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Interventions for the Prevention of Posttraumatic Stress Disorder (PTSD) in Adults After Exposure to Psychological Trauma

Executive Summary

Background—The Condition and Preventive Strategies

Posttraumatic stress disorder (PTSD) may develop following exposure to a traumatic event. According to the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders, Text Revision (DSM-IV-TR),[1] the essential feature of PTSD is the development of characteristic symptoms following exposure to an extreme traumatic stressor. The stressor may include having direct personal experience of an event that involves actual or threatened death or serious injury or other threat to one's physical integrity; witnessing an event that involves death, injury, or a threat to the physical integrity of another person; or learning about unexpected or violent death, serious harm, or threat of death or injury experienced by a family member or other close associate. The DSM-IV-TR also requires that the person's subjective response to the event involve intense fear, helplessness, or horror.

Some traumatic events that are directly experienced or to which individuals can be exposed 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.[1] Psychological trauma is common and

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leads to PTSD in a substantial number of adults exposed to trauma. The 1990–1992 National Comorbidity Survey indicated that 60 percent of men and 51 percent of women reported experiencing at least one

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traumatic event in their lifetimes.[2] Shortly after exposure, many people experience some symptoms of PTSD; in most people, those symptoms resolve within several weeks of the trauma. However, in approximately 10 to 20 percent, PTSD symptoms persist and are associated with impairment in functioning.[3] Although approximately 50 percent of those diagnosed with PTSD improve without treatment in 1 year, 10 to 20 percent develop a chronic unremitting course.[4]

The 2000 National Comorbidity Survey–Replication (NCS-R) estimated lifetime prevalence of PTSD among trauma-exposed adults in the United States to be 6.8 percent (9.7% in women and 3.6% in men) and current (12-month) prevalence to be 3.6 percent (5.2% in women and 1.8% in men), or more than 7.7 million American adults per year.[5-7] Some demographic or occupational groups, such as military personnel, are at higher risk of PTSD because of higher rates of exposure to trauma.

Prevention of PTSD can potentially reduce a significant burden of individual and societal suffering. Two different prevention strategies have been used. The first strategy, universal prevention, is to deliver interventions to all people exposed to a trauma, regardless of symptoms or risk of developing PTSD. The second strategy, targeted prevention, is based on the fact that although many people experience some symptoms of PTSD after trauma, only a relatively small percentage develop the psychiatric disorder of PTSD and its associated disability. The goal of targeted prevention is to identify, from among all people exposed to a trauma, those who are at high risk of developing the disorder of PTSD and then intervene only with those at high risk.

Interventions to prevent PTSD involve various psychological and pharmacological approaches; they also include emerging interventions such as approaches from complementary and alternative medicine. These interventions have been used both separately and in combination. Despite evidence that some early interventions, such as debriefing, are not effective for preventing PTSD or might even cause harm, they are still widely used. Such use indicates that uncertainty and controversy still exist within the field about providing an intervention that intuitively seems as if it should help, and that not enough consideration is given to scientific evidence when weighing intervention benefits and harms.

Scope and Key Questions

This review compares the efficacy, effectiveness, and harms of psychological, pharmacological, and emerging interventions to prevent PTSD in adults. We include studies of both universal and targeted prevention. We also address the clinical importance of effect modifiers or subgroup status that may affect the impact of traumatic exposure on specific outcomes; these include sex, comorbidities, refugee status, and military or civilian status.

Our report is limited to adults who had been exposed to a traumatic event and who received an early intervention designed to prevent progression to PTSD within the first 3 months after the trauma.

We approach each Key Question (KQ) by considering the relevant populations, interventions, comparators, outcomes, timing, and settings (PICOTS). In this review, we address the following KQs:

KQ 1: For adults exposed to psychological trauma, what is the efficacy or comparative effectiveness (or both) of early interventions to prevent PTSD or to improve health outcomes?

KQ 2: For adults exposed to psychological trauma, does timing, intensity, or dosage of intervention have an impact on the effectiveness or harms of approaches to prevent PTSD or to improve health outcomes?

KQ 3: For adults exposed to psychological trauma, how does efficacy, effectiveness, or harms of early interventions to prevent PTSD differ for characteristics of traumatic exposure or subpopulations with respect to:

- demographic groups (defined by age, ethnic and racial groups, and sex),
- psychiatric comorbidities, or
- personal risk factors for developing PTSD (e.g., having a diagnosis of acute stress disorder (ASD) vs. not having the diagnosis)?

KQ 4: For adults exposed to psychological trauma, what are the absolute and comparative risks of harms from early interventions to prevent PTSD?

Figure A depicts the analytic framework for the comparative effectiveness of psychological, pharmacological, and emerging interventions for preventing PTSD in adults after exposure to trauma.

