(1) PTSD severity (BDI-II)</td>
<td>(1) Positive (d=0.29)</td>
</tr>
<tr>
<td>Cloitre et al., 2002</td>
<td>Civilian, n = 58</td>
<td>34 (7.22)</td>
<td>DSM-IV</td>
<td>Childhood abuse</td>
<td>STAIR and Modified PE</td>
<td>Waiting list (Passive)</td>
<td>12 weeks, 16 sessions</td>
<td>(1) Therapeutic alliance (WAI)</td>
<td>(1) Positive (NR)</td>
</tr>
<tr>
<td>Cloitre et al., 2016</td>
<td>Civilian, n = 104</td>
<td>36.48 (9.39)</td>
<td>DSM-IV</td>
<td>Childhood sexual and/or physical abuse occurring before the age of 18</td>
<td>STAIR and PE</td>
<td>STAIR and supportive counselling (Active)</td>
<td>16 weeks and sessions</td>
<td>(1) PTSD severity (CAPS)</td>
<td>(1) None (NR)</td>
</tr>
<tr>
<td>Feeny et al., 2002</td>
<td>Civilian, n = 72</td>
<td>34.9 (10.06)</td>
<td>DSM-III-R</td>
<td>Female victims of sexual and nonsexual assault</td>
<td>PE</td>
<td>SIT (Active) PE and SIT (Active)</td>
<td>9 weeks and sessions</td>
<td>(1) Borderline personality characteristics (SCID-II)</td>
<td>(1) Negative (NR)</td>
</tr>
<tr>
<td>Gobin et al., 2018</td>
<td>Civilian and military, n = 126</td>
<td>Veterans: 42.05 (10.58) Civilians: 47.30 (12.03)</td>
<td>DSM-IV</td>
<td>Physical assault, child sexual abuse, adult sexual assault</td>
<td>CPT via clinical video teleconferencing</td>
<td>Treatment traditional (in-person modality) (Active)</td>
<td>12 weeks and sessions</td>
<td>(1) PTSD severity (CAPS)</td>
<td>(1) None (NR)</td>
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<tr>
<td>Study (year)</td>
<td>Population, sample size</td>
<td>Mean Age (SD)</td>
<td>Diagnostic criterion for PTSD</td>
<td>Type of trauma</td>
<td>Type of intervention</td>
<td>Comparison (active/passive)</td>
<td>Treatment</td>
<td>Independent variables evaluated (instrument)</td>
<td>Influence on CBT response (Effect size)</td>
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<td>Haagen et al., 2017</td>
<td>Civilian and military, n = 72</td>
<td>41.5 (11.3)</td>
<td>DSM-IV-TR</td>
<td>Murder of friends/family, combat situation, physical torture, imprisonment, serious injury, rape or sexual abuse</td>
<td>EMDR</td>
<td>Stabilization therapy (Active)</td>
<td>EMDR: 9 weeks and sessions; Stabilization therapy: 12 weeks and sessions</td>
<td>(1) Presence of depression (HSCL)</td>
<td>(1) Negative (NR)</td>
</tr>
<tr>
<td>Haagenson et al., 2014</td>
<td>Military, n = 81</td>
<td>35.55 (11.05)</td>
<td>DSM-5</td>
<td>Severely traumatised asylum seekers and refugees</td>
<td>Narrative exposure therapy</td>
<td>Treatment as usual (Active)</td>
<td>10 weeks and sessions</td>
<td>(1) Dissociative symptoms such as derealisation and depersonalisation (CAPS)</td>
<td>(1) None (Derealisation: g=1.36; Depersonalisation: g=0.97)</td>
</tr>
<tr>
<td>Hembree et al., 2004</td>
<td>Civilian, n = 75</td>
<td>32 (10)</td>
<td>DSM-IV</td>
<td>Rape or nonsexual assault in adulthood or sexual abuse in childhood</td>
<td>PE</td>
<td>PE with cognitive restructuring (Active)</td>
<td>NR</td>
<td>(1) Comorbid personality disorders (SCID II)</td>
<td>(1) Negative (NR)</td>
</tr>
<tr>
<td>Hembree et al., 2004</td>
<td>Civilian, n = 73</td>
<td>35.7 (10.1)</td>
<td>DSM-III-R</td>
<td>Female assault victims</td>
<td>PE</td>
<td>SIT (Active)</td>
<td>5–6 weeks, 9 sessions</td>
<td>(1) Multiple traumatic events (SAI)</td>
<td>(1) Negative (NR)</td>
</tr>
<tr>
<td>Karatza et al., 2007</td>
<td>Civilian, n = 48</td>
<td>40.6 (11.4)</td>
<td>DSM-IV</td>
<td>Accident, crime, other</td>
<td>EMDR</td>
<td>Treatment as usual (Active)</td>
<td>12 weeks and sessions</td>
<td>(1) PTSD severity (CAPS, IES and PCL)</td>
<td>(1) Positive (NR)</td>
</tr>
<tr>
<td>Knaevelsrud &amp; Maierker, 2007</td>
<td>Civilian, n = 96</td>
<td>35</td>
<td>DSM-IV</td>
<td>Sexual abuse/rape, death of close person, accident, physical disease</td>
<td>Internet-based CBT</td>
<td>Waiting list (Passive)</td>
<td>5 weeks, and 10 sessions</td>
<td>(1) Online therapeutic relationship (WAI)</td>
<td>(1) Positive (NR)</td>
</tr>
<tr>
<td>Lloyd et al., 2014</td>
<td>Military, n = 59</td>
<td>CPT: 53.13 (13.97); Treatment as usual: 53.62 (13.33)</td>
<td>CAPS</td>
<td>Military-related PTSD</td>
<td>OPT</td>
<td>Treatment as usual (Active)</td>
<td>12 sessions, and 6 weeks</td>
<td>(1) Anger (Dimensions of Anger Reactions Scale)</td>
<td>(1) Negative (d=0.36)</td>
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<td>(2) Anxiety (STAI)</td>
<td>(2) None (d=0.76)</td>
