Evidence-based Practice Center Systematic Review Protocol

Project Title: Psychological Treatments and Pharmacological Treatments for Adults with Post-traumatic Stress Disorder (PTSD)

I. Background and Objectives for the Systematic Review

Posttraumatic stress disorder (PTSD) may develop following exposure to a traumatic event. According to the 4th edition of the *Diagnostic and Statistical Manual of Mental Disorders DSM-IV-TR*, the essential feature of PTSD is the development of characteristic symptoms following exposure to an extreme traumatic stressor involving direct personal experience of an event that involves actual or threatened death or serious injury, or other threat to one’s physical integrity; or 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. The full *DSM-IV TR* criteria are listed in Table 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. According to a 2008 Institute of Medicine (IOM) report on the treatment of PTSD, the condition “…develops in a significant minority (up to a third) of individuals who are exposed to extreme stressors, and symptoms of PTSD almost always emerge within days of the trauma.”

PTSD is also highly comorbid with other psychiatric disorders; data from epidemiologic studies have found that a vast majority of individuals with PTSD have another psychiatric disorder, mostly notably substance use disorders and major depressive disorder. Subgroups of people with PTSD that could have differences in their response to various treatments include military personnel or veterans, people with comorbid conditions, gender groups, first responders, refugees, disaster victims, racial and ethnic minorities, and those with different PTSD symptoms.
Table 1. Diagnostic criteria (DSM-IV-TR) for posttraumatic stress disorder

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Symptom or description</th>
</tr>
</thead>
</table>
| Criterion A: Trauma (both) | • Traumatic event that involved actual or threatened death, serious injury, or threat to physical integrity  
• Intense response of fear, helplessness, or horror |
| Criterion B: Re-experiencing symptoms: (one or more) | • 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 |
| Criterion C: Persistent avoidance and numbing: (three or more) | • 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 |
| Criterion D: Hyperarousal: (two or more) | • Difficulty falling or staying asleep  
• Irritability or outburst of anger  
• Difficulty concentrating  
• Hypervigilance  
• Exaggerated startle response |
| Criterion E: Duration of disturbance | • Duration of disturbance symptoms is more than 1 month |
| Criterion F: Clinically significant distress or impairment | • Disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of function |

Prevalence of PTSD

The 2000 National Comorbidity Survey—Replication (NCS-R) estimated lifetime prevalence of PTSD among adults in the United States to be 6.8 percent (9.7 percent in women and 3.4 percent in men) and current (12-month) prevalence to be 3.6 percent (5.2 percent for women and 1.8 percent in men).\(^4\) Military personnel are at elevated risk for exposure to trauma and, thus, PTSD diagnosis. Estimates from the National Vietnam Veterans Readjustment Survey (NVVRS) found a lifetime PTSD prevalence estimate of 18.7 percent and a current PTSD prevalence estimate of 9.1 percent\(^4\) 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. The estimates of PTSD in British combat and noncombat troops that served in Iraq were 6 percent and 3 percent, respectively.\(^5\)

Burden of PTSD

In addition to lost lives due to increased risk of suicide, PTSD is associated with high medical costs and high social costs, because PTSD is a strong risk factor for crime, poor work performance and associated job losses, and familial discord. The economic cost of
the PTSD and depression cases among Operation Enduring Freedom/Operation Iraqi Freedom veterans alone (including medical care, forgone productivity, and lives lost through suicide) is estimated at $4 billion to $6 billion over 2 years.⁶

Many people with PTSD do not seek treatment. Among those who do, many receive inadequate treatment or care that is not empirically based. Several PTSD outcome studies demonstrate the cost-effectiveness of early diagnosis and appropriate treatment, especially when compared with the cost of inadequate or ineffective treatment occurring prior to a correct diagnosis.⁷ In addition to consequences related to PTSD, people affected by these disorders have higher rates of psychiatric comorbidity, suffer decreased role functioning such as work impairment (on average, 3.6 days of work impairment per month), and are associated with many different adverse life-course consequences (e.g., reduced educational attainment, work earnings, marriage attainment, and child rearing).⁸

