Effective Health Care Program

Psychological and Pharmacological Treatments for Adults With Posttraumatic Stress Disorder (PTSD)

Comparative Effectiveness Review
Number 92

Psychological and Pharmacological Treatments for Adults With Posttraumatic Stress Disorder (PTSD)

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Structured Abstract

Objectives. To assess efficacy, comparative effectiveness, and harms of psychological and pharmacological treatments for adults with posttraumatic stress disorder (PTSD).

Data sources. MEDLINE®, Cochrane Library, PILOTS, International Pharmaceutical Abstracts, CINAHL®, PsycINFO®, Web of Science, Embase, U.S. Food and Drug Administration Web site, and reference lists of published literature (January 1980–May 2012).

Review methods. Two investigators independently selected, extracted data from, and rated risk of bias of relevant trials. We conducted quantitative analyses using random-effects models to estimate pooled effects. To estimate medications' comparative effectiveness, we conducted a network meta-analysis using Bayesian methods. We graded strength of evidence (SOE) based on established guidance.

Results. We included 92 trials of patients, generally with severe PTSD and mean age of 30s to 40s. High SOE supports efficacy of exposure therapy for improving PTSD symptoms (Cohen's d -1.27; 95% confidence interval, -1.54 to -1.00); number needed to treat (NNT) to achieve loss of diagnosis was 2 (moderate SOE). Evidence also supports efficacy of cognitive processing therapy (CPT), cognitive therapy (CT), cognitive behavioral therapy (CBT)-mixed therapies, eye movement desensitization and reprocessing (EMDR), and narrative exposure therapy for improving PTSD symptoms and/or achieving loss of diagnosis (moderate SOE). Effect sizes for reducing PTSD symptoms were large (e.g., 28.9- to 32.2-point reduction in Clinician-Administered PTSD Scale [CAPS]; Cohen's d ~ -1.0 or more compared with controls); NNTs were ≤ 4 to achieve loss of diagnosis for CPT, CT, CBT-mixed, and EMDR.

Evidence supports the efficacy of fluoxetine, paroxetine, sertraline, topiramate, and venlafaxine for improving PTSD symptoms (moderate SOE); effect sizes were small or medium (e.g., 4.9- to 15.5-point reduction in CAPS compared with placebo). Evidence for paroxetine and venlafaxine also supports their efficacy for inducing remission (NNTs ~8; moderate SOE). Evidence supports paroxetine's efficacy for improving depression symptoms and functional impairment (moderate SOE) and venlafaxine's efficacy for improving depression symptoms, quality of life, and functional impairment (moderate SOE). Risperidone may help PTSD symptoms (low SOE). Network meta-analysis of 28 trials (4,817 subjects) found paroxetine and topiramate to be more effective than most medications for reducing PTSD symptoms, but analysis was based largely on indirect evidence and limited to one outcome measure (low SOE).

We found insufficient head-to-head evidence comparing efficacious treatments; insufficient evidence to verify whether any treatment approaches were more effective for victims of particular trauma types or to determine comparative risks of adverse effects.

Conclusions. Several psychological and pharmacological treatments have at least moderate SOE supporting their efficacy: exposure, CPT, CT, CBT-mixed therapies, EMDR, narrative exposure therapy, fluoxetine, paroxetine, sertraline, topiramate, and venlafaxine.

Executive Summary

Background

Posttraumatic stress disorder (PTSD) is a mental disorder that 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,"[1] the essential feature of PTSD is the development of characteristic symptoms following exposure to a traumatic stressor. PTSD is characterized by three core symptom clusters: (1) reexperiencing, (2) avoidance or numbing (or both), and (3) hyperarousal. The full DSM-IV-TR criteria are listed in Table A.

Table A. Diagnostic criteria (DSM-IV-TR) for posttraumatic stress disorder

Criterion	Symptom or Description
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: Reexperiencing symptoms (1 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 (3 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 (2 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

DSM-IV-TR = Diagnostic and Statistical Manual of Mental Disorders

Examples of traumatic events include military combat, motor vehicle collisions, violent personal assault, being taken hostage, a terrorist attack, torture, natural or human-caused disasters, and, in some cases, being diagnosed with a life-threatening illness.[1] PTSD develops in up to a third of individuals who are exposed to extreme stressors, and symptoms almost always emerge within days of the exposure.[2] Shortly after exposure to trauma, many people experience some of the symptoms of PTSD; in most people, those symptoms resolve spontaneously in the first several weeks after the trauma. However, in approximately 10 percent to 20 percent of those exposed to trauma, PTSD symptoms persist and are associated with impairment in social or occupational functioning.[3] Although approximately 50 percent of those diagnosed with PTSD improve without treatment in 1 year, 10 percent to 20 percent develop a chronic unremitting course.[4]

The 2000 National Comorbidity Survey—Replication (NCS-R) estimated lifetime prevalence of PTSD among adults in the United States to be 6.8 percent and current (12-month) prevalence to be 3.6 percent.[5] 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 among Vietnam veterans.[5] More recent surveys of military personnel have yielded estimates ranging from 6.2 percent for U.S. service members who fought in Afghanistan to 12.6 percent for those who fought in Iraq.[6]

People with PTSD suffer decreased role functioning, such as work impairment, and experience many other adverse life-course consequences, including job losses; family discord; and reduced educational attainment, work earnings, marriage attainment, and child rearing.[7] PTSD is associated with an increased risk of suicide,[8] high medical costs, and high social costs. Epidemiologic studies have also found that a high percentage of individuals with PTSD have another psychiatric disorder, most notably substance use disorders or major depressive disorder.[9]

Treatment Strategies for PTSD

Treatments available for PTSD span a variety of psychological and pharmacological categories. Specific psychological interventions that have been studied for the treatment of patients with PTSD include the following: brief eclectic psychotherapy; cognitive behavioral therapy (CBT), such as cognitive processing therapy (CPT), cognitive therapy (CT), cognitive restructuring (CR), coping skills therapy (including stress inoculation therapy), and exposure-based therapies; eye movement desensitization and reprocessing (EMDR); hypnosis and hypnotherapy; interpersonal therapy; and psychodynamic therapy. These therapies are designed to minimize the intrusion, avoidance, and hyperarousal symptoms of PTSD by some combination of reexperiencing and working through trauma-related memories and emotions and teaching better methods of managing trauma-related stressors.[2] The therapies are delivered predominantly to individuals; some can also be conducted in a group setting.[10,11]

Many pharmacological therapies have been studied for treatment of patients with PTSD, including selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), other second-generation antidepressants, tricyclic antidepressants, monoamine oxidase (MAO) inhibitors, alpha-blockers, second-generation (atypical) antipsychotics, anticonvulsants (mood stabilizers), and benzodiazepines. Currently, only paroxetine and sertraline are approved by the U.S. Food and Drug Administration for treatment of patients with PTSD.

Existing Guidance

Numerous organizations have produced guidelines for the treatment of patients with PTSD, including the Department of Veterans Affairs and Department of Defense (VA, DoD), the American Psychiatric Association (APA), the United Kingdom's National Institute for Health and Clinical Excellence (NICE), the International Society for Traumatic Stress Studies (ISTSS), the Institute of Medicine (IOM), and the Australian National Health and Medical Research Council.[12-16] All of these guidelines agree that trauma-focused psychological interventions (i.e., those that treat PTSD by directly addressing thoughts, feelings, or memories of the traumatic event) are empirically supported first-line treatments for adults with PTSD, and all, except the IOM report,[2] recognize at least some benefit of pharmacologic treatments for PTSD.

