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## PTSD relapse in Veterans of Iraq and Afghanistan: A systematic review

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### ABSTRACT

This systematic review examines studies published between 2003, the initial invasion of Iraq, and 2018 related to the long-term treatment outcomes for Veterans of Iraq and Afghanistan suffering from combat-related posttraumatic stress disorder (PTSD). More specifically this review attempts to estimate the rate at which Veterans experience the return of symptoms after completing treatment. The review was conducted by the authors in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions*. The literature search identified eight eligible studies, which met the predefined inclusion criteria. Of the included studies a majority were deemed to be at a high risk of attrition bias. In addition, few studies comprehensively reported relevant relapse or recurrence related outcome statistics. The implications of the available evidence base on long-term treatment outcomes are discussed. Recommendations for future studies on relapse and recurrence of PTSD symptoms among Veterans of Iraq and Afghanistan are also presented.

### ARTICLE HISTORY

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### KEYWORDS

PTSD; relapse; recurrence;  
Veteran; military



**What is the public significance of this article?**—It is vital that we understand what characterizes Veterans and soldiers who are hindered by their combat experiences, and how best to help them. Research has already established that Veterans and soldiers seeking treatment for combat trauma face a variety of challenges that civilians do not. As a whole, Veterans are more likely to drop out of treatment before their conditions improve, and those who do complete treatment are less likely to experience a significant improvement than civilian patients. Of the relatively few military patients who complete treatment and experience a significant improvement, little is known about how long this improvement generally lasts.


### Introduction

Posttraumatic stress disorder is a disabling anxiety disorder, emerging after an acutely distressing event of a threatening or catastrophic nature. The core symptoms of the disorder are persistent reexperiencing of the trauma, avoidance of trauma-related stimuli, negative alterations in cognitions and mood, and increased arousal and reactivity. Military personnel, especially those directly involved in combat operations, have been found to be at an increased risk of developing

the disorder. A study from the American Department of Veterans Affairs (VA) examining over 100,000 Veterans indicated that PTSD was the most commonly diagnosed military service-related mental health condition, accounting for more than half of all Veterans diagnosed with a mental health condition (Seal, Bertenthal, Miner, Sen, & Marmar, 2007). In recent years a large number of military personnel have presented with combat related trauma as a result of operations in Iraq and Afghanistan. The Veterans of these conflicts have been exposed to operational stressors that differ meaningfully from those of their predecessors, as well as finding themselves in a markedly different social context (IOM, 2008). These differences may have implications for both how modern Veterans experience their trauma and how they respond to treatment. As a result, ensuring effective and efficient treatment of afflicted service members has become a priority.

Estimates of the prevalence of PTSD among service members vary between studies. An observational study of over 18,000 US Army soldiers returning from Iraq and Afghanistan described the self-reported prevalence of PTSD to be 15% (Thomas et al., 2010). Similarly, a comprehensive study of the prevalence of this disorder among over 13,000

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 Supplemental data for this article can be accessed [here](#).

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Veterans deployed during OEF/OIF indicated an overall rate of 15.8% (Dursa, Reinhard, Barth, & Schneiderman, 2014). An extensive meta-analysis by Hines, Sundin, et al., 2014 estimated a prevalence of 12% amongst combat units and 5% among non-combat units. Although estimates vary, the research literature indicates that Veterans in general, and combat Veterans in particular, are at a much greater risk of being diagnosed with PTSD than civilians (Hines, Sundin, et al., 2014; Fulton et al., 2015). Furthermore, combat-related PTSD is associated with a number of negative consequences in addition to the symptomatology of the disorder itself, such as substance abuse, depression, interpersonal difficulties, and suicidality (Debell et al., 2014; Ramchand, Rudavsky, Grant, Tanielian, & Jaycox, 2015; Stander, Thomsen, & Highfill-McRoy, 2014).

### **Treating PTSD in Veterans and military personnel**

Although research indicates that Veterans and military personnel suffer from PTSD at a higher rate than the civilian population, research also indicates that relatively few seek treatment. A combined systematic review and meta-analysis by Sharp et al. (2015) provides a useful overview. For instance, it is estimated that 40–60% of Veterans that would benefit from treatment do not seek professional help (Hoge et al., 2004; Iversen et al., 2011; Kehle et al., 2010). Studies also indicate that of the small proportion of military personnel afflicted with PTSD that do seek help, a majority receive help from non-clinical sources, such as social workers or chaplains (Hines, Goodwin, et al., 2014; Iversen et al., 2010). Hoge (2011) argues that with current rates of treatment seeking, and a recovery rate of approximately 40%, current treatment strategies will only be able to reach approximately 20% of Veterans in need of PTSD treatment.

Combating the high rate at which military personnel and Veterans withdraw from treatment for PTSD is another critical challenge. A systematic review of dropout from psychotherapy by Goetter et al. (2015) suggested an overall pooled dropout rate of 36% for military personnel. A similar review of nonmilitary PTSD patients estimated a dropout rate of only 18% (Imel, Laska, Jakupcak, & Simpson, 2013). Goetter et al. (2015) also indicated that attrition among soldiers was even higher in routine clinical settings than from clinical trials, and that younger Veterans quit at a higher rate than older Veterans (Goetter et al., 2015). As such, many Veterans unfortunately terminate treatment prematurely, and therefore may not experience significant symptom reduction.