**Treatment of PTSD**

Treatments available for PTSD span a variety of psychological and pharmacological domains. These interventions have been used both separately and in combination with one another, and both appear to be mainstays of treatment in treatment guidelines.⁹-¹⁵ While there is no clearly defined “preferred” approach to manage PTSD, each of these guidelines supports the use of trauma-focused psychological interventions for adults with PTSD, and all recognize at least some benefit of pharmacologic treatments for PTSD. Indeed, some guidelines identify trauma-focused psychological treatments over pharmacological treatments as a preferred first step and view medications as an adjunct or a next-line treatment.¹⁴, ¹⁶ 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 nonphysician mental health provider, psychotherapy options are more likely, while presentation to a physician provider could offer either psychotherapy or pharmacologic therapy, or both. Subsequently, the selection of specific psychotherapies, or specific pharmacologic interventions, may depend to a large degree on the clinician’s training.

**Psychological Interventions**

Specific psychological interventions that have been studied for the treatment of PTSD are described below and include the following: cognitive-behavioral therapy 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; 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.²

_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. Most forms of CBT consist of a minimum of 8-12 weekly sessions lasting 60-90 minutes. CBT can be administered either as group or individual therapy.\(^2, 17\)

**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 (imaginational 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 8-12 weekly or biweekly sessions lasting 60-90 minutes.\(^2, 7, 17\)

**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 and 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 8-12 sessions of 60-90 minutes.\(^2, 17\)

**Coping skills therapy** may include components such as stress inoculation therapy, assertiveness training, biofeedback (including brainwave neurofeedback), or relaxation training. All may use techniques such as education, muscle relaxation training, breathing retraining, role playing, etc., 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 8 60-90 minute sessions, while more comprehensive interventions such as stress inoculation therapy require 10-14 sessions.\(^2, 17\)

**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 bi-weekly sessions over a period of several months to an indefinite period of time.\(^2, 17, 18\)

**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 emotional impact of trauma can be resolved. In the EMDR process, the client 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 client to contemplate memory while focusing on rapid movement of clinicians’ fingers. After 10–12 eye movements (back and forth), the clinician asks the client to rate the strength of the memory and his or her belief in the positive cognition. Although earlier versions of EMDR consisted of 1-3 sessions, current standards consist of 8-12 90-minute weekly sessions.\(^2, 18\)

**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 10-20 weekly sessions in the acute phase followed by a time unlimited maintenance phase.\textsuperscript{20}

*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 varies widely depending on the type of group therapy (e.g., interpersonal process, cognitive-behavioral, peer, education).\textsuperscript{21,22}

*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 exists on the efficacy of hypnosis in treating patients with PTSD.\textsuperscript{2,17} 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 client to adapt to that individual’s needs, rather than approaching the client and his/her issues from a specific psychological orientation. Some therapists adhere largely to a single orientation, such as psychoanalysis or cognitive-behavioral therapy, 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.

**Pharmacologic Interventions**

Pharmacotherapies, including selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, 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.\textsuperscript{2} Currently, only paroxetine and sertraline are approved by the U.S. Food and Drug Administration for treatment of PTSD. Specific medications within these drug classes that have been studied or used in treating PTSD are listed in Table 2.

### Table 2. Medications used in treating PTSD

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selective serotonin reuptake inhibitors</td>
<td>citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline</td>
</tr>
</tbody>
</table>

Source: [www.effectivehealthcare.ahrq.gov](http://www.effectivehealthcare.ahrq.gov)
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### Serotonin and norepinephrine reuptake inhibitors
- desvenlafaxine, venlafaxine, and duloxetine

### Tricyclic antidepressants
- imipramine, amitriptyline, and desipramine

### Monoamine oxidase inhibitors
- phenelzine and brofaromine

### Other second-generation antidepressants
- bupropion, mirtazapine, nefazodone, trazodone

### Alpha blockers
- Prazosin

### Second-generation (atypical) antipsychotics
- olanzapine and risperidone

### Anticonvulsants (mood stabilizers)
- topiramate, tiagabine, lamotrigine, carbamazepine, and divalproex

### Benzodiazepines
- alprazolam, diazepam, lorazepam, and clonazepam

### Other medications
- naltrexone, cycloserine, and inositol

## PTSD Outcomes
One of the primary outcomes in PTSD treatment is symptom reduction, which includes both clinician-rated and self-reported measures. Appendix A, at the end of this report, describes each of the PTSD measures in detail. Some of the most commonly used instruments are listed in the outcomes section of this protocol. In addition to symptom reduction, other outcomes used in practice include prevention/reduction of comorbid medical or psychiatric conditions (e.g., depressive symptoms, anxiety symptoms); remission; improved quality of life; and ability to return to work or return to active duty.

