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LITERATURE REVIEW

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Defining response and nonresponse to posttraumatic stress disorder treatments: A systematic review

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Abstract

There is currently no uniform definition of treatment response for posttraumatic stress disorder (PTSD) to guide researchers and clinicians in the area of posttraumatic mental health. The aim of this systematic review was to explore the operationalization of PTSD treatment response, by reviewing and synthesizing the key criteria used to define treatment response and treatment nonresponse in published trials. Randomized controlled trials (RCTs) assessing the effectiveness of first-line interventions for PTSD were identified for inclusion. Of those, 143 trials provided 226 definitions of treatment response, grouped under five main categories: *treatment response* (n = 181), *remission* (n = 23), *recovery* (n = 5), *treatment nonresponse* (n = 5), *and worsening* (n = 12). Overall, the results showed the PTSD field utilizes diverse and interchangeable operational definitions of treatment response and nonresponse, indicating a need for more precise conceptual definitions and operational criteria. A set of operational research definitions are presented in order to advance the PTSD treatment field.

KEYWORDS

pharmacological interventions, posttraumatic stress disorder, psychological interventions, treatment nonresponse, treatment response

1 | INTRODUCTION

Posttraumatic stress disorder (PTSD) is precipitated by exposure to traumatic events and consists of symptoms of intrusion, avoidance, arousal, negative cognitions, and negative mood (American Psychiatric Association; APA, 2013). PTSD affects approximately 6.8%–9.2% of adults during their lifetime (Kessler et al., 2005; McEvoy, Grove, & Slade, 2011). However, lifetime prevalence estimates are much higher for interpersonal trauma (e.g., rape or torture), as well as combat and military-related trauma (Breslau, Peterson, Poisson, Schultz, & Lucia, 2004; Goldberg et al., 2016). PTSD is also associated with significant mental and physical distress, impairments in functioning, and reduced quality of life (Nemeroff et al., 2006; Olatunji, Cisler, & Tolin, 2007; Rodriguez, Holowka, & Marx, 2012).

Multiple international guidelines for the treatment of PTSD recommend trauma-focused cognitive behavioral therapies as first-line interventions (Forbes et al., 2010). Overall, trauma-focused treatments have demonstrated effectiveness

(Larsen, Fleming, & Resick, 2019), but many individuals fail to improve (Koek et al., 2016). A significant proportion of those who complete a course of psychological or pharmacological treatment still meet criteria for PTSD or are left with residual symptoms (Larsen et al., 2019). Nonresponse to psychotherapies is even higher in military or refugee populations (Gerger, Munder, & Barth, 2014; Steenkamp, Litz, Hoge, & Marmar, 2015).

Despite widespread recognition of the complexity relating to recovery from PTSD, the treatment outcome literature is difficult to interpret because there is a lack of clear guidance on what constitutes treatment response or nonresponse (Forbes et al., 2019; Sippel, Holtzheimer, Friedman, & Schnurr, 2018). Efforts to provide clarity in this space have conceptualized response to treatment as a continuum, ranging from nonresponse to response, remission, and recovery (Smith-Apeldoorn, Veraart, & Schoevers, 2019). *Nonresponse* is defined as achieving minimal to no symptomatic improvement at post-treatment; *treatment response* is typically defined as a significant pre- to post-treatment symptom reduction (usually with the presence of residual symptoms); *remission* is considered improvement to, or attainment of, the asymptomatic stage of the disorder (i.e., no longer meeting formal diagnostic criteria with minimal residual symptoms); *recovery* is sustained remission; and *worsening* (including *relapse*) is usually defined as the exacerbation, deterioration, persistence, or return of clinically significant symptoms during treatment (Smith-Apeldoorn et al., 2019). Of note, the terms treatment nonresponse, treatment resistance, and treatment refractory (i.e., occurrence of an inadequate response following adequate treatment; McFarlane, 2019) are terms often used interchangeably (for a more detailed discussion, see Smith-Apeldoorn et al., 2019). Another common conceptualization of response to treatment is *loss of diagnosis*, defined as the absence of a PTSD diagnosis at post-treatment (Smith-Apeldoorn et al., 2019).

In contrast to clinical practice, in research settings treatment outcomes are typically defined in terms of symptom changes, rather than functional outcomes (Smith-Apeldoorn et al., 2019). Furthermore, when it comes to defining response as an absolute symptom reduction, the decrease in symptoms determined to be statistically significant can fail to translate into clinically meaningful improvement in the day-to-day function of treatment seekers. Many still meet criteria for a diagnosis of PTSD and have persistent problems (Berger et al., 2009).

In addition to the criticism of measuring treatment outcomes in terms of symptom reductions only, other important targets of therapy are overlooked. These include patient-defined treatment goals, quality of life improvement, and social and economic outcomes (e.g., cost-effectiveness; Cuijpers, 2019). While most research has concentrated on PTSD symptom reduction, these additional treatment targets should be incorporated into treatment priorities, preferably through a shared patient–clinician clinical decision-making process.

Public Health Significance

This systematic review synthesized and categorized the ways that PTSD treatment response and nonresponse are operationalized in the literature. The findings revealed diversity and interchangeability among definitions, which impedes the interpretability of treatment outcome research. Clear definitions of these concepts are necessary to inform PTSD treatment planning.

1.1 | Previous attempts to define PTSD treatment response and nonresponse

The issue of response and nonresponse to PTSD treatment has attracted growing interest over the last decade. Most recently, Sippel et al. (2018) argued that it is critical to develop evidence-based benchmarks and differentiate between treatment response and nonresponse. Specifically, they proposed that an operational definition of treatment resistance will stimulate and guide the development and evaluation of novel treatments; will facilitate the examination of the biological mechanisms underlying poor treatment response; and will assist clinicians to better identify treatment-resistant patients (Sippel et al., 2018). The authors proposed a conceptual staged model of treatment-resistant PTSD that incorporates treatment nonresponse criteria. However, their criteria were not based on a systematic review of the evidence. Others have also discussed the issue of differential definitions for treatment response, nonresponse, and resistance. In particular, Koek et al. (2016) reviewed pharmacological interventions for the treatment of patients whose symptoms were resistant to standard PTSD treatments. As part of their review, the authors extracted definitions of prior treatment failure, but conclusions relating to the definition of treatment response or nonresponse were not provided. The current review will examine how treatment nonresponse including treatment resistance is operationalized and defined in PTSD treatment RCTs.

The failure to define what constitutes treatment response from nonresponse in PTSD stands in stark contrast to work in other mental health disorders such as depression (Frank et al., 1991) and obsessive–compulsive disorder (Pallanti et al., 2002), where definitions have been established in order to clearly differentiate and describe the quality of response to treatment. The categories most often reported include treatment response, partial or nonresponse, treatment resistance, remission,

full or partial recovery, and relapse. Operationalization of these categories for PTSD treatment will ultimately help to inform the development of a clinical algorithm, which will guide treatment and optimize treatment decisions in both clinical practice and clinical trials. To the best of our knowledge, there has been no review that has systematically examined how PTSD treatment response and nonresponse are operationalized in both psychological and pharmacological PTSD treatment trials. The aim of this study is to systematically review how PTSD treatment response and nonresponse have been operationalized, and to propose definitions for these constructs to increase the consistency with which they are applied in research and clinical practice.

2 | METHOD

The findings of this review were reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; Moher, Liberati, Tetzlaff, & Altman, 2009). The study protocol was registered with Prospero (registration ID CRD42019119670[1]). The research question was formulated using the Population, Intervention, Comparison, and Outcome (PICO; Schardt, Adams, Owens, Keitz, & Fontelo, 2007) framework in order to structure, contain, and set the scope for the question. Inclusion criteria were as follows:

1. Peer-reviewed randomized controlled trials (RCTs) published in English;
2. Trials that assessed the efficacy of guideline-recommended first-line psychological, pharmacological, or combined interventions;
3. Treatment that included individual and face-to-face mode of delivery;
4. Sample that comprised adults with a primary diagnosis of PTSD.

Guideline-recommended first-line psychological interventions included in this review were as follows: cognitive behavior therapy (CBT), cognitive processing therapy (CPT), cognitive therapy (CT), prolonged exposure (PE), eye movement desensitization and reprocessing (EMDR), brief eclectic psychotherapy (BEP), narrative exposure therapy (NET), and written narrative exposure therapy. First-line pharmacological interventions recommended by treatment guidelines include sertraline, paroxetine, fluoxetine, and venlafaxine (see Table S1 for more details).

The exclusion criteria were any first-line interventions targeting only one of the PTSD symptoms in isolation (e.g., nightmares); interventions that involved only one component of a first-line treatment (i.e., not a full protocol); or interventions delivered in group format or via virtual reality or telehealth/Internet modalities.

2.1 | Search strategy

Relevant RCTs published from inception to December 21, 2018, were identified via PsycINFO, EMBASE, PubMed (including MEDLINE), CINAHL, and Cochrane Central Register of Controlled Trials (CENTRAL). An example search strategy is provided in Table S2.

2.2 | Data extraction

Trials were selected using a two-stage process: title and abstract screening and full-text assessment. Both stages were undertaken using Covidence, an online systematic review information management system (Veritas Health Innovation).

2.3 | Operational definition synthesis

The operational definitions of treatment response and nonresponse were identified and categorized based on the author's own descriptions rather than a priori definitions. Using this bottom-up approach, five categories emerged: *treatment response, remission, recovery, treatment nonresponse,* and *worsening*. Of note, these categories loosely matched the conceptualizations of treatment response and nonresponse outlined in Smith-Apeldoorn et al. (2019).

Once placed in a response category, definitions were further subcategorized based on details reported in the studies. These further categories distinguished between (a) use of a clinician- and self-rated measures; and (b) how studies defined change in PTSD outcomes (i.e., score or percentage reduction, cutoff score, a statistically derived formula, or diagnostic criteria plus functional assessments).

2.4 | Inter-rater reliability

Two independent reviewers completed all screenings. Inter-rater reliability calculated as a percent agreement (Kottner & Streiner, 2011) was high (99.6% for the Stage 1: title/abstract screening, and 93.6% for Stage 2: full-text assessments). In both stages, disagreements were resolved by discussion, and where necessary, arbitration was conducted by another two reviewers. Data extraction was conducted by two reviewers.

3 | RESULTS

From a yield of 10,183 records, 4,679 records were screened on title and abstract and 372 records were screened on

full-text (see the PRISMA flowchart presented in Figure 1). Of those, 192 trials with a total number of 13,789 participants were eligible for inclusion. There was an increase in the use of operational definitions of treatment response or nonresponse over time (pre-2000:7% of studies had definitions; from 2000 to 2010:33% of studies had definitions; and post-2010:60% of studies had definitions). Despite this increase, 40% of trials published post-2010 still failed to operationalize response to treatment. Overall, operational definitions of treatment response or nonresponse were provided in the 143 trials that were included in the qualitative synthesis. The trials that did not provide definitions ($n = 49$) were not included in the qualitative synthesis.