A 2015 review of 36 randomized clinical trials (RCT) examining psychotherapy for military-related PTSD concluded that approximately two-thirds of patients retained their diagnosis after treatment (Steenkamp, Litz, Hoge, & Marmar, 2015). However, the review also indicated that between 49–70% of patients attained meaningful symptom reduction. It has not yet been conclusively established whether outcomes of PTSD treatment are poorer for military than civilian populations, although a growing body of evidence indicates that they are (Bradley et al., 2005; Price, Gros, Strachan, Ruggiero, & Acierno, 2013). If this is the case, it may be necessary to consider novel intervention methods in order to ensure more effective treatment of combat-related PTSD (Steenkamp et al., 2015).

In summary, of the small portion of Veterans suffering from PTSD symptoms who seek and receive treatment, only a slight majority experience symptom reduction, and most retain their diagnosis.

### **Long-term effects of treatment**

In a clinical context, experiencing an increase in mental health symptoms after a period of treatment is referred to as either a relapse or recurrence. The term relapse generally refers to the return of symptoms associated with a treated episode of mental illness, for instance in cases where treatment is terminated prematurely (Hollon, Thase, & Markowitz, 2002). In contrast, the return of symptoms following a period of complete recovery is referred to as a recurrence, and is thought to represent the start of a new and separate episode (Hollon et al., 2002). Unfortunately, as of yet there are few studies which examine the duration of symptom reduction among Veterans after treatment over an extended period of time. For instance, in a recent review by Steenkamp et al. (2015) the follow-up period in RCTs of first-line interventions ranged from no follow-up at all to 12 months, with an average of approximately 5 months. As a result, relatively little is known about the rate at which Veterans diagnosed with combat-related PTSD experience relapse or recurrence after completing treatment.

Ensuring that treatment gains are maintained beyond the treatment period itself is essential to ensuring that adequate care is being provided. Interventions that result in temporary treatment gains, may offer short-lived relief for patients, but may also have negative secondary consequences. Patients may become averse to further treatment attempts or may conversely become dependent on ineffective treatments (Institute of Medicine (US). Committee on Treatment of Posttraumatic Stress Disorder, 2008). Accordingly, the

Institute of Medicine recommends that evaluations of treatment effectiveness should also determine to what extent improvements decline, continue or are maintained (Institute of Medicine (US). Committee on Treatment of Posttraumatic Stress Disorder, 2008). If current treatments of combat-related PTSD are found to be ineffective in ensuring long-term improvements, this would have several important implications. First, such a finding would highlight the need for more robust methods of early relapse detection and prevention. Second, it is essential that Veterans who suffer from the disorder are made aware of what to expect with regards to long term prognosis, also after completing treatment. Finally, if symptom reduction for combat-related PTSD is not maintained over time, necessitating multiple courses of treatment, estimates of the overall societal cost of providing labor intensive care to the Veteran population may be expected to increase.

### **Aims of the systematic review**

In an attempt to summarize what is currently known about the long-term effects of the most commonly used psychotherapies in the treatment of combat-related PTSD among Veterans of Iraq and Afghanistan, this systematic review will present a summary of the available literature. Assessing the long term treatment outcomes for other subgroups of the military clinical population, such as Veterans of other eras of service or Veterans suffering from military sexual trauma, is beyond the scope of the present review. To the knowledge of the authors no such review has been completed in recent years. In particular the review will attempt to summarize what the relapse and recurrence rates of Veterans are indicated to be, as well as what characterizes treatments associated with lower relapse and recurrence rates. The present review was conducted in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins et al., 2019).

## **Methods**

### **Eligibility criteria**

For an RCT to be selected for the review it was required to have (1) a sample consisting primarily of Veterans of military operations in Iraq and Afghanistan; (2) PTSD as an inclusion criterion; (3) a majority of participants that reported combat related trauma; (4) reported symptom scores on standardized clinical measures of PTSD at pretreatment, posttreatment, and for a follow-

up period of at least 6 months after treatment; (5) utilized individual or group therapies that adhered to the British National Institute of Clinical Excellence (NICE), American Psychiatric Association (APA) or Department of Veterans Affairs (VA) guidelines for first-line treatment of PTSD, and did not solely involve pharmacotherapies.

### **Literature search**

The authors searched PubMed, The Published International Literature on Traumatic Stress (PILOTS), PsycNET, and Google Scholar for completed English-language RCTs of psychotherapy for PTSD conducted on military personnel or Veterans published between 2003 (the initial invasion of Iraq) and 2018. The specific search terms for each database used in the literature search, and the resulting number of references, were:

*PubMed (91 results):* “BEST MATCH” (((Randomized controlled trial[Title/Abstract] OR RCT[Title/Abstract] OR Randomized clinical trial[Title/Abstract])) AND (Veteran[Title/Abstract] OR military[Title/Abstract] OR combat[Title/Abstract])) AND (psychotherapy[Title/Abstract] OR PET[Title/Abstract] OR CPT[Title/Abstract] OR CBT[Title/Abstract] OR EMDR[Title/Abstract] OR NET[Title/Abstract])

*PILOTS (144 results):* (ab(randomized controlled trial AND PTSD AND military OR Veteran OR combat) AND ab(PET OR CPT OR CBT OR EMDR)) (After 2001, peer reviewed)