Figure A. Analytic framework for comparative effectiveness of interventions to prevent PTSD in adults after exposure to trauma
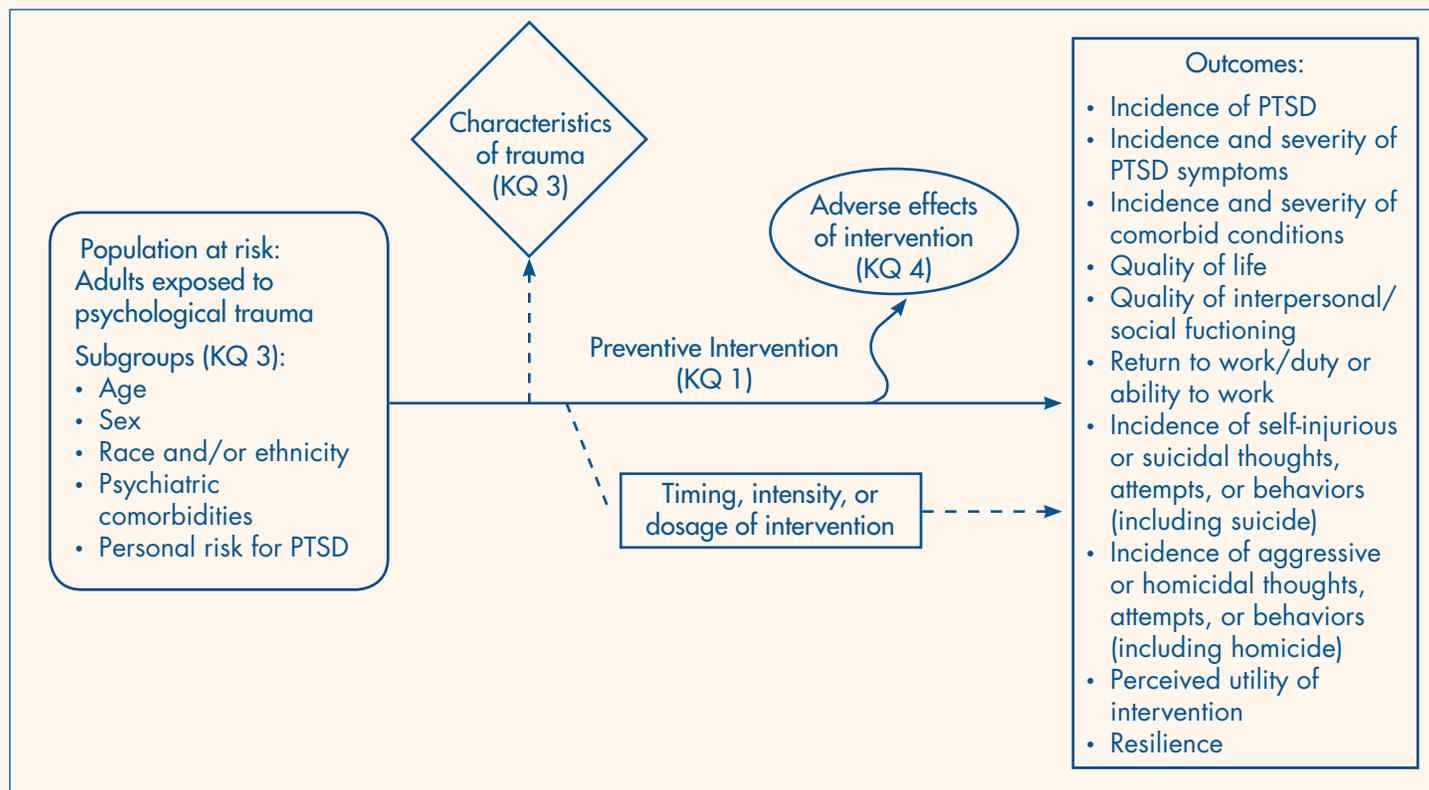
Abbreviations: KQ = Key Question; PTSD = posttraumatic stress disorder.

Methods

Literature Search Strategy

To identify articles relevant to each KQ, we searched PubMed®, CINAHL (Cumulative Index to Nursing and Allied Health Literature), the Cochrane Library, Embase, PILOTS (Published International Literature on Traumatic Stress), International Pharmaceutical Abstracts, PsycINFO®, and Web of Science. We used either Medical Subject Headings (MeSH) or major headings as search terms when available or key words when appropriate, focusing on terms to describe the relevant populations and interventions of interest. We limited the electronic searches to English-language and human-only studies. We searched sources from January 1, 1980, to July 30, 2012. In addition, we manually searched reference lists of pertinent reviews, included trials, and background articles for relevant citations that our searches might have missed. We searched for unpublished studies using ClinicalTrials.gov, the Web site of the U.S. Food and Drug Administration, the World Health Organization's International Clinical Trials Registry Platform, GreyMatters, and OpenGrey.

In addition, the Scientific Resource Center requested scientific information packets from the relevant pharmaceutical companies, asking for any unpublished studies or data relevant for this review.

We developed eligibility criteria with respect to PICOTS and study designs for each KQ. Our population of interest was adults (ages 18 or older) exposed to psychological trauma. We included psychological (e.g., cognitive behavioral therapy, cognitive processing therapy, debriefing), pharmacological (e.g., beta blockers, second-generation antidepressants), and emerging (e.g., yoga, acupuncture) interventions used to prevent PTSD. Both inactive and active comparators of interest were eligible as control interventions. Our outcomes of interest focused on the incidence of PTSD and PTSD-related symptoms; PTSD symptom severity; and quality of life, functional capacity, and other patient-relevant health outcomes. Our subgroups of interest included demographic groups (defined by age, sex, and ethnic or racial groups), populations with psychiatric comorbidities, and populations with different personal risk factors for developing PTSD.

For efficacy and comparative effectiveness, we focused on randomized controlled trials (RCTs) and prospective cohort studies. For assessment of the risk of harms, we also included retrospective controlled cohort studies. For studies to be eligible, the intervention had to be administered within 3 months of the traumatic event.

Two trained members of the research team independently reviewed all titles and abstracts for eligibility against our inclusion/exclusion criteria. We retrieved the full text of all articles included during the title and abstract review phase. If both reviewers agreed that a study did not meet the eligibility criteria, we excluded it. If the reviewers disagreed, conflicts were resolved with a third, senior team member.

