



Evidence-based Practice Center Systematic Review Protocol

Project Title: *Psychological and Pharmacological Treatments for Adults with Posttraumatic Stress Disorder (PTSD): Systematic Review*

Initial publication date if applicable:

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(Amendments Details—see Section VII)

I. Background and Objectives for the Systematic Review

Posttraumatic stress disorder (PTSD) involves a group of symptoms experienced after exposure to a potentially traumatic event that may include re-experiencing the event; avoiding situations that trigger memories of the event; experiencing increased negative feelings and beliefs; and/or experiencing feelings of hyperarousal such as irritability, agitation, anger, or being on alert.¹ The traumatic event (stressor) must involve witnessing an actual or threatened death or serious injury or other threat to one's physical integrity; witnessing an event that involves death, injury, or a threat to the physical integrity of another person; or learning about unexpected or violent death, serious harm, or threat of death or injury experienced by a family member or other close associate.¹

Some traumatic events that are directly experienced include military combat, violent personal assault, being taken hostage, a terrorist attack, torture, natural or manmade disasters, and being diagnosed with a life-threatening illness,² as well as relational trauma such as sexual, physical, and emotional abuse and domestic violence. Not all of those exposed to a potentially traumatic event, however, go on to develop posttraumatic stress symptoms and PTSD. According to one meta-analysis of 35 longitudinal study samples, 28.8 percent (range: 3.1 to 87.5%) of adults exposed to one or more potentially traumatic events meet criteria for PTSD within 1 month of trauma exposure, and 17.0 percent continue to meet criteria for PTSD 12 months following exposure (range: 0.6 to 43.8%).³ PTSD is also highly comorbid with other psychiatric disorders; data from epidemiologic studies indicate that a vast majority of individuals with PTSD have a co-occurring disorder, most notably substance use disorders, mood disorders, anxiety disorders, and suicidality.^{4,5} Subgroups of people with PTSD that could have differences in their response to various PTSD treatments include military personnel and veterans; people with comorbid conditions; gender groups; first responders; refugees; disaster victims; racial and ethnic minorities; and those with different types, severity, or chronicity of PTSD symptoms.

In the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5),¹ PTSD criteria are analogous to, but not exactly the same as, the prior DSM-IV criteria.⁶ In DSM-5, PTSD has four symptom clusters: (1) intrusion (similar to the re-experiencing criterion in DSM-IV), (2) avoidance (without inclusion of numbing symptoms, as in DSM-IV), (3) negative alterations in cognition and mood, and (4) alterations in arousal and reactivity (similar to increased arousal in DSM-IV). These criteria are detailed in Table 1.

Table 1. Diagnostic criteria for PTSD

DSM-IV Criterion	DSM-5 Criterion	Summary of Major Changes in DSM-5
<p>Criterion A: Traumatic event that involved:</p> <ul style="list-style-type: none"> • actual or threatened death, • serious injury, OR • threat to physical integrity <p>AND</p> <p>Intense response of fear, helplessness, or horror</p>	<p>Criterion A: Traumatic event as defined by:</p> <ul style="list-style-type: none"> • direct exposure to, • witnessing indirectly (by learning a close friend or close relative was exposed), OR • repeated/extreme indirect exposure in the course of professional job (not through media) 	<ul style="list-style-type: none"> • Changes to wording of traumatic event exposure specification • DROPPED Intense response of fear, helplessness, or horror criterion
<p>Criterion B: Re-experiencing symptoms (1 or more):</p> <ul style="list-style-type: none"> • Intrusive recollections of events • Recurrent distressing dreams of the event • Acting or feeling as if the traumatic event were recurring • Distress at internal or external reminders of the trauma • Physiological reaction to internal or external reminders 	<p>Criterion B: Intrusion symptoms (1 or more):</p> <ul style="list-style-type: none"> • Recurrent, intrusive memories • Traumatic nightmares • Flashbacks • Intense/prolonged distress after exposure • Physiological reactivity upon exposure to cues 	<ul style="list-style-type: none"> • New title of criterion • Changes to wording of criterion
<p>Criterion C: Persistent avoidance and numbing (3 or more):</p> <ul style="list-style-type: none"> • Avoidance of thoughts, feelings, or conversations associated with trauma • Avoidance of activities, places, or people that arouse recollections of trauma • Failure to recall an important aspect of trauma • Loss of interest or participation in significant activities • Detachment from others • Restricted range of affect • Lost sense of the future 	<p>Criterion C: Persistent effortful avoidance of distressing trauma-related stimuli (1 or more):</p> <ul style="list-style-type: none"> • Trauma-related thoughts/feelings • Trauma-related external reminders <p>Criterion D: Negative cognitions/mood (2 of 7)</p> <ul style="list-style-type: none"> • Inability to recall key features of the trauma • Negative beliefs about oneself, the world • Distorted blame of self, others • Persistent negative trauma-related emotions • Diminished interest • Feeling alienated, detachment/estrangement • Constricted affect 	<ul style="list-style-type: none"> • Split avoidance and negative sequelae into 2 criteria • Changes to wording of specific criterion

Table 1. Diagnostic criteria for PTSD (continued)

DSM-IV Criterion	DSM-5 Criterion	Summary of Major Changes in DSM-5
<p>Criterion D: Hyperarousal (2 or more):</p> <ul style="list-style-type: none"> • Difficulty falling or staying asleep • Irritability or outburst of anger • Difficulty concentrating • Hypervigilance • Exaggerated startle response 	<p>Criterion E: Alterations in arousal and reactivity (2 or more):</p> <ul style="list-style-type: none"> • Irritable or aggressive behavior • Self-destructive/reckless behavior • Hypervigilance • Exaggerated startle response • Problems in concentration • Sleep disturbance 	<ul style="list-style-type: none"> • New title of criterion • Changes to wording of criterion • Added self-destructive/reckless behavior
<p>Criterion E: Duration of disturbance</p> <ul style="list-style-type: none"> • Duration of disturbance symptoms is more than 1 month 	<p>Criterion F: Duration of disturbance</p> <ul style="list-style-type: none"> • Duration of disturbance symptoms is more than 1 month 	None
<p>Criterion F: Clinically significant distress or impairment</p> <ul style="list-style-type: none"> • Duration of disturbance symptoms is more than 1 month 	<p>Criterion G: Clinically significant distress or impairment</p> <ul style="list-style-type: none"> • Duration of disturbance symptoms is more than 1 month 	None
<p>Criterion G: Exclusion criteria</p> <ul style="list-style-type: none"> • Symptoms are not due to medication, substance use, or other illness 	<p>Criterion H: Exclusion criteria</p> <ul style="list-style-type: none"> • Symptoms are not due to medication, substance use, or other illness 	None

DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition; DSM-5 = *Diagnostic and Statistical Manual of Mental Disorders*, 5th Edition; PTSD = posttraumatic stress disorder.