*APA PsycNET (112 results):* Any Field: Any Field: randomized controlled trial OR Any Field: Any Field: randomized clinical trial OR Any Field: Any Field: RCT AND Any Field: Any Field: PTSD OR Any Field: Any Field: post-traumatic stress AND Any Field: Any Field: Veteran OR Any Field: Any Field: military OR Any Field: Any Field: combat AND Any Field: Any Field: psychotherapy OR Any Field: Any Field: PET OR Any Field: Any Field: CPT OR Any Field: Any Field: CBT OR Any Field: Any Field: therapy OR Any Field: Any Field: EMDR OR Any Field: Any Field: NET AND Any Field: Year: 2001 To 9999 AND Peer-Reviewed Journals only

*Google Scholar (First 186 results used, 1770 results total):* PTSD Veteran military combat therapy randomized trial PE OR EMDR OR CPT OR CBT “randomized clinical trial”

### **Study selection and data collection**

The results of the four searches were collated, and duplicates were removed. All titles and abstracts were

screened to remove ineligible studies. For the remaining potentially relevant studies, full-text versions were retrieved and reviewed. The number of full-text papers that were assessed and excluded at each stage, as well as primary reasons for exclusion, were reported in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart. The authors manually extracted the necessary data items to determine the potential eligibility of the identified relevant studies. The data items extracted from potentially relevant studies included whether a study was randomized, the treatment method used, sample size, whether participants were primarily Veterans of Afghanistan and Iraq, the PTSD outcome measure utilized, as well as the length of follow-up.

### Assessing risk of bias

The Cochrane risk of bias tool was used to determine the degree of potential bias. The Cochrane risk of bias tool assesses (1) sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessors; (5) incomplete outcome data; (6) and selective outcome reporting. The first and last author evaluated risk of bias of individual studies independently of each other. Discrepancies were discussed in order to reach consensus.

### Estimates of relapse and recurrence

Comparisons of reported rates of remission, clinically meaningful change and loss of diagnosis at posttreatment and follow-up were considered to estimate recurrence and relapse rates. In this context the term remission refers to a full recovery from previously experienced symptoms, such as scoring below a predefined cutoff point on a given trauma symptom scale. For instance, in the case of the Clinician Administered PTSD Symptom Scale (CAPS) participants scoring at or below 20 points are considered to be in remission (Weathers, Keane, & Davidson, 2001). Similarly, the term clinically meaningful change refers to a decrease in reported trauma symptoms which is thought to be large enough to constitute a meaningful change in the patients experienced symptoms, rather than insignificant fluctuations in symptom severity. For instance, a decrease of 15 points or more in CAPS total score is deemed to represent a clinically meaningful change (Weathers et al., 2001). Finally, loss of diagnosis refers to a decrease in experienced trauma symptoms that is large enough that the participant no longer fulfills the criteria of the PTSD diagnosis. As a given participant may have a score that lies just above or far

above the cutoff point, the amount of improvement necessary to qualify for “loss of diagnosis” will vary. In the case of CAPS the diagnostic cutoff is commonly set at 45 points or less (Weathers, Ruscio, & Keane, 1999). If a participant in a study had experienced one of these three forms of improvement at post-treatment, but no longer did so at follow-up, they were thought to have experienced a relapse or recurrence.

## Results

The literature search returned 533 references which, after removal of duplicates, resulted in 491 unique references. The authors screened the titles and abstracts of these references and identified 75 potentially relevant references. After further assessment, it was concluded that 8 of these potentially relevant studies fulfilled the inclusion criteria and were therefore included in the review. Reasons for exclusion at each stage are described in the PRISMA flow diagram (see Figure 1).

### Excluded studies

Of the 75 potentially relevant articles assessed for eligibility, 67 were excluded after closer examination. Of these, 26 studies were excluded for not being randomized trials, 29 were excluded for not having a sample wherein a majority were Veterans of Iraq and Afghanistan, 4 studies did not require participants to have a diagnosis of PTSD, 2 did not utilize approved treatment methods

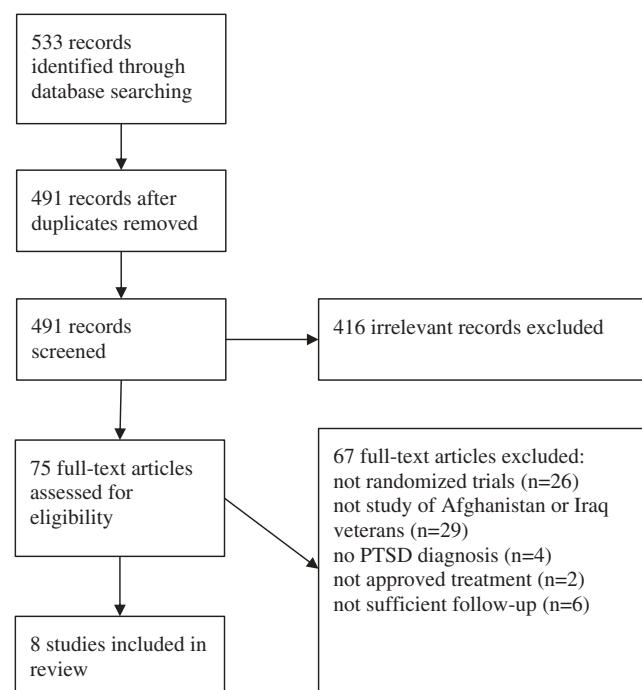


Figure 1. PRISMA flow diagram.



and finally 6 studies did not have sufficient follow-up periods. For specific exclusion reasons for all potentially relevant studies, please refer to the supplemental online material (Appendix A: Characteristics of excluded studies).