Risk-of-Bias Assessment of Individual Studies

To assess the risk of bias (a threat to internal validity) of studies for major outcomes of interest, we used guidance from the AHRQ "Methods Guide for Effectiveness and Comparative Effectiveness Reviews."[8] We assessed selection bias, confounding, performance bias, detection bias, and attrition bias. We included questions about adequacy of randomization, allocation concealment, similarity of groups at baseline, blinding, attrition, whether intention-to-treat (ITT) analysis was used, method of handling dropouts, and treatment fidelity. We rated the studies as low, medium, or high risk of bias. Because our primary outcome of interest was the incidence of PTSD, we adopted a threshold of 20 percent for overall attrition. For outcomes with low event rates, attrition can substantially bias findings.[9]

Two independent reviewers assessed the risk of bias for each study; one of the two reviewers was always an experienced or senior investigator. Disagreements between the two reviewers were resolved by discussion and consensus or by consulting with a third member of the team. If medium or low risk-of-bias studies were available, we omitted from our main analyses studies deemed high risk of bias by two reviewers. Such studies would not have increased the strength of the evidence and the certainty of our conclusions. If we were able to conduct quantitative syntheses, we used high-risk-of-bias studies for sensitivity analyses. In cases in which relevant information was unclear or not reported, we attempted to contact authors to get additional or unpublished information. When successful, we used this information in the findings.

For studies that met inclusion criteria and were of low or medium risk of bias, we extracted important information into evidence tables, which included characteristics of study populations, settings, interventions, comparators, study designs, methods, and results. We did not extract complete data from studies that we rated as high risk of bias.

Data Synthesis

In general, we used a "best evidence" approach to synthesize the available evidence. That is, we prioritized the evidence to emphasize studies that provided the most solid base for conclusions. If we did not find any studies with a low or medium risk of bias rating, we present results of high risk of bias studies. Conversely, if studies with low or medium risk of bias were available, we omitted high risk of bias studies from our syntheses because of the lack of reliability of their findings.

We conducted quantitative syntheses 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., because of 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. For continuous outcomes (e.g., scales for symptom reduction), we used weighted mean differences (WMD). If we had to combine multiple scales in one meta-analysis, we used the standardized mean difference (Cohen's d). For binary outcomes (e.g., incidence of PTSD), we calculated the relative risk (RR) between groups. For each meta-analysis, we conducted sensitivity analyses by adding studies that we rated as high risk of bias. We calculated the chi-squared statistic and the I^2 statistic to assess statistical heterogeneity in effects between studies. Heterogeneity was also explored through sensitivity analyses. Quantitative pairwise meta-analyses were conducted using Stata® version 11.1.

Strength of the Body of Evidence

We graded the strength of evidence (SOE) based on the guidance established for the Evidence-based Practice Center program.[10] 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.

We specified several outcomes a priori (with input from members of a technical expert panel) as important for grading strength of the body of evidence: incidence of PTSD; incidence and severity of PTSD symptoms; measures of depression and anxiety symptoms; quality of life; return to work or duty; incidence of self-injurious or suicidal thoughts, attempts, or behaviors (including suicide); incidence of aggressive or homicidal thoughts, attempts, or behaviors (including homicide); rates of adverse events (overall or for specific events such as organ failure); mortality; and dropout rate because of adverse effects.

Two reviewers assessed each domain for each key outcome and determined an overall SOE grade based on domain ratings. For each assessment one of the two reviewers was always an experienced investigator. In the event of disagreements on the domain or overall grade, they resolved differences by consensus discussion or by consulting with a third, senior investigator. Appendix G in the main report provides the detailed rationale for SOE grades.

Applicability

We assessed applicability of the evidence following guidance from the "Methods Guide for Comparative Effectiveness Reviews."[11] We used 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, race or ethnicity of enrolled populations, few studies enrolling subjects with exposure to certain types of trauma, or few studies distinguishing or reporting the type of traumatic exposure for a heterogeneous population.

Throughout the report, we use the terms "efficacy" and "comparative effectiveness." By efficacy, we mean the efficacy or effectiveness of an intervention tested against some type of inactive control (e.g., placebo or waitlist). By comparative effectiveness we mean the efficacy or effectiveness of an intervention compared with another intervention of interest. In this report, we did not distinguish between explanatory (or efficacy) and pragmatic (or effectiveness) studies.

Results

First, we describe results of the literature searches and ratings of the risk of bias. Second, we present available evidence for each KQ, focusing on efficacy or risk of harms and then comparative effectiveness or risk of harms. Within each section, we discuss evidence on psychological

interventions first, followed by studies on pharmacological interventions, and lastly by studies on emerging interventions. We give SOE grades for major outcomes on which we had any evidence at all; several specified a priori were not present in our evidence base. The main report gives detailed descriptions of included studies in text and in the evidence tables in its Appendix E.

Results of the Literature Searches

We identified 2,563 citations from searches, reviews of reference lists, and grey literature. Overall, we included 19 trials in our main analyses. Another 37 studies otherwise meeting inclusion criteria were omitted from our main analyses because of a high risk of bias. If not stated otherwise, trials described below are of medium risk of bias.

KQ 1: Efficacy and Comparative Effectiveness of Interventions To Prevent PTSD

Efficacy

Thirteen studies addressed efficacy.[12-24] Of these, each involved psychological interventions; one study included a pharmacological intervention, and one evaluated an emerging intervention (collaborative care). These studies were conducted in[15, 18, 23, 24] and outside the United States.[12-14, 16, 17, 19-21] They included a variety of trauma-exposed populations such as victims of crime, motor vehicle accidents (MVAs), other types of accidents, intimate partner violence, sexual assault, and terrorist attacks; critically ill patients; and mothers experiencing traumatic childbirth or caring for a critically ill child. We did not find any evidence on most pharmacological interventions. In addition, we had little or no evidence about terrorist attacks, sexual assault, natural disaster, or combat.