Prevalence of PTSD

The National Comorbidity Survey—Replication conducted between 2001 and 2003 estimated lifetime prevalence of PTSD among adults in the United States to be 6.8 percent (9.7% in women and 3.4% in men) and current (12-month) prevalence to be 3.6 percent (5.2% in women and 1.8% in men).⁷ Military personnel are at elevated risk for exposure to trauma and, thus, at elevated risk for a PTSD diagnosis. Estimates from the National Vietnam Veterans Readjustment Survey found a lifetime PTSD prevalence estimate of 18.7 percent and a current PTSD prevalence estimate of 9.1 percent⁷ among Vietnam veterans. Surveys of military personnel returning from operations in Afghanistan and Iraq have yielded a wide range of estimates—for example, 12.6 percent of U.S. men who fought in Iraq and 6.2 percent of U.S. men who fought in Afghanistan.

Burden of PTSD

The public health importance of this investigation is paramount because PTSD is associated with significant social, personal, and economic costs.⁸ People affected by PTSD have high rates of psychiatric comorbidity; have problems with functioning (e.g., family, work, social); and tend to suffer adverse consequences such as difficulties with educational attainment, work earnings, marriage attainment, and child rearing over the life course.⁸ Almost half (42.6%) of adults with PTSD do not get mental health treatment. Among those who do, only 40.4 percent get minimally adequate treatment: defined by evidence-based guidelines as receiving either appropriate pharmacotherapy for 2 or more months for the focal disorder plus more than four visits to any

type of physician or eight or more psychotherapy visits with any health care or human services professional lasting an average of 30 minutes or more.⁹ Although studies have shown that about 92 percent of adults with lifetime PTSD eventually remit, the median time to remission is 14 years.¹⁰

Treatment of PTSD

Early diagnosis and appropriate treatment of PTSD are critical to reducing the duration and severity of symptoms and associated functional impairment, and appear to be cost-effective.¹¹ Treatment guidelines typically include guidance about both psychological and pharmacological types of treatments.¹²⁻¹⁸ Although there is no clearly defined “preferred” approach to manage PTSD, many of the existing treatment guidelines support the use of trauma-focused psychological treatments for adults with PTSD, and most guidelines recognize at least some benefit of pharmacological treatments for PTSD. Indeed, some guidelines suggest trauma-focused psychological treatments over pharmacological treatments as a preferred first step and medications as an adjunct or a next-line treatment.^{17, 19} Practical considerations or patient preferences may guide treatment decisions. The selection of an initial treatment plan may depend largely on to whom a patient presents for treatment—should a patient present to a provider who does not prescribe medication, psychotherapy options are more likely, while patients who present to a provider who prescribes medication but does not do psychotherapy might receive a pharmacological treatment. Finally, a patient’s coexisting physical or other mental health conditions (e.g., depression, anxiety, serious mental illness, eating disorders, chronic pain, gastrointestinal symptoms, drug or alcohol use disorders, etc.) may influence the type of treatment selected.^{14, 20}

Psychological Interventions

Specific psychological interventions that have been studied for the treatment of PTSD are: cognitive behavioral therapy (CBT) such as cognitive restructuring, cognitive processing therapy, exposure-based therapies, and coping skills therapy (including stress inoculation therapy); psychodynamic therapy; eye movement desensitization and reprocessing (EMDR); interpersonal therapy (IPT); group therapy; hypnosis/hypnotherapy; eclectic psychotherapy; and brainwave neurofeedback. These therapies are designed to minimize the intrusion, avoidance, and hyperarousal symptoms of PTSD by some combination of re-experiencing and working through trauma-related memories and emotions and teaching better methods of managing trauma-related stressors.¹⁶

Cognitive Behavioral Therapy (CBT) uses principles of learning and conditioning to treat disorders and includes components from both behavioral and cognitive therapy. In CBT, components such as exposure, cognitive restructuring, and various coping skills have been used either alone or in combination with one another to treat PTSD. Most forms of CBT consist of a minimum of 8 to 12 weekly sessions lasting 60 to 90 minutes. CBT can be administered either as group or individual therapy.^{16, 18, 21, 22}

Exposure-based therapy involves confrontation with frightening stimuli and is continued until anxiety is reduced. The exposure is based on mental imagery from memory or introduced in scenes presented by the therapist (imaginal exposure). In some cases, exposure is from the actual scene or similar events in life (in vivo exposure). The aim is to extinguish the conditioned emotional response to traumatic stimuli (for the subject to learn that nothing “bad” will happen

during traumatic events), which eventually reduces or eliminates avoidance of feared situations and the affect associated with it. Exposure therapy is typically conducted for 8 to 12 weekly or biweekly sessions lasting 60 to 90 minutes.^{11, 16, 18}

Cognitive restructuring is based on the theory that the interpretation of the event, rather than the event itself, determines an individual's mood. It aims to facilitate relearning thoughts and beliefs generated from a traumatic event, increase awareness of dysfunctional trauma-related thoughts, and correct or replace those thoughts with more adaptive and/or rational cognitions. Cognitive restructuring generally takes place over 8 to 12 sessions of 60 to 90 minutes.^{16, 18}

Coping skills therapy may include components such as stress inoculation therapy, assertiveness training, biofeedback (including brainwave neurofeedback), and relaxation training. All may use techniques such as education, muscle relaxation training, breathing retraining, and role playing to manage anxiety or correct misunderstandings conditioned at the time of trauma. The therapy is designed to increase coping skills for current situations. Most types of coping skills therapies require at least eight 60- to 90-minute sessions, while more comprehensive interventions such as stress inoculation therapy require 10 to 14 sessions.^{16, 18}

Psychodynamic therapy explores the psychological meaning of a traumatic event. The goal is to bring unconscious memories into conscious awareness so that PTSD symptoms are reduced. The therapy presumes the PTSD symptoms are the result of the unconscious memories. Psychodynamic therapy for PTSD would consist of weekly to biweekly sessions over a period of several months to an indefinite period of time.^{16, 18, 21}

Eye movement desensitization and reprocessing (EMDR) combines imaginal exposure with the concurrent induction of saccadic eye movements that are believed to help reprogram brain function so that the emotional impact of trauma can be resolved. In the EMDR process, the patient is instructed to imagine a traumatic memory, engage in negative cognition, and then articulate an incompatible positive cognition (e.g., personal worth). The clinician asks the patient to contemplate memory while focusing on rapid movement of clinicians' fingers. After 10 to 12 eye movements (back and forth), the clinician asks the patient to rate the strength of the memory and his or her belief in the *positive* cognition. Although earlier versions of EMDR consisted of one to three sessions, current standards consist of 8 to 12 90-minute weekly sessions.^{16, 21}

Interpersonal therapy (IPT) is a time-limited, dynamically informed psychotherapy that aims to alleviate patients' suffering and improve their interpersonal functioning. This type of therapy focuses specifically on interpersonal relationships and aims to help patients either improve their interpersonal relationships or change their expectations about them. In addition, it aims to help patients improve their social support so they can better manage their current interpersonal distress. Interpersonal therapy generally requires 10 to 20 weekly sessions in the acute phase followed by a time-unlimited maintenance phase.²³

Group therapy refers to a general class of therapies, rather than to a specific intervention. Trauma-focused group therapy can vary in theory and practice (including the degree of structure) and in its focus on education, cognitive and/or behavior skills, and interpersonal relations/dynamics. It is used for several reasons: (1) cost efficiency; (2) social support; (3) opportunities for acquisition of new information, coping skills, and self-expectations; (4) peer feedback; and (5) exploration of group process and dynamics not possible in individual therapy. Number and length of sessions vary widely depending on the type of group therapy (e.g., interpersonal process, cognitive-behavioral, peer, education).^{24, 25}

Hypnosis may be used as an adjunct to psychodynamic, cognitive-behavioral, or other therapies and has been shown to significantly enhance their efficacy for many clinical conditions; however, little published data exist on the efficacy of hypnosis in treating patients with PTSD.^{16, 18} Number and length of sessions vary widely.