### **Included studies**

The studies included in the present review had the following characteristics (see also supplemental online material Appendix B: Characteristics of included studies):

### **Design**

One of the included studies was a non-inferiority trial (Acierno et al., 2017) while another (Castillo et al., 2016) utilized a wait list control group. A third study (Reger et al., 2016) utilized a combined parallel-group and wait list design, with two arms receiving simultaneous treatment and a third waitlist group serving as a control. The remaining six studies all used a parallel-group design. All included studies were randomized at the participant level.

### **Sample sizes**

In the present review a total of 1041 participants were allocated to 18 conditions across the 8 studies. Sample sizes ranged from 26 (Litz et al., 2012) to 268 participants per study (Resick et al., 2017). Other than the study by Litz et al. (2012) and one additional study which had a sample of 86 participants (Castillo et al., 2016), the remaining six studies all had samples of at least 100 participants (Acierno et al., 2017; Kozel et al., 2018; Reger et al., 2016; Resick et al., 2017, 2015; Rothbaum et al., 2014).

### **Setting**

All included studies were conducted in the USA. Three studies recruited active duty service members via referrals from providers at military medical centers (Reger et al., 2016; Resick et al., 2017, 2015). One of these studies also allowed for self-referral via study advertisements posted within military installations (Reger et al., 2016). Four studies recruited Veterans from Veterans Affairs medical centers and hospitals (Acierno et al., 2017; Castillo et al., 2016; Kozel et al., 2018; Litz et al., 2012). One of these studies also recruited participants from Veteran centers, local universities and colleges with Veteran enrollment, as well as nonprofit Veteran associated service organizations (Kozel et al., 2018). One study did not specify where participants were recruited from (Rothbaum et al., 2014).

### **Participants**

The majority of participants included in the present review were male. The three studies that examined active duty service members (Reger et al., 2016; Resick et al., 2017, 2015) all had samples that were over 90% male. Two studies had samples that were homogenous, with one study using an entirely male sample of Veterans (Litz et al., 2012), and another using an entirely female sample of Veterans (Castillo et al., 2016). Of the remaining three studies, two had Veteran samples that were over 90% male (Acierno et al., 2017; Rothbaum et al., 2014). The final study did not report specific participant gender statistics, but did report having a predominantly male sample of Veterans (Kozel et al., 2018). All participants in all included studies satisfied diagnostic criteria for PTSD. All participants in all but one of the studies also exclusively reported combat-related trauma after deployments to Afghanistan or Iraq. The exception (Acierno et al., 2017) reported that 61% of its participants had been deployed to Afghanistan or Iraq.

### **Exclusion criteria**

The criteria that were used to determine inclusion or exclusion of potential participants varied somewhat between studies, although there were a number of similarities. For instance, all studies reported active psychotic symptoms as an exclusion criteria, and most studies also excluded based on suicidal ideation and substance dependence. All studies required their participants to maintain stable regimes of prescribed psychotropic medications during the treatment period. One of the studies, which utilized repetitive transcranial magnetic stimulation in combination with psychotherapy, also excluded participants based on a number of medical contraindications such as seizures, dementia and pregnancy. Four studies listed traumatic brain injuries as an exclusion criteria in their studies, with one only excluding severe injuries (Resick et al., 2017), and three excluding both moderate and severe traumatic brain injuries (Kozel et al., 2018; Resick et al., 2015; Rothbaum et al., 2014). Finally, five of the studies required their participants to not receive any other psychotherapy for PTSD during the treatment period (Acierno et al., 2017; Castillo et al., 2016; Kozel et al., 2018; Litz et al., 2012; Reger et al., 2016). Of the three remaining studies, one explicitly mentioned allowing participants to undergo parallel treatment (Resick et al., 2017), while the other two made no mention of simultaneous psychotherapies (Resick et al., 2015; Rothbaum et al., 2014).

### **Interventions**

All experimental interventions included in the present review used forms of either exposure therapy or cognitive processing therapy. For more comprehensive descriptions

of the interventions used in the included studies, please refer to the supplemental online material (Appendix B: Characteristics of included studies).

### PTSD Measures

Of the eight studies included in the present review, seven used a clinician-administered measure of PTSD (Castillo et al., 2016; Kozel et al., 2018; Litz et al., 2012; Reger et al., 2016; Resick et al., 2017, 2015; Rothbaum et al., 2014). In five of the studies the clinician administered measure used was the Clinician Administered PTSD Symptom Scale (CAPS) (Castillo et al., 2016; Kozel et al., 2018; Litz et al., 2012; Reger et al., 2016; Rothbaum et al., 2014). Two studies used the Posttraumatic Symptom Scale-Interview Version (PSS-I) (Resick et al., 2017, 2015). Five of the studies with a primary clinician-administered measure of PTSD also reported a secondary self-report measure. These included the original (Kozel et al., 2018), military (Litz et al., 2012), civilian (Reger et al., 2016), and stressor specific (Resick et al., 2017) versions of the PTSD checklist (PCL). Another study used the Posttraumatic Symptom Scale- Self Report Version (PSS-SR) as a secondary outcome measure (Rothbaum et al., 2014). Two studies used a self-report measure as their primary outcome measure, namely the PTSD checklist-military (PCL-M) (Acierno et al., 2017), and the PTSD checklist-stressor specific version (PCL-S) (Resick et al., 2015). Two studies reported rates of diagnostic interrater reliability for clinician administered assessments. Resick et al. (2015) reported good interrater diagnostic reliability ( $\kappa = .83$ ) for the PSS-I based on at least 5% of independent evaluators interviews. Rothbaum et al. (2014) reported 100% interrater reliability for the primary diagnostic assessment which consisted of the Mini-International

Neuropsychiatric Interview (MINI) and CAPS. The remaining six studies did not report any measures of diagnostic interrater reliability.