## Summary of Existing Guidance
Various guidelines and systematic reviews have resulted in contradictory conclusions and recommendations regarding these broad categories of treatments as well as the effectiveness of specific treatments that fit into each of these areas. Clinical uncertainty exists about what treatment to select among all of the reportedly evidence-based approaches. In addition to the clinical uncertainty about the effectiveness of some of the psychological treatments, the effectiveness and potential harms of medications for PTSD are uncertain. 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 the treatment of PTSD, including the American Psychiatric Association (APA), the U.S. Department of Veterans Affairs/U.S. Department of Defense (VA/DoD), the National Institute of Clinical Excellence (NICE) in the United Kingdom, the National Health and Medical Research Council (NHMRC), the International Society for Traumatic Stress Studies (ISTSS), the American Academy of Child and Adolescent Psychiatry (AACAP), and the IOM.

The organizations and guideline developers used different methods, which resulted in conflicting recommendations. Four of these guidelines (VA/DoD, NICE, NHMRC, IOM) were based on rigorous systematic reviews, and the other three guidelines (APA, ISTSS, AACAP) were based on expert consensus and less structured literature reviews.

Source: [www.effectivehealthcare.ahrq.gov](http://www.effectivehealthcare.ahrq.gov)
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The core of the controversy stems from differences in the rating systems each review applied to assess the strength of evidence 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. For example, the IOM Committee on the Treatment of PTSD concluded that the evidence on specific pharmacological drugs was inadequate to determine efficacy in the treatment of PTSD, whereas the VA/DoD clinical practice guideline considered SSRIs to have significant benefit and some other agents to have some benefit for PTSD treatment.

A new review and synthesis of the evidence are needed to address these uncertainties and, as such, are likely to have a significant impact by improving outcomes and reducing variation in treatment guidelines.

II. The Key Questions

**Question 1:** What is the comparative effectiveness of different psychological treatments (including cognitive-behavioral therapy [CBT], such as cognitive restructuring, cognitive processing therapy, exposure-based therapy, and coping skills [including stress inoculation therapy]; psychodynamic therapy; eye movement desensitization and reprocessing [EMDR]; hypnosis/hypnotherapy; interpersonal therapy; group therapy; eclectic psychotherapy; and brainwave neurofeedback) for adults diagnosed with posttraumatic stress disorder (PTSD)?

**Question 2:** What is the comparative effectiveness of different pharmacological treatments (e.g., selective serotonin-reuptake inhibitors [SSRIs]) for adults diagnosed with PTSD?

- As monotherapy compared with monotherapy?
- As augmentation therapy (e.g., adding paroxetine vs. adding sertraline to another ongoing treatment for PTSD)?

**Question 3:** What is the comparative effectiveness of different psychological treatments versus pharmacological treatments for adults diagnosed with PTSD?

**Question 4:** How do combinations of psychological treatments and pharmacological treatments (e.g., CBT plus paroxetine) compare with either one alone (i.e., one psychological or one pharmacological treatment)?

**Question 5:** Are any of the treatment approaches for PTSD more effective than other approaches for victims of particular types of trauma?

**Question 6:** What adverse effects are associated with treatments for adults diagnosed with PTSD?

Population, Interventions, Comparators, Outcome measures, and Setting (PICOS) criteria for the preceding Key Questions are:

Source: www.effectivehealthcare.ahrq.gov
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Population(s):
- Adults with a diagnosis of PTSD based on Diagnostic and Statistical Manual of Mental Disorders criteria.
- Subgroups of interest include military personnel or veterans, people with comorbid conditions, gender groups, first responders, refugees, disaster victims, racial or ethnic minorities, individuals with different PTSD symptoms, complex PTSD (such as those refractory to treatment or high dissociators), those with exposure to childhood trauma or repeat victimization, those with different levels of severity at presentation, and those with chronic PTSD.