We identified trials that reported on one or more of eight different psychological interventions: debriefing, cognitive behavioral therapy (CBT), CBT combined with hypnosis, cognitive therapy (CT), prolonged exposure therapy (PE), psychoeducation, self-help materials, and supportive counseling (SC). The two key outcomes are incidence of PTSD (i.e., preventing PTSD) and reducing the severity of PTSD symptoms. From these studies, we concluded that debriefing is not effective in preventing PTSD or reducing the severity of PTSD symptoms in civilian victims of crime, assault, or accident trauma at 6-month followup (low SOE). We had insufficient data (single study) to determine the efficacy of debriefing at 2- or 6-week or 11-month followup.

From a single study, we concluded that collaborative care (CC), a stepped combination of care management, psychopharmacology, and CBT, produces a greater decrease in PTSD symptom severity at 6, 9, and 12 months after injury than usual care (low SOE).[24] However, data addressing whether groups differed in PTSD diagnosis 12 months after injury were not conclusive (insufficient SOE).

For most other interventions—namely, CBT, CBT combined with hypnosis, CT, PE, psychoeducation, self-help material, SC, and the two pharmaceuticals escitalopram (a selective serotonin reuptake inhibitor [SSRI]) and hydrocortisone—we had single studies with small treatment arms (generally fewer than 80 subjects). This paucity of information led us to conclude that the evidence was insufficient to support their efficacy for preventing PTSD or reducing PTSD symptom severity.

For studies that had assessed the efficacy of interventions in terms of reducing symptoms of anxiety and depression, we found insufficient evidence. Table A summarizes the main findings and the SOE for the efficacy of psychological, pharmacological, and emerging interventions for this section of KQ 1.

Comparative Effectiveness

Eight studies addressed the effectiveness of a psychological intervention compared with another psychological intervention.[13, 17, 20, 21, 25-28] The interventions included Battlemind training, CBT, CBT combined with hypnosis, CT, PE, various forms of debriefing, and SC. One study compared psychological interventions with an SSRI.[20] All these studies were conducted outside the United States and included samples exposed to a variety of traumas, such as combat, crime, physical assault, motor vehicle and other types of accidents, and terrorist attacks. We did not include studies comparing two or more medications; the one study we had identified was rated high risk of bias. We did not identify any studies that evaluated the comparative effectiveness of any emerging interventions.

Our meta-analyses of trials that compared CBT with SC in a sample of participants with ASD found that at both the end of treatment and at 6-month followup, CBT was more effective than SC in reducing the severity of PTSD symptoms as measured by the Impact of Event Scale (IES) (moderate SOE). However, at both the end of treatment and at 6-month followup, CBT was no more effective than SC for preventing PTSD (low SOE), reducing symptoms of anxiety (moderate SOE), or reducing symptoms of depression (low SOE).

Because the knowledge base comprises largely single studies with small sample sizes, we concluded that the evidence was insufficient to determine the comparative effectiveness of most of the psychological interventions in preventing PTSD or reducing PTSD symptom severity.

Only one study compared psychological interventions (CT and PE) with a medication (escitalopram, an SSRI). Because of methods limitations, we could not draw any conclusions about the comparative effectiveness of an SSRI and a psychological intervention.

Table B summarizes the main findings and the SOE for the comparative effectiveness of psychological and pharmacological interventions for this section of KQ 1.

Table A. Summary of findings and strength of evidence for the efficacy of psychological, pharmacological, and emerging interventions to prevent PTSD and reduce PTSD symptom severity

Intervention, Population	Outcome	Results	SOE
CBT, Civilian, mixed trauma types[16]	Incidence of PTSD	Inconclusive, single trial (N=46)	Insufficient
	PTSD symptom severity	Inconclusive, single trial (N=46)	Insufficient
CT, Civilian, mixed trauma types[13, 20]	Incidence of PTSD	Inconclusive, single trial (n=133)	Insufficient
	PTSD symptom severity	Inconclusive, 2 trials (n=193), inconsistent findings at different assessment intervals	Insufficient
CC, Civilian, mixed trauma types requiring hospitalization[24]	Incidence of PTSD	Inconclusive, single trial (N=207)	Insufficient
	PTSD symptom severity	CC produces a greater decrease in PTSD symptom severity at 6, 9, and 12 months after injury than usual care (N=207)	Low
Debriefing, Civilian mixed trauma types[17, 21]	Incidence of PTSD	Debriefing not significantly different than control at multiple followup assessment intervals across 2 trials (n=341)	Low
	PTSD symptom severity	Debriefing not significantly different than control at multiple followup assessment intervals across 2 trials (n=341)	Low
Exposure-based therapies, Civilian, mixed trauma types[13, 18, 20]	Incidence of PTSD	Inconclusive, 3 trials (n=355), inconsistent findings at different assessment intervals	Insufficient
	PTSD symptom severity	Inconclusive, 3 trials (n=355) with different assessment intervals that prevent direct comparisons	Insufficient
Hydrocortisone stress dose, Civilians undergoing high-risk cardiac surgery[22]	Incidence of PTSD	Inconclusive, single trial (n=28)	Insufficient
	PTSD symptom severity	Inconclusive, single trial (n=28)	Insufficient
Psychoeducation, Civilian crime[17] and injury[23] victims	Incidence of PTSD	Inconclusive, 2 trials (N=182) with different assessment intervals that prevent direct comparisons	Insufficient
	PTSD symptom severity	Inconclusive, single trial (n=103)	Insufficient
Self-help materials, Women newly diagnosed with breast cancer[12]	PTSD symptom severity[a]	Inconclusive, single trial (N=49)	Insufficient
SSRI (escitalopram), Civilian, mixed trauma types[20]	Incidence of PTSD	Inconclusive, single trial (n=139)	Insufficient
	PTSD symptom severity	Inconclusive, single trial (n=139)	Insufficient
SC, Women, mixed trauma types[14, 15, 19]	Incidence of PTSD	Inconclusive, single trial (N=103)	Insufficient
	PTSD symptom severity	Inconclusive, 2 trials (n=336), inconsistent findings at different assessment intervals using different outcome measures	Insufficient

[a] Incidence of PTSD not reported.