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<td>(3) Depression (BDI-II)</td>
<td>(3) None (d=0.55)</td>
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<td></td>
<td>(4) Alcohol (Alcohol Use Disorders Identification Test)</td>
<td>(4) None (d=0.23)</td>
<td></td>
</tr>
<tr>
<td>Markowitz et al., 2017</td>
<td>Mainly civilian, n = 110</td>
<td>40.1 (11.6)</td>
<td>DSM-IV</td>
<td>Interpersonal trauma, sexual trauma, and physical trauma</td>
<td>PE</td>
<td>Interpersonal Psychotherapy (Active)</td>
<td>14 weeks and sessions</td>
<td>(1) Type of trauma (LEC)</td>
<td>(1) None</td>
</tr>
<tr>
<td>Price et al., 2012</td>
<td>Military, n = 111</td>
<td>31.66 (8.37)</td>
<td>DSM-IV</td>
<td>Multiple potentially traumatic events</td>
<td>Exposure therapy via telehealth</td>
<td>Exposure therapy inperson (Active)</td>
<td>8 weeks and sessions</td>
<td>(1) Type of trauma (CES)</td>
<td>(1) Negative</td>
</tr>
<tr>
<td>Rauch et al., 2021</td>
<td>Military, n = 196</td>
<td>34.4 (8.4)</td>
<td>DSM-IVTR</td>
<td>Combat-related PTSD</td>
<td>PE plus Placebo</td>
<td>PE + sertraline</td>
<td>12 weeks, and 3 sessions</td>
<td>(1) Alcohol use (number of alcoholic drinks per day)</td>
<td>(1) None (NR)</td>
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<td></td>
<td></td>
<td>(2) Presence of depression (BDI-II)</td>
<td>(2) None (NR)</td>
</tr>
<tr>
<td>Study (year)</td>
<td>Population, sample size</td>
<td>Mean Age (SD)</td>
<td>Diagnostic criterion for PTSD</td>
<td>Type of trauma</td>
<td>Type of intervention</td>
<td>Comparison (active/passive)</td>
<td>Treatment</td>
<td>Independent variables evaluated (instrument)</td>
<td>Influence on CBT response (Effect size)</td>
</tr>
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<tr>
<td>Rizvi et al., 2009</td>
<td>Civilian, n = 145</td>
<td>31.7 (9.8)</td>
<td>CAPS</td>
<td>Discrete incident of completed rape in childhood or adulthood</td>
<td>PE</td>
<td>CPT (Active) Waiting list (Passive)</td>
<td>CPT: 12 weeks and sessions PE: 9 weeks and sessions</td>
<td>(1) Anger (STAXI) (2) Depression severity (BDI)</td>
<td>(1) None (d=0.07) (2) Positive (d=0.05)</td>
</tr>
<tr>
<td>Taylor et al., 2003</td>
<td>Civilian, n = 45</td>
<td>37 (10)</td>
<td>DSM-IV</td>
<td>Sexual assault, physical assault, transport accidents, and being exposed to a sudden death</td>
<td>Exposure therapy</td>
<td>EMDR (Active)</td>
<td>8 weeks and sessions</td>
<td>(1) Multiple traumatic events (CAPS) (2) Dissociative symptoms (CAPS) (3) Anger (PTCI) (4) Depression severity (BDI) (5) Anxiety sensitivity (Anxiety sensitivity Index) (6) Dissociative symptoms (CAPS)</td>
<td>(1) None (NR) (2) None (NR) (3) None (NR) (4) None (NR) (5) None (NR) (6) None (NR)</td>
</tr>
<tr>
<td>Thrasher et al., 2010</td>
<td>Civilian, n = 77</td>
<td>Active treatment: 38.85 (9.92) Relaxation only: 35.60 (10.00)</td>
<td>DSM-III-R</td>
<td>Injury, death, disability</td>
<td>Exposure therapy and/or cognitive restructuring</td>
<td>Waiting list (Passive)</td>
<td>10 weeks and sessions</td>
<td>(1) Type of trauma (CI) (2) Multiple traumatic events (DSM-III-R and CAPS)</td>
<td>(1) None (NR) (2) None (NR)</td>
</tr>
<tr>
<td>Wagner et al., 2012</td>
<td>Civilian, n = 47</td>
<td>27.7 (7.0)</td>
<td>Posttraumatic Diagnostic Scale</td>
<td>Killing of a family member, torture/violence related to war, others</td>
<td>Internet-based CBT</td>
<td>Waiting list (Passive)</td>
<td>5 weeks, and 10 sessions</td>
<td>(1) Therapeutic alliance (WAI)</td>
<td>(1) Positive</td>
</tr>
<tr>
<td>Zandberg et al., 2016</td>
<td>Civilian and military, n = 165</td>
<td>42.78 (9.76)</td>
<td>DSM-IV</td>
<td>Sexual assault, combat, physical assault, other trauma</td>
<td>Placebo and PE Naltrexone and PE (Active) Naltrexone and no PE (Active) Placebo and no PE (Passive)</td>
<td>24 weeks, 18 sessions</td>
<td>(1) Alcohol features (TFBI and PACS) (2) Type of trauma (NR) (3) PTSD severity (PSS-I)</td>
<td>(1) None (NR) (2) Negative (NR) (3) Negative (NR)</td>
<td></td>
</tr>
<tr>
<td>Zang et al., 2019</td>
<td>Civilian, n = 96</td>
<td>32.20 (9.94)</td>
<td>PSS-I</td>
<td>Childhood sexual abuse or adulthood sexual or physical assault</td>
<td>PE with cognitive restructuring</td>
<td>PE (Active) Waiting list (Passive)</td>
<td>8 sessions</td>
<td>(1) Presence of depression (SCID-I) (2) Pretreatment PTSD severity (PSS-SR)</td>
<td>(1) Positive (OR=5.82) (2) None (OR=1.17)</td>
</tr>
</tbody>
</table>

