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

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

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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

Cognitive-behavioral therapy, CBT, posttraumatic stress disorder, PTSD, predictor of response, systematic review

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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[1]. In the general population, the diagnosis of PTSD increases by 13 times the rate of death by suicide when compared with people without PTSD[2]. Although severe, PTSD is quite frequent in the general population worldwide, with a 12 monthly prevalence achieving 3.8% in some European countries[3], and 5% in South American countries[4]. Despite already being highly prevalent, PTSD rates have been increasing among the general population in the last 15 years[5].

The first-line intervention to treat people with PTSD is cognitive-behavioral therapy (CBT)[6]. CBT is effective for treating PTSD symptoms caused by diverse types of trauma and also comorbid disorders frequently associated with PTSD[7]. The basic components of CBT for PTSD include psychoeducation, exposure techniques, cognitive restructuring, and anxiety management[8]. Exposure therapy has sufficient evidence to support its efficacy in treating PTSD showing an important clinical benefit[9]. This treatment involves confronting their fears – either in imaginary or in vivo forms –, varying duration, and the arousal level during exposure[10].

Although CBT is recommended as the first-line intervention for treating PTSD by most guidelines[11,12], many patients continue suffering from the disorder after treatment[13]. Even when treated with prolonged exposure (PE), one of the most effective interventions, not everyone will benefit[14] up to 45% continue to meet the diagnostic criteria for PTSD immediately after therapy, and 44% after 3.5 months of follow-up[15,16]. Although there is little scientific evidence about the predictors of response to CBT[16,17], some studies indicated patient factors as responsible for up to 87% of outcome divergence[18,19]. Previous studies on response predictors have been conducted. However, exclusively investigated biomarkers as possible predictors of response to CBT in the treatment of PTSD[20], or addressed several different psychotherapies[21], or did not perform a systematic review[17].

Therefore, it is necessary to systematically review the literature for randomized controlled trials investigating possible predictors of response to CBT for PTSD[21]. Finding these predictors, the mental health assistants could deliver more refined treatment procedures[17], optimizing the efficacy of PTSD treatment[22]. 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[23]. 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 PTSDpubs (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[24] 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 found 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[25] and was non-significant to CBT, PE, and CPT in six studies[26-31].

The female gender predicted a better response to cognitive therapy and imaginal exposure in only one RCT[32], while it was non-significant to CBT, eye movement desensitization and reprocessing (EMDR), exposure therapy, and (or) cognitive restructuring, CPT in five studies[25,27,29,30,33].

The level of education was non-significant to CBT, PE, and CPT in all three studies[25,28,30].