Beyond that broad agreement, however, lies some disagreement. Various guidelines and systematic reviews have arrived at different conclusions and led to different recommendations

about broad categories of treatments and the effectiveness of specific treatments that fit into these broad categories. Clinical uncertainty exists about what treatment to select among all the evidence-based approaches. However, most 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.[12-14,17] The guideline from the ISTSS acknowledges that practical considerations, such as unavailability of trauma-focused psychological treatment or patient preferences, may guide treatment decisions.[15]

Scope and Key Questions

The main objective of this report is to conduct a systematic review and meta-analysis of the efficacy and comparative effectiveness and harms of psychological and pharmacological interventions for adults with PTSD. In this review, we address the following Key Questions (KQs):

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

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

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

KQ 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)?

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

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

We developed an analytic framework to guide the systematic review process. The population is limited to adults with a diagnosis of PTSD. Because we wanted to assess whether the evidence suggested any differences in response to various treatments for trauma subgroups (e.g., military personnel), we identified subgroups of interest as noted in Figure A.

Methods

Literature Search Strategy

We searched MEDLINE®, the Cochrane Library, the PILOTS database, International Pharmaceutical Abstracts, CINAHL®, PsycINFO®, Web of Science, and Embase for English-language and human-only studies published from January 1, 1980, to May 24, 2012. Searches were run by an experienced information scientist/Evidence-based Practice Center (EPC) librarian and were peer reviewed by another information scientist/EPC librarian. We manually searched

reference lists of pertinent reviews, included trials, and background articles on this topic to look for any relevant citations that our searches might have missed.

Figure A. Analytic framework for the comparative effectiveness of psychological treatments and pharmacological treatments for adults with PTSD
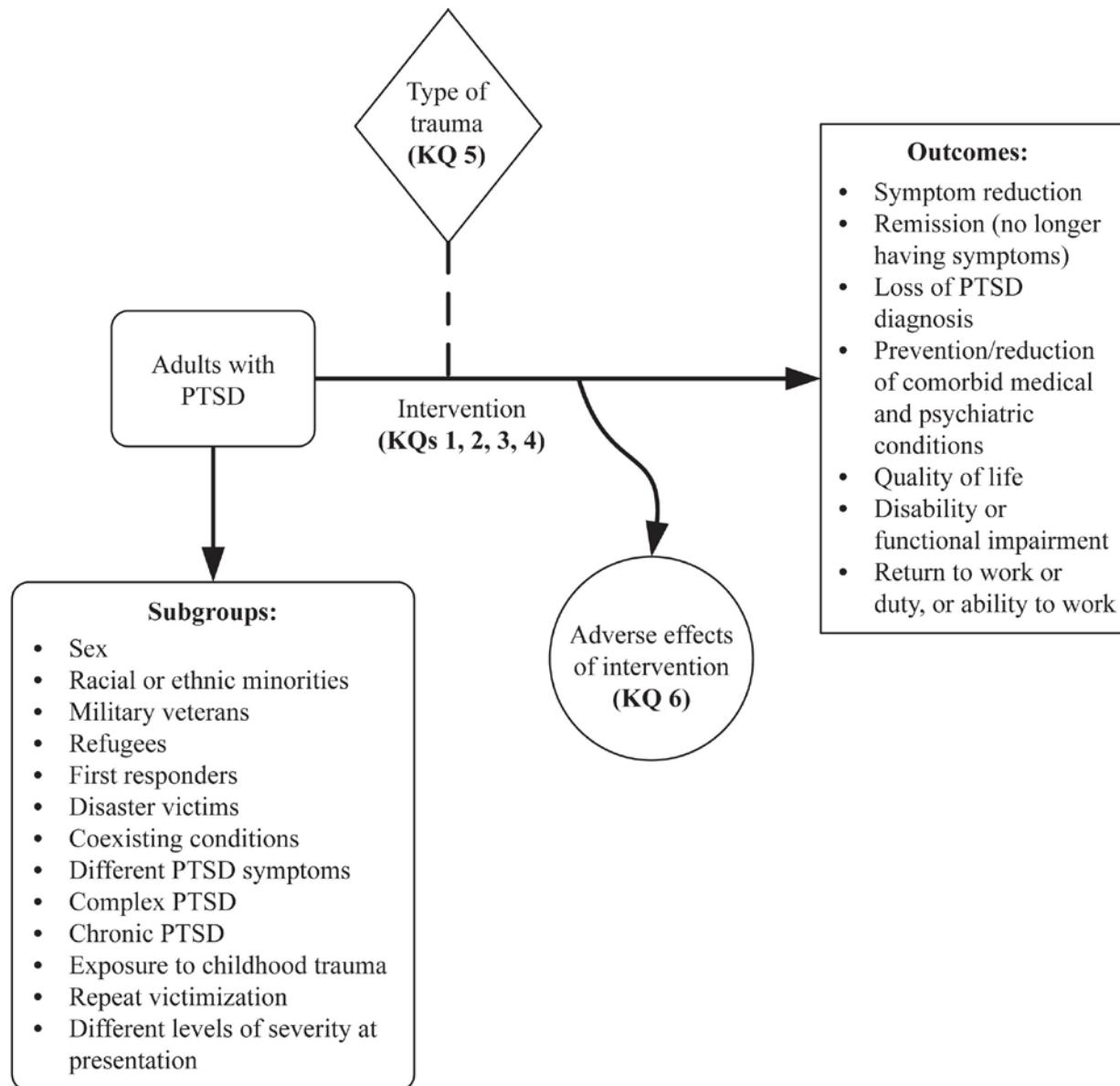
KQ = Key Question; PTSD = posttraumatic stress disorder

We searched for unpublished studies relevant to this review using ClinicalTrials.gov, the Web site for the U.S. Food and Drug Administration, and the World Health Organization's International Clinical Trials Registry Platform.

We developed eligibility (inclusion and exclusion) criteria with respect to PICOTS (populations, interventions, comparators, outcomes, timing, settings), and study designs and durations for each KQ. We included studies enrolling adults with PTSD based on DSM criteria that evaluated one or more of the included psychological or pharmacological interventions

compared with wait list, usual care (as defined by the study), no intervention, placebo, or another psychological or pharmacological intervention. The following psychological treatments were included: brief eclectic psychotherapy; CBT, such as CPT, CT, CR, exposure-based therapies, and coping skills therapies; EMDR; hypnosis or hypnotherapy; interpersonal therapy; and psychodynamic therapy. The following pharmacological treatments were included: SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline), SNRIs (desvenlafaxine, venlafaxine, and duloxetine), other second-generation antidepressants (bupropion, mirtazapine, nefazodone, and trazodone), tricyclic antidepressants (imipramine, amitriptyline, and desipramine), alpha-blockers (prazosin), atypical antipsychotics (olanzapine and risperidone), benzodiazepines (alprazolam, diazepam, lorazepam, and clonazepam), and anticonvulsants/mood stabilizers (topiramate, tiagabine, lamotrigine, carbamazepine, and divalproex).

Studies were required to assess at least one of the following outcomes: PTSD symptoms, remission (no longer having symptoms), loss of PTSD diagnosis, quality of life, disability or functional impairment, return to work or to active duty, or adverse events. Eligible settings included outpatient and inpatient primary care or specialty mental health care settings, community settings (e.g., churches, community health centers, rape crisis centers), and military settings. We included randomized controlled trials (RCTs) of at least 4 weeks in duration for KQs 1 through 5. For KQ 6, on harms, the following were also eligible: nonrandomized controlled trials of any sample size, prospective cohort studies with a sample size of at least 500, and case-control studies with a sample size of at least 500.

Two members of the research team independently reviewed all titles and abstracts (identified through searches) for eligibility against our inclusion/exclusion criteria. Studies marked for possible inclusion by either reviewer were retrieved for full-text review. Two members of the team independently reviewed each full-text article for inclusion or exclusion. If the reviewers disagreed, they resolved conflicts by discussion and consensus or by consulting a third senior member of the team.