Eclectic psychotherapy refers to a general class of therapies rather than to a specific intervention. Eclectic psychotherapy uses techniques drawn from several different theoretical orientations. It allows flexibility in the approach the therapist uses in working with a patient to adapt to that individual's needs, rather than approaching the patient and his/her issues from a specific psychological orientation. Some therapists adhere largely to a single orientation, such as psychoanalysis or CBT but use eclectic techniques as needed. Others self-identify as eclectic in orientation, using whichever techniques work best in any given situation. Number and length of sessions vary widely.

Energy psychology is a holistic method focused on the mind-body connectedness of thoughts, behaviors, sensations, and emotions. Techniques access energy systems via chakra techniques, biofield practices, and meridian interventions while administering psychological treatment. A related treatment, referred to as emotional freedom techniques (EFT), taps various energy points on the skin while focusing on various situations that evoke strong feeling, thoughts, or emotions to shift neurological pathways that facilitate improvements to psychological functioning.

Pharmacological Interventions

Currently, only paroxetine and sertraline are approved by the U.S. Food and Drug Administration for treating PTSD. Other pharmacological agents, including selective serotonin reuptake inhibitors (SSRIs); serotonin and norepinephrine reuptake inhibitors (SRNIs); tricyclic antidepressants (TCAs); other second-generation antidepressants; atypical antipsychotics; anticonvulsants/mood stabilizers; adrenergic agents; benzodiazepines; and other treatments such as naltrexone, cycloserine, and inositol, have also been used to treat PTSD.¹⁶ Specific medications within these drug classes that have been studied or used in treating PTSD are listed in Table 2.

Table 2. Pharmacological agents used in treating PTSD

Class	Drug
SSRIs	Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline
SNRIs	Desvenlafaxine, venlafaxine, and duloxetine
TCAs	Imipramine, amitriptyline, and desipramine
Other second-generation antidepressants	Bupropion, mirtazapine, nefazodone, and trazodone
Alpha blockers	Prazosin
Second-generation (atypical) antipsychotics	Olanzapine, risperidone, ziprasidone, aripiprazole and quetiapine
Anticonvulsants (mood stabilizers)	Topiramate, tiagabine, lamotrigine, carbamazepine, and divalproex
Benzodiazepines	Alprazolam, diazepam, lorazepam, and clonazepam
Other medications	Naltrexone, cycloserine, and inositol

PTSD = posttraumatic stress disorder; SNRI = serotonin and norepinephrine reuptake inhibitors; SSRI = selective serotonin reuptake inhibitor TCA = tricyclic antidepressant.

PTSD Outcomes

The primary outcome in PTSD treatment is symptom reduction. Some of the most commonly used instruments are listed in Appendix A of this protocol. These instruments include both self-reported and clinician-administered instruments that contain items assessing some or all of DSM-IV or DSM-5 symptoms of PTSD such as exposure to a traumatic event, re-experiencing of symptoms, persistent arousal and numbing, and hyperarousal. Some can be administered in as little as 5 minutes, while others take an hour or more to complete. These instruments are valid and reliable, some across multiple subpopulations (e.g., active duty, veterans, trauma survivors, general population). Other outcomes often assessed in clinical practice include prevention/reduction of comorbid medical or psychiatric conditions (e.g., depressive symptoms, anxiety symptoms, remission [reduction in symptoms or loss of PTSD diagnosis]), improved quality of life, reduced functional limitations or disability, and ability to return to work or return to active duty.

Summary of Existing Clinical Practice Guidelines

Various guidelines and systematic reviews have resulted in contradictory conclusions and recommendations regarding the comparative effectiveness and harms of psychological and pharmacological treatments for PTSD. Although various evidence-based approaches to treatment exist, clinical uncertainty about which treatment to select remains. Furthermore, clinicians need to consider patient treatment preferences in treatment selection, given that selecting a treatment a patient does not prefer or value can affect treatment use, dropout rates, adherence to therapy, and/or therapeutic response. A range of organizations have produced guidelines for treating PTSD, including the American Psychiatric Association, the American Psychological Association, the U.S. Department of Veterans Affairs/U.S. Department of Defense, the National Institute of Clinical Excellence in the United Kingdom, the National Health and Medical Research Council, the International Society for Traumatic Stress Studies, the American Academy of Child and Adolescent Psychiatry, the Institute of Medicine, and the World Health Organization.

The organizations and guideline developers used different methods, which resulted in conflicting recommendations. Some are based on rigorous systematic reviews, and others are based on expert consensus and less structured literature reviews.

The core of the controversy stems from differences in the rating systems each review applied to assess the strength of evidence (SOE) of the research data. These methodological differences led to different conclusions and conflicting recommendations. Where one report found evidence to suggest efficacy of a particular treatment, another report deemed the underlying evidence inadequate to address efficacy and, therefore, was unable to make a recommendation.

The prior PTSD systematic review conducted for AHRQ²⁶ concluded that several psychological interventions (exposure therapy, CBT, cognitive therapy, CBT-mixed therapies, EMDR, and narrative exposure therapy) and pharmacological treatments (fluoxetine, paroxetine, sertraline, topiramate, and venlafaxine) have at least moderate SOE in support of their efficacy. The comparative effectiveness of these interventions was not established, however, because few of the trials tested head-to-head comparisons. In addition, evidence was generally insufficient to determine whether any treatment approaches are more effective for victims of particular types of trauma or to determine comparative risks of adverse effects.

In addition to the need to update systematic reviews every few years²⁷ when areas of clinical uncertainty remain, the updated review will also expand the scope of treatment types examined to include one psychological intervention not examined in the prior review, energy psychology/EFT, as well as three atypical antipsychotics, ziprasidone, aripiprazole and quetiapine. Newer studies might also help determine whether the change to DSM-5 criteria to diagnose PTSD has any implications for the efficacy of examined treatments. A synthesis of new and existing evidence is needed to address the uncertainties found at the conclusion to improve the care of those with PTSD and reduce the variation in existing treatment guidelines.

II. The Key Questions

Key Question (KQ) 1: What is the comparative effectiveness of different psychological treatments for adults diagnosed with PTSD?

KQ 1a. How does comparative effectiveness vary by patient characteristics or type of trauma experienced?

KQ 2: What is the comparative effectiveness of different pharmacological treatments for adults diagnosed with PTSD?