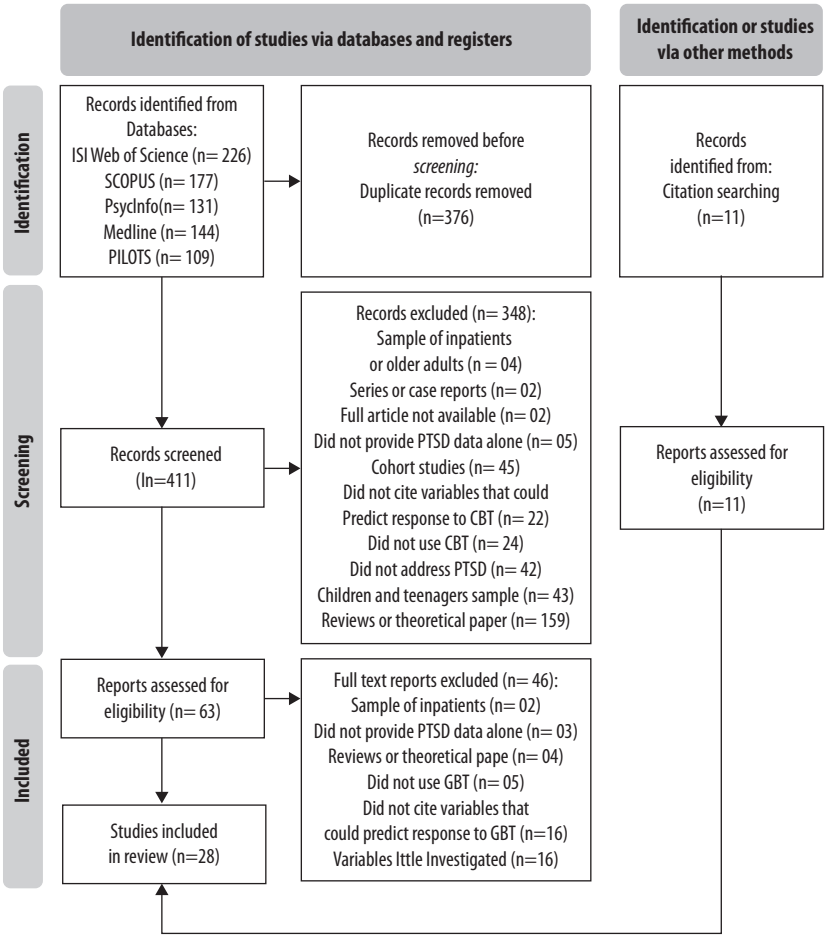

Figure 1. The PRISMA 2020 Flow Diagram illustrating the study selection process.

Table 1. Description of RCTs Investigating Patient-Related Factors as Possible Predictors of Response to CBT

Study (year)	Population, sample size	Mean Age (SD)	Diagnostic criterion for PTSD	Type of trauma	Type of intervention	Comparison (active/passive)	Treatment	Independent variables evaluated (instrument)	Influence on CBT response (Effect size)
Beck et al., 2021	Military n =175	CBT: 54.9 (11.54); Present centered therapy: 57.7 (12.10)	CAPS-5	Combat trauma	CBT	Present centered therapy	16 weeks and 14 sessions	(1) Age (pretreatment assessment)	(1) None (NR)
Karatzias et al., 2007	Civilian, n = 48	40.6 (11.4)	DSM-IV	Accident, crime, other	EMDR	Imaginal exposure + cognitive restructuring (Active)	12 weeks and sessions	(1) Gender (SDQ)	(1) None (NR)
Rauch et al., 2021	Military n =196	34.4 (8.4)	DSM-IV-TR	Combat related PTSD	PE plus placebo	PE + sertraline Sertraline + enhanced medication management	12 weeks, and 3 sessions	(1) Age (NR)	(1) None (NR)
Resick et al., 2020	Military, n =165	34.2 (7.3)	DSM-IV	Combat- related, dath (noncombat), sexual assault, physical assault, and accident	Individual CPT	Group CPT (Active)	12 sessions, and 6 weeks	(1) Younger age (Form developed by the research group) (2) Military and deployment variables (Form developed by the research group)	(1)Positive (NR) (2)None (NR)
Rizvi et al., 2009	Civilian, n =145	31.7 (9.8)	CAPS	Discrete incident of completed rape in childhood or adulthood	PE	CPT (Active) Waiting list (Passive)	CPT: 12 weeks and sessions PE: 9 weeks and sessions	(1) Age (Standardized trauma interview) (2) Level of education (Standardized trauma interview)	(1) None (d=0.41) (2) None (d=0.02)
Ruglass & Yali, 2019	Civilian, n =107	Black/African American: 45.49 (8.77); White/ Caucasian: 44.00 (9.07); Hispanic/Latino: 41.86 (11.10)	SCID-I	Physical assault, sexual assault, accident or disaster, sudden injury or death of other, other	Concurrent Treatment with PE	Relapse Prevention Therapy (Active) Relaxation Groups (Active)	12 weeks	(1) Race/ethnicity (baseline interview)	(1) None (NR)
Tarrier et al., 2000	Civilian, n =62	36.82 (11.60)	DSM III-R	Crime, accident and other	Cognitive therapy	Imaginal exposure (Active)	16 weeks and sessions	(1) Gender (NR)	(1) Positive (NR)
Thrasher et al., 2010	Civilian, n=77	Active treatment: 38.85 (9.92); Relaxation 35.60 (10.00)	DSM-III-R	Injury, death, disability, and disfigurement	Exposure therapy and /or cognitive restructuring	Relaxation Groups (Active)	10 weeks and sessions	(1) Gender (CI) (2) Age (CI)	(1) None (NR) (2) None (NR)
Zandberg et al., 2016	Civilian and military n =165	42.78 (9.76)	DSM-IV	Sexual assault, combat, physical assault, other trauma	Placebo and PE	Naltrexone and PE (Active) Naltrexone and no PE (Active) Placebo and no PE (Passive)	24 weeks, 18 sessions	(1) Level of education (NR)	(1) None (NR)
Zang et al., 2019	Civilian, n=96	32.20 (9.94)	PSS-I	Childhood sexual abuse or adulthood sexual or physical assault	PE with cognitive restructuring	PE with cognitive restructuring Waitlist (Passive)	8 sessions	(1) Age (SAI)	(1) None (OR=0.98)