We designed and used structured data extraction forms to gather pertinent information from each included article, including characteristics of study populations, settings, interventions, comparators, study designs, methods, and results. We extracted the relevant data from each included article into evidence tables. All data abstractions were reviewed for completeness and accuracy by a second member of the team.

Risk-of-Bias Assessment of Individual Studies

To assess the risk of bias (internal validity) of studies, we used predefined criteria based on the Agency for Healthcare Research and Quality (AHRQ) "Methods Guide for Effectiveness and Comparative Effectiveness Reviews,"[18] rating studies as low, medium, or high risk of bias. Two independent reviewers assessed the risk of bias for each study; one of the two reviewers was always an experienced senior investigator. Disagreements between the two reviewers were resolved by discussion and consensus or by consulting a third member of the team. We excluded studies deemed high risk of bias from our main data synthesis; we included them only in sensitivity analyses.

Data Synthesis

We focused first on assessing which interventions have evidence of efficacy by evaluating placebo-controlled studies for the pharmacotherapies and by evaluating wait list, usual care, or

placebo-controlled studies of the psychotherapies (i.e., studies with an inactive control). Then, we assessed head-to-head trials.

We conducted quantitative synthesis using meta-analyses of outcomes reported by multiple studies that were sufficiently homogeneous to justify combining their results. When quantitative synthesis was not appropriate (e.g., due to clinical heterogeneity, insufficient numbers of similar studies, or insufficiency or variation in outcome reporting), we synthesized the data qualitatively. We used random-effects models to estimate pooled effects.[19] For continuous outcomes (e.g., scales for symptom reduction) measured with the same scale (e.g., Clinician-Administered PTSD Scale [CAPS]), we reported the weighted mean difference (WMD) between intervention and control. When multiple scales were combined in one meta-analysis, we used the standardized mean difference (SMD), Cohen's d. For binary outcomes (e.g., remission, loss of PTSD diagnosis, adverse events), we calculated risk differences between groups. For each meta-analysis, we conducted sensitivity analyses by removing each study from the analysis separately and by adding studies excluded for having high risk of bias. To address differences in efficacy by type of trauma, we performed subgroup analyses of our PTSD symptom reduction meta-analyses, stratifying each analysis by the type of trauma experienced by the study population.

For analyses of the efficacy of psychological interventions, we stratified our meta-analyses by comparison group to show how the effect size and confidence interval would differ if we included only studies with a wait list control, as opposed to including those with both wait list and usual care controls. We included only studies with present-centered therapy, supportive therapy, or supportive counseling control groups in sensitivity analyses.

The chi-squared statistic and the I^2 statistic were calculated to assess statistical heterogeneity in effects between studies.[20,21] We examined potential sources of heterogeneity by analysis of subgroups defined by patient population and variation in interventions or controls. Heterogeneity was also explored through sensitivity analyses. Quantitative pairwise meta-analyses were conducted using Stata® version 11.1.

We conducted a network meta-analysis using Bayesian methods[22] to compare pharmacological interventions with one another for their efficacy in improving PTSD symptoms. The analysis included both head-to-head and placebo-controlled trials. We used a random-effects logistic regression model that adjusted for correlations between arms within each study. Our outcome was the mean change from baseline to endpoint in CAPS total score. The network meta-analyses were performed using WinBUGS Version 1.4.3, a Bayesian software package that uses Markov chain Monte Carlo methods.

Strength of the Body of Evidence

We graded the strength of evidence (SOE) as high, moderate, low, or insufficient based on established guidance.[23] This approach incorporates four key domains: risk of bias (which includes study design and aggregate quality), consistency, directness, and precision of the evidence. It also considers other optional domains. Two reviewers assessed each domain for each key outcome and resolved differences by consensus. For each assessment, one of the two reviewers was always an experienced senior investigator. The overall grade was based on a qualitative decision. We graded the SOE for the following outcomes: PTSD symptom reduction, remission, loss of diagnosis, prevention or reduction of comorbid medical or psychiatric conditions, quality of life, disability or functional impairment, return to work or to active duty, and adverse events.

Applicability

We assessed applicability of the evidence following guidance from the "Methods Guide for Effectiveness and Comparative Effectiveness Reviews."[24] We used the PICOTS framework to explore factors that affect applicability.

Results

We included 101 published articles reporting on 92 studies (Figure B). Of the included studies, all were RCTs. Below we summarize the main findings for each KQ by treatment and outcome, and report the SOE for each.

Figure B. Disposition of articles

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┌──────────────────────────────────────────┐
│ # of records identified through database  │
│ searching:                                │
│              21,647                        │
│                                            │
│ Medline®: 1,446                            │
│ IPA, CINAHL®, PsycINFO®: 17,669            │
│ Embase: 353                                │
│ Cochrane Library: 442                      │
│ Web of Science: 1,067                      │
│ PILOTS: 670                                │
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┌──────────────────────────────────────────┐
│ # of additional records identified        │
│ through other sources:                     │
│                67                          │
│                                            │
│ Hand searches of references: 64            │
│ SIPS: 3 publications                       │
└──────────────────────────────────────────┘
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┌──────────────────────────────────────────┐
│ Total # of records after duplicates       │
│ removed:                                   │
│             3,048                          │
└──────────────────────────────────────────┘
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┌──────────────────────────────┐      ┌──────────────────────────┐
│ # of records screened:       │─────▶│ # of records excluded:   │
│           3,048              │      │         2,521            │
└──────────────────────────────┘      └──────────────────────────┘
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┌──────────────────────────────┐      ┌──────────────────────────────────────┐
│ # of full-text articles      │      │ # of full-text articles excluded,     │
│ assessed for eligibility:    │─────▶│ with reasons:                         │
│            527               │      │            380                        │
│                              │      │                                       │
│                              │      │ Wrong study design: 131               │
│                              │      │ No original data: 79                  │
│                              │      │ Wrong PICOTS: 170                     │
└──────────────────────────────┘      └──────────────────────────────────────┘
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                                      ┌──────────────────────────┐
                                      │ High risk of bias:       │
                                 ────▶│         46               │
                                      └──────────────────────────┘
┌──────────────────────────────────┐
│ # of studies (articles) included │          Eligible only for
│ in qualitative synthesis of       │             sensitivity
│ systematic review:                │              analyses
│           92 (101)                │
└──────────────────────────────────┘
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┌──────────────────────────────────────┐
│ # of studies included in quantitative │
│ synthesis of systematic review:       │
│              77ᵃ                       │
└──────────────────────────────────────┘
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PICOTS = populations, interventions, comparators, outcomes, timing, settings; SIPS = scientific information packets
[a]Our main quantitative syntheses included 77 studies with low or medium risk of bias. This total does not include studies with high risk of bias, used only in sensitivity analyses.

Key Question 1. Psychological Treatments

Among the psychological treatments, the strongest evidence of efficacy for improving PTSD symptoms and achieving loss of PTSD diagnosis was for exposure-based therapy (high and moderate SOE, respectively). Evidence of moderate strength also supports the efficacy of CPT, CT, CBT-mixed therapies, EMDR, and narrative exposure therapy for improving PTSD symptoms and/or achieving loss of PTSD diagnosis.

Effect sizes were generally large for psychological treatments, with moderate SOE supporting efficacy for improving PTSD symptoms (e.g., 28.9-point reduction in CAPS and Cohen's d 1.27 for exposure-based therapies), and numbers needed to treat (NNTs) were less than or equal to 4 to achieve one loss of PTSD diagnosis for CPT, CT, exposure, CBT-mixed, and EMDR. Table B summarizes the main findings and SOE for the psychological treatments with evidence of efficacy for the most commonly reported outcomes: PTSD symptoms, loss of PTSD diagnosis, and depression symptoms.