Note. BD-II = Beck depression inventory–II; CAPS = Clinician Administered PTSD Scale; CBT = Cognitive-behavioral therapy; CES = Combat experiences scale; CPT = Cognitive processing therapy; DSM-III-R = Diagnostic and statistical manual of mental disorders, 3rd edition revised; DSM-IV = Diagnostic and statistical manual of mental disorders, 4th ed.; DSM-V = Diagnostic and statistical manual of mental disorders, fifth edition, text revision; DSM-5 = Diagnostic and statistical manual of mental disorders, 5th edition; EMDR = Eye movement desensitization and reprocessing; HSCL = Hopkins symptom checklist; IES = Impact of Events Scale; LEC = Life events checklist; NMR = Negative mood regulation scale; NR = Not reported; OR = Odds ratio; PACS = Penn alcohol craving scale; PCL = PTSD Symptom Checklist; PE = Prolonged exposure; PSS-I = PTSD symptom scale interview; PSS-SR = PTSD Symptom Scale-Self Report; PTCI = Posttraumatic cognitions inventory; SAI = Standardized assault interview; SCID-I = Structured Clinical Interview for DSM-IV for Axis I Disorders; SCID-II = Structured clinical interview for DSM-IV Axis II personality disorders; SCID-IV = Structured clinical interview for DSM-5; ST = Stress inoculation training; STAI = State Trait Anxiety Inventory; STAR = Skills training in affective and interpersonal regulation; STAXI = State-trait anger expression inventory; TFBI = Timeline follow-back interview; WAI = Working alliance inventory.
Hispanic patients were associated with a good response to PE in one study\(^\text{22}\). Race or ethnicity was non-significant to exposure therapy, and (or) cognitive restructuring in two studies\(^\text{30,34}\).