### Treatment completion

Many of the included studies described issues of high dropout rates from both treatment and control conditions. The number of sessions attended in order to be considered a completer differed between studies. As a result the definition of treatment completion provided by the individual studies was used in assessing treatment acceptability.

All included studies minimally reported PTSD outcome measures at pretreatment, posttreatment and at last follow-up. In one study the posttreatment assessment took place one week after the final treatment session (Acierno et al., 2017). In six of the studies the final follow-up assessment took place six months after treatment was completed (Acierno et al., 2017; Castillo et al., 2016; Kozel et al., 2018; Litz et al., 2012; Reger et al., 2016; Resick et al., 2017), while the final two studies conducted the final follow-up assessment 12 months after treatment completion (Resick et al., 2015; Rothbaum et al., Prevalence of bias in studies 2014).

### Risk of bias in included studies

Bias assessments were conducted independently by the first and last author. The results were then compared, and divergent assessments were discussed before a final decision was made. For details on the "Risk of bias" judgments for each study, please refer to the supplemental online material (Appendix A: Characteristics of included studies). The overall assessments of bias in the included studies are presented in Figure 2 and Table 1.

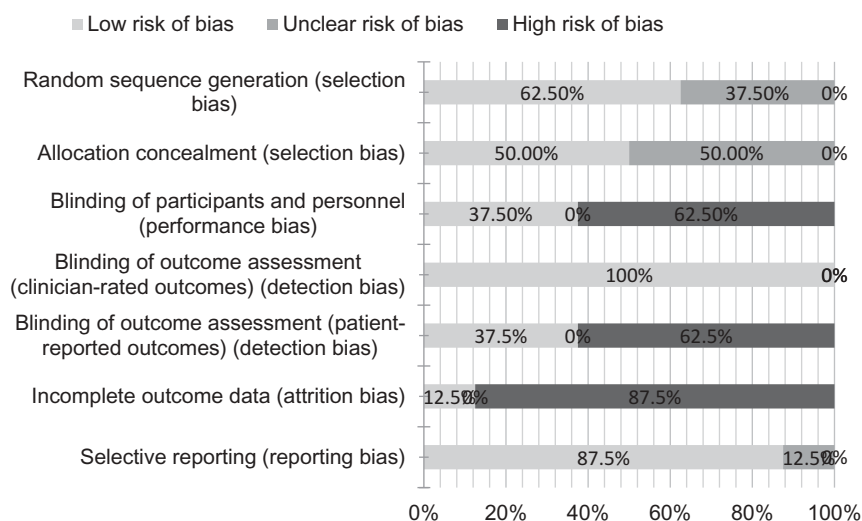


Figure 2. Prevalence of bias in studies.

**Table 1.** Bias assessments of studies.

	Random sequence generation (Selection bias)	Allocation sequence concealment (Selection bias)	Blinding of participants and personnel (Performance bias)	Blinding of outcome assessment (Clinician-rated) (Detection bias)	Blinding of outcome assessment (Patient-reported) (Detection bias)	Incomplete outcome data (Attrition bias)	Selective reporting (Reporting bias)
Acierno et al. (2017)	Low	Low	High	Low	High	High	Low
Castillo et al. (2016)	Unclear	Unclear	High	Low	High	Low	Low
Kozel et al. (2018)	Low	Low	Low	Low	Low	High	Unclear
Litz et al. (2012)	Low	Low	Low	Low	Low	High	Low
Reger et al. (2016)	Low	Low	High	Low	High	High	Low
Resick et al. (2015)	Unclear	Unclear	High	Low	High	High	Low
Resick et al. (2017)	Low	Unclear	High	Low	High	High	Low
Rothbaum et al. (2014)	Unclear	Unclear	Low	Low	Low	High	Low

### Allocation

Four studies specified the method of sequence generation and allocation used and were judged as being at low risk of selection bias (Acierno et al., 2017; Kozel et al., 2018; Litz et al., 2012; Reger et al., 2016). One study was judged to be at low risk of selection bias due to sequence generation and at an unclear risk of selection bias due to potentially inadequate concealment (Resick et al., 2017). Three studies did not adequately describe the method of sequence generation used and were therefore judged as being at unclear risk of selection bias (Castillo et al., 2016; Resick et al., 2015; Rothbaum et al., 2014).

### Blinding

In studies assessing psychotherapy participants and personnel cannot normally be blinded to treatment allocations. As a result, all studies comparing different methods of psychotherapy were judged to be at high risk of performance bias (Acierno et al., 2017; Castillo et al., 2016; Reger et al., 2016; Resick et al., 2017, 2015). The three remaining studies were judged to be at low risk of performance bias (Kozel et al., 2018; Litz et al., 2012; Rothbaum et al., 2014). All eight studies were judged to be at low risk of detection bias with regards to clinician-rated outcomes. With regards to patient-reported outcome measures, the five studies comparing different methods of psychotherapy were also judged to be at high risk of detection bias (Acierno et al., 2017; Castillo et al., 2016; Reger et al., 2016; Resick et al., 2017, 2015).