Evidence was insufficient to determine efficacy for achieving remission for any psychological treatments except CBT-mixed treatments (moderate SOE) because trials typically did not report remission as an outcome. Similarly, evidence for improving other outcomes of interest—anxiety symptoms, quality of life, disability or functional impairment, or return to work or active duty—was generally insufficient (often with no trials reporting those outcomes). A few exceptions emerged: some evidence supported efficacy of CT for improving anxiety symptoms and disability (moderate SOE), efficacy of CBT-mixed treatments and brief eclectic psychotherapy for improving anxiety symptoms (low SOE), efficacy of CBT-mixed treatments for improving disability and functional impairment (low SOE), and efficacy of brief eclectic psychotherapy for improving return to work (low SOE).

Most of the direct head-to-head comparative evidence was insufficient to determine whether psychotherapies differ in effectiveness, with a few exceptions. Evidence of moderate strength supports greater effectiveness (1) for exposure therapy than for relaxation for achieving loss of PTSD diagnosis and improving depression symptoms and (2) for CBT-mixed therapies than for relaxation for improving PTSD symptoms. Evidence of moderate strength also supports similar effectiveness for (1) exposure and exposure plus CR for achieving loss of PTSD diagnosis and (2) seeking safety and active controls (e.g., relapse prevention programs) for PTSD symptom reduction. Table C summarizes the available head-to-head comparative evidence and SOE for improving PTSD symptoms, achieving loss of PTSD diagnosis, and improving depression symptoms (the outcomes most commonly reported). Evidence was insufficient for other outcomes of interest, usually because no trials making the comparison reported those outcomes.

Table B. Summary of findings and strength of evidence for efficacy of psychological treatments for improving PTSD symptoms, achieving loss of PTSD diagnosis, and improving depression symptoms

Intervention	Outcome	Results Effect Size (95% CI)[a]	Strength of Evidence
CPT	PTSD symptoms	SMD, -1.40 (-1.95 to -0.85; 4 trials, N=299) WMD. -32.2 (-46.3 to -18.05;4 trials, N=299)	Moderate
	Loss of diagnosis	0.44 (0.26 to 0.62; 4 trials, N=299); NNT, 3	Moderate
	Depression symptoms	WMD, -10.7 (-16.5 to -4.9; 4 trials, N=299)	Moderate
CT[b]	PTSD symptoms	SMD, -1.22 (-1.91 to -0.53; 3 trials, N=221)	Moderate
	Loss of diagnosis	0.51 (0.24 to 0.78; 3 trials, N=221); NNT, 2	Moderate
	Depression symptoms	SMD, -0.91 (-1.20 to -0.62; 3 trials, N=221)	Moderate
CBT-Exposure	PTSD symptoms	SMD, -1.27 (-1.54 to -1.00; 7 trials, N=387) WMD, -28.9 (-35.5 to -22.3; 4 trials, N=212)	High
	Loss of diagnosis	0.66 (0.42 to 0.91; 3 trials, N=197); NNT, 2	Moderate
	Depression symptoms	WMD, -8.2 (-10.3 to -6.1; 6 trials, N=363)	High
CBT-Mixed	PTSD symptoms	SMD, -1.09 (-1.4 to -0.78; 14 trials, N=825) WMD, -31.1 (-42.6 to -19.6; 8 trials, N=476)	Moderate
	Loss of diagnosis	0.26 (0.11 to 0.41; 6 trials, N=290); NNT, 4	Moderate
	Depression symptoms	WMD, -10.4 (-14.4 to -6.4; 10 trials, N=662)	Moderate
EMDR	PTSD symptoms	SMD, -1.08 (-1.83 to -0.33; 4 trials, N=117)	Low
	Loss of diagnosis	0.64 (0.46 to 0.81; 3 trials, N=95); NNT, 2	Moderate
	Depression symptoms	SMD, -1.13 (-1.52 to -0.74; 4 trials, N=117)	Moderate
Narrative Exposure Therapy	PTSD symptoms	SMD, -1.25 (-1.92 to -0.58; 3 trials, N=227) PDS WMD, -10.2 (-13.1 to -7.4; 3 trials, N=227)	Moderate
	Loss of diagnosis	0.15 (0.01 to 0.30; 3 trials, N=227)	Low
	Depression symptoms	Mixed evidence; 1 trial reported efficacy and 1 reported no difference from comparators; 2 trials, N=75	Insufficient
Brief Eclectic Psychotherapy	PTSD symptoms	Likely small to medium effect size (3 trials, N=96)	Low
	Loss of diagnosis	RD ranged from 0.125 to 0.58 across trials (3 trials, N=96)	Low
	Depression symptoms	3 trials (N=96) found benefits; wide range of effect sizes in the 2 trials reporting sufficient data, from medium to very large	Low

BDI = Beck Depression Inventory; CAPS = Clinician-Administered PTSD Scale; CBT = cognitive behavioral therapy; CI = confidence interval; CPT = cognitive processing therapy; CT = cognitive therapy; EMDR = eye movement desensitization and reprocessing; N = number of subjects; NNT = number needed to treat; PDS = Posttraumatic Diagnostic Scale; PTSD = posttraumatic stress disorder; RD = risk difference; SMD = standardized mean difference; WMD = weighted mean difference
[a]WMD data for PTSD symptoms are mean change from baseline (95% CI, number of trials and number of subjects contributing data) in CAPS score compared with inactive comparators unless another outcome measure is specified; SMD data are Cohen's d—effect sizes. A small effect size is d=0.20, medium effect size is d=0.50, and large effect size is d=0.80.[c] Baseline PTSD severity was generally in the severe (CAPS of 60–79) or extreme (CAPS ≥80) range across the included trials. Using CAPS, PTSD severity has been categorized as asymptomatic/few symptoms (0–19), mild PTSD/subthreshold (20–39), moderate PTSD/threshold (40–59), severe, and extreme.[d] Data for loss of diagnosis are risk difference for treatment compared with inactive comparators unless otherwise specified. WMD data for depression symptoms are mean change from baseline in BDI score compared with inactive comparators unless another outcome measure is specified. SMD data for depression symptoms are Cohen's d.
[b]For the purposes of summarizing results and conclusions, the cognitive therapy category here summarizes evidence from the cognitive therapy studies that were not specifically cognitive processing therapy.
[c]Source: Cohen J. Statistical Power Analysis for the Behavioral Sciences. Hillsdale, NJ: L. Erlbaum Associates; 1988.
[d]Source: Weathers FW, Keane TM, Davidson JRT. Clinician-administered PTSD scale: a review of the first ten years of research. Depress Anxiety. 2001;13(3):132-56.

