



# Effective Health Care Program

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Comparative Effectiveness Review  
Number 92

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



Agency for Healthcare Research and Quality  
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# *Comparative Effectiveness Review*

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Number 92

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

**Prepared for:**

Agency for Healthcare Research and Quality  
U.S. Department of Health and Human Services  
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**Prepared by:**

RTI International–University of North Carolina Evidence-based Practice Center  
Research Triangle Park, NC

**Investigators:**

Daniel E. Jonas, M.D., M.P.H.  
Karen Cusack, Ph.D.  
Catherine A. Forneris, Ph.D., A.B.B.P.  
Tania M. Wilkins, M.S.  
Jeffrey Sonis, M.D., M.P.H.  
Jennifer Cook Middleton, Ph.D.  
Cynthia Feltner, M.D., M.P.H.  
Dane Meredith, M.P.H.  
Jamie Cavanaugh, Pharm.D.  
Kimberly A. Brownley, Ph.D.  
Kristine Rae Olmsted, M.S.P.H.  
Amy Greenblatt, B.A.  
Amy Weil, M.D.  
Bradley N. Gaynes, M.D., M.P.H.

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|   |
|---|
| None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report. |
|---|

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## Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see [www.effectivehealthcare.ahrq.gov/reference/purpose.cfm](http://www.effectivehealthcare.ahrq.gov/reference/purpose.cfm).

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site ([www.effectivehealthcare.ahrq.gov](http://www.effectivehealthcare.ahrq.gov)) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input.

We welcome comments on this systematic review. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to [epc@ahrq.hhs.gov](mailto:epc@ahrq.hhs.gov).

Carolyn M. Clancy, M.D.  
Director  
Agency for Healthcare Research and Quality

Jean Slutsky, P.A., M.S.P.H.  
Director, Center for Outcomes and Evidence  
Agency for Healthcare Research and Quality

Stephanie Chang, M.D., M.P.H.  
Director, EPC Program  
Task Order Officer  
Center for Outcomes and Evidence  
Agency for Healthcare Research and Quality

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The investigators deeply appreciate the considerable support, commitment, and contributions of the EPC staff at RTI International and the University of North Carolina at Chapel Hill. We express our gratitude to the following individuals for their contributions to this project: Carol Woodell, B.S.P.H., our Project Manager; Megan Van Noord, M.S.L.S., and Christiane Voisin, our EPC Librarians; Kathleen Lohr, Ph.D, scientific editor; Jennifer Drolet, Carol Offen, and Wally Campbell, editors; and Loraine Monroe, our EPC publications specialist.

## Key Informants

In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

The list of Key Informants who participated in developing this report follows:

Christine Courtois, Ph.D.  
Principal and Founder of Courtois &  
Associates, PC  
Trauma Treatment, Life Transitions, and  
Wellness Services  
Washington, DC

Jonathan R. Davidson, M.D.  
Professor Emeritus, Psychiatry-Psychiatry &  
Behavioral Sciences and  
Director of the Anxiety and Traumatic  
Stress Program  
Duke University Medical Center  
Durham, NC

Laura Fochtmann, M.D.  
Medical Editor of the American Psychiatric  
Association Practice Guidelines  
Professor of Psychiatry and Director of the  
ECT Service  
Stony Brook University Medical Center  
Stony Brook, NY

Matthew J. Friedman, M.D., Ph.D.  
Executive Director  
National Center for Posttraumatic Stress  
Disorder  
U.S. Department of Veterans Affairs  
Professor of Psychiatry and of  
Pharmacology and Toxicology  
Dartmouth Medical School  
Hanover, NH

Daniel I. Galper, Ph.D.  
Director of Research & Special Projects  
American Psychological Association  
Washington, DC

Rachel Kimerling, Ph.D.  
National Center for Posttraumatic Stress  
Disorder  
VA Palo Alto Health Care System  
Center for Health Care Evaluation  
Palo Alto, CA

## Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

The list of Technical Experts who participated in developing this report follows:

Naomi Breslau, Ph.D.  
Professor of Epidemiology  
Michigan State University  
East Lansing, MI

Melanie S. Harned, Ph.D.  
University of Washington  
Behavioral Research & Therapy Clinics  
Seattle, WA

Jonathan R. Davidson, M.D.  
Professor Emeritus, Psychiatry-Psychiatry &  
Behavioral Sciences and  
Director of the Anxiety and Traumatic  
Stress Program  
Duke University Medical Center  
Durham, NC

Dean G. Kilpatrick, Ph.D.  
Distinguished University Professor of  
Clinical Psychology  
Director, National Crime Victims Research  
& Treatment Center  
Vice-Chair for Research and Research  
Administration  
Department of Psychiatry & Behavioral  
Sciences  
Medical University of South Carolina  
Charleston, SC

Laura Fochtmann, M.D.  
Medical Editor of the American Psychiatric  
Association Practice Guidelines  
Professor of Psychiatry and Director of the  
ECT Service  
Stony Brook University Medical Center  
Stony Brook, NY

Jane Liebschutz, M.D., M.P.H.  
Associate Professor  
Boston University School of Medicine  
Department of Medicine  
Boston, MA

Daniel I. Galper, Ph.D.  
Director of Research & Special Projects  
American Psychological Association  
Washington, DC

## Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report does not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

The list of Peer Reviewers follows:

Laura Fochtmann, M.D.  
Medical Editor of the American Psychiatric  
Association Practice Guidelines  
Professor of Psychiatry and Director of the  
ECT Service  
Stony Brook University Medical Center  
Stony Brook, NY

Matthew J. Friedman, M.D., Ph.D.  
Executive Director, National Center for  
Posttraumatic Stress Disorder  
U.S. Department of Veterans Affairs  
Professor of Psychiatry and of  
Pharmacology and Toxicology  
Dartmouth Medical School  
Hanover, NH

Helena Kraemer, Ph.D.  
Professor Emerita of Biostatistics in  
Psychiatry  
Academy Council, Psychiatry & Behavioral  
Science  
School of Medicine, Stanford University  
Stanford, CA

Jane Liebschutz, M.D., M.P.H.  
Associate Professor  
Boston University School of Medicine  
Department of Medicine  
Boston, MA

Paula Schnurr, Ph.D.  
Deputy Executive Director, VA National  
Center for PTSD  
Research Professor of Psychiatry  
Dartmouth Medical School  
Hanover, NH

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

## 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<sup>®</sup>, Cochrane Library, PILOTS, International Pharmaceutical Abstracts, CINAHL<sup>®</sup>, PsycINFO<sup>®</sup>, 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  $\leq 4$  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.

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- Appendix F. Meta-Analysis
- Appendix G. Strength of Evidence

# 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,”<sup>1</sup> 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)                                 | <ul style="list-style-type: none"> <li>• Traumatic event that involved actual or threatened death, serious injury, or threat to physical integrity</li> <li>• Intense response of fear, helplessness, or horror</li> </ul>   |
| Criterion B: Reexperiencing symptoms (1 or more)           | <ul style="list-style-type: none"> <li>• Intrusive recollections of events</li> <li>• Recurrent distressing dreams of the event</li> <li>• Acting or feeling as if the traumatic event were recurring</li> <li>• Distress at internal or external reminders of the trauma</li> <li>• Physiological reaction to internal or external reminders</li> </ul>   |
| Criterion C: Persistent avoidance and numbing (3 or more)  | <ul style="list-style-type: none"> <li>• Avoidance of thoughts, feelings, or conversations associated with trauma</li> <li>• Avoidance of activities, places, or people that arouse recollections of trauma</li> <li>• Failure to recall an important aspect of trauma</li> <li>• Loss of interest or participation in significant activities</li> <li>• Detachment from others</li> <li>• Restricted range of affect</li> <li>• Lost sense of the future</li> </ul> |
| Criterion D: Hyperarousal (2 or more)                      | <ul style="list-style-type: none"> <li>• Difficulty falling or staying asleep</li> <li>• Irritability or outburst of anger</li> <li>• Difficulty concentrating</li> <li>• Hypervigilance</li> <li>• Exaggerated startle response</li> </ul>  |
| Criterion E: Duration of disturbance                       | <ul style="list-style-type: none"> <li>• Duration of disturbance symptoms is more than 1 month</li> </ul>  |
| Criterion F: Clinically significant distress or impairment | <ul style="list-style-type: none"> <li>• Disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of function</li> </ul>   |

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.<sup>1</sup> 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.<sup>2</sup> 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.<sup>3</sup> 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.<sup>4</sup>



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.<sup>5</sup> 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.<sup>5</sup> 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.<sup>6</sup>

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.<sup>7</sup> PTSD is associated with an increased risk of suicide,<sup>8</sup> 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.<sup>9</sup>

## **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.<sup>2</sup> The therapies are delivered predominantly to individuals; some can also be conducted in a group setting.<sup>10,11</sup>

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.<sup>12-16</sup> 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,<sup>2</sup> 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.<sup>12-14,17</sup> The guideline from the ISTSS acknowledges that practical considerations, such as unavailability of trauma-focused psychological treatment or patient preferences, may guide treatment decisions.<sup>15</sup>

## 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.

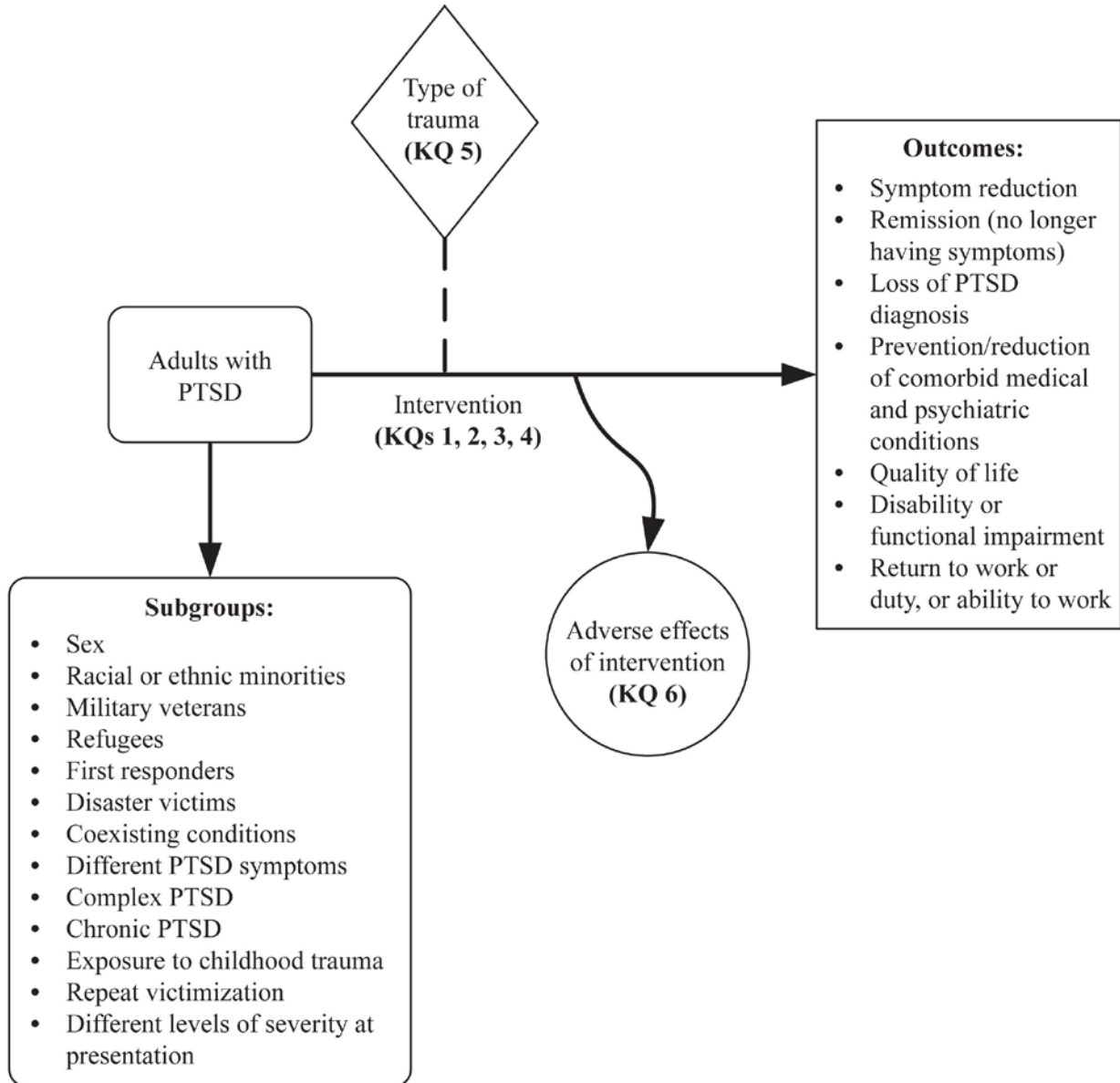
## Methods

### Literature Search Strategy

We searched MEDLINE<sup>®</sup>, the Cochrane Library, the PILOTS database, International Pharmaceutical Abstracts, CINAHL<sup>®</sup>, PsycINFO<sup>®</sup>, 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,”<sup>18</sup> 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.<sup>19</sup> 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.<sup>20,21</sup> 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<sup>®</sup> version 11.1.

We conducted a network meta-analysis using Bayesian methods<sup>22</sup> 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.<sup>23</sup> 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.

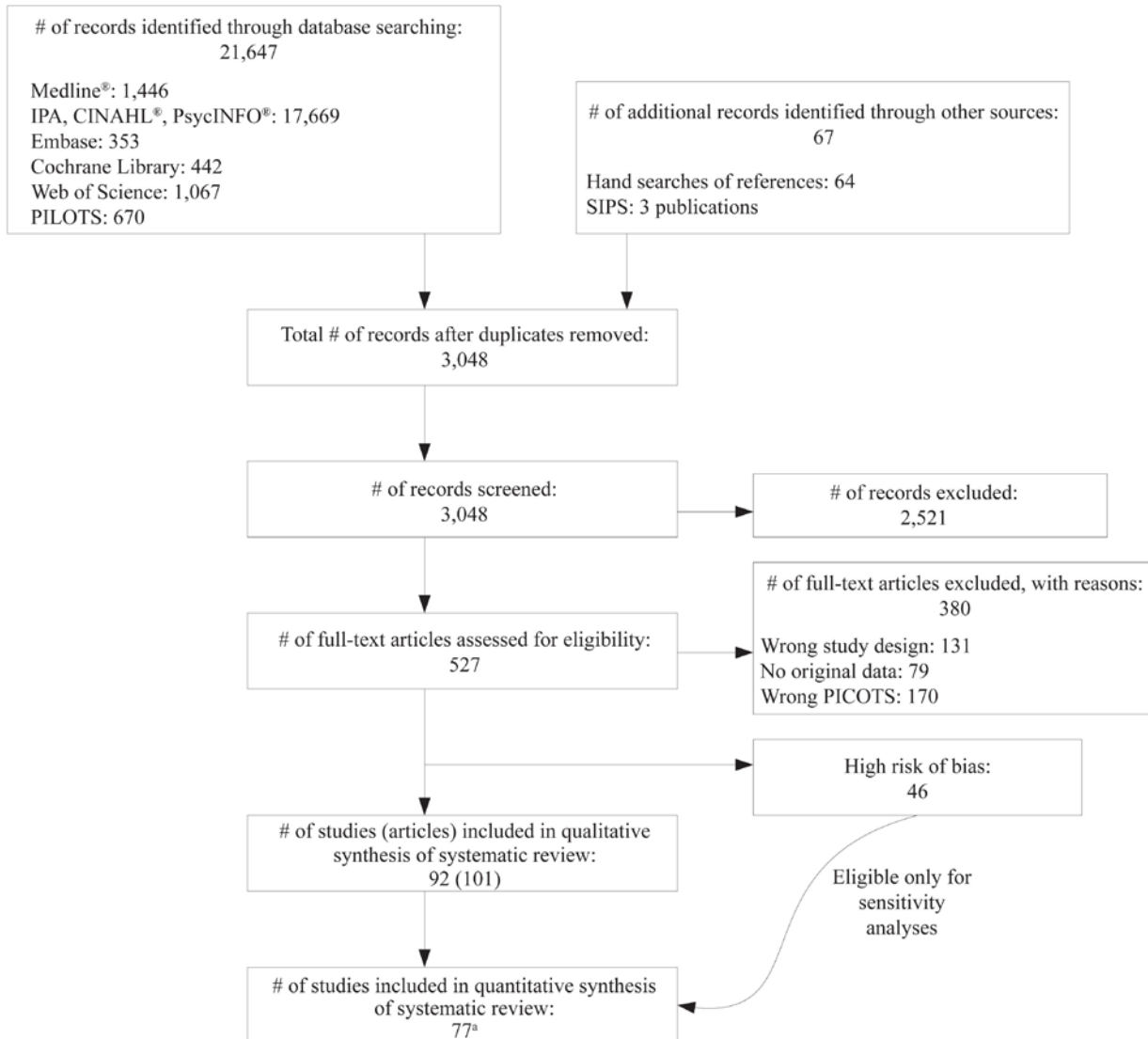
## **Applicability**

We assessed applicability of the evidence following guidance from the “Methods Guide for Effectiveness and Comparative Effectiveness Reviews.”<sup>24</sup> 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**



PICOTS = populations, interventions, comparators, outcomes, timing, settings; SIPS = scientific information packets

<sup>a</sup>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<br>Effect Size (95% CI) <sup>a</sup>  | Strength of Evidence |
|------------------------------|---------------------|---|----------------------|
| CPT                          | PTSD symptoms       | SMD, -1.40 (-1.95 to -0.85; 4 trials, N=299)<br>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 <sup>b</sup>              | 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)<br>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)<br>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)<br>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  
<sup>a</sup>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. <sup>c</sup> 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. <sup>d</sup> 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.

<sup>b</sup>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.

<sup>c</sup>Source: Cohen J. Statistical Power Analysis for the Behavioral Sciences. Hillsdale, NJ: L. Erlbaum Associates; 1988.

<sup>d</sup>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<br>Effect Size (95% CI) <sup>a</sup>   | 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) <sup>b</sup>   | 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 <sup>c</sup> | PTSD symptoms       | SMD, 0.04 (-0.12 to 0.20; 4 trials, N=594)<br>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

<sup>a</sup>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.<sup>d</sup> 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.

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

<sup>c</sup>Active controls were relapse prevention, psychoeducation, and treatment as usual in a VA substance use disorders clinic.

<sup>d</sup>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.

<sup>e</sup>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.

<sup>f</sup>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.<sup>25</sup> 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<br>Effect Size (95% CI) <sup>a</sup>   | Strength of Evidence |
|------------------|----------------|---------------------|--|----------------------|
| Anti-convulsant  | Topiramate     | PTSD symptoms       | WMD, -15.5 (-19.4 to -11.7; 3 trials, N=142)<br>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)<br>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)<br>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)<br>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)<br>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)<br>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)<br>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 <sup>b</sup>  | Moderate             |
|                  |                | Depression symptoms | MADRS WMD, -5.7 (-7.1 to -4.3; 2 trials, N=886)<br>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)<br>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)<br>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

<sup>a</sup>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.<sup>c</sup> 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.<sup>d</sup> For depression symptoms, WMD data are between-group difference for mean change from baseline in BDI, HAMD, or MADRS score—whichever measure is specified.

<sup>b</sup>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).<sup>c</sup> The other trial contributing data for this outcome found similar percentages of subjects achieving remission (33% vs. 14%).<sup>f</sup>

<sup>c</sup>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.

<sup>d</sup>Source: Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. Hillsdale, NJ: L. Erlbaum Associates; 1988.

<sup>e</sup>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.

<sup>f</sup>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.<sup>26</sup> 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 follow up, 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.<sup>27,28</sup> 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.<sup>27</sup> 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.<sup>2,12-15,17</sup> 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<sup>2</sup>) 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.<sup>12-14,17</sup> 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.<sup>15</sup> 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),<sup>29</sup> CBT-mixed (N=45),<sup>30</sup> and topiramate (N=67).<sup>31</sup> For each of the following, two trials focused on combat-related trauma: CPT (total N=119),<sup>32,33</sup> exposure-based therapy (total N=370;<sup>34,35</sup> another study of exposure-based therapy enrolled those with combat- and terror-related PTSD<sup>36</sup>); and fluoxetine (total N=365).<sup>37,38</sup> Three trials assessing sertraline (total N=281) enrolled a majority of subjects with combat-related trauma.<sup>39-41</sup>

## **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.<sup>42</sup> 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.<sup>43-45</sup> 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.<sup>46</sup> 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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# Introduction

## 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,”<sup>1</sup> 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 symptoms; (2) avoidance or numbing symptoms (or both); and (3) hyperarousal symptoms. The full DSM-IV TR criteria are listed in Table 1.

**Table 1. Diagnostic criteria (DSM-IV-TR) for posttraumatic stress disorder**

| Criterion   | Symptom or Description   |
|---|--|
| Criterion A: Trauma (both)                                    | <ul style="list-style-type: none"> <li>• Traumatic event that involved actual or threatened death, serious injury, or threat to physical integrity</li> <li>• Intense response of fear, helplessness, or horror</li> </ul>   |
| Criterion B: Reexperiencing symptoms (one or more)            | <ul style="list-style-type: none"> <li>• Intrusive recollections of events</li> <li>• Recurrent distressing dreams of the event</li> <li>• Acting or feeling as if the traumatic event were recurring</li> <li>• Distress at internal or external reminders of the trauma</li> <li>• Physiological reaction to internal or external reminders</li> </ul>   |
| Criterion C: Persistent avoidance and numbing (three or more) | <ul style="list-style-type: none"> <li>• Avoidance of thoughts, feelings, or conversations associated with trauma</li> <li>• Avoidance of activities, places, or people that arouse recollections of trauma</li> <li>• Failure to recall an important aspect of trauma</li> <li>• Loss of interest or participation in significant activities</li> <li>• Detachment from others</li> <li>• Restricted range of affect</li> <li>• Lost sense of the future</li> </ul> |
| Criterion D: Hyperarousal (two or more)                       | <ul style="list-style-type: none"> <li>• Difficulty falling or staying asleep</li> <li>• Irritability or outburst of anger</li> <li>• Difficulty concentrating</li> <li>• Hypervigilance</li> <li>• Exaggerated startle response</li> </ul>  |
| Criterion E: Duration of disturbance                          | <ul style="list-style-type: none"> <li>• Duration of disturbance symptoms is more than 1 month</li> </ul>  |
| Criterion F: Clinically significant distress or impairment    | <ul style="list-style-type: none"> <li>• Disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of function</li> </ul>   |

Traumatic events that are directly experienced include the following: 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.<sup>1</sup> According to a 2008 Institute of Medicine (IOM) report on the treatment of patients with PTSD, the condition “...develops in a significant minority (up to a third) of individuals who are exposed to extreme stressors, and symptoms of PTSD almost always emerge within days of the trauma.”<sup>2</sup> PTSD is also frequently associated with other psychiatric disorders; data from epidemiologic studies have found that a high percentage of individuals with PTSD have another psychiatric disorder, most notably substance use disorders or major depressive disorder.<sup>3</sup>

## Epidemiology of PTSD

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.<sup>4</sup> Although approximately 50 percent of those diagnosed with PTSD improve without treatment in one year, 10 percent to 20 percent develop a chronic unremitting course.<sup>5</sup>

The 2000 National Comorbidity Survey—Replication (NCS-R) estimated lifetime prevalence of PTSD among adults in the United States to be 6.8 percent (9.7% in women and 3.4% in men) and current (12-month) prevalence to be 3.6 percent (5.2% in women and 1.8% in men).<sup>6</sup> The probability of development of PTSD is a function of both the probability of exposure to traumatic events and the risk of developing PTSD among those exposed to trauma.

Some demographic or occupational groups, such as military personnel, are at higher risk of PTSD because of higher rates of exposure to trauma. 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<sup>6</sup> among Vietnam veterans. Surveys of military personnel returning from operations in Afghanistan and Iraq 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.<sup>7</sup> In addition to lives lost because of the increased risk of suicide,<sup>8</sup> PTSD is associated with high medical costs and high social costs, because PTSD is a strong risk factor for poor work performance and associated job losses and familial discord. The economic cost of the PTSD and depression cases among Operation Enduring Freedom and Operation Iraqi Freedom veterans alone (including medical care, forgone productivity, and lives lost through suicide) is estimated at \$4 billion to \$6 billion over 2 years.<sup>9</sup>

Many people with PTSD do not seek treatment. Among those who do, many receive inadequate treatment or care that is not empirically based. Several PTSD outcome studies demonstrate the cost-effectiveness of early diagnosis and appropriate treatment, especially when compared with the cost of inadequate or ineffective treatment occurring before a correct diagnosis.<sup>10</sup> In addition to consequences related to PTSD, people affected by these disorders have higher rates of psychiatric comorbidity, suffer decreased role functioning such as work impairment (on average, 3.6 days of work impairment per month), and experience many other adverse life-course consequences (e.g., reduced educational attainment, work earnings, marriage attainment, and child rearing).<sup>11</sup>

## **Treatment Strategies for PTSD**

One primary outcome in PTSD treatment is symptom reduction, which includes both clinician-rated and self-reported measures. Appendix A describes each PTSD measure in detail. In addition to symptom reduction, other outcomes used in practice include remission (i.e., no longer having symptoms); loss of PTSD diagnosis; prevention or reduction of coexisting medical or psychiatric conditions (e.g., depressive symptoms, anxiety symptoms); improved quality of life; improved functioning; and ability to return to work or to active duty.

Treatments available for PTSD span a variety of psychological and pharmacological categories. These interventions are used both separately and in combination with one another, and both appear to be mainstays of treatment cited in treatment guidelines.<sup>12</sup> Although no clearly defined “preferred” approach is available for managing patients with PTSD, each of these guidelines supports the use of trauma-focused psychological interventions (i.e., those that treat PTSD by directly addressing thoughts, feelings, or memories of the traumatic event) for adults with PTSD, and all, except the IOM report,<sup>2</sup> recognize at least some benefit of pharmacological treatments for PTSD.<sup>12</sup> Indeed, 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.<sup>13-16</sup> One guideline, from the International Society for Traumatic Stress Studies (ISTSS), recognizes that practical considerations, such as unavailability of trauma-focused psychological treatment or patient preferences, may guide treatment decisions.<sup>17</sup>

## **Psychological Interventions**

Specific psychological interventions that have been studied for the treatment of patients with PTSD are described below. They include the following: brief eclectic psychotherapy; cognitive behavioral therapy (CBT), such as cognitive therapy, cognitive processing therapy, cognitive restructuring, coping skills therapies (including stress inoculation training), 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 either reexperiencing and working through trauma-related memories and emotions, targeting distorted cognitions, teaching better methods of managing trauma-related stressors, or a combination of these approaches.<sup>2</sup> The therapies are delivered predominantly to individuals; some can also be conducted in a group setting.<sup>18,19</sup> We will describe the individual form by default; if the treatment is provided in a group context, we will specifically indicate that.

**Brief eclectic psychotherapy** is a 16-session manualized treatment for PTSD that combines cognitive-behavioral and psychodynamic approaches.<sup>20,21</sup> It consists of (1) psychoeducation, together with a partner or close friend; (2) imaginal exposure preceded by relaxation exercises, focused on catharsis of emotions of grief and helplessness; (3) writing tasks to express aggressive feelings and the use of mementos; (4) domain of meaning, focused on learning from the trauma; and (5) a farewell ritual, to end treatment. It was originally developed as a treatment for police officers, but it has also been used with other trauma samples.

**CBT** is a broad category of therapies based on principles of learning and conditioning and/or cognitive theory to treat disorders and includes components from both behavioral and cognitive therapy. In CBT, components such as exposure, cognitive restructuring, and various coping skills have been used either alone or in combination. Most forms of CBT consist of a minimum of 8 to 12 weekly sessions lasting 60 to 90 minutes. CBT can be administered either as group or individual therapy.<sup>2,17,22,23</sup> It has both specific and nonspecific (i.e., more general or *mixed*) types; three specific types are described below.

*Cognitive therapy* is used to describe interventions that are largely based on the cognitive model, which states that an individual's perception of a situation influences his or her emotional response to it. The general goal of cognitive therapy is to help people identify distorted thinking and to modify existing beliefs, so that they are better able to cope and change problematic behaviors. Cognitive therapy is generally considered to be brief, goal oriented, and time limited. Variants of cognitive therapy have been developed. Among these are cognitive restructuring and cognitive processing therapy.

*Cognitive processing therapy* includes psychoeducation, written accounts about the traumatic event, and cognitive restructuring addressing the beliefs about the event's meaning and the implications of the trauma for one's life.<sup>24</sup> The treatment is based on the idea that affective states, such as depressed mood, can interfere with emotional and cognitive processing of the trauma memory, which can lead to traumatic symptomatology. The manualized treatment is generally delivered over 12 sessions lasting 60 to 90 minutes.<sup>24</sup> (A manualized treatment is based on a

guidebook that defines the specific procedures and tactics used to implement the treatment; the use of a manual facilitates standardization of a therapy across settings and therapists.)

*Cognitive restructuring* is based on the theory that the interpretation of the event, rather than the event itself, determines an individual's mood. It aims to facilitate relearning thoughts and beliefs generated from a traumatic event, to increase awareness of dysfunctional trauma-related thoughts, and to correct or replace those thoughts with more adaptive and rational cognitions. Cognitive restructuring generally takes place over 8 to 12 sessions of 60 to 90 minutes.<sup>2,17</sup>

*Coping skills therapies* may include components such as stress inoculation training, assertiveness training, biofeedback (including brainwave neurofeedback), or relaxation training. These therapies may use techniques such as education, muscle relaxation training, breathing retraining, role playing, or similar interventions to manage anxiety or correct misunderstandings that developed at the time of trauma. The therapy is designed to increase coping skills for current situations. Most types of coping skills therapies require at least eight sessions of 60 to 90 minutes; more comprehensive interventions such as stress inoculation training require 10 to 14 sessions.<sup>2,17</sup> Of note, this category includes a range of active psychotherapeutic treatments (e.g., stress inoculation training) and some comparison treatments that are generally intended as a control group (e.g., relaxation). Consequently, in this report we do not attempt to determine any overall effect for this category (as one would not have sufficient clinical relevance); rather we determine results separately for the various therapies we have included in this category. In addition, not all of these coping skills are CBT—for example, a CBT protocol might include relaxation training, but relaxation is not exclusively CBT.

*Exposure-based therapy* involves confrontation with frightening stimuli related to the trauma and is continued until anxiety is reduced. Imaginal exposure uses mental imagery from memory or introduced in scenes presented to the patient by the therapist. In some cases, exposure is to the actual scene or similar events in life: *in vivo* exposure involves confronting real life situations that provoke anxiety and are avoided because of their association with the traumatic event (e.g., avoidance of tall buildings following experiencing an earthquake). The aim is to extinguish the conditioned emotional response to traumatic stimuli. By learning that nothing “bad” will happen during a traumatic event, the patient experiences less anxiety when confronted by stimuli related to the trauma and reduces or eliminates avoidance of feared situations. Exposure therapy is typically conducted for 8 to 12 weekly or biweekly sessions lasting 60 to 90 minutes.<sup>2,10,17</sup> Prolonged exposure is a manualized intervention including both imaginal and *in vivo* exposure components.<sup>25</sup>

In this report, we include a category for *CBT-mixed therapies* for studies of interventions that use components of CBT, but that don't quite fit cleanly into one of the other categories. The interventions in this category are somewhat heterogeneous in several ways, including how the authors defined and described “cognitive behavioral therapy.” Elements of CBT-mixed interventions may include psychoeducation, self-monitoring, stress management, relaxation training, skills training, exposure (imaginal, *in vivo*, or both), cognitive restructuring, guided imagery, mindfulness training, breathing retraining, crisis/safety planning, and relapse prevention. The studies varied as to how many sessions (if any) were dedicated to these elements and whether homework was assigned as part of the intervention.

In **EMDR** the patient is asked to hold the distressing image in mind, along with the associated negative cognition and bodily sensations, while engaging in saccadic eye movements. After approximately 20 seconds, the therapist asks the patient to “blank it out,” take a deep breath, and note any changes occurring in the image, sensations, thoughts, or emotions. The

process is repeated until desensitization has occurred (i.e., patient reports little or no distress on the Subjective Units of Distress Scale), at which time the patient is asked to hold in mind a previously identified positive cognition, while engaging in saccadic eye movements, and rating the validity of this cognition while going through the procedure as outlined above. The saccadic eye movements were initially theorized to both interfere with working memory and elicit an orienting response, which lowers emotional arousal so that the trauma can be resolved. Although earlier versions of EMDR consisted of 1 to 3 sessions, current standards consist of 8 to 12 weekly 90-minute sessions.<sup>2,22</sup>

**Hypnosis** may be used as an adjunct to psychodynamic, cognitive-behavioral, or other therapies. It has been shown to enhance their efficacy for many clinical conditions.<sup>2,17</sup> Number and length of sessions vary widely.

**Interpersonal therapy** is a time-limited, dynamically informed psychotherapy that aims to alleviate patients' suffering and improve their interpersonal functioning. This type of therapy focuses specifically on interpersonal relationships; its goal is to help patients either improve their interpersonal relationships or change their expectations about them. In addition, it aims to help patients improve their social support so they can better manage their current interpersonal distress. Interpersonal therapy generally requires 10 to 20 weekly sessions in the "acute phase" followed by a time-unlimited "maintenance phase."<sup>26</sup>

**Psychodynamic therapy** explores the psychological meaning of a traumatic event. The goal is to bring unconscious memories into conscious awareness so that PTSD symptoms are reduced. The therapy presumes that the PTSD symptoms are the result of the unconscious memories. Psychodynamic therapy traditionally lasts from 3 months to 7 years.<sup>2,17,22</sup>

## Pharmacological Interventions

Pharmacotherapies, including selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, monoamine oxidase (MAO) inhibitors, other second-generation antidepressants, atypical antipsychotics, anticonvulsants or mood stabilizers, adrenergic agents, benzodiazepines, and other treatments such as naltrexone, cycloserine, and inositol have been studied for treatment of patients with PTSD.<sup>2</sup> Specific medications within these drug classes that have been studied or used in treating PTSD are listed in Table 2. Currently, only paroxetine and sertraline are approved by the U.S. Food and Drug Administration for treatment of patients with PTSD.

**Table 2. Medications that have been used or studied for adults with PTSD**

| Class  | Drug  |
|--|---|
| Selective serotonin reuptake inhibitors          | Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline |
| Serotonin and norepinephrine reuptake inhibitors | Desvenlafaxine, venlafaxine, duloxetine                                   |
| Other second-generation antidepressants          | Bupropion, mirtazapine, nefazodone, trazodone                             |
| Tricyclic antidepressants                        | Imipramine, amitriptyline, desipramine                                    |
| Monoamine oxidase inhibitors                     | Phenelzine, brofaromine   |
| Alpha blockers                                   | Prazosin  |
| Second-generation (atypical) antipsychotics      | Olanzapine, risperidone   |
| Anticonvulsants (mood stabilizers)               | Topiramate, tiagabine, lamotrigine, carbamazepine, divalproex             |
| Benzodiazepines                                  | Alprazolam, diazepam, lorazepam, clonazepam                               |
| Other medications                                | Naltrexone, cycloserine, inositol, guanfacine                             |

## Existing Guidance

Numerous organizations have produced guidelines for the treatment of patients with PTSD, including the American Psychiatric Association (APA), the U.S. Department of Veterans Affairs (VA)/Department of Defense (DoD), the United Kingdom's National Institute for Health and Clinical Excellence (NICE), ISTSS, the IOM, the American Academy of Child and Adolescent Psychiatry (AACAP), and the Australian National Health and Medical Research Council (NHMRC).<sup>12</sup> Four of these guidelines (VA/DoD, NICE, NHMRC, IOM) were based on systematic reviews; the other three guidelines (APA, ISTSS, AACAP) were based on expert consensus and less structured literature reviews.<sup>12</sup>

All of the existing guidelines agree that trauma-focused psychological interventions are effective, empirically supported first-line treatments for PTSD.<sup>12-15,17</sup> Four of the six guidelines (VA/DoD, NICE, NHMRC, and ISTSS) give the strongest level of recommendation for EMDR; the APA guideline gives a second-level recommendation for EMDR, and the IOM guidelines conclude that the evidence is inadequate to determine the efficacy of EMDR, owing to methodological limitations and conflicting findings in the published studies.

There is less agreement in the guidelines about the effectiveness of pharmacotherapy. For example, three of the six guidelines (VA/DoD, APA, ISTSS) give SSRIs the strongest level of recommendation, two guidelines (NICE, NHMRC) give them a second-level recommendation, and one (IOM) concluded that the evidence was insufficient to determine the efficacy of SSRIs and other medications for the treatment of PTSD.

Guidelines have arrived at different conclusions about the efficacy of certain classes of treatment or specific treatments, possibly because of differences in selection criteria and methods used to assess risk of bias of the existing literature. For example, based on its evaluation of attrition rates and handling of missing data, the IOM Committee on the Treatment of PTSD concluded that the evidence on specific pharmacological drugs was inadequate to determine efficacy.<sup>2</sup> The VA/DoD clinical practice guideline, which included some trials that the IOM considered to be flawed, concluded that SSRIs have substantial benefit; and some other agents offer some benefit for PTSD treatment.<sup>13</sup> Of the 14 studies included by the IOM Committee to evaluate the efficacy of SSRI antidepressants, 7 were considered to have major limitations due to high attrition and/or the methods they used to deal with missing data.

As a result of differences in guideline recommendations, some clinical uncertainty exists about what treatment to select among all the evidence-based approaches, particularly when trauma-focused psychological therapy is unavailable or unacceptable to the patient. In addition to the clinical uncertainty about the effectiveness of some of the psychological treatments, the effectiveness and potential harms of medications for PTSD are uncertain. Furthermore, patient preferences need to be incorporated into shared decisionmaking about treatment because they can influence treatment adherence and therapeutic response.

## Scope and Key Questions

A member of the American Psychological Association nominated this topic and the Agency for Healthcare Research and Quality (AHRQ) selected it through the topic prioritization process. Highlighting the timeliness and relevance of this topic, the IOM and various Federal agencies (e.g., the VA Health Administration) have identified PTSD as a priority area for quality improvement and comparative effectiveness research; these decisions are based, in part, on evidence of higher rates of PTSD among service members returning from operations in

Afghanistan and Iraq than previously reported and their increased need for mental health services.<sup>9</sup>

We approach each key question by considering the relevant Populations, Interventions, Comparators, Outcomes, Timing, and Settings (PICOTS). Our report focuses on clinically relevant medications (those that are commonly used, those with sufficient literature for systematic review, and those of greatest interest to the developers of clinical practice guidelines). Further, we also address the clinical importance of moderators or subgroups of patients receiving PTSD treatment, as the evidence allows, such as differences by gender, comorbidities, refugee status, and military, VA, or civilian status. Our report is limited to people with a diagnosis of PTSD; it does *not* address those at risk of developing PTSD or interventions to prevent the development of PTSD.

The main objective of this report is to conduct a systematic review and meta-analysis of the 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)?

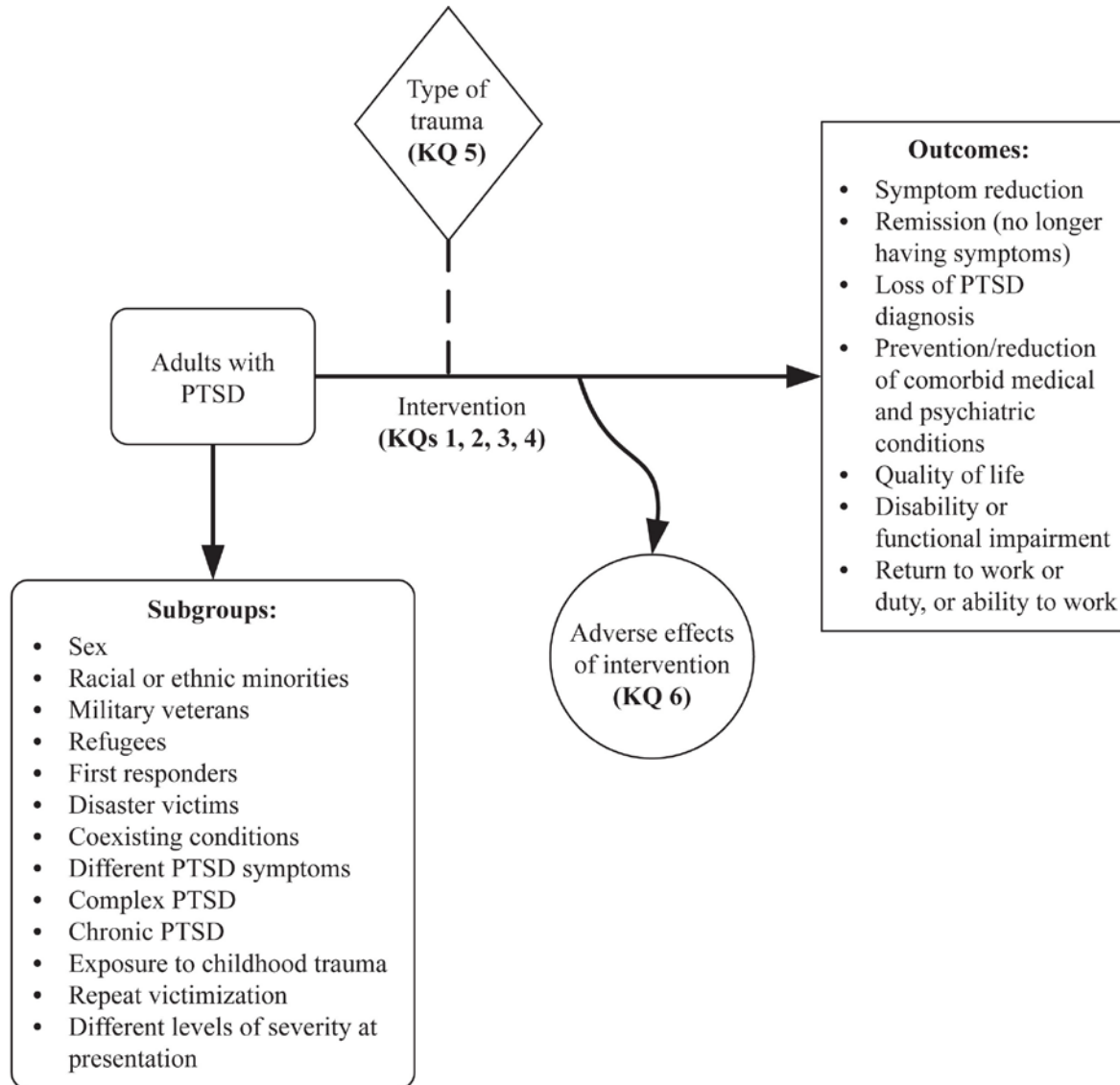
**KQ 5:** Are any of the treatment approaches for PTSD more effective than other approaches for victims of particular types of trauma?

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

## **Analytic Framework**

We developed an analytic framework to guide the systematic review process (Figure 1). The population consists of adult patients with a diagnosis of PTSD. Because we wanted to assess whether the evidence suggested any differences in response to various treatments for trauma subgroups, such as military personnel and those with comorbid psychiatric or medical conditions, we identified subgroups of interest as noted in the figure.

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



KQ = Key Question; PTSD = posttraumatic stress disorder

For each of the first five KQs, the same outcomes of interest are considered. KQ 1 compares the evidence of effectiveness of psychological interventions for improving these outcomes. KQ 2 examines the evidence of effectiveness of pharmacological treatments, considering both strategies that compare a single agent versus another single agent, as well as those that compare augmenting an ongoing treatment with one versus another pharmacological intervention. KQ 3 examines the direct evidence comparing various psychological treatments with pharmacological treatments. KQ 4 considers the evidence comparing combinations of psychological and pharmacological treatments with a single treatment intervention (either one psychological or one pharmacological treatment). KQ 5 considers specific subtypes of trauma, and assesses whether any particular treatment approach is more effective than another for that particular trauma subtype. KQ 6 compares the adverse events associated with the various interventions of interest.

## Methods

The methods for this review follow the methods suggested in the Agency for Healthcare Research and Quality (AHRQ) “Methods Guide for Effectiveness and Comparative Effectiveness Reviews” ([www.effectivehealthcare.ahrq.gov/methodsguide.cfm](http://www.effectivehealthcare.ahrq.gov/methodsguide.cfm)).

### Topic Refinement and Review Protocol

A member of the American Psychological Association nominated the topic of posttraumatic stress disorder (PTSD) in adults; the association aims to use high-quality evidence syntheses to inform guideline development. During the topic development and refinement processes, we engaged in a public process to develop a draft and final protocol for the comparative effectiveness review (CER) process. We generated an analytic framework, preliminary Key Questions (KQs), and preliminary inclusion/exclusion criteria in the form of PICOTS (populations, interventions, comparators, outcomes, timing, settings). The processes were guided by the information provided by the topic nominator, a scan of the literature, methods and content experts, and Key Informants. We worked with six Key Informants during the topic refinement, three of whom were also subsequently members of our Technical Expert Panel (TEP) for this report. Key Informants and TEP members participated in conference calls and discussions through email to review the analytic framework, KQs, and PICOTS; discuss the preliminary assessment of the literature; provide input on the information and categories included in evidence tables; and provide input on the data analysis plan.

Our KQs were posted for public comment on AHRQ’s Effective Health Care Web site from September 6, 2011, through October 4, 2011, and were revised as needed after review of the comments and discussion with the TEP, primarily for clarity and readability. We then drafted a protocol for this CER that was posted on AHRQ’s Effective Health Care Web site on December 20, 2011.

### Literature Search Strategy

#### Search Strategy

To identify articles relevant to each KQ, we searched MEDLINE<sup>®</sup>, the Cochrane Library, the Published International Literature on Traumatic Stress (PILOTS) database, International Pharmaceutical Abstracts, CINAHL<sup>®</sup>, PsycINFO<sup>®</sup>, Web of Science, and EMBASE. The full search strategy is presented in Appendix B. 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 population and interventions of interest. We reviewed our search strategy with the TEP and incorporated their input into our search strategy. 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 limited the electronic searches to English-language and human-only studies. We searched sources for publications from January 1, 1980, to May 24, 2012. The start date was selected based on the introduction of the definition of PTSD as a clinical entity with the publication of DSM-III,<sup>27</sup> the earliest publication date of relevant studies found in previous systematic reviews, and expert opinion regarding when the earliest literature on this topic was published.

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. We imported all citations into an EndNote® X4 electronic database.

We searched for unpublished studies relevant to this review using ClinicalTrials.gov, the Web site for the Food and Drug Administration, and the World Health Organization's International Clinical Trials Registry Platform. In addition, the Scientific Resource Center requested scientific information packets (SIPs) from the relevant pharmaceutical companies, asking for any unpublished studies or data relevant for this CER. We received seven SIPs (from Alkermes, Inc., Forest Laboratories, Janssen Pharmaceuticals, Jazz Pharmaceuticals, Sanofi-Aventis, Valeant Pharmaceuticals International, and Validus Pharmaceuticals); from these materials, we identified three eligible published studies and no eligible unpublished studies. To include information from SIPs, we required that studies meet all inclusion criteria and contain enough information on research methods to be able to assess risk of bias.

## **Inclusion and Exclusion Criteria**

We developed eligibility (inclusion and exclusion) criteria with respect to PICOTS, and study designs and durations for each KQ (Table 3). We did not include studies of complementary and alternative medicine interventions in this review. Due to the already large scope of this review, and time and resources, it was important that we focus on the interventions of greatest interest to stakeholders. During the topic development and refinement process, complementary and alternative interventions were considered, and the general consensus was that such interventions were of less interest than psychological and pharmacological interventions, and less likely to have sufficient evidence for synthesis. Using clinical expert and TEP input about the minimal time required for an adequate therapeutic trial (i.e., the treatment duration needed to show benefits), we required studies to be at least 4 weeks in duration from the time of group assignment.

Observational studies that compare the effectiveness of various treatments for PTSD have a very high risk of selection bias and confounding. We feel that the results should not be used to make decisions about efficacy/effectiveness. For KQ 6, we chose a sample size cutoff of 500 for prospective cohort studies and case-control studies for several reasons: (1) our topic refinement process found a large number of randomized controlled trials in this field and we weighed the tradeoffs between increasing comprehensiveness by reviewing all possible observational studies that present harms and the decreased quality that may occur from increased risk of bias, as well as considering our resource and time constraints; (2) to supplement the trial literature, large observational studies with the lowest potential risk of bias were eligible for inclusion; and (3) our TEP supported this approach.



**Table 3. Eligibility criteria**

| Category      | Inclusion  | Exclusion  |
|---------------|--|--|
| Population    | Adults with PTSD based on “Diagnostic and Statistical Manual of Mental Disorders” criteria   | <ul style="list-style-type: none"> <li>• Children</li> <li>• People at risk of developing PTSD</li> <li>• People with subsyndromal PTSD</li> </ul>                                     |
| Interventions | <p>Psychological interventions including:</p> <ul style="list-style-type: none"> <li>• Brief eclectic psychotherapy</li> <li>• Cognitive-behavioral therapy, such as cognitive restructuring, cognitive processing therapy, exposure-based therapies, and coping skills therapy (may include components such as stress inoculation training, assertiveness training, biofeedback [including brainwave neurofeedback], or relaxation training)</li> <li>• Eye movement desensitization and reprocessing</li> <li>• Hypnosis or hypnotherapy</li> <li>• Interpersonal therapy</li> <li>• Psychodynamic therapy</li> </ul> <p>Pharmacological interventions including:</p> <ul style="list-style-type: none"> <li>• Selective serotonin reuptake inhibitors (SSRIs: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline)</li> <li>• Serotonin and norepinephrine reuptake inhibitors (SNRIs: desvenlafaxine, venlafaxine, and duloxetine)</li> <li>• Other second-generation antidepressants (bupropion, mirtazapine, nefazodone, and trazodone)</li> <li>• Tricyclic antidepressants (imipramine, amitriptyline, and desipramine)</li> <li>• Alpha blockers (prazosin)</li> <li>• Atypical antipsychotics (olanzapine and risperidone)</li> <li>• Benzodiazepines (alprazolam, diazepam, lorazepam, and clonazepam)</li> <li>• Anticonvulsants/mood stabilizers (topiramate, tiagabine, lamotrigine, carbamazepine, and divalproex)</li> </ul> | <ul style="list-style-type: none"> <li>• Complementary and alternative medicine approaches</li> <li>• Psychological or pharmacological interventions not listed as included</li> </ul> |
| Comparators   | <p>By KQ:</p> <ul style="list-style-type: none"> <li>• KQ 1: Psychological interventions listed above compared with one another or with waitlist assignment, usual care (as defined by the study), no intervention, or sham</li> <li>• KQ 2: Pharmacological interventions listed above compared with one another or to placebo</li> <li>• KQ 3: Psychological interventions listed above compared with pharmacologic interventions listed above</li> <li>• KQ 4: Combinations of psychological and pharmacological interventions compared with either one alone (placebo, waitlist assignment, usual care, no intervention, or sham may be used in conjunction with the monotherapy arm)</li> <li>• KQs 5 and 6: All studies including the comparators for KQs 1 through 4 will be eligible</li> </ul>  |  |

**Table 3. Eligibility criteria (continued)**

| Category                                | Inclusion  | Exclusion  |
|---|--|--|
| Outcomes                                | <ul style="list-style-type: none"> <li>• PTSD symptom reduction, both assessor-rated and self-reported: as measured by the Clinician-Administered PTSD Scale (CAPS), and previous versions of the CAPS, such as the Clinician-Administered PTSD Scale Part 2 (CAPS-2); the Impact of Event Scale (IES); the Impact of Event Scale–Revised (IES-R); the Modified PTSD Symptom Scale (MPSS-SR); the self-rated PTSD symptoms Checklist (PCL); the PTSD Symptom Scale–Interview (PSS-I); the PTSD Symptom Scale–Self-report Version (PSS-SR); or the Structured Interview for PTSD (SI-PTSD)</li> <li>• Prevention or reduction of comorbid medical or psychiatric conditions (e.g., coronary artery disease; depressive symptoms; anxiety symptoms; suicidal ideation, plans, or attempts; and substance use, abuse, or dependence)</li> <li>• Remission (no longer having symptoms)</li> <li>• Loss of PTSD diagnosis</li> <li>• Quality of life<sup>a</sup></li> <li>• Disability or functional impairment<sup>a</sup></li> <li>• Return to work or return to active duty</li> <li>• Adverse events: overall adverse events, withdrawals due to adverse events, and specific adverse events (including, but not limited to, disturbed sleep, increased agitation, sedation, weight gain, metabolic side effects, and mortality)</li> </ul> |  |
| Publication language                    | English  | All other languages  |
| Time period                             | 1980 to present; searches to be updated after draft report goes out for peer review  |  |
| Time period                             | 1980 to present; searches to be updated after draft report goes out for peer review  |  |
| Settings                                | <ul style="list-style-type: none"> <li>• Outpatient and inpatient primary care or specialty mental health care settings</li> <li>• Community settings (e.g., churches, community health centers, rape crisis centers)</li> <li>• Military settings</li> </ul>  |  |
| Geography                               | No limits  |  |
| Study duration                          | At least 4 weeks from the time of group assignment for trials  |  |
| Admissible evidence for KQs 1 through 5 | <p>Original research</p> <p>Randomized controlled trials with no sample size limit</p> <p>For KQ 5 (focused on whether any treatment approaches for PTSD are more effective than others for victims of particular types of trauma), information within the trials meeting inclusion criteria for KQs 1 through 4</p>   | <ul style="list-style-type: none"> <li>• Observational studies</li> <li>• Systematic reviews and meta-analyses</li> <li>• Nonsystematic reviews</li> <li>• Editorials</li> <li>• Letters to the editor</li> <li>• Articles rated as high risk of bias<sup>b</sup></li> </ul> |

**Table 3. Eligibility criteria (continued)**

| Category                                       | Inclusion  | Exclusion  |
|--|--|--|
| Admissible evidence for KQ 6 (adverse effects) | <ul style="list-style-type: none"> <li>• Data from trials included in KQs 1 through 4 that reported adverse effects</li> <li>• Nonrandomized controlled trials of any sample size</li> <li>• Prospective cohort studies with an eligible comparison group with a sample size of at least 500</li> <li>• Case-control studies with a sample size of at least 500</li> </ul> | <ul style="list-style-type: none"> <li>• Case series</li> <li>• Case reports</li> <li>• Systematic reviews and meta-analyses</li> <li>• Nonsystematic reviews</li> <li>• Editorials</li> <li>• Letters to the editor</li> <li>• Articles rated as high risk of bias<sup>b</sup></li> <li>• Studies with historical, rather than concurrent, control groups</li> <li>• Pre/post studies without a separate control group</li> </ul> |

## Study Selection

Two trained 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 underwent a full-text review. For studies that lacked adequate information to determine inclusion or exclusion, we retrieved the full text and then made the determination in that phase.

We retrieved the full text of all articles included during the title and abstract review phase. Two trained members of the research team independently reviewed each full-text article for inclusion or exclusion based on the eligibility criteria described above. If both reviewers agreed that a study did not meet the eligibility criteria, we excluded it. If the reviewers disagreed, they resolved conflicts by discussion and consensus or by consulting a third senior member of the review team.

All results in both review stages were tracked in an EndNote® database. We recorded the principal reason that each excluded full-text publication did not satisfy the eligibility criteria (Appendix C).

## Data Extraction

For studies that met our inclusion criteria, we extracted important information into evidence tables. We designed and used structured data extraction forms to gather pertinent information from each article, including characteristics of study populations, settings, interventions, comparators, study designs, methods, and results. Trained reviewers extracted the relevant data from each included article into the evidence tables. All data abstractions were reviewed for completeness and accuracy by a second member of the team. We recorded intention-to-treat results if available. All data abstraction was performed using Microsoft Excel® software. Evidence tables containing all extracted data of included studies are presented in Appendix D, organized by characteristics of included studies, characteristics of study populations, description of interventions, results for benefits, subgroup analyses, and results for harms. Within each of these evidence tables, studies are ordered alphabetically by the last name of the first author.