3.1 | Trial descriptions

The trials included in the qualitative synthesis were from the United States ($n = 76$, 53.1%), Western Europe ($n = 35$, 24.5%), Australia ($n = 7$, 4.9%), Asia ($n = 6$, 4.2%), or other countries ($n = 15$, 10.5%; see Table 1 for further details). The greatest proportion of trials involved samples reporting mixed types of trauma ($n = 73$, 51.1%). Other trauma types included military-related trauma ($n = 30$, 21.0%), man-made disasters including wars, displacement, and terrorism ($n = 18$, 12.6%), and interpersonal violence including sexual violence ($n = 8$, 5.6%). The majority of trials were conducted post-2010 ($n = 84$; 58.7%). Approximately one third of trials

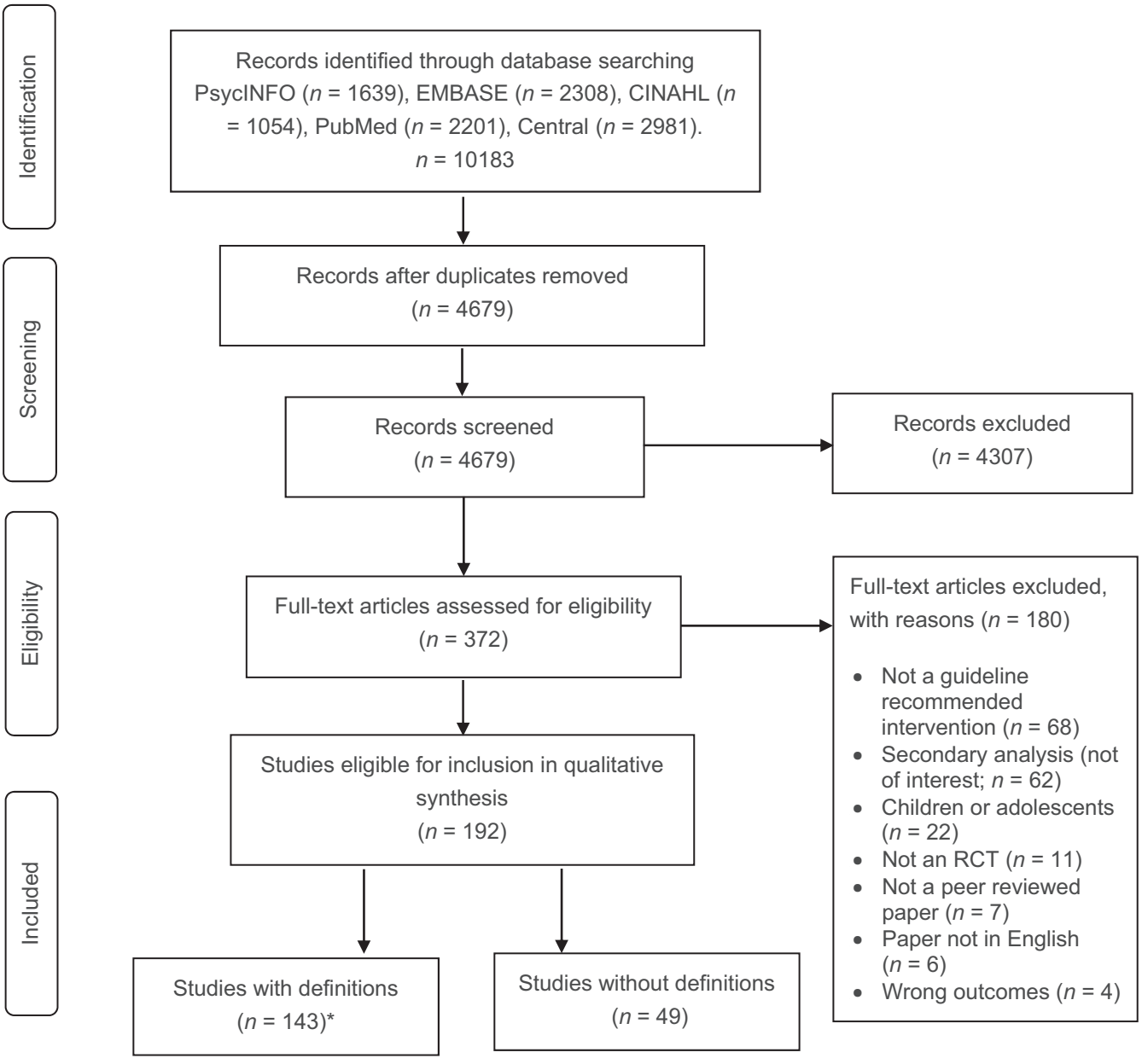

FIGURE 1 PRISMA flowchart

TABLE 1 Study authors definitions of treatment response including loss of diagnosis, remission, recovery, treatment nonresponse, and worsening to PTSD intervention ($n = 143$)

Author[a] *Country*	***N* (Male %)** **Trauma type** **Intervention**	**Treatment response ($n = 98$)**	**Loss of diagnosis ($n = 83$)**	**Remission and Recovery ($n = 28$)**	**Treatment nonresponse and worsening including relapse ($n = 17$)**
Acarturk et al. (2015) *Turkey*	29 (24.1%) Refugees/displacement EMDR versus WL	n/r	Cutoff ≥ 33 points on IES-R (n/r)	n/r	n/r
Acarturk et al. (2016) *Turkey*	98 (25.5%) Refugees/displacement EMDR versus WL	n/r	M.I.N.I. (DSM-IV)	n/r	n/r
Acierno et al. (2016) *US*	232 (94.4%) Military BA-TE* versus BE-TE* telehealth	≥8.8-point reduction on PCL-M (DSM-IV) (Clinically meaningful)	n/r	n/r	n/r
Acierno et al. (2017) *USA*	132 (96.2%) Military PE versus PE telehealth	≥8.8-point reduction on PCL-M (DSM-IV) (Noninferiority margin)	n/r	n/r	n/r
Arntz et al. (2007) *Netherlands*	67 (34.3%) Mixed trauma IE versus IE + IR	n/r	n/r	Cutoff ≤ 20 points on PSS-SR (DSM-III-R) (Recovery)	n/r
Asukai et al. (2010) *Japan*	24 (12.5%) Mixed trauma PE versus TAU	≥15-point reduction on CAPS (DSM-IV) (Clinically meaningful)	CAPS (DSM-IV)	Cutoff < 20 points on CAPS (DSM-IV) (Total remission) Cutoff = 20–25 points on CAPS (DSM-IV) (Near remission)	n/r
Back et al. (2006) *USA*	94 (54.3%) Mixed trauma SRT versus PBO	≥30% reduction on CAPS (DSM-IV) **AND** Rating of 1 or 2 on CAPS Question 20 (DSM-IV)	n/r	n/r	Did not meet response definition (Nonresponder)
Back et al. (2019) *USA*	81 (90.1%) Military COPE versus relapse prevention	n/r	n/r	Cutoff = 50 points on CAPS (DSM-IV) (Remission)	n/r
Beidel et al. (2011) *USA*	35 (100%) Military Exposure* versus TMT	Rating of 1 or 2 on CGI-I	n/r	n/r	Rating of ≥ 3 on CGI-I (Worsening)
Belleville et al. (2018) *Canada*	42 (11.9%) Sexual assault CBT versus CBT + IRT	n/r	CAPS (DSM-IV-TR)	n/r	n/r

(Continues)

TABLE 1 (Continued)

Author[a] *Country*	*N* (Male %) Trauma type Intervention	Treatment response (*n* = 98)	Loss of diagnosis (*n* = 83)	Remission and Recovery (*n* = 28)	Treatment nonresponse and worsening including relapse (*n* = 17)
Bichescu et al. (2007) *Romania*	18 (94.4%) Torture NET versus PsychEdu	n/r	CIDI (DSM-IV)	n/r	n/r
Blanchard et al. (2003) *USA*	98 (26.9%) MVA CBT versus SPT versus WL	n/r	CAPS (DSM-IV)	n/r	Retained full PTSD diagnosis post-treatment (Nonresponder)
Brady et al. (2000) *USA*	187 (26.7%) Mixed trauma SRT versus PBO	≥30% reduction on CAPS (DSM-III-R) **AND** Rating of 1 or 2 on CGI-I (Clinically meaningful)	n/r	n/r	n/r
Bryant et al. (2003) *Australia*	58 (48.3%) Mixed trauma IE versus IE + CR versus SC	Cutoff < 19 points on CAPS (DSM-IV) **AND** Cutoff < 10 points on BDI-2 (Good end-state functioning)	CAPS (DSM-IV)	n/r	n/r
Bryant et al. (2011) *Thailand*	28 (3.6%) Terrorism CBT versus TAU	Cutoff < 19 points on CAPS (DSM-IV) **AND** Cutoff < 10 points on BDI-2 (Good end-state functioning)	n/r	n/r	n/r
Bryant et al. (2013) *Australia*	70 (45.7%) Mixed trauma CBT + SC versus CBT + Skills	Cutoff < 19 points on CAPS (DSM-IV) **AND** Cutoff < 10 points on BDI-2 (Good end-state functioning)	n/r	n/r	n/r
Bryant et al. (2018) *Australia*	100 (77%) Emergency services CBT versus CBT (brief IE) versus WL	n/r	CAPS (DSM-IV)	n/r	n/r
Buhmann et al. (2018) *Denmark*	280 (59%) Refugee/ displacement CBT versus SRT + PsychEdu versus SRT + CBT +PsychEdu versus WL	n/r	Cutoff = 2.5 points on HTQ (ICD-10 and DSM-IV)	n/r	n/r
Butollo et al. (2016) *Germany*	148 (34%) Mixed trauma CPT versus DET	RCI = n/r (PDS and IES-R, DSM-IV)	n/r	PDS (DSM-IV) (Remission)	RCI (=n/r) changed in direction of greater dysfunction (PDS-I, DSM-IV) (Worsening)

(Continues)

TABLE 1 (Continued)

Author[a] *Country*	*N* (Male %) Trauma type Intervention	Treatment response (*n* = 98)	Loss of diagnosis (*n* = 83)	Remission and Recovery (*n* = 28)	Treatment nonresponse and worsening including relapse (*n* = 17)
Carletto et al. (2016) *Italy*	50 (19%) Physical illness EMDR versus RT	n/r	CAPS (DSM-IV)	n/r	n/r
Carlson et al. (1998) *USA*	35 (100%) Military EMDR versus biofeedback-assisted relaxation versus TAU	n/r	CAPS (DSM-IV)	n/r	n/r
Cavaljuga et al. (2003) *Bosnia and Herzegovina*	20 (100%) Military FLX versus AMI	n/r	Cutoff = 2.5 points on HTQ (ICD-10 and DSM-IV)	n/r	n/r
Celik et al. (2011) *Turkey*	50 (n/r) Military PRX versus AMI	≥30% reduction on CAPS (DSM-IV) **AND** Rating of 1 or 2 on CGI-I (Clinically meaningful)	n/r	n/r	n/r
Chard (2005) *USA*	71 (0%) CSA CPT versus MA	Cutoff ≤ 20 points on MPSS (DSM-III) **AND** Cutoff ≤ 10 points on BDI-2 (Good end-state functioning)	CAPS (DSM-IV)	n/r	n/r
Chung et al. (2004) *Korea*	113 (100%) Military SRT versus MRTZ	≥ 30% reduction on CAPS (DSM-IV) **OR** ≥ 50% reduction on HAMD-17 (DSM-IV) **OR** Rating of 1 or 2 on CGI-I	n/r	n/r	Did not meet response definition (Nonresponder)
Cigrang et al. (2017) *USA*	67 (74.6%) Military PE (brief) versus MCC	n/r	PSS-I (DSM-IV)	n/r	n/r
Cloitre et al. (2002) *USA*	58 (0%) CSA/CPA Exposure* + STAIR versus WL	Cutoff < 20 points on MPSS-SR (DSM-IV) **AND** Cutoff < 40 points on STAI–S **AND** Cutoff < 10 points on BDI (Good end-state functioning)	CAPS (DSM-IV)	n/r	Increase in CAPS severity score between baseline and post-treatment (Worsening)