Table C. Summary of findings and strength of evidence for comparative effectiveness of psychological treatments for improving PTSD symptoms, achieving loss of PTSD diagnosis, and improving depression symptoms

Comparison	Outcome	Results Effect Size (95% CI)[a]	Strength of Evidence
CR vs. Relaxation	PTSD symptoms	50% vs. 20% of subjects improved, p=0.04, 1 trial, N=34	Insufficient
	Loss of diagnosis	65% vs. 55% of subjects, p=NS, 1 trial, N=34	Insufficient
	Depression symptoms	BDI (mean improvement): 7 (3 to 11) vs. 17 (11 to 22), 1 trial, N=34	Insufficient
CT vs. Exposure	PTSD symptoms	WMD, 4.8 (-4.5 to 14.2; 2 trials, N=100)	Insufficient
	Loss of diagnosis	RD, 0.13 (-0.06 to 0.32; 2 trials, N=100)	Insufficient
	Depression symptoms	WMD, 2.75 (-1.94 to 7.43; 2 trials, N=100)	Insufficient
Exposure vs. CPT	PTSD symptoms	WMD, 3.97 (-5.95 to 13.9; 1 trial, N=124)	Insufficient
	Loss of diagnosis	0.00 (-0.18 to 0.18; 1 trial, N=124)	Insufficient
	Depression symptoms	WMD, 2.94 (-0.75 to 6.63; 1 trial, N=124)	Insufficient
Exposure vs. Relaxation	PTSD symptoms	WMD, -9.7 (-22.3 to 2.9; 2 trials, N=85)	Insufficient
	Loss of diagnosis	Favors exposure: RD, 0.31 (0.04 to 0.58; 2 trials, N=85)	Moderate
	Depression symptoms	WMD, -5.5 (-10.2 to -0.79; 2 trials, N=85)	Moderate
Exposure vs. SIT	PTSD symptoms	SMD, -0.14 (-0.69 to 0.41; 1 trial, N=51)	Insufficient
	Loss of diagnosis	RD, 0.18 (-0.09 to 0.45; 1 trial, N=51)	Insufficient
	Depression symptoms	WMD, -0.15 (-5.8 to 5.5; 1 trial, N=51)	Insufficient
Relaxation vs. EMDR	PTSD symptoms	SMD, -0.57 (-1.4 to 0.29; 2 trials, N=64)	Insufficient
	Loss of diagnosis	0.34 (-0.04 to 0.72; 2 trials, N=64)	Insufficient
	Depression symptoms	Conflicting findings (2 trials, N=64)	Insufficient
Relaxation vs. CBT-M	PTSD symptoms	Favors CBT-M (2 trials, N=85)[b]	Moderate
	Loss of diagnosis	No included studies reported the outcome	Insufficient
	Depression symptoms	No included studies reported the outcome	Insufficient
Exposure vs. EMDR	PTSD symptoms	No difference found (2 trials, N=91)	Insufficient
	Loss of diagnosis	Both trials favor exposure, but meta-analysis did not find a statistically significant difference and results were imprecise: RD, 0.14 (-0.01 to 0.29; 2 trials, N=91)	Insufficient
	Depression symptoms	No difference (2 trials, N=91)	Insufficient
Exposure vs. Exposure Plus CR	PTSD symptoms	SMD, 0.25 (-0.29 to 0.80; 3 trials, N=259)	Insufficient
	Loss of diagnosis	Similar benefits: RD, -0.01 (-0.17 to 0.14; 3 trials, N=259)	Moderate
	Depression symptoms	WMD, 2.78 (-1.68 to 7.25; 4 trials, N=299)	Insufficient
Brief Eclectic Psychotherapy vs. EMDR	PTSD symptoms	1 trial (N=140) reported more rapid improvement with EMDR but no difference after completion of treatment	Insufficient
	Loss of diagnosis	1 trial (N=140) reported more rapid improvement with EMDR but no difference after completion of treatment	Insufficient
	Depression symptoms	1 trial (N=140) reported more rapid improvement with EMDR but no difference after completion of treatment	Insufficient
Seeking Safety vs. Active Controls[c]	PTSD symptoms	SMD, 0.04 (-0.12 to 0.20; 4 trials, N=594) WMD, 1.45 (-2.5 to 5.4; 3 trials, N=477)	Moderate
	Loss of diagnosis	OR, 1.22 (0.48 to 3.13; 1 trial, N=49)	Insufficient
	Depression symptoms	No trials	Insufficient

BDI = Beck Depression Inventory; CAPS = Clinician-Administered PTSD Scale; CBT-M = cognitive behavioral therapy-mixed; CI = confidence interval; CPT = cognitive processing therapy; CR = cognitive restructuring; CT = cognitive therapy; EMDR = eye movement desensitization and reprocessing; N = number of subjects; NS = not statistically significant; OR = odds ratio; PTSD = posttraumatic stress disorder; RD = risk difference; SIT = stress inoculation training; SMD = standardized mean difference; VA = Department of Veterans Affairs; WMD = weighted mean difference

[a]For PTSD symptoms, WMD data are mean change from baseline (95% CI, number of trials and number of subjects contributing data) in CAPS score compared with inactive comparators unless another outcome measure is specified; SMD data are Cohen's d—effect sizes. Baseline PTSD severity was generally in the severe (CAPS of 60–79) or extreme (CAPS ≥80) range across the

included trials. Using CAPS, PTSD severity has been categorized as asymptomatic/few symptoms (0–19), mild PTSD/subthreshold (20–39), moderate PTSD/threshold (40–59), severe, and extreme.[d] For loss of diagnosis, data are risk difference (95% CI, number of trials and number of subjects contributing data) for the comparison between the 2 therapies unless otherwise specified. For depression symptoms, WMD data are between-group difference for mean change from baseline in BDI score unless another outcome measure is specified. SMD data for depression symptoms are Cohen's d.

[b]Mean CAPS improvement: 38 (95% CI, 26 to 50) vs. 14 (95% CI, 4 to 25) in 1 trial[e] between-group effect size was very large favoring CBT-M (Cohen's d=1.6) in another.[f]

[c]Active controls were relapse prevention, psychoeducation, and treatment as usual in a VA substance use disorders clinic.

[d]Source: Weathers FW, Keane TM, Davidson JRT. Clinician-administered PTSD scale: a review of the first ten years of research. Depress Anxiety. 2001;13(3):132-56.

[e]Source: Marks I, Lovell K, Noshirvani H, et al. Treatment of posttraumatic stress disorder by exposure and/or cognitive restructuring: a controlled study. Arch Gen Psychiatry. 1998 Apr;55(4):317-25. PMID: 9554427.

[f]Source: Hinton DE, Hofmann SG, Rivera E, et al. Culturally adapted CBT (CA-CBT) for Latino women with treatment-resistant PTSD: a pilot study comparing CA-CBT to applied muscle relaxation. Behav Res Ther. 2011 Apr;49(4):275-80. PMID: 21333272.

Note: Table includes rows only for comparisons with any available trials. We found no low or medium risk-of-bias trials making other head-to-head comparisons.

Key Question 2. Pharmacological Treatments

Among pharmacological treatments, we found evidence of moderate strength supporting the efficacy of fluoxetine, paroxetine, sertraline, topiramate, and venlafaxine for improving PTSD symptoms. Risperidone may also have some benefit for reduction of PTSD symptoms (low SOE). Evidence was insufficient to determine whether other medications are efficacious for improving PTSD symptoms. For most of the medications with evidence of efficacy, the mean size of the effect for improving symptoms was small or medium; mean change from baseline in CAPS compared with placebo ranged from -4.9 to -15.5 for the medications with moderate SOE. However, paroxetine and venlafaxine also had evidence of efficacy for inducing remission, with NNTs of ~8 (moderate SOE).

Table D summarizes the main findings and SOE for the pharmacological treatments with evidence of efficacy for the outcomes most commonly reported: PTSD symptoms, remission, and depression symptoms. Unlike the studies of psychological treatments, which often reported loss of PTSD diagnosis as an outcome, evidence in these studies was insufficient to determine efficacy for achieving loss of PTSD diagnosis for any of the pharmacological treatments because studies generally did not report it as an outcome. Similarly, evidence for improving other outcomes of interest was usually insufficient (often with no trials reporting those outcomes). There were a few exceptions, with evidence supporting efficacy of fluoxetine for improving anxiety symptoms (moderate SOE), efficacy of venlafaxine for improving quality of life (moderate SOE), and efficacy of venlafaxine and paroxetine for improving functional impairment for adults with PTSD (moderate SOE).

Little direct comparative evidence (i.e., head-to-head) was available to determine whether pharmacological treatments differ in effectiveness. We identified just three trials meeting inclusion criteria. Of those, just one compared medications that have evidence supporting their efficacy: it compared 12 weeks of venlafaxine, sertraline, and placebo in 538 subjects with a variety of index trauma types.[25] While the point estimate suggested a greater improvement in PTSD symptoms with venlafaxine compared with sertraline, there was no statistically significant difference between the two groups.