## Risk of Bias Assessment of Individual Studies

To assess the risk of bias (i.e., internal validity) of studies, we used predefined criteria based on the AHRQ “Methods Guide for Comparative Effectiveness Reviews,”<sup>28</sup> including questions to assess selection bias, confounding, performance bias, detection bias, and attrition bias (i.e., those about adequacy of randomization, allocation concealment, similarity of groups at baseline, masking, attrition, whether intention-to-treat analysis was used, method of handling dropouts and missing data, validity and reliability of outcome measures, and treatment fidelity). Appendix E provides the 12 specific questions used for evaluating the risk of bias of all included studies. It also includes a table showing the responses to these questions and risk of bias ratings for each study and then an explanation of the rationale for all high risk of bias ratings.

In general terms, results from a study assessed as having low risk of bias are considered to be valid. A study with moderate risk of bias is susceptible to some risk of bias but probably not enough to invalidate its results. A study assessed as high risk of bias has significant risk of bias (e.g., stemming from serious issues in design, conduct, or analysis) that may invalidate its results. We determined the risk of bias rating via appraisal of responses to all 12 questions assessing the various types of bias listed above. We did not use a quantitative approach (e.g., adding up how many favorable or unfavorable responses were given), but we did require favorable responses to at least 10 questions to give a low risk of bias rating, with any unfavorable responses being of relatively minor concern (e.g., lack of provider masking in studies of psychological interventions, which is generally not considered possible).

We gave high risk of bias ratings to studies that we determined to have a fatal flaw (defined as a methodological shortcoming that leads to a very high risk of bias) in one or more categories based on our qualitative assessment. Reasons for high risk of bias ratings included high risk of selection bias due to inadequate method of randomization (e.g., alternating) and resulting baseline differences between groups with no subsequent approach to handle potential confounders, attrition  $\geq 40$  percent or differential attrition  $\geq 30$  percent, risk of attrition bias (attrition over 20% or differential attrition over 15%) along with inadequate handling of missing data (e.g., completers analysis with nothing done to address missing data), and other combinations of multiple risk of bias concerns. Appendix E provides our rationale for each high risk of bias rating.

The majority of studies that we rated as high risk of bias had numerous problems. On average, they received unfavorable responses to 8 of our specific risk of bias assessment questions. All but one study rated as high risk of bias had unfavorable responses to 5 or more questions. For that study, risk of attrition bias was very high (approximately 50% attrition) and we had concerns about selection bias due to baseline differences between groups.<sup>29</sup> The most common methodological shortcomings contributing to high risk of bias ratings were high rates of attrition or differential attrition, inadequate methods used to handle missing data, and lack of intention-to-treat analysis.

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 and main analyses; we included them only in sensitivity analyses.

## Data Synthesis

Because of controversy about whether existing evidence supports the efficacy of many of the included interventions, we decided to focus first on assessing which interventions have evidence of efficacy—by evaluating placebo-controlled studies for the pharmacotherapies and by evaluating waitlist, usual care, or placebo-controlled studies of the psychotherapies (i.e., studies with an inactive control). Then, we assessed head-to-head trials.

To determine the comparative effectiveness of the various interventions, we first focused on direct, comparative evidence if it was available. When direct evidence was not available, we used indirect evidence from, for example, comparisons with placebo. For comparing the efficacy of pharmacological interventions with each other, we conducted a network meta-analysis, including both head-to-head and placebo-controlled trials, as described below.

We conducted quantitative synthesis using meta-analyses of outcomes reported by multiple studies that were homogeneous enough to justify combining their results. To determine whether meta-analyses were appropriate, we assessed the clinical and methodological heterogeneity of the studies under consideration following established guidance.<sup>30</sup> We did this by qualitatively assessing the PICOTS of the included studies, looking for similarities and differences. 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 found sufficient data to conduct meta-analyses for some comparisons of interest for the following outcomes: change in PTSD symptoms (measured by several different instruments, including the Clinician-Administered PTSD Scale [CAPS], Impact of Event Scale [IES], Davidson Trauma Scale [DTS]), remission, loss of PTSD diagnosis, reduction of comorbid depression or anxiety (e.g., measured by Beck Depression Inventory [DBI], Hamilton Depression Scale [HAM-D], Montgomery-Asberg Depression Rating Scale [MADRS], Hamilton Anxiety Scale [HAM-A]), quality of life (e.g., Quality of Life Enjoyment and Life Satisfaction [Q-LES-Q]), functional impairment (e.g., Sheehan Disability Scale [SDS]), rate of withdrawals due to adverse events, and specific adverse events (e.g., headache, nausea, insomnia). For our analyses comparing medications with placebo, we stratified analyses for each drug class by medication to provide pooled point estimates for each medication compared with placebo.

Random-effects models using the inverse-variance weighted method were used to estimate pooled effects.<sup>31</sup> For continuous outcomes (e.g., scales for PTSD symptom reduction) measured with the same scale (e.g., CAPS), we report the weighted mean difference between intervention and control. When multiple scales were combined in one meta-analysis, the standardized mean difference, Cohen's *d*, was used. For binary outcomes (e.g., remission, loss of PTSD diagnosis, adverse events), we calculated risk differences between groups. We calculated rates using the number of all randomized patients as the denominator to reflect a true intention-to-treat analysis. Forest plots graphically summarize results of individual studies and of the pooled analyses (Appendix F).<sup>32</sup>

For analyses of the efficacy of psychological interventions, our main analyses include studies with both waitlist and usual care (or treatment as usual) control groups. We stratified our meta-analyses by comparison group to show how the effect size and confidence interval would differ if we only included studies with a waitlist control, as opposed to including those with both waitlist and usual care controls. The usual care control groups in the included trials were often not described in much detail, making it difficult to determine whether the people in those groups were receiving any care at all. In many studies, usual care groups seemed to be very similar to

waitlist groups (except that usual care groups were not on a waitlist to receive an intervention later). We only included studies with present-centered therapy, supportive therapy, or supportive counseling control groups in sensitivity analyses. In addition, for studies that referred to a control group as usual care or treatment as usual but described a clear intervention received by that group (e.g., the Seeking Safety study where the “treatment as usual” group was enrolled in a residential substance use treatment program<sup>33</sup>), we considered the comparison to be a head-to-head comparison, rather than a comparison with an inactive control.

For analyses comparing medications with placebo, we stratified analyses for each drug class by drug—to provide pooled point estimates for each drug compared with placebo and to show pooled point estimates for the drug class. 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. We restricted stratification by trauma population to interventions that had evidence of efficacy and that had a sufficient number of studies to warrant the stratification.

For each meta-analysis, we conducted two types of sensitivity analyses. First, we calculated a series of pooled effects by removing each study from the analysis separately to determine the influence of each study on the findings. Second, we added studies excluded for having high risk of bias and calculated a pooled effect to determine whether including such studies would have changed conclusions.

The chi-squared statistic and the  $I^2$  statistic (the proportion of variation in study estimates due to heterogeneity) were calculated to assess statistical heterogeneity in effects between studies.<sup>34,35</sup> An  $I^2$  from 0 to 40 percent might not be important, 30 percent to 60 percent may represent moderate heterogeneity, 50 percent to 90 percent may represent substantial heterogeneity, and  $\geq 75$  percent represents considerable heterogeneity.<sup>36</sup> The importance of the observed value of  $I^2$  depends on the magnitude and direction of effects and on the strength of evidence for heterogeneity (e.g., p value from the chi-squared test, or a confidence interval for  $I^2$ ). Whenever we include a meta-analysis with considerable statistical heterogeneity in this report, we provide an explanation for doing so, considering the magnitude and direction of effects.<sup>36</sup> 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, described above. Quantitative pairwise meta-analyses were conducted using Stata<sup>®</sup> version 11.1 (StataCorp LP, College Station, TX).

We conducted a network meta-analysis using Bayesian methods to compare the efficacy of pharmacologic interventions with each other for improving PTSD symptoms. Although there were a few head-to-head trials comparing active interventions, the majority of the evidence base was limited to placebo-controlled comparisons. By performing a network meta-analysis, all the evidence, both direct and indirect, can be incorporated into a single internally consistent model. We used the methods developed and illustrated in NICE Technical Support Document 2, which details the generalized linear modeling framework for network meta-analyses of randomized controlled trials.<sup>37</sup> We used a random effects logistic regression model that adjusted for correlations between arms within each study. Study effect and treatment effect parameters were modeled by noninformative (flat) prior distributions that were normal (0, 10000). For the heterogeneity of the random-effects model, we used a uniform prior distribution centered at zero with sufficiently large variance. The first 20,000 simulations were discarded to allow for model convergence and then a further 80,000 simulations were used in estimating the posterior probabilities. Satisfactory convergence was verified by trace plots and calculation of the Monte

Carlo error for each parameter. We also ran a sensitivity analysis, including studies rated as having a high risk of bias, to assess their impact on the comparative efficacy of the pharmacologic interventions used in treating PTSD. Our outcome in each case was the mean change from baseline to endpoint in CAPS total score, and from the model we calculated pairwise odds ratios with 95% credible intervals, as well as the probability that each drug was the most efficacious. The network meta-analyses were performed using WinBUGS Version 1.4.3, a Bayesian software package that uses Markov chain Monte Carlo (MCMC) methods.

## Strength of the Body of Evidence

We graded the strength of evidence based on the guidance established for the EPC Program.<sup>38</sup> Developed to grade the overall strength of a body of evidence, this approach incorporates four key domains: risk of bias (including study design and aggregate quality), consistency, directness, and precision of the evidence. It also considers other optional domains that may be relevant for some scenarios, such as a dose-response association, plausible confounding that would decrease the observed effect, strength of association (magnitude of effect), and publication bias.

Table 4 describes the grades of evidence that we assigned. We graded the strength of the body of evidence to answer KQs on the comparative effectiveness and harms of the interventions in this review. 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.

**Table 4. Definitions of the grades of overall strength of evidence**

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

Source: Owens et al.<sup>38</sup>

We graded the strength of evidence 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. Appendix G includes tables showing our assessments for each domain and the resulting strength of evidence grades for each KQ, or gazed by intervention-comparison pair and outcome.

## Applicability

We assessed applicability of the evidence following guidance from the “Methods Guide for Comparative Effectiveness Reviews.”<sup>39</sup> 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.

## **Peer Review and Public Commentary**

An external peer review was performed on this report. Peer Reviewers were charged with commenting on the content, structure, and format of the evidence report, providing additional relevant citations, and pointing out issues related to how we conceptualized the topic and analyzed the evidence. Our Peer Reviewers (listed in the front matter) gave us permission to acknowledge their review of the draft. We compiled all comments and addressed each one individually, revising the text as appropriate. AHRQ also provided review from its own staff. In addition, the Scientific Resource Center placed the draft report on the AHRQ Web site ([www.effectivehealthcare.ahrq.gov](http://www.effectivehealthcare.ahrq.gov)) for public review.



# Results

## Introduction

This chapter begins with the results of our literature search and some general description of the included studies. It is then organized by Key Question (KQ) and grouped by intervention (i.e., by type of psychological intervention or by drug class, whichever is relevant). For each KQ, we first give the key points and then proceed with a more detailed synthesis of the literature. Additional details for the studies included in this results chapter are provided in an appendix of evidence tables (Appendix D).

Briefly, we wanted to examine the efficacy and comparative effectiveness of psychological and pharmacological treatments for adults with posttraumatic stress disorder (PTSD). Efficacy of psychological treatments and their comparative effectiveness with each other are addressed in KQ 1. For each type of psychotherapy, we first address efficacy by evaluating studies with inactive comparison groups (e.g., waitlist, usual care). By the term *inactive*, we mean comparators that do not involve a specific psychotherapeutic intervention that may benefit people with PTSD. Of note, we have stratified our meta-analyses by comparison group, to show how the effect size and confidence interval would differ if we only included studies with a waitlist control, as opposed to including those with both waitlist and usual care controls. We then proceed to address comparative effectiveness of a given psychotherapy by evaluating studies with active comparison groups (i.e., head-to-head studies involving other psychotherapies).

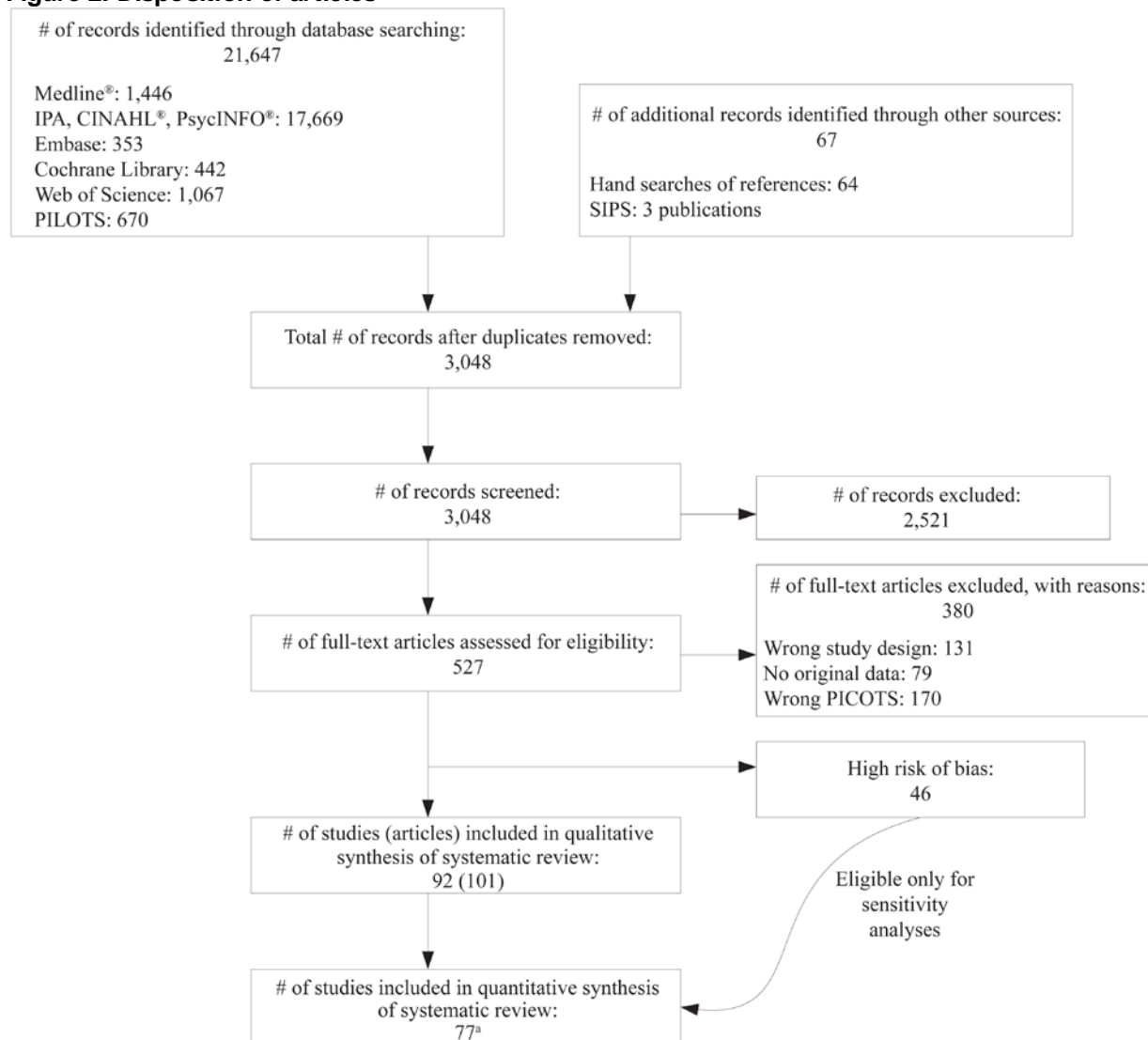
KQ 2 addresses efficacy of pharmacological treatments and their comparative effectiveness with each other. As with KQ 1, we first address efficacy for each type of pharmacotherapy by evaluating studies with placebo controls. We then proceed to address comparative effectiveness by evaluating head-to-head studies (i.e., drug vs. drug).

KQ 3 addresses the direct (head-to-head) evidence on comparative effectiveness of psychological and pharmacological treatments with each other. KQ 4 addresses the direct evidence on comparative effectiveness of combinations of psychological and pharmacological interventions compared with either one alone. KQ 5 addresses whether any of the treatment approaches are more effective than other approaches for victims of particular types of trauma. Finally, KQ 6 synthesizes the evidence on adverse effects associated with treatments for adults with PTSD.

## Results of Literature Searches

Results of our searches appear in Figure 2. We included 101 published articles reporting on 92 studies. Of the included studies, all were randomized controlled trials. We assessed the majority as medium risk of bias. We assessed 4 studies as low risk of bias. Additional details describing the included studies are provided in the relevant sections of this results chapter.

**Figure 2. Disposition of articles**



PICOTS = populations, interventions, comparators, outcomes, timing, settings; SIPS = scientific information packets

<sup>a</sup>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.

Table 5 describes the most common outcome measures used in this literature. For further details about these instruments and scales, see Appendix A. Definitive thresholds for clinically significant changes are not well established for many of these measures, although there are some general guideposts. For example, some suggest that a reduction of 15 points on the CAPS constitutes a clinically significant reduction.<sup>40</sup> However, this cutoff has not been validated and is somewhat uncertain. For the PTSD Checklist, some have considered a reduction of five or more points to indicate a clinically significant response.<sup>41</sup> For the HAM-D and the BDI, a three-point improvement has been considered clinically meaningful.<sup>42</sup> For continuous outcomes for which an SMD was calculated (when data from different scales are combined), an effect size of ~0.5 (a “medium” effect size)<sup>43</sup> or higher has been considered a threshold for clinically significant benefit.

**Table 5. Common outcome measures used in the included trials**

| Abbreviated Name | Complete Name  | Range of Scores  | Improvement Indicated by |
|------------------|--|--|--------------------------|
| BDI              | Beck Depression Inventory                                  | 0 to 63  | Decrease                 |
| CAPS             | Clinician-Administered PTSD Scale                          | 0 to 136   | Decrease                 |
| DGRP             | Duke Global Rating for PTSD scale                          | 1 = very much improved;<br>2 = much improved;<br>> 2 = nonresponders | Decrease                 |
| DTS              | Davidson Trauma Scale                                      | 0 to 136   | Decrease                 |
| GAF              | Global Assessment of Functioning                           | 0 to 100   | Decrease                 |
| HADS             | Hospital Anxiety and Depression Scale                      | 0 to 21  | Decrease                 |
| HAM-A or HAS     | Hamilton Anxiety Scale                                     | 0 to 56  | Decrease                 |
| HAM-D            | Hamilton Depression Scale                                  | 0 to 54  | Decrease                 |
| IES              | Impact of Event Scale                                      | 0 to 75  | Decrease                 |
| IES-R            | Impact of Event Scale-Revised                              | 0 to 88  | Decrease                 |
| MADRS            | Montgomery-Asberg Depression Rating Scale                  | 0 to 60  | Decrease                 |
| MISS or M-PTSD   | Mississippi Scale for Combat-related PTSD                  | 35 to 175  | Decrease                 |
| PCL              | PTSD Checklist   | 17 to 85   | Decrease                 |
| PSS-I            | PTSD Symptom Scale Interview                               | 0 to 51  | Decrease                 |
| PSS-SR           | PTSD Symptom Scale Self-report Version                     | 0 to 51  | Decrease                 |
| PTDS or PDS      | Posttraumatic Diagnostic Scale                             | 0 to 51  | Decrease                 |
| Q-LES-Q-SF       | Quality of Life Enjoyment and Life Satisfaction Short Form | 0 to 70 (raw score)  | Decrease                 |
| SCL-90-R         | Symptom Checklist- 90-Revised                              | 0 to 360   | Decrease                 |
| SDS              | Sheehan Disability Scale                                   | 0 to 30  | Decrease                 |
| SF-12            | Medical Outcome Study Self-Report Form (12 item)           | 0 to 100   | Increase                 |
| SF-36            | 36-Item Short Form Health Survey                           | 0 to 100   | Increase                 |
| SI-PTSD or SIP   | Structured Interview for PTSD                              | 0 to 68  | Decrease                 |
| SPRINT           | Short PTSD Rating Interview                                | 0 to 32  | Decrease                 |
| STAI             | State-Trait Anxiety Inventory                              | 20 to 80   | Decrease                 |
| WAS              | Work and Social Adjustment Scale                           | 0 to 40  | Decrease                 |

## Key Question 1: Comparative Effectiveness of Different Psychological Treatments for Posttraumatic Stress Disorder

We organized this section by type of psychological treatment and present the information in the following order: (1) cognitive behavioral therapy (CBT)-cognitive therapy; (2) CBT-coping skills; (3) CBT-exposure; (4) CBT-mixed therapies; (5) eye movement desensitization and reprocessing (EMDR); and (6) other psychotherapies (Seeking Safety, imagery rehearsal therapy, narrative exposure therapy, brief eclectic psychotherapy). Within each section, we focus first on studies with inactive comparison groups (e.g., waitlist, usual care) to determine whether evidence supports the efficacy of each type of intervention. We then address studies with active

comparison groups (i.e., head-to-head comparative evidence) or we provide cross-references for where those studies are addressed.

Tables describing characteristics of included studies are presented in a similar order. We first give details on studies that use any inactive comparators (in alphabetical order by last name of the first author)—i.e., those about efficacy—and then the details on any additional studies that only included active comparators.

In the bulleted text below we summarize the main overall key points and then the key points for each type of psychotherapy and report the strength of evidence (SOE) where appropriate. The primary outcomes of interest for determining whether treatments are effective for adults with PTSD are improving PTSD symptoms, inducing remission, and losing PTSD diagnosis; we focus more on these outcomes than on other outcomes in the key points. We also comment on other outcomes of interest, such as prevention or reduction of coexisting medical or psychiatric conditions (especially depression symptoms), quality of life, disability or functional impairment, and return to work or active duty. The findings in these key points are primarily based on meta-analyses of the trials that we rated low or medium risk of bias; those trials are cited in the detailed synthesis and related tables. In the detailed synthesis section for each treatment, we provide section headers for each outcome reported (PTSD symptoms, remission, loss of PTSD diagnosis, prevention or reduction of coexisting medical or psychiatric conditions, quality of life, disability or functional impairment, and return to work or active duty). If an outcome does not appear, no trial reported data on it.

## **Key Points: Overall—Efficacy**

- The strongest evidence of efficacy for improving PTSD symptoms is for exposure-based therapy (high SOE).
- Evidence also supports the efficacy of exposure-based therapy for achieving loss of PTSD diagnosis, with a number needed to treat (NNT) of 2 (moderate SOE).
- Evidence of moderate strength also supports the efficacy of cognitive processing therapy, cognitive therapy, CBT-mixed interventions, EMDR, and narrative exposure therapy for improving PTSD symptoms and/or achieving loss of PTSD diagnosis.
- For improving PTSD symptoms, the effect sizes were very large for most of the psychological interventions with evidence of efficacy (e.g., 28.9-point reduction in CAPS and Cohen's  $d = 1.27$  for exposure).
- For achieving loss of PTSD diagnosis, NNTs were  $\leq 4$ .
- Evidence was insufficient to determine efficacy for achieving remission for most psychological interventions, as trials typically did not report remission as an outcome.
- Evidence was insufficient to determine efficacy of relaxation, stress inoculation training, Seeking Safety, or imagery rehearsal therapy.

Table 6 summarizes the efficacy and SOE for psychological treatments for improving PTSD symptoms, inducing remission, and achieving loss of PTSD diagnosis.

**Table 6. Summary of efficacy and strength of evidence of psychological treatments for adults with PTSD for improving PTSD symptoms, remission, and loss of PTSD diagnosis**

| Treatment                      | PTSD Symptoms <sup>a</sup>  | Remission (No Longer Having Symptoms) <sup>b</sup><br>(Risk Difference) | Loss of PTSD Diagnosis <sup>b</sup><br>(Risk Difference)           |
|--------------------------------|---|---|--|
| Cognitive processing therapy   | SMD -1.40 (-1.95, -0.85); 4 trials, N=299<br>WMD -32.2 (-46.3, -18.05); 4 trials, N=299<br>Moderate SOE   | Insufficient SOE  | 0.44 (0.26, 0.62); 4 trials, N=299;<br>NNT 3<br>Moderate SOE       |
| Cognitive therapy <sup>c</sup> | SMD -1.22 (-1.91, -0.53); 3 trials, N=221<br>Moderate SOE   | Insufficient SOE  | 0.51 (0.24, 0.78); 3 trials, N=221<br>NNT 2<br>Moderate SOE        |
| Stress inoculation training    | PSS-I for stress inoculation training vs. waitlist<br>Baseline: 29.4 vs. 32.9;<br>Endpoint: 12.9 vs. 26.9;<br>p<0.05; 1 trial, N = 41<br>Insufficient SOE | Insufficient SOE  | 0.42, P<0.001; 1 trial, N=41<br>Insufficient SOE                   |
| Relaxation                     | 1 trial, N=25<br>Insufficient SOE   | 1 trial, N=25<br>Insufficient SOE                                       | 1 trial, N=25<br>Insufficient SOE                                  |
| CBT-exposure                   | SMD -1.27 (-1.54, -1.00); 7 trials, N=387<br>WMD -28.9 (-35.5, -22.3); 4 trials, N=212<br>High SOE  | Insufficient SOE  | 0.66 (0.42, 0.91); 3 trials, N=197;<br>NNT 2<br>Moderate SOE       |
| CBT-mixed                      | SMD -1.09 (-1.4, -0.78); 14 trials, N=825<br>WMD -31.1 (-42.6, -19.6) 8 trials, N=476<br>Moderate SOE   | Ranged from 0.4 to 0.82 across trials (2 trials, N=114)<br>Moderate SOE | 0.26 (0.11, 0.41); 6 trials, N=290;<br>NNT 4<br>Moderate SOE       |
| EMDR                           | SMD -1.08 (-1.83, -0.33); 4 trials, N=117<br>Low SOE  | Insufficient SOE  | 0.64 (0.46, 0.81); 3 trials, N=95;<br>NNT 2<br>Moderate SOE        |
| Seeking Safety <sup>d</sup>    | WMD -9.14, p<0.01; 1 trial, N=107<br>Insufficient SOE   | Insufficient SOE  | Insufficient SOE   |
| Imagery rehearsal therapy      | WMD -21, p=0.001; 1 trial, N=168<br>Insufficient SOE  | Insufficient SOE  | Insufficient SOE   |
| Narrative exposure therapy     | SMD -1.25 (-1.92, -0.58); 3 trials, N=227<br>PDS, WMD -10.2 (-13.1, -7.4); 3 trials, N=227<br>Moderate SOE  | Insufficient SOE  | 0.15 (0.01, 0.30); 3 trials, N=227<br>Low SOE                      |
| Brief eclectic psychotherapy   | Likely small to medium effect size; 3 trials, N=96<br>Low SOE   | 0.125 (1 trial, N=30)<br>Insufficient SOE                               | Ranged from 0.125 to 0.58 across trials; 3 trials, N=96<br>Low SOE |
| Trauma affect regulation       | 1 trial, N=146<br>Insufficient SOE  | 1 trial, N=146<br>Insufficient SOE                                      | 1 trial, N=146<br>Insufficient SOE                                 |

CAPS = Clinician-Administered PTSD Scale; CBT = cognitive behavioral therapy; CI = confidence interval; EMDR = eye movement desensitization and reprocessing; N = number of subjects; NNT = number needed to treat; NR = not reported; NS = not statistically significant; PDS = Posttraumatic Diagnostic Scale; PSS-I = PTSD Symptom Scale Interview; SMD, standardized mean difference; SOE = strength of evidence; WMD = weighted mean difference

<sup>a</sup>WMD data are mean change from baseline (95% CI); also given are the number of trials and number of subjects contributing data, specifically in CAPS scores 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, a medium effect size is d=0.50, and a large effect size is d=0.80.43

Across the included trials, baseline PTSD severity was generally in the severe (CAPS of 60-79) or extreme (CAPS ≥80) range. Using CAPS, PTSD severity has been categorized as asymptomatic or few symptoms (0-19), mild PTSD or subthreshold (20-39), moderate PTSD or threshold (40-59), severe, and extreme.<sup>40</sup>

<sup>b</sup>Data are risk differences (95% CI); number of trials; number of subjects contributing data; and number needed to treat for treatment compared with inactive comparators.

<sup>c</sup>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

<sup>d</sup>Several other trials with Seeking Safety arms were included in our review besides the one that contributed to this table. However, those trials compared Seeking Safety with other active interventions (generally other interventions targeting substance use disorders) and were unable to establish efficacy for these outcomes. See the section titled Detailed Synthesis: Other Psychological Interventions for details.

## **Key Points: Overall—Comparative Effectiveness**

- Most of the direct head-to-head comparative evidence was insufficient to determine whether psychotherapies differ for improving outcomes.
- With few trials and few total subjects, most of our meta-analyses of head-to-head trials were underpowered to detect anything but medium to large differences.
- Head-to-head evidence was insufficient to determine whether exposure therapy is more or less effective than cognitive processing therapy, cognitive therapy (CT), stress inoculation training, or EMDR.
- Exposure therapy was more effective than relaxation for achieving loss of PTSD diagnosis (risk difference [RD], 0.31; 95% confidence interval [CI], 0.04 to 0.58; 2 trials, N=85, moderate SOE) and for improving depression symptoms.
- For exposure therapy compared with exposure plus cognitive restructuring (CR), evidence supported a conclusion of no significant difference between treatments for achieving loss of diagnosis (RD, -0.01; 95% CI, -0.17 to 0.14; 3 trials, N=146). Although point estimates favored exposure plus CR, evidence was insufficient to determine comparative effectiveness for reduction of PTSD symptoms or depression symptoms, largely because of imprecision.
- CBT-mixed interventions resulted in greater improvements in PTSD symptoms than relaxation interventions (moderate SOE).
- For seeking safety compared with active controls (relapse prevention, psychoeducation, and treatment as usual in a VA substance use disorders clinic), evidence supported a conclusion of no significant difference between treatments for PTSD symptom reduction.

Table 7 summarizes the available head-to-head evidence and SOE for improving PTSD symptoms, inducing remission, and achieving loss of PTSD diagnosis.

**Table 7. Summary of comparative effectiveness from head-to-head trials and strength of evidence for improving PTSD symptoms, remission, and loss of PTSD diagnosis**

| Treatment   | PTSD Symptoms <sup>a</sup>   | Remission (No Longer Having Symptoms) <sup>b</sup> | Loss of PTSD Diagnosis <sup>b</sup>                                       |
|---|--|--|---|
| CR vs. relaxation   | 50% vs. 20% of subjects improved, p=0.04, 1 trial, N=34<br>Insufficient SOE                          | Insufficient SOE                                   | 65% vs. 55% of subjects, p=NS, 1 trial, N=34<br>Insufficient SOE          |
| CT vs. exposure   | WMD 4.8 (-4.5, 14.2); 2 trials, N=100<br>Insufficient SOE  | Insufficient SOE                                   | RD 0.13 (-0.06, 0.32); 2 trials, N=100<br>Insufficient SOE                |
| Exposure vs. CPT  | WMD 3.97 (-5.95, 13.9); 1 trial, N=124<br>Insufficient SOE   | Insufficient SOE                                   | RD 0.00 (-0.18, 0.18); 1 trial, N=124<br>Insufficient SOE                 |
| Exposure vs. relaxation   | WMD -9.7 (-22.3, 2.9); 2 trials, N=85<br>Insufficient  | Insufficient SOE                                   | Favors exposure: RD 0.31 (0.04, 0.58); 2 trials, N=85<br>Moderate SOE     |
| Exposure vs. SIT  | SMD -0.14 (-0.69, 0.41); 1 trial, N=51<br>Insufficient SOE   | Insufficient SOE                                   | RD 0.18 (-0.09, 0.45); 1 trial, N=51<br>Insufficient SOE                  |
| Relaxation vs. EMDR   | SMD -0.57 (-1.4, 0.29)<br>SMD -0.3 (-0.8, 0.2); 2 trials, N=64 <sup>c</sup><br>Insufficient SOE      | Insufficient SOE                                   | RD 0.34 (-0.04, 0.72); 2 trials, N=64<br>Insufficient SOE                 |
| Relaxation vs. CBT-M  | Favors CBT-M; 2 trials, N=85 <sup>d</sup><br>Moderate SOE  | Insufficient SOE                                   | Insufficient SOE  |
| Exposure vs. EMDR   | No difference found; 2 trials, N=91<br>Insufficient SOE  | Insufficient SOE                                   | RD 0.14 (-0.01, 0.29); 2 trials, N=91<br>Insufficient SOE                 |
| Exposure vs. exposure plus CR   | SMD 0.25 (-0.29, 0.80); 3 trials, N=259<br>Insufficient SOE  | Insufficient SOE                                   | Similar benefits: RD -0.01 (-0.17, 0.14); 3 trials, N=259<br>Moderate SOE |
| Brief eclectic psychotherapy vs. EMDR                                 | 1 trial, N=140<br>Insufficient SOE <sup>e</sup>  | Insufficient SOE                                   | 1 trial, N=140<br>Insufficient SOE <sup>e</sup>                           |
| Seeking safety vs. active controls (e.g., relapse prevention program) | SMD 0.04 (-0.12 to 0.20); 4 trials, N=594<br>WMD 1.45 (-2.5 to 5.4; 3 trials, N=477)<br>Moderate SOE | Insufficient SOE                                   | OR 1.22 (0.48 to 3.13; 1 trial, N=49)<br>Insufficient SOE                 |

CI = confidence interval; CPT = cognitive processing therapy; CR = cognitive restructuring; CT = cognitive therapy; EMDR = eye movement desensitization and reprocessing; N = number of subjects; NR = not reported; NS = not statistically significant; RD = risk difference; SIT = stress inoculation training; SOE = strength of evidence; WMD = weighted mean difference

<sup>a</sup>Weighted mean difference (WMD) data are mean change from baseline (95% CI); also given are the number of trials and number of subjects contributing data, specifically in scores on the Clinician-Administered PTSD Scale (CAPS). Standardized mean difference (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.<sup>43</sup> 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 or few symptoms (0-19), mild PTSD or subthreshold (20-39), moderate PTSD or threshold (40-59), severe, and extreme.<sup>40</sup>

<sup>b</sup>Unless otherwise specified, data are RDs (95% CI); number of trials; number of subjects contributing data; for the comparison between the two therapies.

<sup>c</sup>We report two SMDs here: we ran two meta-analyses because one of the two trials reported two measures of PTSD symptoms.<sup>44</sup> The first SMD is from our meta-analysis using the Mississippi Scale for Combat Related PTSD from the trial reporting two measures; the second is using the Impact of Event Scale (IES) from that trial. The other trial reported the CAPS.<sup>45</sup>

<sup>d</sup>Mean CAPS improvement: 38 (95% CI, 26 to 50) vs. 14 (95% CI, 4 to 25) in one trial;<sup>46</sup> between-group effect size was very large favoring CBT-M (Cohen's d = 1.6) in another.<sup>47</sup>

<sup>e</sup>Due to unknown consistency (with data from a single trial<sup>48</sup>), risk of bias, and imprecision, we graded the evidence as insufficient to determine the comparative effectiveness of brief eclectic psychotherapy and EMDR. The trial reported greater improvements from baseline to the first assessment for those treated with EMDR than for those treated with brief eclectic psychotherapy, but no significant difference between groups at the second assessment, after both groups had completed treatment (see Detailed Synthesis: Other Psychological Treatments section for details).

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

## **Key Points: CBT—Cognitive Therapy**

- Evidence supports the efficacy of cognitive processing therapy for improving PTSD symptoms (WMD, -32.2 compared with waitlist or usual care), achieving loss of PTSD diagnosis, and improving depression symptoms for adults with PTSD (moderate SOE).
- For achieving loss of diagnosis, 44 percent more subjects treated with cognitive processing therapy than subjects in control groups achieved the outcome. This translates to a NNT of 3.
- For cognitive processing therapy, evidence was insufficient for remission and for other outcomes (such as anxiety symptoms, quality of life, disability or functioning, and return to work or active duty).
- Evidence supports the efficacy of other CT interventions (i.e., that were not cognitive processing therapy) for improving PTSD symptoms, achieving loss of PTSD diagnosis, improving depression and anxiety symptoms, and reducing disability for adults with PTSD (moderate SOE).

## **Key Points: CBT—Coping Skills**

- Evidence was insufficient to determine efficacy of relaxation or stress inoculation training for adults with PTSD. One trial comparing prolonged exposure, stress inoculation training, prolonged exposure plus stress inoculation training, and waitlist suggests that stress inoculation training may be efficacious.<sup>49</sup>

## **Key Points: CBT—Exposure**

- Evidence supports the efficacy of exposure therapy for improving PTSD symptoms (standardized mean difference [SMD], -1.27; 95% CI, -1.54 to -1.00; 7 trials, N=387; high SOE), achieving loss of PTSD diagnosis (moderate SOE), and improving depression symptoms for adults with PTSD (high SOE).
- For achieving loss of PTSD diagnosis, 66 percent more subjects treated with exposure than subjects in waitlist control groups achieved the outcome (RD, 0.66; 95% CI, 0.42 to 0.91; 3 trials, N=197). This translates to a NNT of 2.
- Evidence was insufficient for other outcomes (remission, anxiety, quality of life, disability or functional impairment, and return to work or active duty).
- Most efficacy evidence comes from trials of prolonged exposure, which combines imaginal and in vivo exposure.

## **Key Points: CBT—Mixed**

- Evidence<sup>25,46,47,49-69</sup> supports the efficacy of CBT-mixed treatments for improving PTSD symptoms (mean change from baseline in CAPS: WMD, -31.1; 8 trials, N=476; mean change from baseline in any PTSD symptom measure: SMD, -1.09; 14 trials, N=825, moderate SOE).



- Evidence also supports the efficacy of CBT-mixed interventions for achieving loss of PTSD diagnosis (moderate SOE), remission (moderate SOE), reduction of depression symptoms (moderate SOE), reduction of disability or functional impairment (low SOE), and anxiety symptoms (low SOE).
- For achieving loss of diagnosis, 26 percent more subjects treated with CBT-mixed therapies than subjects in inactive control groups achieved the outcome (RD, 0.26; 6 trials, N=290). This translates to a NNT of 4.

### **Key Points: Eye Movement Desensitization and Reprocessing (EMDR)**

- Evidence supports the efficacy of EMDR for reduction of PTSD symptoms, but SOE is low because of some inconsistency and imprecision.
- Evidence supports the efficacy of EMDR for achieving loss of PTSD diagnosis and improving depression symptoms (moderate SOE for both); 64 percent more subjects treated with EMDR experienced this outcome than did subjects in waitlist control groups. This translates to a NNT of 2.
- Evidence was insufficient to determine the efficacy of EMDR for other outcomes (remission, anxiety, quality of life, disability or functioning, and return to work or active duty).

### **Key Points: Other Psychological Therapies**

- Evidence supports the efficacy of narrative exposure therapy for improving PTSD symptoms (Posttraumatic Diagnostic Scale [PDS], mean change from baseline: WMD, -10.2; 95% CI, -13.1 to -7.4; 3 trials, N=227, moderate SOE) and for achieving loss of PTSD diagnosis (RD, 0.15; 95% CI, 0.01 to 0.30; 3 trials, N=227, low SOE).
- Some evidence (3 trials, N=96) supports the efficacy of brief eclectic psychotherapy for improving PTSD symptoms, achieving loss of diagnosis, reducing depression and anxiety symptoms, and returning to work (all low SOE).
- Evidence was insufficient to determine the efficacy of Seeking Safety or imagery rehearsal therapy.

## **Detailed Synthesis: CBT—Cognitive Therapy**

### **Characteristics of Trials**

Table 8 summarizes the characteristics of the nine cognitive therapy (CT) trials meeting our inclusion criteria. Five trials included a comparison with a waitlist condition (two of which also included an active comparison arm).<sup>52,70-73</sup> Two trials included a comparison with usual care or treatment as usual.<sup>74,75</sup> Two trials included only comparisons with active interventions.<sup>46,76</sup> Further details describing the included trials are provided in Appendix D.

**Table 8. Characteristics of included cognitive therapy trials**

| Study   | Arm (N)  | Duration (Followup)  | Population Trauma Type              | Baseline PTSD Severity <sup>a</sup>                            | Mean Age (Y) | % F | % Non-white | Risk of Bias |
|---|--|--|-------------------------------------|--|--------------|-----|-------------|--------------|
| Chard et al., 2005 <sup>71</sup>  | CPT (36)<br>MA (35)                            | 17 weeks (3 and 12 months)   | Female<br>Childhood sexual abuse    | 65.5 to 68.3   | 33           | 100 | 19          | Medium       |
| Resick et al., 2002 <sup>72</sup><br>Resick, et al., 2003 <sup>77</sup><br>Resick, et al., 2012 <sup>78</sup> | CPT (62)<br>PE (62)<br>MA (47)                 | 6 weeks (3 and 9 months, 5 to 10 years)                              | Female<br>Sexual assault            | 69.9 to 76.6   | 32           | 100 | 29          | Medium       |
| Monson et al., 2006 <sup>70</sup>   | CPT (30)<br>WL (30)                            | 10 weeks (1 month)   | Male and female<br>Combat           | 76.7 to 79.1   | 54           | 10  | 4           | Medium       |
| Forbes et al., 2012 <sup>74</sup>   | CPT (30)<br>TAU (29)                           | 12 weeks (3 months)  | Male and female<br>Military related | 65.8 to 75.5   | 53           | 3   | 0           | Medium       |
| Marks et al., 1998 <sup>46</sup><br>Lovell, et al., 2001 <sup>79</sup>  | PE (23)<br>CR (13)<br>CR+PE (24)<br>Relax (21) | 10 sessions <sup>b</sup><br>(mean of 16 weeks), (1, 3, and 6 months) | Male and female<br>Mixed            | NR   | 38           | 36  | NR          | Medium       |
| Ehlers et al., 2003 <sup>73</sup>   | CT (28)<br>SHB (28)<br>RA (29)                 | Mean of 9 weeks, 0 to 3 booster sessions (3, 6, and 9 months)        | Male and female<br>MVA              | PDS (frequency) 30.0<br>PDS (distress) 30.8                    | 39           | 72  | 97          | Medium       |
| Ehlers et al., 2005 <sup>52</sup>   | CT (14)<br>WL (14)                             | 4 to 12 weeks plus up to 3 monthly boosters (3 and 6 months)         | Male and female<br>Mixed            | CAPS (frequency) 31.6 to 42.0<br>CAPS (intensity) 29.0 to 36.5 | 37           | 54  | 4           | Medium       |
| Mueser et al., 2008 <sup>75</sup>   | CT (54)<br>UC (54)                             | 12 to 16 sessions <sup>c</sup>                                       | Male and female<br>Mixed            | 74.5 to 76.2   | 44           | 79  | 16          | Medium       |
| Tarrier et al., 1999 <sup>76,80</sup>   | IE (35)<br>CT (37)                             | 16 sessions (112 days) (6 and 12 months)                             | Male and female<br>Mixed            | 71.1 to 77.8   | 39           | 42  | NR          | Medium       |

CAPS-SX = Clinician Administered PTSD Scale for DSM-IV: One-Week Symptom Status Version; CPT = cognitive processing therapy; CT = cognitive therapy; CR = cognitive restructuring; IE = imaginal exposure; MA = minimal attention (a type of waitlist group); MVA = motor vehicle accident; N = total number randomized/assigned to intervention and control groups; NR = not reported; PE = prolonged exposure; PTSD = posttraumatic stress disorder; RA = repeated assessments (a type of waitlist group); relax = relaxation; SHB = self-help booklet based on principles of CBT; UC = usual care; WL = waitlist; y = year

<sup>a</sup>Data reported are mean CAPS total or range of mean CAPS total scores across groups unless otherwise specified.

<sup>b</sup>Number of treatment sessions is reported when duration of treatment was not specified.

Three trials compared cognitive processing therapy with a waitlist control.<sup>70-72</sup> Of these, one trial enrolled male (n=54) and female (n=6) military veterans;<sup>70</sup> one enrolled women with histories of childhood sexual abuse (n=71);<sup>71</sup> and one enrolled subjects with histories of adult sexual assault (n=121).<sup>72</sup> All three trials were conducted in the United States. The subjects in the trial enrolling military veterans had a higher average age (54 years) than those in the other two trials (~32 years). Subjects were allowed to participate in two of the trials if they had been on a stable medication regimen for 2 or 3 months.<sup>70,71</sup> Subjects were excluded from the trial enrolling those with histories of adult sexual assault if they were in an abusive relationship or were being stalked. The primary outcomes for the trials were the Clinician Administered PTSD Scale

(CAPS), PTSD Checklist (PCL), Modified PTSD Symptom Scale (MPSS), and PTSD Symptom Scale (PSS).

One trial compared cognitive processing therapy with usual treatment at veterans' community-based counseling services.<sup>74</sup> The trial randomized 59 people with military-related PTSD living in three states in Australia.

Two trials from the same research group in the United Kingdom compared cognitive therapy (CT) treatments with waitlist controls. The first enrolled survivors of motor vehicle accidents, and compared CT with a waitlist condition of repeated symptom assessments and with a self-help booklet, "Understanding Your Reactions to Trauma" (SHB group), which the authors reported was based on cognitive behavioral principles for treating patients with PTSD.<sup>73</sup> This study was designed as an "early intervention" and included only subjects who started therapy within 6 months of their MVA. Subjects were excluded from the study if they had been unconscious for more than 15 minutes after the accident or had no memory of it. The second trial from the same research group compared CT with waitlist.<sup>52</sup> The trial enrolled 28 consecutive referrals from General Practitioners and Community Mental Health Teams. Subjects were required to have PTSD resulting from trauma that occurred at least 6 months before study entry.

Another trial of CT randomized 108 people with PTSD from various traumatic events to 12 to 16 sessions of CT or usual care.<sup>75</sup> In addition to PTSD, all subjects also had diagnoses of either major mood disorder (85%) or schizophrenia or schizoaffective disorder (15%). The therapy intervention was a program involving CT that had previously been designed and pilot tested for PTSD in people with severe mental illness.<sup>75</sup>

Of the two trials that included only comparisons with active interventions, one four-arm study compared prolonged exposure alone, CR alone, prolonged exposure and CR together, and a relaxation group;<sup>46</sup> the other compared CT with imaginal exposure (IE).<sup>76,80</sup> Both enrolled heterogeneous samples of men and women in the United Kingdom who had experienced a variety of traumatic events (physical assault, witnessing a trauma, road accident, nonroad accident, sexual assault, being held hostage, bombing, combat, and "miscellaneous";<sup>46</sup> crime, accident, and other events<sup>76,80</sup>).

## **Results for Cognitive Therapy Compared With Inactive Comparators**

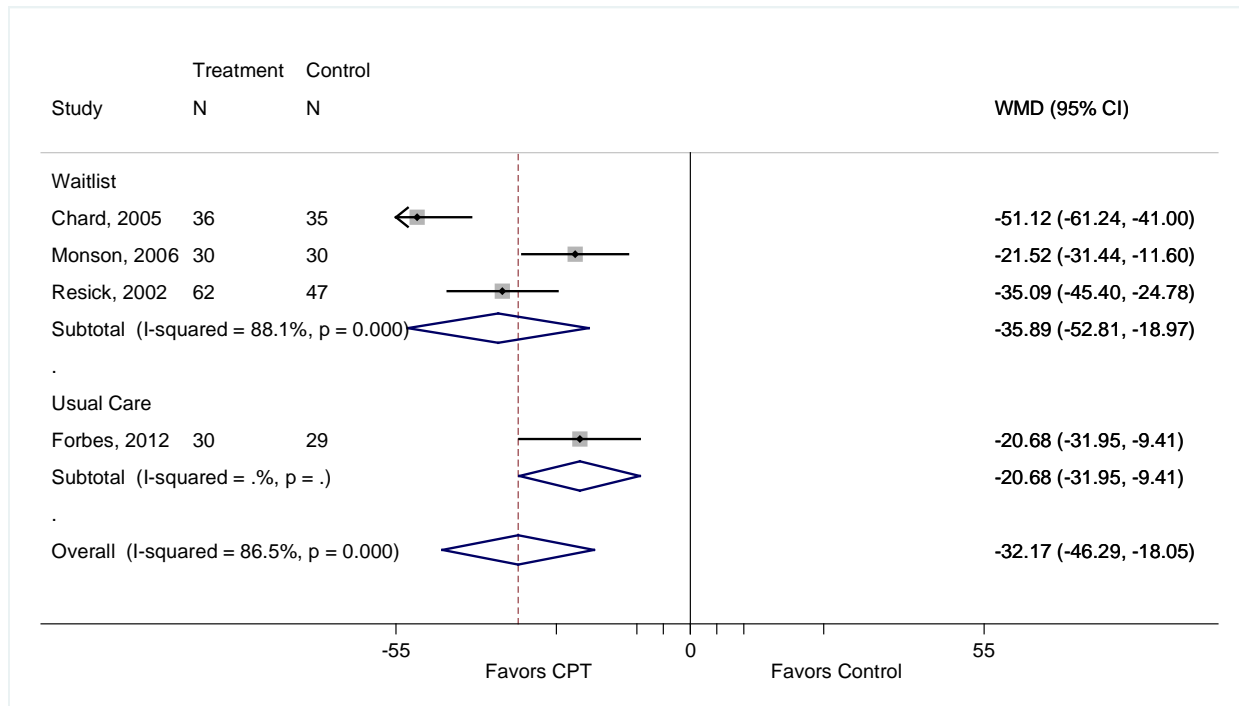
Under each outcome header below, we first present our data synthesis for studies of cognitive processing therapy. Then we present results for the other CT studies with inactive comparator groups.<sup>52,73,75</sup>

### **PTSD Symptom Reduction**

All included trials reported measures of PTSD symptom reduction. Of the four trials comparing cognitive processing therapy with controls, all found that subjects in the active treatment arm had a greater reduction in symptoms of PTSD than those in control groups.<sup>70-74</sup>

Our meta-analysis of CAPS scores (Figure 3) found a much greater reduction in PTSD symptoms for subjects treated with cognitive processing therapy than for those in control groups (WMD, -32.2; corresponding Cohen's  $d = -1.40$ ; 95% CI, -1.95 to -0.85; Appendix F). The meta-analysis had considerable statistical heterogeneity ( $I^2=86.5\%$ ), but the direction of effects was consistent. The differences were only in the magnitude of benefit; all trials found moderate or large magnitudes of benefit. The pooled effect size was slightly larger when only including the three studies with a waitlist comparator (WMD, -35.9) than when also including the one study with a usual care comparator.

**Figure 3. Mean change from baseline in CAPS for cognitive processing therapy compared with controls, by type of comparator**



Note: Timing of outcome assessment: 17 weeks (Chard, 2005),<sup>71</sup> 10 weeks (Monson, 2006),<sup>70</sup> 6 weeks (Resick, 2002),<sup>72</sup> 12 weeks (Forbes, 2012).<sup>74</sup>

For two of the three trials comparing cognitive processing therapy with waitlist control, the authors reported that changes were maintained at a 3-month posttreatment followup.<sup>71,72</sup> In one trial, subjects continued to improve from posttreatment to the 3-month followup ( $p=0.02$ ); no significant difference on CAPS scores was observed between the 3-month and 1-year follow-up points.<sup>71</sup> In the other trial, both of the active interventions exhibited a strong decrease in CAPS scores from baseline to posttreatment ( $p<0.0001$ ) with some increase from posttreatment to the 3-month assessment ( $p<0.005$ ), and no change between 3 and 9 months.<sup>72</sup> A later publication from the trial reported that decreases in symptoms were maintained throughout a long-term followup of 5 to 10 years after participation in the study.<sup>78</sup>

The study comparing cognitive processing therapy with usual care reported similar, but slightly lower CAPS scores, at 3-month posttreatment followup compared with posttreatment assessments for both study groups.<sup>74</sup>

Each of the four trials involving cognitive processing therapy also reported one other measure of PTSD symptom reduction. The trials used several different measures (PCL,<sup>70,74</sup> MPSS,<sup>71</sup> and PSS<sup>72</sup>)—see Appendix D for details.

Overall, we concluded that evidence of moderate strength supports the efficacy of cognitive processing therapy for reduction of PTSD symptoms based on consistent and direct evidence from four trials. Even though findings were not precise, the differences in magnitudes of benefit suggest a moderate or large benefit.

All three studies comparing other CT interventions (i.e., that were not cognitive processing therapy) with inactive control groups reported greater improvement for those treated with CT than those in control groups.<sup>52,73,75</sup> The trial involving CT, self-help booklet, or repeated assessments as an early intervention measured PTSD symptoms with the PDS (Posttraumatic

Diagnostic Scale) and CAPS; data were reported separately for “CAPS assessor frequency” and “CAPS assessor intensity.” The CT group showed better outcomes on all PTSD symptom measures at posttreatment followup and 3- and 9-month followup ( $p < 0.001$ ).<sup>73</sup> The trial using CT for those with severe mental illness showed that CT was more effective than treatment as usual in decreasing total-CAPS score ( $p = 0.005$ ).

Our meta-analysis of PTSD symptom measures found a greater reduction in PTSD symptoms for subjects treated with CT than for those in waitlist, self-help booklet, and usual care control groups (Cohen’s  $d = -1.22$ ; 95% CI,  $-1.91$  to  $-0.53$ , using the CAPS intensity scores from Ehlers et al. 2003 and Ehlers et al. 2005 and using the total CAPS from Mueser et al. 2008, Appendix F). The meta-analysis had considerable statistical heterogeneity ( $I^2 = 79.6\%$ ), but the direction of effects was consistent. When only compared with waitlist controls, the effect size was larger (Cohen’s  $d = -1.54$ ; 95% CI,  $-2.17$  to  $-0.92$ ; Appendix F).

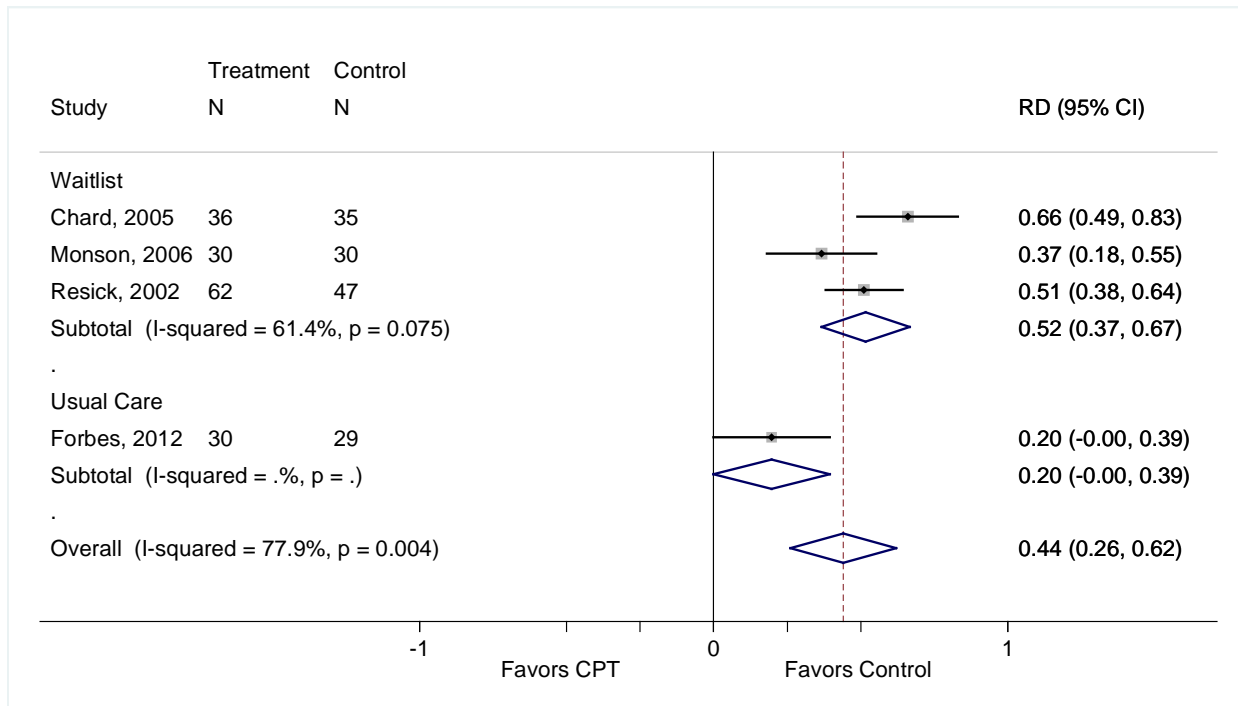
Overall, we concluded that evidence of moderate strength supports the efficacy of CT for reduction of PTSD symptoms based on consistent and direct evidence. Even though findings were not precise, the differences in magnitudes of benefit suggest a moderate or large benefit.