(Continues)

TABLE 1 (Continued)

Author[a] *Country*	*N* (Male %) Trauma type Intervention	Treatment response (*n* = 98)	Loss of diagnosis (*n* = 83)	Remission and Recovery (*n* = 28)	Treatment nonresponse and worsening including relapse (*n* = 17)
Cloitre et al. (2010) *USA*	104 (0%) CSA/CPA Exposure* + STAIR versus STAIR + SC versus Exposure* + SC	n/r	CAPS (DSM-IV)	Cutoff < 20 points on CAPS (DSM-IV) (Remission)	≥7-point (1 *SD*) increase on CAPS severity score between post-treatment baseline (Worsening)
Coffey et al. (2016) *USA*	126 (54%) Mixed trauma M-PE versus M-PE + MET-PTSD versus HLS	>2 *SD* reduction on IES (DSM-IV) Cutoff = 20.23 points (Clinically meaningful)	n/r	n/r	n/r
Connor et al. (1999) *USA*	54 (9%) Mixed trauma FLX versus PBO	Rating of 1 or 2 on Duke Improvement Scale	n/r	n/r	Did not meet response definition (Nonresponder)
Cottraux et al. (2008) *France*	60 (30%) Mixed trauma CBT versus RST	Cutoff < 44 points on PCL-S (DSM-IV) (General criterion of improvement) Cutoff < 35 points on PCL-S (DSM-IV) (More stringent criterion of improvement)	n/r	n/r	n/r
Crocker et al. (2018) *USA*	74 (87.8%) Military CPT versus CPT (Smart)	Cutoff < 50 points on PCL-S (DSM-IV) **AND** ≥10-point reduction on PCL-S (DSM-IV) (Clinically meaningful)	n/r	n/r	n/r
Davidson et al. (2001) *USA*	208 (22.1%) Mixed trauma SRT versus PBO	≥30% reduction on CAPS (DSM-III-R) **AND** Rating of 1 or 2 on CGI-I (Clinically meaningful)	n/r	n/r	n/r
Davidson et al. (2005) *USA*	62 (49.2%) Mixed trauma FLX versus PBO	n/r	n/r	n/r	Rating of ≥4 on GCI-I **OR** ≥2-point increase on CGI-I (Relapse)
Davidson, Baldwin, et al. (2006) *Multiple countries (56 sites)*	329 (45.9%) Mixed trauma VLFX versus PBO	≥30% reduction on CAPS (DSM-IV)	n/r	Cutoff ≤ 20 points on CAPS (DSM-IV) (Remission)	n/r

(Continues)

TABLE 1 (Continued)

Author[a] *Country*	*N* (Male %) Trauma type Intervention	Treatment response (*n* = 98)	Loss of diagnosis (*n* = 83)	Remission and Recovery (*n* = 28)	Treatment nonresponse and worsening including relapse (*n* = 17)
Davidson, Rothbaum, et al. (2006) *USA*	538 (n/r) Mixed trauma VLFX versus SRT versus PBO	n/r	n/r	Cutoff ≤ 20 points on CAPS (DSM-IV) (Remission)	n/r
de Bont et al. (2013) *Netherlands*	10 (20%) Mixed trauma PE versus EMDR	n/r	CAPS (DSM-IV)	n/r	n/r
De Kleine et al. (2012) *Netherlands*	*N* = 75 (M: 19.4%) Mixed trauma PE + PBO versus PE + DCS	≥10-point reduction on CAPS (DSM-IV-TR)	n/r	Cutoff < 20 points on CAPS (Remission)	n/r
Difede et al. (2007) *USA*	31 (97%) Terrorism CBT versus TAU	≥10-point reduction on CAPS (DSM-IV-TR) (Clinically meaningful)	CAPS (DSM-IV-TR)	n/r	n/r
Dunne et al. (2012) *Australia*	26 (50%) MVA CBT (TF) versus WL	RCI = 7.8 points (PDS, DSM-IV) (Clinically meaningful)	SCID (DSM-IV)	n/r	n/r
Ehlers et al. (2003) *UK*	85 (n/r) MVA CT versus SHB versus Repeated assessments	≥50% reduction on PDS (DSM-IV) Cutoff < 14 points on PDS (DSM-IV) **AND** Cutoff < 2 points on CAPS Global Severity (DSM-IV) **AND** Cutoff < 12 points on BDI **AND** Cutoff < 12 points on BAI (Good end-state functioning)	PDS (DSM-IV) **AND** Cutoff ≥ 14 points on PDS (DSM-IV) **OR** CAPS (DSM-IV) **AND** Rating of ≥ 2 on CAPS global severity scale (DSM-IV)	n/r	n/r
Ehlers et al. (2005) *UK*	28 (46.4%) Mixed trauma CT versus WL	≥50% reduction on PDS (DSM-IV) Cutoff < 14 points on PDS (DSM-IV) **AND** Cutoff < 2 points on PDS-distress scale (DSM-IV) **AND** Cutoff < 12 points on BDI **AND** Cutoff < 12 points on BAI (Good end-state functioning)	PDS (DSM-IV) **AND** Cutoff > 2 points on PDS-distress scale (DSM-IV) **AND** Cutoff ≥ 14 points on PDS (DSM-IV)	n/r	n/r

(Continues)

TABLE 1 (Continued)

Author[a] *Country*	*N* (Male %) Trauma type Intervention	Treatment response (*n* = 98)	Loss of diagnosis (*n* = 83)	Remission and Recovery (*n* = 28)	Treatment nonresponse and worsening including relapse (*n* = 17)
Ehlers et al. (2014) *UK*	121 (41.3%) Mixed trauma CT (intensive) versus CT versus SC versus WL	n/r	CAPS (DSM-IV) **AND** Cutoff ≥ 1 for both frequency and intensity on CAPS (DSM-IV) **AND** Rating of 1 or 2 on CAPS global severity scale (DSM-IV)	Cutoff < 20 points on CAPS (DSM-IV) **AND** Cutoff < 11 points on PDS (DSM-IV) (Remission)	>6.15-point increase on PDS (DSM-IV) from baseline **AND** >10-point increase on CAPS (DSM-IV) from baseline (Worsening)
Ertl et al. (2011) *Uganda*	85 (44.7%) Mixed trauma NET versus academic catch-up versus WL	≥15-point reduction on CAPS (DSM-IV) (Clinically meaningful)	CAPS (DSM-IV)	n/r	n/r
Fecteau et al. (1999) *Canada*	20 (30%) MVA CBT versus WL	RCI = 11.09 points (CAPS, DSM-IV) (Clinically meaningful)	CAPS (DSM-IV)	n/r	n/r
Feeny et al. (2002) *USA*	72 (0%) Mixed trauma PE versus SIT versus PE + SIT versus WL	Cutoff ≤ 20 points on PSS-I (DSM-III-R) **AND** Cutoff ≤ 40 points on STAI-S **AND** Cutoff ≤ 10 points on BDI (Good end-state functioning)	PSS-I (DSM-III-R)	n/r	n/r
Feng et al. (2018) *China*	240 (29.6%) Mixed trauma SRT + S-TEAS versus CBT + S-TEAS versus SRT + A-TEAS versus CBT + A-TEAS	≥30% reduction on CAPS (DSM-IV) (Clinically meaningful)	n/r	Cutoff ≤ 20 points on CAPS (DSM-IV) (Remission)	n/r

(Continues)

TABLE 1 (Continued)

Author[a] *Country*	*N* (Male %) Trauma type Intervention	Treatment response (*n* = 98)	Loss of diagnosis (*n* = 83)	Remission and Recovery (*n* = 28)	Treatment nonresponse and worsening including relapse (*n* = 17)
Feske et al. (2008) *USA*	21 (0%) Mixed trauma PE versus TAU	RCI = n/r (PDS-I and IES-R, DSM-IV) ≥2 *SD* reduction on PDS-I and IES-R (DSM-IV) Cutoff = n/r (Clinically meaningful)	n/r	Reliable improvement **AND** PDS-I and IES-R scores move from statistically belonging to the dysfunctional population distribution at pretest to the functional population distribution at posttest (Recovery)	RCI (=n/r) changed in direction of greater dysfunction (PDS-I, DSM-IV) (Worsening)
Foa et al. (1991) *USA*	45 (0%) Sexual assault PE versus SIT versus SC versus WL	>2 *SD* decrease (assessment measure/score n/r) Cutoff = n/r (Clinically meaningful)	Clinical interview (DSM-III)	n/r	n/r
Foa et al. (1999) *USA*	96 (0%) Mixed trauma PE versus SIT versus PE + SIT versus WL	Cutoff ≤ 20 points on PSS-I (DSM-III-R) **AND** Cutoff ≤ 40 points on STAI-S **AND** Cutoff ≤ 10 points on BDI (Good end-state functioning)	PSS-I (DSM-III-R)	n/r	n/r
Foa et al. (2013) *USA*	165 (65.5%) Mixed trauma PE + PBO versus PE + NLTX versus SC + NLTX versus SC + PBO	Cutoff ≤ 10 points on PSS-I (DSM-IV) (Low severity)	n/r	n/r	n/r
Foa et al. (2018) *USA*	370 (88%) Military PE (intensive) versus PE versus PCT versus MCC	One-half *SD* decrease Cutoff = 3.18 points (PSS-I, DSM-IV-TR) Cutoff = 7.9 points (PCL-S, DSM-IV-TR) (Minimal clinically important difference)	PSS-I (DSM-IV-TR)	n/r	n/r
Fonzo et al. (2017) *USA*	66 (34.8%) Mixed trauma PE versus WL	n/r	n/r	Cutoff < 20 points on CAPS (DSM-IV) (Remission)	n/r

(Continues)

TABLE 1 (Continued)

Author[a] *Country*	*N* (Male %) Trauma type Intervention	Treatment response (*n* = 98)	Loss of diagnosis (*n* = 83)	Remission and Recovery (*n* = 28)	Treatment nonresponse and worsening including relapse (*n* = 17)
Forbes et al. (2012) *Australia*	59 (96.6%) Military CPT versus TAU	>12-point reduction on CAPS (DSM-IV) (Clinically meaningful)	CAPS (DSM-IV)	Cutoff < 20 points on CAPS (DSM-IV) (Remission)	n/r
Ford et al. (2018) *USA*	31 (100%) Military PE versus TARGET	>12-point reduction on CAPS (DSM-IV) (Clinically meaningful)	CAPS (DSM-IV)	n/r	n/r
Friedman et al. (2007) *USA*	169 (79.9%) Mixed trauma SRT versus PBO	≥30% reduction on CAPS (DSM-III-R) **AND** Rating of 1 or 2 on CGI-I (Clinically meaningful)	n/r	n/r	n/r
Galovski et al. (2012) *USA*	100 (31%) Mixed trauma M-CPT versus SMDT	Cutoff ≤ 20 points on PDS **AND** Cutoff ≤ 18 points on BDI-2 (Good end-state functioning)	CAPS (DSM-IV)	n/r	n/r
Gersons et al. (2000) *Netherlands*	42 (88.1%) Emergency Services BEP versus WL	n/r	SI-PTSD (DSM-III-R)	n/r	n/r
Haller et al. (2016) *USA*	123 (88.6%) Mixed trauma I-CBT versus M-CPT	≥10-point reduction on PCL-C (DSM-IV) (Clinically meaningful) ≥5-point reduction on PCL-C (DSM-IV) (Minimum threshold)	n/r	n/r	n/r
Harned et al. (2014) *USA*	26 (0%) Mixed trauma DBT-PE* + DBT versus DBT	RCI = 10.5 points (PSS-I, DSM-IV) >2 *SD* reduction on PSS-I (DSM-IV) Cutoff ≤ 14.9 points (Clinically meaningful)	n/r	PSS-I (DSM-IV) **AND** Achieving both reliable and clinically significant improvement (Recovery)	n/r
Hensel-Dittmann et al. (2011) *Germany*	28 (n/r) Refugee/displacement NET versus SIT	n/r	CAPS (DSM-IV)	n/r	n/r
Hertzberg et al. (2000) *USA*	12 (100%) Military FLX versus PBO	Rating of 1 or 2 on Duke Improvement Scale	n/r	n/r	Rating of > 2 on Duke Improvement Scale (Nonresponder)