Table D. Summary of findings and strength of evidence for efficacy of pharmacological treatments for improving PTSD symptoms, achieving remission, and improving depression symptoms

Medication Class	Medication	Outcome	Results Effect Size (95% CI)[a]	Strength of Evidence
Anti-convulsant	Topiramate	PTSD symptoms	WMD, -15.5 (-19.4 to -11.7; 3 trials, N=142) SMD, -0.96 (-1.89 to -0.03; N=142)	Moderate
		Remission	42% vs. 21%, p=0.295 (1 trial, N=40)	Insufficient
		Depression symptoms	BDI, -8.5 vs. -3.9, p=0.72 (1 trial, N=35) HAMD, -50.7% vs. -33.3%, p=0.253 (1 trial, N=40)	Insufficient
Anti-psychotic	Risperidone	PTSD symptoms	WMD, -4.60 (-9.0 to -0.2; 4 trials, N=419) SMD, -0.26 (-0.52 to -0.00; 4 trials, N=419)	Low
		Remission	No included studies reported the outcome	Insufficient
		Depression symptoms	HAMD, -3.7 vs. -1.4, p >0.05 (1 trial, N=65)	Insufficient
SNRI	Venlafaxine ER	PTSD symptoms	WMD, -7.2 (-11.0 to -3.3; 2 trials, N=687) SMD, -0.28 (-0.43 to -0.13; 2 trials, N=687)	Moderate
		Remission	RD, 0.12 (0.05 to 0.19; 2 trials, N=687); NNT, 9	Moderate
		Depression symptoms	HAMD WMD, -2.08 (-3.12 to -1.04; 2 trials, N=687)	Moderate
SSRI	Fluoxetine	PTSD symptoms	WMD, -6.97 (-10.4 to -3.5; 4 trials, N=835) SMD, -0.31 (-0.44 to -0.17; 5 trials, N=889)	Moderate
		Remission	13% vs. 10%, p=0.72 (1 trial, N=52)	Insufficient
		Depression symptoms	MADRS WMD, -2.4 (-3.7 to -1.1; 2 trials, N=712) SMD, -0.20 (-0.40 to -0.00; 3 trials, N=771)	Moderate
SSRI	Paroxetine	PTSD symptoms	WMD, -12.6 (-15.7 to -9.5; 2 trials, N=886) SMD, -0.49 (-0.61 to -0.37; 2 trials, N=886)	Moderate
		Remission	0.129 (p=0.008; 2 trials, N=346); NNT, 8[b]	Moderate
		Depression symptoms	MADRS WMD, -5.7 (-7.1 to -4.3; 2 trials, N=886) SMD, -0.49 (-0.64 to -0.34; 2 trials, N=886)	Moderate
SSRI	Sertraline	PTSD symptoms	WMD, -4.9 (-7.4 to -2.4; 7 trials, N=1,085) SMD, -0.25 (-0.42 to -0.07; 8 trials, N=1,155)	Moderate
		Remission	24.3% vs. 19.6%, p=NS (NR) (1 trial, N=352)	Insufficient
		Depression symptoms	HAMD WMD, -0.77 (-2.1 to 0.55; 5 trials, N=1,010) SMD, -0.13 (-0.32 to 0.06; 7 trials, N=1,085)	Low

BDI = Beck Depression Inventory; CAPS = Clinician-Administered PTSD Scale; CAPS-2 = Clinician-Administered PTSD Scale Part 2; CI = confidence interval; ER = extended release; HAMD = Hamilton Depression Rating Scale; MADRS = Montgomery-Åsberg Depression Rating Scale; N = number of subjects; NNT = number needed to treat; NR = not reported; NS = not statistically significant; PTSD = posttraumatic stress disorder; RD = risk difference (for medication compared with placebo); SMD = standardized mean difference; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; WMD = weighted mean difference

[a]For PTSD symptoms, WMD data are mean change from baseline (95% CI, number of trials and number of subjects contributing data) in CAPS score compared with placebo. Baseline PTSD severity was generally in the severe (CAPS of 60–79) or extreme (CAPS ≥80) range across the included trials. Using CAPS, PTSD severity has been categorized as asymptomatic/few symptoms (0–19), mild PTSD/subthreshold (20–39), moderate PTSD/threshold (40–59), severe, and extreme.[c] SMD data are Cohen's d—effect sizes. A small effect size is d=0.20, medium effect size is d=0.50, and large effect size is d=0.80.[d] For depression symptoms, WMD data are between-group difference for mean change from baseline in BDI, HAMD, or MADRS score—whichever measure is specified.

[b]The best available evidence is from a trial of paroxetine (N=323) that defined remission as a CAPS-2 total score less than 20 and found that a significantly greater proportion of paroxetine-treated subjects achieved remission compared with placebo at week 12 (29.4% vs. 16.5%, p=0.008).[e] The other trial contributing data for this outcome found similar percentages of subjects achieving remission (33% vs. 14%).[f]

[c]Source: Weathers FW, Keane TM, Davidson JRT. Clinician-administered PTSD scale: a review of the first ten years of research. Depress Anxiety. 2001;13(3):132-56.

[d]Source: Cohen J. Statistical Power Analysis for the Behavioral Sciences. Hillsdale, NJ: L. Erlbaum Associates; 1988.

[e]Source: Tucker P, Zaninelli R, Yehuda R, et al. Paroxetine in the treatment of chronic posttraumatic stress disorder: results of a placebo-controlled, flexible-dosage trial. J Clin Psychiatry. 2001 Nov;62(11):860-8. PMID: 11775045.

[f]Source: Simon NM, Connor KM, Lang AJ, et al. Paroxetine CR augmentation for posttraumatic stress disorder refractory to prolonged exposure therapy. J Clin Psychiatry. 2008 Mar;69(3):400-5. PMID: 18348595.

Our network meta-analysis of 28 trials (4,817 subjects) found paroxetine and topiramate to be more effective for reducing PTSD symptoms than most other medications included in the analysis (low SOE). When compared with medications with at least moderate SOE supporting efficacy, paroxetine was more effective than sertraline (WMD, -7.6; 95% credible interval [CrI], -12 to -2.8), but was not significantly different from the others (low SOE). When compared with medications with moderate SOE supporting efficacy, topiramate was more effective than fluoxetine (WMD, 8.6; 95% CrI, 2.4 to 14.9), sertraline (WMD, 11; 95% CrI, 5.7 to 16.6), and venlafaxine (WMD, -8.8; 95% CrI, -15 to -2.5) but was not significantly different from paroxetine (low SOE).

Key Question 3. Psychotherapy Compared With Pharmacotherapy

We found just one trial (N=88) meeting inclusion criteria that directly compared a psychological treatment with a pharmacological treatment. It compared EMDR, fluoxetine, and placebo.[26] The trial found that EMDR- and fluoxetine-treated subjects had similar improvements in PTSD symptoms, rates of remission, and loss of PTSD diagnosis at the end of treatment. At 6-month followup, those treated with EMDR had higher remission rates and greater reductions in depression symptoms than those who received fluoxetine. We concluded that the head-to-head evidence was insufficient to draw any firm conclusions about comparative effectiveness, primarily due to unknown consistency (with data from just one study) and lack of precision.

Key Question 4. Combinations of Psychological Treatments and Pharmacological Treatments Compared With Either One Alone

Two trials provided limited information related to this KQ.[27,28] The most relevant trial (N=37) found greater improvement in PTSD symptoms (CAPS, -51.1 vs. -29.8; p = 0.01) and greater likelihood of remission for those treated with both prolonged exposure and paroxetine than for those treated with prolonged exposure plus placebo.[27] Evidence was limited by unknown consistency (single trial), attrition, and lack of precision. Overall, evidence was insufficient to determine whether combinations of psychological treatments and pharmacological treatments are better than either one alone when initiating treatment.