KQ 2a. How does comparative effectiveness vary by patient characteristics or type of trauma experienced?

KQ 3: What is the comparative effectiveness of different psychological treatments and pharmacological treatments for adults diagnosed with PTSD?

KQ 3a. How does comparative effectiveness vary by patient characteristics or type of trauma experienced?

KQ 4: What adverse events (AEs) are associated with treatments for adults diagnosed with PTSD?

Contextual Question (CQ):

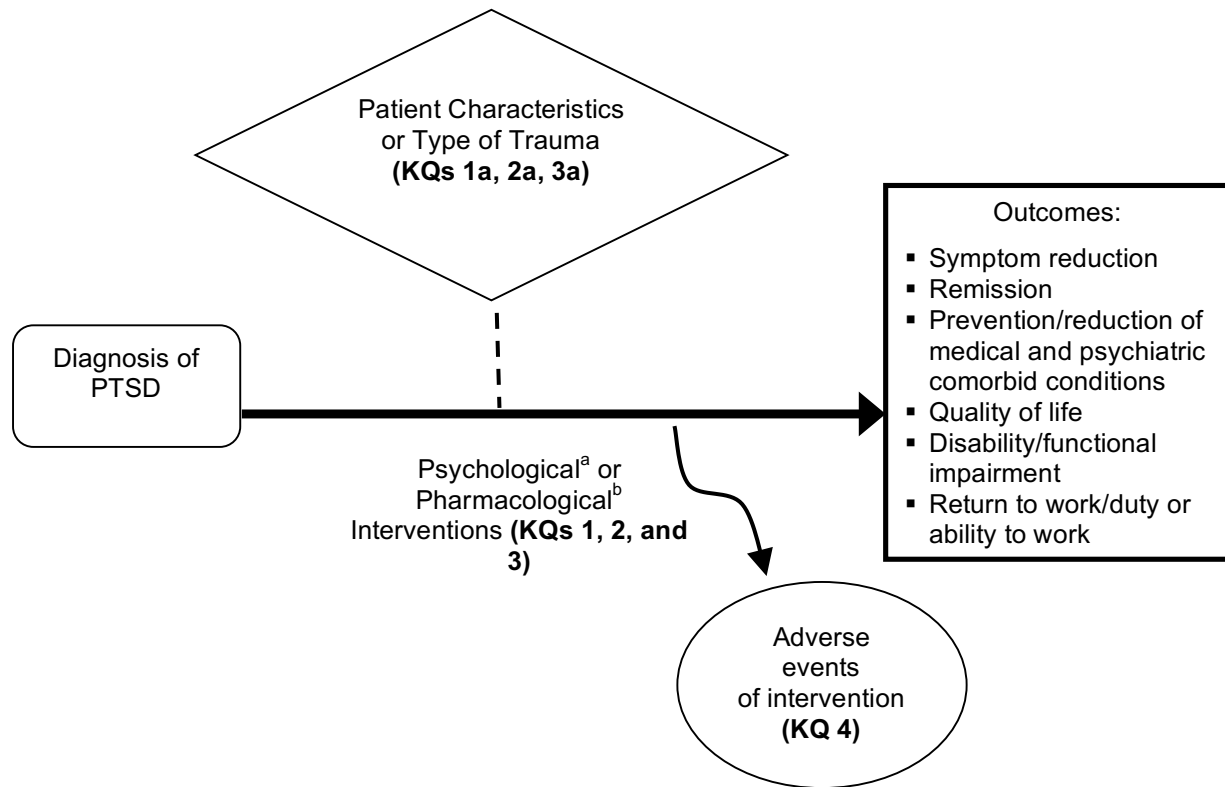
CQ1a. What are the components of effective psychological treatments (e.g., frequency or intensity of therapy, and/or aspects of the therapeutic modality)?

CQ 1b. For psychological interventions that are effective in trial settings, what is the degree of fidelity when implemented in clinical practice settings?

III. Analytic Framework

Figure 1 depicts the draft analytic framework for the comparative effectiveness of psychological treatments and pharmacological treatments for adults with PTSD. The KQs are displayed within the PICOTS context described in the previous section. Beginning with a population of adults diagnosed with PTSD, the figure illustrates the effect of psychological and pharmacological interventions on outcomes of PTSD, including symptom reduction and remission, prevention or reduction of medical and psychiatric comorbid conditions, quality of life, disability/functional impairment, and ability to work or return to work or duty (KQ 1, KQ 2, and KQ 3). Patient characteristics or type of trauma are explored as potential moderators of these interventions in KQ 1a, KQ 2a, and KQ 3a. Finally, KQ 4 examines the AEs of these interventions.

Figure 1. Analytic framework for the comparative effectiveness of psychological treatments and pharmacological treatments for adults with PTSD



^a Psychological treatments for PTSD including brief eclectic psychotherapy, CBT including cognitive restructuring, cognitive processing therapy, exposure-based therapy, coping skills therapy (including stress inoculation therapy), psychodynamic therapy, EMDR, IPT, group therapy, hypnosis or hypnotherapy, and energy psychology (including EFT)

^b Pharmacological treatments for PTSD including SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline), SNRIs (desvenlafaxine, venlafaxine, and duloxetine), tricyclic antidepressants (imipramine, amitriptyline, and desipramine), other second-generation antidepressants (bupropion, mirtazapine, nefazodone, and trazodone), alpha blockers (prazosin), atypical antipsychotics (olanzapine, risperidone, ziprasidone, aripiprazole and quetiapine), benzodiazepines (alprazolam, diazepam, lorazepam, and clonazepam), anticonvulsants/mood stabilizers (topiramate, tiagabine, lamotrigine, carbamazepine, and divalproex)

KQ = Key Question; PTSD = posttraumatic stress disorder.