### **Loss of PTSD Diagnosis**

All trials in this section reported data on posttreatment diagnostic status. The four trials that compared people receiving cognitive processing therapy with controls reported a reduction in the number of subjects meeting the criteria for PTSD at the end of treatment and at later follow-up assessments in both the cognitive processing therapy and control groups, with fewer subjects meeting diagnostic criteria in the intervention arm than in the control arm.

Our meta-analysis for achieving loss of PTSD diagnosis (Figure 4) found that 52 percent more subjects treated with cognitive processing therapy achieved loss of PTSD diagnosis than subjects in waitlist groups (RD, 0.52). This translates to a NNT of 2. When also including the study with a usual care comparator, the effect size decreased to 44 percent (Figure 4).

**Figure 4. Loss of PTSD diagnosis for cognitive processing therapy compared with controls, by type of comparator**



Note: Timing of outcome assessment: 17 weeks (Chard, 2005),<sup>71</sup> 12 sessions (Monson, 2006),<sup>70</sup> 6 weeks (Resick, 2002),<sup>72</sup> 12 weeks (Forbes, 2012).<sup>74</sup>

All three trials comparing cognitive processing therapy with waitlist reported posttreatment follow-up assessments indicating that, over time, the changes seen in loss of PTSD diagnosis were maintained. One trial reported that 30 percent of subjects treated with cognitive processing therapy and 3 percent of waitlist subjects did not meet criteria for PTSD diagnosis 1 month posttreatment ( $p=0.01$ ).<sup>70</sup>

Two of the cognitive processing therapy trials reported posttreatment followups of 3 months or longer. In one trial, 93 percent of subjects treated with cognitive processing therapy (and 36 percent of those in the minimal attention group) no longer met criteria for PTSD posttreatment; later values for the intervention group were 97 percent at 3 months posttreatment and 94 percent at 1-year followup.<sup>71</sup> Another trial reported that 58 percent and 55 percent of subjects treated with cognitive processing therapy no longer met criteria for PTSD at 3 and 9 months after treatment, respectively (immediately posttreatment, 53% no longer met criteria for PTSD).<sup>72</sup> A later publication from the trial reported that 77.8 percent no longer met criteria for PTSD at long-term followup of 5 to 10 years after participation in the study.<sup>73,78</sup> From the above findings and our meta-analysis, evidence of moderate strength supports the efficacy of cognitive processing therapy for achieving loss of PTSD diagnosis. This grade is based on consistent, direct, and fairly precise evidence from four trials.

All three studies comparing other CT interventions (i.e., that were not cognitive processing therapy) with inactive control groups reported data on loss of PTSD diagnosis.<sup>52,73,75</sup> The study comparing CT, a self-help booklet, and repeated assessments reported that 78.6 percent and 89.3 percent of subjects treated with CT no longer met criteria for PTSD at 3 and 9 months after treatment, respectively.<sup>73</sup> The study comparing CT for people with severe mental illness with

treatment as usual reported that 63.3 percent and 72.7 percent of subjects treated with CT no longer met criteria for PTSD at 3 and 6 months after treatment, respectively.<sup>75</sup>

Our meta-analysis for achieving loss of PTSD diagnosis found that 51 percent (95% CI, 24% to 78%) more subjects treated with CT achieved loss of PTSD diagnosis than subjects in waitlist, self-help booklet, and usual care control groups by 3 months after treatment (Appendix F). This translates to a NNT of 2. The meta-analysis had considerable statistical heterogeneity ( $I^2=84.7\%$ ), but the direction of effects was consistent. When only compared with waitlist controls, the effect size was larger (risk difference 0.66; 95% CI, 0.50 to 0.82;  $I^2=0\%$ , Appendix F).

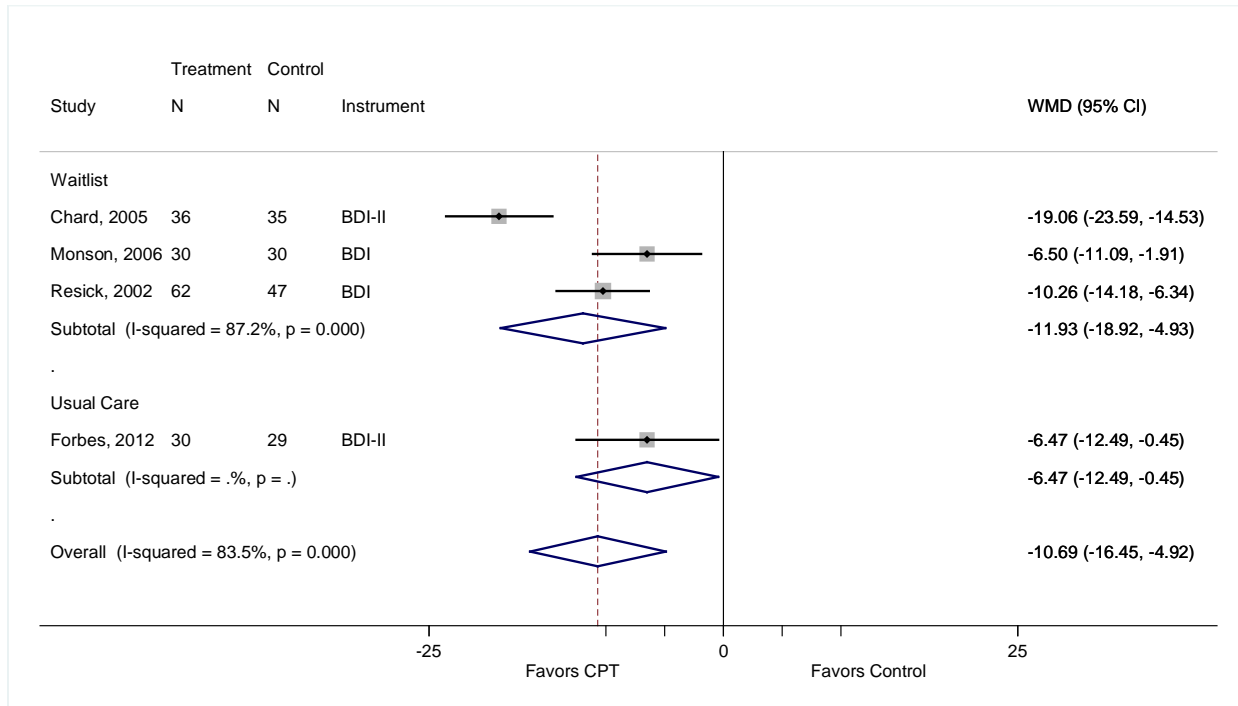
Overall, we concluded that evidence of moderate strength supports the efficacy of CT for achieving loss of PTSD diagnosis based on consistent and direct evidence.

### **Prevention or Reduction of Comorbid Medical or Psychiatric Conditions**

All cognitive therapy trials assessed the impact on coexisting psychiatric conditions— anxiety, depression, or both. No trial reported the reduction or prevention of a comorbid medical condition as one of their outcomes of interest. All trials assessed the impact of cognitive therapy on symptoms of depression as measured by the Beck Depression Inventory (BDI) or BDI-II. Of the four studies comparing people receiving cognitive processing therapy with those in a control group, all found that subjects in the active treatment arm had a greater reduction in symptoms of depression than those in the control arm.<sup>70-74</sup>

Our meta-analysis of cognitive processing therapy trials reporting BDI or BDI-II scores (Figure 5) found greater improvement for subjects treated with cognitive processing therapy than for those in the waitlist groups (WMD, -11.9; 95% CI, -18.9 to -4.9). When including the study with a usual care comparison<sup>71</sup> the magnitude of benefit decreased slightly (WMD, -10.7; 95% CI, -16.5 to -4.9). The statistical heterogeneity in the analysis was considerable. Regardless of the reason, all four trials found substantial benefits for reducing depression symptoms in adults with PTSD.

**Figure 5. Mean change from baseline in depression (measured by the Beck Depression Inventory) for cognitive processing therapy compared with control, by type of comparator**



Note: Timing of outcome assessment: 17 weeks (Chard, 2005),<sup>71</sup> 12 sessions (Monson, 2006),<sup>70</sup> 6 weeks (Resick, 2002),<sup>72</sup> 12 weeks (Forbes, 2012).<sup>74</sup>

These changes were maintained from the posttreatment assessment at 3 months<sup>72-74</sup> and 9 months<sup>72</sup> in two trials. In another trial, the pre- to posttreatment effect size was 1.00; this figure declined to 0.49 at the 3-month follow-up interval.<sup>70</sup> The authors attributed this trend to improving depression scores in the waitlist group, not to worsening of depression in the cognitive processing therapy group.

From the above findings and our meta-analysis, we concluded that evidence of moderate strength supports the efficacy of cognitive processing therapy for reducing depression symptoms. This determination is based on consistent, direct, and precise evidence from four trials.

Two trials of cognitive processing therapy assessed anxiety as an outcome using<sup>73</sup> the State-Trait Anxiety Inventory (STAI).<sup>70,74</sup> One found cognitive processing therapy to be no more effective in reducing symptoms of anxiety than waitlist;<sup>70</sup> the other found greater improvement in anxiety for subjects treated with cognitive processing therapy than those receiving usual treatment from intake to posttreatment (p=0.018).<sup>73,74</sup> We concluded that evidence is insufficient to determine the efficacy of cognitive processing therapy for reducing anxiety symptoms, based on lack of consistency and imprecise findings of two trials.

All three studies comparing other CT interventions (i.e., that were not cognitive processing therapy) with inactive control groups assessed both depression and anxiety symptoms.<sup>52,73,75</sup> In the study comparing CT to self-help booklet and repeated assessment, greater improvement in anxiety (Beck Anxiety Inventory [BAI]) and depression (BDI) were seen among those treated with CT compared with either the self-help booklet or repeated assessments at both 3 and 9 months (p<0.001 for both assessments).<sup>73</sup> The study comparing CT for the mentally ill with treatment as usual was effective for reducing depression (BDI-II), anxiety (BAI), and overall psychiatric symptoms (BPRS).<sup>75</sup>



Our meta-analysis of depression symptom measures found a greater reduction in depression symptoms for subjects treated with CT than for those in waitlist, self-help booklet, and usual care control groups (Cohen's  $d = -0.91$ ; 95% CI, -1.20 to -0.62, Appendix F). When only compared with waitlist controls, the effect size was larger (Cohen's  $d = -1.06$ ; 95% CI, -1.52 to -0.60, Appendix F).

Our meta-analysis of anxiety symptom measures found a greater reduction in anxiety symptoms for subjects treated with CT than for those in waitlist, self-help booklet, and usual care control groups (Cohen's  $d = -0.93$ ; 95% CI, -1.36 to -0.50, Appendix F). When only compared with waitlist controls, the effect size was larger (Cohen's  $d = -1.20$ ; 95% CI, -1.67 to -0.73, Appendix F).

Overall, we concluded that evidence of moderate strength supports the efficacy of CT for reducing depression and anxiety symptoms based on consistent and direct evidence.

### **Quality of Life**

One trial of cognitive processing therapy assessed quality of life using the Abbreviated Dyadic Adjustment Scale (ADAS) and the short form of the World Health Organization Quality of Life Scale (WHOQOL).<sup>74</sup> The trial reported significant time by condition interactions for social quality of life measures, but not for physical quality of life measures. With data from a single trial ( $N=59$ ), unknown consistency, and imprecision, evidence was insufficient to determine the efficacy of cognitive processing therapy for improving quality of life.

The trial comparing CT for people with severe mental illness with treatment as usual reported outcomes using the SF-12. The CT group had slightly better quality-of-life outcomes than the usual care group for the SF-12 Physical Component ( $p=0.002$ ), but not for the Mental Component ( $p=0.13$ ). With data from a single trial, unknown consistency, and imprecision, evidence was insufficient to determine the efficacy of this particular CT treatment for improving quality of life.

### **Disability or Functional Impairment**

None of the trials that assessed cognitive processing therapy reported outcomes for this category.

Two studies comparing other CT interventions (i.e., that were not cognitive processing therapy) with inactive control groups assessed disability using the Sheehan Disability Scale.<sup>52,73</sup> The trial evaluating CT, a self-help booklet, and repeated assessments measured disability or functional impairment with the Sheehan Disability Scale at posttreatment and at 3- and 9-month follow-up assessments.<sup>73</sup> At 3 and 9 months, those in the CT group had greater reduction in disability scores than those in the repeat assessments group ( $p<0.001$ ). The trial comparing CT with a waitlist control also reported greater reduction in disability scores for those in the CT group at 3 months ( $p<0.0005$ ).<sup>52</sup>

Our meta-analysis of disability measures found a greater improvement for subjects treated with CT than for those in waitlist and self-help booklet control groups (Cohen's  $d = -1.13$ ; 95% CI, -1.76 to -0.51, Appendix F). When only compared with waitlist controls, the effect size was larger (Cohen's  $d = -1.41$ ; 95% CI, -2.41 to -0.41, Appendix F).

Overall, we concluded that evidence of moderate strength supports the efficacy of CT for reducing disability based on consistent and direct evidence.

## Results for Cognitive Therapy Compared With Active Comparators

Three trials compared CT with exposure therapy.<sup>46,72,76</sup> Assessment of these studies appears in the CBT-Exposure section below.

One trial compared CR (N=13) with a relaxation group (N=21) and a combination of prolonged exposure and CR (N=24);<sup>46</sup> these results appear in the CBT-Coping Skills section (below). The authors did not report data on the comparative effectiveness of CR and the combination of prolonged exposure and CR. Briefly, because of unknown consistency, imprecision, and data from a single trial (with 13 CR subjects), we conclude that evidence is insufficient about the comparative effectiveness of CR relative to either relaxation or the prolonged exposure-CR combination for reducing PTSD symptoms.

## Detailed Synthesis: CBT—Coping Skills

### Characteristics of Trials

Table 9 summarizes the characteristics of the four trials meeting our inclusion criteria.<sup>44-46,49</sup> Further details describing the included studies are provided in Appendix D.

The trials in this section had a “coping skills” arm(s)—either relaxation training or stress inoculation training. Stress inoculation training is a cognitive behavioral intervention for PTSD in which the basic goal is to help subjects gain confidence in their ability to cope with anxiety and fear stemming from trauma-related reminders. In stress inoculation training, the therapist helps patients increase their awareness of trauma-related cues for fear and anxiety. In addition, clients learn a variety of coping skills that are useful in managing anxiety, such as muscle relaxing and deep breathing.

**Table 9. Characteristics of included coping skills trials**

| Study  | Arm (N)  | Duration (Followup)   | Population Trauma Type                | Baseline PTSD Severity <sup>a</sup> | Mean Age (Y) | % F | % Non-white | Risk of Bias |
|--|--|---|---------------------------------------|-------------------------------------|--------------|-----|-------------|--------------|
| Carlson et al., 1998 <sup>44</sup>                                     | Relax (13)<br>EMDR (10)<br>TAU (12)            | 6 weeks<br>(3 and 9 months)   | Male<br>Vietnam<br>combat<br>veterans | M-PTSD<br>117.5 to<br>119.4         | 48.5         | 0   | 45.7        | Medium       |
| Marks et al., 1998 <sup>46</sup><br>Lovell, et al., 2001 <sup>79</sup> | Relax (21)<br>PE (23)<br>CR (13)<br>CR+PE (24) | 10 sessions <sup>b</sup><br>(mean of 16 weeks) (1, 3, and 6 months) | Male and female<br>Mixed              | NR                                  | 38           | 36  | NR          | Medium       |
| Taylor et al., 2003 <sup>45</sup>                                      | Relax (19)<br>PE (22)<br>EMDR (19)             | 8 weeks<br>(1 and 3 months)   | Male and female<br>Mixed              | NR                                  | 37           | 75  | 23          | Medium       |
| Foa et al., 1999 <sup>49</sup><br>Zoellner et al., 1999 <sup>81</sup>  | SIT (26)<br>PE (25)<br>PE+SIT (30)<br>WL (15)  | 9 weeks<br>(3, 6, and 9 months)                                     | Female<br>Assault                     | PSS-I<br>29.4 to 32.9               | 35           | 100 | 36          | Medium       |

CBT-M = cognitive behavioral therapy mixed; CR = cognitive restructuring; EMDR = eye movement desensitization and reprocessing; F = female; M-PTSD = Mississippi Scale for Combat-related PTSD; N = total number randomized/assigned to intervention and control groups; NR = not reported; PE = prolonged exposure; PSS-I = PTSD Symptom Scale—Interview; PTSD = posttraumatic stress disorder; relax = relaxation; SIT = stress inoculation training; TAU = treat as usual; y = year

<sup>a</sup>Data reported are mean CAPS or range of mean CAPS scores across groups unless otherwise specified.

<sup>b</sup>Number of treatment sessions is reported when duration of treatment was not specified.

Two of the four trials compared coping skills interventions with inactive comparators.<sup>44,49</sup> One compared prolonged exposure, stress inoculation training, combined prolonged exposure and stress inoculation training, and a waitlist group<sup>49</sup> and the other compared relaxation, EMDR, and treatment as usual.<sup>44</sup> Both trials were conducted in the United States; one enrolled women who were victims of sexual or nonsexual assault<sup>49</sup> and the other enrolled male combat veterans.<sup>44</sup> Duration of treatment ranged from 6 to 9 weeks and both studies included posttreatment follow-up assessments at 3 months, although one study also conducted assessments at 6 and 12 months.<sup>49</sup> The primary outcome measure for one study was the PSS-I;<sup>49</sup> for the other it was the CAPS.<sup>44</sup>

All four included trials made comparisons with active psychotherapy interventions, such as prolonged exposure or EMDR. Three were conducted in the United States<sup>44,46,49</sup> and one in Canada.<sup>45</sup> Sample sizes ranged from 35 to 96. Duration of treatment ranged from 6 to 16 weeks. All four trials included posttreatment follow-up assessments at 3 months; three conducted follow-up assessments as far out as 12 months.<sup>46</sup> One study enrolled male combat veterans;<sup>44</sup> one enrolled victims of sexual and nonsexual assault;<sup>49</sup> the other two enrolled heterogeneous groups of subjects with a variety of index trauma types (e.g., physical assault, road accidents, nonroad accident, witnessing a trauma or homicide, sexual assault, being held hostage, bombing, combat). Mean age for subjects in three trials was mid- to late 30s; one sample included slightly older males (age 45 to 52).<sup>44</sup> In two trials, 75 percent or more of subjects were female.<sup>45,49</sup> The primary outcome for three trials was the CAPS; one study used the PSS-I.<sup>49</sup>

We rated five coping skills trials otherwise meeting criteria for this section as high risk of bias (Table 10). Two of the five trials compared coping skills interventions with inactive comparators.<sup>44,49</sup> One compared prolonged exposure, stress inoculation training, combined prolonged exposure and stress inoculation training, and a waitlist group<sup>49</sup> and the other compared relaxation, EMDR, and treatment as usual.<sup>44</sup> Both trials were conducted in the United States; one enrolled women who were victims of sexual or nonsexual assault and the other enrolled male combat veterans.<sup>44</sup> Duration of treatment ranged from 6 to 9 weeks and both studies included posttreatment follow-up assessments at 3 months, although one study also conducted assessments at 6 and 12 months.<sup>49</sup> The primary outcome measure for one study was the PSS-I;<sup>49</sup> for the other it was the CAPS.<sup>44</sup> We excluded them from our main data synthesis and used them only for sensitivity analyses.

**Table 10. Characteristics of coping skills trials excluded from main analyses because of high risk of bias**

| Study                                     | Arm (N)                                   | Duration (Followup)          | Population Trauma Type                            | Baseline PTSD Severity <sup>a</sup>         | Mean Age (Y) | % F | % Non-white | Risk of Bias |
|---|---|------------------------------|---|---|--------------|-----|-------------|--------------|
| Zlotnick et al., 1997 <sup>82</sup>       | Affect management (17)<br>WL (16)         | 15 weeks                     | Female<br>Childhood sexual abuse                  | DTS<br>66.9 to 74.7                         | 39           | 100 | 3           | High         |
| Echeburua et al., 1996 <sup>83</sup>      | CBT-M (10)<br>CBT Cope (10)               | 57 weeks                     | Female<br>Sexual assault                          | NR  | 22           | 100 | NR          | High         |
| Echeburua et al., 1997 <sup>84</sup>      | CBT-M (10)<br>Relax (10)                  | 6 weeks                      | Female<br>Sexual assault                          | NR  | 20           | 100 | NR          | High         |
| Foa et al., 1991 <sup>85</sup>            | SIT (17)<br>PE (14)<br>SC (14)<br>WL (10) | 9 weeks                      | Female<br>Assault                                 | Interviewer severity rating<br>24.4 to 25.8 | 32           | 100 | 27          | High         |
| Hensel-Dittman et al., 2011 <sup>86</sup> | NET (15)<br>SIT (13)                      | 4 weeks<br>(6 and 12 months) | Male and female<br>Experienced organized violence | 85.2 to 96.5                                | NR           | NR  | NR          | High         |

CBT Cope = cognitive behavioral therapy-coping skills; CBT-M = cognitive behavioral therapy mixed; DTS = Davidson Trauma Scale; F = female; N = total number randomized/assigned to intervention and control groups; PE = prolonged exposure; PTSD = posttraumatic stress disorder; relax = relaxation; SIT = stress inoculation training; SC = supportive counseling; WL = waitlist; y = year

<sup>a</sup>Data reported are mean CAPS or range of mean CAPS scores across groups unless another instrument is specified.

## Results for Coping Skills Compared With Inactive Comparators

### PTSD Symptom Reduction

Both trials that compared a coping skills intervention with inactive comparators reported measures of symptom reduction (Table 11).<sup>44,49</sup> The trial that compared prolonged exposure, stress inoculation training, combined prolonged exposure and stress inoculation training, and waitlist found greater improvement in PTSD symptoms for subjects treated with stress inoculation training than for those in the waitlist group.<sup>49</sup>

The trial that compared relaxation, EMDR, and treatment as usual found no statistically significant difference between relaxation and treatment as usual using the Impact of Event Scale (IES)-total (Table 11).<sup>44</sup> Using the Mississippi scale, both groups had a similar small decrease in symptoms.

Neither study reported follow-up data after the posttreatment assessment for the inactive comparator group—only the active intervention groups were assessed.

For stress inoculation training, with data from a single trial (N=41 subjects in the stress inoculation training and waitlist arms combined), unknown consistency, and imprecision, evidence was insufficient to determine its efficacy. However, the single trial of stress inoculation training suggests that it may be efficacious, but further research is needed to confirm or refute the findings. For relaxation, the trial provides insufficient evidence to determine the efficacy of relaxation—evidence was inconsistent and imprecise.

**Table 11. Results at end of treatment for PTSD symptoms for coping skills interventions compared with inactive controls**

| Study   | Arm (N)                                       | Outcome Measure(s)         | Baseline Value             | End of Treatment Value | P Value |
|---|---|----------------------------|----------------------------|------------------------|---------|
| Carlson et al., 1998 <sup>44</sup>                              | Relax (13)<br>EMDR (10)<br>TAU (12)           | M-PTSD                     | Relax: 119.4<br>TAU: 117.9 | 114.2<br>112.9         | NS      |
|   |   | PSTD symptoms <sup>a</sup> | Relax: 6.8<br>TAU: 7.5     | 4.7<br>6.2             | NR      |
|   |   | IES-Total                  | Relax: 52.9<br>TAU: 52.8   | 44.5<br>38.7           | NS      |
| Foa, 1999 et al., <sup>49</sup><br>Zoellner, 1999 <sup>81</sup> | SIT (26)<br>PE (25)<br>PE+SIT (30)<br>WL (15) | PSS-I                      | SIT: 29.4<br>WL 32.9       | 12.9<br>26.9           | <0.05   |

EMDR = eye movement desensitization and reprocessing; IES = Impact of Event Scale; M-PTSD = Mississippi Scale for Combat-related PTSD; N = total number randomized/assigned to intervention and control groups; NR = not reported; NS = not significant; PE = prolonged exposure; PSS-I = Posttraumatic Stress Disorder Symptom Scale-Interview; PTSD = posttraumatic stress disorder; relax = relaxation; SIT = stress inoculation training; TAU = treatment as usual; WL = waitlist

<sup>a</sup>This was a global self-rating on a 0-10 scale with 10 = “worst.”

Note: results are only presented for the relevant arms for this section (coping skills and inactive comparators); values entered are means unless otherwise specified; p values are for the comparison between coping skills and inactive comparators.

### Loss of PTSD Diagnosis

Both trials reported loss of diagnosis. In one trial, 42 percent of the subjects in the stress inoculation training group and 0 percent in the waitlist group lost their PTSD diagnosis ( $p < 0.001$ ).<sup>49</sup>

In the other trial, 2 of 9 patients in the relaxation group who completed treatment (out of 13 patients randomized to relaxation) no longer met criteria for PTSD diagnosis. The study did not report data for the treatment as usual group.

For stress inoculation training, with data from a single trial (N=41 subjects in the stress inoculation training and waitlist arms combined), unknown consistency, and imprecision, evidence was insufficient to determine its efficacy. However, the single trial of stress inoculation training suggests that it may be efficacious, but further research is needed to confirm or refute the findings.

### Prevention or Reduction of Comorbid Medical or Psychiatric Conditions

Both trials reported on coexisting anxiety and depression symptoms (Table 12).<sup>44,49</sup> The trial that included stress inoculation training and waitlist arms found that subjects treated with stress inoculation training had greater reduction in their symptoms of depression than those in the waitlist group; reduction in anxiety symptoms was not statistically significantly different between groups.<sup>49</sup>

The trial comparing relaxation and treatment as usual found a reduction in both depression and anxiety symptoms in the relaxation group; however, the authors reported no statistically significant between-group difference on measures of anxiety and did not provide data on between-group differences for depression.<sup>44</sup>

**Table 12. Results at end of treatment for depression and anxiety symptoms for coping skills interventions compared with inactive controls**

| Study   | Arm (N)                                       | Outcome Measure(s)  | Baseline Value           | End of Treatment Value | P Value |
|---|---|---------------------|--------------------------|------------------------|---------|
| Carlson et al., 1998 <sup>44</sup>                                    | Relax (13)<br>EMDR (10)<br>TAU (12)           | BDI                 | Relax: 23.6<br>TAU: 24.0 | 15.8<br>23.5           | NR      |
|   |   | STAI-State subscale | Relax: 58.2<br>TAU: 58.2 | 46.3<br>51.4           | NS      |
|   |   | STAI-Trait subscale | Relax: 58.0<br>TAU: 61.7 | 50.8<br>55.8           | NS      |
| Foa et al., 1999 <sup>49</sup><br>Zoellner et al., 1999 <sup>81</sup> | SIT (26)<br>PE (25)<br>PE+SIT (30)<br>WL (15) | BDI                 | SIT: 21.7<br>WL: 25.2    | 10.1<br>22.1           | <0.05   |
|   |   | STAI-State subscale | SIT: 51.5<br>WL: 51.4    | 39.1<br>50.4           | 0.14    |

BDI = Beck Depression Inventory; EMDR = eye movement desensitization and reprocessing; N = total number randomized/assigned to intervention and control groups; NR = not reported; NS = not statistically significant; PE = prolonged exposure; relax = relaxation; SIT = stress inoculation training; STAI = State-Trait Anxiety Inventory; TAU = treatment as usual; WL = waitlist

Note: results are only presented for the relevant arms for this section (coping skills and inactive comparators); values entered are means unless otherwise specified; P values are for the comparison between coping skills and inactive comparators.

For stress inoculation training, with data from a single trial (N=41 subjects in the stress inoculation training and waitlist arms combined), unknown consistency, and imprecision, evidence was insufficient to determine its efficacy. The single trial of stress inoculation training suggests that it may be efficacious, but further research is needed to confirm or refute the findings.

Neither trial reported data on the prevention or reduction of a coexisting medical condition.

## Results for Coping Skills Compared With Active Comparators

Of the four included trials comparing a coping skills therapy with an active comparator, three included comparisons with exposure-based interventions;<sup>45,46,49</sup> two included comparisons with EMDR;<sup>44, 45</sup> two included comparisons with CBT-mixed therapies;<sup>46,49</sup> and one included a comparison with CR.<sup>46</sup> For assessment of the comparisons with exposure-based therapies, see the CBT Exposure section (below). For assessment of the comparisons with CBT-mixed therapies, see the CBT-Mixed section (below). For assessment of the comparisons with EMDR, see the EMDR section (below).

One trial comparing a relaxation intervention with CR randomly assigned subjects (N=81) to prolonged exposure, CR, prolonged exposure plus CR, or relaxation.<sup>46</sup> In summary, direct evidence was insufficient to determine the comparative effectiveness of CR and relaxation. Consistency of the evidence is unknown (limited to this single trial) and results were imprecise, with 34 total subjects in the CR and relaxation groups. Of note, indirect evidence (described in other sections of this report) from comparisons with inactive controls (e.g., waitlist) was insufficient to determine the efficacy of relaxation. In addition, the head-to-head trial described here reported outcomes for the relaxation group that were consistently less favorable than those for the other three groups.

## **PTSD Symptom Reduction**

The trial defined the percentage of patients whose PTSD symptoms improved using the CAPS and IES based on a criterion of 2 standard deviations or more improvement since week 0. Using the IES, the authors reported that 50 percent of the subjects in the CR group and 20 percent of the subjects in the relaxation group improved ( $p=0.04$ ).<sup>46</sup>

The trial also reported data on end-state function, determined by a 50 percent drop in PTSD Symptoms Scale, a BDI score of 7 or less, and a STAI score of 35 or more at week 11. A higher percentage of subjects were improved in the prolonged exposure, CR, and prolonged exposure plus CR arms than in the relaxation arm, but the differences were not statistically significant (53% vs. 32% vs. 32% vs. 15%,  $p=NS$ ).

## **Loss of PTSD Diagnosis**

At week 11, more subjects in the CR group than in the relaxation group no longer met criteria for PTSD; the difference was not statistically significant (65% vs. 55%,  $p=NS$ ).

## **Prevention or Reduction of Comorbid Medical or Psychiatric Conditions**

Subjects treated with relaxation did consistently less well than comparators on the BDI; mean change scores for exposure therapy were 13 (95% CI, 8 to 18); for CR, 17 (95% CI, 11 to 22); prolonged exposure plus CR, 18 (95% CI, 13 to 23); and for relaxation, 7 (95% CI, 3 to 11).<sup>46</sup>

The trial did not report on anxiety symptoms or medical conditions.

## **Detailed Synthesis: CBT—Exposure**

### **Characteristics of Trials**

Table 13 summarizes the characteristics of the 15 trials meeting our inclusion criteria. Further details are provided in Appendix D. Of the 15 included trials, 11 compared exposure therapy (imaginal, in vivo, or prolonged exposure [which includes both components]) with waitlist,<sup>25,46,49,72,87,88</sup> usual care,<sup>89</sup> treatment as usual,<sup>90</sup> present-centered therapy,<sup>91,92</sup> or supportive counseling.<sup>63</sup> Among these studies, many also included active comparators, including EMDR,<sup>45,87</sup> relaxation,<sup>45</sup> CR or CT,<sup>46,72,76</sup> prolonged exposure plus CR,<sup>25,46</sup> stress inoculation training,<sup>49</sup> and prolonged exposure plus stress inoculation training.<sup>49</sup> Two of the 10 prolonged exposure studies had only active comparators—1 compared prolonged exposure with EMDR and relaxation;<sup>45</sup> the other compared prolonged exposure, prolonged exposure plus CR, imaginal exposure, and in vivo exposure.<sup>66</sup> One additional study compared virtual reality with imaginal exposure and waitlist among combat veterans in Portugal.<sup>93</sup> Finally, 1 study compared a version of prolonged exposure conducted in a group setting with present-centered therapy.<sup>92</sup>

**Table 13. Characteristics of included CBT-exposure trials**

| Study   | Arm (N)  | Duration (Followup)                                       | Population Trauma Type              | Baseline PTSD Severity <sup>a</sup> | Mean Age (Y) | % F | % Non-white | Risk of Bias |
|---|--|---|-------------------------------------|-------------------------------------|--------------|-----|-------------|--------------|
| Basoglu et al., 2007 <sup>88</sup>  | In vivo (16)<br>WL (15)                          | 1 session <sup>b</sup> (4, 8, 12, 24 weeks and 12 months) | Male and female<br>Natural disaster | 62.3 to 63.1                        | 34           | 87  | NR          | Medium       |
| Foa et al., 1999 <sup>49</sup><br>Zoellner et al., 1999 <sup>81</sup>   | PE (25)<br>SIT (26)<br>PE+SIT (30)<br>WL (15)    | 9 weeks (3, 6, and 9 months)                              | Female<br>Assault                   | PSS-I<br>29.4 to 32.9               | 35           | 100 | 36          | Medium       |
| Foa et al., 2005 <sup>25</sup>  | Total 190<br>PE (NR)<br>PE+CR (NR)<br>WL (NR)    | 12 weeks; 9 to 12 weekly sessions (3, 6, and 12 months)   | Female<br>Assault                   | PSS-I<br>31.1 to 34.0               | 31           | 100 | 51          | Medium       |
| Gamito et al., 2010 <sup>93</sup>   | VR (5)<br>IE (2)<br>WL (3)                       | 12 sessions <sup>b</sup>                                  | Male<br>Combat                      | NR                                  | 64           | 0   | NR          | Medium       |
| Resick et al., 2002 <sup>72</sup><br>Resick, et al., 2003 <sup>77</sup><br>Resick, et al., 2012 <sup>78</sup> | PE (62)<br>CPT (62)<br>WL (47)                   | 6 weeks (3 and 9 months, 5 to 10 years)                   | Female<br>Sexual assault            | 69.9 to 76.6                        | 32           | 100 | 29          | Medium       |
| Rothbaum et al., 2005 <sup>87</sup>   | PE (24)<br>EMDR (26)<br>WL (24)                  | 4.5 weeks (6 months)                                      | Female<br>Sexual assault            | Data reported in graphs only        | 34           | 100 | 32          | Medium       |
| Asukai et al., 2010 <sup>89</sup>   | PE (12)<br>UC (12)                               | 8 to 15 weekly sessions (3 and 12 months)                 | Male and female<br>Mixed            | 84.3 to 84.6                        | 29           | 88  | 100         | Medium       |
| Nacasch et al., 2011 <sup>90</sup>  | PE (15)<br>TAU (15)                              | 9 to 15 weeks (12 months)                                 | Male and female<br>Combat           | PSS-I<br>36.8 to 37.1               | 34           | NR  | 100         | Medium       |
| Schnurr et al., 2003 <sup>92</sup>  | Group exposure (180)<br>PCT (180)                | 30 weeks, 5 subsequent monthly boosters (12 months total) | Male<br>Combat                      | 80.4 to 82.1                        | 51           | 0   | 34          | Low          |
| Schnurr et al., 2007 <sup>91</sup>  | PE (141)<br>PCT (143)                            | 10 weeks (3 and 6 months)                                 | Female<br>Mixed                     | 77.6 to 77.9                        | 45           | 100 | 46          | Medium       |
| Bryant et al., 2003 <sup>63</sup>   | IE (20)<br>IE+CR (20)<br>SC (18)                 | 8 weeks   | Male and female<br>Mixed            | CAPS-I intensity<br>32.5 to 32.9    | 35           | 52  | NR          | Medium       |
| Bryant et al., 2008 <sup>66</sup>   | PE (31)<br>PE+CR (28)<br>IE (31)<br>In vivo (28) | 8 weeks   | Male and female<br>Mixed            | 71.4 to 76.8                        | 37           | NR  | 8           | Medium       |



**Table 13. Characteristics of included CBT-exposure trials (continued)**

| Study   | Arm (N)  | Duration (Followup)   | Population Trauma Type   | Baseline PTSD Severity <sup>a</sup> | Mean Age (Y) | % F | % Non-white | Risk of Bias |
|---|--|---|--------------------------|-------------------------------------|--------------|-----|-------------|--------------|
| Marks et al., 1998 <sup>46</sup><br>Lovell et al., 2001 <sup>79</sup> | PE (23)<br>CR (19)<br>PE+CR (24)<br>Relax (21) | 10 sessions <sup>b</sup><br>mean of 16 weeks (1, 3, and 6 months) | Male and female<br>Mixed | CAPS Severity 2.6 to 3.2            | 38           | 36  | NR          | Medium       |
| Tarrier et al., 1999 <sup>76,80</sup>                                 | IE (35)<br>CT (37)                             | 16 sessions (112 days) (6 and 12 months)                          | Male and female<br>Mixed | 71.1 to 77.8                        | 39           | 42  | NR          | Medium       |
| Taylor et al., 2003 <sup>45</sup>                                     | PE (22)<br>EMDR (19)<br>Relax (19)             | 6 months  | Male and female<br>Mixed | NR                                  | 37           | 75  | 23          | Medium       |

CAPS = Clinician Administered PTSD Scale; CPT = cognitive processing therapy; CR = cognitive restructuring; EMDR = eye movement desensitization and reprocessing; F = female; IE = imaginal exposure; In vivo = in vivo exposure; PCT = present-centered therapy (a type of supportive therapy); NR = not reported; PE = prolonged exposure; PSS-I = PTSD Symptom Scale—Interview; relax = relaxation; SIT = stress inoculation training; SC = supportive control; TAU = treatment as usual; UC = usual care; WL = waitlist; y = year

<sup>a</sup>Data reported are mean CAPS or range of mean CAPS scores across groups unless another instrument is specified.

<sup>b</sup>Number of treatment sessions is reported when duration of treatment was not specified.

These trials generally enrolled subjects with severe or extreme PTSD symptoms. The majority of the trials assessing exposure therapy were conducted in the United States; 1 each was conducted in Japan,<sup>89</sup> Canada,<sup>45</sup> Israel,<sup>90</sup> the United Kingdom,<sup>46</sup> and Australia.<sup>63</sup> Sample sizes ranged from 24 to 284. Each trial included posttreatment followups after 3, 6, 9, or 12 months. Seven of the trials enrolled a heterogeneous group of subjects with a variety of index trauma types (e.g., accident, disaster, physical assault, sexual assault, witnessing death or serious injury); 4 trials enrolled a majority of subjects with sexual assault-related PTSD;<sup>25,49,72,87</sup> 2 enrolled subjects with combat-related PTSD;<sup>90,92,93</sup> 1 enrolled subjects with combat- or terror-related PTSD;<sup>90</sup> and 1 enrolled natural disaster victims.<sup>88</sup> Mean age ranged from 27 to 63. Eight trials enrolled two-thirds or more female subjects. The primary outcome for the majority of trials was some version of the CAPS (CAPS, CAPS-2, or CAPS-Sx); 3 trials identified the PSS-I as the primary outcome measure.<sup>25,49,90</sup>

Regarding the type of exposure therapy evaluated by the included trials, the majority evaluated prolonged exposure. One trial compared a modified version of prolonged exposure conducted in a group format to an inactive control condition for combat veterans (group exposure vs. PCT).<sup>92</sup> Four examined imaginal exposure.<sup>63,66,76,93</sup> Of these 4, 1 trial (N=10) compared imaginal exposure with virtual reality exposure and waitlist;<sup>93</sup> 1 (N=68) compared it with imaginal exposure plus cognitive restructuring and supportive control;<sup>63</sup> 1 (N=72) compared it with cognitive therapy;<sup>76</sup> and 1 compared it with prolonged exposure, prolonged exposure plus cognitive restructuring, and in vivo exposure.<sup>66</sup> Of these 4 trials, 2 were conducted in Australia, 1 in Portugal, and 1 in England. One trial assessed in vivo exposure compared with waitlist among natural disaster victims in Turkey.<sup>88</sup>

Twelve trials otherwise meeting criteria for this section were rated high risk of bias (Table 14); we excluded them from our main data synthesis but used them in sensitivity analyses.

**Table 14. Characteristics of CBT-exposure trials excluded from main analyses because of high risk of bias**

| Study                                | Arm (N)  | Duration (Followup)  | Population Trauma Type               | Baseline PTSD Severity <sup>a</sup>                         | Mean Age (Y) | % F | % Non-white | Risk of Bias |
|--------------------------------------|--|--|--------------------------------------|---|--------------|-----|-------------|--------------|
| Difede et al., 2007 <sup>94</sup>    | CBT-exp (13)<br>WL (8)   | 24 weeks   | World Trade Center attack            | 69.3 to 71.8  | 46           | 14  | 24          | High         |
| Johnson et al., 2006 <sup>95</sup>   | Randomized (Total: 51) <sup>b</sup><br>PE (Unclear)<br>CM (Unclear)<br>EMDR (Unclear)<br>WL (14) | Mean number of weekly sessions <sup>c</sup><br>PE: 9.66<br>EMDR: 6.33<br>WL: 5.89 (3 months) | Female<br>Mixed                      | 61.8 to 82.0  | 39           | 100 | 17          | High         |
| Keane et al., 1989 <sup>96</sup>     | Flooding (11)<br>WL (13)   | 14 to 16 sessions <sup>b</sup> (6 months)  | Male<br>Combat                       | PTSD Symptom Checklist<br>36.4 to 36.5                      | 35           | 0   | 21          | High         |
| Foa et al., 1991 <sup>85</sup>       | SIT (17)<br>PE (14)<br>SC (14)<br>WL (10)  | 9 weeks  | Female<br>Sexual abuse, assault      | Calculation of interviewer severity rating<br>24.4 to 25.78 | 32           | 100 | 27          | High         |
| Feske et al., 2008 <sup>97</sup>     | PE (11)<br>UC (13)   | 6 months   | NR                                   | PDS-I<br>34.9 to 35.2                                       | 43           | 100 | 95          | High         |
| McLay et al., 2011 <sup>98</sup>     | VR-exposure (10)<br>TAU (10)   | 10 weeks   | Active duty service members          | 82.8 to 83.5  | 24           | 5   | NR          | High         |
| Ready et al., 2010 <sup>99</sup>     | VR (6)<br>PCT (5)  | 10 sessions (6 months)   | Male<br>Combat                       | 93.8  | 58           | 0   | 46          | High         |
| Arntz et al., 2007 <sup>100</sup>    | CBT-exp (42)<br>CBT-exp (29)<br>Cross-over (17)  | 10 weeks (1 month)   | Mixed                                | PSS-SR<br>25.0 to 29.4                                      | 35           | 66  | 28          | High         |
| Brom et al., 1989 <sup>101</sup>     | Desen (31)<br>Hypno (29)<br>PsychEd (29)   | 15 session (3 months)  | Netherlands<br>Mixed                 | IES<br>46.3 to 50.8   | 42           | 79  | NR          | High         |
| Beidel et al., 2011 <sup>102</sup>   | CBT-M (18)<br>Exposure (17)  | 17 weeks   | Male<br>Combat                       | 84.9 to 90.6  | 59           | 0   | 0           | High         |
| Ironson et al., 2002 <sup>103</sup>  | EMDR (10)<br>PE (12)   | 6 weeks (3 months)   | Domestic violence/child sexual abuse | PSS-SR<br>26.6 to 34.6                                      | NR           | 77  | NR          | High         |
| Paunovic et al., 2001 <sup>104</sup> | Exposure (10)<br>CBT-M (10)  | 16 to 20 weeks (6 months)  | Male and female<br>Refugees          | 95.1 to 98.4  | 38           | 15  | NR          | High         |

CBT-M = cognitive behavioral therapy mixed; CAPS = Clinician Administered PTSD Scale for DSM-IV; CPT = cognitive processing therapy; CM = Counting Method; CR = cognitive restructuring; desen = desensitization; EMDR = eye movement desensitization and reprocessing; F = female; f/u = follow-up; hypno = hypnotherapy; IES = Impact of Event Scale; PCT = present-centered therapy (a type of supportive therapy); NR = not reported; PE = prolonged exposure; PSS = PTSD symptom scale; PsychEd = psychoeducation; relax = relaxation; SC = supportive control; SIT = stress inoculation training; UC = usual care; WL = waitlist; y = year

<sup>a</sup>Data reported are mean CAPS or range of mean CAPS scores across groups unless another instrument is specified.

<sup>b</sup>The number of participants randomized to each active treatment group was not reported. A total of 27 participants from the active treatment groups were analyzed, 9 in each treatment group.

<sup>c</sup>Number of treatment sessions is reported when duration of treatment was not specified.

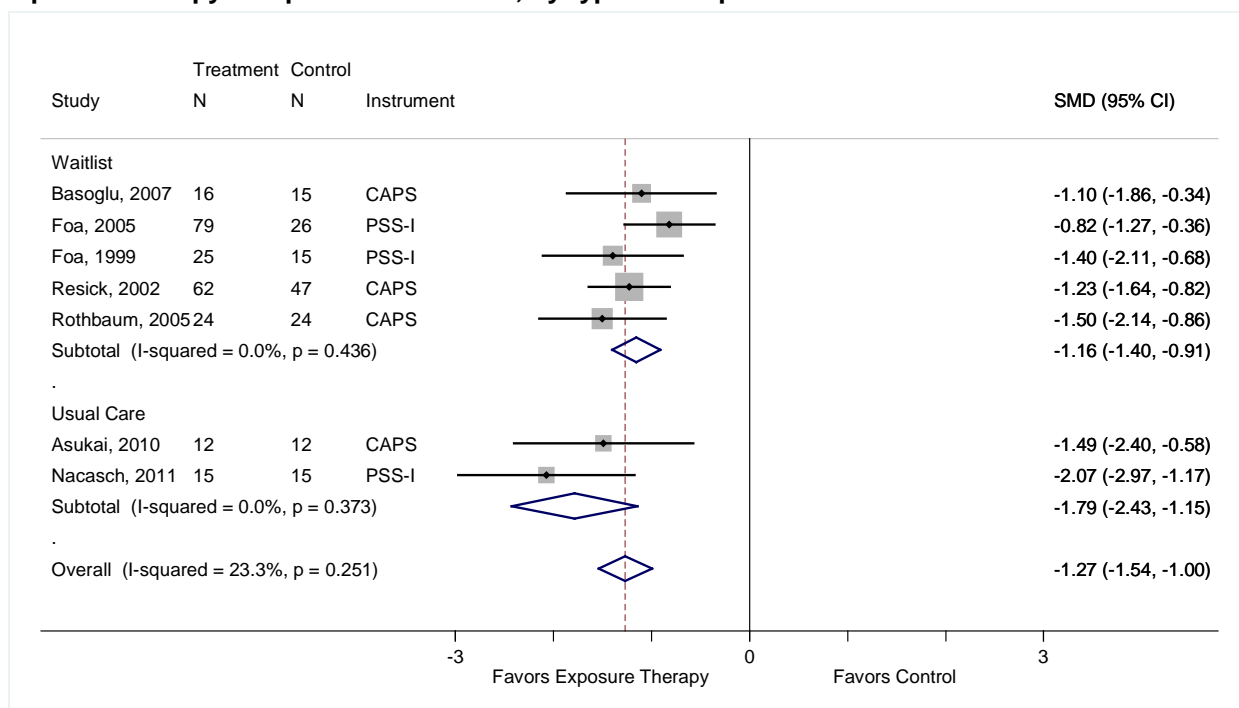
## Results for Exposure Therapy Compared With Inactive Controls

### PTSD Symptom Reduction

Eight of the 11 trials comparing various exposure therapies with an inactive comparator reported measures of PTSD symptom change. All 8 reported greater improvement in PTSD symptoms in the exposure group than in the control group.<sup>25,49,72,87-91</sup>

Our meta-analysis including all trials with sufficient data (available outcome measures were CAPS and PSS-I) (Figure 6) that compared exposure therapy with waitlist or usual care found a greater reduction in PTSD symptoms for subjects treated with exposure than for those in control groups; the effect size was very large (SMD -1.27).<sup>89,91</sup>

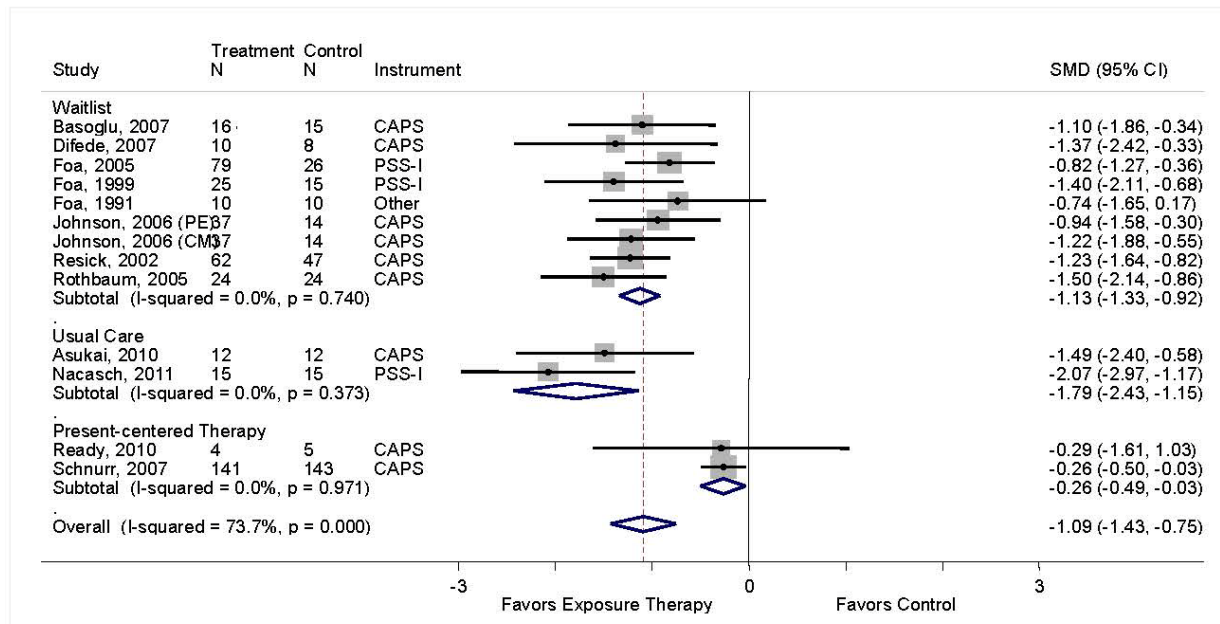
**Figure 6. Mean change from baseline to end of treatment in PTSD symptoms (any measure) for exposure therapy compared with control, by type of comparator**



Note: Timing of outcome assessment: 8 weeks (Basoglu, 2007),<sup>88</sup> 12 weeks (Foa, 2005),<sup>25</sup> 9 weeks (Foa, 1999),<sup>49</sup> 6 weeks (Resick, 2002),<sup>72</sup> 4.5 weeks (Rothbaum, 2005),<sup>87</sup> “post-treatment” or 8 to 15 weeks (Asukai, 2010),<sup>89</sup> 9 to 15 weeks (Nacasch, 2011).<sup>90</sup>

Sensitivity analyses that added trials comparing exposure therapy with present-centered therapy, those rated as high risk of bias, or both had little impact on the results; effect sizes were still large, ranging from -1.19 to -1.09 (Appendix F and Figure 7).

**Figure 7. Sensitivity analysis for mean change from baseline to end of treatment in PTSD symptoms (any measure) for exposure therapy compared with control, by type of comparator: including present-centered therapy comparators and high risk of bias studies**



Note: Timing of outcome assessment: 8 weeks (Basoglu, 2007),<sup>88</sup> 24 weeks (Difede 2007),<sup>94</sup> 12 weeks (Foa, 2005),<sup>25</sup> 9 weeks (Foa, 1999<sup>49</sup> and Foa, 1991<sup>85</sup>), 6 to 9 sessions (Johnson, 2006),<sup>95</sup> 6 weeks (Resick, 2002),<sup>72</sup> 4.5 weeks (Rothbaum, 2005),<sup>87</sup> “post-treatment” or 8 to 15 weeks (Asukai, 2010),<sup>89</sup> 9 to 15 weeks (Nacasch, 2011),<sup>90</sup> 10 sessions (Ready 2010),<sup>99</sup> 10 weeks (Schnurr 2007).<sup>91</sup>

Our meta-analysis of the trials reporting CAPS scores found a 28.9-point greater reduction for subjects treated with exposure than for those in control groups (WMD, -28.9; 95% CI, -35.5 to -22.3; 4 trials, N=212, Appendix F).

Sensitivity analyses that added trials comparing exposure therapy with present-centered therapy, those rated as high risk of bias, or both had little impact on the results; effect sizes were still large, ranging from -24 to -27.9 (Appendix F).

In general, the effects for reduction of PTSD symptoms were maintained at longer-term followup of 3, 6, 9, or 12 months.

Overall, we concluded that the SOE is high to support the efficacy of exposure therapy for reduction of PTSD symptoms. This conclusion is based on consistent, direct, and precise evidence from trials that used common comparators and found large effect sizes.

### Loss of PTSD Diagnosis

Five of the trials comparing people receiving exposure therapy with those in inactive control groups reported on achieving loss of diagnosis. In each one, a substantial percentage of participants treated with exposure therapy lost their PTSD diagnosis (range, 41% to 95%); this was a significantly higher percentage than among controls.

Our meta-analysis for achieving loss of diagnosis found that 66 percent more subjects treated with exposure therapy achieved loss of PTSD diagnosis than in waitlist control groups over 4 to 9 weeks (RD, 0.66; 95% CI, 0.42 to 0.91; 3 trials, N=197, Appendix F). This translates to a NNT of 2. Our sensitivity analysis adding trials that compared exposure therapy with present-centered

therapy or with supportive control (there were not sufficient data to conduct sensitivity analyses by adding high risk of bias trials) resulted in a reduced effect size (RD 0.46, Appendix F).

### **Prevention or Reduction of Comorbid Conditions**

Eight trials reported on changes in depression symptoms.<sup>25,49,72,87-91</sup> All reported a significantly greater decrease in depression symptoms for exposure intervention patients than for controls. Results of our meta-analysis indicated a greater reduction in BDI scores for subjects treated with exposure than for those in waitlist or usual care groups (WMD, -8.2; 95% CI, -10.3 to -6.1;  $I^2=0%$ ,  $N=363$ , Appendix F). Together, these trials provide high SOE of the efficacy of exposure therapy for decreasing symptoms of depression in adults with PTSD.

No trial reported on anxiety symptoms or coexisting medical conditions.

### **Quality of Life**

No studies of exposure therapy meeting inclusion criteria and with a waitlist or usual care control reported quality of life outcomes. One trial comparing prolonged exposure with present-centered therapy included a measure of quality of life.<sup>91</sup> The study reported that groups did not differ across time (Cohen's  $d = 0.09$ , NS). Evidence was insufficient (because of unknown consistency and imprecision) to determine the efficacy of exposure therapy for improving quality-of-life outcomes.

### **Disability or Functional Impairment**

One trial comparing in vivo exposure with waitlist included a measure of work and social adjustment.<sup>88</sup> It found that in vivo exposure led to greater improvement in functional impairment than the waitlist control at 4 weeks (Cohen's  $d = 0.8$ ) and 8 weeks (Cohen's  $d = 0.6$ ).

One trial comparing prolonged exposure, prolonged exposure plus CR, and waitlist ( $N=190$ ) included the Social Adjustment Scale. The trial reported numerically greater improvements for the two intervention groups than for the waitlist group, but the differences were not statistically significant (see Appendix D for details).