Abbreviations: CBT = cognitive behavioral therapy; CC = collaborative care; CT = cognitive therapy; N = entire sample; n = subset of sample; PTSD = posttraumatic stress disorder; SC = supportive counseling; SOE = strength of evidence; SSRI = selective serotonin reuptake inhibitor.

Table B. Summary of findings and strength of evidence for the comparative effectiveness of psychological, pharmacological, and emerging interventions to prevent PTSD and reduce PTSD symptom severity

Intervention, Population	Outcome	Results	SOE
Battlemind training vs. standard brief, UK military service members[28]	PTSD symptom severity	Inconclusive, single trial (n=2,443)	Insufficient
CBT vs. CBT+Hypnosis, Civilian, mixed trauma types[27]	Incidence of PTSD	Inconclusive, single trial (n=63)	Insufficient
	PTSD symptom severity	Inconclusive, single trial (n=63)	Insufficient
CBT vs. SC, Civilian, mixed trauma types with ASD[25-27]	Incidence of PTSD	CBT not significantly different than SC at end of treatment (RR, 0.27; 95% CI [0.05 to 1.29]; I2=71.8%) or at 6 months (RR, 0.46; 95% CI [0.21 to 1.01]; I2=44.9%); 3 trials (n=105)	Low
	PTSD symptom severity	Greater reduction for CBT than for SC on IES-I at the end of treatment (WMD, -7.85; 95% CI [-11.18 to -4.53]; I2=1.3%) and at 6 months (WMD, -8.19; 95% CI [-11.79 to -4.58]; I2=6.8%); 3 trials (n=105)	Moderate
		Greater reduction for CBT than for SC on IES-A at end of treatment (WMD, -14.04; 95% CI [-19.37 to -8.71]; I2=53.8%) and 6 months (WMD, -9.94; 95% CI [-15.06 to -4.83]; I2=44.0%); 3 trials (n=105)	
CBT+Hypnosis vs. SC, Civilian, mixed trauma types[27]	Incidence of PTSD	Inconclusive, single trial (n=54)	Insufficient
	PTSD symptom severity	Inconclusive, single trial (n=54)	Insufficient
CT vs. PE Civilian, mixed trauma types[13, 20]	Incidence of PTSD	Inconclusive, 2 trials (n=163), inconsistent findings at different assessment intervals; 1 trial used a "completer analysis	Insufficient
	PTSD symptom severity	Inconclusive, 2 trials (n=163), inconsistent findings at different assessment intervals; 1 trial used a "completer analysis"	Insufficient
CT vs. SSRI (escitalopram). Civilian, mixed trauma types[20]	Incidence of PTSD	Inconclusive, single trial (n=54)	Insufficient
	PTSD symptom severity	Inconclusive, single trial (n=54)	Insufficient
Emotional debriefing vs. Educational debriefing Civilian, mixed trauma types[21]	Incidence of PTSD	Inconclusive, single trial (n=155)	Insufficient
	PTSD symptom severity	Inconclusive, single trial (n=155)	Insufficient
PE vs. SSRI (escitalopram) Civilian, mixed trauma types[20]	Incidence of PTSD	Inconclusive, single trial (n=71)	Insufficient
	PTSD symptom severity	Inconclusive, single trial (n=71)	Insufficient
Psychoeducation vs. Debriefing combined with psychoeducation Civilian, crime victims[17]	Incidence of PTSD	Inconclusive, single trial (n=106)	Insufficient
	PTSD symptom severity	Inconclusive, single trial (n=106)	Insufficient

Abbreviations: ASD = acute stress disorder; CBT = cognitive behavioral therapy; CBT+Hypnosis = CBT combined with hypnosis; CI = confidence interval; CT = cognitive therapy; IES-A = Impact of Event Scale-Avoidance subscale; IES-I = Impact of Event Scale-Intrusions subscale; n = subset of sample; PE = prolonged exposure therapy; PTSD = posttraumatic stress disorder; RR = relative risk; SC = supportive counseling; SOE = strength of evidence; SSRI = selective serotonin reuptake inhibitor; UK = United Kingdom; WMD = weighted mean difference.

KQ 2: Impact of Timing, Intensity, and Dosing

The evidence is scarce on the impact of timing, intensity, and dosing on the effectiveness or risk of harms of interventions used to prevent PTSD. Overall, studies addressed timing and dosing questions;[29-32] two were rated as high risk of bias.[30, 31] We found no studies on the impact of intensity of intervention for any psychological or emerging interventions. Table C summarizes the main findings and the SOE for KQ 2 for incidence of PTSD and PTSD symptom severity.

Table C. Summary of evidence of the impact of timing, intensity, and dosing on the effectiveness of interventions and strength of evidence			
Intervention, Population	**Outcome**	**Results**	**SOE**
Debriefing (CISD) timing (early vs. late), Robbery victims[29]	PTSD symptom severity	Inconclusive, single trial (N=77)	Insufficient
Pharmacological sedation depth (light vs. deep) Critically ill patients[32]	Incidence of PTSD	Inconclusive, single trial (N=137)	Insufficient

Abbreviations: CISD = critical incident stress debriefing; N = entire sample; PTSD = posttraumatic stress disorder; SOE = strength of evidence.