Key Question 5. Victims of Particular Types of Trauma

Overall, evidence was insufficient to make definitive conclusions about whether any treatment approaches are more effective for victims of particular types of trauma. Analyses were generally not powered to detect anything but large differences. Also, many factors other than trauma type varied across the studies included in our subgroup analyses. Findings should be considered hypothesis generating. Most of the subgroup analyses (those reported by included studies and those that we conducted of our meta-analyses) found similar benefits for victims of different trauma types.

Key Question 6. Adverse Effects of Treatments

Overall, evidence was insufficient to determine comparative rates of adverse events for various interventions. For psychological treatments, the vast majority of studies reported no information about adverse effects. With such a small proportion of trials reporting data, evidence

was insufficient to draw conclusions about withdrawals due to adverse events, mortality, suicide, suicidal ideation, self-harmful behaviors, or other specific adverse events.

For pharmacological treatments, very few studies reported any information about mortality, suicide, suicidal ideation, or self-harmful behaviors (insufficient SOE). For *most* other adverse effects, risk of bias of included studies, inconsistency or unknown consistency, and lack of precision all contributed to the insufficient SOE determinations. Study durations ranged from 8 to 24 weeks and were generally not designed to assess adverse events. Adverse events were often not collected using standardized measures, and methods for systematically capturing adverse events often were not reported.

Focusing on the medications with moderate SOE supporting efficacy—topiramate, venlafaxine, fluoxetine, paroxetine, and sertraline—most of the evidence was insufficient to determine whether risks were increased, often primarily due to lack of precision. For withdrawals due to adverse events, we found similar rates (within 1 percent to 2 percent) for subjects treated with fluoxetine, sertraline, and venlafaxine compared with those who received placebo (low SOE). We found a 4-percent higher rate of withdrawals due to adverse events with paroxetine than with placebo (moderate SOE). For most of the specific adverse events, point estimates favored placebo (more adverse events with medications), but differences were not statistically significant. We found a small increase (~5 percent) in the risk of nausea for fluoxetine (low SOE); an increase (of 10 percent to 13 percent) in the risk of nausea, dry mouth, and somnolence for paroxetine (low SOE); between 7 percent and 12 percent increases in the risk of nausea, diarrhea, fatigue, and decreased appetite for sertraline (moderate SOE); and an increased risk (of 6 percent to 10 percent) of nausea, dry mouth, and dizziness for subjects treated with venlafaxine compared with those who received placebo (moderate SOE). Evidence suggests no difference in risk of headache or somnolence between subjects treated with venlafaxine compared with those who received placebo (low SOE). Findings were insufficient to determine whether the risks of other adverse events are increased.

Discussion

Existing guidelines and systematic reviews agree that some psychological therapies are effective treatments for adults with PTSD.[2,12-15,17] Our findings support this assertion in that we found evidence to support the efficacy of several psychological treatments for adults with PTSD. Further, we found that exposure therapy was the only treatment with high SOE supporting its efficacy (based primarily on studies of prolonged exposure).

Most guidelines and systematic reviews (with the exception of the IOM report[2]) recognize some benefit of pharmacological treatments. Our findings support this assertion. We found evidence of moderate strength supporting the efficacy of fluoxetine, paroxetine, sertraline, topiramate, and venlafaxine.

Some guidelines identify psychological treatments over pharmacological treatments as the preferred first step and view medications as an adjunct or a next-line treatment.[12-14,17] We found insufficient direct evidence (from head-to-head trials) to support this approach. Indirect evidence suggests that psychological treatments are more effective than pharmacological ones because effect sizes for reduction of PTSD symptoms are much larger in trials of the efficacious psychological treatments. However, conclusions based on naive indirect comparisons can be flawed, primarily because it is difficult to determine the similarity of populations across two somewhat different bodies of literature (i.e., studies of psychological treatments and those of pharmacological treatments).

Although patients enrolled in trials of psychological and pharmacological treatments had similar average ages and similar baseline PTSD severity, different types of patients may have been recruited for studies or may have been willing to be enrolled in studies of psychological treatments than for studies of medications. For example, it was often hard to determine how many previous treatments subjects had not responded to, and studies of medications may have enrolled more "treatment-resistant" subjects. Further, the study designs used for pharmacological treatments could be considered more rigorous in some ways (e.g., generally with masking of patients, providers, and outcome assessors) than those of psychological treatments (e.g., generally with no masking of patients or providers). Thus, further studies are needed to confirm or refute whether psychological treatments are truly more effective first-line treatments.

Although the evidence supports the efficacy of several types of psychological and pharmacological treatments for PTSD, clinical uncertainty exists about what treatment to select for individual patients. Practical considerations, such as presence or lack of availability of psychological treatments and patient preferences, may guide treatment decisions.[15] If numerous treatments are available and patients do not have a preference for a particular type of treatment, decisionmaking in the absence of direct evidence from head-to-head trials can be challenging. Nevertheless, choices must be made for patients who need treatment. Given the findings, the magnitude of benefit and SOE found for exposure therapy support its use as a first-line treatment for PTSD. However, other factors must be considered in selecting a treatment for PTSD, including patient preference, access to treatment, and clinical judgment about the appropriateness of an intervention. For example, a majority of the studies reviewed in this report excluded patients with presenting issues such as substance dependence or suicidality. (See the Applicability section in the Discussion chapter of the full report for additional details on the proportion of studies with various exclusion criteria.) Most clinicians would agree that stabilization of these issues should occur before initiating trauma-focused therapy.

If one decides to pursue treatment with a medication, paroxetine and venlafaxine may have the best evidence supporting their efficacy. Unlike the other medications with evidence of efficacy for improving PTSD symptoms, they both also have evidence of efficacy for achieving remission, with NNTs ~8 to achieve one remission. In addition, paroxetine has evidence supporting its efficacy for improving depression symptoms and functional impairment (moderate SOE); and venlafaxine has evidence supporting its efficacy for improving depression symptoms, quality of life, and functional impairment (moderate SOE). Further, our network meta-analysis found paroxetine to be one of the best treatments.

Our results are based on studies we rated low or medium for risk of bias. To determine whether this influenced conclusions, we conducted sensitivity analyses by adding studies rated as high risk of bias. These sensitivity analyses did not produce significantly different results for our pairwise meta-analyses; point estimates and confidence intervals were generally very similar, and the sensitivity analyses did not alter any of our main conclusions.

Further, it does not appear that any particular types of studies were more likely to be excluded. For example, the proportions of included studies and excluded studies that focused on combat-related trauma or veterans were similar.

Applicability

The included studies assessing efficacious treatments generally enrolled subjects from outpatient settings who had severe to extreme PTSD symptoms. Most studies included participants with chronic PTSD. However, studies inconsistently reported, and had wide

variation in, the time between incident trauma and trial entry. The mean age of subjects was generally in the 30s to 40s, but some studies enrolled slightly older populations. We found studies of people with a wide range of trauma exposures, and many enrolled a heterogeneous group of subjects with a variety of index trauma types. Evidence was insufficient to determine whether findings are applicable to all those with PTSD or whether they are applicable only to certain groups. Evidence was insufficient to determine whether any treatment approaches are more or less effective for specific subgroups, including victims of particular types of trauma. (See KQ 5.)