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

Study (year)	Population, sample size	Mean Age (SD)	Diagnostic criterion for PTSD	Type of trauma	Type of intervention	Comparison (active/ passive)	Treatment	Independent variables evaluated (instrument)	Influence on CBT response (Effect size)
Assmann et al., 2021	Civilian (155)	38.54 (11.17)	CAPS-5	Childhood trauma	EMDR	Imagery rescripting (Active)	6 weeks, and 12 sessions	(1) Presence of Depression (BDI-II)	(1) None (d=1.22)
Beck, et al., 2021	Military (175)	CBT: 54.9 (11.54); Present centered therapy: 57.7 (12.10)	CAPS-5	Combat trauma	CBT	Present centered therapy (Active)	16 weeks, and 14 sessions	(1) PTSD severity (PCL-5) (2) Depression severity (BDI-II) (3) Type of trauma (Traumatic Life Events Checklist (TLEQ)	(1) Positive (d=1.31) (2) None (NR) (3) None (NR)
Bosch et al., 2020	Civilian and military, n = 126	46.5 (11.9)	CAPS-IV	Neglect, sexual abuse, and physical abuse	CPT via videoteleconferencing	CPT inperson (Active)	12 sessions, once or twice per week	(1) Type of trauma (Childhood traumatic events)	(1)Negative (NR)
Cahill et al., 2003	Civilian, n = 67	34.6 (10.5)	DSM-III-R	Female assault victims	PE	SIT (Active) PE and SIT (Active)	5 weeks, 9 sessions	(1) Anger (STAEI)	(1) None (d=3.43)
Cloitre et al., 2017	Civilian, n = 104	36.48 (9.39)	DSM-IV	Childhood sexual and/ or physical abuse	STAIR	Narrative therapy (Active)	16 weeks and sessions	(1) Depression severity (BDI-II)	(1) Positive (d=0.29)
Cloitre et al., 2002	Civilian, n = 58	34 (7.22)	DSM-IV	Childhood abuse	STAIR and Modified PE	Waiting list (Passive)	12 weeks, 16 sessions	(1) Therapeutic alliance (WAI)	(1) Positive (NR)
Cloitre et al., 2016	Civilian, n = 104	36.48 (9.39)	DSM-IV	Childhood sexual and/ or physical abuse occurring before the age of 18	STAIR and PE	STAIR and supportive counselling (Active)	16 weeks and sessions	(1) PTSD severity (CAPS) (2) Presence of depression (BDI-II) (3) Dissociation (Dissociation subscale of the Trauma Symptoms Inventory) (4) Anger (STAEI) (5) Negative mood regulation (NMR)	(1) None (NR) (2) None (NR) (3) None (NR) (4) None (NR) (5) None (NR)
Feeny et al., 2002	Civilian, n = 72	34.9 (10.06)	DSM-III-R	Female victims of sexual and nonsexual assault	PE	SIT (Active) PE and SIT (Active) Waiting list (Passive)	9 weeks and sessions	(1) Borderline personality characteristics (SCID-II)	(1) Negative (NR)
Gobin et al., 2018	Civilian and military, n = 126	Veterans: 42.05 (10.58) Civilians: 47.30 (12.03)	DSM-IV	Physical assault, child sexual abuse, adult sexual assault)	CPT via clinical vídeo teleconferencing	Treatment traditional (in-person modality) (Active)	12 weeks and sessions	(1) PTSD severity (CAPS) (2) Presence of depression (BDI-II)	(1) Negative (NR) (2) None (NR)