(Continues)

TABLE 1 (Continued)

Author[a] *Country*	*N* (Male %) Trauma type Intervention	Treatment response (*n* = 98)	Loss of diagnosis (*n* = 83)	Remission and Recovery (*n* = 28)	Treatment nonresponse and worsening including relapse (*n* = 17)
Hien et al. (2015) *USA*	69 (19%) Mixed trauma SRT + SS versus PBO + SS	>15-point reduction on CAPS (DSM-IV-TR) (Clinically meaningful)	n/r	n/r	n/r
Hinton et al. (2005) *USA*	40 (40%) Refugees/displacement CBT versus delayed treatment	>15-point reduction on CAPS (DSM-IV) (Clinically meaningful)	CAPS (DSM-IV)	n/r	n/r
Hogberg et al. (2007) *Sweden*	24 (79.2%) Occupation-based EMDR versus WL	>2 *SD* reduction on IES (DSM-IV) Cutoff = n/r (Clinically meaningful)	SCID (DSM-IV)	n/r	n/r
Ironson et al. (2002) *USA*	22 (22.7%) Mixed trauma EMDR versus PE	>70% reduction on PSS-SR (DSM-III-R)	n/r	n/r	n/r
Jacob et al. (2014) *Rwanda*	76 (43 widows; 33 orphans; 7.9%) Refugees/displacement NET versus WL	RCI = 17.7 points (CAPS, DSM-IV-TR) (Clinically meaningful)	CAPS (DSM-IV-TR)	n/r	n/r
Karatzias et al. (2011) *UK*	46 (43.5%) Mixed trauma EMDR versus EFT	>2 *SD* reduction on CAPS and PCL-C (DSM-IV) Cutoff = n/r (Clinically meaningful)	n/r	n/r	n/r
Kozel et al. (2018) *USA*	103 (n/r) Military CPT + rTMS versus CPT + sham	Cutoff = 7.9 points (PCL, DSM-IV) Cutoff = 10.4 points (CAPS, DSM-IV) (Minimally clinically important difference)	n/r	n/r	n/r
Langkaas et al. (2017) *Norway*	65 (42%) Mixed trauma PE versus IR	RCI = 8 points (PSS-I, DSM-IV) **AND** Cutoff ≤ 23 points (PSS-I, DSM-IV) (Clinically meaningful)	n/r	Clinically significant differences based on RCI were used to differentiate between recovered, improved, not reliably changed, and deteriorated (Recovery)	RCI (= 8) changed in direction of greater dysfunction (PSS-I, DSM-IV) (Worsening)
Lee et al. (2002) n/r	24 (54.2%) Mixed trauma PE + SIT versus EMDR	>2 *SD* reduction on IES (DSM-III-R) Cutoff < 37 points (Clinically meaningful)	SI-PTSD (DSM-III-R)	n/r	n/r

(Continues)

TABLE 1 (Continued)

Author[a] *Country*	*N* (Male %) Trauma type Intervention	Treatment response (*n* = 98)	Loss of diagnosis (*n* = 83)	Remission and Recovery (*n* = 28)	Treatment nonresponse and worsening including relapse (*n* = 17)
Li et al. (2017) *China*	72 (87.5%) Mixed trauma SRT versus PBO	≥30% reduction on IES-R (DSM-IV)	n/r	n/r	n/r
Lindauer et al. (2008) *Netherlands*	20 (50%) Mixed trauma BEP versus WL	n/r	SI-PTSD (DSM-IV)	n/r	n/r
Lindauer, Gersons et al. (2005) *Netherlands*	24 (45.8%) Mixed trauma BEP versus WL	n/r	SI-PTSD (DSM-IV)	n/r	n/r
Lindauer, Vlieger et al. (2005) *Netherlands*	18 (44.4%) Mixed trauma BEP versus WL	n/r	SI-PTSD (DSM-IV)	n/r	n/r
Litz et al. (2012) *USA*	26 (100%) Military Exposure* + PBO versus Exposure* + DCS	≥10-point reduction on CAPS (DSM-IV)	CAPS (DSM-IV)	n/r	n/r
Maercker et al. (2006) *Germany*	48 (23.8%) MVA CBT versus WL	n/r	CAPS (DSM-IV)	n/r	n/r
Maieritsch et al. (2016) *USA*	90 (93.3%) Military CPT versus CPT telehealth	≥10-point reduction on CAPS (DSM-IV-TR)	n/r	n/r	n/r
Marcus et al. (1997) *USA*	67 (20.9%) Mixed trauma EMDR versus TAU	n/r	n/r (DSM-III-R)	n/r	n/r
Markowitz et al. (2015) *USA*	110 (30%) Mixed trauma PE versus IPT versus RT	>30% reduction on CAPS (DSM-IV) >15-point reduction on CAPS (DSM-IV) (Clinically meaningful)	n/r	Cutoff < 20 points on CAPS (DSM-IV) (Remission)	n/r

(Continues)

TABLE 1 (Continued)

Author[a] *Country*	*N* (Male %) Trauma type Intervention	Treatment response (*n* = 98)	Loss of diagnosis (*n* = 83)	Remission and Recovery (*n* = 28)	Treatment nonresponse and worsening including relapse (*n* = 17)
Marks et al. (1998) *UK*	87 (64%) Mixed trauma PE + IE versus CR versus PE + IE + CR versus RT	>50% reduction on PSS (DSM-III-R) **AND** Cutoff ≤ 7 points on BDI **AND** Cutoff ≥ 35 points on STAI (Good end-state functioning) ≥2 *SD* reduction on CAPS (DSM-III-R) Cutoff = n/r **AND** ≥2 *SD* reduction on IES (DSM-III-R) Cutoff = n/r **AND** ≤3 on GHQ Global Improvement Subscale	CAPS (DSM-III-R)	n/r	n/r
Marshall et al. (2001) *USA*	563 (31.6%) Mixed trauma PRX (20 mg) versus PRX (40 mg) versus PBO	Rating of 1 or 2 on CGI-I	n/r	n/r	n/r
Marshall et al. (2007) *USA*	52 (32.7%) Mixed trauma PRX versus PBO	Rating of 1 or 2 on CGI-I	CAPS (DSM-IV)	n/r	n/r
Martenyi et al. (2002) *Belgium, Bosnia, Croatia, Yugoslavia, Israel and South Africa*	301 (81%) Mixed trauma FLX versus PBO	≥50% reduction on TOP-8 (DSM-IV) **AND** Rating of 1 or 2 on CGI-S	n/r	n/r	n/r
Martenyi et al. (2007) *USA*	411 (28.5%) Mixed trauma FLX (20 mg/day) versus FLX (40 mg/day) versus PBO	≥50% reduction on TOP-8 (DSM-IV) **AND** Rating of 1 or 2 on CGI-S **AND** No longer meeting diagnostic criteria on CAPS (DSM-IV)	CAPS (DSM-IV)	n/r	n/r
McDonagh et al. (2005) *USA*	74 (0%) CSA CBT versus PCT versus WL	n/r	CAPS (DSM-IV)	n/r	n/r
McGovern et al. (2011) *USA*	53 (43.4%) Mixed trauma I-CBT + TAU versus AC + TAU	≥15 point reduction on CAPS (DSM n/r) (Clinically meaningful)	CAPS (DSM n/r)	n/r	n/r

(Continues)

TABLE 1 (Continued)

Author[a] *Country*	*N* (Male %) Trauma type Intervention	Treatment response (*n* = 98)	Loss of diagnosis (*n* = 83)	Remission and Recovery (*n* = 28)	Treatment nonresponse and worsening including relapse (*n* = 17)
McGovern et al. (2015) *USA*	221 (40.7%) Mixed trauma I-CBT + TAU versus AC + TAU versus TAU	≥15-point reduction on CAPS (DSM-IV) (Clinically meaningful)	n/r	n/r	n/r
McLay et al. (2017) *USA*	81 (96.3%) Military Exposure therapy* versus VR-EXP	≥30% reduction on CAPS (DSM-IV)	n/r	Cutoff ≤ 20 points on CAPS (DSM-IV) (Remission)	n/r
Mills et al. (2012) *Australia*	103 (37.9%) Mixed trauma COPE versus TAU	≥15 point reduction on CAPS (DSM-IV-TR) **AND** 1-point change on CIDI (Clinically meaningful)	CAPS (DSM-IV-TR)	n/r	n/r
Monson et al. (2006) *USA*	60 (90%) Military CPT versus WL	RCI = 12-point (CAPS, DSM-IV-TR)	CAPS (DSM-IV-TR)	n/r	n/r
Morland et al. (2015) *USA*	126 (0%) Mixed trauma CPT versus CPT telehealth	≥10-point reduction on CAPS (DSM-IV) (Clinically meaningful)	CAPS (DSM-IV)	n/r	n/r
Mueser et al. (2008) *USA*	108 (21.3%) Mixed trauma CBT versus TAU	n/r	CAPS (DSM-IV)	n/r	n/r
Mueser et al. (2015) *USA*	201 (33%) n/r CBT versus CBT (brief)	n/r	CAPS (DSM-IV)	n/r	n/r
Nacasch et al. (2015) *Israel*	40 (61.5%) Mixed trauma PE versus PE (brief IE)	RCI = 7 points (PSS-I, DSM-IV) (Clinically meaningful)	n/r	n/r	n/r
Neuner et al. (2004) *Uganda*	43 (37.2%) Refugees/displacement NET versus SC versus PsychEdu	n/r	CIDI (DSM-IV)	n/r	n/r
Neuner et al. (2008) *Uganda*	277 (48.7%) Refugees/displacement NET versus FTC versus monitoring	n/r	PDS (DSM-IV)	n/r	n/r
Neuner et al. (2010) *Germany*	32 (68.8%) Refugees/displacement NET versus TAU	n/r	PDS (DSM-IV)	n/r	n/r

(Continues)

TABLE 1 (Continued)