One RCT addressed the impact of timing of a psychological intervention.[29] Immediate debriefing (within 10 hours) compared with late debriefing (after 48 hours) led to significantly fewer posttraumatic symptoms that victims experienced (insufficient SOE). No evidence was available on the impact of timing for any other psychological, pharmacological, or emerging interventions or any other outcomes.

In one RCT, dosing of sedation (light vs. deep) in critically ill patients did not affect posttraumatic symptoms, depression, or anxiety (insufficient evidence).[32] We did not find any eligible evidence on the effect of dosing for any other pharmacological or emerging interventions to prevent PTSD.

KQ 3: Subgroups

Evidence is also sparse on whether the effect of early interventions differs among groups defined by sociodemographic characteristics, psychiatric diagnoses and comorbidities, personal risk factors for developing PTSD, or types of trauma. Eight studies met our inclusion criteria for subgroup analyses,[12, 17, 18, 21, 28, 29, 33, 34] but we rated two as high risk of bias.[33, 34] Table D summarizes the main findings and the SOE for KQ 3 for two main categories of outcomes—the numbers of PTSD symptoms and depression symptoms. We report the outcomes in terms of whether the subgroup characteristic, such as sex, modified the effect of any intervention(s)—that is, whether individuals in the intervention and control subgroups did or did not differ at various followup measurements.

Two trials reported consistent results that effects of early psychological interventions on PTSD symptoms were similar for men and women.[17, 29] However, because neither trial reported the magnitude of the estimated effect or its precision, we graded the SOE as low.

One trial tested the effect of a debriefing intervention—critical incident stress debriefing (CISD)—in subgroups with a history of either depression or child abuse, but it did not report magnitude or precision of effects (SOE insufficient in all cases).[17]

One trial reported that the severity of trauma exposure did not modify the effect of Battlemind training among United Kingdom returning military service members (insufficient SOE).[28]

One trial reported that PE reduced symptoms of PTSD among survivors of sexual assault but not physical assault or motor vehicle accidents (SOE insufficient).[18]

Table D. Summary of evidence and strength of evidence for the effect of early interventions in various subgroups

Subgroup; Intervention; Population	Outcome	Results	SOE
Demographic groups: sex; CBT, CISD; Crime victims[17, 29]	Incidence of PTSD	No evidence	Insufficient
	PTSD symptom severity	The effect of CBT or CISD did not differ between men and women; 2 trials (N=234), consistent findings	Low
Type of trauma; PE, Mixed civilian trauma[18]	Incidence of PTSD	Inconclusive, single trial (N=137)	Insufficient
	PTSD symptom severity	Inconclusive, single trial (N=137)	Insufficient
Psychiatric diagnosis: previous depression; Debriefing; Crime victims[17]	Incidence of PTSD	No evidence	Insufficient
	PTSD symptom severity	Inconclusive, single trial (N=157)	Insufficient
History of child abuse[a]; psychoeducation vs. debriefing combined with psychoeducation; Crime victims[17]	Incidence of PTSD	No evidence	Insufficient
	PTSD symptom severity	Inconclusive, single trial (N=157)	Insufficient
Severity of baseline distress[a]; Debriefing, self-help workbook; Crime victims, women with breast cancer[12, 21]	Incidence of PTSD	No evidence	Insufficient
	PTSD symptom severity	Inconsistent findings, 2 trials (N=285); 1 trial reported that debriefing increased PTSD symptoms among those with high baseline PTSD arousal symptoms; and 1 trial reported that a self-help workbook decreased PTSD symptoms to a greater extent in those with high baseline PTSD symptom severity	Insufficient
Severity of combat exposure[a]; UK military service members[28]	Incidence of PTSD	No evidence	Insufficient
	PTSD symptom severity	Inconclusive, single trial (n=2,443)	Insufficient

[a] Personal risk factor for PTSD.

Abbreviations: CBT = cognitive behavioral therapy; CISD = critical incident stress debriefing; N = entire sample; n = subset of sample; PE = prolonged exposure therapy; PTSD = posttraumatic stress disorder; SOE = strength of evidence; UK = United Kingdom.

Two trials provided inconsistent findings on whether baseline severity of PTSD symptoms modified the effect of two different psychological interventions (SOE insufficient).[12, 21]

KQ 4: Risk of Harms

Little evidence exists addressing either the general or the comparative risks of harms from early interventions to prevent PTSD. Four studies assessed harms;[21, 32, 35, 36] two were rated as high risk of bias.[21, 32] For most interventions, no evidence was available. Table E summarizes the main findings and the SOE for KQ 4.

Table E. Summary of findings and strength of evidence about harms

Intervention, Population	Outcome	Results	SOE
Emotional debriefing vs. no debriefing, Civilian, medical trauma[21]	PTSD symptom severity	For subgroup with hyperarousal, inconclusive, single trial (N=236), inconsistent findings at different assessment intervals	Insufficient
Pharmacological sedation (light vs. deep), Critically ill patients[32]	Mortality	Inconclusive, single trial (N=137)	Insufficient
	Incidence of adverse events	Inconclusive, single trial (N=137)	Insufficient

Abbreviations: N = entire sample; PTSD = posttraumatic stress disorder; SOE = strength of evidence.

A three-armed RCT (low risk of bias) considered absolute risk of greater severity of PTSD symptoms in patients presenting to an outpatient psychiatric clinic after psychological trauma.[21] In a subgroup of patients with early hyperarousal, those receiving emotional debriefing experienced higher PTSD severity at 6 weeks than those not receiving such debriefing. The investigators did not find this difference in this subgroup at either 2 weeks or 6 months or in any other subgroups (insufficient evidence). We found no other trials of psychological or pharmacological interventions that provided information on risks of early interventions.