Interventions:
- Psychological interventions including:
  - CBT, such as cognitive restructuring and cognitive processing therapy, exposure-based therapies, and coping skills therapy [may include components such as stress inoculation therapy, assertiveness training, biofeedback (including brainwave neurofeedback), or relaxation training].
  - Psychodynamic therapy
  - EMDR
  - Interpersonal therapy
  - Group therapy
  - Hypnosis/hypnotherapy
  - Eclectic psychotherapy
- Pharmacological interventions including:
  - SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline)
  - Serotonin and norepinephrine reuptake inhibitors (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 and risperidone)
  - Benzodiazepines (alprazolam, diazepam, lorazepam, and clonazepam)
  - Anticonvulsants/mood stabilizers (topiramate, tiagabine, lamotrigine, carbamazepine, and divalproex)

Comparators:
- Comparators include:
  - Psychological treatments (listed above) with one another
  - Pharmacological treatments (listed above) with one another
  - Psychological treatments with pharmacological treatments (listed above)
  - Combinations of psychological and pharmacological treatments with either type of treatment alone
  - Pharmacological treatments with placebo
Psychological treatments with waiting list assignment, usual care, no intervention, or sham

- We will focus on direct/comparative evidence when available. When direct evidence is not available, we will use indirect evidence to inform the assessment of comparative effectiveness (i.e., from comparisons with placebo, waiting list assignment, usual care, no intervention, or sham).

- Interventions and Comparators by Key Question (KQ)
  - KQ 1: Psychological interventions listed above compared to one another or to waiting list assignment, usual care (as defined by the study), no intervention, or sham.
  - KQ 2: Pharmacological interventions listed above compared to one another or to placebo.
  - KQ 3: Psychological interventions listed above compared to pharmacologic interventions listed above.
  - KQ 4: Combinations of psychological and pharmacological interventions compared to either one alone (placebo, waiting list assignment, usual care, no intervention, or sham may be used in conjunction with the monotherapy arm).
  - KQ 5: All studies included for KQs 1 through 4 will be eligible.
  - KQ 6: All studies included for KQs 1 through 4 will be eligible.

- **Outcome measures:**
  - PTSD symptom reduction, both assessor-rated and self-reported, as measured by the Clinician-Administered PTSD Scale (CAPS), the Clinician-Administered PTSD Scale Part 2 (CAPS-2), the Impact of Events Scale (IES), the Impact of Events Scale–Revised (IES-R), the Modified PTSD Symptom Scale (MPSS-SR), the self-rated PTSD symptoms Checklist (PCL), the PTSD Symptom Scale–Interview (PSS-I), the PTSD Symptom Scale–Self-report Version (PSS-SR), or the Structured Interview for PTSD (SI-PTSD)
  - Prevention/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 (no longer having symptoms)
  - Improved quality of life
  - Disability/functional impairment
  - Return to work/return to active duty
  - Adverse events: overall adverse events, withdrawals due to adverse events, and specific adverse events (including, but not limited to, disturbed sleep, increased agitation, sedation, weight gain, metabolic side effects, and mortality)

- **Settings:**
  Settings include outpatient and inpatient primary care or specialty mental health care settings, community settings (e.g., churches, community health centers, rape crisis centers), or military 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 PICOS 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, KQ 3, and KQ 4). Type of trauma as a potential moderator of these interventions is explored in KQ 5. KQ 6 looks at the adverse effects of these interventions. Finally, subgroups within the overall population include military personnel or veterans, first responders, disaster victims, refugees, those with comorbid conditions, those with different PTSD symptoms, men/women, and race/ethnicity.

Source: www.effectivehealthcare.ahrq.gov
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IV. Methods

A. Criteria for Inclusion/Exclusion of Studies in the Review. Table 3 presents the inclusion/exclusion criteria for this review. We do not repeat all of the PICOS information related to the inclusion/exclusion criteria; Table 3 supplements the information outlined above in the PICOS.