Study (year)	Population, sample size	Mean Age (SD)	Diagnostic criterion for PTSD	Type of trauma	Type of intervention	Comparison (active/ passive)	Treatment	Independent variables evaluated (instrument)	Influence on CBT response (Effect size)
Haagen et al., 2017	Civilian and military, n = 72	41.5 (11.3)	DSM-IV-TR	Murder of friends/ family , combat situation, physical torture, imprisonment , serious injury, rape or sexual abus	EMDR	Stabilization therapy (Active)	EMDR: 9 weeks and sessions; Stabilizatio n therapy: 12 weeks and sessions	(1) Presence of depression (HSCL) (2) Depression severity (HSCL)	(1) Negative (NR) (2) Negative (NR)
Halvorsen et al., 2014	Military, n = 81	35.55 (11.05)	DSM-5	Severely traumatised asylum seekers and refugees	Narrative exposure therapy	Treatment as usual (Active)	10 weeks and sessions	(1) Dissociative symptoms such as derealisation and depersonalisation (CAPS)	(1) None (Derealisation: g=1.36; Depersonalisation: g=0.97)
Hembree et al., 2004	Civilian, n = 75	32 (10)	DSM-IV	Rape or nonsexual assault in adulthood or sexual abuse in childhood	PE	PE with cognitive restructuring (Active)	NR	(1) Comorbid personality disorders (SCID II)	(1) Negative (NR)
Hembree et al., 2004	Civilian, n = 73	35.7 (10.1)	DSM–III–R	Female assault victims	PE	SIT (Active)	5–6 weeks, 9 sessions	(1) Multiple traumatic events (SAI)	(1) Negative (NR)
Karatzias et al., 2007	Civilian, n = 48	40.6 (11.4)	DSM-IV	Accident, crime, other	EMDR	Treatment as usual (Active)	12 weeks and sessions	(1) PTSD severity (CAPS, IES and PCL)	(1) Positive (NR)
Knaevelsrud & Maercker, 2007	Civilian, n = 96	35	DSM-IV	Sexual abuse/ rape, death of close person, accident, physical disease	Internet-based CBT	Waiting list (Passive)	5 weeks, and 10 sessions	(1) Online therapeutic relationship (WAI)	(1) Positive (NR)
Lloyd et al., 2014	Military, n = 59	CPT: 53.13 (13.97); Treatment as usual: 53.62 (13.33)	CAPS	Military-related PTSD	CPT	Treatment as usual (Active)	12 sessions, and 6 weeks	(1) Anger (Dimensions of Anger Reactions Scale) (2) Anxiety (STAI) (3) Depression (BDI-II) (4) Alcohol (Alcohol Use Disorders Identification Test)	(1) Negative (d=0.36) (2) None (d=0.76) (3) None (d=0.55) (4) None (d=0.23)
Markowitz et al., 2017	Mainly civilian, n = 110	40.1 (11.6)	DSM-IV	Interpersonal trauma, sexual trauma, and physical trauma	PE	Interpersonal Psychotherapy (Active)	14 weeks and sessions	(1) Type of trauma (LEC)	(1) None
Price et al., 2012	Military, n = 111	31.66 (8.37)	DSM-IV	Multiple potentially traumatic events	Exposure therapy via telehealth	Exposure therapy inperson (Active)	8 weeks and sessions	(1) Type of trauma (CES)	(1) Negative
Rauch et al., 2021	Military, n = 196	34.4 (8.4)	DSM-IVTR	Combat-related PTSD	PE plus Placebo	PE + sertraline Sertraline + Enhanced Medication management	12 weeks, and 3 sessions	(1) Alcohol use (number of alcoholic drinks per day) (2) Presence of depression (BDI-II)	(1) None (NR) (2) None (NR)

Study (year)	Population, sample size	Mean Age (SD)	Diagnostic criterion for PTSD	Type of trauma	Type of intervention	Comparison (active/ passive)	Treatment	Independent variables evaluated (instrument)	Influence on CBT response (Effect size)
Rizvi et al., 2009	Civilian, n = 145	31.7 (9.8)	CAPS	Discrete incident of completed rape in childhood or adulthood	PE	CPT (Active) Waiting list (Passive)	CPT: 12 weeks and sessions PE: 9 weeks and sessions	(1) Anger (STAXI) (2) Depression severity (BDI)	(1) None (d=0.07) (2) Positive (d=0.05)
Taylor et al., 2003	Civilian, n = 45	37 (10)	DSM-IV	Sexual assault, physical assault, transport accidents, and being exposed to a sudden death	Exposure therapy	EMDR (Active)	8 weeks and sessions	(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)	(1) None (NR) (2) None (NR) (3) None (NR) (4) None (NR) (5) None (NR) (6) None (NR)
Thrasher et al., 2010	Civilian, n = 77	Active treatment: 38.85 (9.92) Relaxation only: 35.60 (10.00)	DSM-III-R	Injury, death, disability	Exposure therapy and/or cognitive restructuring	Waiting list (Passive)	10 weeks and sessions	(1) Type of trauma (CI) (2) Multiple traumatic events (DSM-III-R and CAPS)	(1) None (NR) (2) None (NR)
Wagner et al., 2012	Civilian, n = 47	27.7 (7.0)	Posttraumatic Diagnostic Scale	Killing of a family member, torture/violence, sexual violence related to war, others	Internet-based CBT	Waiting list (Passive)	5 weeks, and 10 sessions	(1) Therapeutic alliance (WAI)	(1) Positive
Zandberg et al., 2016	Civilian and military, n = 165	42.78 (9.76)	DSM-IV	Sexual assault, combat, physical assault, other trauma	Placebo and PE	Naltrexone and PE (Active) Naltrexone and no PE (Active) Placebo and no PE (Passive)	24 weeks, 18 sessions	(1) Alcohol features (TFBI and PACS) (2) Type of trauma (NR) (3) PTSD severity (PSS-I)	(1) None (NR) (2) Negative (NR) (3) Negative (NR)
Zang et al., 2019	Civilian, n = 96	32.20 (9.94)	PSS-I	Childhood sexual abuse or adulthood sexual or physical assault	PE with cognitive restructuring	PE (Active) Waiting list (Passive)	8 sessions	(1) Presence of depression (SCID-I) (2) Pretreatment PTSD severity (PSS-SR)	(1) Positive (OR=5.82) (2) None (OR=1.17)