We recognize the hypothesis that treatments proven to be effective for adults with PTSD should be applicable to all adults with PTSD, but we did not find evidence to confirm or refute this hypothesis. For example, there was often very little evidence from subjects with combat-related trauma that contributed to assessments of the efficacious treatments, making it difficult to determine with any certainty whether findings are applicable to adults with PTSD from combat-related trauma. None of the included studies of paroxetine or venlafaxine enrolled a population with combat-related trauma. In addition, just one included trial for each of the following treatments focused on combat-related trauma: EMDR (N=35),[29] CBT-mixed (N=45),[30] and topiramate (N=67).[31] For each of the following, two trials focused on combat-related trauma: CPT (total N=119),[32,33] exposure-based therapy (total N=370;[34,35] another study of exposure-based therapy enrolled those with combat- and terror-related PTSD[36]); and fluoxetine (total N=365).[37,38] Three trials assessing sertraline (total N=281) enrolled a majority of subjects with combat-related trauma.[39-41]

Limitations of the Comparative Effectiveness Review Process

The scope of this review was limited to studies that enrolled adults with PTSD. AHRQ has commissioned a separate report focused on children.[42] We did not attempt to review literature on treatments for acute stress disorder or on interventions aimed to *prevent* PTSD for people exposed to trauma. Further, we did not review literature on complementary and alternative medicine treatments.

For KQs 1 through 5, we included RCTs with no sample size limit; we did not allow for inclusion of observational studies because observational studies that compare the effectiveness of various treatments for PTSD have a very high risk of selection bias and confounding. We believe that the results of such studies should not be used to make decisions about efficacy or effectiveness. For KQ 6, focused on harms, we allowed for observational studies to be included if they were prospective cohort studies or case-control studies with a sample size of 500 or greater. We set this criterion for two main reasons: (1) our topic refinement process found a large number of RCTs in this field, and we weighed the tradeoffs between increasing comprehensiveness by reviewing all possible observational studies that present harms information 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. Nevertheless, this approach may have led to the exclusion of some observational studies that could provide useful information.

For harms, it is also possible that useful information could have been provided by studies conducted in other populations (i.e., those without PTSD). For example, many studies of some medications reviewed in this report enrolled patients with depression. Such studies could provide important information about adverse effects of those medications.

Our network meta-analysis used methods that allowed for the inclusion of data from head-to-head and placebo-controlled trials. However, very few head-to-head trials were identified for inclusion. The findings have low SOE, given that they were based primarily on indirect evidence. Indirect comparisons, in general, have to be interpreted cautiously because the validity of results is based on assumptions that cannot be verified, particularly the assumption that study populations were similar. Also, our network meta-analysis was based on a single outcome (reduction of PTSD symptoms as measured by CAPS) and does not capture other important information—for example, that moderate SOE supports the efficacy of paroxetine and venlafaxine for achieving remission (with NNTs of ~8), but evidence is insufficient to determine the efficacy of other medications for achieving remission.

Finally, publication bias and selective reporting are potential limitations.

Limitations of the Evidence Base

The evidence base was inadequate to draw conclusions for many of the questions or subquestions of interest. In particular, we found very few head-to-head studies of treatments. We found too few (and sometimes zero) studies with low or medium risk of bias to determine (1) whether some of the psychological and pharmacological treatments are efficacious or not; (2) comparative effectiveness of most of the treatments; (3) whether treatments differ in effectiveness for specific groups, such as those with different types of trauma; and (4) risk of adverse effects for most treatments.

Many of the trials assessing treatments for adults with PTSD had methodological limitations that introduced some risk of bias. We excluded 46 articles from our main data synthesis because of high risk of bias. High risk of bias was most frequently due to high rates of attrition or differential attrition and inadequate methods used to handle missing data. Another common methodological limitation was the lack of masking of outcome assessors. High attrition rates are not uncommon in studies of psychiatric conditions.[43-45] It is unknown whether the attrition rates were due to the underlying condition—given that some of the key features of PTSD are avoidance, loss of interest, and detachment—or to the treatments (e.g., adverse effects, worsening of symptoms).

The heterogeneity of populations enrolled in the included studies makes it challenging to determine whether findings are applicable to all adults with PTSD or only to certain subgroups (e.g., those with particular trauma types). Many studies enrolled subjects with a wide variety of trauma types (e.g., sexual abuse, nonsexual abuse, combat, motor vehicle accident, natural disaster). We generally found insufficient evidence to determine whether treatments differ in efficacy for specific groups. (See the Applicability section in the Discussion chapter of the full report.)

Reporting of previous treatments and ongoing treatments (i.e., cointerventions) was variable across the included studies. We were often unable to determine whether subjects had received any previous treatments for PTSD and whether they were allowed to continue treatments that might be effective for PTSD during studies.

For many of the treatments, studies did not include any followup after completion of treatment to assess whether benefits were maintained. This was particularly true for the pharmacological treatments because trials generally reported outcomes after 8 to 12 weeks of treatment. In addition, pharmaceutical companies funded the majority of trials assessing medications.

Future Research

We identified numerous gaps in the evidence that future research could address. The full report provides additional details. Key future research that would fill the evidence gaps we identified include comparisons of (1) the psychological treatments with the best evidence of efficacy; (2) the medications with moderate strength of evidence supporting their efficacy (fluoxetine, paroxetine, sertraline, topiramate, and venlafaxine); (3) the psychological and pharmacological treatments with the best evidence of efficacy (e.g., exposure therapy compared with paroxetine); or (4) combinations of the psychological and pharmacological treatments with the best evidence of efficacy compared with either one alone (e.g., exposure plus paroxetine compared with either one alone). Future studies could also evaluate promising therapies that have some evidence suggesting possible efficacy or could evaluate new therapies that may be applicable to broader populations or to specific populations (e.g., those with particular comorbid conditions). Future trials could also include prespecified subgroup analyses to explore differences in effectiveness for specific subgroups, or trials could enroll patients all with the same type of trauma to determine whether treatments are effective for that group. Regarding adverse events, future studies could include validated measures of adverse effects, including assessment of mortality, suicide, suicidal ideation, self-harmful behaviors, and hospitalizations.

Some additional considerations for future research involve methodological improvements. Development of methods to minimize attrition could help to reduce the risk of bias in studies of treatments for adults with PTSD.[46] Also, using best approaches to handling of missing data, such as multiple imputation, could reduce risk of bias. To more completely assess benefits of treatments, studies could include measures of remission and loss of PTSD diagnosis (frequently not reported) in addition to measures of PTSD symptoms (more commonly reported). Also, previous studies rarely assessed adverse effects with adequate rigor. Future studies could include longer followup of subjects, validated measures of adverse events and methods for systematically capturing adverse events, and more complete reporting of adverse events. Moreover, methods to minimize attrition and to obtain more complete followup data will be important to better understand the risk of adverse effects for treatments.

For potential future comparative effectiveness research, perhaps head-to-head trials should be conducted by investigators at clinical equipoise and free of any vested interest in particular treatments. Some of the current literature was conducted by investigators with strong potential conflicts of interest (e.g., developers of a particular treatment).

Conclusions

Several psychological and pharmacological treatments have at least moderate SOE supporting their efficacy for improving outcomes for adults with PTSD. These include exposure-based therapy, CPT, CT, CBT-mixed therapies, EMDR, narrative exposure therapy, fluoxetine, paroxetine, sertraline, topiramate, and venlafaxine. Head-to-head evidence was insufficient to determine the comparative effectiveness of these treatments. For exposure-based therapy, CPT, CT, CBT-mixed therapies, and EMDR, effect sizes for improving PTSD symptoms were large (Cohen's d from 1.08 to 1.40; reduction in CAPS from 28.9 to 32.2), and NNTs to achieve loss of diagnosis were 4 or less. For fluoxetine, paroxetine, sertraline, topiramate, and venlafaxine, effect sizes for improving symptoms were smaller (reduction in CAPS compared with placebo from 4.9 to 15.5). Paroxetine and venlafaxine also had evidence of efficacy for inducing remission, with NNTs of ~8. 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.

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