Table 3. Inclusion/exclusion criteria

<table>
<thead>
<tr>
<th>Category</th>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Adults with PTSD, as defined above in the PICOS</td>
<td></td>
</tr>
<tr>
<td>Geography</td>
<td>No limits</td>
<td></td>
</tr>
<tr>
<td>Time period</td>
<td>1980–present; searches to be updated after draft report goes out for peer review</td>
<td></td>
</tr>
<tr>
<td>Study duration</td>
<td>At least 4 weeks from the time of group assignment for trials</td>
<td></td>
</tr>
<tr>
<td>Settings</td>
<td>As defined above in the PICOS</td>
<td></td>
</tr>
<tr>
<td>Interventions</td>
<td>As defined above in the PICOS</td>
<td></td>
</tr>
<tr>
<td>Outcomes</td>
<td>As listed above under the PICOS</td>
<td></td>
</tr>
<tr>
<td>Publication language</td>
<td>English</td>
<td>All other languages†</td>
</tr>
<tr>
<td>Admissible evidence (study design and other criteria)</td>
<td>Original research For KQs 1 through 5, eligible study designs include: • Randomized controlled trials. For KQ 5 (focused on whether there are any treatment approaches for PTSD that are more effective for victims of particular types of trauma), we will evaluate the information within the trials meeting inclusion criteria for KQs 1 through 4. A number of the subgroups of interest will be addressed by this KQ (e.g., military/combat vs. noncombat trauma, first responders, refugees, disaster victims, those with exposure to childhood trauma, those with repeat victimization) For KQ 6 (focused on adverse effects), we will evaluate the trials included in KQs 1 through 4 that report adverse effects. In addition, we will include nonrandomized controlled trials of any sample size, prospective cohort studies with an eligible comparison group with a sample size of at least 500, and case-control studies with a sample size of at least 500. We will not include observational studies with a sample size of less than 500 or for other KQs due to the risk of bias being too high to provide valid and reliable evidence for the other KQs.‡</td>
<td>• Case series • Case reports • Systematic reviews and meta-analyses • Nonsystematic reviews • Editorials • Letters to the editor • Articles to the editor • Articles rated poor during quality assessment • Studies with historical, rather than concurrent, control groups • Pre-post studies without a separate control group</td>
</tr>
</tbody>
</table>

† Due to limited time and resources, we will only include studies published in English.
‡ 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 6, we have chosen a sample size cutoff.
of 500 for prospective cohort studies and case-control studies for several reasons: (1) our topic refinement process found a large number of trials in this field and we weighed the tradeoffs between increasing comprehensiveness by reviewing all possible observational studies that present harms and the decreased quality that may occur from increased risk of bias, as well as considering our resource and time constraints; (2) related to the previous point, we decided to include large observational studies with the lowest potential risk of bias to supplement the trial literature; and (3) our TEP supported this approach.

Abbreviations: KQ = key question; PICOS = populations, interventions, comparators, outcomes, and setting; TEP = Technical Expert Panel.

**B. 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.

1. 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. Relevant terms are listed in Table 4. We will also search the Cochrane Library, the Cochrane Central Trials Registry, the Cumulative Index to Nursing and Allied Health Literature, and PsycInfo by using analogous search terms. We will conduct quality checks to ensure that the known studies (i.e., studies included in the previous review on alcohol misuse and those identified during Topic Nomination and Refinement) are identified by the search. If they are not, we will revise and rerun our searches.

2. We will search the literature published in 1980 and later. This 1980 search date was selected based on the introduction/definition of PTSD as a clinical entity and based on the earliest publication date of relevant studies found in previous systematic reviews and expert opinion about when the earliest literature on this topic was published.

3. 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 assessment of internal validity/quality. Sources of gray literature include ClinicalTrials.gov, the FDA Web site, and pharmaceutical companies’ dossiers (for pharmacotherapies of interest).

4. We will review our search strategy with the Technical Expert Panel (TEP) and supplement it as needed according to their recommendations. In addition, to attempt to avoid retrieval bias, we will manually search the reference lists of landmark studies and background articles on this topic to look for any relevant citations that electronic searches might have missed.
5. We will also conduct an updated literature search (of the same databases searched initially) concurrent with the peer review process. We will investigate any literature the peer reviewers or the public suggest and, if appropriate, will incorporate them into the final review. Appropriateness will be determined by the same methods described above.