IV. Methods

Criteria for Inclusion/Exclusion of Studies in the Review

Table 3. Inclusion/exclusion criteria

PICOTS	Inclusion	Exclusion
Population	<p>Adults 18 years or older with PTSD based on any DSM diagnostic criteria</p> <p>Subgroups of interest (KQs 1a, 2a, 3a) include those distinguished by patient characteristics (e.g., gender, age, race/ethnicity, comorbid mental and physical health conditions, employment types requiring trauma exposure [for example, first responders], severity of trauma experienced, different symptoms of PTSD, dissociation, and/or psychosis, PTSD symptom chronicity or severity) or type of trauma experienced (e.g., military/combat, natural disaster, war, political instability, relational [physical, emotional, or sexual abuse or exposure to domestic violence], repeat victimizations, cumulative).</p>	All other
Intervention	<p>Psychological interventions: Brief eclectic psychotherapy, CBT including cognitive restructuring, cognitive processing therapy, exposure-based therapy, coping skills therapy (e.g., stress inoculation therapy, assertiveness training, biofeedback, relaxation training), psychodynamic therapy, EMDR, IPT, group therapy, hypnosis or hypnotherapy, and energy psychology (including EFT)</p> <p>Pharmacological interventions: SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline), SNRIs (desvenlafaxine, venlafaxine, and duloxetine), tricyclic antidepressants (imipramine, amitriptyline, and desipramine), other second-generation antidepressants (bupropion, mirtazapine, nefazodone, and trazodone), alpha blockers (prazosin), atypical antipsychotics (olanzapine, risperidone, ziprasidone, aripiprazole and quetiapine), benzodiazepines (alprazolam, diazepam, lorazepam, and clonazepam), anticonvulsants/mood stabilizers (topiramate, tiagabine, lamotrigine, carbamazepine, and divalproex)</p>	<p>Complementary and alternative medicine approaches</p> <p>Psychological or pharmacological interventions not listed as included</p>
Comparator	<p>KQ 1 (1a): Psychological interventions listed above compared with one another, waiting list assignment, usual care (as defined by the study), no intervention, or sham. KQ 2 (2a): Pharmacological interventions listed above compared with one another or placebo. KQ 3 (3a): Psychological interventions listed above compared with pharmacological interventions listed above. KQ 4: Any intervention listed above</p>	All other comparisons
Outcomes	<p>KQs 1–3: PTSD symptom reduction (see Appendix A for a list of measures), prevention or reduction of comorbid medical or psychiatric conditions (e.g., coronary artery disease; depressive symptoms; anxiety symptoms; suicidal ideation/plans/attempts; and substance use, abuse, or dependence), remission (i.e., no longer having symptoms or loss of PTSD diagnosis), quality of life, disability or functional impairment, return to work or active duty status</p> <p>KQ 4: Overall and specific AEs (e.g., disturbed sleep, increased agitation, sedation, weight gain, metabolic side effects, and mortality), withdrawals due to AEs</p>	All other outcomes

Time frame	Studies published from 2012 to the present will be searched to identify new studies meeting the review criteria. Findings of these newly identified studies will be synthesized with those from studies included in the prior review that continue to meet the new review criteria. At least 4 weeks study duration after randomization	Less than 4 weeks
Settings	Outpatient and inpatient primary care or specialty mental health care; community settings e.g., churches, community health centers, rape crisis centers), military settings	Other settings
Study design	KQs 1–3: Randomized controlled trials (RCTs) of any sample size, systematic reviews (for references) KQ 4: AE data from trials for KQs 1–3, systematic reviews and meta-analyses (for references), nonrandomized controlled trials, prospective cohort studies with an eligible comparison group and a sample size of at least 500, ^a case-control studies with a sample size of at least 500 ^a	All other designs and studies using included designs that do not meet the sample size criterion
Language	Studies published in English ^b	Studies published in languages other than English

^a Observational studies that compare the effectiveness of various treatments for PTSD have a very high risk of selection bias and confounding. We feel that the results should not be used to make decisions about efficacy/effectiveness. For KQ 4, we have chosen a sample size cutoff of 500 for prospective cohort studies and case-control studies for several reasons: (1) the topic refinement process done for the prior review that we are currently updating found a large number of trials in this field, and it was determined that increasing comprehensiveness by reviewing all possible observational studies that present harms was outweighed by the potential decreased quality/increased risk of bias of these studies; (2) the threshold of 500 will ensure only the inclusion of large observational studies with the lowest potential risk of bias to supplement the trial literature; and (3) the Technical Expert Panel of the prior project supported this approach.

^b Due to limited time and resources, we will include only studies published in English.

AE = adverse events; CBT = cognitive behavioral therapy; DSM = *Diagnostic and Statistical Manual*; EFT = emotional freedom therapy; EMDR = eye movement desensitization and reprocessing; IPT = interpersonal therapy; KQ = Key Question; PICOTS = populations, interventions, comparators, outcomes, timing, and setting; PTSD = posttraumatic stress disorder; RCT = randomized controlled trial; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions

We will systematically search, review, and analyze the scientific evidence for each KQ. We will take the following steps to perform the literature search.

To identify articles relevant to each KQ, we will begin with a focused MEDLINE search using a variety of terms, medical subject headings (MeSH), and major headings and limiting the search to English-language and human-only studies. We list relevant terms to include in Appendix B. We will also search the Cochrane Library, the Cochrane Central Trials Registry, the Cumulative Index to Nursing and Allied Health Literature, PsycINFO, and the Published International Literature on Traumatic Stress (PILOTS) database by using analogous search terms. We will conduct quality checks to ensure that we identify known studies (i.e., studies included in the previous review) by our search. If not, we will revise and rerun our searches. Because the prior review's literature searches ended in May 2012, we plan to search the literature published since January 2012 to account for lags in indexing published studies. An experienced librarian familiar with systematic reviews will design and conduct all searches in consultation with the review

team. Because we did not include studies testing energy psychology/EFT interventions or those testing the efficacy of the atypical antipsychotics ziprasidone, aripiprazole, or quetiapine as part of the prior review, we will conduct a separate search using these terms crossed with PTSD terms, and we will not impose a publication date limit on this separate search so we can capture all pertinent studies ever published. We will search the gray literature for unpublished studies relevant to this review and will include studies that meet all the inclusion criteria and contain enough methodological information for assessing internal validity/quality. Sources of gray literature include ClinicalTrials.gov, pharmaceutical companies' dossiers (for pharmacotherapies of interest), and scientific evidence and data received in response to Federal Register notice requests.

We will also conduct an updated literature search (of the same databases searched initially) concurrent with the draft report peer/public review process. We will investigate any literature the peer reviewers or the public suggest and, if appropriate, will incorporate them into the final review. We will identify all eligible studies using the same criteria described above.

To answer the CQ, we will search our included psychological treatment studies as well as reviews captured by our search that discuss components of effective psychological treatments such as frequency or intensity of therapy and/or aspects of the therapeutic modality. In addition, for psychological interventions that are effective in trial settings, we will look for evidence that describes the degree of fidelity to protocol when interventions are implemented into clinical practice.

Data Abstraction and Data Management

Two trained research team members will independently review all titles and abstracts identified through searches for eligibility against our inclusion/exclusion criteria using Abstrackr.²⁸ Studies marked for possible inclusion by either reviewer will undergo a full-text review. For studies without adequate information to determine inclusion or exclusion, we will retrieve the full text and then make the determination. All results will be tracked in an EndNote[®] bibliographic database (Thomson Reuters, New York, NY).

We will retrieve and review the full text of all titles included during the title/abstract review phase. Two trained team members will independently review each full-text article for inclusion or exclusion based on the eligibility criteria described above. All articles included in the prior PTSD systematic review also will be reevaluated for inclusion based on the inclusion and exclusion criteria of this updated review. If both reviewers agree that a study does not meet the eligibility criteria, the study will be excluded. If the reviewers disagree, conflicts will be resolved by discussion and consensus or by consulting a third member of the review team. As described above, all results will be tracked in an EndNote database. We will record the reason why each excluded full-text publication or publication included in the prior PTSD review did not satisfy the eligibility criteria so that we can later compile a comprehensive list of such studies.

For studies that meet our inclusion criteria, we will abstract relevant information into evidence tables. We will design data abstraction forms to gather pertinent information from each article, including characteristics of study populations, settings, interventions, comparators, study designs, methods, and results. Trained reviewers will extract the relevant data from each included article into the evidence tables. A second member of the team will review all data abstractions for completeness and accuracy.