A summary of the RCTs investigating all patient-related factors, the effect size of each variable, and their impact on CBT response can be found in table 1.

### Clinical and treatment characteristics

Depression as a comorbidity was found to predict good response to prolonged exposure (PE) with cognitive restructuring in one study\(^\text{31}\), a worse response to EMDR in one study\(^\text{32}\), and was non-significant to skills training for affective and interpersonal regulation (STAIR) with exposure, EMDR, CPT, exposure therapy and (or) cognitive restructuring, and CBT in five studies\(^\text{27,29,36-39}\).

Depression severity predicted a better response to STAIR, narrative therapy, PE, and CPT in two studies\(^\text{38,40}\), a worse response to EMDR in one study\(^\text{32}\), and non-significant to CBT and PE in three studies\(^\text{26,30,41}\).

The severity of PTSD at baseline predicted a good response to CBT, EMDR, imaginal exposure, and cognitive restructuring in two studies\(^\text{26,31}\), a worse response to CPT and PE in two studies\(^\text{30,37}\), and was found non-significant to PE with cognitive restructuring and STAIR with exposure in two studies\(^\text{31,36}\).

Regarding the type of trauma, combat trauma was associated with a worse response to exposure therapy in two studies\(^\text{30,42}\) and non-significant to CBT in one study\(^\text{38}\). The injury was a predictor of worse response to PE and stress inoculation training in one study\(^\text{41}\), and non-significant to exposure therapy and (or) cognitive restructuring in two studies\(^\text{39,44}\). Sexual trauma was found as a predictor of bad response to PE in one study\(^\text{30}\) and was non-significant to PE in another one\(^\text{44}\).

Anger was a predictor of worse response to CPT in one study\(^\text{18}\) and was non-significant to STAIR with exposure and CPT in four studies\(^\text{28,36,41,45}\).

Multiple traumatic events predicted a worse response to CPT, PE and stress inoculation training in two studies\(^\text{43,46}\), and was non-significant to CPT, exposure therapy and (or) cognitive restructuring, and EMDR in two studies\(^\text{28,41}\).

Alcohol use was non-significant to PE and CPT in all three studies\(^\text{27,30,38}\). Dissociative symptoms were also not significant for STAIR with PE, EMDR, and PE in all three studies\(^\text{36,41,47}\).

Anxiety sensitivity predicted a worse response to PE in only one study\(^\text{40}\) and was non-significant to CPT and exposure therapy in two studies\(^\text{30,41}\).

Comorbid personality disorders predicted a worse response to PE, cognitive restructuring, and stress inoculation training in two studies\(^\text{48,49}\), and were non-significant to PE in one study\(^\text{39}\).

Therapeutic alliance predicted a good response to internet-based CBT, EMDR, and modified PE in all three studies\(^\text{50-52}\).

A summary of the RCTs investigating clinical and treatment characteristics variables, the effect size of each variable, and their impact on CBT response can be found in table 2.

### Risk of bias

The results of the assessment of the methodological quality of the 27 selected studies are shown in figures 2 and 3. Of these, eight showed a low risk of bias, 19 showed some concerns, and only one showed a high potential risk of bias. Eleven studies adequately described the randomization process. Two studies showed deviations from the intended interventions. Only one study did not include sufficient outcome data in the final analysis. In 25 studies, there were no errors in the measurement of the outcome. There was the risk of bias in the selection of the reported outcome in only two studies.

Of the three studies that evaluated the therapeutic alliance as a predictor of good response, two studies\(^\text{30,51}\) showed some concerns, and only one\(^\text{51}\) showed a high risk of bias regarding the randomization process, deviations from intended interventions, and errors in the measurement of results.