Evidence was insufficient (because of inconsistency and imprecision) to determine the efficacy of exposure therapy for improving disability or functional impairment.

## **Results for Exposure Therapy Compared With Active Comparators: Exposure Therapy Versus Cognitive Therapy**

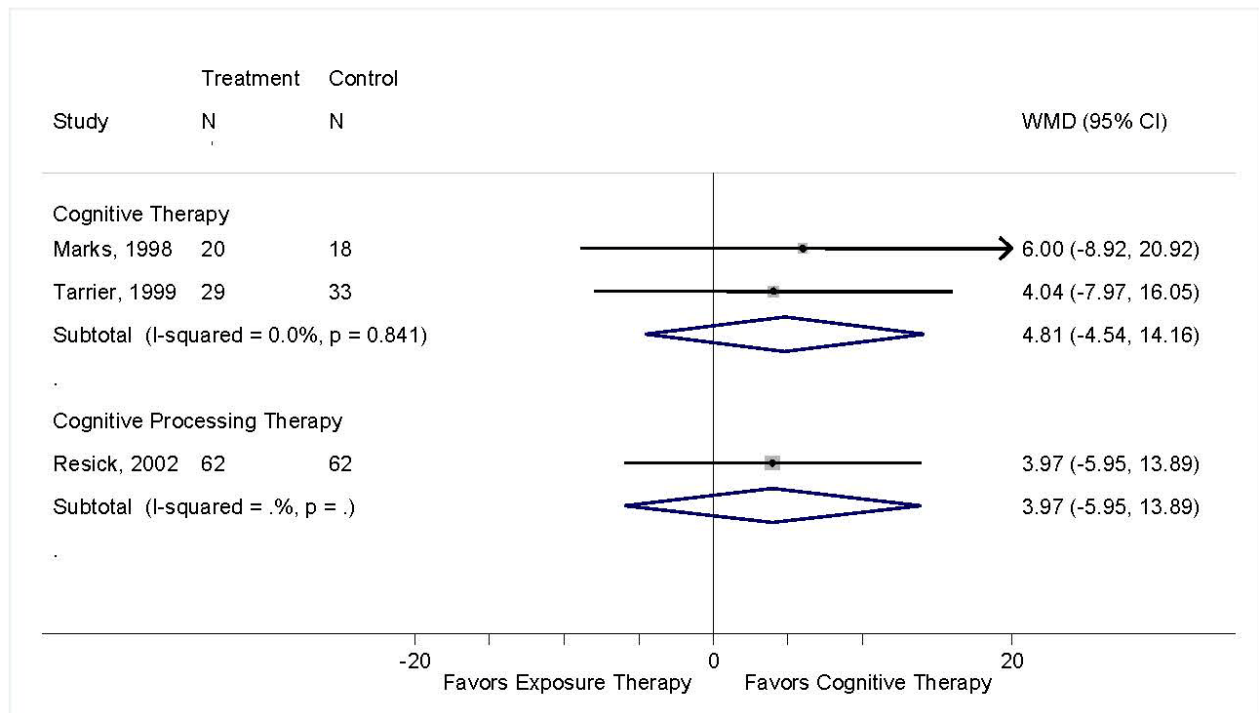
Three trials compared exposure therapy and either CR, CT, or cognitive processing therapy.<sup>46,72,76</sup> Of these, one compared prolonged exposure with CR,<sup>46</sup> one compared imaginal exposure with CT,<sup>76</sup> and one compared prolonged exposure with cognitive processing therapy.<sup>72</sup> The results from these head-to-head trials did not find either treatment to be statistically significantly better than the other. Our meta-analyses (below) for some outcomes found point estimates favoring exposure therapies (loss of PTSD diagnosis) and for other outcomes favoring cognitive therapies (reduction of PTSD symptoms and depression symptoms). We concluded that the evidence was largely insufficient to determine the comparative effectiveness of therapies for each individual outcome. Nevertheless, considering all of the outcomes across these studies suggests that if a difference in effectiveness exists between treatments, it is small.

## PTSD Symptom Reduction

All three trials found that both exposure therapies and cognitive therapies led to substantial decreases in PTSD symptoms from baseline to posttreatment, with no statistically significant difference between the interventions.

Results of our meta-analyses (Figure 8) found no statistically significant difference between exposure therapy and CT (WMD, 4.8; 95% CI, -4.5 to 14.2) or between exposure therapy and cognitive processing therapy (WMD, 3.97; 95% CI, -5.95 to 13.9). Mainly because of imprecision of these findings, we concluded that these trials provide insufficient head-to-head data to determine whether exposure therapy is better or worse than cognitive therapy for reducing PTSD symptoms.

**Figure 8. Mean change from baseline in CAPS for exposure therapy compared with cognitive therapy**



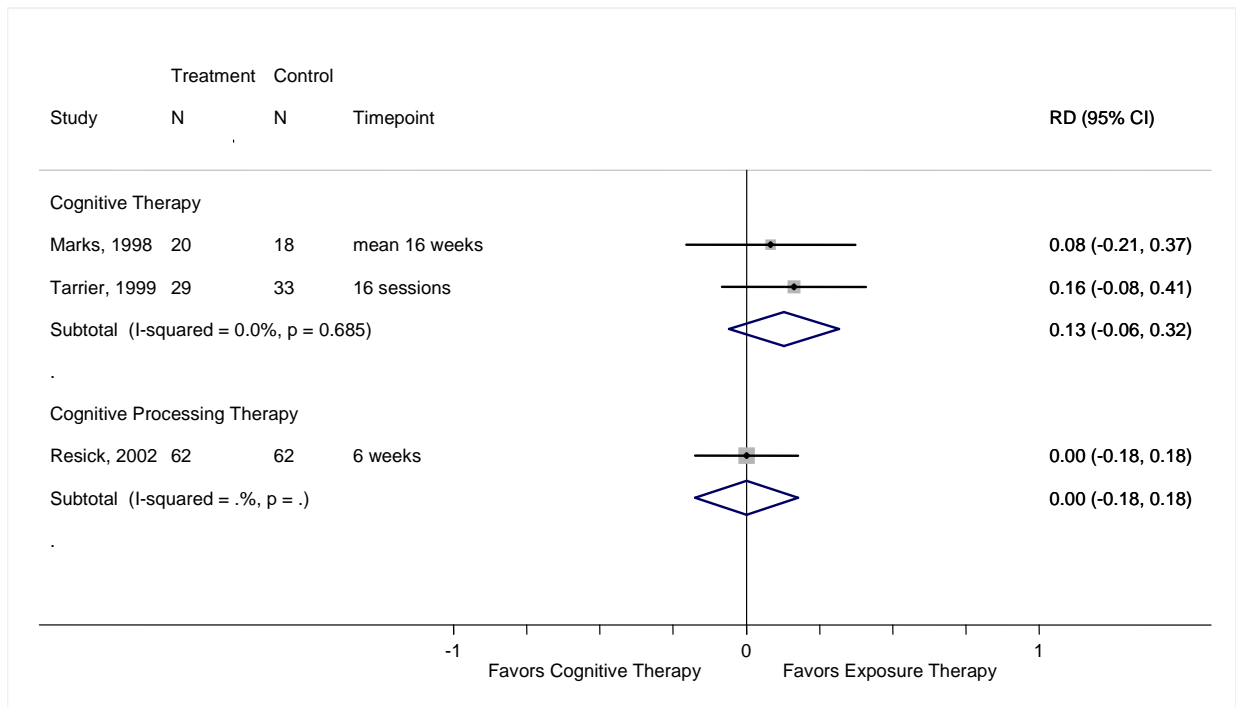
Note: Timing of outcome assessment: mean 16 weeks (Marks, 1998),<sup>46</sup> following 16 sessions (Tarrier, 1999),<sup>80</sup> 6 weeks (Resick, 2002).<sup>72</sup>

## Loss of PTSD Diagnosis

All three trials reported data on achieving loss of PTSD diagnosis.<sup>46,72,76</sup> Loss of PTSD diagnosis for exposure therapy-treated subjects was equal to or greater than that for CT-treated subjects in all three trials (range 53% to 75%).

Our meta-analysis (Figure 9) found no statistically significant difference between exposure therapy and CT (RD, 0.13; 95% CI, -0.06 to 0.32) or between exposure therapy and cognitive processing therapy (RD 0.0).

**Figure 9. Loss of PTSD diagnosis for exposure therapy compared with cognitive therapy**

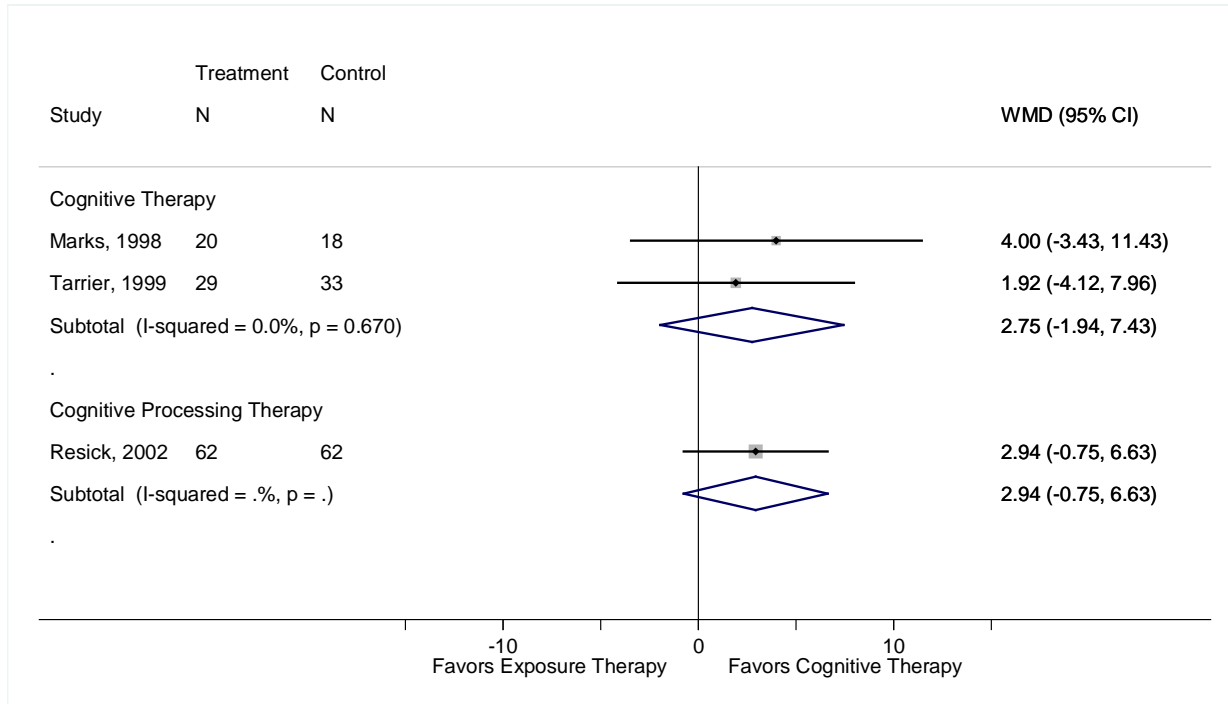


### Prevention or Reduction of Comorbid Conditions

All three trials used the BDI to measure change in depression symptom scores. Although point estimates favored CT and cognitive processing therapy, no study found a statistically significant difference between the interventions.

Our meta-analysis (Figure 10) found no statistically significant difference between interventions. The point estimates favored CT (WMD 2.75) and cognitive processing therapy (WMD 2.94). We concluded, however, that evidence is insufficient (mainly because of imprecision) to determine whether either treatment is more effective for reducing depressive symptoms.

**Figure 10. Mean change in Beck Depression Inventory for exposure therapy compared with cognitive therapy**



Note: Timing of outcome assessment: mean 16 weeks (Marks, 1998),<sup>46</sup> following 16 sessions (Tarrier, 1999),<sup>80</sup> 6 weeks (Resick, 2002).<sup>72</sup>

One trial comparing imaginal exposure with CT used the Beck Anxiety Inventory as a measure of anxiety symptoms.<sup>76</sup> It found no significant difference between groups posttreatment or at 12-month followup.

No trial reported on reduction or prevention of a comorbid medical condition as one of their outcomes of interest.

### **Return to Work or Active Duty**

One trial of CT and imaginal exposure (N=72) reported the impact of interventions on one of these outcomes.<sup>76</sup> The percentage of patients working was significantly better at 6-month followup (40%) than before treatment (15%); differences between treatment groups were not statistically significant (CT, 37%; imaginal exposure, 44%).

### **Results for Exposure Therapy Compared With Active Comparators: Exposure Therapy Versus Coping Skills Therapies**

Three trials compared exposure therapy with a coping skills therapy.<sup>45,46,49</sup> One compared prolonged exposure with stress inoculation training and two compared prolonged exposure with relaxation.

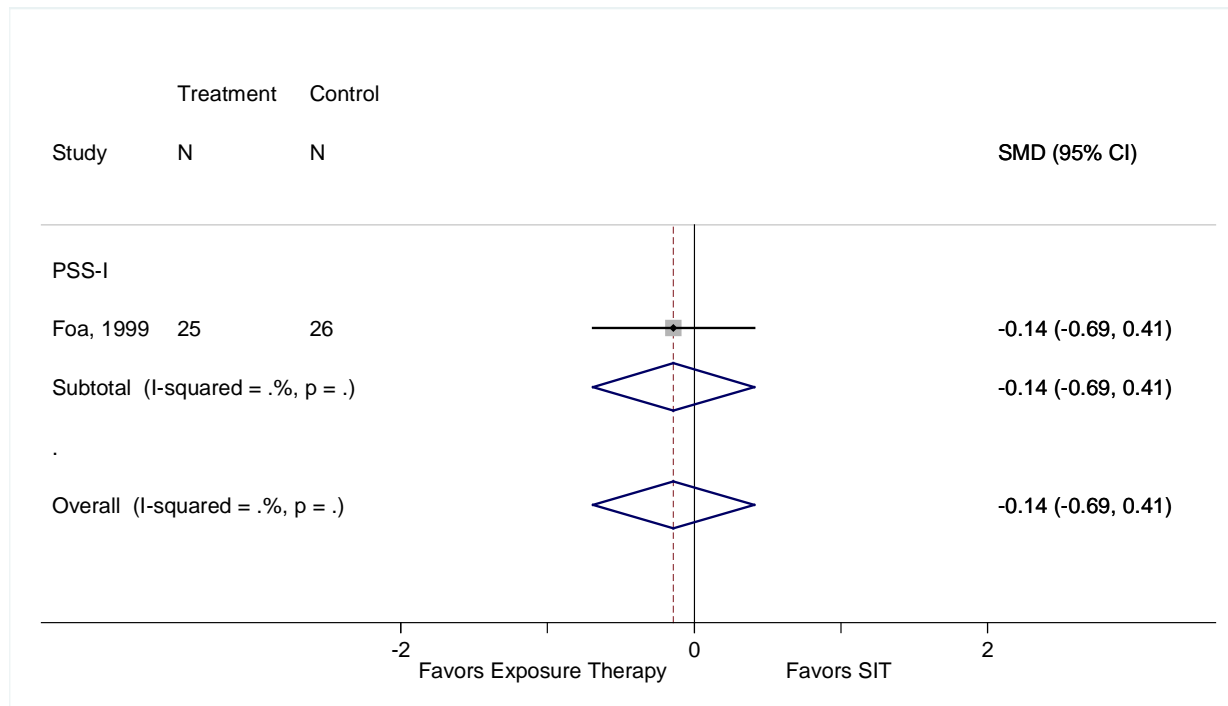
### **PTSD Symptom Reduction**

Figure 11 shows results from the trial comparing prolonged exposure with stress inoculation training. Results did not show a statistically significant difference between treatments.



Sensitivity analysis including trials rated as high risk of bias found no difference between treatments (SMD 0.04, 95% CI, -0.46 to 0.54, 2 trials, N=75, Appendix F).

**Figure 11. Mean change from baseline in PTSD symptoms for exposure therapy compared with stress inoculation training**



Note: Timing of outcome assessment: 9 weeks

Our meta-analysis of the two studies comparing exposure therapy with relaxation found a summary effect favoring exposure, but the difference was not statistically significant (WMD - 9.7, 95% CI, -22.3, 2.9, 2 trials, N=85, Appendix F).

We concluded that the data are insufficient to determine the comparative effectiveness of exposure relative to stress inoculation training or relaxation for reducing PTSD symptoms, mainly because of imprecision. The analyses were underpowered to detect a small or medium difference in effect size.

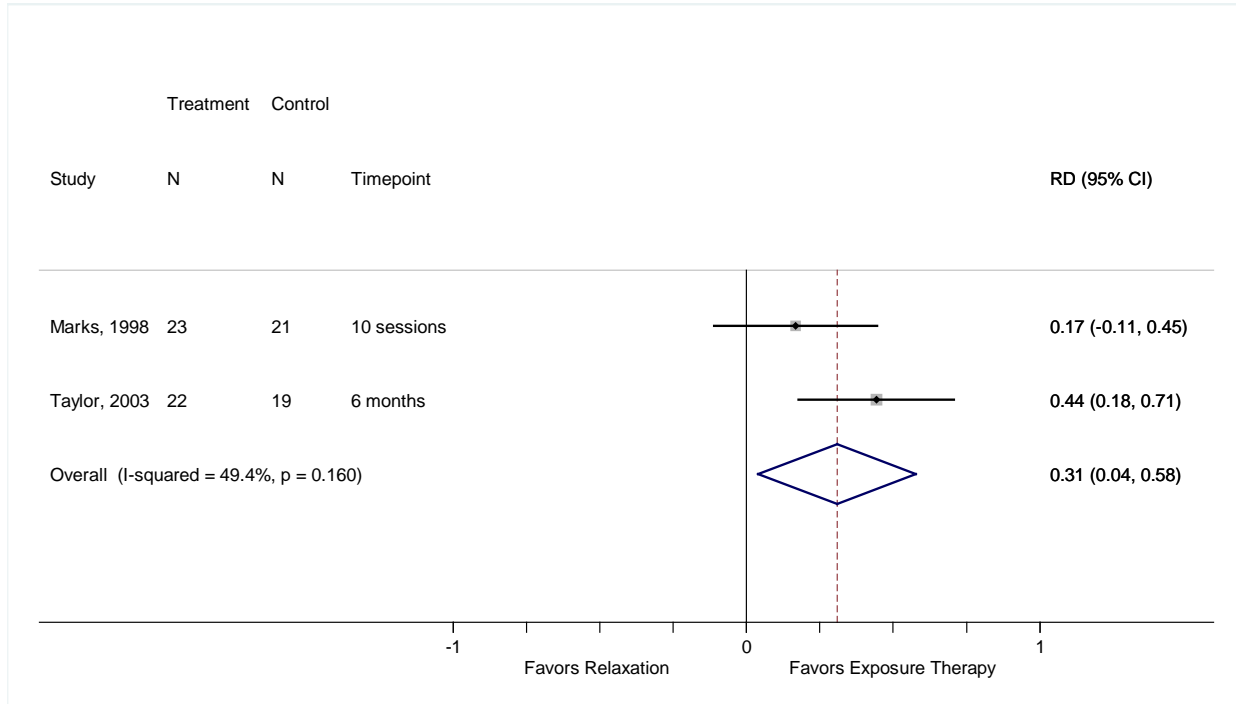
### Loss of PTSD Diagnosis

All three trials reported data on achieving loss of PTSD diagnosis.<sup>45,46,49</sup> In each study, a greater proportion of subjects treated with exposure lost their PTSD diagnosis at posttreatment (87%, 60%, and 75%, respectively) than subjects receiving coping skills interventions (40%, 42%, and 55%, respectively).

The trial comparing prolonged exposure with stress inoculation training found no statistically significant difference between the two therapies (RD, 0.18 favoring exposure therapy; 95% CI, -0.09 to 0.45, N=51, Appendix F). Sensitivity analysis including trials rated as high risk of bias (which added 1 trial to the analysis) found that 26 percent more patients treated with exposure lost their PTSD diagnosis than patients treated with stress inoculation training (RD, 0.26; 95% CI, -0.04 to 0.48, 2 trials, N=75, Appendix F).

Our meta-analysis of the trials comparing exposure with relaxation (Figure 12) found that 31 percent more patients treated with exposure lost their PTSD diagnosis than patients treated with relaxation.

**Figure 12. Loss of PTSD diagnosis for exposure therapy compared with relaxation**



We concluded that the data are insufficient to determine the comparative effectiveness of exposure relative to stress inoculation training for achieving loss of PTSD diagnosis, because of unknown consistency and imprecision. The analyses were underpowered to detect a small or medium difference in effect size.

Taken together, consistent, direct, precise findings indicate that exposure therapy is more effective for achieving loss of PTSD diagnosis than relaxation (moderate SOE).

### Prevention or Reduction of Comorbid Conditions

All three studies reported BDI-related measures of depression symptoms.<sup>45,46,49</sup> The trial comparing exposure with stress inoculation training found no difference between treatments (WMD, -0.15; 95% CI, -5.8 to 5.5, Appendix F).

Our meta-analysis comparing exposure therapy with relaxation found that subjects treated with exposure therapy had greater reduction in depression symptoms than those treated with relaxation (WMD, -5.5; 95% CI, -10.2 to -0.79; 2 trials, N=85, Appendix F).

Because of inconsistency and imprecision, the evidence was insufficient to determine whether exposure therapy is more effective than stress inoculation training for reducing depression symptoms.

Consistent, direct, precise findings indicate that exposure therapy is more effective for improving depression symptoms than relaxation (moderate SOE).

## Results for Exposure Therapy Compared With Active Comparators: Exposure Therapy Compared With Eye Movement Desensitization and Reprocessing

Two trials (total N=91) compared prolonged exposure with EMDR.<sup>45,87</sup>

### PTSD Symptom Reduction

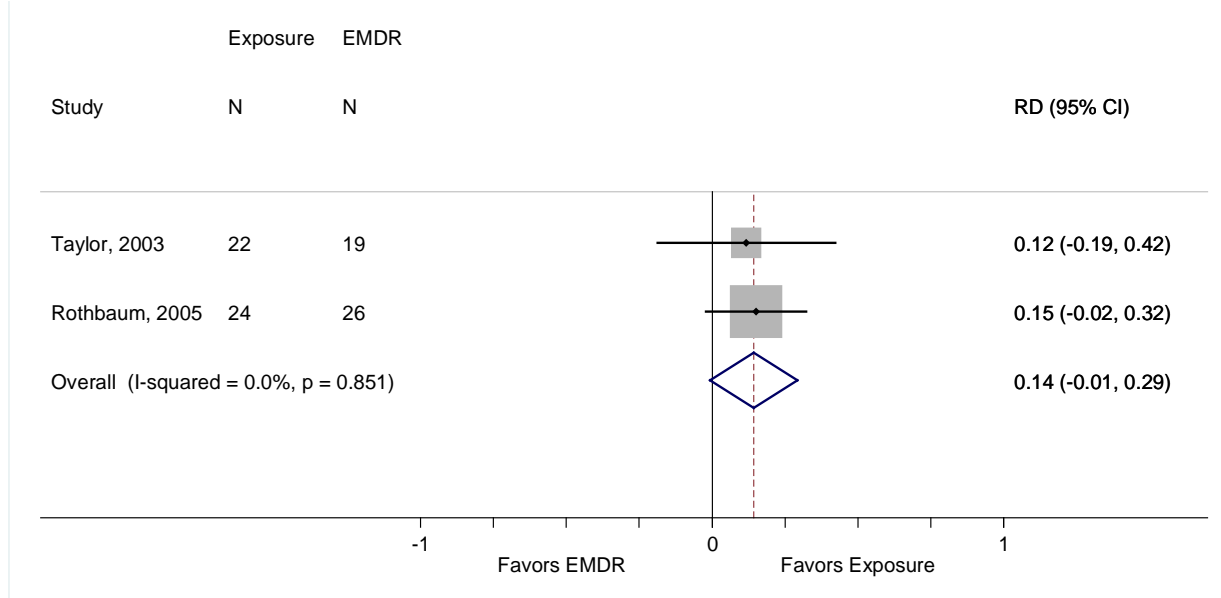
Both trials found that prolonged exposure and EMDR led to significant decreases in CAPS scores from baseline to end of treatment, but found no statistically significant difference between interventions. In one trial, prolonged exposure led to greater reductions in re-experiencing and avoidance symptoms of PTSD among completers.<sup>45</sup> The results of these two trials provide insufficient data on the comparative effectiveness of prolonged exposure over EMDR for reducing PTSD symptoms, mainly because of imprecision.

### Loss of PTSD Diagnosis

In both trials, more participants in the prolonged exposure group than in the EMDR group achieved loss of PTSD diagnosis (~88% vs. ~60%,  $p>0.05$ ;<sup>45</sup> 95% vs. 75%,  $p=0.108$ <sup>87</sup>).

Our meta-analysis of these two trials (Figure 13) did not find a statistically significant difference between treatments.

**Figure 13. Percentage of subjects achieving loss of diagnosis for exposure compared with EMDR**



Note: Timing of outcome assessment: 8 weeks (Taylor, 2003),<sup>45</sup> 4.5 weeks (Rothbaum, 2005).<sup>87</sup>

### Prevention or Reduction of Comorbid Conditions

Both trials used the BDI to assess change in depression symptom scores. In both trials, prolonged exposure and EMDR led to significant decreases in these symptoms, but the intervention groups did not differ on this measure.<sup>45,87</sup>

## Results for Exposure Therapy Compared With Active Comparators: Exposure Therapy Versus Exposure Plus Cognitive Restructuring

Four trials compared exposure therapy with exposure plus CR.<sup>25,46,63,66</sup>

## PTSD Symptom Reduction

Two trials found no difference between subjects treated with exposure and those treated with exposure plus CR on measures of PTSD symptom reduction.<sup>25,46</sup> Another trial found no difference at the end of treatment but an advantage for exposure plus CR at posttreatment followup.<sup>63</sup> Finally, one trial found that exposure plus CR led to significantly greater decreases in PTSD symptoms at the end of treatment.<sup>66</sup>

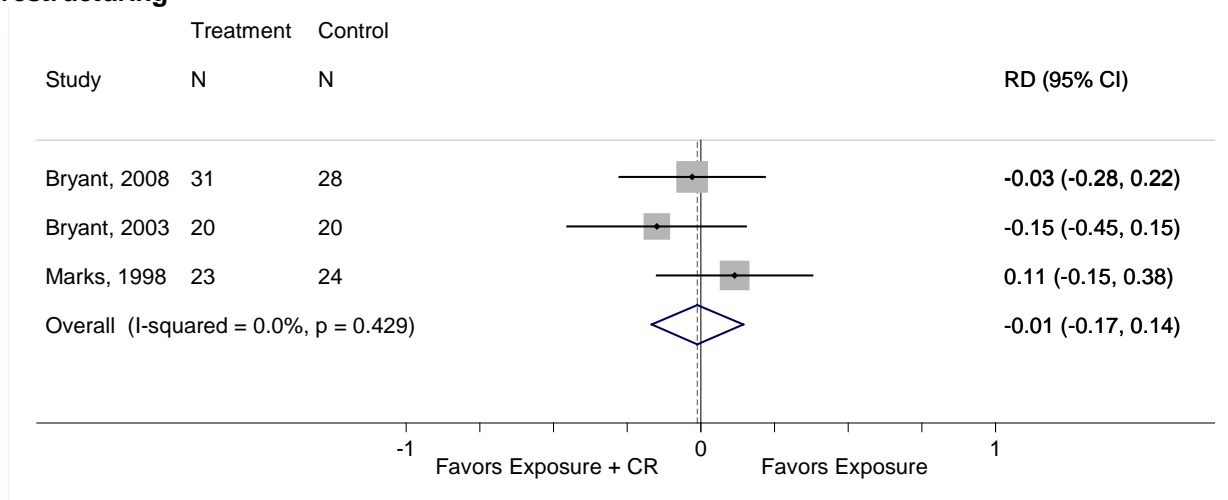
Our meta-analysis of PTSD symptom reduction found no statistically significant difference between therapies (SMD, 0.25; 95% CI, -0.29 to 0.80; 3 trials, N=259, Appendix F). On this basis, we concluded that evidence is insufficient to determine the comparative effectiveness of exposure with exposure plus CR for reducing PTSD symptoms, as the evidence was both inconsistent and imprecise.

## Loss of PTSD Diagnosis

Three of these four trials reported data on achieving loss of PTSD diagnosis.<sup>46,63,66</sup> Only one found greater benefit for exposure plus CR over exposure alone (69% lost diagnosis vs. 37%).<sup>66</sup>

Results of our meta-analysis (Figure 14) indicate that the two interventions did not differ for achieving loss of PTSD diagnosis (RD, -0.01; 95% CI, -0.17 to 0.14; 3 trials, N=146). Taken together, consistent evidence ( $I^2=0\%$ ) from three trials supports a conclusion of no significant difference for achieving loss of PTSD diagnosis for exposure therapy alone compared with exposure plus CR (moderate SOE).

**Figure 14. Loss of PTSD diagnosis for exposure compared with exposure plus cognitive restructuring**



Note: Timing of outcome assessment: 8 weeks (Bryant, 2008<sup>66</sup> and Bryant, 2003<sup>63</sup>), mean 16 weeks (Marks, 1998).<sup>46</sup>

## Prevention or Reduction of Comorbid Conditions

All four trials used the BDI as a measure of change in depression symptoms. Each found no statistically significant difference between interventions from baseline to the end of treatment.

Our meta-analysis found no statistically significant difference between groups for change in BDI score (WMD, 2.78; 95% CI, -1.68 to 7.25; 4 trials, N=299, Appendix F). Overall we concluded that evidence is insufficient to determine comparative effectiveness of exposure and exposure plus CR, largely because of inconsistent results and imprecision.

## **Results for Exposure Therapy Compared With Active Comparators: Prolonged Exposure Versus Imaginal Exposure Versus In Vivo Exposure**

One trial (N=58) compared prolonged exposure, imaginal exposure alone, and in vivo exposure alone.<sup>66</sup> All three types of exposure therapy led to substantial decreases in PTSD symptoms, but the authors found no significant differences between the three groups. In addition, the proportions of subjects who no longer met criteria for PTSD after treatment did not differ significantly (41% vs. 37% vs. 35%); the groups also did not differ with respect to reduction in BDI scores. We concluded that evidence is insufficient to determine the comparative effectiveness of these three types of exposure based on this single trial.

## **Detailed Synthesis: CBT—Mixed Interventions**

### **Characteristics of Trials**

Table 15 summarizes the characteristics of the 23 trials meeting our inclusion criteria. Further details about these trials appear in Appendix D. The trials in this section are somewhat heterogeneous in several ways: how authors define and describe “cognitive behavioral therapy,” duration of the intervention, and mode of delivery. Elements of the CBT arm of the studies considered here include: psychoeducation, self-monitoring, stress management, relaxation training, skills training, exposure (imaginal, or in vivo, or both), cognitive restructuring, guided imagery, mindfulness training, breathing retraining, crisis/safety planning, and relapse prevention. The studies varied as to how many sessions (if any) were dedicated to these elements and whether homework was assigned as part of the intervention.

**Table 15. Characteristics of included CBT-mixed intervention trials**

| Study   | Arm (N)   | Duration (Followup)  | Population Trauma Type                  | Baseline PTSD Severity <sup>a</sup> | Mean Age (Y) | % F | % Non-white | Risk of Bias |
|---|---|--|---|-------------------------------------|--------------|-----|-------------|--------------|
| Blanchard et al., 2003 <sup>50</sup>                                  | CBT-M (27)<br>SC (27)<br>WL (24)                                      | 8 to 12 weeks (3 months)   | Male and female MVA                     | 65.0 to 68.2                        | 41           | 73  | 10.2        | Medium       |
| Cloitre et al., 2002 <sup>51</sup>                                    | CBT-M (31)<br>WL (27)   | 12 months  | Female Childhood abuse                  | 69                                  | 34           | 100 | 54          | Medium       |
| Fecteau et al., 1999 <sup>53</sup>                                    | CBT-M (22)<br>WL (21)   | 4 weeks (6 months)   | Male and female MVA                     | 70.9 to 77.3                        | 41           | 70  | NR          | Medium       |
| Foa et al., 2005 <sup>25</sup>  | Total 190<br>PE (NR)<br>CBT-M <sup>b</sup><br>(PE+CR) (NR)<br>WL (NR) | 12 weeks, 9 to 12 weekly sessions (3, 6, and 12 months)                          | Female Assault                          | PSS-I<br>31.1 to 34.0               | 31           | 100 | 51          | Medium       |
| Foa et al., 1999 <sup>49</sup><br>Zoellner et al., 1999 <sup>81</sup> | PE (25)<br>SIT (26)<br>CBT-M <sup>b</sup><br>(PE+SIT) (30)<br>WL (15) | 9 weeks (3, 6, and 12 months)  | Female Assault                          | PSS-I<br>29.4 to 32.9               | 35           | 100 | 36          | Medium       |
| Hinton et al., 2005 <sup>54</sup>                                     | CBT-M (20)<br>WL (20)   | 12 weeks   | Male and female Cambodian refugees      | 74.9 to 75.9                        | 52           | 60  | 100         | Medium       |
| Hollifield et al., 2007 <sup>55</sup>                                 | Acupuncture (29)<br>CBT-M (28)<br>WL (27)                             | 12 weeks (3 months)  | Male and female Mixed                   | PSS-SR<br>30.8 to 32.5              | 42           | 48  | 24          | Medium       |
| Kubany et al., 2003 <sup>56</sup>                                     | CBT-M (19)<br>WL (18)   | 8 to 11 sessions <sup>c</sup> (3 months)   | Female Interpersonal violence           | 80.1 to 80.2                        | 35           | 100 | 51          | Medium       |
| Kubany et al., 2004 <sup>69</sup>                                     | CBT-M (63)<br>WL (62)   | 4 to 5.5 weeks (3 and 6 months)  | Female Interpersonal violence           | 74.1 to 74.4                        | 42           | 100 | 47          | Medium       |
| Liedl et al., 2011 <sup>57</sup>                                      | CBT-M (12)<br>CBT-M (12)<br>WL (12)                                   | 10 sessions <sup>c</sup> (mean of 4.8 months) (3 months)                         | Male and female Refugees w/chronic pain | PDS<br>25.6 to 31.2                 | 42           | 43  | NR          | Medium       |
| McDonagh et al., 2005 <sup>58</sup>                                   | CBT-M (29)<br>PCT (22)<br>WL (23)                                     | 14 weeks (3 and 6 months)  | Female Childhood sexual abuse           | 67.7 to 72.0                        | 41           | 100 | 7           | Medium       |
| Spence et al., 2011 <sup>59</sup>                                     | CBT-M (23)<br>WL (21)   | 8 weeks (3 months)   | Male and female Mixed                   | PCL-C<br>57.0 to 60.8               | 43           | 81  | NR          | Medium       |
| van Emmerik et al., 2008 <sup>60</sup>                                | CBT-M (41)<br>Writing (44)<br>WL (40)                                 | 5 sessions <sup>c</sup> (mean of 119.5 days), 91 to 973 days                     | Male and female Mixed                   | IES<br>46.4 to 49.1                 | 40           | 67  | NR          | Medium       |
| Johnson et al., 2011 <sup>61</sup>                                    | CBT-M (35)<br>UC (35)   | 8 months (1 week, 3 and 6 months)  | Female Interpersonal violence           | 53.3 to 62.7                        | 33           | 100 | 57          | Medium       |
| Kruse et al., 2009 <sup>62</sup>                                      | CBT-M (35)<br>UC (35)   | Weekly for 3 months; then once every 2 weeks for a total of 25 hours (12 months) | Male and female Refugees                | NR                                  | 45           | 67  | NR          | Medium       |

**Table 15. Characteristics of included CBT-mixed intervention trials (continued)**

| Study   | Arm (N)  | Duration (Followup)   | Population Trauma Type                   | Baseline PTSD Severity <sup>a</sup>              | Mean Age (Y) | % F | % Non-white | Risk of Bias |
|---|--|---|--|--|--------------|-----|-------------|--------------|
| Bryant et al., 2003 <sup>63</sup>                                     | IE (20)<br>CBT-M <sup>b</sup> (IE+CR) (20)<br>SC (18)                  | 8 weeks (6 months)  | Male and female<br>Mixed                 | CAPS-I<br>32.5 to 32.9<br>CAPS-F<br>36.0 to 38.3 | 35           | 52  | NR          | Medium       |
| Cottraux et al., 2008 <sup>64</sup>                                   | CBT-M (31)<br>SC (29)  | 16 weeks (1 and 24 months)  | Male and female<br>Mixed                 | PCLS<br>60.8                                     | 39           | 70  | NR          | Medium       |
| Litz et al., 2007 <sup>65</sup>                                       | CBT-M (24)<br>SC (21)  | 8 weeks (3 and 6 months)  | Male and female<br>Combat                | PSS-I<br>26.7 to 29.2                            | 39           | 22  | 30          | Medium       |
| Bryant et al., 2008 <sup>66</sup>                                     | PE (31)<br>CBT-M <sup>b</sup> (Exp+CR) (28)<br>IE (31)<br>In vivo (28) | 8 weeks (6 months)  | Male and female<br>Mixed                 | 71.4 to 76.8                                     | 37           | NR  | 8           | Medium       |
| Cloitre et al., 2010 <sup>67</sup>                                    | CBT-M (33)<br>CBT-M (38)<br>CBT-M (33)                                 | 16 weeks (3 and 6 months)   | Female<br>Mixed childhood abuse          | 63.1 to 64.5                                     | 36           | 100 | 64          | Medium       |
| Hinton et al., 2009 <sup>68</sup>                                     | CBT-M (12)<br>CBT-M (12)   | 12 weeks  | Cambodian refugees<br>Witnessed genocide | 75.4 to 77.3                                     | 50           | 60  | 100         | Medium       |
| Hinton et al., 2011 <sup>47</sup>                                     | CBT-M (12)<br>Relax (12)   | 14 weeks (12 weeks)   | Female<br>Trauma NR                      | PCL<br>69.8 to 71.1                              | 50           | 100 | 100         | Medium       |
| Marks et al., 1998 <sup>46</sup><br>Lovell et al., 2001 <sup>79</sup> | PE (23)<br>CR (13)<br>CBT-M <sup>b</sup> (CR+PE) (24)<br>Relax (21)    | 10 sessions <sup>c</sup> (mean of 16 weeks), (1, 3, and 6 months) | Male and female<br>Mixed                 | CAPS Severity<br>2.6 to 3.2                      | 38           | 36  | NR          | Medium       |

CBT-M = cognitive behavioral therapy-mixed; CR = cognitive restructuring; F = female; IE = imaginal exposure; IES = Impact of Event Scale; in vivo = in vivo exposure; MVA = motor vehicle accident; NR = not reported; PCL-C = Posttraumatic Stress Disorder Checklist-Civilian Version; PCLS = Post-Traumatic Stress Disorder Checklist Scale; PDS = Posttraumatic Stress Diagnostic Scale; PE = prolonged exposure; PSS-I = PTSD Symptom Scale—Interview; PSS-SR = Posttraumatic Symptom Scale-Self Report; relax = relaxation; SC = supportive control; SIT = stress inoculation training; UC = usual care; WL = waitlist; writing = structured writing therapy; y = year

<sup>a</sup>Data reported are mean CAPS or range of mean CAPS scores across groups unless another instrument is specified.

<sup>b</sup>The information provided after CBT-M indicates the content of the mixed intervention (see abbreviations below).

<sup>c</sup>Number of treatment sessions is reported when duration of treatment was not specified.

Eighteen of these 23 trials included an inactive comparator, such as a waitlist (13 trials), usual care (2 trials), or supportive control (3 trials).<sup>25,49-51,53-65,69</sup> Ten of the 24 trials made comparisons with active interventions (i.e., other psychotherapies).<sup>25,46,47,49,58,60,63,66-68</sup> Of these 10 trials, 5 included an exposure-based intervention as the comparison;<sup>25,46,49,63,66</sup> 1 used “structured writing therapy”;<sup>60</sup> 1 used a present-centered therapy;<sup>58</sup> 2 used relaxation;<sup>46,47</sup> and 2 used another CBT-mixed intervention.<sup>67,68</sup>

Of the 18 trials with *inactive* comparators, 11 were conducted in the United States; 1 was conducted in Switzerland,<sup>57</sup> 1 in Canada,<sup>53</sup> 1 in the Netherlands,<sup>60</sup> 2 in Australia,<sup>59,63</sup> 1 in Germany,<sup>62</sup> and 1 in France.<sup>64</sup> Sample sizes ranged from 23 to 190. Duration of treatment ranged from 4 to 16 weeks. All trials also included posttreatment follow-up assessments after 1, 3, 6, 9, or 12 months, although the follow-up interval for 1 was unclear.<sup>60</sup> The majority of trials enrolled a heterogeneous group of subjects with a variety of index trauma types (e.g., childhood abuse

[physical, sexual, or mental], physical assault, road accidents, nonroad accident, sexual assault, being held hostage, bombing, combat, witnessing genocide, nonsexual assault, and motor vehicle accidents). Mean age ranged from 30 to 50 years. Most trials enrolled a large majority of female subjects. The primary outcome measure for 9 of these trials was some version of the CAPS (CAPS, CAPS-2, or CAPS-Sx);<sup>50,51,53, 2001,54,56,58,61,63,69</sup> 4 trials used a form of the PSS (PSS-I or PSS-SR);<sup>25,49,55,65</sup> 1 trial used the PDS;<sup>57</sup> 2 trials used the PCL;<sup>59,64</sup> 1 trial used the Harvard Trauma Questionnaire (HTQ);<sup>62</sup> and 1 the IES.<sup>60</sup>

Of the 10 trials with *active* comparators, 6 were conducted in the United States; 1 was conducted in the United Kingdom;<sup>46</sup> 1 in the Netherlands;<sup>60</sup> and 2 in Australia.<sup>63,66</sup> Sample sizes ranged from 24 to 190. Duration of treatment ranged from 8 to 16 weeks. All trials also included posttreatment follow-up assessments. The majority of trials enrolled a heterogeneous group of subjects with a variety of index trauma types. Mean age ranged from 33.2 to 51.4. Most trials enrolled a large majority of female subjects. The primary outcome for 6 trials was some version of the CAPS (CAPS, CAPS-2, or CAPS-Sx); 2 used the PSS-I,<sup>25,49</sup> 1 the PCL,<sup>47</sup> and 1 the IES.<sup>60</sup>

Ten trials otherwise meeting criteria for this section were rated high risk of bias (Table 16). We excluded them from our main data synthesis but used them in sensitivity analyses.

**Table 16. Characteristics of CBT-mixed intervention trials excluded from main analyses because of high risk of bias**

| Study                                | Arm (N)   | Duration (Followup)                                  | Population Trauma Type                        | Baseline PTSD Severity <sup>a</sup> | Mean Age (Y) | % F  | % Non-white | Risk of Bias |
|--------------------------------------|---|--|---|-------------------------------------|--------------|------|-------------|--------------|
| Beck et al., 2009 <sup>105</sup>     | CBT-M (17)<br>MCC (16)                                      | 14 weeks<br>(3 months)                               | Male and female<br>MVA                        | 57.3 to 57.8                        | 43           | 82   | 11          | High         |
| Power et al., 2002 <sup>106</sup>    | EMDR (39)<br>CBT-M <sup>p</sup><br>(Exp+CR) (37)<br>WL (29) | 10 weeks   | Male and female<br>Mixed                      | IES<br>32.6 to 35.1                 | 39           | 42   | NR          | High         |
| Difede et al., 2007 <sup>107</sup>   | CBT-M (15)<br>TAU (16)                                      | 12 weeks (12<br>to 13 weeks)                         | Disaster workers<br>World Trade Center attack | 50.5 to 51.7                        | 46           | 3    | 23          | High         |
| Ulmer et al., 2011 <sup>108</sup>    | CBT-M (12)<br>UC (9)  | 6 biweekly sessions, over<br>12 weeks                | Male and female<br>Recently deployed veterans | PCL-M<br>63.1 to 63.4               | 46           | 31.8 | 66.6        | High         |
| Beidel et al., 2011 <sup>102</sup>   | CBT-M (18)<br>Exp (17)                                      | 17 weeks   | Male<br>Combat                                | 84.9 to<br>90.6                     | 59           | 0    | 0           | High         |
| Devilley et al., 1999 <sup>109</sup> | CBT-M (15)<br>EMDR (17)                                     | 9 sessions <sup>c</sup> (2<br>weeks and 3<br>months) | Male and female<br>Mixed                      | IES<br>48.4 to 54.1                 | 39           | 65   | NR          | High         |
| Echeburua et al., 1996 <sup>83</sup> | CBT-M (10)<br>CBT Cope (10)                                 | 5 weeks (1, 3,<br>6, and 12<br>months)               | Female<br>Sexual assault                      | NR                                  | 22           | 100  | NR          | High         |



**Table 16. Characteristics of CBT-mixed intervention trials excluded from main analyses because of high risk of bias (continued)**

| Study                                | Arm (N)                                       | Duration (Followup)              | Population Trauma Type             | Baseline PTSD Severity <sup>a</sup> | Mean Age (Y) | % F | % Non-white | Risk of Bias |
|--------------------------------------|---|----------------------------------|------------------------------------|-------------------------------------|--------------|-----|-------------|--------------|
| Echeburu et al., 1997 <sup>84</sup>  | CBT-M (10)<br>Relax (10)                      | 6 weeks (1, 3, 6, and 12 months) | Female<br>Sexual abuse/<br>assault | NR                                  | 20           | 100 | NR          | High         |
| Lee et al., 2002 <sup>110</sup>      | EMDR (12)<br>CBT-M <sup>b</sup> (SIT+PE) (12) | 7 weeks (3 months)               | Male and female<br>Mixed           | IES 55.3                            | 35           | 46  | NR          | High         |
| Paunovic et al., 2001 <sup>104</sup> | Exp (10)<br>CBT-M (10)                        | 16 to 20 weeks (6 months)        | Male and female<br>Refugees        | 95.1 to 98.4                        | 38           | 15  | NR          | High         |

CBT Cope = cognitive behavioral therapy-coping skills; CBT-M = cognitive behavioral therapy-mixed; CR = cognitive restructuring; EMDR = eye movement desensitization and reprocessing; exp = exposure therapy; IES = Impact of Event Scale; MCC = minimum contact comparison group; NR = not reported; PCL-M = PTSD Checklist-Military Version; PE = prolonged exposure; relax = relaxation; SIT = stress inoculation training; TAU = treatment as usual; UC = usual care; WL = waitlist; y = year

<sup>a</sup>Data reported are mean CAPS or range of mean CAPS scores across groups unless another instrument is specified.

<sup>b</sup>The information provided after CBT-M indicates the content of the mixed intervention (see abbreviations below).

<sup>c</sup>Number of treatment sessions is reported when duration of treatment was not specified.

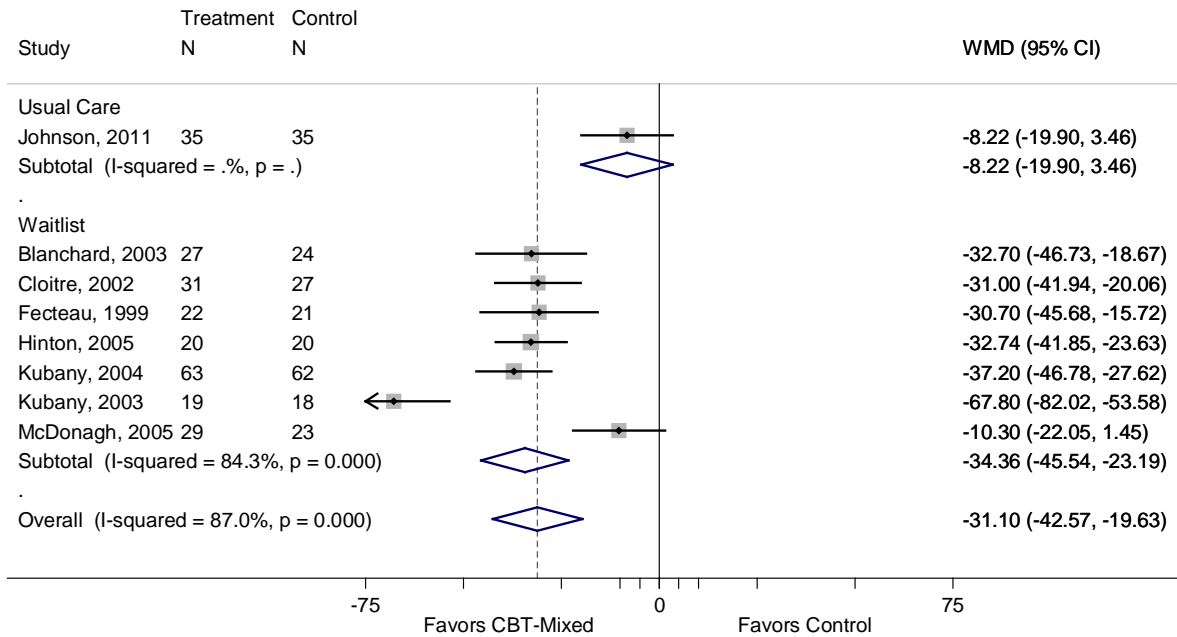
## Results for CBT-Mixed Interventions Compared With Inactive Comparators

### PTSD Symptom Reduction

Of 18 trials with inactive comparators, 8 reported the CAPS and gave sufficient data to include in meta-analyses. Among these 8 trials, 6 reported reductions in CAPS scores that were statistically significant.

Our meta-analysis (Figure 15) found greater reduction in PTSD symptoms for CBT-mixed interventions than for inactive controls (WMD, -31.1). Statistical heterogeneity was substantial ( $I^2=87%$ ). Much of the heterogeneity may be explained by the diversity of both interventions (as explained above, these interventions used various CBT components). Five trials found a similarly large improvement in CAPS for CBT-mixed intervention groups compared with waitlist controls—about a 30-point greater reduction.<sup>50,51,53,54,69</sup> One trial with a waitlist control found even greater benefits (about a 68 point reduction).<sup>56</sup> Two of the 8 trials found little to no benefit.<sup>58,61,75</sup> One of these compared CBT-mixed interventions with usual care (in which the control patients were often receiving some form of treatment) rather than with waitlist; this likely biased results toward the null.<sup>61,75</sup>

**Figure 15. Mean change from baseline in CAPS for CBT-mixed interventions compared with control, by comparator**



Note: Timing of outcome assessment: 7 weeks (Johnson, 2011),<sup>61</sup> 8 to 12 weeks (Blanchard, 2003),<sup>50</sup> 12 weeks (Cloitre, 2002),<sup>51</sup> 4 weeks (Fecteau, 1999),<sup>53</sup> 12 weeks (Hinton, 2005),<sup>54</sup> 4 to 5.5 weeks (Kubany, 2004),<sup>69</sup> 4.5 months (Kubany, 2003),<sup>56</sup> 14 weeks (McDonagh, 2005).<sup>58</sup>

Sensitivity analyses including high risk of bias studies or adding studies with supportive counseling control groups and sensitivity analyses removing each individual study one at a time did not result in any significant differences in findings (Appendix F).

For posttreatment followup at 3 to 6 months, just 2 of the 8 trials reported sufficient CAPS data to permit meta-analysis (Appendix F).<sup>50,61</sup> Of these, 1 found significant differences between a CBT-mixed intervention and waitlist (WMD, -22; 95% CI, -36.4 to -7.6).<sup>50</sup> One found no significant difference between a CBT-mixed intervention and usual care (WMD, 1.41; 95% CI, -9.8 to 12.6).<sup>61</sup> Thus, drawing any strong conclusions about whether reduction of symptoms is maintained at long-term followup is difficult. A third trial reported 3- and 6-month follow-up data, reporting no significant differences between groups, but the control group had all received the intervention by that time.<sup>69</sup>

We conducted additional meta-analyses to calculate an effect size (Cohen's d) for change in PTSD symptoms using additional outcome measures reported across all trials with waitlist (CAPS, PSS-I, IES, PCL, PDS). Our meta-analysis found greater reduction in PTSD symptoms for CBT-mixed interventions compared with waitlist (13 trials) and usual care (1 trial) controls, with a very large effect size (SMD, -1.09; 95% CI, -1.4 to -0.78; 14 trials, N=825, Appendix F). Similar to the meta-analysis in Figure 15, statistical heterogeneity was substantial ( $I^2=75.3%$ ). However, also like that analysis, the differences in findings were in the magnitude (not the direction) of the effect; all point estimates favored CBT-mixed interventions, and the vast majority of individual trials reached statistical significance. When the 2 trials with sufficient data with supportive counseling comparators were also included, the effect size decreased slightly

(SMD -0.98; 95% CI, -1.28 to -0.68, Appendix F). Sensitivity analyses including high risk of bias studies were similar (Appendix F).

For posttreatment followup at 3 to 6 months, just 4 of the trials reported sufficient data about PTSD symptom measures to permit meta-analysis. Thus, determining with confidence how much of the reduction in symptoms is maintained at long-term followup is difficult, partly because of potential for reporting bias (with the other trials not reporting sufficient data). Of the 4, 3 found statistically significant differences between CBT-mixed interventions and waitlist<sup>50,55</sup> or supportive counseling,<sup>65</sup> and 1 found no difference between a CBT-mixed intervention and usual care; meta-analysis of the 4 trials found that improvements were maintained, but with a smaller effect size, although still in the medium to large range (SMD, -1.02; 95% CI, -1.43 to -0.61 for the 2 trials with waitlist control; -0.65; 95% CI, -1.21 to -0.09 when including all 4 trials; Appendix F).

Overall, we concluded that evidence of moderate strength supports the efficacy of CBT-mixed interventions for reducing PTSD symptoms. Although magnitude of the effect was somewhat inconsistent, trials were consistent in the direction of effect; our meta-analyses provided fairly precise estimates with moderate to large effect sizes.

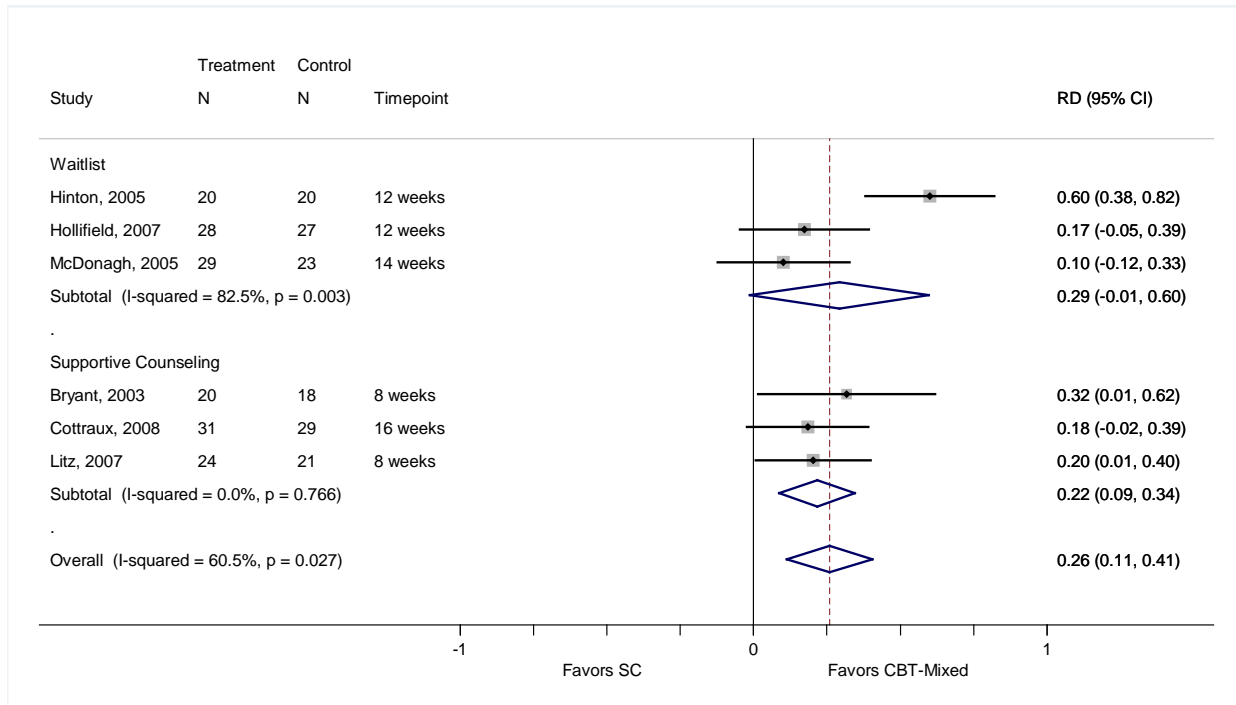
### **Remission (No Longer Having Symptoms)**

Two trials comparing CBT-mixed interventions with an inactive comparator reported data on remission of PTSD.<sup>59,62</sup> Both trials reported that greater percentages of subjects in CBT-mixed groups than controls achieved remission (61% vs. 21%,  $p=NR$  using the PCL;<sup>59</sup> 82.4% vs. 0%,  $p<0.001$  using the HTQ<sup>62</sup>). Evidence of moderate strength supports the efficacy of CBT-mixed interventions for achieving remission.