Note. BDI-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; DSMIV- TR = Diagnostic and statistical manual of mental disorders, fourth 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-IV; SIT = Stress inoculation training; STAI = State Trait Anxiety Inventory; STAIR = Skills training in affective and interpersonal regulation; STAXI = State-trait anger expression inventory; TFBI = Timeline follow-back interview; WAI = Working alliance inventory.

Table 3. Number of RCTs Investigating Each Possible Predictor of Response to CBT In Patients With PTSD

Possible Predictor investigated	Number of RCTs
Age	7
Alcohol use	3
Anger	5
Anxiety	3
Comorbid personality disorders	3
Depression severity	6
Dissociative symptoms	3
Gender	6
Level of education	3
Multiple traumatic events	4
Presence of depression	8
PTSD severity	6
Race or ethnicity	3
Therapeutic relationship	3
Type of trauma	6

Hispanic patients were associated with a good response to PE in one study[27]. Race or ethnicity was non-significant to exposure therapy, and (or) cognitive restructuring in two studies[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[31], a worse response to EMDR in one study[35], 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[27,29,36-39].

Depression severity predicted a better response to STAIR, narrative therapy, PE, and CPT in two studies[28,40], a worse response to EMDR in only one study[32], and non-significant to CBT and PE in three studies[26,30,41].

The severity of PTSD at baseline predicted a good response to CBT, EMDR, imaginal exposure, and cognitive restructuring in two studies[26,33], a worse response to CPT and PE in two studies[30,37], and was found non-significant to PE with cognitive restructuring and STAIR with exposure in two studies[31,36].

Regarding the type of trauma, combat trauma was associated with a worse response to exposure therapy in two studies[30,42] and non-significant to CBT in one study[26]. The injury was a predictor of worse response to PE and stress inoculation training in one study[43], and non-significant to exposure therapy and (or) cognitive restructuring in two studies[29,44]. Sexual trauma was found as a predictor of bad response to PE in one study[30] and was non-significant to PE in another one[44].

Anger was a predictor of worse response to CPT in one study[38] and was non-significant to STAIR with exposure and CPT in four studies[28,36,41,45].

Multiple traumatic events predicted a worse response to CPT, PE and stress inoculation training in two studies[43,46], and was non-significant to CPT, exposure therapy and (or) cognitive restructuring, and EMDR in two studies[29,41].

Alcohol use was non-significant to PE and CPT in all three studies[27,30,38]. Dissociative symptoms were also not significant for STAIR with PE, EMDR, and PE in all three studies[36,41,47].

Anxiety sensitivity predicted a worse response to PE in only one study[30] and was non-significant to CPT and exposure therapy in two studies[38,41].

Comorbid personality disorders predicted a worse response to PE, cognitive restructuring, and stress inoculation training in two studies[48,49], and were non-significant to PE in one study[30].