### Incomplete outcome data

Seven studies clearly reported drop-out and loss to follow-up and performed intention-to-treat (ITT) analyses on all randomized participants (Castillo et al., 2016; Kozel et al., 2018; Litz et al., 2012; Reger et al., 2016; Resick et al., 2017, 2015; Rothbaum et al., 2014). However, five of these studies had such high rates of data-loss that they were automatically judged to be at high risk of attrition bias (Kozel et al., 2018; Litz et al.,

2012; Reger et al., 2016; Resick et al., 2017, 2015; Rothbaum et al., 2014). One study reported conducting a modified ITT analysis, and was therefore judged to be at a high risk of attrition bias (Acierno et al., 2017).

### Selective reporting

For seven studies, all prespecified PTSD-related outcome measures were reported at all prespecified time-points, and were therefore judged to be at low risk of reporting bias (Acierno et al., 2017; Castillo et al., 2016; Litz et al., 2012; Reger et al., 2016; Resick et al., 2017, 2015; Rothbaum et al., 2014). One study was judged to be at an unclear risk of reporting bias (Kozel et al., 2018).

### Measures of relapse and recurrence

Only one study reported rates of remission, clinically meaningful change and loss of diagnosis at both post-treatment and last follow-up (Castillo et al., 2016). One study reported both changes in clinically meaningful change and loss of diagnosis, but did not report these statistics at last follow-up for the group receiving prolonged exposure therapy combined with d-cycloserine (Litz et al., 2012). One study reported clinically meaningful change at post-treatment and follow-up for all conditions (Resick et al., 2015). Another study reported rates of clinically meaningful change for all conditions, but only at posttreatment (Reger et al., 2016). Two studies reported loss of diagnosis both at posttreatment and last follow up for all treatment conditions (Resick et al., 2017; Rothbaum et al., 2014). Finally, two studies did not report any rates of remission, clinically meaningful change or loss of diagnosis for any treatment conditions at any time points (Acierno et al., 2017; Kozel et al., 2018).

### Effects of interventions

Only one study was not deemed to be at a high risk of attrition bias (Castillo et al., 2016). It was however



**Table 2.** Relapse and recurrence statistics.

Source	Participants	Conditions	Longest follow-up (Mo)	Drop-out (%)	Remission, post/follow-up	Clinically meaningful change, post/follow-up	Loss of diagnosis, post/follow-up
Acierno et al. (2017)	68	PE-IP	6	13 (19.1)	-	-	-
	64	PE-HBT	6	22 (32.8)	-	-	-
Castillo et al. (2016)	44	3 module	6	12 (27.3)	13.52%/12.62%	77.38%/73.10%	51.86%/46.29%
	42	Waitlist	-	7 (16.7)	-	-	-
Kozel et al. (2018)	54	CPT + rTMS	6	22 (40.7)	-	-	-
	49	CPT + sham	6	19 (38.8)	-	-	-
Litz et al. (2012)	13	PE + d-cycloserine	6	4 (30.8)	-	30%/-	33.3%/-
	13	PE + placebo	6	3 (23.1)	-	70%/66%	36.4%/50%
Reger et al. (2016)	54	VRE	6	24 (44.4)	-	56.67%/-	-
	54	PE	6	22 (40.7)	-	65.63%/-	-
	54	Waitlist	6	7 (13.0)	-	21.28%/-	-
	54	CPT-C	6	7 (13.5)	-	49%/56%	-
Resick et al. (2015)	56	PCT	12	15 (26.8)	-	34%/50%	-
	52	G-CPT	12	7 (13.5)	-	-	-
Resick et al. (2017)	133	CPT	6	30 (45.1)	-	-	37%/39%
	135	VRE + d-cycloserine	6	53 (39.3)	-	-	49%/43%
Rothbaum et al. (2014)	53	VRE + placebo	12	25 (47.2)	-	-	21.4%/52.9%
	50	VRE + Alprazolam	12	15 (30.0)	-	-	25.7%/36.4%
	53	VRE + placebo	12	19 (35.9)	-	-	26.5%/45%

judged to be at a high risk of performance bias, as well as an unclear risk of selection bias. The study reported overall rates of remission, clinically meaningful change and loss of diagnosis, both at posttreatment and at the last follow-up assessment, indicating a slight decrease in all three measures. However, as the study utilized a waitlist condition, no such long-term outcome statistics were available for a control group. As such no useful comparison of relevant outcome measures is possible based on the literature included in the present review. For an overview of relapse and recurrence related outcome statistics for all included studies, please refer to Table 2.