### **Loss of PTSD Diagnosis**

Six trials reported sufficient data on achieving loss of PTSD diagnosis to permit meta-analysis.<sup>54,55,58,63-65</sup> Our meta-analysis (Figure 16) found that 26 percent more CBT-mixed intervention subjects than waitlist or supportive counseling control subjects achieved loss of PTSD diagnosis (29% when just pooling the three trials with waitlist controls). This translates to a NNT of 4 (and was also 4 when only considering the waitlist controls). We concluded that evidence of moderate strength supports the efficacy of CBT-mixed interventions for achieving loss of PTSD diagnosis.

**Figure 16. Loss of PTSD diagnosis for CBT-mixed interventions compared with control, by type of comparator**



Two of the trials also reported 3- to 6-month followup data. These findings suggested that the improvements from the CBT-mixed interventions were sustained over time. Our meta-analysis of these trials found a similar result (RD, 0.24; 95% CI, 0.04 to 0.43; Appendix F).

Overall, we concluded that evidence of moderate strength supports the efficacy of CBT-mixed interventions for achieving loss of PTSD diagnosis. Although the magnitude of the effect was somewhat inconsistent across trials, the direction of effect was consistent; results of our meta-analyses provided a fairly precise estimate of the effect.

### **Prevention or Reduction of Comorbid Medical or Psychiatric Conditions**

Twelve of the 18 trials that compared CBT-mixed interventions with an inactive control reported data on depression symptoms using the BDI. All but one of these reported point estimates favoring subjects treated with CBT-mixed interventions; the vast majority reported these findings to be statistically significant. Meta-analysis of these trials found greater improvement in depression symptoms for subjects treated with CBT-mixed interventions than for those in control groups (BDI, mean change from baseline; WMD, -10.4; 95% CI, -14.4 to -6.4; 10 trials, N=662; Appendix F). Sensitivity analysis including two trials with supportive counseling controls found similar results (WMD -9.23; 95% CI, -13.0 to -5.5, Appendix F).

Four of the trials reported sufficient 3- to 6-month postintervention follow-up data for meta-analysis. Meta-analysis of the four trials found that improvements were maintained, but with a slightly smaller effect size (WMD, -5.1; 95% CI, -8.1 to -2.1; Appendix F).

Overall, evidence of moderate strength supports the efficacy of CBT-mixed interventions for improvement in depression symptoms for adults with PTSD. Although the magnitude of the effects across trials was somewhat inconsistent, trials were consistent in the direction of effect, and results of our meta-analyses provided a fairly precise estimate of the effect.

A number of trials also reported reduction in anxiety symptoms; a variety of different measures were used (see Appendix D for details). The most commonly reported measure was the STAI, reported with sufficient data for meta-analysis by 4 of the trials that compared CBT-mixed interventions with an inactive condition. Meta-analysis of these 4 trials found greater improvement in anxiety symptoms for subjects treated with CBT-mixed interventions than for those in control groups (STAI, mean change from baseline; WMD, -11.2; 95% CI, -20 to -2.4; 4 trials, N=172; Appendix F). Based on data from medium risk-of-bias trials, some inconsistency in findings, and imprecision, we determined that the SOE supporting the efficacy of CBT-mixed interventions for improvement in anxiety symptoms for adults with PTSD is low.

### **Quality of Life**

Three trials reported data on quality of life.<sup>58,62,64</sup> All three used different measures of quality of life. Two trials found no differences between groups; one reported some differences between groups. Taken together, this evidence is insufficient to determine the efficacy of CBT-mixed interventions for improving quality of life.

One trial (N=60) found no significant difference in change from baseline on the Marks' Quality of Life Scale (-6.7 vs. -9.6, p=0.26);<sup>64</sup> another found no difference in change from baseline on the Quality of Life Inventory (QOLI: 3.4 vs. 0.4, p=0.63).<sup>58</sup> One trial (N=70) enrolling Bosnian refugees reported positive effect sizes for both the mental and the physical component summary scales of the SF-36 for CBT subjects compared with usual care subjects (Cohen's d = 2.1 vs. -0.1, p<0.001, and 1.4 vs. 0.2, p<0.001, respectively).<sup>62,75</sup>

### **Disability or Functional Impairment**

Five trials reported data on disability or functional impairment<sup>50,51,55,59,64</sup> using a variety of measures (Table 17).

**Table 17. Results at end of treatment for disability or functional impairment outcomes for CBT-mixed interventions compared with inactive controls**

| Study                                 | Arm (N)                                       | Outcome measure(s)                      | Baseline Value          | End of Treatment Value  | Change From Baseline | P Value | Effect Size (Cohen's d) |
|---------------------------------------|---|---|-------------------------|-------------------------|----------------------|---------|-------------------------|
| Blanchard et al., 2003 <sup>50</sup>  | CBT-M (27)<br>WL (24)                         | GAF                                     | CBT-M: 53.9<br>WL: 56.0 | 75.8<br>60.4            | NR                   | <0.05   | NR                      |
| Cloitre, 2002 <sup>51</sup>           | CBT-M (31)<br>WL (27)                         | IIP                                     | CBT-M: 1.88<br>WL: 1.70 | CBT-M: 1.06<br>WL: 1.60 | NR                   | 0.01    | NR                      |
|                                       |   | SAS-SR                                  | CBT-M: 2.44<br>WL: 2.57 | CBT-M: 2.06<br>WL: 2.47 |                      | 0.02    |                         |
|                                       |   | ISEL                                    | CBT-M: 24<br>WL: 23     | CBT-M: 30<br>WL: 23     |                      | 0.01    |                         |
| Hollifield et al., 2007 <sup>55</sup> | Acupuncture (29)<br>CBT mixed (28)<br>WL (27) | SDI                                     | CBT-M: 4.09<br>WL: 4.0  | 3.3<br>3.96             | NR                   | <0.05   | 0.76<br>0.04            |
| Spence et al., 2011 <sup>59</sup>     | CBT-M (23)<br>WL (21)                         | SDS                                     | 18.17<br>19.42          | 13.22<br>18.11          | NR                   | 0.07    | 0.62                    |
| Cottraux et al., 2008 <sup>64</sup>   | CBT-M (31)<br>SC (29)                         | Global Phobic Disability Subscale of FQ | NR                      | 4.4<br>4.0              | -2.14<br>-2.0        | 0.86    | NR                      |

CBT-M = cognitive behavioral therapy mixed; FQ = Fear Questionnaire (a self-rating inventory for evaluation of agoraphobia, social phobia, blood-injury phobia, anxiety-depression, and global phobic disability); GAF = global assessment of functioning; IIP = Inventory of Interpersonal Problems; ISEL Interpersonal Support Evaluation List; NR = not reported; SAS-SR = Social Adjustment Scale-Self Report; SC = supportive control; SDI = Sheehan Disability Inventory; SDS = Sheehan Disability Scale; UC = usual care; WL = waitlist

Note: results are only presented for the relevant arms for this section (CBT-M and inactive comparators); values entered are means unless otherwise specified; P values are for the comparison between CBT-M and inactive comparators.

Four of the five trials compared CBT-mixed interventions with waitlist controls; one compared a CBT-mixed intervention with standard care. All four trials with waitlist controls found greater improvements in disability or functional outcomes for subjects who received CBT-mixed interventions—all but one reached statistical significance,<sup>59</sup>  $p=0.07$ ). The trial that compared CBT-mixed with standard care found similar changes in both groups.<sup>64</sup> Taken together, results suggest CBT-mixed interventions are efficacious for reducing disability and functional impairment; SOE was low because of some inconsistency and imprecision (low SOE).

## Results for CBT-Mixed Interventions Compared With Active Comparators

Of the 10 trials comparing a CBT-mixed intervention with an active comparator, 5 compared it with an exposure-based intervention.<sup>25,46,49,63,66</sup> Assessment of head-to-head comparisons with exposure-based interventions is covered in the CBT Exposure section (above). Several of the other trials made comparisons with interventions for which we did not aim to assess comparative effectiveness<sup>57,58,60,67</sup> (e.g., comparisons with other CBT-mixed interventions<sup>57,67</sup> or “structured writing therapy”).<sup>60</sup> In this section, we address the 2 trials comparing CBT-mixed interventions and relaxation interventions.<sup>46,47</sup>

### PTSD Symptom Reduction

Both trials reported that CBT-mixed interventions were more effective than relaxation in reducing symptoms of PTSD. One reported improvement from baseline in CAPS scores of 38

(95% CI, 26 to 50) for the CBT group and 14 (95% CI, 4 to 25) for relaxation.<sup>46</sup> The other trial used the PCL as the outcome measure and found a large effect size favoring subjects treated with CBT (between-group effect size:  $d = 1.6$ ). These between-group treatment differences were maintained at followup ( $p < 0.05$ ). From these two trials, we concluded that CBT-mixed interventions are more effective than relaxation for improving PTSD symptoms (moderate SOE).

### **Disability or Functional Impairment**

One trial reported data on disability or functional impairment using the GHQ Global Improvement measure.<sup>46</sup> A greater percentage of subjects in the CBT arm than in the relaxation arm improved functioning, but the difference was not statistically significant (70% to 80% vs. 50% to 55%, respectively,  $p = \text{NS}$ ). Evidence from this single trial was insufficient to determine whether CBT-mixed interventions are more effective than relaxation for improving disability or functional impairment because of unknown consistency (single study) and imprecision.

## **Detailed Synthesis: Eye Movement Desensitization and Reprocessing (EMDR)**

### **Characteristics of Trials**

Table 18 summarizes the characteristics of the seven trials meeting our inclusion criteria. Further details describing the included trials are provided in Appendix D. Five trials had an inactive comparator, such as waitlist,<sup>87,111,112</sup> usual care<sup>44</sup> or placebo.<sup>113</sup> Four had active comparisons with either prolonged exposure,<sup>45,87</sup> brief eclectic psychotherapy,<sup>48</sup> or relaxation.<sup>44,45</sup>

Four of the five trials with inactive comparators were conducted in the United States; one was conducted in Sweden.<sup>111</sup> Sample sizes ranged from 21 to 88. Duration of treatment ranged from 4 to 8 weeks. All but one of the studies<sup>111</sup> included posttreatment followups after 3, 6, or 9 months. Two of the trials enrolled a heterogeneous group of subjects with a variety of index trauma types (e.g., sexual assault, physical assault, witnessing traumatic events, accidents, and combat); one trial enrolled a majority of subjects with combat-related PTSD;<sup>44</sup> one enrolled Swedish public transportation workers who witnessed train accidents or were physically assaulted;<sup>111</sup> and two enrolled female victims of sexual assault.<sup>87,112</sup> Mean age was roughly similar across trials, ranging from 34 to 49 years. Three trials enrolled 75 percent or more female subjects.<sup>87,112,113</sup> The primary outcome for the majority of trials was some version of the CAPS (CAPS, CAPS-2, or CAPS-Sx); two trials identified other primary outcomes, including the PSS-I,<sup>112</sup> or IES.<sup>111</sup>

**Table 18. Characteristics of included EMDR trials**

| Study                                    | Arm (N)                                      | Duration (Followup)                       | Population Trauma Type                  | Baseline PTSD Severity <sup>a</sup> | Mean Age (Y) | % F | % Non-white | Risk of Bias |
|--|--|---|---|-------------------------------------|--------------|-----|-------------|--------------|
| Hogberg et al., 2007 <sup>111</sup>      | EMDR (13)<br>WL (11)                         | 2 months                                  | Swedish public transportation employees | IES<br>39                           | 43           | 21  | NR          | Medium       |
| Rothbaum et al., 1997 <sup>112</sup>     | EMDR (11)<br>WL (10)                         | 4 weeks (3 months)                        | Female Sexual assault                   | PSS-I<br>33.3 to<br>39.0            | 35           | 100 | NR          | Medium       |
| Rothbaum et al., 2005 <sup>87</sup>      | PE (24)<br>EMDR (26)<br>WL (24)              | 4.5 weeks (6 months)                      | Female Sexual assault                   | Data reported in graphs only        | 34           | 100 | 32          | Medium       |
| van der Kolk et al., 2007 <sup>113</sup> | EMDR (29)<br>Fluoxetine (30)<br>Placebo (29) | 8 weeks (6 months)                        | Male and female Mixed                   | 71.2                                | 36           | 83  | 33          | Medium       |
| Carlson et al., 1998 <sup>44</sup>       | EMDR (10)<br>Relaxation (13)<br>TAU (12)     | Twice a week for 6 weeks (3 and 9 months) | Male Vietnam combat veterans            | M-PTSD<br>117.9 to<br>119.4         | 49           | 0   | 46          | Medium       |
| Nijdam et al., 2012 <sup>48</sup>        | BEP (70)<br>EMDR (70)                        | 17 weeks                                  | Male and female Mixed                   | IES-R<br>72.8 to<br>79.9            | 38           | 56  | 100         | Medium       |
| Taylor et al., 2003 <sup>45</sup>        | PE (22)<br>EMDR (19)<br>Relaxation (19)      | 8 weeks (1 and 3 months)                  | Male and female Mixed                   | NR                                  | 37           | 75  | 23          | Medium       |

BEP = brief eclectic psychotherapy; CAPS = Clinician-Administered Post Traumatic Stress Disorder Scale; CI = confidence interval; EMDR = eye movement desensitization and reprocessing; F = female; IES = Impact of Event Scale; M-PTSD = Mississippi Scale for Combat-Related Post Traumatic Stress Disorder; N = total number randomized/assigned to intervention and control groups; NA = not applicable; NR = not reported; PE = prolonged exposure; PSS-I = Post Traumatic Stress Disorder Symptom Scale-Interview; TAU = treatment as usual; WL = waitlist; y = year  
<sup>a</sup>Data reported are mean or range of mean scores across groups for the PTSD measure listed.

Among the trials described above, two also included an active comparator arm of either prolonged exposure<sup>87</sup> or relaxation.<sup>44</sup> One other trial compared EMDR with either prolonged exposure or relaxation in a sample (N=60) of individuals with PTSD from mixed trauma types.<sup>45</sup> Treatment duration was 8 weeks with a follow-up assessment at 3 months. Seventy-five percent of the sample was female.

Eight trials otherwise meeting criteria for this section were rated high risk of bias (Table 19), and thus were not included in our main data synthesis, and were only included in sensitivity analyses.



**Table 19. Characteristics of EMDR trials excluded from main analyses because of high risk of bias**

| Study                                 | Arm (N)  | Duration (Followup)  | Population Trauma Type                               | Baseline PTSD Severity <sup>a</sup> | Mean Age (Y) | % F | % Non-white | Risk of Bias |
|---------------------------------------|--|--|--|-------------------------------------|--------------|-----|-------------|--------------|
| Johnson et al., 2006 <sup>95</sup>    | Randomized (Total: 51) <sup>b</sup><br>PE (Unclear)<br>CM (Unclear)<br>EMDR (Unclear)<br>WL (14) | Mean number of weekly sessions <sup>c</sup><br>PE: 9.66<br>EMDR: 6.33<br>WL: 5.89 (3 months) | Female<br>Mixed                                      | 61.8 to 82.0                        | 39           | 100 | 17          | High         |
| Power et al., 2002 <sup>106</sup>     | EMDR (39)<br>EXP+CR (37)<br>WL (29)  | 10 weeks (15 months)   | Male and female<br>Mixed                             | IES<br>32.6 to 35.1                 | 40           | 42  | NR          | High         |
| Marcus et al., 1997 <sup>114</sup>    | EMDR (NR)<br>UC (NR)   | NR - Variable number of sessions   | Male and female<br>Mixed                             | IES<br>46.1 to 49.7                 | 42           | 79  | 34          | High         |
| Zimmerman et al., 2007 <sup>115</sup> | EMDR (40)<br>UC (49)   | Twice a week for 68 days (12 to 60 months)   | Male and female<br>Mixed (91% male, German soldiers) | IES<br>36.1<br>NR                   | 28           | 9   | NR          | High         |
| Deville et al., 1999 <sup>109</sup>   | EMDR (11)<br>CBT-M (12)  | 9 weeks (3 months)   | Australian male and female<br>Mixed                  | IES<br>48.4 to 54.1                 | 38           | 75  | NR          | High         |
| Ironson et al., 2002 <sup>103</sup>   | EMDR (10)<br>PE (12)   | 6 weeks (3 months)   | Domestic violence<br>Childhood sexual abuse          | PSS-SR<br>26.6 to 34.6              | NR           | 77  | NR          | High         |
| Karatzias et al., 2011 <sup>116</sup> | EMDR (23)<br>EFT (23)  | 8 weeks (3 months)   | Male and female<br>Mixed                             | 70.7 to 66.1                        | 40           | 57  | NR          | High         |
| Lee et al., 2002 <sup>110</sup>       | EMDR (12)<br>SITPE (12)  | 7 weeks (3 months)   | Australian male and female<br>Mixed                  | IES<br>55.3                         | 35           | 46  | NR          | High         |

CAPS = Clinician-Administered Post Traumatic Stress Disorder Scale; CBT-M = cognitive behavioral therapy-mixed; CI = confidence interval; CR = cognitive restructuring; EFT = Emotional Freedom Techniques; EMDR = eye movement desensitization and reprocessing; F = female; IES = Impact of Event Scale; MISS = Mississippi Scale for Combat-Related Post Traumatic Stress Disorder; N = total number randomized/assigned to intervention and control groups; NA = not applicable; NR = not reported; PE = prolong exposure; PTSD = posttraumatic stress disorder; PSS-SR = Post Traumatic Stress Disorder Symptom Scale-Self-Report; SITPE = stress inoculation training with prolonged exposure; TAU = treatment as usual; UC = usual care; WL = waitlist; y = year

<sup>a</sup>Data reported are mean score or range of mean scores across groups for the PTSD measure listed.

<sup>b</sup>The number of participants randomized to each active treatment group was not reported. A total of 27 participants from the active treatment groups were analyzed, 9 in each treatment group.

<sup>c</sup>Number of treatment sessions is reported when duration of treatment was not specified.

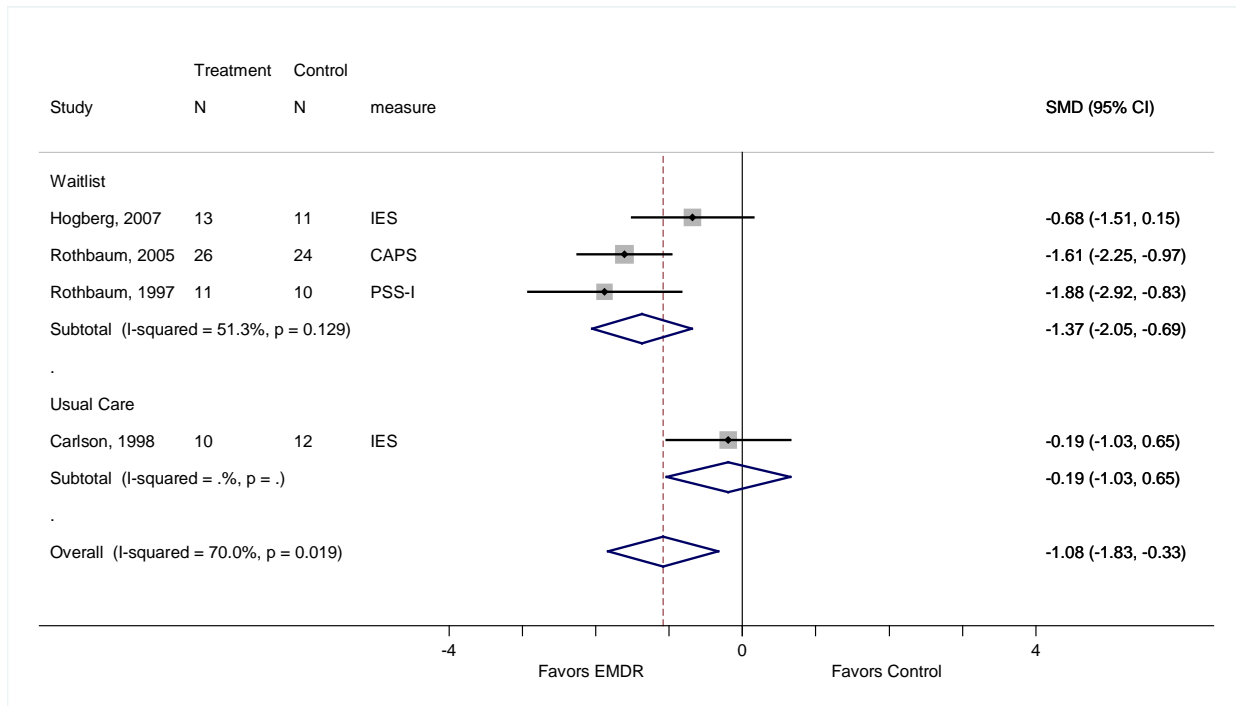
## Results for EMDR Compared With Inactive Comparators

### PTSD Symptom Reduction

All seven trials measured PTSD symptom change. Of the trials comparing EMDR with either a waitlist, usual care, or a placebo, all found a greater reduction in PTSD symptom score for EMDR than for comparators.<sup>44,87,111-113</sup> Not all differences reached statistical significance within individual studies, and point estimates varied widely across trials.

Our meta-analysis (Figure 17) found greater reduction in PTSD symptoms for EMDR than for controls (SMD, -1.08). Treatment gains were maintained for studies reporting followup at 3, 6, or 9 months.

**Figure 17. Mean change from baseline in PTSD symptoms for EMDR compared with control, by type of comparator**



Note: Timing of outcome assessment: 2 months (Hogberg, 2007),<sup>111</sup> 4.5 weeks (Rothbaum, 2005),<sup>87</sup> 4 weeks (Rothbaum, 1997),<sup>112</sup> 6 weeks (Carlson, 1998).<sup>44</sup>

The effect size we report here is Cohen’s d—a small effect size is 0.2, medium is 0.5, and large is 0.8. Thus, the pooled effect size was very large. However, statistical heterogeneity was substantial ( $I^2=70\%$ ) and the confidence interval ranged from almost a small effect size to a very large one.

Our sensitivity analysis including the placebo-controlled trial<sup>113</sup> resulted in a slightly lower effect size (SMD, -0.92; 95% CI, -1.55 to -0.29, Appendix F). Our sensitivity analysis also including trials with high risk of bias found a slightly larger benefit of EMDR. The confidence interval ranged from a medium to very large effect size (SMD, -1.13; 95% CI, -1.62 to -0.64; eight trials, N=361; Appendix F).

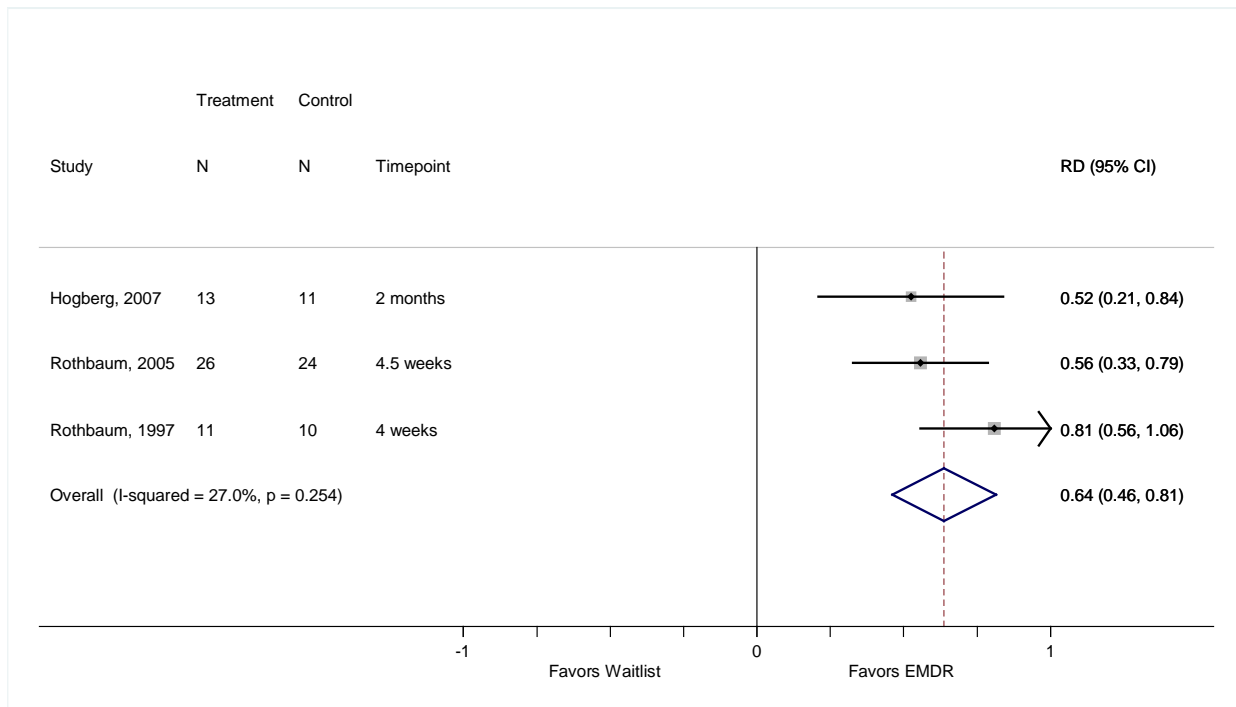
Overall, we concluded that the evidence supports the efficacy of EMDR over inactive controls for reduction of PTSD symptoms. However, the SOE is low because of lack of consistency and imprecision.

### Loss of PTSD Diagnosis

Of the studies that compared EMDR with waitlist, all three reported sufficient data to permit meta-analysis. All three found a greater reduction in the number of subjects meeting criteria for PTSD at posttreatment and at follow-up assessments in the EMDR groups than in control groups.<sup>87,111,112</sup>

Our meta-analysis (Figure 18) found 64 percent more subjects treated with EMDR than in waitlist control groups achieved loss of PTSD diagnosis. This translates to a NNT of 2. Sensitivity analyses removing each study one at a time, adding the placebo-controlled trial,<sup>113</sup> and adding high risk of bias trials produced similar results (RDs ranged from 0.46 to 0.68, Appendix F).

**Figure 18. Loss of PTSD diagnosis for EMDR compared with control (all were waitlist controls)**



We concluded evidence of moderate strength supports the efficacy of EMDR for achieving loss of PTSD diagnosis. This conclusion is based on direct, fairly precise evidence from randomized controlled trials.

## Prevention or Reduction of Comorbid Medical or Psychiatric Conditions

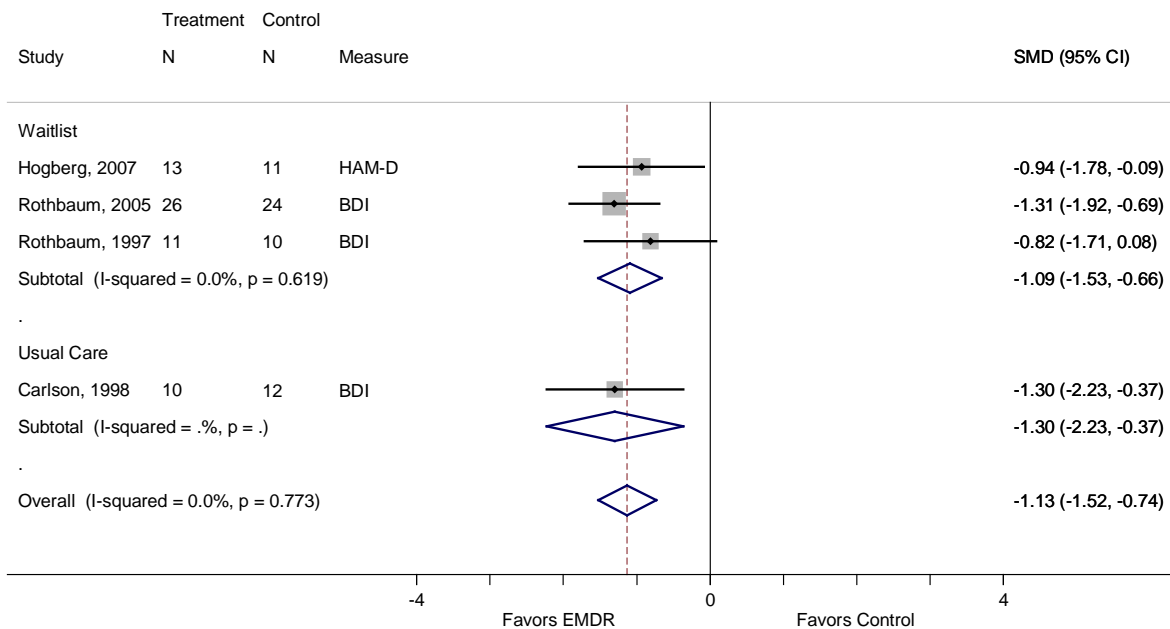
All five studies comparing EMDR with inactive control conditions included a measure of depression symptoms (BDI or HAM-D). Each found greater decreases in symptom scores for EMDR than for inactive controls.

Our meta-analysis (Figure 19) found EMDR had a greater reduction in depression scores than did inactive controls, with a large effect size (SMD, -1.13). Our sensitivity analysis including high-risk-of-bias trials and the placebo-controlled trial found a smaller, but still large, effect size (SMD, -0.87; 95% CI, -1.34 to -0.39, Appendix F).

Overall, we concluded that consistent, direct, and precise evidence supports the efficacy of EMDR over inactive controls for reducing depression symptoms (moderate SOE).

Three trials used STAI to assess anxiety symptoms. Our meta-analysis found that EMDR improved anxiety symptoms more than inactive controls, although results did not reach statistical significance (WMD, -11.1; 95% CI, -23.1 to 0.90; three trials, N=93; Appendix F). Overall findings were inconsistent and imprecise, however, leading us to conclude that evidence is insufficient to determine the efficacy of EMDR over inactive controls for this outcome.

**Figure 19. Mean change from baseline in depression symptoms for EMDR compared with control, by type of comparator**



Note: Timing of outcome assessment: 2 months (Hogberg, 2007),<sup>111</sup> 4.5 weeks (Rothbaum, 2005),<sup>87</sup> 4 weeks (Rothbaum, 1997),<sup>112</sup> 6 weeks (Carlson, 1998).<sup>44</sup>

### Results for EMDR Compared With Active Comparators: Relaxation

Of the trials comparing EMDR with an active comparator, two compared EMDR and exposure therapy<sup>45,87</sup> as assessed in the CBT Exposure section (above); one trial compared EMDR with brief eclectic psychotherapy<sup>48</sup> as assessed in the brief eclectic psychotherapy section below. Two trials compared EMDR and relaxation.<sup>44,45</sup>

### PTSD Symptom Reduction

One trial found no statistically significant difference in PTSD symptom reduction between subjects treated with EMDR (N=22) and those treated with relaxation (N=19) using the CAPS<sup>45</sup>; one found that EMDR (N=10) led to greater PTSD symptom reduction than relaxation (N=13) on the Mississippi Scale for Combat Related PTSD, but not on the IES.<sup>44</sup>

Pooled analyses of these two trials favored EMDR but found no statistically significant difference (SMD, -0.57; 95% CI, -1.44 to 0.29 using the Mississippi Scale for Combat Related PTSD from the study reporting two measures; SMD, -0.3; 95% CI, -0.8 to 0.2 using the IES; Appendix F). We concluded that evidence is insufficient to determine the comparative effectiveness of EMDR and relaxation for reducing PTSD symptoms; evidence was inconsistent and imprecise.

### Loss of PTSD Diagnosis

Two trials comparing EMDR with relaxation both reported achieving loss of PTSD diagnosis at some assessments.<sup>44,45</sup> One reported loss of diagnosis at the end of treatment—finding 60 percent of subjects treated with EMDR and 40 percent of subjects treated with relaxation no longer met criteria for PTSD diagnosis.<sup>45</sup>

Both studies reported loss of diagnosis at 3 months after treatment. Our meta-analysis of 3-month follow-up data (using intention-to-treat data, assuming those lost to followup still had a PTSD diagnosis) found a greater percentage of subjects treated with EMDR than with relaxation no longer having a PTSD diagnosis, but the difference was not statistically significant (RD, 0.34; 95% CI, -0.04 to 0.72; Appendix F). Overall, because of lack of consistency and imprecision, evidence is insufficient to draw conclusions about the comparative effectiveness of EMDR and relaxation for achieving loss of PTSD diagnosis.

### **Prevention or Reduction of Comorbid Medical or Psychiatric Conditions**

Both trials used the BDI to measure depression symptoms; one also reported on anxiety symptoms using the STAI.<sup>44</sup> Neither trial found a statistically significant difference between groups for reducing depression symptoms. One trial reported a large between-group effect size (>0.90 using BDI) that was not statistically significant.<sup>44</sup> The other trial did not report data for the depression symptoms measure.<sup>45</sup>

The study reporting anxiety symptoms (N=23) found that relaxation was less effective than EMDR (Cohen's  $d=1.15$ ,  $p<0.01$ ) for reducing symptoms of anxiety at the end of treatment.<sup>44</sup>

Because of limited evidence from two trials, lack of consistency, and imprecision, head-to-head evidence was insufficient to determine whether EMDR is more effective than relaxation for improving depression or anxiety symptoms.

## **Detailed Synthesis: Other Psychological Interventions**

### **Characteristics of Trials**

Table 20 summarizes the characteristics of 14 trials meeting our inclusion criteria. Further details describing the included studies are provided in Appendix D.

Four trials assessed the efficacy of a short-term manualized cognitive behavior treatment for people with PTSD and substance use disorders called Seeking Safety; three different active control approaches were designed to treat substance use disorders alone or to provide psychoeducation about women's health issues.<sup>33,117,118</sup> One of these three trials compared the addition (to treatment as usual) of a voluntary Seeking Safety intervention with a treatment as usual control group, which comprised incarcerated women enrolled in a residential substance use treatment program in a minimum security wing;<sup>33</sup> the relatively large "dose" of treatment as usual along with the voluntary dose of Seeking Safety could bias results toward the null. Another active control involved treatment as usual in a substance use disorder clinic at a Veteran's Administration outpatient mental health clinic.<sup>119</sup> Three of the trials enrolled women generally in their 30s; one enrolled male veterans with a mean age of 54.<sup>119</sup> Sample sizes ranged from 49 to 353;<sup>33,117,118</sup> one of these was a pilot study (N=49) that may have been underpowered.<sup>33</sup> One trial enrolled a sample of incarcerated women;<sup>33</sup> two enrolled community-based samples of women seeking substance abuse treatment.<sup>117,118</sup> Follow-up assessments were conducted at 3 and 6 months in all trials; one study each conducted additional assessments at 9 months<sup>117</sup> or 12 months.<sup>118</sup> In addition to assessing the effectiveness of Seeking Safety on symptoms of PTSD, all four trials assessed its effectiveness on substance use. One of the trials used less than half of the Seeking Safety model (only 12 of the 25 sessions/topics) and a large proportion of patients were either abstinent from substances at baseline or had very low levels of use, which could bias results toward the null.<sup>118</sup>

Two other trials describe an intervention called imagery rehearsal therapy.<sup>120,121</sup> This approach is described as a “cognitive-behavioral technique” based on the notion that “waking activity can influence the content of night-time dreams.”<sup>120</sup> Imagery rehearsal therapy targets trauma-related nightmares and, by doing so, attempts to reduce the severity of PTSD and improve the quality of sleep. Both trials were conducted in the United States. One trial of this approach versus waitlist involved women with a mean age of about 38 generally with moderate to very severe PTSD primarily associated with a history of sexual trauma (N=168).<sup>121</sup> The other trial compared this approach with psychoeducation in male Vietnam-era combat veterans with a mean age of about 60 (N=124).<sup>120</sup> Subjects were excluded if they had medical disorders known to affect sleep (e.g., narcolepsy, untreated sleep apnea). All subjects were screened for undiagnosed sleep apnea. Both trials allowed subjects to continue with psychotherapy and medication throughout the study. Both trials conducted follow-up assessments at 3 and 6 months after treatment ended.

**Table 20. Characteristics of included studies of other psychological interventions**

| Study                                | Arm (N)  | Treatment Duration (Followup)   | Population Trauma Type                            | Baseline PTSD Severity <sup>a</sup> | Mean Age (Y) | % F | % Non-white | Risk of Bias |
|--------------------------------------|--|---|---|-------------------------------------|--------------|-----|-------------|--------------|
| Ford et al., 2011 <sup>122</sup>     | Trauma Affect Regulation (48)<br>PCT (53)<br>WL (45)         | 12 sessions <sup>b</sup> (3 and 6 months)                                       | Female<br>Victimization or incarceration          | 61.9 to 68.7                        | 31           | 100 | 59          | Medium       |
| Gersons et al., 2000 <sup>21</sup>   | BEP (22)<br>WL (20)  | 16 weeks (3 months)   | Male and female police officers<br>Trauma type NR | NR                                  | 37           | 12  | NR          | Medium       |
| Lindauer et al., 2005 <sup>123</sup> | BEP (12)<br>WL (12)  | 16 weeks  | Male and female<br>Mixed                          | NR                                  | 39           | 54  | NR          | Medium       |
| Schnyder et al., 2011 <sup>124</sup> | BEP (16)<br>MA (14)  | 16 weeks (6 months) <sup>c</sup>  | Male and female<br>Mixed                          | 73.4 to 78.6                        | 40           | 47  | NR          | Medium       |
| Nijdam et al., 2012 <sup>48</sup>    | BEP (70)<br>EMDR (70)  | 16 weeks  | Male and female<br>Mixed                          | IES-R<br>72.8 to 79.9               | 38           | 56  | 100         | Medium       |
| Krakov et al., 2001 <sup>121</sup>   | IRT (88)<br>WL (80)  | 3 sessions—2 sessions 1 week apart and 1 session 3 weeks later (3 and 6 months) | Female<br>Sexual abuse/assault                    | 79.6 to 81.9                        | 38           | 100 | 21          | Medium       |
| Cook et al., 2010 <sup>120</sup>     | IRT (61)<br>PsychEd (63)                                     | 6 weeks (1, 3, and 6 months)  | Male<br>Combat                                    | 79.5 to 81.3                        | 59           | 0   | 58          | Medium       |
| Neuner et al., 2008 <sup>125</sup>   | NET (111)<br>Trauma Couns (111)<br>MG (no intervention) (55) | 3 weeks (6 months)  | Male and female<br>Rwandan and Somali refugees    | PDS<br>21.3 to 26.7                 | 35           | 51  | 100         | Medium       |
| Neuner et al., 2010 <sup>126</sup>   | NET (16)<br>TAU (16)   | Weekly or bi-weekly sessions (median 9) <sup>d</sup>                            | Male and female<br>Asylum seekers                 | PDS<br>36.9 to 38.9                 | 31           | 31  | NR          | Medium       |

**Table 20. Characteristics of included studies of other psychological interventions (continued)**

| Study  | Arm (N)  | Treatment Duration (Followup)  | Population Trauma Type                               | Baseline PTSD Severity <sup>a</sup> | Mean Age (Y) | % F | % Non-white | Risk of Bias |
|--|--|--------------------------------|--|-------------------------------------|--------------|-----|-------------|--------------|
| Neuner et al., 2004 <sup>127</sup>                                   | NET (17)<br>Trauma Couns (14)<br>PsychEd (12)                      | 3 to 4 weeks (4 and 12 months) | Male and female<br>Sudanese refugees                 | PDS<br>19.5 to 25.2                 | 33           | 61  | 100         | Medium       |
| Boden et al., 2012 <sup>119</sup>                                    | SS (59)<br>TAU (58)  | 12 weeks                       | Male<br>Combat                                       | IES-R<br>46.8 to 47.7               | 54           | 0   | 74          | Medium       |
| Hien et al., 2004 <sup>117</sup>                                     | Total 107 <sup>e</sup><br>SS (unclear)<br>RPC (unclear)<br>SC (32) | 12 weeks                       | Female<br>Mixed<br>w/substance<br>abuse<br>disorders | 70.4 to 73.9                        | 37           | 100 | 63          | Medium       |
| Hien et al., 2009 <sup>118</sup><br>Hien et al., 2012 <sup>128</sup> | SS (176)<br>PsychEd <sup>f</sup> (177)                             | 6 weeks                        | Female<br>Mixed                                      | 61.6 to 64.2                        | 39           | 100 | 54          | Medium       |
| Zlotnick et al., 2009 <sup>33</sup>                                  | SS (27)<br>RPC (22)  | 6 to 8 weeks (3 and 6 months)  | Female<br>Mixed                                      | 64.4 to 69.4                        | 35           | 100 | 53          | Medium       |

BEP = brief eclectic psychotherapy; F = female; IRT = imagery rehearsal therapy; MA = minimal attention (inactive control group); MG = no-treatment monitoring group; N = total number randomized/assigned to intervention and control groups; NET = narrative exposure therapy; NR = not reported; PCT = present-centered therapy; PDS = Posttraumatic Stress Diagnostic Scale; PTSD = posttraumatic stress disorder; PsychEd = psychosocial education; RPC = relapse prevention condition; SC = standard care; SS = Seeking Safety; TAU = treatment as usual; trauma couns = trauma counseling; WL = waitlist; y = year  
<sup>a</sup>Data reported are mean CAPS total or range of mean CAPS total scores across groups unless otherwise specified.

<sup>b</sup>Number of treatment sessions is reported when duration of treatment was not specified.

<sup>c</sup>Only the BEP group had a follow-up assessment; the control group did not.

<sup>d</sup>Treatment was terminated at the discretion of the therapist; range of 5-17 sessions provided.

<sup>e</sup>The article did not report the numbers randomized to each group. It reported the numbers analyzed in each group (41, 34, and 32, respectively). It describes baseline data for 107 subjects analyzed. Of the 128 women who met full study eligibility criteria, 115 (90%) agreed to participate, and 96 of these women were randomly assigned to the two active treatment (SS and RPC). Thirty-two of the 128 women became the community care comparison group; they were not randomized to that group.

<sup>f</sup>Psycho Ed in this study is "Women's Health Education" (WHE).

Note: When mean data for baseline PTSD severity were not reported for the total sample but were presented for each study arm, we provide the range across arms.

Three trials assessed the effectiveness of narrative exposure therapy for PTSD among asylum seekers and refugees. Narrative exposure therapy is described as a "standardized short-term approach based on the principles of cognitive-behavioral exposure therapy by adapting the classical form of exposure therapy to meet the needs of traumatized survivors of war and torture."<sup>127</sup> All three trials were conducted by the same group of researchers. Sample sizes ranged from 32 to 277. Duration of treatment was usually 3 to 5 weeks. All three trials used the PDS to assess PTSD symptom severity. All samples contained males (25% to 69%) and females (31% to 75%) who were generally in their early to mid-30s. One trial compared narrative exposure therapy (n=17), supportive trauma counseling (n=14), and psychoeducation (n=12) in a Ugandan refugee settlement with Sudanese refugees.<sup>127</sup> The second trial was also conducted in a Ugandan refugee settlement and compared narrative exposure therapy (n=111), trauma counseling (n=111), and a nontreatment symptom monitoring group (n=55) among Rwandan and Somali refugees.<sup>125</sup> The primary focus of this trial was to examine whether trained lay

counselors can carry out effective treatment of PTSD in a refugee settlement as this might have important implications in resource-poor countries experiencing conflict. The third trial compared narrative exposure therapy (n=16) with treatment as usual (n=16) in a sample of asylum seekers living in Germany who were originally from Turkey, the Balkans, or Africa.<sup>126</sup> Treatment as usual included “psychotherapy with a focus on stabilizing methods (n=6) and psychoactive medication (n=12).”

Four trials assessed brief eclectic psychotherapy, a manualized intervention that combines cognitive-behavioral and psychodynamic approaches for treating patients with PTSD. Three of the four compared brief eclectic psychotherapy with waitlist<sup>21,123</sup> or minimal attention<sup>124</sup>; one compared it with EMDR.<sup>48</sup> Three trials were conducted by the same research group in the Netherlands; one with police officers<sup>21</sup> and the other two with heterogeneous group of subjects with a variety of index trauma types.<sup>48,123</sup> One trial enrolled a diverse group of predominantly Swiss citizens (63.3%).<sup>124</sup> Brief eclectic psychotherapy was conducted for 16 weeks in all four studies. Mean age was similar in all four trials (35 to 40 years of age). Twelve subjects (40.0%) of the Swiss sample were taking psychotropic medications, “mostly antidepressants.”

One trial compared trauma affect regulation (Trauma Affect Regulation: Guide for Education and Therapy [TARGET]) with present-centered therapy and with waitlist.<sup>122</sup> The trial enrolled mothers with victimization-related PTSD, primarily low-income and ethnoracial minorities.

Five trials otherwise meeting criteria for this section were rated high risk of bias (Table 21), and thus were not included in our main data synthesis, and were only included in sensitivity analyses.

**Table 21. Characteristics of other psychological intervention trials excluded from main analyses because of high risk of bias**

| Study                                     | Arm (N)                                      | Treatment Duration (Followup)                     | Population Trauma Type                            | Baseline PTSD Severity <sup>a</sup> | Mean Age (Y) | % F | % Non-white | Risk of Bias |
|---|--|---|---|-------------------------------------|--------------|-----|-------------|--------------|
| Wagner et al., 2007 <sup>129</sup>        | BA (4)<br>TAU (4)                            | 4 to 6 sessions <sup>b</sup>                      | Male and female<br>Recently Injured               | PCL<br>54.2 to 55.5                 | 34           | 38  | 50          | High         |
| Brom et al., 1989 <sup>101</sup>          | TD (31)<br>Hypno (29)<br>PDT (29)<br>WL (23) | ~4 months—only gave mean # of sessions (3 months) | Male and female<br>Mixed                          | NR                                  | 42           | 79  | NR          | High         |
| Krupnick et al., 2008 <sup>130</sup>      | IPT (32)<br>WL (16)                          | 16 weeks (4 months)                               | Female<br>Mixed                                   | 62.6 to 65.2                        | 32           | 100 | 94          | High         |
| Bichescu et al., 2007 <sup>131</sup>      | NET (9)<br>PED (9)                           | 10 weeks—5 NET sessions, 1 PED session (6 months) | Male and female<br>Political detainees            | CIDI - PTSD<br>11.4 to 11.9         | 69           | 6   | NR          | High         |
| Hensel-Dittman et al., 2011 <sup>86</sup> | NET (15)<br>SIT (13)                         | 4 weeks (6 and 12 months)                         | Male and female<br>Experienced organized violence | 85.2 to 96.5                        | NR           | NR  | NR          | High         |

BA = behavioral activation; CAPS = Clinician-Administered Post Traumatic Stress Disorder Scale; CIDI = Composite International Diagnostic Interview – PTSD section; F = female; hypno = hypnotherapy; IPT = interpersonal therapy; N = total number randomized/assigned to intervention and control groups; NET = narrative exposure therapy; NR = not reported; PCL = PTSD Checklist; PED = psychoeducation only; PDT = psychodynamic therapy; PTSD = posttraumatic stress disorder; SIT = stress inoculation training; TAU = treatment as usual; TD = trauma desensitization; WL = waitlist; y = year

<sup>a</sup>Data reported are mean CAPS or range of mean CAPS scores across groups unless another instrument is specified.

<sup>b</sup>Number of treatment sessions is reported when duration of treatment was not specified.



## Seeking Safety

### PTSD Symptom Reduction

Of the four Seeking Safety trials, one compared this approach, standard community treatment, and relapse prevention for women with both PTSD and substance use disorders (N=128).<sup>117</sup> Women in the active treatment arm had a greater reduction in symptoms of PTSD than those in the standard community treatment arm (CAPS frequency and intensity, reduction from baseline to posttreatment -15.02 vs. -5.88,  $p < 0.01$ ), and subjects in the standard community treatment arm had worse PTSD severity at the end of treatment and at 3- and 6-month followup (as measured by a standardized composite score for PTSD severity).

All four trials of Seeking Safety found that the intervention reduced symptoms of PTSD; however, between-group differences were not statistically significant, and point estimates favored control groups rather than Seeking Safety for several of the trials.<sup>33,117-119</sup>

Our meta-analysis of mean change from baseline in CAPS scores (reported by three of the trials) found no difference between Seeking Safety and active controls (WMD, 1.45; 95% CI, -2.5 to 5.4;  $I^2 = 0\%$ ; three trials, N=477; Appendix F). Similarly, our meta-analysis of PTSD symptom reduction using any measure found no difference (SMD, 0.04; 95% CI, -0.12 to 0.2;  $I^2 = 0\%$ ; four trials, N=594; Appendix F).

For followup at the end of treatment, all three trials comparing Seeking Safety with relapse prevention reported improvement in PTSD symptoms for both groups, but they found no between-group difference. This was maintained in all three trials at 3- and 6-month followup, and at 9-month<sup>117</sup> and 12-month<sup>118</sup> followup as well.

Overall, we concluded that evidence is insufficient to determine the efficacy of Seeking Safety for reduction of PTSD symptoms. One trial found Seeking Safety to be efficacious compared with standard care.<sup>117</sup> Overall, evidence was limited to one trial designed to assess efficacy, consistency was unknown, and findings were imprecise.

Four trials of Seeking Safety compared with active controls (e.g., relapse prevention) found no differences, providing evidence of moderate strength supporting similar effectiveness for PTSD symptom reduction for people with PTSD and substance use disorders.

### Loss of PTSD Diagnosis

The trial that compared Seeking Safety with standard community treatment did not report on achieving loss of diagnosis. The trial of Seeking Safety compared with relapse prevention (N=49) reported loss of PTSD diagnosis.<sup>33</sup> At 3-month followup, 39 percent of the women in Seeking Safety and 43 percent of the women in the relapse prevention group met criteria for PTSD. At 6 months, the figures were 53 percent (of women available for followup) in both groups. Their analysis indicated no significant difference in the odds of meeting criteria for PTSD between the two conditions across all points in time (odds ratio for Seeking Safety vs. relapse prevention = 1.22; 95% CI, 0.48 to 3.13). We concluded that evidence is insufficient to support the efficacy of Seeking Safety for achieving loss of PTSD diagnosis (no studies available addressing efficacy); one trial found no difference between Seeking Safety and relapse prevention, but consistency is unknown and findings were imprecise.

### Prevention or Reduction of Comorbid Medical or Psychiatric Conditions

The trial that compared Seeking Safety with standard community treatment reported that subjects in the intervention arm had a greater reduction in substance use or abuse than those in

standard community treatment ( $p < 0.001$ ).<sup>117</sup> This effect was maintained at the 6-month follow up ( $p < 0.05$ ) but not at the 9-month assessment ( $p = 0.06$ ).

Three Seeking Safety trials reported outcome data on substance use or abuse and found no between-group differences for the active treatment arms in the respective studies. One study sample comprised incarcerated women with no access to substances<sup>33</sup> and two studies enrolled those in community-based substance use or abuse treatment programs.<sup>117,118</sup> Substance use outcome measures included abstinence<sup>33,118</sup> and substance use severity.<sup>33,117</sup> One trial reported no statistically significant differences between Seeking Safety and relapse prevention<sup>117</sup> but did not provide a statistical measure. Another trial reported no between-group differences on several measures of substance use or abuse; Anxiety Stress Index (ASI) composite score for drug ( $p = 0.71$ ), ASI composite score for alcohol ( $p = 0.48$ ), and weeks abstinent ( $p = 0.20$ ).<sup>33</sup> Abstinence rates were not significantly different for Seeking Safety and Women's Health Education (WHE) at 12-month follow up.<sup>118</sup> Overall, evidence did not support a difference in effectiveness between Seeking Safety interventions and active controls for reducing substance use for people with PTSD.

The trial conducted in male veterans reported better drug use outcomes for those in the Seeking Safety group than in the treatment as usual group ( $p < 0.05$ ), but found no difference between groups for alcohol use outcomes (alcohol use decreased equally in both groups).<sup>119</sup>

## **Imagery Rehearsal Therapy**

### **PTSD Symptom Reduction**

Both trials assessing imagery rehearsal therapy reported measures of PTSD symptoms. The trial (N=168) with a waitlist control reported that the intervention was more effective than waitlist for reducing symptoms of PTSD as measured by the CAPS (mean change -32.3 vs. -11.3,  $p = 0.001$ ).<sup>121</sup> We determined that evidence from this one trial was insufficient to determine the efficacy of imagery rehearsal therapy for reducing PTSD symptoms.

In the trial comparing this intervention and an active comparator (psychoeducation), the authors reported no significant between-group difference in CAPS scores (mean change 7.3 vs. 4.6, Chi-square=0.20).<sup>120</sup> The evidence was insufficient to determine whether imagery rehearsal therapy and psychoeducation differ in reducing PTSD symptoms; consistency is unknown (single study) and findings were imprecise.

### **Prevention or Reduction of Comorbid Medical or Psychiatric Conditions**

Both trials assessed the effectiveness of imagery rehearsal therapy for reducing depression symptoms; one used the BDI<sup>120</sup> and the other used the HAM-D.<sup>121</sup> The trial comparing imagery rehearsal therapy with a waitlist (N=168) found the intervention to be more effective than waitlist for reducing symptoms of depression (HAM-D, effect sizes reported as Cohen d, 0.57 vs. 0.33,  $p = \text{NS}$  between groups).<sup>121</sup> This trial also assessed symptoms of anxiety using the HAM-A. Anxiety symptoms improved in the therapy group ( $d = 0.39$ ) and worsened in the waitlist group ( $d = -0.16$ ,  $p = 0.04$ ). Evidence was insufficient to determine the efficacy of imagery rehearsal therapy for reducing depression or anxiety symptoms because of unknown consistency (single study), imprecision, and small difference in effect sizes between the intervention and waitlist.

The trial comparing imagery rehearsal therapy with psychoeducation, reported no statistically significant difference between groups for reducing symptoms of depression (BDI scores) at the end of treatment or at any follow-up assessment.<sup>120</sup> Mean change scores were as follows: 1

month, -2.69 vs. -1.2 (p=NS); 3 months, -2.05 vs. 0.25 (p=NS); and 6 months, -1.83 vs. -0.14 (p=NS).

### Quality of Life

Both trials of imagery rehearsal therapy reported the SF-36 among outcome measures. Neither study found the therapy to be more effective than the comparator for improving quality of life. One trial did not report data;<sup>121</sup> the other reported mean change scores for the SF-36 Physical Component at 1 month (2.31 vs. -1.69, p=NR), 3 months (0.55 vs. -2.57, p=NR), and 6 months (-1.37 vs. 1.32, p=NR); it also reported data for the SF-36 Mental Component at 1 month (2.64 vs. -1.68, p=NR), 3 months (1.29 vs. -0.52, p=NR), and 6 months (2.46 vs. 0.26, p=NR).<sup>120</sup> Evidence from these two trials was insufficient to determine the efficacy or comparative effectiveness of imagery rehearsal therapy because of unknown consistency (only one study reported data) and imprecision.