Author[a] *Country*	*N* (Male %) Trauma type Intervention	Treatment response (*n* = 98)	Loss of diagnosis (*n* = 83)	Remission and Recovery (*n* = 28)	Treatment nonresponse and worsening including relapse (*n* = 17)
Nidich et al. (2018) *USA*	203 (83.2%) Military PE versus TM versus PsychEdu	≥10-point reduction on CAPS (DSM-IV) **OR** ≥10-point reduction on PCL-M (DSM-IV) **OR** ≥10-point reduction on PHQ-9 (Clinically meaningful)	n/r	n/r	n/r
Nijdam et al. (2012) *Netherlands*	140 (43.6%) Mixed trauma BEP versus EMDR	n/r	SI-PTSD (DSM-IV)	n/r	n/r
Onder et al. (2006) *Turkey*	103 (49.5%) Natural disaster FLX versus moclobemide versus TNP	≥50% reduction on CAPS (DSM-IV) **OR** Rating of 1 or 2 on CGI-S	n/r	n/r	n/r
Orang et al. (2018) *Iran*	45 (0%) IPV NET versus TAU	RCI = 15 points (PSS-I, DSM-IV) (Clinically meaningful)	PSS-I (DSM-IV)	n/r	n/r
Pacella et al. (2012) *USA*	65 (63.1%) Mixed trauma PE versus Monitoring	Cutoff ≤ 20 points on HIV-related PSS-I (DSM-IV) **AND** Cutoff ≤ 20 points on non–HIV-related PSS-I (DSM-IV) **AND** Cutoff ≤ 16 points on CES-D (Good end-state functioning)	PDS (DSM-IV)	n/r	n/r
Panahi et al. (2011) *Iran*	70 (100%) Military SRT versus PBO	≥30% reduction on IES-R (DSM-IV) **AND** Rating of 1 or 2 on CGI-I	n/r	n/r	n/r
Paunovic et al. (2011) *Sweden*	29 (41.4%) Mixed trauma Exposure inhibition Therapy* versus WL	n/r	Cutoff ≥ 44 points on CAPS (DSM-IV) **OR** Cutoff ≥ 39 points on CAPS (DSM-IV) **OR** Cutoff ≥ 27 points on CAPS (DSM-IV)	n/r	n/r

(Continues)

TABLE 1 (Continued)

Author[a] *Country*	*N* (Male %) Trauma type Intervention	Treatment response (*n* = 98)	Loss of diagnosis (*n* = 83)	Remission and Recovery (*n* = 28)	Treatment nonresponse and worsening including relapse (*n* = 17)
Popiel et al. (2015) *Poland*	228 (n/r) MVA PE versus PRX versus PE + PRX	n/r	n/r	CAPS (DSM-IV) **AND** Absence of the minimal number of symptoms required for a PTSD diagnosis on PDS (Remission)	> 1 *SD* increase in number of PTSD symptoms (PDS, DSM-IV) (Relapse)
Powers et al. (2015) *USA*	9 (11.1%) n/r PE versus PE + exercise	Cutoff ≤ 10 points on PSS-I (DSM-IV) (Good end-state functioning)	n/r	n/r	n/r
Rauch et al. (2015) *US*	36 (91.7%) Military PE versus PCT	≥10-point reduction on CAPS (DSM-IV) (Clinically meaningful) ≥50% reduction on CAPS (DSM-IV)	CAPS (DSM-IV)	n/r	n/r
Rauch et al. (2018) *USA*	223 (87%) Military SRT versus PE + PBO versus PE + SRT	≥50% reduction on CAPS (DSM-IV-TR) ≥20-point reduction on CAPS (DSM-IV-TR) **OR** Cutoff ≤ 35 points on CAPS (DSM-IV-TR) (Clinically meaningful)	n/r	Cutoff ≤ 35 points on CAPS (DSM-IV-TR) (Remission)	n/r
Reger et al. (2016) *USA*	162 (96.3%) Military PE versus VR-EXP versus WL	RCI = 1.65 points (CAPS, DSM-IV) >2 *SD* reduction on CAPS (DSM-IV) Cutoff = 52.78 points (Clinically meaningful)	n/r	n/r	RCI (=1.65) changed in direction of greater dysfunction (CAPS, DSM-IV) (Worsening)
Resick et al. (2002) *USA*	171 (0%) Sexual assault CPT versus PE versus MA	Cutoff ≤ 20 points on PSS (DSM-IV) **AND** Cutoff ≤ 10 points on BDI (Good end-state functioning)	CAPS (DSM-IV)	n/r	n/r
Resick et al. (2008) *USA*	150 (0%) Mixed trauma CPT versus CPT-C versus Written accounts	n/r	CAPS (DSM-IV)	n/r	n/r

(Continues)

TABLE 1 (Continued)

Author[a] *Country*	*N* (Male %) Trauma type Intervention	Treatment response (*n* = 98)	Loss of diagnosis (*n* = 83)	Remission and Recovery (*n* = 28)	Treatment nonresponse and worsening including relapse (*n* = 17)
Resick et al. (2017) *USA*	268 (91%) Mixed trauma CPT versus CPT group	n/r	PSS-I (DSM-IV)	n/r	n/r
Rothbaum et al. (2006) *USA*	65 (35.4%) Mixed trauma PE + SRT versus SRT	>1 *SD* reduction on SIP (DSM-IV) Cutoff < 14 points (Excellent responders) Cutoff ≥ 14 points (Partial responders)	n/r	n/r	n/r
Roy et al. (2010) *USA*	29 (89.7%) Military IE versus VR-EXP	>30% reduction on CAPS (DSM-IV)	n/r	n/r	n/r
Sack et al. (2016) *Germany*	139 (36%) Mixed trauma EMDR versus EMDR hand moving versus EMDR nonmoving hand	≥20-point reduction on CAPS (DSM-IV) (Clinically meaningful)	SCID-PTSD assessment (DSM-IV)	n/r	n/r
Sannibale et al. (2013) *Australia*	62 (47%) Mixed trauma I-CBT versus alcohol support	Cutoff < 37 points on CAPS (DSM-IV) (Clinically meaningful)	CAPS (DSM-IV)	n/r	n/r
Schaal et al. (2009) *Rwanda*	26 (38.5%) Refugees/displacement NET versus IPT	n/r	CAPS (DSM-IV)	n/r	n/r
Schacht et al. (2017) *USA*	58 (21%) Mixed trauma PE versus PE with incentives	≥15-point reduction on CAPS (DSM-IV) (Clinically meaningful)	n/r	n/r	n/r
Schneier et al. (2012) *USA*	37 (45.9%) Terrorism PE + PRX versus PE + PBO	Rating of 1 or 2 on CGI-C	n/r	Cutoff ≤ 20 points on CAPS (DSM-IV) **AND** Rating of 1 on CGI-C (Remission)	n/r
Schneier et al. (2015) *USA*	36 (36.1%) Mixed trauma SRT + PBO versus SRT + MRTZ	>30% reduction on CAPS (DSM-IV) **AND** Rating of 1 or 2 on CGI-I	n/r	Cutoff < 20 points on CAPS (DSM-IV) (Remission)	n/r

(Continues)

TABLE 1 (Continued)

Author[a] *Country*	*N* (Male %) Trauma type Intervention	Treatment response (*n* = 98)	Loss of diagnosis (*n* = 83)	Remission and Recovery (*n* = 28)	Treatment nonresponse and worsening including relapse (*n* = 17)
Schnurr et al. (2007) *USA*	284 (0%) Mixed trauma PE versus PCT	≥10-point reduction on CAPS (DSM-IV)	CAPS (DSM-IV)	Cutoff < 20 points on CAPS (DSM-IV) (Remission)	n/r
Schnyder et al. (2011) *Switzerland*	30 (53.3%) Mixed trauma BEP versus MA	≥1 *SD* reduction on CAPS (DSM-IV) Cutoff = 18 points	CAPS (DSM-IV)	Cutoff < 20 points on CAPS (DSM-IV) (Remission)	n/r
Seo et al. (2010) *Korea*	40 (30%) Mixed trauma PRX versus MRTZ	≥30% reduction on CAPS (DSM-IV)	n/r	n/r	n/r
Sloan et al. (2018) *USA*	126 (52.4%) Mixed trauma CPT versus WET	RCI = 13 points (CAPS, DSM-V)	CAPS (DSM-V)	n/r	n/r
Stenmark et al. (2013) *Norway*	81 (69.1%) Refugees/displacement NET versus TAU	>2 *SD* reduction on CAPS (DSM-IV) Cutoff = n/r (Clinically meaningful)	CAPS (DSM-IV)	n/r	n/r
Tarrier et al. (1999) *UK*	72 (58%) Mixed trauma IE versus CT	Rating of 0 or 1 on CAPS Global Severity (DSM-III-R) **AND** Rating of 0 or 1 on CAPS Global Improvement (DSM-III-R) (Clinically meaningful)	CAPS (DSM-III-R)	n/r	n/r
Ter Heide et al. (2011) *Netherlands*	20 (60%) Refugees/displacement EMDR versus stabilization	n/r	SCID-I (DSM-IV)	n/r	n/r
Ter Heide et al. (2016) *Netherlands*	72 (72.2%) Refugees/displacement EMDR versus stabilization	≥10-point reduction on CAPS (DSM-IV-TR) (Clinically meaningful)	CAPS (DSM-IV-TR)	n/r	≥ 10-point increase on CAPS (DSM-IV-TR) (Worsening)
Triffleman et al. (2000) *USA*	19 (47.4%) n/r I-CBT versus 12-step facilitation	n/r	CAPS (DSM-IV)	n/r	n/r
Tucker et al. (2001) *USA and Canada*	323 (34.2%) Mixed trauma PRX versus PBO	Rating of 1 or 2 on CGI-I	n/r	Cutoff < 20 points on CAPS (DSM-IV) (Remission)	n/r

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TABLE 1 (Continued)

Author[a] *Country*	*N* (Male %) Trauma type Intervention	Treatment response (*n* = 98)	Loss of diagnosis (*n* = 83)	Remission and Recovery (*n* = 28)	Treatment nonresponse and worsening including relapse (*n* = 17)
Tuerk et al. (2018) *USA*	26 (100%) Military PE + PBO versus PE + yohimbine HCl	>1 *SD* reduction on PCL-M (DSM-IV-TR) Cutoff = n/r	CAPS (DSM-IV-TR)	n/r	n/r
Van Den Berg et al. (2015) *Netherlands*	155 (45.8%) Mixed trauma PE versus EMDR versus WL	n/r	CAPS (DSM-IV-TR)	Cutoff < 20 points on CAPS (DSM-IV-TR) (Remission)	n/r
van Denderen et al. (2018) *Netherlands*	85 (26%) Homicide bereavement EMDR + CBT versus CBT + EMDR versus WL (EMDR + CBT) versus WL (CBT + EMDR)	>2 *SD* reduction on IES (version not reported) Cutoff = 23 points (Clinically meaningful)	n/r	n/r	n/r
Van der Kolk et al. (2007) *USA*	88 (17%) Mixed trauma EMDR versus FLX versus PBO	n/r	CAPS (DSM-IV)	Cutoff < 20 points on CAPS (DSM-IV) (Remission)	n/r
Wells et al. (2015) *UK*	32 (62.5%) Mixed trauma PE versus metacognitive therapy versus WL	RCI = 10 points (IES, DSM-IV) >2 *SD* reduction (IES, DSM-IV) Cutoff ≤ 32 points (Clinically meaningful)	SCID (DSM-IV-R)	Achieving reliable change and clinically meaningful change (Recovery)	RCI (= 10) changed in direction of greater dysfunction (IES, DSM-IV) (Worsening)
Yehuda et al. (2014) *USA*	52 (89.2%) Military PE versus MA	n/r	CAPS (DSM-IV)	n/r	n/r
Yehuda et al. (2015) *USA*	24 (n/r) Mixed trauma PE + PBO versus PE + hydrocortisone	n/r	CAPS (DSM-IV)	n/r	n/r
Yuen et al. (2015) *USA*	52 (98.1%) Military PE versus PE telehealth	n/r	CAPS (DSM-IV)	n/r	n/r
Ziemba et al. (2014) *USA*	18 (90%) Military CBT versus CBT telehealth	≥15-point reduction on CAPS (DSM-IV-TR) (Clinically meaningful)	n/r	n/r	n/r