## Discussion

### Lack of research

The present review identified relatively few eligible studies on the topic of long-term treatment outcomes for PTSD among Veterans of Iraq and Afghanistan. In addition, few of these eligible studies consistently reported relevant relapse and recurrence related outcome statistics, such as rates of clinically meaningful change, loss of diagnosis, or remission. Only three studies reported a relevant outcome statistic for all conditions and at both post-treatment and follow-up. No study reported all three outcome statistics for more than one condition, and no study reported actual rates of relapse or recurrence. As such, it was not possible to estimate an overall relapse or recurrence rate. However, based on the studies returned by the literature search, certain observations may be made about the research

that is currently available. A sizable number of studies have been conducted on PTSD among Veterans in general, and in recent years on Veterans of Iraq and Afghanistan in particular. The literature search returned 34 potentially relevant RCTs that were conducted on Veterans suffering from PTSD, eight of which were included in the final review. The average follow-up period for these 34 studies was four months, with 19 of the studies not meeting the minimum criteria of six months, and eight of the studies reporting no follow-up period at all. Similarly, 22 of the studies either did not report what conflict their participants had been deployed to, or reported that a majority of their participants had deployed to other theaters than Iraq and Afghanistan. In summary, a minority of the studies returned by the literature search were conducted primarily on Veterans of Iraq and Afghanistan, and most had follow-up periods that were too short to assess long-term outcomes. These tendencies may represent two potential deficits in the available literature on PTSD treatment among Veterans.

### Quality of current research

In addition to the small number of eligible studies available on the present topic, the quality of the studies that are available should be addressed. In particular, the included studies are characterized by high risk of performance and attrition bias. Although a risk of performance bias is inherent to most studies that compare psychotherapeutic interventions, the high rate of

attrition bias may indicate a much more serious concern. It is important to note the distinction between dropout and loss of data. Although the decision of participants to terminate treatment may often be beyond the control of researchers, the same does not necessarily apply to the collection of follow-up data. The Institute of Medicine argues that studies that either exceed a 15% difference in data-loss between groups, or exceeds 40% data-loss in any group, automatically indicates a high risk of bias, regardless of the analytic methods used to handle the missing data (Institute of Medicine (US). Committee on Treatment of Posttraumatic Stress Disorder, 2008). The average loss of data at final follow-up for the included studies was 48%, with three studies reporting loss of data that exceeded 60%. In accordance with the Institute of Medicine, these rates of data-loss are so high that results will be at high risk of bias, regardless of the analytic methods employed (Institute of Medicine (US). Committee on Treatment of Posttraumatic Stress Disorder, 2008). As a result, even if the literature search had returned a larger number of eligible but methodologically similar studies, little could be reliably concluded based on their results anyway. In summary, high rates of data-loss lead to an increased risk of attrition bias which poses a serious threat to the quality of the available research. This may in turn have implications for the validity of conclusions drawn on the basis of such research.

### **Exclusion criteria**

With regards to the quality of currently available research, the variety in the participant exclusion criteria used in the included studies should also be stressed. Participant characteristics such as substance dependence and traumatic brain injuries (TBI) are particularly prevalent comorbidities among active duty soldiers and Veterans (Hoge et al., 2004; Seal et al., 2007), and are thought to influence a participant's ability to effectively engage in treatment (Bryant & Hopwood, 2006; Ouimette, Goodwin, & Brown, 2006). A disparity within the literature with regards to whether participants should be excluded on the basis of these factors or not is problematic for several reasons.

First, the exclusion of participants based on highly comorbid factors which are thought to both affect a large portion of the clinical population and hinder effective treatment, may lead to misleading estimates of treatment efficacy and dramatically limit the generalizability of results. Conversely, overinclusion of participants with a variety of potentially confounding secondary conditions will impede any meaningful discoveries about

PTSD as an independent disorder. As a result, conflicting inclusion criteria may therefore also lead to conflicting conclusions regarding treatment efficacy.

Secondly, estimates of total treatment efficacy based on meta-analysis or systematic reviews will be of limited use if the samples of the included studies are too different to be compared. These issues highlight the importance of identifying and separately examining the largest subgroups within the clinical population with regards to comorbid disorders. Studies of patients suffering only from PTSD, but none of the most prevalent comorbid disorders, will be unable to assess what constitutes effective treatment for patients with comorbid disorders. Ideally the available body of research would be both extensive and diverse enough to include both studies with strict inclusion criteria, enabling observation of PTSD as an independent disorder, as well as studies specifically aimed toward furthering our understanding of patients with the most common and disruptive comorbid disorders.

Another aspect of participant selection that is worth noting are the diagnostic criteria for PTSD, as considerable changes were made to these criteria in the newest edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; Pai, Suris, & North, 2017). These changes may in turn have implications for the diagnostic assessments that are made in selecting study participants. As the present review includes studies that were published both before and after the release of the DSM-5, it is pertinent to evaluate to what extent this may have influenced the utility of the review. In the present review all included studies describe having utilized diagnostic criteria based on the DSM-IV. As such, there is no reason to believe that a comparison of study results would be complicated by differing diagnostic criteria. Such a comparison is however complicated by the inconsistent reporting of interrater diagnostic reliability in the included studies. As a majority did not report any such measures, it is difficult to assess whether participant selection was based on accurate diagnostic assessments.

In summary, a disparity in participant exclusion criteria and inadequate reporting of diagnostic interrater reliability may pose a threat to the generalizability and utility of study results. As an understanding of what constitutes effective treatment for patients both with and without comorbid disorders is vital, it is important that a consensus on exclusion criteria is agreed upon, and that studies are conducted on all sub-groups.

### **Definition of relapse and recurrence**

The comprehensive summary by the Institute of Medicine (2008) on modern PTSD research argues that there is no generally accepted or used definition of recovery within

the field of psychological trauma. To the knowledge of the author, no widely accepted definitions of trauma-related relapse or recurrence currently exists either. As with the term “recovery”, there may be many similarities between trauma-related relapse and recurrence, and the empirically supported, and accepted definitions of similar terms within the literature on other disorders. However, as of now there is not sufficient evidence to conclude that this is the case. As such, the development of empirically supported and consistent definitions of relapse-related terms would facilitate more methodologically robust studies of the disorder in the future.