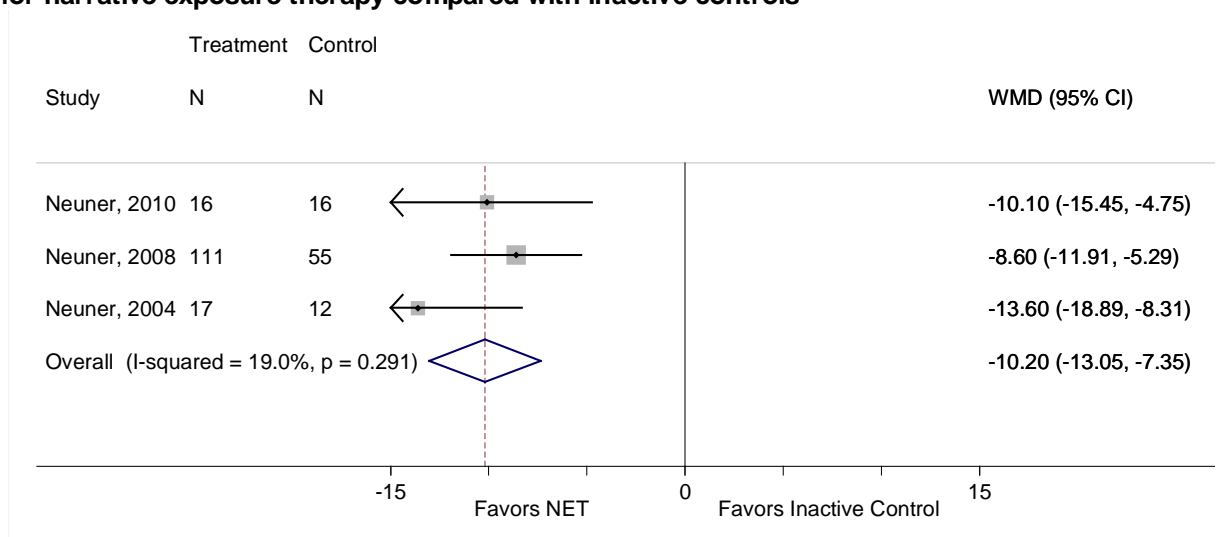
### Narrative Exposure Therapy

#### PTSD Symptom Reduction

All three trials assessing narrative exposure therapy used the PDS to measure PTSD symptom reduction. All three compared narrative exposure therapy with an inactive comparator;<sup>125-127</sup> two compared it with at least one other active intervention not directed at treating PTSD.<sup>125,127</sup> All trials found that this intervention reduced symptoms of PTSD more than inactive comparators.

Our meta-analysis (Figure 20) found about a 10-point greater improvement in change from baseline to end of treatment for narrative exposure therapy than for inactive control groups for PDS score (corresponding Cohen’s d -1.25; 95% CI, -1.92 to -0.58, Appendix F). Analyses removing each individual study one at a time did not yield any significant differences in findings (Appendix F).

**Figure 20. Mean change from baseline to end of treatment in PTSD symptoms (measured by PDS) for narrative exposure therapy compared with inactive controls**



Note: Timing of outcome assessment: after 5 to 17 sessions (Neuner, 2010),<sup>126</sup> 3 weeks (Neuner, 2008),<sup>125</sup> 3 to 4 weeks (Neuner, 2004).<sup>127</sup>

One trial reported a reduction (but no data) in PTSD symptoms for subjects in the intervention group at 6 months after the end of treatment;<sup>126</sup> another reported that the intervention was significantly better in reducing symptoms of PTSD than no treatment (i.e., monitoring group) from baseline to 6-month followup (d=1.4 and 0.08, respectively, p<0.001).<sup>125</sup> One year post-treatment data were reported by one trial; subjects in the narrative exposure group had better improvement on the PDS than those in the inactive treatment group (d=1.6 and -0.09, respectively, p<0.01).<sup>127</sup>

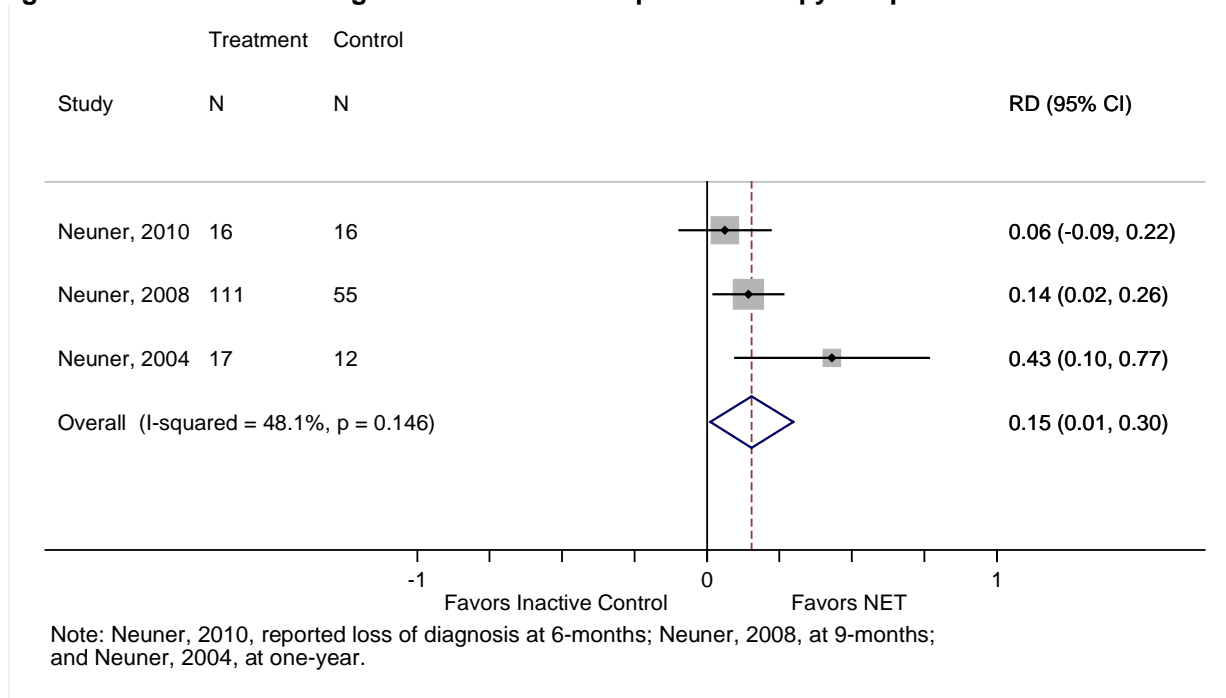
Overall, we concluded that evidence of moderate strength supports the efficacy of narrative exposure therapy for reducing PTSD symptoms, based on consistent, direct, and precise evidence from three trials.

### Loss of PTSD Diagnosis

All three trials of narrative exposure therapy and an inactive control reported data on achieving loss of PTSD diagnosis.<sup>125-127</sup> Two of these also had at least one other active intervention not directed at treating PTSD.<sup>125,127</sup> All three trials found point estimates favoring narrative exposure therapy.

Our meta-analysis (Figure 21) found that 15 percent more subjects were no longer diagnosed with PTSD at the end of treatment for narrative exposure therapy than for inactive comparator groups.

**Figure 21. Loss of PTSD diagnosis for narrative exposure therapy compared with inactive controls**



### Prevention or Reduction of Comorbid Medical or Psychiatric Conditions

Two trials evaluated the effectiveness of narrative exposure therapy on coexisting psychiatric conditions;<sup>126,127</sup> one used the HSCL-25 Depression scale<sup>126</sup> the other used the SRQ-20.<sup>127</sup> One trial reported greater improvement in depression for subjects treated with narrative exposure therapy than for those receiving treatment as usual (HSCL-25 Depression scale, between-group

effect size, Cohens  $d = 0.54$ ,  $p = \text{NR}$ ).<sup>126</sup> The other trial found no significant differences among narrative exposure therapy, trauma counseling, or psychoeducation on the SRQ-20 (reductions from 2.2 to 3.3 across groups,  $p = \text{NS}$ ).<sup>127</sup> Using this same measure, narrative exposure therapy was no more effective than trauma counseling or psychoeducation in reducing the number of cases classified as suffering from a severe mental illness ( $p = 0.08$ ) at 1-year followup.

Overall, we concluded that evidence is insufficient to determine the efficacy of narrative exposure therapy for preventing or reducing coexisting psychiatric conditions. Evidence from two trials was inconsistent and imprecise.

One trial ( $N = 32$ ) evaluated the effectiveness of narrative exposure therapy on pain as assessed by part C of the Composite International Diagnostic Interview (CIDI-C) Pain score.<sup>126</sup> Whether all of the subjects in this sample had pain was unclear, but the authors stated that 79 percent of their sample reported physical torture experiences. The between-group effect size of narrative exposure therapy and treatment as usual for the CIDI Pain score was  $d = 0.65$  (for CIDI-C pain score, a significant time by treatment interaction was found,  $p = 0.034$ , but no significant main effect of time,  $p = 0.46$ , or treatment,  $p = 0.35$ ). We concluded that evidence is insufficient to determine the efficacy of narrative exposure therapy for preventing or reducing pain. Evidence was imprecise and consistency is unknown.

## Quality of Life

One trial evaluated quality of life using the Psychological Health subscale from the Medical Outcomes Study Short Form 12.<sup>127</sup> Narrative exposure therapy was more effective for improving quality of life than trauma counseling (effect sizes pre- to posttreatment:  $-0.6$  and  $0.1$ , respectively,  $p < 0.01$ ) but not more effective than psychoeducation ( $p = 0.54$ ). We concluded that evidence is insufficient to determine the efficacy of narrative exposure therapy for improving quality of life. Evidence was imprecise and consistency is unknown.

## Brief Eclectic Psychotherapy

### PTSD Symptom Reduction

Three trials reported measures of PTSD symptom reduction for brief eclectic psychotherapy compared with an inactive comparator.<sup>21,123,124</sup> In all three trials (using different outcome measures), brief eclectic psychotherapy was effective in reducing symptoms of PTSD. One reported greater reduction in symptoms measured by the SI-PTSD Reexperiencing score (Cohen's  $d = 0.45$ ), Avoidance score ( $d = 0.52$ ), and Hyperarousal score ( $d = 0.39$ ) (for Cohen's  $d$ ,  $0.2$  would indicate a small effect size;  $0.5$  a medium effect size).<sup>123</sup> Another used the CAPS (change from baseline to end of treatment:  $-17.8$  vs.  $-7$ ).<sup>124</sup> The third study reported change in the frequency of symptoms within each symptoms cluster and found that brief eclectic psychotherapy was effective in eliminating reexperiencing symptoms ( $p < 0.01$  at end of treatment and at 3-month followup), was not effective in reducing the number of avoidance symptoms ( $< 3$  avoidance symptoms) at the end of treatment, but was effective at 3-month followup ( $p < 0.001$ ), and was effective in reducing the number of hyperarousal symptoms ( $< 2$  avoidance symptoms) ( $p < 0.01$  at end of treatment and  $p < 0.05$  at 3-month followup).<sup>21</sup> Based on these three trials, we concluded that consistent, direct evidence supports the efficacy of brief eclectic psychotherapy for reducing PTSD symptoms, likely with a small to medium effect size (low SOE). However, the evidence was imprecise. Each trial reported different outcome measures, and data were not sufficient to determine the effect size accurately.

The trial comparing brief eclectic psychotherapy with EMDR reported that both treatments were equally effective in reducing PTSD symptom severity, but that EMDR resulted in faster recovery.<sup>48</sup> The study reported improvement in PTSD symptoms in both groups using the IES-R and the SI-PTSD, but greater improvement from baseline to the first assessment for those treated with EMDR than for those treated with brief eclectic psychotherapy (SI-PTSD, mean estimated between-group difference 10.80; 95% CI 6.37 to 15.23)<sup>48</sup> The between-group difference was no longer significant at the second assessment, conducted after both groups had completed treatment.

Due to unknown consistency (with data from a single trial), risk of bias, and imprecision, we graded the evidence as insufficient to determine the comparative effectiveness of brief eclectic psychotherapy and EMDR.

### **Remission (No Longer Having Symptoms)**

One trial (N=30) reported data on symptom remission. At the end of treatment, 2 of 16 subjects (12.5% ) in the group receiving brief eclectic psychotherapy were described as being in complete remission based on a total CAPS score of <20.<sup>124</sup> At 6-month followup, 3 subjects (18.8%) were fully remitted. None of the subjects in the waitlist group achieved complete remission. We concluded that evidence from this single trial was insufficient to determine the efficacy of brief eclectic psychotherapy for remission of PTSD symptoms. Consistency is unknown (single study) and findings were imprecise.

### **Loss of PTSD Diagnosis**

All three trials reported that brief eclectic psychotherapy was more effective than waitlist in reducing the proportion of subjects who continued to meet criteria for PTSD at the end of treatment and at followup. One trial (N=30), using a definition of CAPS<50 found more subjects receiving the intervention than on the waitlist lost their diagnosis of PTSD (2 subjects, 12.5% vs. 0 subjects, 0%).<sup>124</sup> The other two trials used the SI-PTSD to determine PTSD diagnosis. One trial (N=24) reported that 83.3 percent of subjects receiving brief eclectic psychotherapy and 25 percent on a waitlist ( $p<0.05$ ) no longer met criteria for PTSD at the end of treatment.<sup>123</sup> The other trial (N=42) reported that 91 percent of subjects receiving the intervention and 50 percent on a waitlist ( $p<0.01$ ) lost their diagnosis at the end of treatment; these changes were essentially maintained at 3-month followup (96% versus 35%,  $p<0.01$ ).<sup>21</sup> We concluded that evidence supports the efficacy of brief eclectic psychotherapy for achieving loss of PTSD diagnosis; however, findings from three trials (total N=96) were inconsistent (ranging from a small effect to a large effect) and imprecise (low SOE).

The trial comparing brief eclectic psychotherapy with EMDR reported that both treatments had similar benefits for achieving loss of diagnosis, but that EMDR resulted in earlier benefits.<sup>48</sup> The study reported more improvement (a higher rate of achieving loss of PTSD diagnosis) among completers for the EMDR group than for the brief eclectic psychotherapy group at the first assessment (92.2% vs. 52.3%,  $p<0.001$ ), but found no significant difference between groups at the second assessment (93.7% vs. 85.7%,  $p=0.30$ ), conducted after both groups had completed treatment. These results included 51 out of 70 and 44 out of 70 subjects (not accounting for missing data from dropouts) in the EMDR and brief eclectic psychotherapy groups at the first assessment and 48 out of 70 and 42 out of 70 at the second assessment, respectively. Due to unknown consistency (with data from a single trial), risk of bias, and imprecision, we graded the

evidence as insufficient to determine the comparative effectiveness of brief eclectic psychotherapy and EMDR.

### **Prevention or Reduction of Comorbid Medical or Psychiatric Conditions**

All three trials comparing brief eclectic psychotherapy with waitlist reported on reduction of depression and anxiety. Two used the Hospital Anxiety and Depression Scale (HADS) as an outcome measure. Both reported that brief eclectic psychotherapy was more effective than the waitlist in reducing symptoms of depression at the end of treatment and at later followup (Cohen's  $d = 1.0$  for both time points in one trial<sup>124</sup> and  $d=0.38$  for the other<sup>123</sup>). One trial used the SCL-90 as a multidimensional indicator of psychopathology and reported that brief eclectic psychotherapy was more effective than waitlist in reducing symptoms of depression at the end of treatment (data NR,  $p<0.01$ ); this change was maintained at the 3-month followup.<sup>21</sup>

Two trials reported that brief eclectic psychotherapy was more effective than waitlist in reducing symptoms of anxiety as assessed by the HADS (Cohen's  $d = 0.8$ ,  $p<0.05$ ; and  $d = 0.9$ ,  $p<0.05$  for one trial at the end of treatment and at followup<sup>124</sup>; for the other trial  $d = 0.54$ <sup>123</sup>). The trial using the SCL-90 reported that brief eclectic psychotherapy was more effective than waitlist in reducing symptoms of anxiety at the end of treatment and at 3-month followup (data NR,  $p$ -values of  $< 0.05$  and  $<0.01$ ).<sup>21</sup>

Evidence (low SOE) supports the efficacy of brief eclectic psychotherapy for reducing depression or anxiety symptoms. Although these trials (total  $N=96$ ) support efficacy, the evidence was somewhat inconsistent and imprecise; effect sizes and outcomes not reported in one trial and ranged from a medium to a very large effect in the other two.

The trial comparing brief eclectic psychotherapy with EMDR reported measures of depression and anxiety symptoms (using the HADS depression and the HADS anxiety).<sup>48</sup> Similar to findings for other outcomes (e.g. PTSD symptoms), the study reported greater improvement from baseline to the first assessment for those treated with EMDR than for those treated with brief eclectic psychotherapy, but no significant difference between groups at the second assessment (see Appendix D for detailed data).

Due to unknown consistency (with data from a single trial), risk of bias, and imprecision, we graded the evidence as insufficient to determine the comparative effectiveness of brief eclectic psychotherapy and EMDR.

### **Return to Work or Active Duty**

Two trials reported outcomes related to work—one reported the percentage of subjects on sick leave;<sup>123</sup> the other reported the percentage who had returned to work.<sup>21</sup> The former trial ( $N=24$ ) found fewer subjects on sick leave for the brief eclectic psychotherapy group compared with those on the waitlist, but the difference was not statistically significant ( $d=0.33$ ,  $p=0.06$ ).<sup>123</sup> The other trial ( $N=42$ ) reported a statistically significant difference between the groups at the end of treatment—86 percent of the intervention group and 60 percent of the waitlist group had returned to work ( $p<0.05$ ).<sup>21</sup> Together, evidence from these two trials suggests that brief eclectic psychotherapy is efficacious for improving return to work; SOE is low, primarily because of imprecision.

## Trauma Affect Regulation

### PTSD Symptom Reduction

The trial comparing trauma affect regulation, present-centered therapy, and waitlist reported greater improvement in PTSD symptoms for those treated with trauma affect regulation than those in the waitlist group (CAPS mean change from baseline: -23.6 vs. -6.2,  $p < 0.001$ ).<sup>122</sup>

For this outcome and the others (below) from this trial, due to unknown consistency (with data from a single trial), risk of bias, and imprecision, we graded the evidence as insufficient to determine the efficacy of trauma affect regulation.

### Remission

The trial reported that more people in the trauma affect regulation group than in the waitlist group achieved full remission at posttreatment (21% vs. 0%,  $p < 0.001$ ).

### Loss of Diagnosis

The trial reported that more people in the trauma affect regulation group than in the waitlist group achieved loss of diagnosis at posttreatment (35% vs. 11%).

#### Prevention or Reduction of Comorbid Medical or Psychiatric Conditions

The trial reported greater improvement in depression symptoms and anxiety symptoms for the trauma affect regulation group than for the waitlist group (BDI: -4.4 vs. -0.3,  $p < 0.01$ ; STAI: -6.7 vs. -0.4,  $p = 0.19$ ).

## Key Question 2. Comparative Effectiveness of Different Pharmacological Treatments for Adults With PTSD

For this question, we included placebo-controlled trials (indirect evidence) and head-to-head trials (direct evidence) of pharmacotherapies. First, we evaluated the evidence of efficacy for the included medications (compared with placebo) and then assessed the direct evidence and conducted network meta-analysis to utilize both the indirect and direct evidence to inform a determination of the comparative effectiveness of pharmacotherapies. In the bulleted text below we summarize the main overall key points and then the key points for each medication class and report the strength of evidence (SOE) where appropriate.

The primary outcomes of interest for determining whether treatments are effective for adults with PTSD are improving PTSD symptoms, inducing remission, and losing PTSD diagnosis; we focus more on these outcomes than on other outcomes in the key points. We also comment on other outcomes of interest, such as prevention or reduction of coexisting medical or psychiatric conditions, quality of life, disability or functional impairment, and return to work or active duty. The findings in these key points are primarily based on meta-analyses of the trials that we rated low or medium risk of bias described later in the detailed synthesis sections of the chapter. Those trials are cited in the detailed synthesis and related tables. In the detailed synthesis section for each treatment, we provide section headers for each outcome reported (PTSD symptoms, remission, loss of PTSD diagnosis, prevention or reduction of coexisting medical or psychiatric conditions, quality of life, disability or functional impairment, and return to work or active duty). If an outcome does not appear, no trial reported data on it.



## Key Points: Overall—Efficacy

- Evidence supports the efficacy of fluoxetine, paroxetine, sertraline, topiramate, and venlafaxine for improving PTSD symptoms (moderate SOE).
- Evidence suggests that risperidone may have some, albeit minimal, benefit for reduction of PTSD symptoms (low SOE).
- Evidence was insufficient to determine efficacy for other medications.
- For the medications with evidence of efficacy, the mean size of the effect for improving symptoms was small or medium (mean change from baseline in the Clinician-Administered PTSD Scale [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 numbers needed to treat (NNTs) of ~8 (moderate SOE).

Table 22 summarizes the efficacy and SOE for all included medications for improving PTSD symptoms, inducing remission, and achieving loss of PTSD diagnosis.

**Table 22. Summary of efficacy and strength of evidence of pharmacologic treatments for adults with PTSD, by drug class**

| Medication Class | Medication     | PTSD Symptoms <sup>a</sup>   | Remission (No Longer Having Symptoms) <sup>b</sup> | Loss of PTSD Diagnosis |
|------------------|----------------|--|--|------------------------|
| Alpha blocker    | Prazosin       | WMD -8.9 (-22.1 to 4.3, N=50)<br>SMD -0.40 (-0.97 to 0.16, N=50)<br>Insufficient SOE     | Insufficient SOE                                   | Insufficient SOE       |
| Anti-convulsant  | Divalproex     | WMD 1.40 (-8.22 to 11.02, N=85)<br>SMD 0.06 (-0.36 to 0.49, N=85)<br>Insufficient SOE    | Insufficient SOE                                   | Insufficient SOE       |
| Anti-convulsant  | Lamotrigine    | Insufficient SOE   | Insufficient SOE                                   | Insufficient SOE       |
| Anti-convulsant  | Tiagabine      | WMD -0.50 (-7.12 to 6.12, N=232)<br>SMD -0.02 (-0.28 to 0.24, N=232)<br>Insufficient SOE | Insufficient SOE                                   | Insufficient SOE       |
| Anti-convulsant  | Topiramate     | WMD -15.5 (-19.4 to -11.7, N=142)<br>SMD -0.96 (-1.89 to -0.03, N=142)<br>Moderate SOE   | Insufficient SOE                                   | Insufficient SOE       |
| Anti-psychotic   | Olanzapine     | WMD -12.1 (-23.3 to -0.97, N=19)<br>SMD -0.14 (-1.80, 1.53, N=34)<br>Insufficient SOE    | Insufficient SOE                                   | Insufficient SOE       |
| Anti-psychotic   | Risperidone    | WMD -4.60 (-9.0 to -0.2, N=419)<br>SMD -0.26 (-0.52 to -0.00, N=419)<br>Low SOE          | Insufficient SOE                                   | Insufficient SOE       |
| Benzo-diazepines | All            | Insufficient SOE   | Insufficient SOE                                   | Insufficient SOE       |
| SNRI             | Desvenlafaxine | Insufficient SOE   | Insufficient SOE                                   | Insufficient SOE       |
| SNRI             | Duloxetine     | Insufficient SOE   | Insufficient SOE                                   | Insufficient SOE       |
| SNRI             | Venlafaxine ER | WMD -7.2 (-11.0 to -3.3, N=687)<br>SMD -0.28 (-0.43 to -0.13, N=687)<br>Moderate SOE     | 0.12 (95% CI, 0.05 to 0.19); NNT 9<br>Moderate SOE | Insufficient SOE       |
| SSRI             | Citalopram     | WMD +7.98 (-10.1 to 26.0, N=35)<br>SMD +0.34 (-0.40, 1.08, N=35)<br>Insufficient SOE     | Insufficient SOE                                   | Insufficient SOE       |
| SSRI             | Fluoxetine     | WMD -6.97 (-10.4 to -3.5, N=835)<br>SMD -0.31 (-0.44 to -0.17, N=889)<br>Moderate SOE    | Insufficient SOE                                   | Insufficient SOE       |

**Table 22. Summary of efficacy and strength of evidence of pharmacologic treatments for adults with PTSD, by drug class (continued)**

| Medication Class | Medication  | PTSD Symptoms <sup>a</sup>   | Remission (No Longer Having Symptoms) <sup>b</sup> | Loss of PTSD Diagnosis |
|------------------|-------------|--|--|------------------------|
| SSRI             | Paroxetine  | WMD -12.6 (-15.7 to -9.5, N=886)<br>SMD -0.49 (-0.61 to -0.37, N=886),<br>Moderate SOE | 0.129 (p=0.008); NNT 8<br>Moderate SOE             | Insufficient SOE       |
| SSRI             | Sertraline  | WMD -4.9 (-7.4 to -2.4, N=1085)<br>SMD -0.25 (-0.42 to -0.07, N=1155)<br>Moderate SOE  | Insufficient SOE                                   | Insufficient SOE       |
| TCA              | All         | Insufficient SOE   | Insufficient SOE                                   | Insufficient SOE       |
| Other SGA        | Bupropion   | WMD +4.7 (NR, N=30)<br>SMD 0.23 (-0.55 to 1.00, N=30)<br>Insufficient SOE              | Insufficient SOE                                   | Insufficient SOE       |
| Other SGA        | Mirtazapine | WMD -9.5 (NR, p=NS, N=29)<br>SMD -0.27 (-1.08 to 0.54, N=29)<br>Insufficient SOE       | Insufficient SOE                                   | Insufficient SOE       |
| Other SGA        | Nefazodone  | Insufficient SOE   | Insufficient SOE                                   | Insufficient SOE       |
| Other SGA        | Trazodone   | Insufficient SOE   | Insufficient SOE                                   | Insufficient SOE       |

CAPS = Clinician-Administered PTSD Scale; CI = confidence interval; N = number of subjects; NNT = number needed to treat; NR = not reported; NS = not statistically significant; PTSD = posttraumatic stress disorder; SGA = second-generation antidepressant; SMD = standardized mean difference; SNRI = serotonin and norepinephrine reuptake inhibitors; SOE = strength of evidence; SSRI = selective serotonin reuptake inhibitors; TCA = tricyclic antidepressant; WMD = weighted mean difference  
<sup>a</sup>WMD data are mean change from baseline (95% CI, 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.<sup>40</sup> SMD data are Cohen's d effect sizes. A small effect size is d=0.20, a medium effect size is d=0.50, and a large effect size is d=0.80.<sup>43</sup>

<sup>b</sup>Data are risk difference for medication compared with placebo.

## Key Points: Overall—Comparative Effectiveness

- Very few head-to-head trials were identified.
  - One four-arm trial enrolling veterans with comorbid alcohol dependence compared **desipramine with paroxetine** (N=88) and found similar reduction in PTSD symptoms (CAPS, mean change from baseline from -33.2 to -36.4) and depression symptoms, but found greater improvement in alcohol use outcomes for those treated with desipramine than those treated with paroxetine (low SOE).<sup>132</sup>
  - Evidence from one large, multicenter (59 sites) trial comparing **venlafaxine ER, sertraline**, and placebo (N=538) found no statistically significant difference between venlafaxine and sertraline (moderate SOE).<sup>133</sup>
- Our network meta-analysis of 28 trials (4,817 subjects) found paroxetine and topiramate to yield greater improvement in PTSD symptoms than most other medications (low SOE; primarily based on indirect evidence).
  - When compared with other medications with moderate SOE supporting efficacy, paroxetine was more effective than sertraline (weighted mean difference [WMD], -7.6; 95% credible interval [CrI], -12 to -2.8), but was not significantly different from fluoxetine, topiramate, or venlafaxine (low SOE).
  - When compared with other 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 Points: Alpha Blockers

- Evidence was insufficient to determine efficacy of **prazosin** for improving outcomes for adults with PTSD. Improvement in PTSD symptoms was greater for subjects treated with prazosin than for those who received placebo, but the difference did not reach statistical significance and findings were imprecise (CAPS mean change from baseline compared with placebo, WMD, -8.86; 95% CI, -22.06 to 4.33; standardized mean difference [SMD], -0.40; 95% CI, -0.97 to 0.16, two trials, N=50).

## Key Points: Anticonvulsants

- Consistent, direct, fairly precise evidence from three trials supported the efficacy of **topiramate** for reduction of PTSD symptoms (CAPS mean change from baseline compared with placebo, WMD, -15.53; 95% CI, -19.40 to -11.65; SMD -0.96; 95% CI -1.89 to -0.03; N=142, moderate SOE). Evidence was insufficient to determine the efficacy of topiramate for improving other outcomes for adults with PTSD.
- Evidence was insufficient to determine the efficacy of **divalproex, lamotrigine, or tiagabine**. Consistency is unknown (with either zero or one trials contributing data for each medication) and findings were imprecise.

## Key Points: Atypical Antipsychotics

- Evidence from two small trials (total N=34) was insufficient to determine whether **olanzapine** is efficacious for improving PTSD symptoms, inducing remission, or for improving other outcomes for adults with PTSD.
- Existing evidence suggested that **risperidone** has little or no clinically significant benefit for reduction of PTSD symptoms on average (CAPS mean change from baseline compared with placebo: WMD, -4.60; 95% CI, -9.01 to -0.20; SMD, -0.26; 95% CI, -0.52 to -0.00, four trials, N=419, low SOE). Although subjects treated with risperidone had a statistically significant reduction in PTSD symptoms compared with those receiving placebo, trials had medium risk of bias, the magnitude of difference was small and likely not clinically significant, and findings were imprecise.

## Key Points: Benzodiazepines

- No studies with low or medium risk of bias (insufficient SOE).

## Key Points: Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs)

- Consistent, direct, precise evidence supports the efficacy of **venlafaxine ER** for improving PTSD symptoms (CAPS mean change from baseline: WMD, -7.2; 95% CI, -11.0 to -3.3; two trials, N=687), inducing remission (risk difference 0.12; 95% CI, 0.05 to 0.19; NNT 9), improving quality of life, and improving disability or functional impairment (moderate SOE).
- No trials that assessed **desvenlafaxine** or **duloxetine** (insufficient SOE).

## Key Points: Selective Serotonin Reuptake Inhibitors (SSRIs)

- Evidence was insufficient to determine the efficacy of **citalopram**.
- **PTSD symptoms**: consistent, direct, and precise evidence from trials supports the efficacy of **fluoxetine, paroxetine, and sertraline** for improving PTSD symptoms (moderate SOE). The magnitude of benefit is in the small to medium range—CAPS mean change from baseline compared with placebo from -4.9 (95% CI, -7.4 to -2.4; seven trials, N=1,085) for sertraline to -12.6 (95% CI, -15.7 to -9.5; two trials, N=886) for paroxetine (Cohen's d from -0.25 to -0.49).
- **Remission (no longer having symptoms)**: consistent, direct, precise information from two trials (N=346) supports the efficacy of **paroxetine** for achieving remission—best evidence found 12.9 percent more subjects treated with paroxetine than with placebo achieved remission,<sup>134</sup> NNT 8 (moderate SOE). Evidence was insufficient to determine the efficacy of **fluoxetine** or **sertraline** for achieving remission because of unknown consistency and imprecision.
- **Depression symptoms**: both **fluoxetine** and **paroxetine** improve depression symptoms for adults with PTSD (moderate SOE). Evidence for **sertraline** does not support its efficacy for improving depression symptoms for adults with PTSD (low SOE).
- **Anxiety symptoms**: greater improvement in anxiety symptoms for subjects treated with **fluoxetine** than for subjects who received placebo (moderate SOE). Evidence was insufficient to determine the efficacy of **paroxetine** (no trials reported) or **sertraline** (two trials, N=377, with inconsistent and imprecise findings).
- **Disability or functional impairment**: insufficient evidence to determine the efficacy of **fluoxetine** and **sertraline**. For **paroxetine**, consistent, direct, and precise findings support its efficacy (mean change from baseline in the Sheehan Disability Scale (SDS): WMD, -2.3; 95% CI, -3.3 to -1.4; two trials, N=886, moderate SOE).
- **Achieving loss of PTSD diagnosis, improving quality of life, or return to work or active duty**: evidence was insufficient for all SSRIs.

## Key Points: Tricyclic Antidepressants (TCAs)

- Insufficient SOE to determine efficacy. We found no studies with low or medium risk of bias.

## Key Points: Other Second-Generation Antidepressants

- Insufficient SOE to determine efficacy of **bupropion, mirtazapine, nefazodone, or trazodone**.

## Detailed Synthesis: Placebo-Controlled Trials of Alpha-Blockers

### Characteristics of Trials

We found two studies that met our inclusion criteria for this section (Table 23). Both trials were conducted within VA Medical Centers in the United States and compared prazosin with placebo. Both enrolled subjects with moderate to severe PTSD. Both enrolled all or a large majority of male subjects; average age was similar (53 to 56 years). Trial durations were 20 weeks<sup>135</sup> and 8 weeks.<sup>136</sup> Further details describing the included trials are provided in Appendix D.

**Table 23. Characteristics of included placebo-controlled trials of alpha-blockers**

| Study                               | Arm Dose mg/day (N)                       | Duration (Weeks) | Population Trauma Type                   | Baseline PTSD Severity <sup>a</sup> | Mean Age (Y) | % F | % Non-white | Risk of Bias |
|-------------------------------------|---|------------------|--|-------------------------------------|--------------|-----|-------------|--------------|
| Raskind et al., 2003 <sup>135</sup> | Prazosin (2 to 10mg) (5)<br>Placebo (5)   | 20               | Male<br>Combat<br>veterans               | 79.1<br>to 83.6                     | 53           | 0   | NR          | Medium       |
| Raskind et al., 2007 <sup>136</sup> | Prazosin (2 to 15mg) (20)<br>Placebo (20) | 8                | Male and<br>female<br>Combat<br>veterans | 70.0                                | 56           | 5   | 35          | Medium       |

CAPS = Clinician Administered PTSD Scale; F = female; mg = milligram; N = total number randomized/assigned to intervention and control groups; NR = not reported; PTSD = posttraumatic stress disorder; y = year

<sup>a</sup>Data reported are mean CAPS or range of mean CAPS scores across groups unless otherwise specified.

Note: When mean data for baseline PTSD severity were not reported for the total sample but were presented for each study arm, we provide the range across arms.

## Results for Placebo-Controlled Trials of Alpha-Blockers

### PTSD Symptom Reduction

Both trials reported numerically greater improvements in CAPS for subjects treated with prazosin than for those receiving placebo.<sup>135,136</sup> Similarly, our meta-analyses found greater improvement in PTSD symptoms for subjects treated with prazosin, but the difference did not reach statistical significance and findings were imprecise (mean reduction in CAPS: WMD, -8.86, 95% CI, -22.06 to 4.33; SMD -0.40, 95% CI, -0.97 to 0.16, two trials, N=50, Appendix F). Overall, the evidence from two trials was insufficient to determine efficacy of prazosin for improving outcomes for adults with PTSD, primarily because of imprecision.

### Prevention or Reduction of Comorbid Medical or Psychiatric Conditions

One of the included studies (N=40) reported the Hamilton Depression Scale (HAM-D) to assess depression.<sup>136</sup> The study found that patients treated with prazosin had a greater reduction in depression symptoms than those administered placebo, but the difference between groups was not statistically significant (-5.6 vs. -0.6,  $p = 0.08$ ). We concluded that evidence is insufficient for determining whether prazosin is effective for improving depression symptoms for adults with PTSD; consistency is unknown (single study) and findings were imprecise.

## Detailed Synthesis: Placebo-Controlled Trials of Anticonvulsants/Mood Stabilizers

### Characteristics of Trials

Table 24 summarizes the five trials that met inclusion criteria. Further details are provided in Appendix D. The trials enrolled subjects with moderate to severe PTSD. Three were conducted in the United States; one in Iran;<sup>137</sup> and one in Brazil.<sup>138</sup> Sample sizes ranged from 35 to 232. Treatment duration ranged from 8 to 12 weeks. Two of the included studies focus on combat-related PTSD;<sup>137,139</sup> three enrolled a heterogeneous group of subjects with a variety of index trauma types (e.g., physical and sexual assault/violence, witnessing harm or death, combat, natural disaster, childhood sexual abuse, childhood physical abuse, motor vehicle accident).<sup>138,140,141</sup> The trials generally recruited middle-aged adults, with mean ages ranging from ~40 to ~55 years. Three trials enrolled at least two-thirds female subjects;<sup>138,140,141</sup> two

enrolled all or nearly all males. The primary outcome for all five trials was some version of the CAPS.

**Table 24. Characteristics of included placebo-controlled trials of anticonvulsants, by drug**

| Study                                  | Arm Dose mg/day (N)                            | Duration (Weeks) | Population Trauma Type             | Baseline PTSD Severity <sup>a</sup> | Mean Age (Y) | % F | % Non-white | Risk of Bias |
|--|--|------------------|------------------------------------|-------------------------------------|--------------|-----|-------------|--------------|
| Davis et al., 2008 <sup>139</sup>      | Divalproex (1000 to 3000) (44)<br>Placebo (41) | 8                | Male and female<br>Combat veterans | 75.2 to 77.3                        | 55           | 2   | NR          | Low          |
| Davidson et al., 2007 <sup>140</sup>   | Tiagabine (4 to 16) (116)<br>Placebo (116)     | 12               | Male and female<br>Mixed           | 82.6                                | 42.6         | 66  | NR          | Medium       |
| Akuchekian et al., 2004 <sup>137</sup> | Topiramate (12.5 to 500) (34)<br>Placebo (33)  | 12               | Male<br>Combat veterans            | 49.8                                | 40           | 0   | 100         | Medium       |
| Tucker et al., 2007 <sup>141</sup>     | Topiramate (25 to 400) (20)<br>Placebo (20)    | 12               | Male and female<br>Mixed           | 88.3 to 91.1                        | 41           | 79  | 11          | Medium       |
| Yeh et al., 2011 <sup>138</sup>        | Topiramate (25 to 200) (17)<br>Placebo (18)    | 12               | Male and female<br>Mixed           | 66.1 to 78.8                        | 40           | 68  | NR          | Medium       |

CAPS = Clinician Administered PTSD Scale; F = female; mg = milligram; N = total number randomized/assigned to intervention and control groups; NR = not reported; PTSD = posttraumatic stress disorder; y = year

<sup>a</sup>Data reported are mean CAPS or range of mean CAPS scores across groups unless otherwise specified.

We rated three trials otherwise meeting criteria for this section as high risk of bias (Table 25). We excluded them from our main data synthesis, and used them only in sensitivity analyses. Appendix E provides additional rationale for risk of bias assessments. Briefly, the trials deemed high risk of bias only analyzed subjects who completed treatment (did not use an intention-to-treat analysis) or had very high attrition or differential attrition rates.

**Table 25. Characteristics of placebo-controlled trials of anticonvulsants excluded because of risk of bias**

| Study                                 | Arm Dose mg/day (N)                          | Duration (Weeks) | Population Trauma Type   | Baseline PTSD Severity <sup>a</sup> | Mean Age (Y) | % F | % Non-white | Risk of Bias |
|---------------------------------------|--|------------------|--------------------------|-------------------------------------|--------------|-----|-------------|--------------|
| Hamner et al., 2009 <sup>142</sup>    | Divalproex <sup>b</sup> (16)<br>Placebo (13) | 10               | Male and female<br>Mixed | 77.1                                | 52           | 4   | 7           | High         |
| Hertzberg et al., 1999 <sup>143</sup> | Lamotrigine (25 to 500) (11)<br>Placebo (4)  | 12               | Male and female<br>Mixed | SI-PTSD<br>44.3                     | 43           | 36  | 71          | High         |
| Lindley et al., 2007 <sup>144</sup>   | Topiramate (50 to 200) (20)<br>Placebo (20)  | 7                | Male<br>Combat veterans  | 61.6                                | 53           | 0   | 37.5        | High         |

CAPS = Clinician Administered PTSD Scale; F = female; mg = milligram; N = total number randomized/assigned to intervention and control groups; NR = not reported; PTSD = posttraumatic stress disorder; SI-PTSD = Structured Interview for PTSD; y = year

<sup>a</sup>Data reported are mean CAPS or range of mean CAPS scores across groups unless otherwise specified.

<sup>b</sup>Dose not reported; serum trough between 50-125 mcg/ml.

## Results of Placebo-Controlled Trials of Anticonvulsants/Mood Stabilizers

### PTSD Symptom Reduction

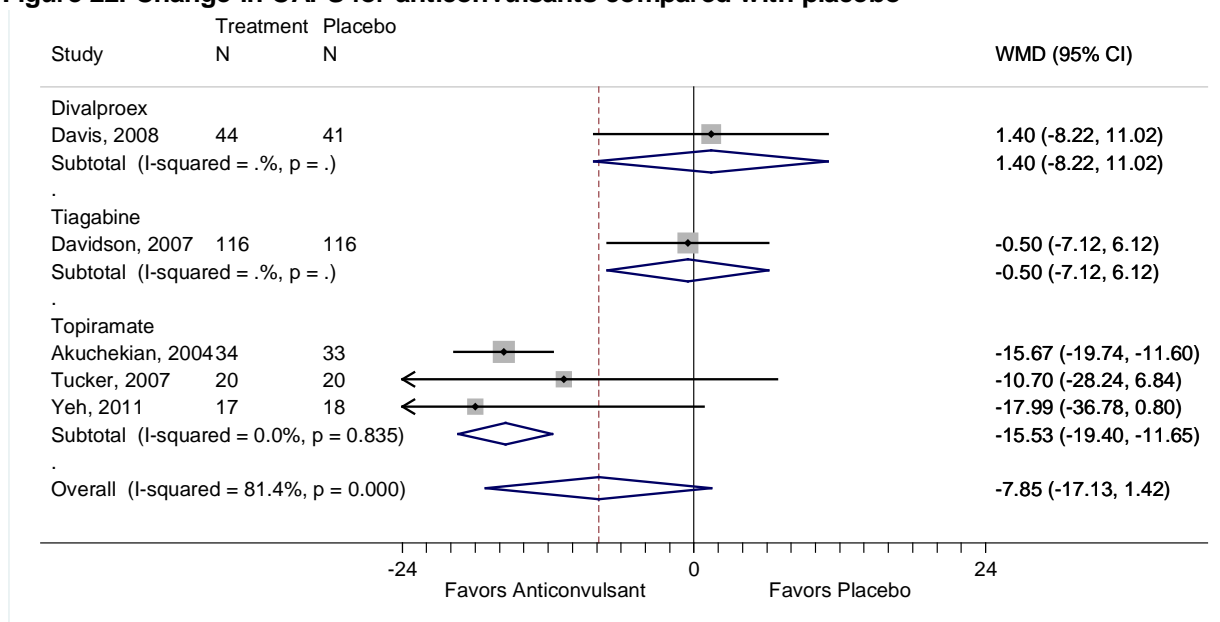
All five of the included studies reported CAPS. Our meta-analyses (Figure 22 and Appendix F) found topiramate to improve PTSD symptoms more than placebo (WMD, -15.53; SMD, -0.96; 95% CI, -1.89 to -0.03). A sensitivity analysis adding the topiramate trial rated high risk of bias<sup>144</sup> did not significantly change the results (WMD, -15.29; 95% CI, -19.00 to -11.57; I<sup>2</sup> 0%, four trials, N=182, Appendix F). Overall, we concluded that evidence of moderate strength supports the efficacy of topiramate for reducing PTSD symptoms; evidence was consistent, direct, and fairly precise.

Evidence was insufficient to determine the efficacy of divalproex or tiagabine for improvement in PTSD symptoms. Consistency is unknown (with just one study contributing data for each medication) and findings were imprecise.

Three studies, one each for divalproex, tiagabine, and topiramate, reported data from the Treatment Outcome PTSD scale (TOP-8) as an additional measure of PTSD symptoms. The studies examining tiagabine and divalproex did not find a difference between those receiving medication and those receiving placebo. The study of tiagabine simply stated that the reduction in TOP-8 score was not significant compared to baseline.<sup>140</sup> The study of divalproex reported a TOP-8 mean change from baseline of -4.0 for those receiving divalproex and -3.9 for those receiving placebo (p=NS).<sup>139</sup>

The only study of topiramate reporting TOP-8 found greater improvement in symptoms for those receiving topiramate than for those receiving placebo (mean percentage change from baseline: -67.9 vs. -41.6, p=0.023).<sup>141</sup>

**Figure 22. Change in CAPS for anticonvulsants compared with placebo**



Note: Timing of outcome assessment: 8 weeks (Davis, 2008),<sup>139</sup> 12 weeks (Davidson, 2007;<sup>140</sup> Akuchekian, 2004;<sup>137</sup> Tucker, 2007;<sup>141</sup> Yeh, 2011<sup>138</sup>).

## **Remission (No Longer Having Symptoms)**

Two studies reported PTSD remission rates; one study of tiagabine<sup>140</sup> and one of topiramate.<sup>141</sup> Both of the studies defined remission as a CAPS score less than 20. Neither study found a statistically significant difference between anticonvulsants and placebo. The former (N=232) reported similar remission rates for tiagabine and placebo (16% vs. 14%,  $p=0.88$ ). The latter (N=40) reported higher remission rates for those treated with topiramate than those who received placebo, although the difference was not statistically significant (42% vs. 21%,  $p=0.295$ ). Overall, evidence was insufficient to determine the efficacy of either tiagabine or topiramate for inducing remission, largely due to unknown consistency (with just one study contributing data for each medication) and imprecision.

## **Prevention or Reduction of Comorbid Medical or Psychiatric Conditions**

Three studies reported depression symptoms—one assessed divalproex<sup>139</sup> and two assessed topiramate.<sup>138,141</sup> All three used different outcome measures. None of the studies reported statistically significant reductions in depression for an anticonvulsant compared with placebo, although all point estimates favored anticonvulsants. The trial comparing divalproex with placebo (N=85) reported no significant difference for mean improvement in Montgomery-Asberg Depression Rating Scale (MADRS) scores (-5.1 vs. -4.5).<sup>139</sup> One trial of topiramate (N=40) reported no significant difference between topiramate and placebo for HAM-D score (mean percentage change from baseline: -50.7 vs. -33.3,  $p=0.25$ );<sup>141</sup> the other (N=35) found no significant difference between topiramate and placebo for Beck Depression Inventory (BDI) score (mean change from baseline: -8.5 vs. -3.9,  $p=0.72$ ).<sup>138</sup>

Overall, evidence is insufficient to determine the efficacy of any of the anticonvulsants for reducing depression symptoms; just one study reported each outcome measure (MADRS, HAM-D, and BDI), consistency is unknown, and results were imprecise.

Two trials reported on anxiety. Both used the Hamilton Anxiety Scale (HAM-A), and neither found statistically significant reductions in anxiety. The first (N=85) reported similar changes for divalproex and placebo (mean change from baseline: -15.1 vs. -16.5,  $p = NS$ ).<sup>139</sup> The other (N=40) found no statistically significant difference between topiramate and placebo (mean percentage change from baseline: -53.9 and -40.0, with  $p=0.33$ ).<sup>141</sup> Overall, evidence is insufficient to determine the efficacy of any of the anticonvulsants for preventing or reducing anxiety. Consistency is unknown (one trial each for divalproex and topiramate) and findings were imprecise.

## **Disability or Functional Impairment**

Two studies, one of tiagabine (N=232) and one of topiramate (N=40), reported the SDS.<sup>140,141</sup> Both trials reported similar changes between subjects treated with medication and those treated with placebo (see Appendix D for details). Overall, evidence is insufficient to determine the efficacy of any of the anticonvulsants for improving disability or functional impairment. Consistency is unknown (one trial each for tiagabine and topiramate) and findings were imprecise.



# Detailed Synthesis: Placebo-Controlled Trials of Atypical Antipsychotics

## Characteristics of Trials

Table 26 summarizes the characteristics of the seven trials meeting our inclusion criteria. Further details describing the included trials are provided in Appendix D.

**Table 26. Characteristics of included placebo-controlled trials of atypical antipsychotics, by drug**

| Study                                   | Arm Dose mg/day (N)                         | Duration (Weeks) | Population Trauma Type    | Baseline PTSD Severity <sup>a</sup> | Mean Age (Y) | % F | % Non-white | Risk of Bias |
|---|---|------------------|---------------------------|-------------------------------------|--------------|-----|-------------|--------------|
| Butterfield et al., 2001 <sup>145</sup> | Olanzapine (5 to 20) (10)<br>Placebo (5)    | 10               | Male and female<br>Mixed  | SIP<br>39.7 to 45.9                 | 43           | 93  | 46          | Medium       |
| Stein et al., 2002 <sup>146</sup>       | Olanzapine (10 to 20) (10)<br>Placebo (9)   | 8                | Male<br>Combat veterans   | 84.0 to 86.1                        | 52           | 0   | NR          | Medium       |
| Bartzokis et al., 2005 <sup>147</sup>   | Risperidone (1 to 3) (33)<br>Placebo (32)   | 16               | Male<br>Combat veterans   | 98.6 to 102.2                       | 52           | 0   | 32          | Medium       |
| Hamner et al., 2003 <sup>148</sup>      | Risperidone (1 to 6) (20)<br>Placebo (20)   | 5                | Male<br>Combat veterans   | 89.1 to 90.3                        | 52           | 0   | 54          | Medium       |
| Krystal et al., 2011 <sup>149</sup>     | Risperidone (1 to 4) (147)<br>Placebo (149) | 24               | Male and female<br>Combat | 78.2                                | 54           | 3   | 34          | Low          |
| Monnelly et al., 2003 <sup>150</sup>    | Risperidone (0.5 to 2)(8)<br>Placebo (8)    | 6                | Male<br>Combat veterans   | PCL-M<br>72 to 73                   | 51           | 0   | 20          | Medium       |
| Reich et al., 2004 <sup>151</sup>       | Risperidone (0.5 to 8) (12)<br>Placebo (9)  | 8                | Female<br>Childhood abuse | 65.5 to 73.9                        | 28           | 100 | 14          | Medium       |

CAPS = Clinician Administered PTSD Scale; F = female; mg = milligram; N = total number randomized/assigned to intervention and control groups; NR = not reported; PCL-M = PTSD Checklist – Military Version; PTSD = posttraumatic stress disorder; TOP-8 = Treatment Outcome PTSD Scale; y = year

<sup>a</sup>Data reported are mean CAPS or range of mean CAPS scores across groups unless otherwise specified.

Note: When mean data for baseline PTSD severity, sex, or race were not reported for the total sample but were presented for each study arm, we provide the range across arms.

Most of the trials compared risperidone with placebo. Two compared olanzapine with placebo. All included trials were conducted in the United States. Sample sizes ranged from 15 to 65. Duration of treatment ranged from 5 weeks to 6 months. Most trials enrolled a majority of males with combat-related trauma;<sup>146-150</sup> one enrolled females with childhood abuse-related trauma;<sup>151</sup> and one enrolled males and females with mixed types of trauma, 53 percent of which had rape as the index trauma.<sup>145</sup> One trial exclusively enrolled subjects with PTSD and concurrent psychotic features.<sup>148</sup> Subjects with a history of schizophrenia, bipolar disorder, or recent substance abuse/dependence were frequently excluded.<sup>145,148,150,151</sup> The majority of trials permitted cointerventions. Three trials permitted continuation of antidepressants and anxiolytics as long as doses were stable prior to enrollment;<sup>148,150,151</sup> one also allowed the continuation of lithium and carbamazepine in one subject.<sup>148</sup> One trial required all subjects to be nonresponsive to 12 weeks of SSRI therapy (4 weeks at optimal doses) and subjects continued on their SSRI during the trial.<sup>146</sup> One trial required intolerance, nonresponse, or inadequate response to antidepressants prior to enrollment, but allowed patients to take any medications deemed

appropriate during the trial (including adrenergic drugs, antidepressants, anxiolytics, and mood stabilizers).<sup>149</sup> Two trials did not address use of cointerventions.<sup>145,147</sup> Mean age was similar across most trials, generally ranging from 43 to 54. Mean age in one trial was slightly lower, at 27.<sup>151</sup> Two trials enrolled a majority of females, 93 to 100 percent.<sup>145,151</sup>

The primary outcome for most trials was some version of the CAPS (CAPS total, CAPS-1, CAPS-2).<sup>145-149,151</sup> The primary outcomes in one trial were reduction in irritability using the Overt Aggression Scale-Modified for Outpatients (OAS-M) and PTSD symptoms using the PTSD Checklist – Military Version (PCL-M).<sup>150</sup>

We rated two trials<sup>152,153</sup> otherwise meeting criteria for this section as rated high risk of bias (Table 27). We excluded them from our main data synthesis and used them only in sensitivity analyses.

**Table 27. Characteristics of placebo-controlled trials of atypical antipsychotics excluded from main analyses because of high risk of bias**

| Study                                | Arm dose mg/day (N)                                     | Duration (weeks) | Population Trauma Type   | Baseline PTSD Severity <sup>a</sup> | Mean Age (Y) | % F | % Non-white | Risk of Bias |
|--------------------------------------|---|------------------|--------------------------|-------------------------------------|--------------|-----|-------------|--------------|
| Padala et al., 2006 <sup>153</sup>   | Risperidone (0.5 to 8) (11)<br>Placebo (9)              | 12               | Female<br>Mixed          | 79.3 to 80.6                        | 41           | 100 | 30          | High         |
| Rothbaum et al., 2008 <sup>152</sup> | Risperidone (0.5 to 3) (9)<br>Placebo (11) <sup>b</sup> | 16               | Male and female<br>Mixed | 56 to 60                            | 34           | 80  | 30          | High         |

CAPS = Clinician Administered PTSD Scale; F = female; mg = milligram; N = total number randomized/assigned to intervention and control groups; NR = not reported; PTSD = posttraumatic stress disorder; y = year

<sup>a</sup>Data reported are mean CAPS or range of mean CAPS scores across groups unless another instrument is specified.

<sup>b</sup>This study did not report the number randomized in each group. Overall 25 were randomized; the n reported is the number of participants analyzed in each group.

## Results of Placebo-Controlled Trials of Atypical Antipsychotics

### PTSD Symptom Reduction

For olanzapine, one trial<sup>146</sup> (N=19) found some benefit for reduction of PTSD symptoms as measured by CAPS compared with placebo (-14.8 vs. -2.67, p<0.05). Another trial<sup>145</sup> (N=15) found no statistically significant difference between olanzapine and placebo on three different measures of PTSD symptoms: Davidson Trauma Scale (-34.2 vs. -39.8, p=NR), Treatment Outcome PTSD Scale (-6.7 vs. -11.3, p=NR), and Short Post-Traumatic Stress Disorder Rating Interview (-13.6 vs. -14.3, p=NR).<sup>145</sup> Overall, evidence from these two trials (total N=34) was insufficient to determine whether olanzapine is efficacious for improving PTSD symptoms; consistency is unknown (with just one trial reporting each outcome) and findings were imprecise. Our meta-analysis found no statistically significant difference between olanzapine and placebo for PTSD symptom reduction (SMD, -0.14; 95% CI, -1.80 to 1.53; N=34; Appendix F).

For risperidone, four trials assessed PTSD symptom reduction. Our meta-analysis found a statistically significant reduction in PTSD symptoms compared with placebo, as measured by improvement in CAPS (four trials, N=419; WMD, -4.60; 95% CI, -9.01 to -0.20; I<sup>2</sup> 22.3%; SMD, -0.26; 95% CI, -0.52 to -0.00; Appendix F). Although the finding was statistically significant, the magnitude of difference was small and it is unclear whether it is clinically significant. Some suggest that a reduction of 15 points on the CAPS constitutes a clinically significant reduction.<sup>40</sup> However, the value representing a clinically significant reduction has not been validated and is somewhat uncertain. Our sensitivity analysis (adding high risk of bias

trials) found a similar, but slightly reduced magnitude of difference, but the difference was no longer statistically significant. (five trials, N=444; WMD,-4.00, 95% CI, -8.48 to 0.49; I<sup>2</sup> 23.1%; Appendix F).