Table 4. PubMed proposed literature search terms

| Interventions | Psychological intervention terms: "cognitive therapy" [MeSH] OR "cognitive restructuring" OR "cognitive processing therapy" OR "exposure-based therapy" OR "exposure based therapy" OR "exposure therapy" OR "exposure-based psychotherapy" OR "exposure based psychotherapy" OR "exposure-based psychological therapy" OR "exposure based psychological therapy" OR "exposure psychological therapy" OR "prolonged exposure therapy" OR "prolonged exposure psychotherapy" OR "prolonged exposure psychological therapy" OR "imaginal exposure" OR "in vivo exposure therapy" OR "coping skills therapy" OR "stress inoculation therapy" OR "stress inoculation training" OR "assertiveness training" OR "psychodynamic therapy" OR "psychodynamic psychotherapy" OR "psychoanalytic therapy" OR "psycho-analytic therapy" OR "psychoanalytic psychotherapy" OR "Eye Movement Desensitization Reprocessing" [MeSH] OR "interpersonal therapy" OR "interpersonal psychotherapy" OR "group therapy" OR "group psychotherapy" OR "group psychological therapy" OR "family therapy" OR "marital therapy" OR "hypnosis" [MeSH] OR "eclectic therapy" OR "eclectic psychotherapy" OR "biofeedback, psychology" [MeSH] OR Pharmacologic intervention terms: "citalopram" OR "escitalopram" OR "fluoxetine" OR "fluvoxamine" OR "paroxetine" OR "sertraline" OR "desvenlafaxine" OR "venlafaxine" OR "duloxetine" OR "imipramine" OR "amlodipine" OR "desipramine" OR "bupropion" OR "mirtazapine" OR "nelfazodone" 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"
| Limits | Humans; NOT [Addresses, autobiography, bibliography, biography, case reports, classical article, congresses, dictionary, editorial, festschrift, in vitro, interactive tutorial, interview, lectures, legal cases, legislation, letter, news, newspaper article, patient education handout, periodical index, portraits, twin study, webcasts] English language; NOT [All Child: 0-17 years] Publication Date from 1980/01/01 to [date of search]


Source: www.effectivehealthcare.ahrq.gov
Published Online: December 20, 2011
C. 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. 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. 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 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 important 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.
D. Assessment of Methodological Quality of Individual Studies. To assess the quality (internal validity) of studies, we will use predefined criteria based on those developed by the U.S. Preventive Services Task Force (USPSTF) (ratings: good, fair, poor) and the University of York Centre for Reviews and Dissemination.23, 24 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.
E. Data Synthesis. If we find three or more similar 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 pharmacologic interventions with each other if we identify a sufficient number of studies with a common comparator (e.g., placebo). For all analyses, we will use random-effects models to estimate pooled or comparative effects. In order to determine whether quantitative analyses are appropriate, we will assess the clinical and methodological heterogeneity of the studies under consideration following established guidance. 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 strength of evidence 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.

F. Grading the Evidence for Each Key Question. We will grade the strength of evidence based on the guidance established for the Evidence-based Practice Center Program. Developed to grade the overall strength of a body of evidence, this approach incorporates four key domains: risk of bias (includes study design and aggregate quality), consistency, directness, and precision of the evidence. 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, strength of association (magnitude of effect), and publication bias.
Table 5 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 strength of evidence 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 adverse events.

Table 5. Definitions of the grades of overall strength of evidence

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
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<tbody>
<tr>
<td>High</td>
<td>High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.</td>
</tr>
<tr>
<td>Moderate</td>
<td>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.</td>
</tr>
<tr>
<td>Low</td>
<td>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.</td>
</tr>
<tr>
<td>Insufficient</td>
<td>Evidence either is unavailable or does not permit estimation of an effect.</td>
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</tbody>
</table>

G. Assessing Applicability. We will assess applicability of the evidence following guidance from the Methods Guide for Effectiveness and Comparative Effectiveness Reviews. We will use the PICOTS framework to explore factors that affect applicability. Some factors identified a priori that may limit the applicability of evidence include the following: age of enrolled populations; sex of enrolled populations (e.g., few women may be enrolled in the studies); race/ethnicity of enrolled populations; few studies enrolling subjects with exposure to certain types of trauma; or few studies distinguishing/reporting the type of traumatic exposure for a heterogeneous population.

V. References

Source: www.effectivehealthcare.ahrq.gov
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VI. Definition of Terms
None.

Source: www.effectivehealthcare.ahrq.gov
Published Online: December 20, 2011
VII. Summary of Protocol Amendments

In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale.

VII. Summary of Protocol Amendments

None.

VIII. Review of Key Questions

For all EPC reviews, key questions were reviewed and refined as needed by the EPC with input from Key Informants and the Technical Expert Panel (TEP) to assure that the questions are specific and explicit about what information is being reviewed. In addition, for Comparative Effectiveness reviews, the key questions were posted for public comment and finalized by the EPC after review of the comments.