Therapeutic alliance predicted a good response to internet-based CBT, EMDR, and modified PE in all three studies[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[50,51] showed some concerns, and only one[52] 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[5,53], 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

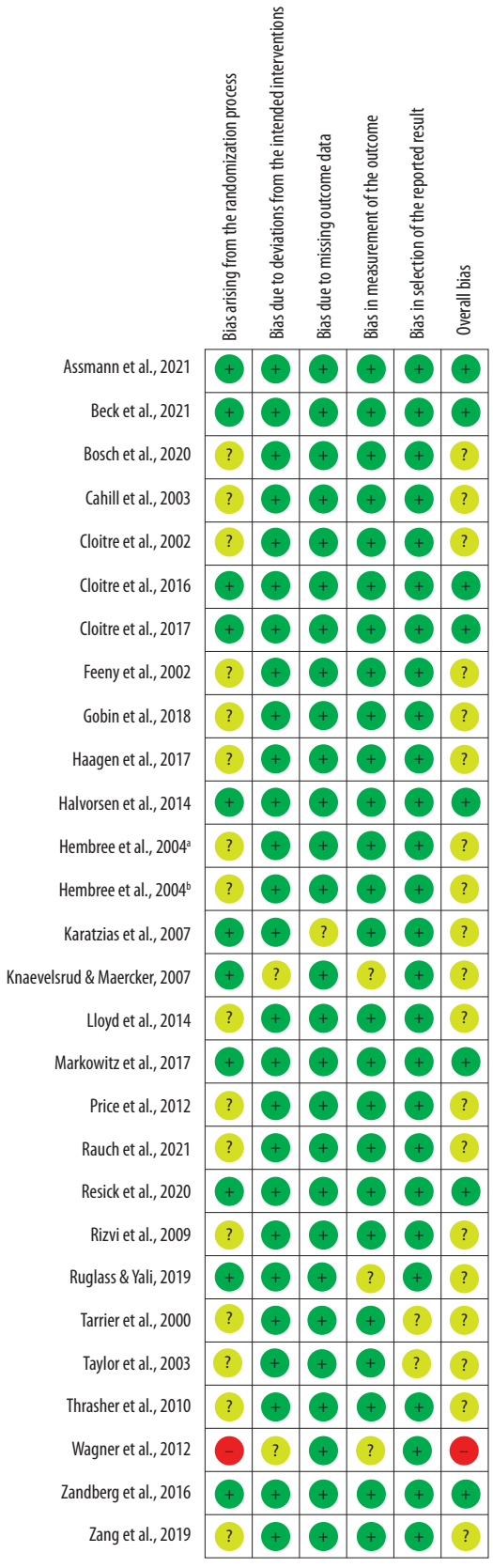

Figure 2. Risk of bias summary for Randomized Controlled Trials (RoB 2.0 tool); +: low risk of bias; –: high risk of bias; ?: some concerns for potential risk of bias.

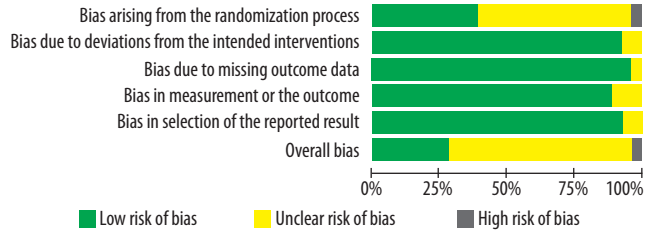

Figure 3. Risk of bias graph for randomized controlled trials (RoB 2.0 tool).

characteristics that could reliably predict the response to CBT in patients with PTSD.

Even the most frequently investigated variable (presence of depression) showed conflicting results. Contrary to our results, a review found the presence of depression to be a predictor of worse response. However, more research is needed, given that those who responded to therapy did not necessarily have lower levels of depression symptoms[21].

In contrast to the previous findings on combat trauma as a predictor of good response to treatment[54,55], most studies in the present review have indicated that variable as a predictor of worse response to CBT. Noteworthy, the present study presents a sample that is composed mainly of men (75.72%) with comorbidities such as depression and alcohol dependence, which could explain this difference.

In a narrative review published in 2008, Schottenbauer *et al.*[17] 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. While our systematic review corroborates the first part, we did not find that PTSD severity could predict a worse response to CBT. Contrary to Schottenbauer *et al.*[17], 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)[21], 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[50-52]. In line with this, Brady *et al.* (2015)[56] 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[57]. 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[58]. It is noteworthy that it is possible to establish a healthy therapeutic alliance for face-to-face and online treatment[51,59,60]. 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 impaired 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[36,37,61].

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 Mendlowicz – 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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