(Continues)

TABLE 1 (Continued)

Author[a] *Country*	*N* (Male %) Trauma type Intervention	Treatment response (*n* = 98)	Loss of diagnosis (*n* = 83)	Remission and Recovery (*n* = 28)	Treatment nonresponse and worsening including relapse (*n* = 17)
Zoellner et al. (1999) *USA*	95 (0%) Mixed trauma CBT versus WL	Cutoff ≤ 20 points PSS-I (DSM-III-R) **AND** Cutoff ≤ 40 points on STAI-S **AND** Cutoff ≤ 10 points on BDI (Good end-state functioning)	n/r	n/r	n/r
Zoellner et al. (2018) *USA*	200 (24.5%) Mixed trauma PE versus SRT	Cutoff < 24 points on PSS-I (DSM-IV) **AND** Rating of < 4 on CGI-I	PSS-I (DSM-IV)	n/r	n/r
Zohar et al. (2002) *Israel*	42 (88.2%) Military SRT versus PBO	≥30% reduction on CAPS (DSM-III-R) **OR** Rating of 1 or 2 on CGI-I **OR** Both of the above (Clinically meaningful)	n/r	n/r	n/r

Abbreviations: AC, addictive counseling; AMI, amitriptyline; A-TEAS, active transcutaneous electrical acupoint stimulation; BAI, Beck Anxiety Inventory; BA-TE, behavioral activation and therapeutic exposure; BDI, Beck Depression Inventory; BEP, brief eclectic psychotherapy; CAPS, Clinician-Administered PTSD Scale; CBT (TF) = trauma-focused cognitive behavioral therapy; CBT, cognitive behavioral therapy; CES-D, Center for Epidemiological Studies—Depression Scale; CGI-C, Clinical Global Impressions Scale—Change; CGI-I, Clinical Global Impressions Scale—Improvement; CGI-S, Clinical Global Impressions Scale—Severity; CIDI, Composite International Diagnostic Interview; COPE, Concurrent Treatment of PTSD and Substance Use Disorders Using Prolonged Exposure; CPA, childhood physical abuse; CPT (smart) = CPT + cognitive rehabilitation strategies; CPT, cognitive processing therapy; CPT-C, cognitive processing therapy—cognitive therapy only; CR, cognitive restructuring; CSA, childhood sexual abuse; CT, cognitive therapy; DBT, dialectical behavior therapy; DCS, D-cycloserine; DET, dialogical exposure therapy; DSM, Diagnostic and Statistical Manual of Mental Disorders; EFT, emotional freedom techniques; EMDR, eye movement desensitization and reprocessing; FLX, fluoxetine; FTC, flexible trauma counseling; GHQ, General Health Questionnaire; HAMD, Hamilton Rating Scale for Depression; HIV, human immunodeficiency virus; HLS, Health Information Control; HTQ, Harvard Trauma Questionnaire; I-CBT, integrated cognitive behavioral therapy; ICD-10, International Classification of Diseases—10th Revision; IE, imaginal exposure; IES, Impact of Event Scale; IES-R, Impact of Event Scale—Revised; IPT, interpersonal psychotherapy; IPV, intimate partner violence; IR, imagery rescripting; IRT, imagery rehearsal therapy; M.I.N.I., The Mini-International Neuropsychiatric Interview; MA, minimal attention; MCC, minimal contact control; M-CPT, modified cognitive processing therapy; MET-PTSD, Trauma-Focused Motivational Enhancement Session; M-PE, Modified PE; MPSS, Modified Posttraumatic Stress Disorder Symptom Scale; MPSS-SR, Modified Posttraumatic Stress Disorder Symptom Scale—Self-report; MRTZ, mirtazapine; MVA, motor vehicle accident; n/r, not reported; NET, narrative exposure therapy; NLTX, naltrexone; PBO, Placebo; PCL, PTSD Checklist; PCL-C, PTSD Checklist—Civilian; PCL-M, PTSD Checklist—Military; PCL-S, PTSD Checklist—Stressor-Specific; PCT, present-centered therapy; PDS, Posttraumatic Diagnostic Scale; PDS-I, Posttraumatic Diagnostic Scale—Interview; PE, prolonged exposure; PHQ, Patient Health Questionnaire; PRX, paroxetine; PSS, Posttraumatic Stress Disorder Symptom Scale; PSS-I, Posttraumatic Stress Disorder Symptom Scale—Interview; PSS-SR, Posttraumatic Stress Disorder Symptom Scale—Self-Report; PsychEdu, psychoeducation; PTSD, posttraumatic stress disorder; RCI, Reliable Change Index; RST, Rogerian supportive therapy; RT, relaxation therapy; rTMS, repetitive transcranial magnetic stimulation; SC, supportive counseling; SCID, Structured Clinical Interview for DSM-IV Axis I Disorders; *SD*, standard deviation; SHB, Self-help Booklet; SIP, Structured Interview for PTSD; SI-PTSD, Structured Interview for PTSD; SIT, stress inoculation training; Skills, emotion regulation skills; SMDT, symptom-monitoring delayed treatment; SPT, supportive psychotherapy; SRT, sertraline; SS, safety seeking; STAIR, Skills Training in Affective and Interpersonal Regulation; STAI–S, State-Trait Anxiety Inventory—State subscale; S-TEAS, simulated transcutaneous electrical acupoint stimulation; TARGET, Trauma Affect Regulation: Guide for Education and Therapy; TAU, treatment as usual; TM, transcendental meditation; TMT, trauma management therapy; TNP, tianeptine; TOP-8, Treatment Outcome PTSD Rating Scale; VLFX, venlafaxine; VR-EXP, virtual reality exposure; WET, written exposure therapy; WL, wait list.

*Exposure intervention based on PE.

[a]Reference list can be requested from lead author.

identified their population as chronic (n = 51, 35.7%; commonly defined as PTSD diagnosis longer than 6 months, but in some instances, as short as 3 months), while a small number involved a treatment-resistant population (n = 2, 0.7%).

3.2 | Interventions

Two thirds of trials involved first-line psychological interventions (n = 105, 73.4%), while a smaller proportion involved first-line pharmacological (n = 23, 16.1%) or combined interventions (n = 15, 10.5%). Of the psychological trials, prolonged exposure (n = 41, 39%) and cognitive behavior therapy (n = 22, 21%) were the most common interventions. Of the pharmacological trials, the most common interventions were sertraline (n = 9, 39.1%) and fluoxetine (n = 7, 30.4%). The majority of the chronic PTSD trials (n = 33, 64.7%) investigated the efficacy of psychological interventions, followed by pharmacological interventions (n = 15, 29.4%) and combined interventions (n = 3, 5.9%).

3.3 | Operationalization of response to treatment

Figure 2 represents the synthesized categories and subcategories of response to treatment definitions. From the 143 trials included in this review, 226 definitions were extracted, matching the following five categories: *treatment response* (n = 181), *remission* (n = 23), *recovery* (n = 5), *treatment nonresponse* (n = 5), and *worsening* (n = 12). There were no trials that defined all five categories, but one trial defined four categories (Wells, Walton, Lovell, & Proctor, 2015). Approximately three-quarters of trials (n = 106, 74.1%) only defined treatment response (including loss of diagnosis). Nineteen trials (13.3%) differentiated between treatment response and remission, four trials (2.8%) between treatment response and recovery, and 15 trials (10.5%) between treatment response and nonresponse.

The author-defined definitions used by each trial included in the qualitative synthesis are presented in Table 1.

3.4 | Treatment response definitions

In the treatment response category, 79 trials (80.1%) defined response using a reduction of PTSD symptom severity, 12 trials (12.2%) used a reduction of PTSD symptom severity plus improvement in functioning, and seven trials (7.1%) assessed improvement in functioning only. Further information on how these reductions or improvements were defined is presented below.

3.4.1 | Reduction of PTSD symptom severity

The majority of trials based their definition(s) of treatment response on the reduction of PTSD symptom severity (n = 79) in terms of: (a) a minimum score reduction on a clinician-rated or self-report PTSD measure ("minimum score reduction," n = 20); (b) a cutoff score on a clinician-rated or self-report PTSD measure, using a predefined statistical formula ("cutoff score derived from a predefined statistical formula," n = 17); (c) a minimum percentage reduction on a clinician-rated or self-report PTSD measure scores ("minimum percentage reduction," n = 10); or (d) meeting a predefined cutoff score for a clinician-rated or self-report PTSD measure ("cutoff score," n = 10). These four subcategories are further elaborated below with examples.

Minimum score reduction (clinician-rated)

The Clinician-Administered PTSD Scale (CAPS) was the only clinician-rated measure used, with trials requiring a minimum score reduction of either 10 points (n = 8), 12 points (n = 2), 15 points (n = 9), or 20 points (n = 1).

Cutoff score derived from a predefined statistical formula (clinician-rated)

Jacobson and Truax's (1991) formula was predominately used for definitions using a cutoff score derived from a statistical formula. The formula is used to determine whether a change in an individual's score is *clinically* significant. An individual is considered to have made clinically significant improvement if their post-treatment scores move outside the range of the population of those with a disorder, or within the range of scores of the population with no disorder (Jacobson & Truax, 1991).

Most frequently, a 2 standard deviation reduction between pre- and post-treatment scores on a clinician-rated PTSD measure was used to confirm change (n = 8). Formulas using reductions of 1 or 0.5 standard deviation (n = 3) were also used to identify minimal clinically meaningful differences. These less conservative formulas were chiefly confined to noninferiority trials. Second, the formula can be used to determine whether the magnitude of change is statistically reliable, which uses the Reliable Change Index (RCI). The RCI can be calculated by dividing the difference between pretreatment and post-treatment scores by the standard error of the difference between the two scores (Jacobson & Truax, 1991). Twelve trials used RCI definitions, with reliable change scores ranging from 11.09 to 17.70 points on CAPS (CAPS-V = 13.0; CAPS-IV = 11.09; and CAPS-IV-TR = 12.0 and 17.7), and from 7 to 15 on the PTSD Symptom Scale—Interview (PSS-I).