### **Quality of outcome statistics**

Although changes in outcome related statistics such as rates of remission, clinically meaningful change and loss of diagnosis are the most common indicators of the total rate of relapse or recurrence within a clinical sample, these are inaccurate estimates as they do not include individual patient statistics. Consequently, a comparison of what percentage of participants experienced clinically significant improvement at post-treatment compared to final follow-up constitutes a poor statistic of overall relapse or recurrence rates. This estimate will, for instance, potentially be affected by the number of participants who did not experience a significant amount of improvement by the end of treatment, but did experience a spontaneous improvement during the follow-up period. In addition, an assessment of changes in clinically significant improvement rates takes into account all participants, whether they experienced an improvement or not. An estimate of relapse or recurrence would ideally only take into account individuals who achieved responder status by the end of treatment, and then assess what percentage of these individuals maintained their responder status at the final assessment. As such, an outcome statistic that would more accurately reflect relapse or recurrence rates in future studies would be the proportion of participants who did not maintain a clinically significant improvement, loss of diagnosis or remission at the last data collection point. The utility of such a measure would, however, necessitate long enough follow-up periods for impending relapses or recurrences to be observed. More systematic reporting of what portion of participants that have received treatment for PTSD earlier, would also be of interest. Finally, recording which of these previously treated participants have experienced a symptom free period in the interim would enable researchers to determine whether participants are currently experiencing a relapse or recurrence. In summary, if future research is to provide accurate assessments of long-term treatment outcomes and overall estimates of relapse and recurrence rates,

more accurate long-term statistics of relapse and recurrence must be reported.

### **Limitations**

There are several limitations to the present systematic review. First, the small number of eligible studies constitutes a major limitation with regards to estimating an overall relapse and recurrence rate. Second, the systematic review would ideally utilize a longer follow-up period than 6 months as an inclusion criterion. This may very well be too short a period of time to reliably observe impending recurrences or relapses. In comparison, the Institute of Medicine refers to long-term effects of treatment as those that persist beyond 12 months (Institute of Medicine (US). Committee on Treatment of Posttraumatic Stress Disorder, 2008). Third, the search engine strategy that was implemented in the present review yielded an 85% irrelevant record result. One could therefore argue that further attempts could have been made to refine the strategy. However, to our knowledge such a high rate of irrelevant record results is not uncommon for systematic literature searches. Fourth, the entirety of the sample in this review consists of American Veterans and active duty military personnel. This is not surprising as a majority of the international troops deployed to both Afghanistan and Iraq during the last two decades have been American. All the same, the review would be strengthened by the inclusion of studies examining military personnel from other NATO member countries deployed to the same areas of conflict. A comparison of outcome measures in the context of Veteran nationality would also be of great interest, with regard to both cultural and clinical differences in treating combat-related PTSD. The inclusion of both active duty personnel and Veterans in the review may also constitute a potential limitation. It is conceivable that long term treatment outcomes and rates of relapse/recurrence for these groups are not directly comparable, given that active duty soldiers are at higher risk of redeploying. This may in turn increase the likelihood of future relapse/recurrence. As such, one could argue that separate analyses should be conducted for each of these subgroups. Fifth, the review would be strengthened by including studies of other empirically supported treatment methods. In particular, one could argue that eye movement desensitization and reprocessing (EMDR) is a common psychotherapeutic treatment that is missing from the present review. Lastly, as argued above, the current literature and therefore this review is limited by inaccurate and inconsistently reported statistics of relapse and recurrence.

### Implications for future research

The aforementioned flaws in current research on the topic of relapse and recurrence among Veterans, as well as the general shortage of available studies, indicate several recommendations for future research on the subject. In order to contribute to valid estimates of long term treatment efficacy and relapse/recurrence, future studies should seek to conduct randomized controlled trials, as many of the studies excluded from the present review were done so on the basis of lacking randomization. Similarly, future studies should seek to extend the follow-up period after completed treatment, so as to better outline long term outcomes and allow for impending relapses and recurrences to be observed. With regards to follow-up, the present review also highlights the importance of developing methods aimed toward limiting the high rate of data loss in clinical trials of Veterans, so as to avoid being at an automatic risk of attrition bias. In addition, it is advisable that researchers strive to use more accurate statistics of relapse and recurrence, and report them more consistently. Furthermore, the development of trauma specific definitions of relapse and recurrence would greatly improve the quality of future research on the topic. Finally, an empirically founded consensus among researchers with regards to exclusion criteria for participants, as well as conducting separate studies on the largest currently excluded subgroups within the clinical population would be beneficial.

In conclusion, the present review was unable to surmise any meaningful estimate of PTSD relapse or recurrence rates among Veterans of Iraq and Afghanistan based on the available studies. This is, in and of itself, an important finding, as it highlights a deficiency in recent research on this important clinical population. Based on the large body of research that was returned by the literature search and subsequently excluded from the review, as well as an assessment of risk of bias in the studies that were included, the present review outlines a number of areas of improvement and recommendations for future studies.

### Disclosure statement

The authors have no involvement in any organizations or entities with any financial or non-financial interests in the subject matter or materials discussed in this manuscript.

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