One randomized open-label trial considered comparative risk of harms from light versus deep sedation for patients requiring mechanical ventilation.[32] The two groups did not differ with regard to rates of mortality (either during their stays in the intensive care unit or in their overall hospitalization) or in the incidence of adverse events (organ dysfunction, hypertension, and tachycardia) (insufficient evidence).

High-Risk-of-Bias Studies

Table 7 in the main report presents a summary of the study designs, prevention type (i.e., universal or targeted), study comparisons, results, and methodological shortcomings of the 37 studies we rated as high risk of bias. In most cases, we had data from studies of either low or medium risk of bias, and we did not include these high-risk-of-bias studies in our analyses. For some interventions, however, we found only high-risk-of-bias studies. We summarize their findings in the main report.

Discussion

Key Findings and Strength of Evidence

In this comprehensive comparative effectiveness review (CER), we conducted a systematic review of the efficacy, comparative effectiveness, and harms of psychological,

pharmacological, and emerging interventions for the prevention of PTSD in adults exposed to psychological trauma. Overall, for most interventions and outcomes of interest, evidence was either entirely lacking or insufficient to draw conclusions. In addition, in the available body of evidence, the majority of eligible studies were fraught with methodological shortcomings and were rated as high risk of bias. Consequently, we are able to draw only a few conclusions with some degree of certainty:

- CC is effective at reducing the severity of PTSD symptoms for civilian victims of injuries requiring inpatient surgical admission at 6-month, 9-month, and 12-month followup (low SOE, one RCT).

- Debriefing is not effective in reducing either the incidence of PTSD or severity of PTSD or depressive symptoms in civilian victims of crime, assault, or accident trauma at 6-month followup (low SOE, two RCTs).

- In individuals with ASD, a meta-analysis found that adults who received CBT had greater reductions in severity of PTSD symptoms than those who received SC (moderate SOE, three RCTs). Differences between CBT and SC with respect to preventing PTSD (low SOE, three RCTs), reducing the severity of depression symptoms (low SOE, three RCTs), or reducing the severity of anxiety symptoms (moderate SOE, three RCTs) also favored CBT; results, however, did not reach statistical significance.

- The effectiveness of psychological interventions to prevent PTSD does not differ between men and women (low SOE).

For many interventions we did not have sufficient evidence to draw conclusions about either efficacy or comparative effectiveness. How available results from some head-to-head studies might be extrapolated to comparisons with other interventions remains unclear. Consistent with

other reviews,[37-39] we also concluded that psychological debriefing is not useful for preventing PTSD. One of these reviews also concluded that debriefing could actually be harmful to participants and should cease;[38] we cannot confirm this conclusion from our evidence base.

Our primary outcome measures were prevention of PTSD as a DSM-IV-TR disorder (defined as incidence of PTSD) and reduction of PTSD symptom severity. Most of the studies we reviewed, however, determined PTSD symptom scores without establishing the incidence of PTSD. Whether such findings can be extrapolated reliably to differences in the incidence of PTSD remains unclear on the basis of our results.

Overall, two major limitations characterize this body of evidence. First, for many interventions, the evidence was insufficient on the efficacy, comparative effectiveness, or risk of harms of interventions. Despite our eligibility criteria, including observational studies for effectiveness and harms, we could not draw conclusions for or against benefits and harms for the majority of our interventions of interest. Even when studies assessing the effectiveness of an intervention were available, they often did not assess harms. Although lack of evidence cannot be equated with lack of effectiveness or harms, incautious use of interventions without proven net benefit has the potential to cause more harms than benefits.[38]

Second, available evidence frequently showed shortcomings in study methods. Of 56 studies meeting our eligibility criteria, we rated 37 as high risk of bias using standard criteria and only 3 as low risk of bias. Studies assessed as high risk of bias have significant flaws of various types (stemming from serious errors in design, conduct, or analysis) that may invalidate their results. Consequently, the evidence base for most of the major outcomes we sought to review was insufficient to draw conclusions. The SOE grades for only a few outcomes for only a few interventions could be rated as low or moderate, indicating reasonable confidence in effect estimates of those studies.

Which early psychological or pharmacological interventions would be most effective and least harmful in preventing PTSD among all adults exposed to trauma cannot be specified from our results. Among adults exposed to trauma who meet criteria for ASD, however, our findings support the use of brief CBT interventions over SC for reducing PTSD symptom severity, although the SOE supporting this conclusion is low. Our results did not identify any class of drugs that has been shown to be effective in preventing PTSD.

We found that being male or female did not modify the effect of early intervention among crime victims (low SOE), suggesting that clinicians may not need to take the sex of a patient into consideration when choosing a preventive intervention for crime victims. Whether that observation would generalize to other types of trauma is unclear. We found no evidence about which early interventions are more or less effective for other subgroups of interest.

Evidence addressing the absolute risks or comparative risks of harms from early interventions intended to prevent PTSD was similarly insufficient.

Applicability

The included studies covered diverse populations exposed to a wide range of traumas and not diagnosed with PTSD, but the findings may not generalize to survivors of terrorist attack, natural disaster, sexual assault, or combat who were underrepresented or unrepresented. In addition, there were too few data to assess whether outcomes differed according to type of trauma or specific demographic factors such as age, since only adults over age 18 years were studied. Many of the included studies were conducted outside the United States with civilian populations (not U.S. military abroad), but there were too few data to analyze whether cross-cultural differences in setting or intervention delivery systems had any impact on outcome. Generally, the findings reflect interventions that were representative of those used in the treatment of PTSD, outcomes that were derived using clinically meaningful and valid measures, and settings that provided real-world context; but, because there is no accepted "usual clinical care" model for preventing PTSD in trauma victims, we cannot draw conclusions about the applicability of the findings to primary care or any other specific setting in which trauma victims present for care. Finally, with respect to the comparative effectiveness of two or more treatments, our meta-analyses indicated some benefit of CBT over SC in reducing PTSD severity in trauma victims who met criteria for ASD.[25-27] However, because individuals with ASD constitute the minority of those who later develop PTSD,[40-43] these findings may not generalize to the broader population of individuals at risk for developing PTSD.