Minimum percentage reduction (clinician-rated)

Of the ten trials that defined treatment response as a percentage reduction in PTSD symptom severity, the majority used

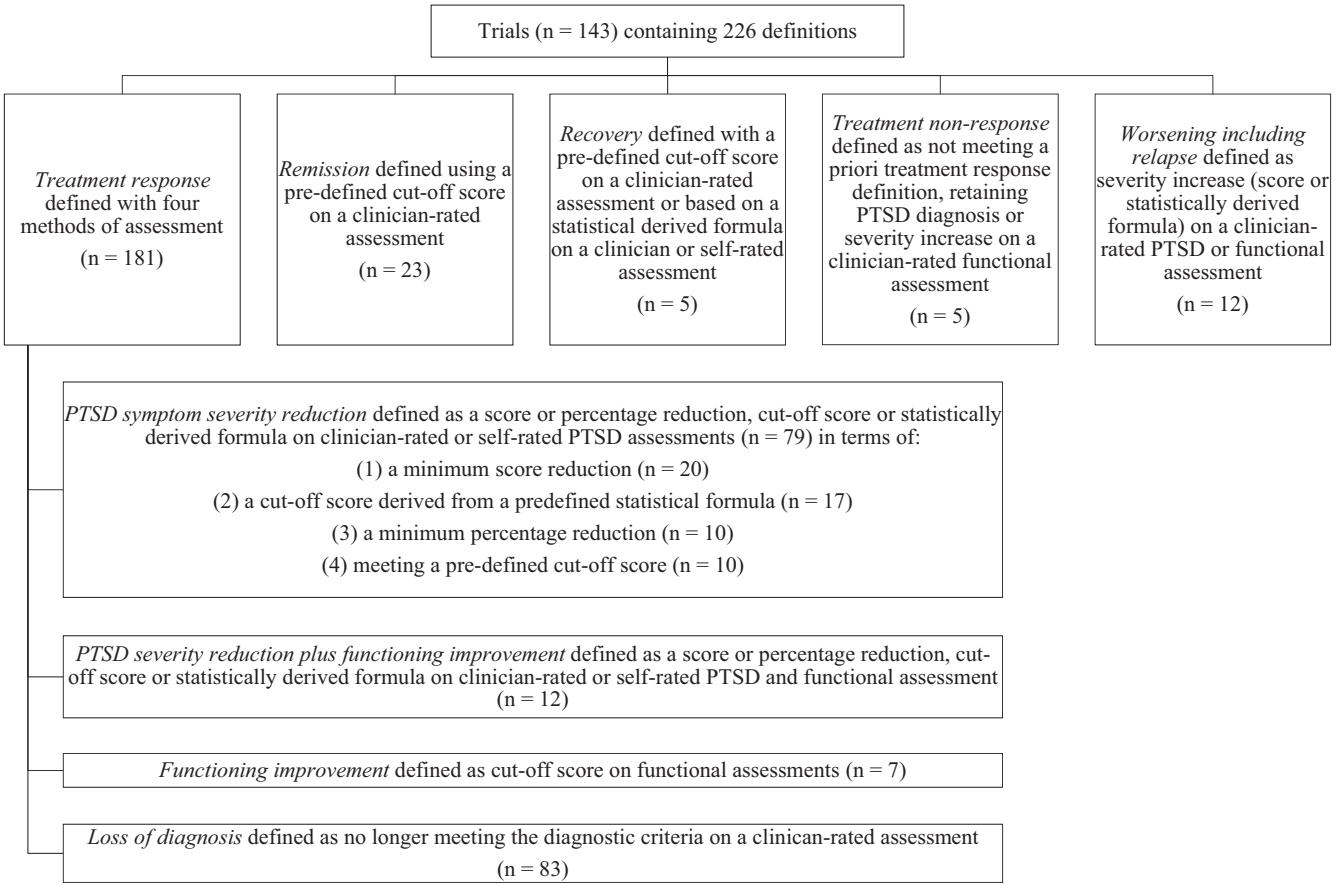

FIGURE 2 Definitions of treatment response and nonresponse used within the synthesized trials included in the review

a 30% reduction on CAPS-IV ($n = 6$) to indicate significant improvement. Two studies examining pharmacological interventions (Martenyi, Brown, & Caldwell, 2007; Martenyi, Brown, Zhang, Prakash, & Koke, 2002) used a 50% reduction to indicate treatment response.

Cutoff scores (clinician-rated)

Ten trials used a predefined cutoff score on a clinician-rated measure. The majority of these trials operationalized treatment response as a score of ≤20 on either the CAPS-IV or PSS-I. Weathers, Keane, and Davidson (2001) suggest that a score of ≤19 on the CAPS-IV indicates that a patient is asymptomatic or has few symptoms, whereas Foa (1995; Foa et al., 1999) suggests that a score of ≤20 on the PSS-I and PSS-Self-Report (PSS-SR) indicates "good end-state functioning," which is presumably synonymous with remission or recovery.

Self-rated outcomes

In comparison with definitions of treatment response derived from clinician-rated assessments, definitions based on self-report evaluations were used less frequently and varied widely. For example, out of 26 trials that used self-report assessments when defining treatment response, seven included definitions based on threshold score reductions (5.0 and 8.8 points on the PTSD Checklist [PCL]; and 20 points on the Posttraumatic Diagnostic Scale [PDS], PSS-SR, or the Modified Posttraumatic Stress Disorder Symptom Scale [MPSS-SR]). Four trials used threshold percentage reductions (30% on the Impact of Event Scale—Revised [IES]; 50% on PDS; or 70% on PSS-SR), and two trials used cutoff scores (44 points or 50 points on the PCL). Nine studies used sample mean cutoff scores to define treatment response. These mainly incorporated a 2 standard deviation reduction on IES scores, and therefore, there was a range of cutoffs used among the trials to indicate clinically significant change. Only one trial used a RCI of a 10-point decrease on the IES to indicate treatment response (Wells et al., 2015).

3.4.2 | Definitions incorporating a reduction in PTSD symptom severity plus improvement in function

The most comprehensive definitions of treatment response ($n = 12$) incorporated a combination of clinician-rated or self-report PTSD symptom severity outcomes and functional outcomes. The most common of these definitions combined a 30% or greater reduction on the CAPS with a Clinical Global Impression of Improvement (CGI-I) rating of 1 or 2 ($n = 8$). Two other trials used the clinician-rated PSS-I or the

self-report IES/IES-Revised in conjunction with either the CGI-I or the General Health Questionnaire (GHQ) global improvement scale to define treatment response (Marks, Lovell, Noshirvani, Livanou, & Thrasher, 1998; Zohar et al., 2002). One trial provided a definition, which included both the assessor's CAPS global severity rating and the participants' own CAPS global improvement rating (Tarrier et al., 1999), and another provided a definition, which included both clinician-rated PTSD outcomes (CAPS 2) and the GHQ global improvement scale (Marks et al., 1998).

3.4.3 | Defining treatment response as improvement in function only

PTSD treatment response was also defined in terms of only functional improvement in seven trials. Most trials used the CGI-I ($n = 5$), and one used the Duke Improvement Scale ($n = 1$). In all of these trials, treatment responders were categorized using a global improvement score of 1 (very much improved) or 2 (much improved), or an improved rating of two or more points ($n = 1$). Six of the seven trials that used functional improvement to measure treatment response examined pharmacological interventions, including fluoxetine (Connor et al., 1999; Hertzberg, Feldman, Beckham, Kudler, & Davidson, 2000) and paroxetine (Marshall, Beebe, Oldham, & Zaninelli, 2001; Marshall et al., 2007; Schneier et al., 2012; Tucker et al., 2001).

3.4.4 | Treatment response as loss of diagnosis

Response to treatment was operationalized as loss of diagnosis in 83 (58%) trials. The most common of these definitions were based on the CAPS diagnostic criteria ($n = 54$). A further twenty-three trials defined response as loss of diagnosis based on clinician-rated assessments other than the CAPS—most commonly the PDS or the Structured Clinical Interview for DSM-IV (SCID). Only three trials went beyond the diagnostic criteria by pairing loss of diagnosis with a cutoff score in the definition (i.e., score of <45 or <50 on the CAPS; Monson et al., 2006; Schnurr et al., 2007; Schnyder, Müller, Maercker, & Wittmann, 2011). Six studies defined loss of diagnosis using self-report assessment cutoff scores (i.e., <2.5 on the Harvard Trauma Questionnaire [HTQ], <14 on the PDS, and <20 on the PSS-SR).

3.5 | Remission definitions

Response to treatment was operationalized and labeled as remission in 23 trials. In contrast to other definitions, there was more consistency in the definition of remission with 16 trials (69.6%) using a score of ≤20 points on the CAPS as the cutoff. Two trials used less stringent CAPS cutoff scores to define remission, namely ≤35 points (Rauch et al., 2018) or ≤50 points (Back et al., 2019), while Ehlers et al. (2014) used both a 20-point cutoff score on the CAPS and a score of <11 on the PDS in their trial. Three studies (Butollo, Karl, König, & Rosner, 2016; Harned, Korslund, & Linehan, 2014; Popiel, Zawadzki, Pragłowska, & Teichman, 2015) defined treatment response as "remission" and described remission as not meeting PTSD criteria in the last month. However, they did not provide details of which cutoff scores were used. Global functioning was only considered in the definition of remission in one trial. Schneier et al. (2012) defined treatment response as ≤20 points on the CAPS and a rating of 1 (*very much improved*) on the CGI-Change.

3.6 | Recovery definitions

Five trials offered definitions of recovery, with two trials using the Jacobson and Truax's (1991) reliable change formula to identify reliably and clinically significant indices of change to indicate recovery. Two trials identified recovery as change on a clinician-rated assessment (i.e., >10.5-point reduction and a cutoff score of ≤14.9 in PSS-I; Feske, 2008; Harned et al., 2014), and one trial used a self-rated assessment (i.e., 10-point reduction and cutoff score of ≤32 on IES; Wells et al., 2015). The fourth trial calculated clinically significant differences based on the RCI (8-point reduction on PSS-I) to differentiate between improved, recovered, not reliably changed, and deteriorated (Langkaas et al., 2017). The fifth trial offered a definition of recovery, which was a score of ≤20 points on the PSS-SR (Arntz, Tiesema, & Kindt, 2007). It should be noted that there was some overlap in the way in which recovery and remission were defined. For example, three studies described remission as not meeting PTSD criteria in the last month (cutoff score details were not provided), while one study defined recovery as having a score of ≤20 points on the PSS-SR.

3.7 | Treatment nonresponse definitions

Nonresponse was defined in five trials as failure to meet the treatment response definition (Back, Brady, Sonne, & Verduin, 2006; Blanchard et al., 2003; Chung et al., 2004; Connor et al., 1999) or as a deterioration in function only (Duke Improvement Scale > 2; Hertzberg et al., 2000). No studies provided operational definitions of treatment resistance.

3.8 | Worsening (including relapse) definitions

Worsening was defined in 10 trials primarily as a reliable change in the direction of greater dysfunction, based on the Jacobson and Truax (1991) formula (RCI ranged between 1.65 and 10), as an increase in severity of symptoms from baseline to post-treatment on a clinician-rated assessment (e.g., PDS > 6.15; CAPS-IV > 10 points), or as a decline in function only (≥3 points on CGI-I). Finally, symptom exacerbation or relapse was defined in two trials as an increase in symptom severity scores, with either an increase in one standard deviation on the PDS (Popiel et al., 2015) or a score increase indicative of decline in function on the CGI (i.e., a score ≥ 4 at post-treatment or a ≥ 2-point increase on the CGI relative to improvement status at week 24; Davidson et al., 2005).

4 | DISCUSSION

As far as the present authors are aware, this is the first systematic review to comprehensively consider how response and nonresponse to PTSD treatment have been operationalized in PTSD treatment trials. It was concerning to find that a substantial number of eligible research trials ($n = 49$) investigating the efficacy of PTSD interventions did not operationalize treatment response (and therefore were excluded from the qualitative synthesis). As trial reporting standards have been introduced and become commonplace, we have seen an improvement in the utilization of the operational definitions over time. Nevertheless, our findings show that of trials published within the last 10 years, more than a quarter still failed to operationalize treatment response or nonresponse. Trials that did not operationalize treatment response typically used statistical tests to show between-group differences, and concluded that there was significant benefit, decreases in PTSD symptoms, or differences in rates of a PTSD diagnosis. Some trials also stated that there was a greater treatment response for one group over another. However, none of these trials paired this wording with definitions of numerical scores or changes in diagnosis status on validated measures to operationalize treatment response. This represents a major methodological concern and undermines efforts to examine the comparative efficacy of treatments across trials when these terms are not defined. It is essential that future studies of PTSD treatment include these important definitions to help determine the effectiveness of the treatments.