One trial (N=16) found a statistically significant change in the PCL-M for risperidone compared to placebo (-10.0 vs. -0.50, p=0.02).<sup>150</sup>

Overall, evidence suggests little or no clinically significant benefit for reducing PTSD symptoms for risperidone (low SOE). Although subjects treated with risperidone had a greater reduction in PTSD symptoms than those who received placebo that was statistically significant, the magnitude of difference was small (-4.60 points on CAPS) and possibly not clinically significant.

## **Prevention or Reduction of Comorbid Medical or Psychiatric Conditions**

For olanzapine, one trial (N=19) found a greater reduction of depression symptoms than for placebo measured by the change in the Center for Epidemiologic Studies Depression Scale (-5.25 vs. -4.88, p<0.03).<sup>146</sup> Overall, evidence from this trial was insufficient to determine whether olanzapine is efficacious for improving depression symptoms.

For risperidone compared with placebo, two trials assessed reduction of coexisting psychiatric conditions.<sup>147,148</sup> One assessed depression symptoms and anxiety symptoms;<sup>147</sup> the other assessed psychosis.<sup>148</sup>

The first trial (N=65) did not find a statistically significant reduction in depression symptoms as measured by the HAM-D (-3.7 vs. -1.4, p>0.05). However, it did report greater reduction in anxiety for those treated with risperidone than for those treated with placebo using the HAM-A (-7.4 vs. -2.0, p<0.001).<sup>147</sup> The other trial (N=40) examined the effect of risperidone compared with placebo on psychosis. All patients included in the trial had current psychotic features and had a baseline score of ≥60 on the total Positive and Negative Syndrome Scale for psychosis (PANSS). The trial found greater reduction in psychosis for subjects treated with risperidone than for those treated with placebo (-10.0 vs. -2.3, p≤0.05).<sup>148</sup>

Overall, evidence from two trials (total N=105) was insufficient to determine whether risperidone is efficacious for improving coexisting psychiatric conditions. Individual trials had medium risk of bias, consistency is unknown (one trial contributing data for each outcome), and findings were imprecise.

## **Disability or Functional Impairment**

One trial (N=15) found no difference in disability, as measured by the SDS, between olanzapine and placebo (-7.7 vs. -8.0, p>0.05).<sup>145</sup> Evidence is insufficient to determine whether olanzapine is efficacious for reducing disability in patients with PTSD.

## **Detailed Synthesis: Placebo-Controlled Trials of Benzodiazepines**

### **Characteristics of Trials**

We found no studies with low or medium risk of bias meeting our inclusion criteria. We identified one trial otherwise meeting criteria for this section that we rated as high risk of bias (Table 28). Thus, we did not include it in our main our data synthesis.<sup>154</sup> The identified study was a 12-week randomized, double-blind crossover trial of alprazolam and placebo (N=16). The study was conducted in Israel and enrolled a heterogeneous group of subjects with a variety of index trauma types (e.g., military combat stress, industrial accident, automobile accident,

terrorist bomb in bus). Appendix E provides additional rationale for risk of bias assessments. Briefly, the trial had high attrition, high risk of measurement bias, and high risk of selection bias. In addition, it did not report information needed to determine comparability of treatment groups.

**Table 28. Characteristics of placebo-controlled trials of benzodiazepines excluded from main analyses because of high risk of bias**

| Study                             | Arm Dose mg/day (N)                      | Duration (Weeks) | Population Trauma Type   | Baseline PTSD Severity  | Mean Age (Y) | % F | % Non-white | Risk of Bias |
|-----------------------------------|--|------------------|--------------------------|-------------------------|--------------|-----|-------------|--------------|
| Braun et al., 1990 <sup>154</sup> | Alprazolam (1.5 to 6) (7)<br>Placebo (9) | 12               | Male and female<br>Mixed | PTSD-Scale 30.0 to 30.9 | 38           | NR  | NR          | High         |

F = female; mg = milligram; N = total number randomized/assigned to intervention and control groups; NR = not reported; PTSD = posttraumatic stress disorder; PTSD-Scale = Posttraumatic Stress Disorder Scale; y = year

Note: When mean data for baseline PTSD severity were not reported for the total sample but were presented for each study arm, we provide the range across arms.

## PTSD Symptom Reduction, Remission, and Other Outcomes

With no low or medium risk of bias studies identified, evidence is insufficient to determine the efficacy of benzodiazepines for improving outcomes for adults with PTSD.

## Detailed Synthesis: Selective Serotonin Reuptake Inhibitors (SSRIs)

### Characteristics of Trials

Table 29 summarizes the characteristics of the 16 trials meeting our inclusion criteria. Further details describing the trials are provided in Appendix D.

**Table 29. Characteristics of included placebo-controlled trials of selective serotonin reuptake inhibitors, by drug**

| Study   | Arm Dose mg/day (N)   | Duration (Weeks) | Population Trauma Type                              | Baseline PTSD Severity <sup>a</sup> | Mean Age (Y) | % F | % Non-white | Risk of Bias |
|---|---|------------------|---|-------------------------------------|--------------|-----|-------------|--------------|
| Tucker et al., 2003 <sup>155</sup><br>Tucker et al., 2004 <sup>156</sup>        | Citalopram (20 to 50) (25)<br>Sertraline (50 to 200) (23)<br>Placebo (10) | 10               | Male and female<br>Mixed                            | 83.9 to 94.2                        | 39           | 74  | 14          | Medium       |
| Connor et al., 1999 <sup>157</sup><br>Meltzer-Brody et al., 2000 <sup>158</sup> | Fluoxetine (10 to 60) (27)<br>Placebo (27)                                | 12               | Male and female<br>Mixed                            | DTS 73.7 to 79.4                    | 37           | 91  | 7           | Medium       |
| Martenyi et al., 2002 <sup>159</sup> ,<br>Martenyi et al., 2006 <sup>160</sup>  | Fluoxetine (20 to 80) (226)<br>Placebo (75)                               | 12               | Male and female<br>Combat and victim/witness of war | 80.5 to 81.3                        | 38           | 19  | 9           | Medium       |
| Martenyi et al., 2007 <sup>161</sup>  | Fluoxetine (20) (163)<br>Fluoxetine (40) (160)<br>Placebo (88)            | 12               | Male and female<br>Mixed                            | 75 to 79                            | 41           | 72  | 23          | Medium       |
| van der Kolk et al., 1994 <sup>162</sup>  | Fluoxetine (20 to 60) (33)<br>Placebo (31)                                | 5                | Male and female<br>Mixed (48% combat)               | NR                                  | 40           | 34  | NR          | Medium       |
| van der Kolk et al., 2007 <sup>113</sup>  | Fluoxetine (30) (29)<br>EMDR (29)<br>Placebo (29)                         | 8 <sup>b</sup>   | Male and female<br>Mixed                            | 71.2                                | 36           | 83  | 33          | Medium       |

**Table 29. Characteristics of included placebo-controlled trials of selective serotonin reuptake inhibitors, by drug (continued)**

| Study                                | Arm Dose mg/day (N)   | Duration (Weeks) | Population Trauma Type  | Baseline PTSD Severity <sup>a</sup> | Mean Age (Y) | % F                     | % Non-white | Risk of Bias |
|--------------------------------------|---|------------------|---|-------------------------------------|--------------|-------------------------|-------------|--------------|
| Marshall et al., 2001 <sup>163</sup> | Paroxetine (20) (188)<br>Paroxetine (40) (187)<br>Placebo (188)   | 12               | Male and female<br>Mixed  | 74.3 to<br>75.3                     | 42           | NR<br>(~<br>2:1<br>F:M) | <10%        | Medium       |
| Simon et al., 2008 <sup>164</sup>    | Paroxetine (12.5 to 62.5)<br>(11)<br>Placebo (14)   | 10               | Male and female<br>Mixed (60% exposure<br>to war; combat % NR),<br>refractory to exposure | SPRINT<br>16.1 to 17                | 46           | 56                      | 26          | Medium       |
| Tucker et al., 2001 <sup>134</sup>   | Paroxetine (20 to 50)<br>(163)<br>Placebo (160)   | 12               | Male and female<br>Mixed  | 73.2 to<br>74.3                     | 41           | 66                      | 28          | Medium       |
| Brady et al., 2000 <sup>165</sup>    | Sertraline (25 to 200)<br>(94)<br>Placebo (93)  | 12               | Male and female<br>Mixed  | 75.1 to<br>76.6                     | 40           | 73                      | 16          | Medium       |
| Brady et al., 2005 <sup>166</sup>    | Sertraline (150) (49)<br>Placebo (45)   | 12               | Male and female<br>Mixed, alcohol<br>dependence   | 57.6 to<br>60.1                     | 37           | 46                      | NR          | Medium       |
| Davidson et al., 2001 <sup>167</sup> | Sertraline (25 to 200)<br>(100)<br>Placebo (108)  | 12               | Male and female<br>Mixed  | 73.5 to<br>73.9                     | 37           | 78                      | 17          | Medium       |
| Davidson et al., 2006 <sup>133</sup> | Total (538) <sup>c</sup> Venlafaxine<br>(37.5 to 375) (179)<br>Sertraline (25 to 200)<br>(173)<br>Placebo (179) | 12               | Male and female<br>Mixed  | ~82                                 | NR           | NR                      | NR          | Medium       |
| Friedman et al., 2007 <sup>168</sup> | Sertraline (25 to 200)<br>(86)<br>Placebo (83)  | 12               | Male and female<br>Mixed (71% combat)   | 72.1 to<br>73.8                     | 46           | 20                      | 71          | Medium       |
| Panahi et al., 2011 <sup>169</sup>   | Sertraline (50 to 200)<br>(35)<br>Placebo (35)  | 10               | Male<br>Combat  | IES-R<br>65.1 to<br>65.4            | 46           | 0                       | 100         | Medium       |
| Zohar et al., 2002 <sup>170</sup>    | Sertraline (50 to 200)<br>(23)<br>Placebo (19)  | 10               | Male and female<br>Israeli military<br>veterans   | 91.2 to<br>93.3                     | 40           | 12                      | NR          | Medium       |

CAPS = Clinician Administered PTSD Scale; DTS = Davidson Trauma Scale; EMDR = eye movement desensitization and reprocessing; F = female; mg = milligram; N = total number randomized/assigned to intervention and control groups; NR = not reported; PTSD = posttraumatic stress disorder; SPRINT = Short PTSD Rating Interview; y = year

<sup>a</sup>Data reported are mean CAPS or range of mean CAPS scores across groups unless otherwise specified.

<sup>b</sup>Study was 8 weeks of treatment, but also included a 6-month post-treatment followup.

<sup>c</sup>The Ns for each are the number analyzed; the number randomized to each group was not reported (overall N was 538; 531 were included in the analysis).

The vast majority were conducted in the United States; one in Israel;<sup>170</sup> one in Iran;<sup>169</sup> one in the United States and Canada;<sup>134</sup> and one in Europe, Israel, and South Africa.<sup>159</sup> Sample sizes ranged from 12 to 563. Duration of treatment ranged from 5 to 12 weeks. The majority of trials enrolled a heterogeneous group of subjects with a variety of index trauma types (e.g., sexual abuse, nonsexual abuse, combat, injury, motor vehicle accident, natural disaster); five trials enrolled a majority of subjects with combat-related PTSD;<sup>159,168-171</sup> one enrolled 60 percent exposed to war;<sup>164</sup> and one enrolled just under half of subjects with combat-related PTSD.<sup>162</sup> One study enrolled subjects with PTSD and coexisting alcohol dependence.<sup>166</sup> Mean age was very

similar across trials, ranging from 36 to 46. Nine trials enrolled two-thirds or more female subjects.<sup>113,134,155,157,161,163,165,167,172</sup>

The primary outcome for the majority of trials was some version of the CAPS (CAPS, CAPS-2, or CAPS-Sx); five trials identified other primary outcomes, including TOP-8,<sup>159,161</sup> DTS,<sup>171</sup> Duke Global Rating for PTSD,<sup>157</sup> IES,<sup>169</sup> or SPRINT.<sup>164</sup>

We rated two trials<sup>171,172</sup> otherwise meeting criteria for this section as high risk of bias (rationale in Appendix E) (Table 30). We excluded them from our main data synthesis and used them only for sensitivity analyses.

**Table 30. Characteristics of placebo-controlled trials of SSRIs excluded from main analyses because of high risk of bias**

| Study                                 | Arm Dose mg/day (N)                        | Duration (Weeks) | Population Trauma Type   | Baseline PTSD Severity <sup>a</sup> | Mean Age (Y) | % F | % Non-white | Risk of Bias |
|---------------------------------------|--|------------------|--------------------------|-------------------------------------|--------------|-----|-------------|--------------|
| Hertzberg et al., 2000 <sup>171</sup> | Fluoxetine (10 to 60) (6)<br>Placebo (6)   | 12               | Male<br>Combat veterans  | DTS<br>106 to 111                   | 46           | 0   | 58          | High         |
| Marshall et al., 2007 <sup>172</sup>  | Paroxetine (10 to 60) (25)<br>Placebo (27) | 10               | Male and female<br>Mixed | 82.8 to 84.2                        | 40           | 67  | 75          | High         |

CAPS = Clinician Administered PTSD Scale; DTS = Davidson Trauma Scale; F = female; mg = milligram; N = total number randomized/assigned to intervention and control groups; PTSD = posttraumatic stress disorder; y = year

<sup>a</sup>Data reported are mean CAPS or range of mean CAPS scores across groups unless another instrument is specified.

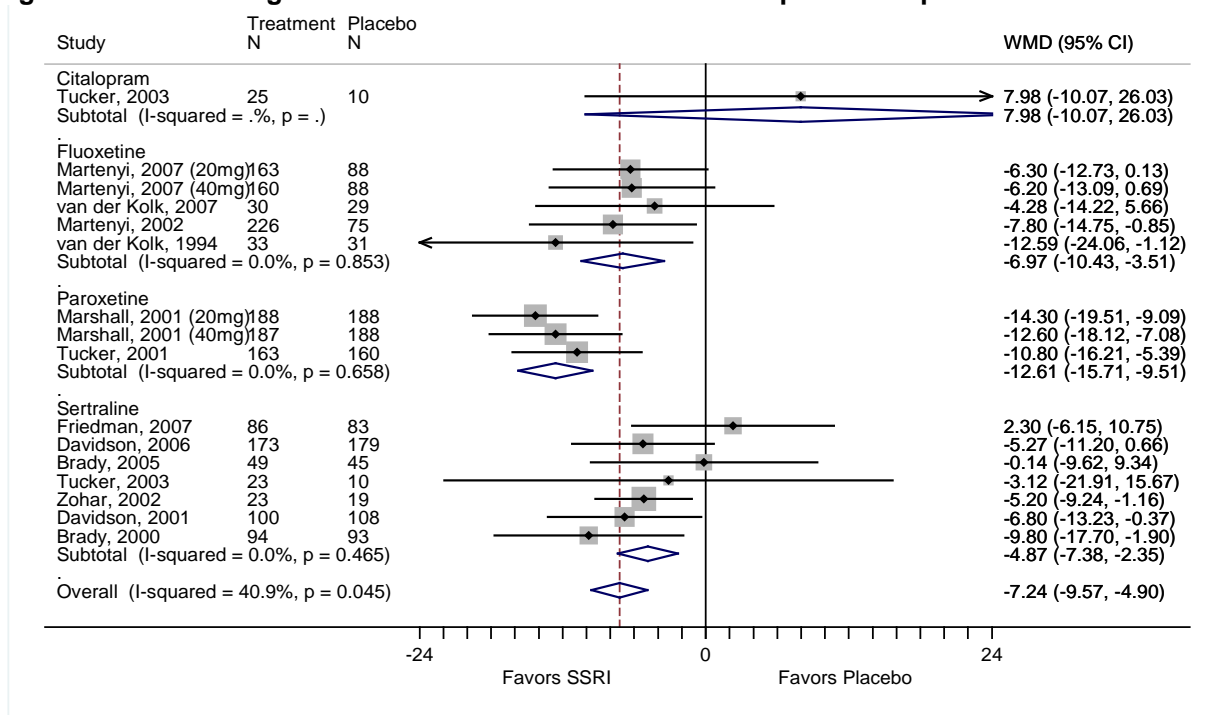
Note: When mean data for baseline PTSD severity were not reported for the total sample but were presented for each study arm, we provide the range across arms.

## Results of Placebo-Controlled Trials of SSRIs

### PTSD Symptom Reduction

Our meta-analyses found fluoxetine, paroxetine, and sertraline to improve PTSD symptoms, as measured by improvement in CAPS, more than placebo (Figure 23). We found no statistically significant difference between citalopram and placebo, and results favored placebo (one trial). Magnitude of benefit ranged from a difference of -4.9 for sertraline to -12.6 for paroxetine compared with placebo. The meta-analyses for change in CAPS did not have significant statistical heterogeneity for any of the individual medications compared with placebo ( $I^2=0\%$  for each). Analyses removing each individual study one at a time did not result in any significant differences in findings (Appendix F). Sensitivity analyses adding the trials rated high risk of bias with available data did not significantly change the results (Appendix F).

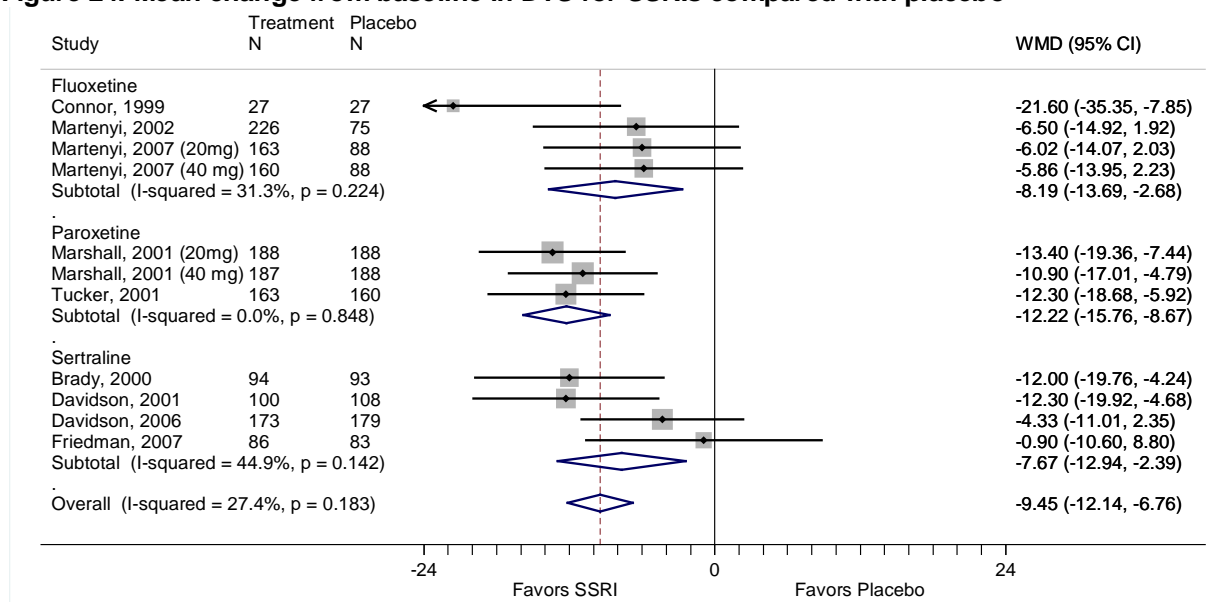
**Figure 23. Mean change from baseline in CAPS for SSRIs compared with placebo**



Note: Timing of outcome assessment: 10 weeks (Tucker, 2003;<sup>155</sup> Zohar, 2002<sup>170</sup>), 12 weeks (Martenyi, 2007;<sup>161</sup> Martenyi, 2002;<sup>159</sup> Marshall, 2001;<sup>163</sup> Tucker, 2001;<sup>134</sup> Brady, 2005;<sup>166</sup> Brady, 2000;<sup>165</sup> Davidson, 2001;<sup>167</sup> Friedman, 2007;<sup>168</sup> Davidson, 2006<sup>133</sup>), 8 weeks (van der Kolk, 2007),<sup>113</sup> 5 weeks (van der Kolk, 1994).<sup>162</sup>

The second most frequently reported measure of PTSD symptoms was the Davidson Trauma Scale (DTS). Our meta-analyses of mean change from baseline in DTS found similar results as those for CAPS, with fluoxetine, paroxetine, and sertraline improving PTSD symptoms more than placebo (Figure 24). Magnitude of benefit ranged from -7.7 (95% CI, -12.9 to -2.4, four trials, N=916) for sertraline to -12.2 (95% CI, -15.8 to -8.7, two trials, N=886) for paroxetine compared with placebo. Sensitivity analyses adding the trials rated high risk of bias with available data did not significantly change the results (Appendix F).

**Figure 24. Mean change from baseline in DTS for SSRIs compared with placebo**



Note: Timing of outcome assessment: 12 weeks for all included studies.

Fewer studies reported other measures of PTSD symptoms, such as the IES, TOP-8, SI-PTSD, or Duke Global rating. Overall, findings on these measures were consistent with those of the CAPS and DTS. Five trials that compared citalopram with placebo (one trial) and/or sertraline with placebo measured improvement in PTSD symptoms with the Impact of Event Scale (IES).<sup>155,165,167-169</sup> One trial found no statistically significant difference between citalopram and placebo (WMD, 7.8; 95% CI, -4.8 to 20.5, N=35). Our meta-analysis found greater improvement in symptoms measured with the IES for subjects treated with sertraline than for those who received placebo (WMD, -3.96; 95% CI, -6.0 to -1.9;  $I^2=0\%$ , five trials, N=667; Appendix F). Using the TOP-8 as a measure of PTSD symptoms, one trial<sup>159,160</sup> found greater improvement with fluoxetine compared with placebo (WMD, -2.3; 95% CI, -3.5 to -1.1, N=301); our meta-analysis of trials comparing paroxetine with placebo found greater improvement with paroxetine (WMD, -3.3; 95% CI, -4.2 to -2.4;  $I^2=0\%$ , two trials<sup>134,163</sup> contributing three comparisons, N=886, Appendix F). A single included trial reported each of the following outcomes as a measure of PTSD symptoms: SI-PTSD (aka SIP),<sup>157</sup> Duke Global rating,<sup>157</sup> SPRINT,<sup>164</sup> and the Mississippi Scale for Combat-related PTSD<sup>168</sup>—details for these outcomes are available in Appendix D.

Our meta-analyses using any measure of PTSD symptom reduction found effect sizes (i.e., Cohen's d; SMD) of -0.31 (95% CI, -0.44 to -0.17), -0.49 (95% CI, -0.61 to -0.37), and -0.25 (95% CI, -0.42 to -0.07) for fluoxetine, paroxetine, and sertraline, respectively (Appendix F).

Overall, we determined that the evidence from trials is consistent, direct, and precise and supports the efficacy of fluoxetine, paroxetine, and sertraline for improving PTSD symptoms (moderate SOE). The magnitude of benefit is in the small to medium range. Evidence was insufficient to determine the efficacy of citalopram for improving PTSD symptoms.

### Remission (No Longer Having Symptoms)

Four trials reported remission using varying definitions of remission; one of fluoxetine,<sup>113</sup> two of paroxetine,<sup>134,164</sup> and one of sertraline.<sup>133</sup> Three of the trials defined remission as a score of less than 20 on some version of the CAPS. For all four trials, point estimates favored SSRIs.



All four trials reported that greater proportions of subjects treated with SSRIs achieved remission than subjects who received placebo; differences between groups ranged from 3 percent to 19 percent, but often did not reach statistical significance. Some of the trials were underpowered to detect anything but a very large difference for remission.

One trial of fluoxetine randomized 88 subjects to eye movement desensitization and reprocessing (EMDR), fluoxetine, or placebo and defined remission (i.e., percent asymptomatic) as CAPS total score less than 20. It reported that a greater percentage of subjects treated with fluoxetine achieved remission than subjects who received placebo, but findings did not achieve statistical significance (13% vs. 10%,  $p=0.72$ , 58 subjects total in the fluoxetine and placebo groups). The evidence was insufficient to determine the efficacy of fluoxetine for achieving remission because of unknown consistency and imprecision.

For paroxetine, two trials reported remission. Both trials reported a similar between-group difference in the percentage of subjects achieving remission. One enrolled subjects refractory to prolonged exposure therapy ( $N=23$ ). It defined remission as a SPRINT score less than 6.<sup>164</sup> It found 33 percent (3 out of 9) of subjects in the paroxetine group and 14 percent (2 out of 14) of the placebo group achieved remission ( $p=0.34$ ). The difference did not reach statistical significance; the trial was underpowered to detect anything but a large difference for this outcome. The other trial ( $N=323$ )<sup>134</sup> defined remission as a CAPS-2 total score less than 20 and found that a significantly greater proportion of paroxetine-treated subjects achieved remission than placebo subjects at week 12 (29.4% vs. 16.5%,  $p=0.008$ ). The difference (12.9% difference between paroxetine and placebo) would translate to a NNT of 8. With consistent, direct, precise information from two trials, we determined that evidence supports the efficacy of paroxetine for achieving remission (moderate SOE).

The fourth trial ( $N=538$ ) reporting remission randomized subjects to sertraline, venlafaxine, or placebo.<sup>133</sup> It defined remission as CAPS-SX<sub>17</sub> score less than 20. At week 12, remission rates were numerically greater for patients treated with sertraline than for patients who received placebo, but the difference did not reach statistical significance (24.3% vs. 19.6%,  $p=NS$ , 352 subjects total in the sertraline and placebo arms). The evidence was insufficient to determine the efficacy of fluoxetine for achieving remission because of unknown consistency and imprecision.

### **Loss of PTSD Diagnosis**

A single trial comparing EMDR ( $N=29$ ), fluoxetine ( $N=30$ ), and placebo ( $N=29$ ) found no statistically significant difference between the three groups for the percentage of subjects achieving loss of diagnosis after 8 weeks of treatment (76% vs. 73% vs. 59%, respectively,  $p=0.23$  for fluoxetine compared with placebo).<sup>113</sup> The evidence was insufficient to determine the efficacy of fluoxetine for achieving loss of diagnosis because of imprecision and unknown consistency.

### **Prevention or Reduction of Comorbid Medical or Psychiatric Conditions**

Many of the included trials reported reduction of depression symptoms using various outcome measures: just two measures, HAM-D and MADRS, were reported with sufficient data to conduct meta-analyses—six trials reported the HAM-D<sup>133,162,165-168</sup> and five reported MADRS.<sup>134,160,161,163,170</sup> Most of the trials assessed fluoxetine, paroxetine, or sertraline. Evidence from one trial ( $N=35$ )<sup>155</sup> was insufficient to determine efficacy of citalopram for reducing comorbid depression in adults with PTSD.

Our meta-analysis of trials reporting MADRS found greater improvement in depression symptoms for subjects treated with fluoxetine than for those who received placebo (MADRS, mean change from baseline: WMD -2.4, 95% CI, -3.7 to -1.1;  $I^2=0\%$ , two trials, N=712, Appendix F) and for subjects treated with paroxetine than for those who received placebo (MADRS, mean change from baseline: WMD, -5.7; 95% CI, -7.1 to -4.3;  $I^2=0\%$ , two trials, N=886, Appendix F). Overall, consistent, direct, precise evidence provided moderate SOE that both fluoxetine and paroxetine improve depression symptoms for adults with PTSD.

For sertraline, data were available for meta-analysis of five trials reporting the HAM-D. Our meta-analysis found no statistically significant difference between sertraline and placebo (HAM-D, mean change from baseline: WMD, -0.77; 95% CI, -2.1 to 0.55;  $I^2=25\%$ , five trials, N=1,010, Appendix F). Point estimates favored sertraline for three of the individual trials; they favored placebo for the other two. One trial reporting MADRS found greater improvement in depression symptoms for subjects treated with sertraline than for those who received placebo (WMD, -3.2; 95% CI, -5.2 to -1.2; N=42).<sup>170</sup> Taken together, primarily because of lack of consistency and imprecision, the evidence for sertraline does not support its efficacy for improving depression symptoms for adults with PTSD (low SOE).

Our meta-analyses using any measure for depression symptom reduction found effect sizes (i.e., Cohen's d; SMD) of -0.04 (95% CI, -0.77 to 0.70), -0.20 (95% CI, -0.40 to -0.00), -0.49 (95% CI, -0.64 to -0.34), and -0.13 (95% CI, -0.32 to 0.06) for citalopram, fluoxetine, paroxetine, and sertraline, respectively (Appendix F).

Four of the included trials assessed anxiety symptoms using the HAM-A.<sup>159,161,167,168</sup> Two trials compared fluoxetine with placebo<sup>159,161</sup> and two compared sertraline with placebo.<sup>167,168</sup> Our meta-analysis found greater improvement in anxiety symptoms for subjects treated with fluoxetine than for those who received placebo (WMD, -2.1; 95% CI, -3.2 to -0.9;  $I^2=0\%$ , two trials, N=712, Appendix F). Evidence for fluoxetine was consistent, direct, and precise (moderate SOE). The two trials that compared sertraline with placebo reported mixed results; one favored sertraline and one favored placebo. Meta-analysis of the two trials had substantial heterogeneity (WMD, 0.19; 95% CI, -3.14 to 3.51;  $I^2=68.3\%$ , 2 trials, N=377). Overall, evidence from these two trials was inconsistent and imprecise; thus, evidence is insufficient to determine the efficacy of sertraline for reducing anxiety symptoms in subjects with PTSD.

## Quality of Life

Three included trials assessed quality of life; two trials of sertraline used the Q-LES-Q<sup>133,165</sup> and one of fluoxetine used the SF-36.<sup>160</sup> Results of our meta-analysis found no statistically significant difference between sertraline and placebo (mean change in Q-LES-Q: WMD, 4.9; 95% CI, -0.88 to 10.7, two trials, N=539). The analysis found substantial statistical heterogeneity ( $I^2=72.6\%$ ). This could be explained by differences in the enrolled populations—one trial enrolled male and females with comorbid alcohol dependence. Overall, because of inconsistency and imprecision, evidence was insufficient to determine the efficacy of sertraline for improving quality of life.

The SF-36 was reported as an outcome in a subgroup analysis of subjects with combat-related PTSD in one trial (N=144 of the 301 from the main trial).<sup>160</sup> It reported greater improvement in the mental health subscore of the SF-36 for those treated with fluoxetine than for those who received placebo (15.5 vs. 0.33,  $p<0.001$ ) and no difference between groups for the physical functioning subscore (8.62 vs. 8.07,  $p=0.891$ ). This evidence was insufficient to determine the efficacy of fluoxetine for improving quality of life.

## Disability or Functional Impairment

Four trials assessed disability using the Sheehan Disability Scale (SDS); one trial of fluoxetine,<sup>157</sup> two trials of paroxetine,<sup>134,163</sup> and one of sertraline.<sup>133</sup> Evidence from one trial each for fluoxetine and sertraline provided insufficient evidence to determine their efficacy for reducing disability (detailed results provided in Appendix D and Appendix F). For paroxetine, consistent, direct, precise findings support its efficacy for improving disability or functioning (mean change from baseline in SDS: WMD, -2.3; 95% CI, -3.3 to -1.4; two trials, N=886, Appendix F, moderate SOE).

## Detailed Synthesis: Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs)

### Characteristics of Trials

Table 31 summarizes the characteristics of the two trials meeting our inclusion criteria. Further details describing the included trials are provided in Appendix D. Both trials evaluated venlafaxine extended release. One was a 12-week trial conducted in the United States<sup>133</sup> and one was a 24-week multinational collaboration of 56 outpatient psychiatric clinic sites in South America, Europe, Mexico, and South Africa.<sup>173</sup> The U.S.-based trial had an active comparator arm (sertraline) as well as a placebo comparison. Both trials enrolled a heterogeneous group of subjects with a variety of index trauma types (e.g., sexual abuse, nonsexual abuse, combat, injury, motor vehicle accident, natural disaster), and very few subjects with combat-related PTSD (9% to 12%). The primary outcome for both trials was the CAPS.

**Table 31. Characteristics of included placebo-controlled trials of SNRIs**

| Study                                | Arm Dose mg/day (N)  | Duration (Weeks) | Population Trauma Type   | Baseline PTSD Severity <sup>a</sup> | Mean Age (Y) | % F | % Non-white | Risk of Bias |
|--------------------------------------|--|------------------|--------------------------|-------------------------------------|--------------|-----|-------------|--------------|
| Davidson et al., 2006 <sup>173</sup> | Venlafaxine ER (37.5 to 300) (161)<br>Placebo (168)  | 24               | Male and female<br>Mixed | 81 to 82.9                          | 41           | 54  | NR          | Medium       |
| Davidson et al., 2006 <sup>133</sup> | Total (538) <sup>b</sup><br>Venlafaxine (37.5 to 375) (179)<br>Sertraline (25 to 200) (173)<br>Placebo (179) | 12               | Male and female<br>Mixed | ~82                                 | NR           | NR  | NR          | Medium       |

CAPS = Clinician Administered PTSD Scale; F = female; mg = milligram; N = total number randomized/assigned to intervention and control groups; NR = not reported; PTSD = posttraumatic stress disorder; y = year

<sup>a</sup>Data reported are mean CAPS or range of mean CAPS scores across groups unless another instrument is specified.

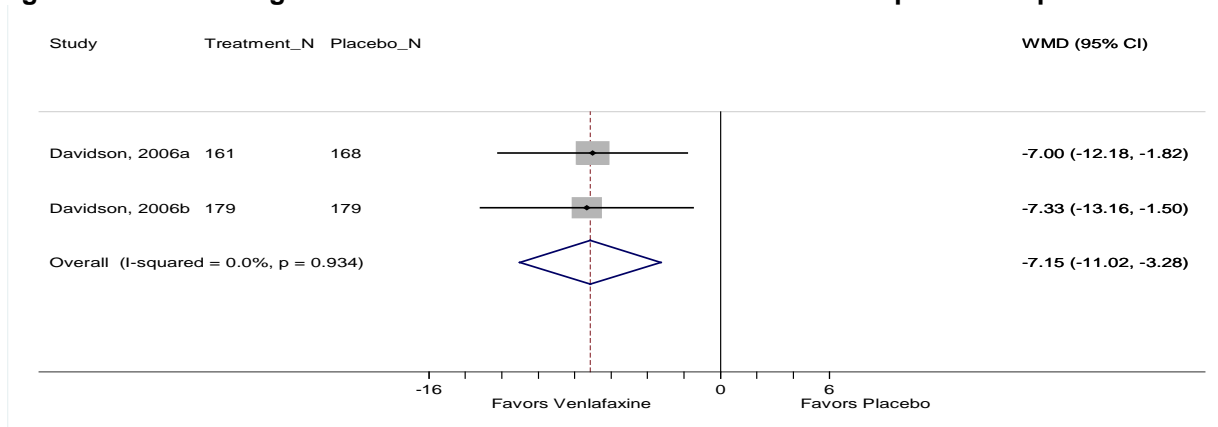
<sup>b</sup>The Ns for each are the number analyzed; the number randomized to each group was not reported (overall N was 538; 531 were included in the analysis).

## Results of Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs)

### PTSD Symptom Reduction

Both trials reported similar improvement in CAPS. Our meta-analysis found venlafaxine to improve PTSD symptoms more than placebo (WMD -7.15, 95% CI, -11.02 to -3.28, Figure 25; SMD -0.28, 95% CI, -0.43 to -0.13, Appendix F).

**Figure 25. Mean change from baseline in CAPS for venlafaxine ER compared with placebo**



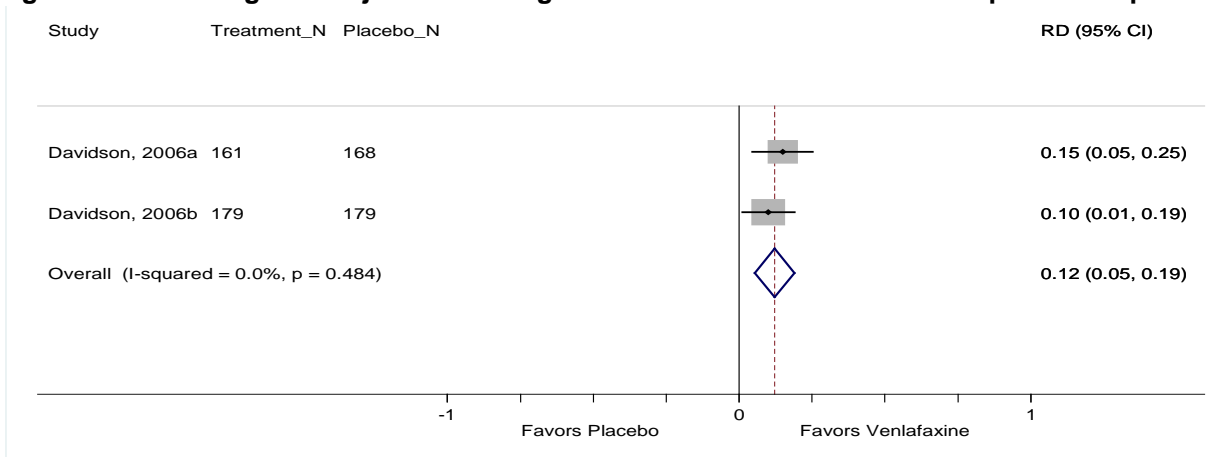
Note: Timing of outcome assessment: 24 weeks (Davidson, 2006),<sup>173</sup> 12 weeks (Davidson, 2006).<sup>133</sup>

The U.S.-based trial also reported the Davidson Trauma Scale (DTS) total score, finding greater improvement in symptoms with venlafaxine than with placebo (-42.9 vs. -34.6, p=0.015).

#### Remission (No Longer Having Symptoms)

Both trials reported remission, defined as CAPS-Sx total score of 20 or less, and both found that more subjects receiving venlafaxine achieved remission than those receiving placebo. Our meta-analysis for remission at 12 weeks found that 12 percent more subjects receiving venlafaxine achieved remission than those receiving placebo (Figure 26). This would translate to a NNT of 9.

**Figure 26. Percentage of subjects achieving remission for venlafaxine ER compared with placebo**



Note: Timing of outcome assessment: 24 weeks (Davidson, 2006),<sup>173</sup> 12 weeks (Davidson, 2006).<sup>133</sup>

One of the trials<sup>173</sup> also reported that about 13 percent more subjects in the venlafaxine group than the placebo group achieved remission at 24 weeks (50.9% vs. 37.5%).

### Prevention or Reduction of Comorbid Medical or Psychiatric Conditions

Both trials assessed depression using the HAM-D, and both reported a statistically significant reduction with venlafaxine compared with placebo. Our meta-analysis found about a 2-point greater reduction in HAM-D with venlafaxine than with placebo (WMD, -2.08; 95% CI, -3.12 to -1.04; I<sup>2</sup>=0%, Appendix F).

## Quality of Life

Both trials reported a statistically significant improvement in quality of life with venlafaxine compared with placebo, as measured by the Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form (Q-LES-Q-SF). Our meta-analysis found a 3.4-point greater improvement in Q-LES-Q-SF with venlafaxine than with placebo (WMD, 3.42; 95% CI, 1.58 to 5.26;  $I^2 = 0\%$ , Appendix F).

## Disability or Functional Impairment

Both trials reported a statistically significant improvement in functional impairment with venlafaxine than with placebo, as measured by the Sheehan Disability Scale (SDS). Our meta-analysis found about a 2-point greater improvement in SDS with venlafaxine than with placebo (WMD, -2.06; 95% CI, -3.28 to -0.84;  $I^2 = 0\%$ , Appendix F). Similarly, our meta-analyses found greater improvement in Global Assessment of Functioning (GAF) with venlafaxine than with placebo (WMD, 3.41; 95% CI, 1.41 to 5.40,  $I^2 = 0\%$ , Appendix F).

## Detailed Synthesis: Placebo-Controlled Trials of Tricyclic Antidepressants

We did not find any trials comparing tricyclic antidepressants with placebo or other medications that had low or medium risk of bias. We rated three trials otherwise meeting criteria for this section as high risk of bias (Table 32). Appendix E provides additional rationale for risk of bias assessments. Briefly, the trials only analyzed subjects who completed treatment (did not use an intention-to-treat analysis) and/or had very high dropout rates.

Overall evidence was insufficient to make conclusions about the efficacy of any tricyclic antidepressants for treating PTSD in adults (insufficient SOE).

**Table 32. Characteristics of placebo-controlled trials of tricyclic antidepressants excluded because of high risk of bias**

| Study  | Arm Dose mg/day (N)                                       | Duration (Weeks) | Population Trauma Type  | Baseline PTSD Severity | Mean Age (Y) | % F | % Non-white | Risk of Bias |
|--|---|------------------|-------------------------|------------------------|--------------|-----|-------------|--------------|
| Davidson et al., 1990 <sup>174</sup><br>Davidson et al., 1993 <sup>175</sup> | Amitriptyline (50 to 300) (33)<br>Placebo (29)            | 8                | NR<br>Combat veterans   | IES 33.1               | 49           | NR  | NR          | High         |
| Reist et al., 1989 <sup>176</sup>  | Total (27)<br>Desipramine (50 to 200)(NR)<br>Placebo (NR) | 4                | Male<br>Combat veterans | IES 55.2 to 56.2       | 38           | 0   | NR          | High         |
| Kosten et al., 1991 <sup>177</sup>   | Imipramine (50 to 300) (23)<br>Placebo (19)               | 8                | Male<br>Combat veterans | IES 35.6               | 39           | 0   | NR          | High         |

F = female; IES = Impact of Event Scale; mg = milligram; N = total number randomized/assigned to intervention and control groups; NR = not reported; PTSD = posttraumatic stress disorder; y = year

Note: When mean data for baseline PTSD severity were not reported for the total sample but were presented for each study arm, we provide the range across arms.

## Detailed Synthesis: Placebo-Controlled Trials of Other Second-Generation Antidepressants

### Characteristics of Trials

Table 33 summarizes the characteristics of the two trials that met our inclusion criteria. Further details describing the included trials are provided in Appendix D.

**Table 33. Characteristics of included placebo-controlled trials of other second-generation antidepressants**

| Study                                | Arm Dose mg/day (N)  | Duration (Weeks) | Population Trauma Type   | Baseline PTSD Severity | Mean Age (Y) | % F | % Non-white | Risk of Bias |
|--------------------------------------|--|------------------|--------------------------|------------------------|--------------|-----|-------------|--------------|
| Becker et al., 2007 <sup>178</sup>   | Total (30) <sup>a</sup><br>Bupropion (100 to 300) (18)<br>Placebo (10) | 8                | Male and female<br>Mixed | NR                     | 50           | 21  | 71          | Medium       |
| Davidson et al., 2003 <sup>179</sup> | Total (29) <sup>b</sup><br>Mirtazapine (15 to 45) (17)<br>Placebo (9)  | 8                | Male and Female<br>Mixed | SPRINT<br>21.7 to 25.0 | 46           | NR  | NR          | Medium       |

F = female; mg = milligram; N = total number randomized/assigned to intervention and control groups; NR = not reported; PTSD = posttraumatic stress disorder; SPRINT = Short PTSD Rating Interview; y = year

<sup>a</sup>Thirty subjects were randomized; exact numbers randomized to each group NR; authors report that 18 received bupropion and 10 received placebo; 2 dropped out prior to treatment.

<sup>b</sup>A total of 29 subjects were randomized: 3 subjects dropped out early, 17 received mirtazapine, and 9 received placebo.

Note: When mean data for baseline PTSD severity were not reported for the total sample but were presented for each study arm, we provide the range across arms.

Of the two included placebo-controlled trials, one assessed bupropion (N=30)<sup>178</sup> and one assessed mirtazapine (N=29).<sup>179</sup> Both were conducted in the United States. Treatment duration was 8 weeks. Both enrolled a heterogeneous group of subjects with a variety of index trauma types (e.g., military combat or war trauma, childhood sexual abuse, physical abuse, rape, motor vehicle accident, witnessing a trauma, death or suicide of a loved one). The trials generally recruited middle-aged adults, with mean ages ranging from ~43 to ~50 years. The trial of bupropion recruited subjects from a VA Medical Center and from the community.<sup>178</sup> The trial of mirtazapine recruited subjects by advertisements or from the clinical practice of the investigators.<sup>179</sup>

We rated one trial comparing nefazodone with placebo<sup>29</sup> otherwise meeting criteria for this section as high risk of bias (Table 34). We excluded it from our main data synthesis and used it only for sensitivity analyses.

**Table 34. Characteristics of placebo-controlled trials of other second-generation antidepressants excluded from main analyses because of high risk of bias**

| Study                            | Arm Dose mg/day (N)                          | Duration (Weeks) | Population Trauma Type | Baseline PTSD Severity <sup>a</sup> | Mean Age (Y) | % F | % Non-white | Risk of Bias |
|----------------------------------|--|------------------|------------------------|-------------------------------------|--------------|-----|-------------|--------------|
| Davis et al., 2004 <sup>29</sup> | Nefazodone (100 to 600) (27)<br>Placebo (15) | 12               | Male and female Mixed  | 81.0 to 83.2                        | 54           | 2.4 | 46          | High         |

F = female; mg = milligram; N = total number randomized/assigned to intervention and control groups; NR = not reported; PTSD = posttraumatic stress disorder; y = year

<sup>a</sup>Data reported are mean CAPS or range of mean CAPS scores across groups unless another instrument is specified.

## Results of Placebo-Controlled Trials of Other Second-Generation Antidepressants

### PTSD Symptom Reduction

Both included trials reported measures of PTSD symptoms.<sup>178,179</sup> For all but one of the measures of PTSD symptoms, neither trial found statistically significant differences between medication and placebo groups.

The trial comparing bupropion with placebo found no statistically significant difference between groups for improvement in PTSD symptoms, assessed by mean reduction in CAPS (-12.33; SD, 24.12 vs. -16.99; SD, 11.26) or DTS (-13.22; SD, 21.62 vs. -10.6; SD, 29.20).<sup>178</sup> Both groups improved.

The trial comparing mirtazapine with placebo reported three measures of PTSD symptoms: SPRINT, SIP, and DTS.<sup>179</sup> For SPRINT and DTS, results were not statistically significantly different between groups (-9.3 vs. -5.6,  $p=0.20$  and -20.7 vs. -11.2,  $p=0.20$ , respectively). However, the trial reported statistically significant differences between groups for the SIP, favoring those treated with mirtazapine (-17.3 vs. -6.5,  $p=0.04$ ).

Overall, we found insufficient evidence to determine the efficacy of either bupropion or mirtazapine for improving PTSD symptoms. Evidence was limited to one trial for each medication, consistency was thus unknown, and findings were imprecise.

### Prevention or Reduction of Comorbid Medical or Psychiatric Conditions

Both trials reported measures of reduction of depression and/or anxiety.<sup>178,179</sup> Neither reported prevention or reduction of comorbid medical conditions. The trial of bupropion reported similar decreases in depression scores for the intervention group and the control group (mean change in BDI: -3.22 vs. -3.61,  $p=NS$ ). The trial of mirtazapine found a greater reduction in depressive symptoms using the Hospital Depression Scale (HADS-D), but the difference between mirtazapine-treated subjects and those receiving placebo was not statistically significant (-2.2 vs. -0.5,  $p=0.08$ ).

The trial of mirtazapine reported greater reduction in anxiety for subjects treated with mirtazapine than for those receiving placebo, using the Hospital Anxiety Scale (HADS-A) (-2.8 vs. -1.2,  $p<0.05$ ).<sup>179</sup>

Overall, we found insufficient evidence to determine the efficacy of either bupropion or mirtazapine for prevention or reduction of comorbid medical or psychiatric conditions for adults with PTSD. Evidence was limited to one small medium-risk-of-bias trial for each medication, consistency was thus unknown, and findings were imprecise.

## Detailed Synthesis: Head-to-Head Pharmacotherapy Trials

### Characteristics of Trials

Table 35 summarizes the three trials that met inclusion criteria. Further details are provided in Appendix D. The trials enrolled subjects with severe to extreme PTSD symptomatology. All were conducted in the United States. Sample sizes ranged from 59 to 538. Treatment duration ranged from 10 to 12 weeks. One of the included trials enrolled veterans with comorbid alcohol dependence;<sup>132</sup> the other two enrolled a heterogeneous group of subjects with a variety of index trauma types. The trial enrolling veterans randomized subjects to paroxetine plus naltrexone, paroxetine plus placebo, desiprimine plus naltrexone, or desiprimine plus placebo.<sup>132</sup> The primary outcome for all five trials was some version of the CAPS.

**Table 35. Characteristics of included head-to-head pharmacotherapy trials**

| Study  | Arm Dose mg/day (N)  | Duration (Weeks) | Population Trauma Type                        | Baseline PTSD Severity <sup>a</sup> | Mean Age (Y) | % F | % Non-white | Risk of Bias |
|--|--|------------------|---|-------------------------------------|--------------|-----|-------------|--------------|
| Petrakis et al., 2012 <sup>132</sup>                                     | Paroxetine (40) + Naltrexone (50) (22)<br>Paroxetine (40) + Placebo (20)<br>Desiprimine (200) + Naltrexone (50) (22)<br>Desipramine (200) + Placebo (24) | 12               | Male and female Veterans w/alcohol dependence | 62.5 to 77.8                        | 47           | 9   | 25          | Medium       |
| Davidson et al., 2006 <sup>133</sup>                                     | Total (538) <sup>b</sup> Venlafaxine (37.5 to 375) (179)<br>Sertraline (25 to 200) (173)<br>Placebo (179)  | 12               | Male and female Mixed                         | ~82                                 | NR           | NR  | NR          | Medium       |
| Tucker et al., 2003 <sup>155</sup><br>Tucker et al., 2004 <sup>156</sup> | Citalopram (20 to 50) (25)<br>Sertraline (50 to 200) (23)<br>Placebo (10)  | 10               | Male and female Mixed                         | 83.9 to 94.2                        | 39           | 74  | 14          | Medium       |

F = female; mg = milligram; N = total number randomized/assigned to intervention and control groups; NR = not reported; PTSD = posttraumatic stress disorder; y = years

<sup>a</sup>Data reported are mean CAPS or range of mean CAPS scores across groups unless otherwise specified.

<sup>b</sup>The Ns for each are the number analyzed; the number randomized to each group was not reported (overall N was 538; 531 were included in the analysis).

We rated three trials otherwise meeting criteria for this section as high risk of bias (Table 36). We excluded them from our main data synthesis. Appendix E provides additional rationale for risk of bias assessments. Briefly, the trials deemed high risk of bias only analyzed subjects who completed treatment (did not use an intention-to-treat analysis) and/or had very high overall and differential attrition rates.



**Table 36. Characteristics of head-to-head pharmacotherapy trials excluded because of high risk of bias**

| Study                              | Arm Dose mg/day (N)   | Duration (Weeks) | Population Trauma Type                | Baseline PTSD Severity <sup>a</sup> | Mean Age (Y) | % F | % Non-white | Risk of Bias |
|------------------------------------|---|------------------|---------------------------------------|-------------------------------------|--------------|-----|-------------|--------------|
| Spivak et al., 2006 <sup>180</sup> | Reboxetine (8) (20)<br>Fluvoxamine (150) (20)                             | 8                | Male and female MVA                   | 74.9 to 81.8                        | 40           | 46  | NR          | High         |
| Kosten et al., 1991 <sup>177</sup> | Imipramine (50 to 300) (23)<br>Phenelzine (15 to 75) (19)<br>Placebo (18) | 8                | Male Combat veterans                  | IES 30.0 to 36.5                    | 39           | 0   | 13          | High         |
| McRae et al., 2004 <sup>181</sup>  | Nefazodone (100 to 600) ( )<br>Sertraline (50 to 200)( )                  | 12               | Male and female Outpatient special MH | 68.9 to 73.8                        | 40           | 77  | NR          | High         |

CAPS = Clinician Administered Post traumatic stress disorder Scale; F = female; IES = Impact of Event Scale; mg = milligram; N = total number randomized/assigned to intervention and control groups; NR = not reported; PTSD = posttraumatic stress disorder; y = year

<sup>a</sup>Data reported are mean CAPS or range of mean CAPS scores across groups unless otherwise specified.

Note: When mean data for baseline PTSD severity were not reported for the total sample but were presented for each study arm, we provide the range across arms.

## Results of Head-to-Head Pharmacotherapy Trials

### PTSD Symptom Reduction

All three included trials assessed PTSD symptom reduction. Outcome measures included versions of the CAPS,<sup>132,133,155</sup> the DTS,<sup>133</sup> and the IES.<sup>155</sup> The four-arm trial enrolling veterans with PTSD and comorbid alcohol dependence (N=88) reported similar improvements in PTSD symptoms for all treatment groups (CAPS, mean change from baseline: -33.5 vs. -33.2 vs. -35.7 vs. -36.4, p NS). With evidence from one trial, unknown consistency, and imprecise findings, we concluded that evidence of low strength indicates no difference between desipramine and paroxetine for reducing PTSD symptoms in adults with PTSD and coexisting alcohol dependence.

The trial comparing venlafaxine ER, sertraline, and placebo (N=538) reported similar improvements in PTSD symptoms for both active treatment arms using the CAPS-SX<sub>17</sub> (mean change from baseline: -41.5 vs. -39.4, p=0.49) and the DTS (-42.9 vs. -38.9, p=0.25).<sup>133</sup> Results favored venlafaxine ER and differences between venlafaxine ER and placebo reached statistical significance (CAPS-SX<sub>17</sub> -41.5 vs. -34.2, p=0.015; DTS -42.9 vs. -34.6, p=0.015), whereas those between sertraline and placebo did not (CAPS-SX<sub>17</sub> -39.4 vs. -34.2, p=0.081; DTS -38.9 vs. -34.6, p=0.203). Although evidence is from a single trial, and consistency is unknown, direct and precise findings suggest no significant difference between venlafaxine ER and sertraline for reducing PTSD symptoms (moderate SOE).

The trial comparing sertraline, citalopram, and placebo (N=58) found greater improvement in CAPS for those treated with sertraline than for citalopram or placebo, but differences did not reach statistical significance (-41.8 vs. -30.7 vs. -38.7, p=NS). It also reported no statistically significant differences between groups for change in IES, although the greatest numerical reduction was seen in the placebo group (-29.1 vs. -19.3 vs. -33.2, p=NS).<sup>155</sup> Evidence was from a single trial, consistency is unknown, and findings were imprecise (insufficient SOE).

## Remission (No Longer Having Symptoms)

Just one of the included head-to-head trials reported remission—the trial comparing venlafaxine ER, sertraline, and placebo (N=538).<sup>133</sup> It defined remission as a CAPS-SX<sub>17</sub> score of  $\leq 20$ . By week 12, 30.2 percent of subjects treated with venlafaxine, 24.3 percent of subjects treated with sertraline, and 19.6 percent of those receiving placebo achieved remission ( $p < 0.05$  for venlafaxine ER vs. placebo;  $p = \text{NS}$  for sertraline vs. placebo or venlafaxine vs. sertraline).

## Prevention or Reduction of Comorbid Medical or Psychiatric Conditions

All three trials assessed reduction of depression symptoms. Outcome measures included the HAM-D<sup>132,133</sup> and the BDI.<sup>155</sup> The four-arm trial enrolling veterans with PTSD and coexisting alcohol dependence (N=88) reported similar improvements in PTSD symptoms for all treatment groups (HAM-D, mean change from baseline: -3.9 vs. -2.7 vs. -2.6 vs. -4.2,  $p = \text{NS}$ ). With evidence from one trial, unknown consistency, and imprecise findings, we concluded that evidence of low strength indicates no difference between desipramine and paroxetine for reduction of depression symptoms in adults with PTSD and coexisting alcohol dependence.

The trial comparing venlafaxine ER, sertraline, and placebo (N=538)<sup>133</sup> reported similar findings for reduction of depression as it reported for reduction of PTSD symptoms, with results favoring the venlafaxine ER group, but reaching statistically significant differences only for the comparison between venlafaxine and placebo (mean change from baseline in HAM-D: -7.09 vs. -6.42 vs. -5.54,  $p = 0.38$  for venlafaxine vs. sertraline,  $p = 0.04$  for venlafaxine vs. placebo,  $p = 0.24$  for sertraline vs. placebo).