### DISCUSSION

Although cognitive-behavioral therapy is considered the first-line treatment for posttraumatic stress disorder\(^\text{3,31}\), no systematic review has previously investigated the predictors of CBT response in PTSD patients. Our systematic review of the literature showed that, until now, there are no variables related to the patient, as well as clinical and treatment characteristics.
Predictors of response to CBT found mixed results regarding a variety of variables. In a narrative review published in 2008, Schottenbauer et al. found mixed results regarding a variety of variables such as type of trauma, presence of depression, anxiety, guilt, anger, and comorbid personality disorders. Therefore, no definitive conclusion could be drawn regarding the potential of these variables in predicting the response to CBT in patients with PTSD. However, the authors have suggested that the severity of PTSD at baseline could predict a worse response to CBT. Contrary to Schottenbauer et al., we have only included RCTs in our review, given this design’s reliability and level of scientific evidence, which could explain this difference. In a narrative review published in 2008, Schottenbauer et al. found mixed results regarding a variety of variables such as type of trauma, presence of depression, anxiety, guilt, anger, and comorbid personality disorders. Therefore, no definitive conclusion could be drawn regarding the potential of these variables in predicting the response to CBT in patients with PTSD. However, the authors have suggested that the severity of PTSD at baseline could predict a worse response to CBT. Contrary to Schottenbauer et al., we have only included RCTs in our review, given this design’s reliability and level of scientific evidence, which could explain this divergent result. Our finding is consistent with Dewar et al. (2019), who found heterogeneous results in the severity of PTSD symptoms.

The only variable that predicted a good response to CBT in PTSD patients was the therapeutic relationship. All three RCTs (comprising a total of 201 patients) found that a good therapeutic relationship can foresee a good response. In line with this, Brady et al. (2015) found that a better quality of the collaborative working relationship between patients and therapists was related to a better response to therapy. The therapeutic relationship can be known as the collaborative bond between therapist and patient that develops through trust, and it is indispensable for the therapeutic process. An adequate therapeutic alliance is needed to...
incorporate a sense of safety, support, caring, and compassion in the trauma narrative. This new information may be critical to reconsolidate the trauma memory in a manner that regularizes the emotional experience associated with the trauma. It is noteworthy that it is possible to establish a healthy therapeutic alliance for face-to-face and online treatment. Therefore, it is not surprising that the therapeutic alliance has proven to be a predictor of a good response, but only three RCTs have been evaluated. Additional studies should be conducted to improve the understanding of this variable as a response predictor and thus optimize the effectiveness of PTSD treatment.

To identify studies with the most reliable results, we critically assessed the risk of bias of all included studies. Overall, the methodological quality of the studies was good. Of the three studies that evaluated the therapeutic relationship, two showed some concerns, and one study showed a high risk of bias. Although a single study showed a high risk of bias, it is in line with the other two that also evaluated therapeutic relationships as a predictor variable of good response to CBT.

Some limitations of this systematic review should be considered. First, each variable had its relationship with the outcome investigated by a small number of RCTs. Second, there is methodological heterogeneity among selected studies regarding the type of technique (cognitive restructuring, exposure in vivo, imaginal, in group, individual), duration of treatment (varying between five and 24 weeks), and type of comparison (treatment active and passive). Ideally, we should compare more homogeneous groups of traumatized patients receiving similar CBT techniques, however, the small number of studies investigating each predictor impairs these analyses. Finally, these factors mentioned above precluded us from performing a meta-analytic study.

CONCLUSIONS

Although numerous variables have shown conflict in the results, this does not mean that there is no precise predictor of response to CBT. The most promising variable, despite weak scientific evidence, is the therapeutic relationship. Therefore, more RCTs should be performed to definitively clarify the role of this variable as a predictor of the response to CBT in patients suffering from PTSD. The identification of this and other predictors would guide clinicians to prescribe the best-personalized treatment for each patient and therefore abbreviate the time of the disorder.

INDIVIDUAL CONTRIBUTIONS

Jéssica Paiva – Conceptualization, methodology, study selection, and data extraction.

Marina Melani – Study selection, data extraction, and editing.

Raquel Gonçalves – Writing, critical review, and editing.

Mariana Luz – Writing, critical review, and editing.

Mauro Mendelowicz – Writing, critical review, and editing.

Ivan Figueira – Writing, critical review, and editing.

Cheyenne von Arcosy – Writing and editing.

Paula Ventura – Conceptualization, methodology, writing, and editing.

William Berger – Supervision, conceptualization, methodology, writing, critical review, and editing.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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REFERENCES

Predictors of response to CBT