In this systematic review, the most popular categories used to describe treatment response were as follows: *treatment response, remission, recovery, treatment nonresponse,* and *worsening*. The review identified a preference across PTSD trials to operationalize treatment response using either a predetermined percentage or score reduction in symptom severity, or a cutoff symptom score on a clinician-rated assessment. Several concerns arise from these approaches. First, the validity of the method by which these definitions have been formulated is dubious. For example, with one exception (i.e., CAPS 10-point benchmark; Schnurr & Lunney, 2016) the nominated cutoff scores reported across trials were not empirically derived, instead appearing to have been arbitrarily chosen. The findings highlight a need to: (a) empirically identify and test the validity of different cutoff scores for different assessment tools (e.g., CAPS versus PSS-I) and different versions of the tools (e.g., CAPS-IV versus CAPS-5), ensuring all are anchored to some form of discernible "difference" in the clinical picture; and (b) empirically differentiate between different cutoff scores relating to different categories of treatment response.

A second concern relates to the fact that definitions based on symptom severity reductions do not take into consideration baseline symptom severity (Yehuda & Hoge, 2016). Using these methods, a person with severe PTSD may achieve symptom improvement, but still exhibit significant levels of symptomatology and functional impairment or retain the clinical diagnosis. A 10-point reduction on CAPS, for example, is unlikely to be deemed a significant clinical treatment response for clients with severe PTSD symptomatology scoring 60 or 70 on the CAPS at baseline. As such, the individual finds themselves in the confused position of being both "a treatment success" but continuing to be heavily burdened by ill health and associated disability. Thus, incorporating a symptoms' cutoff in addition to amount of symptom improvement could be a useful way to define treatment response to avoid this problem. Furthermore, a better understanding of residual symptoms may help further clarify which symptoms continue to affect quality of life and predict the likelihood of relapse or other long-term outcomes (Larsen et al., 2019). They also can inform which treatment strategies are most helpful and consequently lead to a better understanding of the mechanisms of change and longitudinal course of PTSD. This would not only allow for improvements to treatment response definitions, but also may assist in improving treatment outcomes through augmented treatments specifically targeting residual symptoms (Metcalf et al., 2019).

Consistent with the views expressed previously (e.g., Schnurr, Hayes, Lunney, McFall, & Uddo, 2006; Schnurr & Lunney, 2016; Sippel et al., 2018), it is somewhat concerning that the most common PTSD treatment response is defined in terms of symptom severity scores or percentage reductions alone, in the absence of other meaningful treatment outcomes. Yehuda and Hoge (2016) commented on the need to expand treatment outcomes beyond symptom reductions and incorporate other meaningful goals related to physical

health, well-being, interpersonal connections, and functioning in vocational or social settings. A similar sentiment has been supported by Schnurr and Lunney (2016), who conceptualized meaningful improvement to reflect real-world quality of life impacts (i.e., improvements in social, occupational, emotional, physical and social functioning, and life satisfaction), rather than the degree of change in PTSD symptom severity, as this has been found to not necessarily result in improvements across quality of life domains. There is evidence that improvements in functioning and quality of life do not necessarily occur at the same rate or trajectory as the amelioration of symptoms (Keller, 2003). Such outcomes are often recognized by patients as more important and meaningful than symptom relief (Cuijpers, 2019). It is our view that definitions of treatment response should systematically incorporate assessments of function. However, in the absence of a gold-standard assessment of functionality (Lam, Parikh, Michalak, Dewa, & Kennedy, 2015), an appropriate tool must be selected depending on the specific research question, and taking into consideration the patient-reported outcomes.

Ultimately, the treatment goal for any physical or mental health condition should be remission and finally recovery, or in simple terms, the absence of ill health and a return to pre-illness functioning (Crosby, Kolotkin, & Williams, 2003). In the current review, remission was consistently operationalized as achieving a score of 20 points or less on the CAPS. However, the remission definitions used in trials did not specify how long symptoms must be absent for across a specific time period, which is problematic if distinction is to be drawn between loss of diagnosis and remission. Furthermore, in some trials, remission and recovery referred to unique concepts, while in others, the terms were used interchangeably.

There was little discussion in reviewed trials of how treatment nonresponse and worsening are determined. The few studies that provided a definition commonly defined it as a deterioration in symptom severity, or as not achieving the definition of treatment response. This reflects the general lack of discussion around the quality of negative outcomes in PTSD clinical trials (Yehuda & Hoge, 2016). Increased focus on the issue of treatment nonresponse is recommended given that just as the quality of treatment response varies between groups and individuals, there is equal variability between groups and individuals in the quality of nonresponse (e.g., partial response versus no change versus worsening following treatment). This in turn will guide the personalization of treatment, and may also suggest a need for new and novel treatment approaches (Sippel et al., 2018).

Critically, failure to reach agreed-upon and accepted definitions of treatment response and nonresponse is not without consequences, with the greatest real-world impact experienced in clinical practice. In this context, debate and delay in determining treatment response and when or when not to intervene undermines aspirations to assertively intervene in a timely fashion when a first-line treatment fails (i.e., secondary prevention). This, in turn, unnecessarily exposes treatment seekers to risks of complications and comorbidity associated with treatment delay (Wang et al., 2005) and significant burden associated with the duration of untreated illness (McFarlane, 2019). Poorly specified outcomes are also problematic because they can lead to distortion of the true efficacy of interventions. Our recommendation is that the CONSORT reporting guidelines for research trials include a requirement for clearly defined and operationalized treatment outcomes that address the quality of treatment response and, as importantly, treatment nonresponse.

4.1 | Operational definitions for consideration

To move the trauma field forward, it is essential that there are clearly defined and operationalized treatment response categories. One way of agreeing-upon definitions for these terms is to use a consensus-driven approach. Based on our findings, we propose a set of consensus-driven operational definitions (and depicted in Figure 3).

- *Treatment response* as measured on a clinician- and self-rated scale is a reduction in an individual's baseline symptomatology of ≥30%–50%. On CAPS, a *clinically meaningful response* is indicated by a minimum score reduction of ≥15 points. A more rigorous form of treatment response should also include a range of functional and quality of life outcomes (e.g., interpersonal, social and occupational functioning, coping skills) and other indicators of a "good end-state function" (e.g., depression and anxiety symptoms; Cuijpers, 2019; Yehuda & Hoge, 2016). Inclusion of functional and quality of life outcomes in research will help to ensure that treatment outcomes that are clinically meaningful for the patient, and in clinical settings, will inform treatment decisions by patients and providers (Stefanovics, Rosenheck, Jones, Huang, & Krystal, 2018).
- *Remission* is defined as obtaining a score of ≤20 points on the CAPS.
- *Recovery* is defined as maintaining a score of ≤20 points on the CAPS at a time point of at least 6 months after treatment completion.
- *Treatment nonresponse* definitions should make the distinction between nonresponse, worsening, and treatment resistance. *Nonresponse* should be defined as failure to meet the treatment response criteria, while *worsening* should be differentiated from temporary symptom exacerbation

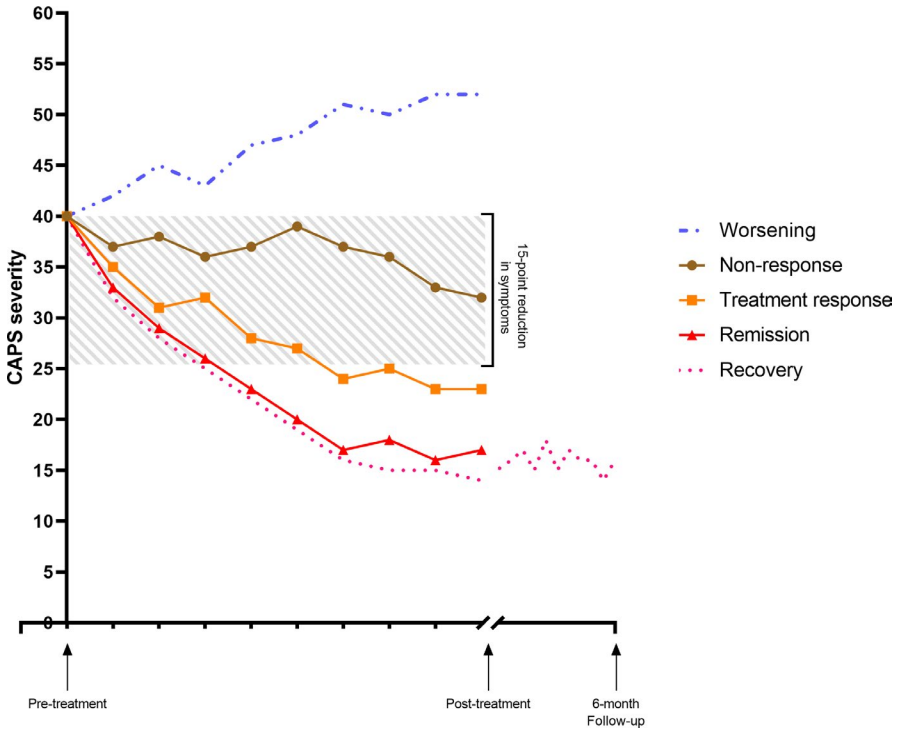

FIGURE 3 Operational definitions of treatment response and nonresponse categories proposed based on the findings of the review

(Foa, Zoellner, Feeny, Hembree, & Alvarez-Conrad, 2002) and defined as persistent deterioration of symptoms. We suggest that the field further investigates whether there is a cutoff score that best represents worsening. This should also take into account issues such as reduction in function and quality of life or increases in disability. Finally, *treatment resistance* should be defined as lack of clinically meaningful improvement despite provision of adequate treatment (Sippel et al., 2018). Sippel et al. (2018) propose a staged model to guide research and clinical management. Specifically, Stage 1 treatment-resistant PTSD should be defined as nonresponse to two evidence-based treatments for PTSD, each delivered with high fidelity and at an effective dose. Stage 2 treatment-resistant PTSD is defined as nonresponse to at least three evidence-based treatments.

Operationalization of these constructs will also help to facilitate the development of clinical algorithms to guide decision-making and treatment planning (Forbes et al., 2019). For example, an algorithm for treatment-resistant PTSD has been developed (Dunlop, Kaye, Youngner, & Rothbaum, 2014), which focuses on treatments with proven efficacy that the patient has failed to respond to, to determine whether the patient is treatment-resistant. This work needs to be extended and built upon with high-quality trials to test the utility of the proposed models. No algorithms currently exist to guide decision-making and treatment planning for those who are treatment-resistant and experience nonresponse or worsening, representing a major shortcoming for the PTSD field.

4.2 | Strengths and limitations

A strength of this review was the inclusion of a large number of trials providing treatment response and nonresponse definitions for both psychological and pharmacological interventions for PTSD. Limitations of the review include restricting the inclusion to interventions with strong recommendations from PTSD guidelines and restricting the review to RCT methodologies.

5 | CONCLUSION

This review identified significant diversity in the definitions of treatment response and nonresponse. It is clear that the field of PTSD treatment is in need of a shared understanding of these concepts to increase agreement and communication among clinicians and researchers. The next step required is for researchers to test our proposed definitions to empirically validate them. Standardizing operational definitions of treatment response and nonresponse is essential for the interpretation of research findings, their translation into clinical practice, and improving comparability and generalization.

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ENDNOTE

[1] http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42019119670.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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