Research Gaps

The most striking finding from this review is the paucity of high-quality evidence to address each of the four Key Questions. As a result of the small number of studies of low or moderate risk of bias that assessed different interventions, no findings from the included studies

could be graded as high SOE. With respect to differences between interventions in PTSD-specific benefits, we had only one finding with moderate SOE (that CBT is more effective than SC in reducing symptoms of PTSD for individuals with ASD) and one with low SOE (that collaborative care produces a greater decrease in PTSD symptom severity after injury compared with usual care). All other findings for incidence of PTSD or PTSD symptom severity were graded as having insufficient strength of evidence.

Specific and important methodological flaws that we identified included the following:

• Inadequate randomization procedures

• High rates of attrition

• Inadequate statistical approaches for data analysis (e.g., lack of ITT analysis, or lack of statistical adjustment for significant between-group differences at baseline)

An important task of systematic reviews is to assess whether design and conduct of included studies provide adequate protection against bias. The methodological shortcomings of many studies conducted to test interventions to prevent PTSD substantially limit our confidence that results accurately reflect the truth. Therefore, the focus of this report is on evidence from studies rated as having low or medium risk of bias.

Future studies on early interventions to prevent PTSD should institute procedures to avoid or minimize these methodological problems if possible. Adequate and concealed methods of randomization should be relatively easy to implement. Statistical consultation can help investigators use more appropriate methods than "completers analysis" or "last observation carried forward" for handling missing data.

Minimizing attrition, however, may be more difficult to achieve, for multiple reasons. Adults exposed to trauma may have difficulty building the commitment required for long-term followup because their first contact with the research team occurs at a time when they are likely to be highly distressed. Survivors who are exposed to traumas that disrupt community infrastructure, such as natural disasters, are likely to be highly mobile and difficult to locate for followup interviews. Specific protocols for minimizing attrition in studies of traumatized populations may help maintain high rates of followup.[44]

Among the 19 studies that we included and rated as low or medium risk of bias, there was frequently insufficient or no evidence to address KQ 2 (timing and dose of intervention), KQ 3 (effectiveness in subgroups), or KQ 4 (harms). Future research can fill the gaps in multiple ways. For KQ 2, future studies could evaluate the comparative effectiveness of the same intervention given at different time intervals after exposure to trauma, while incorporating inactive control interventions. For studies in which the timing of the intervention is not explicitly randomized, investigators could measure the time between trauma exposure and intervention and carry out preplanned subgroup analyses by time to intervention. Investigators could also attempt to recruit sample sizes that provide sufficient power to detect prespecified group-by-intervention interaction effects. All the following subgroups could be considered: (1) demographic groups: sex, race, or ethnicity; (2) types of trauma; and (3) severity of trauma and severity of baseline distress. In examining harms or unintended side effects of both psychological and pharmacological treatments, researchers should identify potential adverse effects before starting their study and use or adapt validated instruments to measure adverse effects.

Psychological first aid has gained rapid acceptance as a universal intervention for people in the acute aftermath of trauma, but no studies of this intervention met inclusion criteria for our review. Although psychological first aid was not designed as an intervention to reduce the incidence of PTSD, it may have beneficial or adverse effects on mental health among trauma survivors.[45, 46] Rigorous studies of psychological first aid should be conducted.

One key research gap for studies of targeted prevention is the limited ability to identify people who are at high risk of developing PTSD shortly after they have been exposed to trauma. The development of a clinical prediction rule to identify, shortly after exposure to trauma, the relatively small percentage of such individuals who will develop PTSD would be an enormous help to the field.

We recommend that additional work be devoted to developing a clinical prediction rule based on inclusion of key variables that, together, are highly predictive of PTSD. Those variables could include pretrauma factors, event characteristics, and peri-event responses. An ideal prediction rule would have strong ability to discriminate between people who do or do not develop PTSD, be composed of a relatively small number of variables that can be measured easily and quickly, and produce results that are easily interpretable by health care providers who interact with survivors shortly after they are exposed to trauma. After a clinical prediction rule has been derived and validated in populations exposed to a variety of trauma types, it should be evaluated, in a randomized trial, to determine whether use of the rule, in concert with an intervention to reduce the incidence of PTSD, results

in reduced incidence of PTSD. We believe that this is a promising approach to realizing the potential of targeted strategies for preventing PTSD.

Conclusions

Evidence supporting the efficacy of most interventions used to prevent PTSD is lacking. If available in a given setting, brief trauma-focused CBT might be the preferable choice for reducing PTSD symptom severity in adults with ASD; CC may be helpful for reducing PTSD symptom severity post-injury; and debriefing is not an effective prevention intervention.

Our findings highlight the inherent difficulties of conducting research on prevention interventions— difficulties that are often more challenging for mental-health-related research than for research on medical or other health-related issues. Our body of evidence was highly limited because of the paucity of methodologically sound studies. Although disappointing, our findings underscore the need for ongoing research efforts in the field of PTSD prevention. Our findings lead us to conclude that developing a clinical prediction algorithm to identify those who are at high risk of developing PTSD after trauma exposure is perhaps a more crucial next step in the field of PTSD prevention than continuing to study which interventions are more effective than others. The ability to identify people most at risk for developing PTSD and then to evaluate the effectiveness of prevention interventions in those individuals should be the focus of future clinical and research efforts.

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