Assessment of Methodological Risk of Bias of Individual Studies

To assess the risk of bias (i.e., internal validity) of RCTs, we will use the same criteria used in the 2013 AHRQ review by Jonas and colleagues,²⁶ which were based on the Agency for Healthcare Quality and Research (AHRQ) *Methods Guide for Comparative Effectiveness Reviews*. These criteria are similar to the ROBINS-1²⁹ tool (for observational studies) and the Cochrane RCT tool³⁰ (for RCTs). For both RCTs and observational studies, ROB assessment will include questions to assess selection bias, confounding, performance bias, detection bias, and attrition bias; concepts covered include those about adequacy of randomization (for RCTs only), similarity of groups at baseline, masking, attrition, whether intention-to-treat analysis was used, method of handling dropouts and missing data, validity and reliability of outcome measures, and treatment fidelity.³¹

In general terms, a “good” study has the least bias, and its results are considered to be valid. A “fair” study is susceptible to some bias but probably not sufficient enough to invalidate its results. A “poor” study has significant bias (e.g., stemming from serious errors in design or analysis) that may invalidate its results.

Two independent reviewers will assign quality ratings for each study. Disagreements between the two reviewers will be resolved by discussion and consensus or by consulting a third member of the team. We will give a good quality rating to studies that meet all criteria. Fair quality ratings will be given to studies that presumably fulfill all quality criteria but do not report their methods sufficiently to answer all of our questions. We will give a poor quality rating to studies that have a fatal flaw (defined as a methodological shortcoming that leads to a very high risk of bias) in one or more categories and will exclude them from our analyses. We will reassess risk of bias in a random sample of 10 studies included in the prior review that continue to meet the inclusion and exclusion criteria of this update to confirm consistency between the prior review and this updated review.

Data Synthesis

We will summarize all included studies in narrative form and in summary tables that tabulate the important features of the study populations, design, intervention, outcomes, setting (including geographic location), and results. All new qualitative and quantitative analyses will synthesize relevant studies included in the 2013 systematic review and this update as a single body of evidence.

If we find three or more studies for a comparison of interest, we will consider quantitative analysis (i.e., meta-analysis) of the data from those studies. We will also consider conducting mixed treatment comparisons meta-analysis using Bayesian methods to compare the pharmacological interventions with each other if we identify at least three studies that tested the same intervention with a common comparator (e.g., placebo). For all analyses, we will use random-effects models to estimate pooled or comparative effects. To determine whether quantitative analyses are appropriate, we will assess the clinical and methodological heterogeneity of the studies under consideration following established guidance.³² We will do this by qualitatively assessing the PICOTS of the included studies, looking for similarities and differences. If we conduct quantitative syntheses (i.e., meta-analysis), we will assess statistical heterogeneity in effects between studies by calculating the chi-squared statistic and the I^2 statistic (the proportion of variation in study estimates due to heterogeneity). The importance of the observed value of I^2 depends on the magnitude and direction of effects and on the SOE for

heterogeneity (e.g., p-value from the chi-squared test or a confidence interval for I^2). If we include any meta-analyses with considerable statistical heterogeneity in this report, we will provide an explanation for doing so, considering the magnitude and direction of effects. We will also examine potential sources of heterogeneity using sensitivity analysis or analysis of subgroups. We plan to stratify analyses and/or perform subgroup analyses when possible and appropriate to examine clinical heterogeneity. Planned stratifications or categories for subgroup analyses include the subgroups listed in the analytic framework and geographic location of studies. When quantitative analyses are not appropriate (e.g., due to heterogeneity, insufficient numbers of similar studies, or insufficiency or variation in outcome reporting), we will synthesize the data qualitatively.

Grading the SOE for Major Comparisons and Outcomes

We will grade the SOE based on the guidance established for the Evidence-based Practice Center (EPC) Program.³³ Developed to grade the overall strength of a body of evidence, this approach incorporates five key domains: risk of bias (includes study design and aggregate quality), consistency, directness, precision of the evidence, and reporting bias. It also considers other optional domains that may be relevant for some scenarios, such as a dose-response association, plausible confounding that would decrease the observed effect, and strength of association (magnitude of effect).

Table 4 describes the grades of evidence that can be assigned. Grades reflect the strength of the body of evidence to answer KQs on the comparative effectiveness, efficacy, and harms of the interventions included in this review. Two reviewers will assess each domain for each key outcome, and differences will be resolved by consensus. We will grade the SOE for the outcomes deemed to be of greatest importance to decisionmakers and those most commonly reported in the literature. We expect these to include PTSD symptom reduction, quality of life, disability/functional impairment, and AEs.

Table 4. Definitions of the grades of overall SOE³⁴

Grade	Definition
High	High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate.
Low	Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit estimation of an effect.

SOE = strength of evidence.

Assessing Applicability

We will assess the applicability of individual studies as well as the applicability of a body of evidence following guidance from the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.³⁵ For individual studies, we will examine conditions that may limit applicability based on the PICOTS structure. Some factors identified a priori that may limit the applicability of evidence include the following: age of enrolled population, index type of trauma experienced (including military-related or combat-related trauma), severity of trauma, and setting

of enrolled populations (e.g., active duty, veteran). We also will consider whether findings of intervention studies that used DSM-IV criteria for PTSD can extend to individuals meeting DSM-5 criteria for PTSD.

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VI. Definition of Terms

We will define important terms in the full report.

VII. Summary of Protocol Amendments

No protocol amendments to date.

If we need to amend this protocol, we will give the date of each amendment, describe the change, and give the rationale in this section. Changes will not be incorporated into the protocol.

Example table below:

Table 5. Example table

Date	Section	Original Protocol	Revised Protocol	Rationale
This should be the effective date of the change in protocol	Specify where the change would be found in the protocol	Describe the language of the original protocol.	Describe the change in protocol.	Justify why the change will improve the report. If necessary, describe why the change does not introduce bias. Do not use justification as “because the AE/TOO/TEP/Peer reviewer told us to” but explain what the change hopes to accomplish.

VIII. Key Informants/Technical Experts and Review of Key Questions

Key Informants are the end users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions.

Technical Experts constitute a multidisciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, and outcomes and identify particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development.

Key Informants and Technical Experts were included in a multi-stakeholder virtual workshop by PCORI in December 2016. The workshop reviewed scoping for the updated review, prioritization of key questions, a discussion of where the evidence based has accumulated since the prior review and emerging issues in PTSD. This PTSD protocol was developed based upon findings from the multi-stakeholder virtual workshop. Key Informants and Technical Experts do not do analysis of any kind nor do they contribute to the writing of the report. They have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

IX. Peer Reviewers

Peer Reviewers, representing the diversity of perspectives included in the definition of “Key Informants” and “Technical Experts” above, are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft report in preparation of the final report. Peer Reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers. The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published 3 months after the publication of the evidence report.

Potential Peer Reviewers must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than \$10,000. Peer Reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

X. EPC Team Disclosures

No team members have financial conflicts of interest.