IX. Key Informants

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. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform health care decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high-priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The Task Order Officer (TOO) and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Experts

Technical Experts comprise a multidisciplinary group of clinical, content, and methodologic experts who provide input in defining populations, interventions, comparisons, or outcomes as well as identifying particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore, study questions, design, and/or methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not perform analysis of any kind nor contribute to the writing of the report, and they have not reviewed the report, except as given the opportunity to do so through the public review mechanism.
Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Peer Reviewers

Peer Reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodologic expertise. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. Peer Reviewers do not participate in writing or editing of the final report or other products. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual Reviewers. The dispositions of the peer review comments are documented and will, for Comparative Effectiveness Reviews (CERs) and Technical briefs, be published 3 months after the publication of the Evidence report.

Potential 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.

XII. EPC Team Disclosures

With the exception of the following, the team had no interests to disclosure:

- Co-Investigator A’s Statement of Disclosure of Business and Professional Interest:
  - Editorial Board for Medscape Psychiatry and Mental Health, a continuing medical education organization

- Co-Investigator B’s Statement of Disclosure of Business and Professional Interest:
  - Member, Binge Eating Disorder Association Scientific Advisory Board

XIII. Role of the Funder

This project was funded under Contract No. 290-2007-10056 I from the Agency for Healthcare Research and Quality. U.S. Department of Health and Human Services. The TOO reviewed contract deliverables for adherence to contract requirements, including the objectivity and independence of the research process and the methodological quality of the report. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.
Appendix A. PTSD outcome measures

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Description</th>
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| **Clinician-Administered PTSD Scale (CAPS)**<sup>2, 28</sup> | • Gold standard for PTSD assessment and diagnosis for military and civilian and trauma survivors.  
• 30-item structured interview that corresponds to the DSM-IV criteria for PTSD.  
• 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 5 associated symptoms (guilt over acts, survivor guilt, gaps in awareness, depersonalization, and derealization).  
• Can be used to make a current or lifetime diagnosis of PTSD or to assess symptoms over the past week.  
• 45–60-minute administration by trained (para)professionals. |
| **Clinician-Administered PTSD Scale Part 2 (CAPS-2)**<sup>28</sup> | • Assesses 1-week symptom status. |
| **Davidson Trauma Scale (DTS)**<sup>29, 30</sup> | • 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 clients 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)**<sup>2</sup> | • 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)**<sup>31</sup> | • 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)**<sup>12</sup> | • 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)**<sup>2</sup> | • 43-item self-report measure used to assess PTSD symptoms and associated features, including signs of distress and functional problems. |
| **Minnesota Multiphasic Personality Inventory, Keane PTSD Scale**<sup>2</sup> | • Self-report questionnaire.  
• Originally composed of 29 items, revised for MMPI-2 by deleting 3 item repetitions.  
• 46 MMPI items.  
• Norms available for different populations. |
| **Mississippi Scale for Combat-related PTSD (M-PTSD)**<sup>2</sup> | • 35-item self-report questionnaire used to assess DSM-III combat-related PTSD and related features (depression, suicidality, and substance abuse).  
• 10–15-minute administration. |
| **Modified PTSD Symptom Scale (MPSS-SR)**<sup>33</sup> | • 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 |
<table>
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<tr>
<th>Outcome Measure</th>
<th>Description</th>
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| Penn Inventory for Posttraumatic Stress², ³⁴         | • 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)²               | • 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)³⁵                                | • 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: PCL-M (military), PCL-C (civilian), and PCL-S (specific).  
• 5–10-minute administration. |
| PTSD Interview (PTSD-I)²                              | • 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. |
| PTSD Symptom Scale-Interview (PSS-I)³⁷               | • 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)³⁸     | • 17-item scale used to diagnosis 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)³⁹     | • 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 client's symptoms meet DSM criteria B, C, and D for PTSD.  
• 20–30-minute administration |
| Structured Clinical Interview (SCID) PTSD Module², ⁴⁰ | • 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 Checkli-90-Revised (SCL-90-R)⁷               | • 90-item self-report questionnaire used to assess a broad range of psychological problems, symptoms of psychopathology, patient progress, and treatment outcomes.  
• 12–15-minute administration. |