XI. Role of the Funder

This project was completed under Contract No. HHS A290201500011I HHS A29032010T from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services, through funds provided by a partnership with the Patient-Centered Outcomes Research Institute (PCORI). The AHRQ TOO reviewed contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by PCORI, the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

XII. Registration

This protocol will be registered in the international prospective register of systematic reviews (PROSPERO).

Appendix A. PTSD outcome measures

Outcome Measure	Description
Clinician-Administered PTSD Scale (CAPS) ³⁶	<ul style="list-style-type: none"> • Gold standard for PTSD assessment and diagnosis for military, civilian, and trauma survivors. • 30-item structured interview that corresponds to the DSM-IV criteria for PTSD. • Asks respondent to think of up to three traumatic events to keep in mind during the interview. • Can be used to make a current or lifetime diagnosis of PTSD or to assess symptoms over the past week. • In addition to PTSD symptoms, CAPS assesses the impact of symptoms on social and occupational functioning, improvement in symptoms since a previous CAPS administration, overall response validity, overall PTSD severity, and frequency and intensity of five associated symptoms (guilt over acts, survivor guilt, gaps in awareness, depersonalization, and derealization). Separate frequency and intensity scores are calculated. • 45- to 60-minute administration by trained (para) professionals.
Clinician-Administered PTSD Scale Part 2 (CAPS-5) ³⁶	<ul style="list-style-type: none"> • Updates CAPS with assessment of symptoms required to meet DSM-5 PTSD diagnosis. • 30-item structured interview. • Asks respondents to think of a single index trauma to serve as the basis for symptom inquiry. • Past week, past month, and worst month (lifetime) PTSD can be estimated. • A single severity score is calculated based on symptom frequency and intensity. • 45- to 60-minute administration by trained (para) professionals.
Davidson Trauma Scale (DTS) ³⁷	<ul style="list-style-type: none"> • 17-item, self-rating scale used to assess DSM-IV PTSD criteria (B-D). • Each item corresponds to a DSM-IV symptom of PTSD, and each symptom is rated in terms of frequency and severity. • Can be used to screen patients at initial evaluation, evaluate psychopathology in trauma victims, assess the effectiveness of treatment, and predict treatment success. • Scale covers the following types of trauma: accident, combat, sexual, criminal assault, natural disaster, torture, burns, loss of property, near-death experiences, and bereavement. • Approximately 10-minute administration.
Diagnostic Interview Schedule (DIS) ³⁸	<ul style="list-style-type: none"> • Assesses DSM III-R/IV symptomatology and can be used for PTSD diagnosis. • Semistructured interview. • Requires patient to associate each symptom with a specific traumatic event. • 15-minute administration by lay-trained interviewers.
Impact of Events Scale (IES) ³⁹	<ul style="list-style-type: none"> • 15-item self-reported measure used to assess the frequency with which experiences of “intrusions,” “avoidance,” and emotional numbing related to stressful events occurred in the last week. • A total distress score is calculated by summing all 15 item responses.
Impact of Events Scale-Revised (IES-R) ⁴⁰	<ul style="list-style-type: none"> • 22-item self-report measure that assesses subjective distress caused by traumatic events. • Items correspond directly to 14 of the 17 DSM-IV symptoms of PTSD.
Los Angeles Symptom Checklist (LASC) ³⁸	<ul style="list-style-type: none"> • 43-item self-report measure used to assess PTSD symptoms and associated features, including signs of distress and functional problems.

Outcome Measure	Description
Minnesota Multiphasic Personality Inventory, Keane PTSD Scale ³⁸	<ul style="list-style-type: none"> • Self-report questionnaire. • Originally composed of 29 items, revised for MMPI-2 by deleting three item repetitions. • 46 MMPI items. • Norms available for different populations.
Mississippi Scale for Combat-related PTSD (M-PTSD) ³⁸	<ul style="list-style-type: none"> • 35-item self-report questionnaire used to assess DSM-III combat-related PTSD and related features (depression, suicidality, and substance abuse). • 10- to 15-minute administration.
Modified PTSD Symptom Scale (MPSS-SR) ⁴¹	<ul style="list-style-type: none"> • 17-item self-report measure that assesses the 17 DSM-III-R symptoms of PTSD. • This scale is a modification of the PTSD Symptom Scale. • The major modifications are that the items are not keyed to any particular traumatic event and that the MPSS-SR includes severity ratings in addition to the original measure's frequency ratings for each item. • It can be used to make a preliminary determination of the diagnosis of PTSD using either DSM-III-R criteria or a frequency, severity, or total score cutoff scores. • It can be scored as a continuous measure of PTSD symptom severity.
Penn Inventory for Posttraumatic Stress ^{38, 42}	<ul style="list-style-type: none"> • 26-item self-report questionnaire primarily used with male patients, including accident victims, veterans, and general psychiatric patients. • It does not assess all of the 17 DSM symptoms of PTSD and includes items that are not directly related to DSM criteria (e.g., self-knowledge).
Posttraumatic Diagnostic Scale (PTDS) ³⁸	<ul style="list-style-type: none"> • 17 questions, including 12-item checklist of traumatic events used to assess DSM-IV PTSD criteria. • Assesses frequency of PTSD symptoms in the past month and self-ratings of impairment across 9 areas of functioning. • Has been validated across several populations, including combat veterans and sexual and nonsexual-assault survivors.
PTSD Checklist (PCL) for DSM-IV ⁴³	<ul style="list-style-type: none"> • 17-item self-report measure of the 17 DSM-IV symptoms of PTSD. • The PCL has been used to screen individuals for PTSD, diagnose PTSD, and monitor symptom change during and after treatment. • There are three versions of the PCL for DSM-IV: PCL-M (military), PCL-C (civilian), and PCL-S (specific). • 5- to 10-minute administration.
PTSD Checklist for DSM-5 ⁴⁴ (PCL-5)	<ul style="list-style-type: none"> • 20-item self-report measure of the 20 DSM-5 symptoms of PTSD. • The PCL-5 can be used to make provisional PTSD diagnoses, screen for PTSD, or monitor symptom change before and after treatment. • There is only one version of the PCL-5; it is most similar to the PCL-S for DSM-IV. • 5- to 10-minute administration. • Can be administered in three formats. • Score should be interpreted by a clinician.
PTSD Interview (PTSD-I) ^{38, 45}	<ul style="list-style-type: none"> • Structured clinical interview. • Patients given a copy of scale to read along with interviewer and asked to give subjective ratings for each symptom. • Administered by trained subprofessionals.

Outcome Measure	Description
PTSD Symptom Scale-Interview (PSS-I) ⁴⁶	<ul style="list-style-type: none"> • 17-item semistructured interview that assesses the presence and severity of DSM-IV PTSD symptoms related to a single identified traumatic event in individuals with a known trauma history. • Each item is assessed with a brief, single question. • Interviewees are asked about symptoms they have experienced in the past 2 weeks. • Approximately 20-minute administration.
PTSD Symptom Scale-Self-report Version (PSS-SR) ⁴⁷	<ul style="list-style-type: none"> • 17-item scale used to diagnose PTSD according to DSM-III-R criteria. • Assess the severity of PTSD symptoms (consist of the same 17 items as the PSS-I).
Structured Interview for PTSD (SI-PTSD or SIP) ⁴⁸	<ul style="list-style-type: none"> • Assesses the 17 PTSD symptoms as well as survival and behavioral guilt. • For each item, the interviewer assigns a severity rating that reflects both frequency and intensity. • Item responses can be used to make a determination about whether patient's symptoms meet DSM criteria B, C, and D for PTSD. • 20- to 30-minute administration.
Structured Clinical Interview (SCID) PTSD Module ^{38, 49}	<ul style="list-style-type: none"> • Semistructured interview used to assess the prevalence, absence, and subthreshold presence of PTSD used across trauma populations. • It consists of separate modules corresponding to categories of diagnoses. • 25-minute administration.
Symptom Checklist-90-Revised (SCL-90-R) ³⁸	<ul style="list-style-type: none"> • 90-item self-report questionnaire used to assess a broad range of psychological problems, symptoms of psychopathology, patient progress, and treatment outcomes. • 12- to 15-minute administration.

DSM = *Diagnostic and Statistical Manual*; PTSD = posttraumatic stress disorder.

Appendix B. PubMed search strategy

Search	Query
#1	Search ("Stress Disorders, Post-Traumatic"[Mesh] OR "post-traumatic stress disorder"[All Fields] OR "post-traumatic stress disorders"[All Fields] OR "posttraumatic stress disorder"[All Fields] OR "posttraumatic stress disorders"[All Fields] OR (disorder* AND "post-traumatic"[tiab]) OR "Stress Disorders, Traumatic"[Mesh:NOEXP] OR "Combat Disorders"[Mesh] OR PTSD) OR "stress disorder"[All Fields] OR "traumatic event"[All Fields] OR "traumatic incident"[All Fields])
#2	Search (("implosive therapy"[MeSH Terms] OR "implosive therapy"[All Fields] OR ("exposure"[tiab] AND ("therapy"[tiab] OR "psychotherapy"[tiab])) OR "imaginal exposure" OR "Biofeedback, Psychology"[Mesh] OR biofeedback or neurofeedback OR "Relaxation Therapy"[Mesh] OR "relaxation training"[All Fields] OR "cognitive therapy"[MeSH] OR cognitive restructur*[tiab] OR cognitive processing therap*[tiab] OR "Adaptation, Psychological"[Mesh] OR coping skill*[tiab] OR "stress inoculation" OR "assertiveness training" OR (psychodynamic[All Fields] AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields])) OR (psychodynamic[All Fields] AND ("psychotherapy"[MeSH Terms] OR "psychotherapy"[All Fields])) OR (("psychoanalytic"[All Fields] AND "psychotherapy"[All Fields]) OR "psychoanalytic psychotherapy"[All Fields]) OR (("psycho-analytic"[All Fields] AND "psychotherapy"[All Fields]) OR "psycho-analytic psychotherapy"[All Fields]) OR (("psycho-analytic"[All Fields] AND "psychotherapy"[All Fields]) OR "psycho-analytic psychotherapy"[All Fields]) OR "psychoanalytic therapy" OR "psycho-analytic therapy" OR "Eye Movement Desensitization Reprocessing"[MeSH] OR "EMDR"[tiab] OR "Psychotherapy"[Mesh] OR "brief eclectic psychotherapy" OR "interpersonal therapy" OR "interpersonal psychotherapy" OR "family therapy"[tiab] OR "marital therapy"[tiab] OR "group therapy" OR "group psychotherapy" OR "group psychological therapy" OR "Hypnosis"[Mesh] OR hypnotherapy OR "energy psychology"[All Fields] OR EFT OR "emotional freedom techniques"[All Fields])
#3	Search (#1 and #2)
#4	Search ("Benzodiazepines"[Mesh] OR "Antidepressive Agents, Tricyclic"[Pharmacological Action] OR "Anticonvulsants"[Pharmacological Action] OR "Adrenergic alpha-Antagonists"[Pharmacological Action] OR "Antipsychotic Agents"[Pharmacological Action] OR "Antidepressive Agents"[Pharmacological Action])
#5	Search ("Serotonin Uptake Inhibitors"[Mesh] OR "Serotonin Uptake Inhibitors" [Pharmacological Action] OR "Serotonin and Noradrenaline Reuptake Inhibitors"[Mesh] OR SSRI* OR SNRI* OR "citalopram" OR "escitalopram" OR "fluoxetine" OR "fluvoxamine" OR "paroxetine" OR "sertraline" OR "desvenlafaxine" OR "venlafaxine" OR "duloxetine" OR "imipramine" OR "amitriptyline" OR "desipramine" OR "bupropion" OR "mirtazapine" OR "nefazodone" OR "trazodone" OR "prazosin" OR "olanzapine" OR "risperidone" OR "benzodiazepines" [MeSH] OR "alprazolam" OR "diazepam" OR "lorazepam" OR "clonazepam" OR "topiramate" OR "tiagabine" OR "lamotrigine" OR "carbamazepine" OR "divalproex" OR "ziprasidone" OR "aripiprazole" OR "quetiapine")
#6	Search (#4 or #5)
#7	Search (#1 and #6)
#8	Search (#3 or #7)
#9	Search (#3 or #7) Filters: Humans
#10	Search (#3 or #7) Filters: Humans; English
#11	Search (#3 or #7) Filters: Humans; English; Adult: 19+ years
#12	Search (#11 NOT (letter[pt] OR newspaper article[pt] OR editorial[pt] OR comment[pt]))
#13	Search (((randomized[title/abstract] OR randomised[title/abstract]) AND controlled[title/abstract] AND trial[title/abstract]) OR (controlled[title/abstract] AND trial[title/abstract]) OR "controlled

Search	Query
	clinical trial"[publication type] OR "Randomized Controlled Trial"[Publication Type] OR "Single-Blind Method"[MeSH] OR "Double-Blind Method"[MeSH] OR "Random Allocation"[MeSH])
#14	Search (#12 and #13)
#15	Search (("review"[Publication Type] AND "systematic"[tiab]) OR "systematic review"[All Fields] OR ("review literature as topic"[MeSH AND "systematic"[tiab]))
#16	Search ("meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[All Fields])
#17	Search (#12 and (#15 or #16))
#18	Search ("Comparative Study"[Publication Type] OR "comparative study" OR case control stud* OR "Case-Control Studies"[Mesh])
#19	Search (#12 and #18)
#20	Search ("Cohort Studies"[Mesh] OR "cohort effect"[MeSH Term] OR cohort*[tiab] OR "prospective studies"[MeSH] OR (prospective*[All Fields] AND cohort[All Fields] AND (study[All Fields] OR studies[All Fields])))
#21	Search (#12 and #20)
#22	Search (#14 or #17 or #19 or #21)
#23	Search (#14 or #17 or #19 or #21) Filters: Publication date from 2012/01/01 to 2017/12/31