The trial comparing sertraline, citalopram, and placebo (N=58) reported similar reduction in depression symptoms for all groups (BDI, mean change from baseline: -13.4 vs. -16.1 vs. -15.6,  $p = \text{NR}$ ).<sup>155</sup> It also reported change in systolic and diastolic blood pressure, but it was not clear if any enrolled subjects had hypertension; the reported information is not useful to inform the question of whether treatments reduced coexisting hypertension. Evidence was from a single trial, consistency is unknown, and findings were imprecise.

The four-arm trial enrolling veterans with PTSD and coexisting alcohol dependence (N=88) also reported alcohol use outcomes, finding greater reduction in the percentage of heavy drinking days ( $p = 0.009$ ) and drinks per drinking days ( $p = 0.027$ ) for subjects receiving desipramine than for those receiving paroxetine.<sup>132</sup> The data were not reported for drinking outcomes (shown in figure only for drinks per week—all groups ended up less than 20 standard drinks per week, from baselines above 70 drinks per week, and it appears that the desipramine groups ended up in the 0 to 10 drinks per week range and the paroxetine groups ended up in the 10-20 range at the 12-week endpoint). Overall, the trial provides some evidence of a slightly greater benefit for drinking outcomes for those treated with desipramine than for those treated with paroxetine. We concluded that evidence was of low strength; consistency is unknown (single study), and findings were imprecise.

## Quality of Life

One trial assessed quality of life using the Q-LES-Q.<sup>133</sup> The trial comparing venlafaxine ER, sertraline, and placebo (N=538) reported similar findings for improvement in quality of life as it reported for other outcomes, with results favoring the venlafaxine ER group, but reaching statistically significant differences only for the comparison between venlafaxine and placebo (Appendix D).

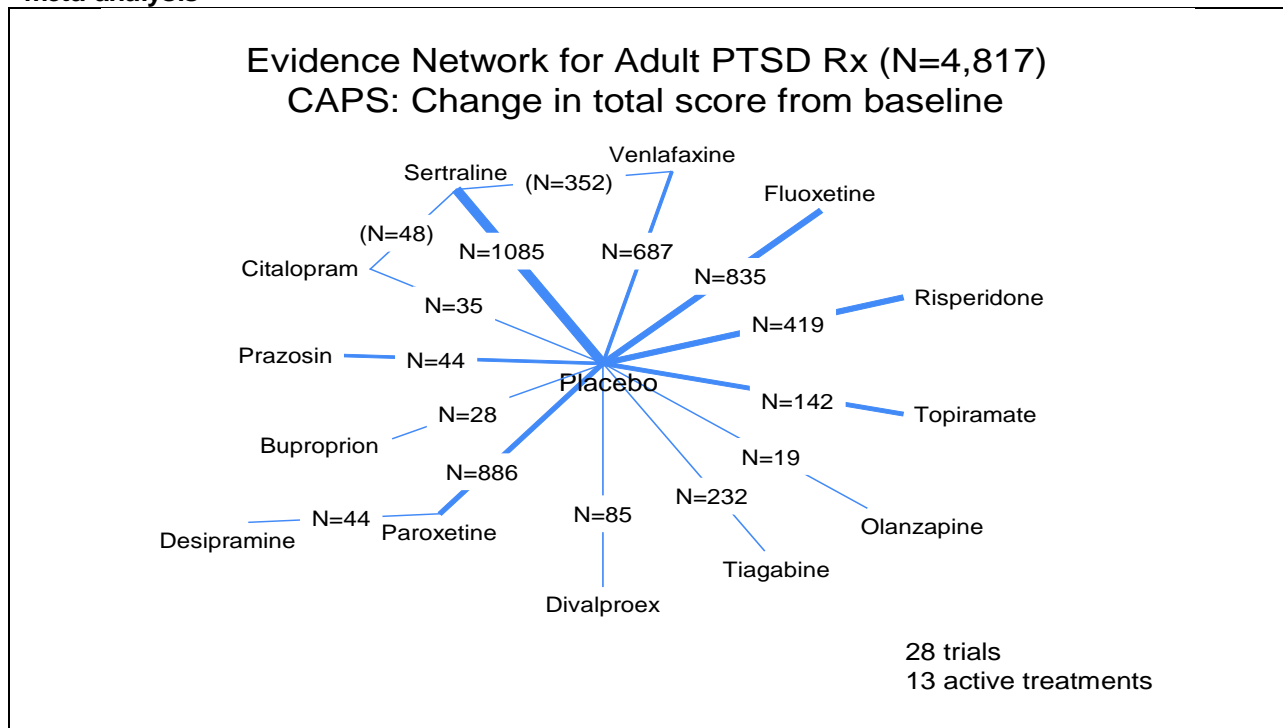
## Disability or Functional Impairment

One trial assessed disability, using the Sheehan Disability Scale (SDS) and the Global Assessment of Functioning (GAF).<sup>133</sup> The trial comparing venlafaxine ER, sertraline, and placebo (N=538) reported similar findings for improvement in disability as it reported for other outcomes, with results from the SDS showing benefit for the venlafaxine ER group, but reaching statistically significant differences only for the comparison between venlafaxine and placebo (Appendix D). For the GAF none of the between-group differences were statistically significant. Although evidence is from a single trial, and consistency is unknown, direct and precise findings suggest no significant difference between venlafaxine ER and sertraline for reducing PTSD symptoms (moderate SOE).

## Network Meta-Analysis of Pharmacotherapy Trials

We conducted network meta-analyses using Bayesian methods for the PTSD symptoms outcome, measured by mean change from baseline in CAPS compared with placebo. The analysis included 28 trials and 13 active treatments (4,817 subjects) incorporating both direct and indirect evidence from the trials included in the previous sections of this Key Question (KQ). A network diagram illustrates the number of subjects contributing to each comparison; thickness of lines connecting each drug-drug or drug-placebo is directly proportional to the number of trials with available data for that comparison (Figure 27).

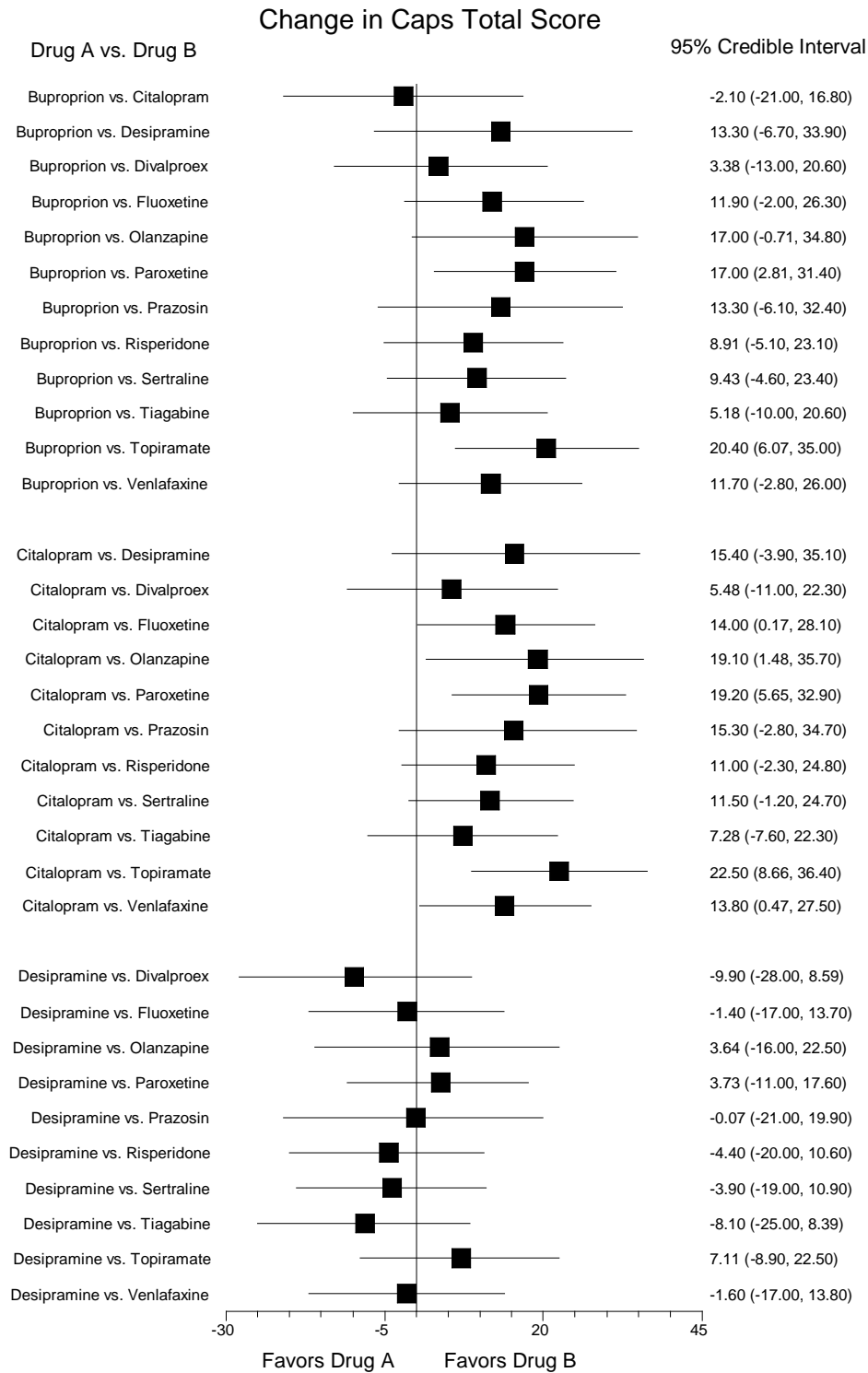
**Figure 27. Evidence network: comparisons, and number of subjects for each, included in network meta-analysis**



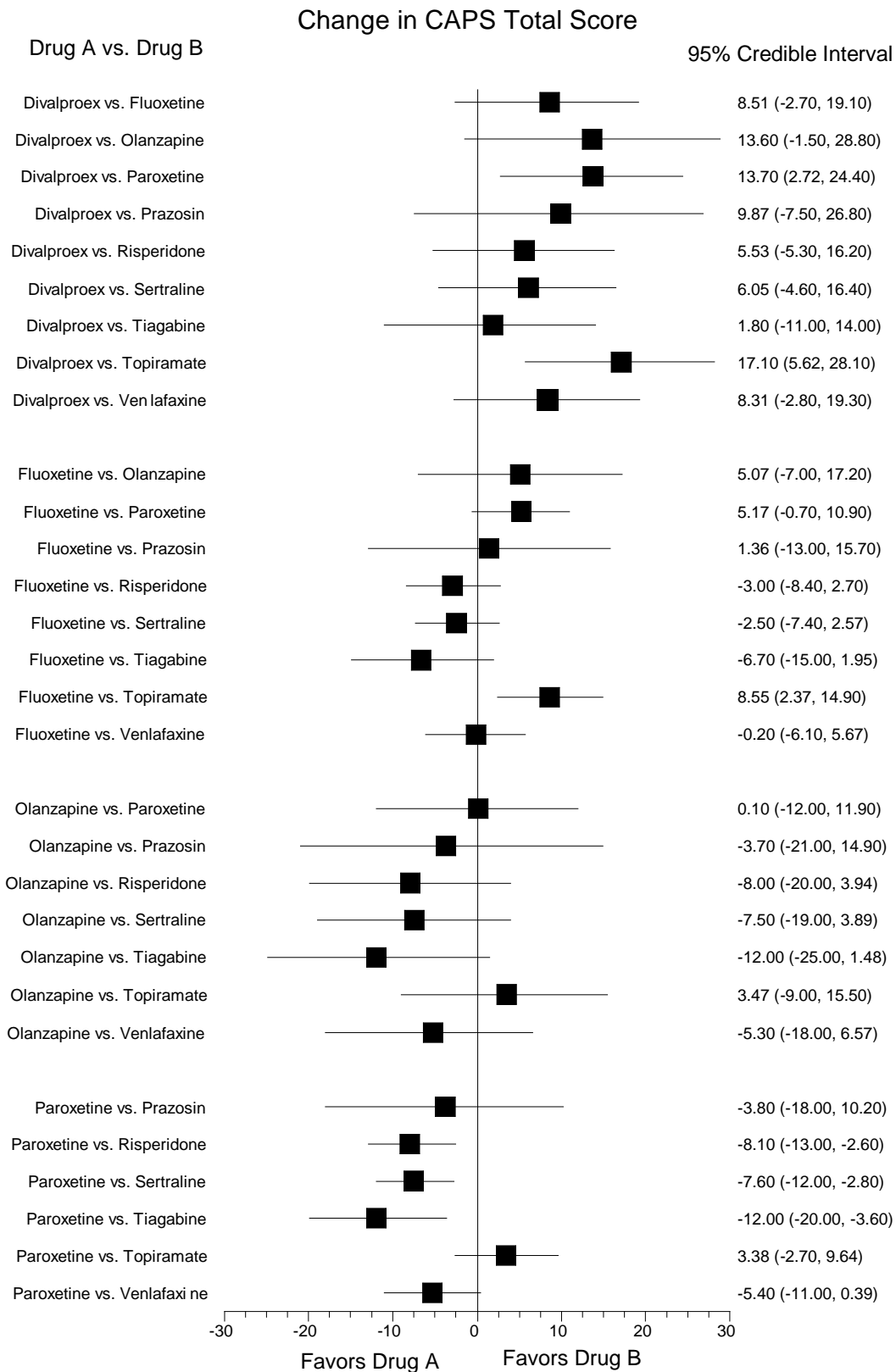
Findings from our network meta-analysis are presented in Figure 28, showing the difference between each pair of treatments for change from baseline in total CAPS score (WMD and 95% credible interval [CrI] for each comparison). Our network meta-analysis found paroxetine and

topiramate to be more effective for reducing PTSD symptoms than most other medications included in the analysis. When compared with other medications with

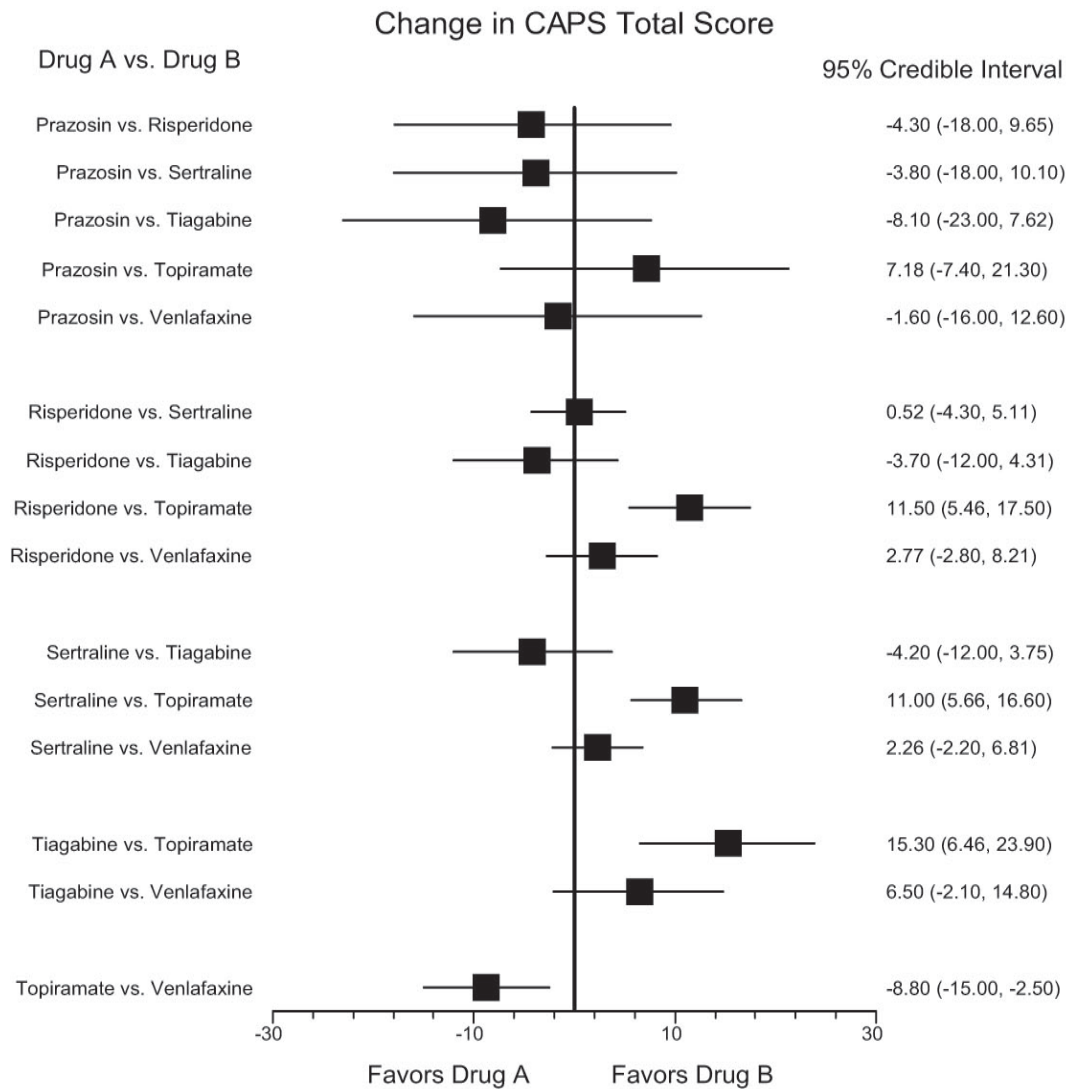
**Figure 28. Results of network meta-analysis comparing improvement in PTSD symptoms (change in CAPS total score)**



**Figure 28. Results of network meta-analysis comparing improvement in PTSD symptoms (change in CAPS total score) (continued)**



**Figure 28. Results of network meta-analysis comparing improvement in PTSD symptoms (change in CAPS total score) (continued)**



moderate SOE of efficacy for improving PTSD symptoms (based on our findings in previous sections of this KQ), paroxetine was more effective than sertraline (WMD -7.6, 95% CrI -12 to -2.8), but was not significantly different from fluoxetine, topiramate, or venlafaxine. When compared with other medications with moderate SOE of 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. Results of our sensitivity analysis adding in studies rated as high risk of bias were similar to those for the main analysis (Appendix F).

It appears that paroxetine and topiramate were found to be more effective than most other medications mainly due to the magnitude of effects and the precision in the individual trials that compared each of them with placebo. Two trials (total N=886) contributed data for paroxetine compared with placebo—the effect sizes in those trials were greater on average (WMD -12.6, 95% CI, -15.7, -9.5) than those for most other medications. Three trials (total N=142) contributed data for topiramate compared with placebo—the effect sizes in those three trials

were greater on average (WMD, -15.5, 95% CI, -19.4 to -11.7) than those for all other medications.

Three head-to-head comparisons contributed data, but the majority of evidence in the network meta-analysis was indirect evidence (from placebo-controlled trials). Thus, we consider the findings to be of low SOE. Indirect comparisons, in general, have to be interpreted cautiously because the validity of results is based on assumptions that cannot be completely verified—particularly the similarity of study populations.

### Key Question 3. Psychotherapy Versus Pharmacotherapy for Adults With PTSD

This Key Question (KQ) focused on studies that directly compared a psychological treatment with a pharmacological treatment.

#### Key Points

- Just one trial (N=88) included a head-to-head comparison of a psychotherapy (eye movement desensitization and reprocessing [EMDR]) and a pharmacotherapy (paroxetine). We concluded that the head-to-head evidence was insufficient to draw any firm conclusions about comparative effectiveness because of risk of bias, unknown consistency (with data from just one study), and imprecision.
- 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.

#### Detailed Synthesis

##### Characteristics of Trials

We found one medium risk of bias trial meeting our inclusion criteria. Table 37 summarizes the characteristics of the trial. Further details are provided in Appendix D.

**Table 37. Characteristics of included studies directly comparing psychotherapy with pharmacotherapy**

| Study                             | Arm (N)   | Duration (Followup) | Population Trauma Type   | Baseline PTSD Severity <sup>a</sup> | Mean Age (Y) | % F | % Non-white | Risk of Bias |
|-----------------------------------|---|---------------------|--------------------------|-------------------------------------|--------------|-----|-------------|--------------|
| van der Kolk, 2007 <sup>113</sup> | Fluoxetine (30) <sup>b</sup><br>EMDR (29)<br>Placebo (29) | 8 weeks (6 months)  | Male and female<br>Mixed | 71                                  | 36           | 83  | 33          | Medium       |

CAPS = Clinician-Administered Post Traumatic Stress Disorder Scale; EMDR = eye movement desensitization and reprocessing; F = female; mg = milligram; N = total number randomized/assigned to intervention and control groups; PTSD = posttraumatic stress disorder; y = year

<sup>a</sup>Data reported are mean CAPS total score (1 week). The mean CAPS total score (1 month) was 74.0.

<sup>b</sup>Titration from 10mg/day to max 60 mg/day (mean = 30 mg/day, mode = 40mg/day).

The included trial was conducted in the United States, and randomized subjects to 8 weeks of fluoxetine, EMDR, or placebo.<sup>113</sup> The results related to placebo comparisons are included in KQs 1 and 2. Participants were a heterogeneous group of males and females with a variety of index

trauma types (described as child sexual abuse, child physical abuse, adult sexual assault, adult physical assault, domestic violence, other adult victimization, traumatic loss, war/terrorism/violence, and injury/accident). All were studied in an outpatient specialty mental health setting and were followed for 6 months after treatment ended. The primary outcome was reduction in PTSD symptoms according to the total Clinician-Administered Post Traumatic Stress Disorder Scale (CAPS) score. Secondary outcomes included depression as measured by the Beck Depression Inventory (BDI).

One trial (N=21) comparing paroxetine with cognitive behavioral therapy (CBT)<sup>182</sup> otherwise meeting criteria for this section was rated high risk of bias (Table 38), and thus was not included in our data synthesis.

**Table 38. Characteristics of trials directly comparing psychotherapy with pharmacotherapy excluded from main analyses because of high risk of bias**

| Study                                   | Arm (N)                                  | Duration (Followup)       | Population Trauma Type   | Baseline PTSD Severity <sup>a</sup> | Mean Age (Y) | % F | % Non-white | Risk of Bias |
|---|--|---------------------------|--------------------------|-------------------------------------|--------------|-----|-------------|--------------|
| Frommberger et al., 2004 <sup>182</sup> | Paroxetine (11) <sup>b</sup><br>CBT (10) | 12 weeks (3 and 6 months) | Male and female<br>Mixed | 65.0 to 70.5                        | 43           | 57  | NR          | High         |

CAPS = Clinician-Administered Post Traumatic Stress Disorder Scale; CBT = cognitive behavioral therapy; F = female; mg = milligram; N = total number randomized/assigned to intervention and control groups; NR = not reported; PTSD = posttraumatic stress disorder; y = year

<sup>a</sup>Data reported are mean CAPS total score (CAPS-1 and CAPS-2; time frame [1 week or 1 month] not specified).

<sup>b</sup>Titrated from 10 mg/day to max 50 mg/day (mean = 28 mg/day).

## Results for Psychotherapy Versus Pharmacotherapy

### PTSD Symptom Reduction

The CAPS total score (1 month) was used to assess PTSD symptoms at study entry and followup. The CAPS total score (1 week) was used to assess PTSD symptoms at pre- and posttreatment. After 8 weeks of treatment, the CAPS total score (1 week) was not statistically significantly different between those treated with EMDR and those treated with fluoxetine (32.55 vs. 42.67, respectively,  $p=0.13$ , intention-to-treat analysis, adjusted for baseline). At 6-month posttreatment followup, the CAPS total score (1 month) was significantly lower in the EMDR-treated group than in the fluoxetine-treated group (25.79 vs. 42.12,  $p<0.005$ , intention-to-follow analysis including 85% of randomized subjects, adjusted for baseline). Effect sizes for PTSD symptom reduction favoring EMDR over fluoxetine were larger among participants with adult-onset vs. child-onset traumas.

### Remission

Remission rates favored EMDR-treated subjects compared with fluoxetine-treated subjects at end of treatment, but the difference was not statistically significant (28% vs. 13%,  $p=0.17$ , intention-to-treat analysis). Remission rates were higher for those treated with EMDR than for those treated with fluoxetine at posttreatment followup (58% vs. 0%,  $p<0.001$ , intention-to-follow analysis including 85% of randomized subjects).

### Loss of PTSD Diagnosis

The percentages of subjects no longer meeting diagnostic criteria for PTSD were similar for EMDR compared with fluoxetine at end of treatment (76% vs. 73%,  $p=0.82$ , intention-to-treat



analysis); results at followup found no statistically significant difference (88% vs. 73%,  $p=0.20$ , intention-to-follow analysis including 85% of randomized subjects).

### **Prevention or Reduction of Comorbid Medical or Psychiatric Conditions**

The mean (SD) BDI scores were similar for EMDR compared to fluoxetine at baseline (16.2 vs. 18.2,  $p=NS$ ). At end of treatment, point estimates favored of those treated with EMDR, but differences were not statistically significant (9.10 vs. 13.00,  $p=0.08$ , intention-to-treat analysis). At followup, depression symptom scores were lower in the EMDR-treated group than in the fluoxetine-treated group (5.25 vs. 14.00,  $p<0.001$ , intention-to-follow analysis including 85% of randomized subjects).

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

For this question, we included studies that randomized subjects to the combination of a psychological and a pharmacological treatment compared with either one alone. The intention was to inform whether clinicians should start treatment with combinations of therapies at the outset as opposed to starting with a single modality.

### **Key Points**

- Overall, evidence was insufficient to determine whether combinations of psychological treatments and pharmacological treatments are better than either one alone when initiating treatment.
- Two trials provided limited information related to this Key Question (KQ). Although both trials used prolonged exposure therapy as the psychological treatment, the trials differed in type of trauma population included and the timing of initiating the other intervention.
- The trial most relevant for this KQ ( $N=37$ ) found greater improvement in PTSD symptoms (Clinician-Administered PTSD Scale [CAPS] -51.1 vs. -29.8,  $p = 0.01$ ) and greater likelihood of remission for those treated with both prolonged exposure and paroxetine than those treated with prolonged exposure plus placebo.<sup>183</sup> Evidence was limited by unknown consistency (single trial), attrition, and imprecision.

## **Detailed Synthesis**

### **Characteristics of Trials**

Table 39 summarizes the characteristics of the two trials meeting our inclusion criteria. Further details describing the trials are provided in Appendix D. Both were conducted in the United States.

**Table 39. Characteristics of included trials assessing combinations of treatments compared with either one alone**

| Study                                | Arm Dose mg/day (N)                                       | Duration (Followup)         | Population Trauma Type                       | Baseline PTSD Severity <sup>a</sup> | Mean Age (Y) | % F | % Non-white | Risk of Bias |
|--------------------------------------|---|-----------------------------|--|-------------------------------------|--------------|-----|-------------|--------------|
| Schneier et al., 2012 <sup>183</sup> | PE+paroxetine 12.5 to 50 (19)<br>PE+placebo (18)          | 10 to 22 weeks <sup>b</sup> | Male and female<br>World Trade Center Attack | 65.4 to 72.6                        | 50           | 54  | 32          | Medium       |
| Rothbaum et al., 2006 <sup>184</sup> | Sertraline 25 to 200+PE (34)<br>Sertraline 25 to 200 (31) | 6 weeks                     | Male and female<br>Mixed                     | SIP 15.3 <sup>c</sup>               | 39           | 65  | 20          | Medium       |

CAPS = Clinician-Administered Post Traumatic Stress Disorder Scale; F = female; mg = milligram; N = total number randomized/assigned to intervention and control groups; PE = prolonged exposure; PTSD = posttraumatic stress disorder; SIP = Structured Interview for PTSD; y = year

<sup>a</sup>Data reported are mean CAPS or range of mean CAPS scores across groups unless another instrument is specified.

<sup>b</sup>Those who completed 10 weeks of treatment were offered an additional 12 weeks of double-blind treatment of paroxetine or placebo alone.

<sup>c</sup>The 15.3 was the mean SIP score at randomization. The mean at the start of the open-label phase was 35.9.

One trial (N=37) compared 10 weeks of prolonged exposure (10 sessions) plus paroxetine with prolonged exposure plus placebo in adult survivors of the World Trade Center attack of September 11, 2001, with chronic PTSD.<sup>183</sup> After 10 weeks of prolonged exposure plus paroxetine or placebo, subjects were offered 12 additional weeks of randomized treatment; 13 subjects in each group began the additional 12 weeks (11 in each group completed it). Adequacy of prior PTSD treatment was not systematically documented, but 15 subjects had been previously medicated for PTSD—9 of these reported prior SSRI treatment—and 20 had previously received psychotherapy, but none reported an adequate course of at least 10 sessions of trauma-focused CBT. The primary outcomes were CAPS score and remission status at weeks 5 and 10.

The other trial (N=65) enrolled subjects with chronic PTSD for 10 weeks of open-label sertraline, followed by randomization to 5 additional weeks of sertraline alone or sertraline plus 10 sessions of twice weekly prolonged exposure.<sup>184</sup> The trial provides limited information about whether to start treatment with combinations of therapies at the outset as opposed to starting with a single modality, primarily because all subjects were treated with 10 weeks of sertraline prior to randomization. This trial was therefore more relevant for the question of whether prolonged exposure adds benefit for people who have been treated with (and responded to) sertraline. Subjects had a variety of types of index traumas including sexual assault (24), nonsexual assault (16), death of another (14), motor vehicle accident (6), combat exposure (1), house fire (1), airplane crash (1), discovering a parent after a nonfatal overdose (1), and a police officer who felt he came close to shooting an unarmed suspect (1). The main outcomes were the Structured Interview for PTSD (SIP) (for PTSD symptoms), the Beck Depression Inventory (BDI), and the State-Trait Anxiety Inventory-State-Anxiety (STAI-S).

We rated one trial otherwise meeting criteria for this section as high risk of bias. We excluded it from our main data synthesis (Table 40). It compared sertraline plus CBT with sertraline alone.<sup>185</sup> We excluded it from our main data synthesis.

**Table 40. Characteristics of trials assessing combinations of treatments compared with either one alone excluded from main analyses because of high risk of bias**

| Study                               | Arm<br>mg/day (N)  | Duration<br>(Followup) | Population<br>Trauma<br>Type                 | Baseline<br>PTSD<br>Severity | Mean<br>Age (Y) | % F | % Non-<br>white | Risk of<br>Bias |
|-------------------------------------|--|------------------------|--|------------------------------|-----------------|-----|-----------------|-----------------|
| Otto et al.,<br>2003 <sup>185</sup> | Sertraline 50 to<br>200+CBT (5)<br>Sertraline 50 to<br>200 (5) | NR                     | Female<br>Cambodian<br>refugees <sup>a</sup> | NR                           | 47              | 100 | 100             | High            |

CBT = cognitive behavioral therapy; F = female; mg = milligram; N = total number randomized/assigned to intervention and control groups; NR = not reported; PTSD = posttraumatic stress disorder; y = year

<sup>a</sup>Subjects still met criteria for PTSD despite pharmacotherapy with clonazepam in combination with an adequate dose of an SSRI other than sertraline.

## Results for Combinations of Psychological Treatments and Pharmacological Treatments Compared With Either One Alone

### PTSD Symptom Reduction

Both trials reported some measure of PTSD symptoms. The trial comparing prolonged exposure (10 sessions) plus paroxetine with prolonged exposure plus placebo in adult survivors of the World Trade Center attack reported greater improvement in symptoms for those treated with both paroxetine and prolonged exposure (CAPS, mean change from baseline to week 10: -51.1 vs. -29.8,  $p=0.01$ ). The evidence from this single trial is insufficient to determine whether the combination is better than prolonged exposure alone for improving PTSD symptoms (due to risk of bias, unknown consistency with data from a single study, and attrition—with 13 subjects completing the trial in each group out of 19 and 18, respectively).

The trial comparing sertraline plus prolonged exposure with sertraline alone provides limited information related to this KQ, primarily because all subjects were treated with 10 weeks of sertraline prior to randomization. The trial therefore is more relevant for the question of whether prolonged exposure adds benefit for people who have been treated with (and responded to) sertraline. For subjects enrolled in the trial, PTSD symptoms decreased from a mean of 35.9 on the Structured Interview for PTSD (SIP), indicating moderate to severe PTSD, to a mean of 15.3 at the point of randomization, indicating mild (rarely and/or not bothersome) PTSD. After randomization, the sertraline plus prolonged exposure group had greater improvement than the group that continued only sertraline (SIP, within-group mean reduction from baseline 5.9 with  $p<0.001$  vs. -0.3,  $p = \text{NS}$ ), although the difference between groups was not statistically significant.

### Remission (No Longer Having Symptoms)

The trial comparing prolonged exposure (10 sessions) plus paroxetine with prolonged exposure plus placebo in adult survivors of the World Trade Center attack reported more subjects in the former group achieving remission (intention-to-treat sample: 42.1% vs. 16.7%, modeled data adjusted for baseline values: OR 12.6; 95% CI, 1.23 to 129), defined as a CAPS score less than 20 and a CGI-C of 1 (very much improved). The findings are limited by the small sample size and missing data—data were available for 13 subjects in each group (out of 19 and 18, respectively). The very wide confidence interval reflects the limited precision of this estimate. Evidence is insufficient to determine whether the combination is better than prolonged exposure

alone for remission (because of unknown consistency with data from a single study, missing data, attrition, and imprecision).

### **Prevention or Reduction of Comorbid Medical or Psychiatric Conditions**

Both trials reported measures of reduction of comorbid psychiatric conditions. The trial comparing prolonged exposure (10 sessions) plus paroxetine with prolonged exposure plus placebo in adult survivors of the World Trade Center attack reported no statistically significant difference in reduction of depression symptoms between groups (HAM-D, -9.2 vs. -5.2,  $p=0.14$ ; modeled data: OR, 0.74; 95% CI, 0.50 to 1.11). The findings are limited by the small sample size and missing data—data were available for 27 out of 37 subjects. The wide confidence interval reflects the limited precision of this estimate. We concluded that evidence is insufficient to determine whether the combination is better than prolonged exposure alone for reduction of depressive symptoms (because of unknown consistency with data from a single study, missing data, and imprecision).

The trial comparing sertraline plus prolonged exposure with sertraline alone found no statistically significant difference between treatment groups for reduction of depression symptoms (change from week 10 to week 15 for mean BDI, -3.2 vs. +0.3,  $p=NS$ ) or anxiety (change from week 10 to week 15 for mean STAI-S, -3.9 vs. 0,  $p=NS$ ); in both cases, point-estimates favored the sertraline plus prolonged exposure group. As described above, this trial provides limited information related to this KQ, primarily because all subjects were treated with 10 weeks of sertraline prior to randomization. Overall, evidence was insufficient to determine whether the combination is better than sertraline alone for reduction of depression or anxiety in people with PTSD (because of the study design, unknown consistency with data from a single study, and imprecision).

### **Quality of Life**

The trial comparing prolonged exposure (10 sessions) plus paroxetine with prolonged exposure plus placebo in adult survivors of the World Trade Center attack reported greater improvement in quality of life for those in the combination treatment group (increase in Q-LES-Q: 20.8 vs. 9.4,  $p=0.02$ ). The findings are limited by the small sample size and missing data/high risk of attrition bias—data were available for just 9 subjects in the combination group and 10 in the prolonged exposure plus placebo group (out of 19 and 18, respectively). In addition, evidence is from a single study. Thus, consistency is unknown and findings have not been reproduced. Thus, evidence is insufficient to determine whether the combination is better than prolonged exposure alone for improving quality of life.

## **Key Question 5. Are Any Treatment Approaches More Effective for Victims of Particular Types of Trauma?**

This Key Question (KQ) evaluated whether any of the treatments are more effective than other treatments for victims of particular types of trauma, such as military/combat trauma, first responders, refugees, disaster victims, assault survivors, and those with exposure to childhood trauma or repeat victimization. For this question, we used two general sources of information: (1) included studies—subgroup analyses reported by individual studies that focus on subjects with a particular type of trauma or comparative effectiveness studies that compared two or more treatments within a group of subjects all with the same trauma type, and (2) subgroup analyses (stratified analyses by trauma type) of our meta-analyses of reduction in PTSD symptoms for the

treatments found to be efficacious in KQs 1 and 2. For the latter, we only had sufficient data to conduct analyses for exposure-based therapy for female assault compared with other trauma types, CBT-mixed therapies for various trauma types, EMDR for female sexual assault compared with other trauma types, and SSRIs for combat trauma compared with mixed trauma (studies enrolling heterogeneous populations). There were often insufficient numbers of trials conducted in subjects with any particular type of trauma to conduct any meaningful stratified analyses and trials often enrolled heterogeneous populations of subjects with a variety of index trauma types (e.g., sexual abuse, nonsexual abuse, combat, injury, motor vehicle accident, natural disaster).

## Key Points

- 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. In addition, many other factors (other than trauma type) vary across studies included in our subgroup analyses. Findings should be considered hypothesis-generating.
- Subgroup analyses from one trial (N=169) that compared cognitive processing therapy, prolonged exposure, and waitlist found that cognitive processing therapy and prolonged exposure had similar effectiveness for participants with a history of child sexual abuse and participants whose sexual abuse occurred during adulthood.<sup>77</sup>
- Subgroup analyses from one trial (N=88) that compared EMDR, fluoxetine, and placebo found that treatments were less effective for those with child-onset trauma.<sup>113</sup> In addition, it found that EMDR was more effective than paroxetine at 6-month posttreatment followup for those with either child- or adult-onset trauma.
- Our subgroup analyses (of our meta-analyses of reduction in PTSD symptoms stratified by trauma type) found no significant difference in efficacy of
  - fluoxetine, paroxetine, or sertraline for studies enrolling mixed trauma populations compared with those enrolling only subjects with combat-related trauma,
  - exposure therapy for studies enrolling females with assault or sexual abuse compared with those enrolling subjects with combat-related trauma or other trauma types, or
  - CBT-mixed therapies for studies enrolling subjects with a history of childhood sexual or physical abuse, females with assault or interpersonal violence, or refugees compared with those enrolling subjects with other trauma types.
- Our subgroup analyses found a trend toward greater efficacy of EMDR for studies enrolling females with a history of sexual assault than for those enrolling subjects with other trauma types—EMDR was found to be efficacious for both groups, but found a large effect size for females with a history of sexual assault (SMD, -1.68; 95% CI, -2.23 to -1.13; two trials, N=71) and a small to medium effect size (that did not reach a statistically significant benefit) for those with other trauma types (SMD, -0.44; 95% CI, -1.03 to 0.15; two trials, N=46).
- For first responders, disaster victims, or those with repeat victimization, we found no studies meeting our inclusion criteria addressing whether any treatment approaches are more or less effective, and data were insufficient to conduct any meaningful subgroup analyses (stratified analyses of our meta-analyses) or to perform meta-regression to explore whether any treatment approaches are more or less effective for these groups.

## Detailed Synthesis: Trauma Type

### Characteristics of Included Studies

Table 41 summarizes the characteristics of the two included studies. Both were randomized controlled trials or subgroup analyses of trials that have been described in previous parts of this report. Study treatment durations ranged from 6 to 8 weeks, with posttreatment follow-up periods from 6 to 9 months. Both studies enrolled subjects with severe PTSD symptoms at baseline. Both used the Clinician-Administered PTSD Scale (CAPS) as the primary outcome measure. Additional details describing the included studies can be found in Appendix D.

**Table 41. Characteristics of studies that evaluated specific trauma types**

| Study   | Arm (N)                                      | Duration (Followup)      | Population Trauma Type   | Baseline PTSD Severity <sup>a</sup> | Mean Age (Y) | % F | % Non-white | Risk of Bias |
|---|--|--------------------------|--|-------------------------------------|--------------|-----|-------------|--------------|
| Resick et al., 2002 <sup>72</sup><br>Resick, et al., 2003 <sup>77</sup> | CPT (62)<br>PE (62)<br>WL (47)               | 6 weeks (3 and 9 months) | Female<br>Sexual assault<br>Subgroup analysis: history of child sexual abuse   | 69.9 to 76.6                        | 32           | 100 | 29          | Medium       |
| van der Kolk et al., 2007 <sup>113</sup>                                | EMDR (29)<br>Fluoxetine (30)<br>Placebo (29) | 8 weeks (6 months)       | Male and female<br>Mixed subgroup analysis: child-onset and adult-onset trauma | 71.2                                | 36           | 83  | 33          | Medium       |

CPT = cognitive processing therapy; EMDR = eye movement desensitization and reprocessing; F = female; N = total number randomized/assigned to intervention and control groups; PE = prolonged exposure; PTSD = posttraumatic stress disorder; WL = waitlist; y = year

<sup>a</sup>Data reported are mean CAPS total or range of mean CAPS total scores across groups unless otherwise specified.

One study compared cognitive processing therapy, prolonged exposure, and waitlist in women with a history of sexual assault and conducted a subgroup analysis for those with a history of childhood sexual abuse (subgroup analysis used data from 121 of the 171 women randomized in the original trial).<sup>72,77</sup> Forty-one percent of all study participants had been sexually abused as children. Participants had slightly more than 14 years of education on average. Time since rape ranged from 3 months to 33 years, with a mean of 8.5 years. Participants with a history of childhood sexual assault reported significantly greater criminal victimization histories than their counterparts with no childhood sexual assault history (number of times victimized, childhood physical abuse, robbery, kidnapping, rape prior to index rape, attempted rape, sexual assault, minor physical assault, and attempted murder). The two groups were similar in terms of age, race, education, and months since index rape.

The other study compared EMDR, fluoxetine, and placebo in subjects with a variety of trauma types including child sexual abuse, child physical abuse, child sexual and physical abuse, adult sexual assault, adult physical assault, domestic violence, other adult victimization, traumatic loss, war/terror/violence, and injury/accident.<sup>113</sup> Participants had experienced mixed trauma exposure at least 1 year prior to intake. For 50 percent of enrolled subjects, trauma onset occurred prior to age 18. The authors reported subgroup analyses for those with child-onset trauma and those with adult-onset trauma.

## **Exposure to Childhood Trauma**

For the study that compared cognitive processing therapy, prolonged exposure, and waitlist, the main analyses found that those who were randomized to one of the active treatments (i.e., cognitive processing therapy or prolonged exposure) had significant reductions in PTSD symptoms and comorbid depression compared with those who were assigned to a waitlist. The subgroup analysis comparing participants with a history of child sexual abuse to those whose sexual abuse occurred during adulthood found that cognitive processing therapy and prolonged exposure had similar effectiveness for both groups.<sup>77</sup>

For the study that compared EMDR, fluoxetine, and placebo, the main analyses 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 (see KQ 3 for additional details). At 6-month followup, more than twice the percentage of participants with adult-onset trauma than with child-onset trauma achieved asymptomatic functioning (75% versus 33%, respectively) in the EMDR group. No participants achieved this level of relief in the fluoxetine or placebo group. For most child-onset trauma participants, neither treatment produced complete remission of PTSD symptoms.

Our subgroup analyses for reduction of PTSD symptoms found no statistically significant difference in efficacy of CBT-mixed therapies for studies enrolling subjects with a history of childhood sexual or physical abuse (SMD, -0.95; 95% CI, -1.93 to 0.02; two trials, N=110) compared with those enrolling subjects with other trauma types (Appendix F). Confidence intervals were wide and overlapped in all cases.

## **Combat-Related Trauma**

We found no studies meeting our inclusion criteria addressing whether any treatment approaches are more or less effective for those with combat-related trauma.

Our subgroup analyses for reduction of PTSD symptoms found no significant difference in efficacy of exposure therapy for studies enrolling subjects with combat-related trauma (just one trial with N=30) compared with those enrolling females with assault or sexual abuse or other trauma types (Appendix F). Confidence intervals were wide and overlapped (for sexual abuse/assault and other types of trauma).

Our subgroup analyses for reduction of PTSD symptoms (change from baseline in CAPS scores) found no statistically significant difference in efficacy of fluoxetine, paroxetine, or sertraline for studies enrolling mixed trauma populations compared with those enrolling only subjects with combat-related trauma (Appendix F). Confidence intervals were wide and overlapped (for mixed and combat-related trauma) in all cases. For example, pooled point estimates for fluoxetine were not significantly different for studies enrolling mixed trauma populations (WMD, -5.9; 95% CI, -10.1 to -1.6) compared with those enrolling only subjects with combat-related trauma (WMD, -9.1; 95% CI, -15.0 to -3.1). Point estimate sometimes favored mixed populations and sometimes favored combat-related trauma populations. The sertraline subgroup analysis for combat-related trauma studies (two trials, total N=211) did not find a statistically significant reduction in PTSD symptoms for those with combat-related trauma (WMD, -2.4; 95% CI, -9.5 to 4.7); however, the confidence interval is wide and overlaps the confidence interval for mixed populations (WMD, -5.8; 95% CI, -9.3 to -2.4).

## **First Responders**

We found no studies meeting our inclusion criteria addressing whether any treatment approaches are more or less effective for first responders. In addition, data were insufficient to conduct any subgroup analyses (stratified analyses of our meta-analyses) or to perform meta-regression to explore whether any treatment approaches are more or less effective for first responders.

## **Refugees**

We found no studies meeting our inclusion criteria addressing whether any treatment approaches are more or less effective for refugees.

Our subgroup analyses for reduction of PTSD symptoms found no statistically significant difference in efficacy of CBT-mixed therapies for studies enrolling refugees (SMD, -1.26; 95% CI, -3.16 to 0.64; two trials, N=64) compared with those enrolling subjects with other trauma types (Appendix F). Confidence intervals were wide and overlapped in all cases.

## **Disaster**

We found no studies meeting our inclusion criteria addressing whether any treatment approaches are more or less effective for disaster victims. In addition, data were insufficient to conduct any subgroup analyses (stratified analyses of our meta-analyses) or to perform meta-regression to explore whether any treatment approaches are more or less effective for disaster victims.

## **Assault or Sexual Abuse**

We found no studies meeting our inclusion criteria addressing whether any treatment approaches are more or less effective for assault survivors.

Our subgroup analyses for reduction of PTSD symptoms found no significant difference in efficacy of exposure therapy for studies enrolling females with assault or sexual abuse (SMD, -1.17; 95% CI, -1.47 to -0.88; four trials) compared with those enrolling subjects with combat-related trauma or other trauma types (Appendix F). Confidence intervals were wide and overlapped (for sexual abuse/assault and other types of trauma).

Our subgroup analyses for reduction of PTSD symptoms found no statistically significant difference in efficacy of CBT-mixed therapies for studies enrolling females with assault or interpersonal violence (SMD, -1.27; 95% CI, -2.16 to -0.37; four trials, N=252) compared with those enrolling subjects with other trauma types (Appendix F). Confidence intervals were wide and overlapped (for female assault/violence and other trauma types) in all cases.

Our subgroup analyses for reduction of PTSD symptoms found greater efficacy of EMDR for studies enrolling females with a history of sexual assault (two trials) than for those enrolling subjects with other trauma types (one trial each for mixed, public transportation workers, and combat-related trauma). Analyses found a large effect size (for benefit for EMDR) for females with a history of sexual assault (SMD, -1.68; 95% CI, -2.23 to -1.13; two trials, N=71) and a small to medium effect size (that did not reach a statistically significant benefit) for those with other trauma types (SMD, -0.44; 95% CI, -1.03 to 0.15; two trials, N=46, Appendix F). We also conducted sensitivity analyses including studies rated high risk of bias. The sensitivity analyses found no significant difference by trauma type. Although the summary effect size was in the same direction, point estimates moved closer together and confidence intervals overlapped (Appendix F).



## Repeat Victimization

We found no studies meeting our inclusion criteria addressing whether any treatment approaches are more or less effective for those with repeat victimization. In addition, data were insufficient to conduct any subgroup analyses (stratified analyses of our meta-analyses) or to perform meta-regression to explore whether any treatment approaches are more or less effective for those with repeat victimization.

## Limitations

We found insufficient data to conduct meaningful subgroup analyses (stratified analyses of our meta-analyses) or meta-regressions for many of the treatments with evidence of efficacy and for many of the trauma types. For example, for cognitive processing therapy, our meta-analysis for PTSD symptom reduction (CAPS scores) included four trials. All four trials found moderate to large benefits of cognitive processing therapy, but with differences in magnitude of benefit (from -20.7 to -51.1). We wanted to explore whether cognitive processing therapy is more or less efficacious for victims of particular types of trauma, but the four trials enrolled populations with three different trauma types (adult sexual assault,<sup>72</sup> childhood sexual abuse,<sup>71</sup> or military<sup>70,74</sup>). With just one trial each for three different trauma types and all finding moderate to large benefits, we can't say with confidence if cognitive processing therapy works more or less for those with various trauma types. However, we observed a larger effect size for those with childhood sexual abuse than for military veterans (and those confidence intervals did not overlap).

As another example, we concluded that evidence supports the efficacy of topiramate for reduction of PTSD symptoms. We wanted to explore whether it is more or less efficacious for victims of particular types of trauma, but we found insufficient data to do so. Our meta-analysis for reduction of symptoms (measured by CAPS) for topiramate included three trials enrolling either mixed populations (two trials<sup>138,141</sup>) or those with combat-related trauma (one trial<sup>137</sup>)—and all three trials found similar results. Similarly, we found insufficient data for venlafaxine—with just two trials, both enrolling a heterogeneous group of subjects with a variety of index trauma types, and both with almost identical findings.

Frequently, trials enrolled heterogeneous populations of subjects with a variety of index trauma types (e.g., sexual abuse, nonsexual abuse, combat, injury, motor vehicle accident, natural disaster). Our ability to make definitive conclusions was limited by heterogeneity of enrolled populations. With individual patient data from trials, additional analyses might be possible. Further, there were often no trials for a given treatment enrolling an entire group of subjects with a particular trauma type. When there were some trials doing so, there were often insufficient numbers of trials (or with few total subjects) conducted in subjects with a particular type of trauma to conduct any meaningful subgroup analyses (stratified analyses of our meta-analyses).

## Key Question 6. Adverse Effects of Treatments for PTSD

For this question, we evaluated the trials included in Key Questions (KQs) 1 through 4. In addition, we searched for nonrandomized controlled trials and observational studies (specifically, prospective cohort studies with an eligible comparison group, and case-control studies). We did not find any nonrandomized trials or observational studies meeting our inclusion criteria (e.g., prospective cohort studies or case-control studies with a sample size of at least 500; see the Methods section). Therefore, the results for this question are based on the trials included in KQs

1 through 4. Throughout this KQ we often describe risks of various adverse events—risks reported are absolute risk differences between intervention and control.

## Key Points: General

- Adverse events were often not collected using standardized measures and methods for systematically capturing adverse events were often not reported.
- Overall, evidence was insufficient to determine comparative rates of adverse events for various interventions—very little head-to-head data were available.

## Key Points: Psychological Treatments

- The vast majority of trials 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.

## Key Points: Pharmacological Treatments

- **Mortality, suicidality, or self-harmful behaviors:** evidence was insufficient to determine whether risk was increased with any of the medications.
- **Withdrawals due to adverse events:** evidence was insufficient to determine whether rates differ between most medications and placebo, mainly because of imprecision. For fluoxetine, sertraline, and venlafaxine, evidence of low strength suggests similar rates (within 1% to 2%) for subjects treated with medication and those who received placebo. For paroxetine, evidence suggests a 4 percent higher rate of withdrawals due to adverse events with paroxetine than with placebo (risk difference [RD], 0.04; 95% confidence interval [CI], 0.00 to 0.07; moderate strength of evidence [SOE]).
- **Specific adverse events**—focusing on medications with evidence of efficacy:
  - For **topiramate**, evidence was insufficient to determine whether the risk of specific adverse events is increased compared with placebo for adults with PTSD.
  - For **fluoxetine**, evidence suggests a small increase (~5%) in the risk of nausea (RD, 0.05; 95% CI, 0.00 to 0.09; low SOE), but was insufficient to determine whether the risk of other specific adverse events is increased.
  - For **paroxetine**, evidence suggests an increase (of 10% to 13%) in the risk of nausea, dry mouth, and somnolence (low SOE), but was insufficient to determine whether the risk of other specific adverse events is increased.
  - For **sertraline**, we found between 7 percent and 12 percent increases in the risk of nausea, diarrhea, fatigue, and decreased appetite (moderate SOE). Findings were insufficient to determine whether the risks of other adverse events are increased.
  - For **venlafaxine**, we found an increased risk (of 6% to 10%) 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.
- Risk of bias of included studies, inconsistency, and imprecision all contributed to the insufficient SOE determinations for most adverse effects.

- Study durations ranged from 8 to 24 weeks and were generally not designed to assess adverse events.

## Detailed Synthesis: Psychological Treatments

### Characteristics of Trials

The included trials are described in KQ 1 on efficacy and comparative effectiveness of pharmacological interventions. Very few of the included trials reported any information about adverse events. One of the 8 included trials of cognitive therapies and none of the 4 included trials of relaxation or stress inoculation training reported any information about adverse events. One trial of cognitive processing therapy reported only that no treatment-related adverse events occurred during the trial.<sup>74</sup> Three of the 15 included trials of exposure therapies, 5 of the 23 trials of CBT-mixed interventions, 1 of the 7 trials of EMDR, and 2 of the 14 trials of other psychological interventions (trauma affect regulation, Seeking Safety, narrative exposure therapy, brief eclectic psychotherapy, imagery rehearsal therapy) reported some information about withdrawals due to adverse events or specific adverse events. Two of the 14 trials of other psychological interventions reported that no treatment-related adverse outcomes were observed during the trials.<sup>119,122</sup> Additional details about the specific number of adverse events reported in each included trial are available in Appendix D.

### Withdrawals Due to Adverse Events

Just 3 of the 23 included trials of CBT-mixed interventions<sup>50,55,64</sup> and 1 of the 7 of EMDR<sup>111</sup> reported any information about withdrawals due to adverse events. None of the trials of other psychological interventions reported withdrawals due to adverse events. With such a small proportion of trials reporting data, evidence was insufficient to draw conclusions. Any conclusions would be highly subject to reporting bias.

### Mortality

Just three of the included trials from KQ 1 reported any information about mortality—one compared prolonged exposure (n=141) with present-centered therapy (n=143);<sup>91</sup> one compared group exposure (n=180) with present-centered therapy (n=180);<sup>92</sup> and one (n=190) compared prolonged exposure, prolonged exposure plus cognitive restructuring, and waitlist.<sup>25</sup> The latter trial reported one postrandomization removal from the trial due to death caused by an unrelated medical condition, but the trial did not report which group the death was in.<sup>25</sup> The trial that compared prolonged exposure with present-centered therapy reported two nonsuicide deaths in the present-centered group and none in the exposure group.<sup>91</sup> The trial that compared group exposure with present-centered therapy reported four deaths in the present-centered group and none in the exposure group.<sup>92</sup>

### Suicide, Suicidal Ideation, or Self-Harmful Behaviors

Four of the included trials from KQ 1 reported any information—one compared prolonged exposure (n=141) with present-centered therapy (n=143);<sup>91</sup> one compared group exposure (n=180) with present-centered therapy (n=180);<sup>92</sup> one (N=32) compared narrative exposure therapy with treatment as usual;<sup>126</sup> and one (N=190) compared prolonged exposure, prolonged exposure plus cognitive restructuring, and waitlist.<sup>25</sup> The latter trial reported that four participants had severe depression and suicidal ideation that required immediate intervention, but

the trial did not report which groups they were in.<sup>25</sup> The trial that compared prolonged exposure with present-centered therapy reported one suicide attempt in the exposure group and three in the present-centered group.<sup>91</sup> The trial that compared group exposure with present-centered therapy reported no suicides in the group exposure arm and one in the present-centered arm.<sup>92</sup> The trial that compared narrative exposure therapy with treatment as usual reported two hospital admissions for suicidal ideation in the narrative exposure therapy group and none in the treatment as usual group.<sup>126</sup>

### **Other Specific Adverse Events**

No information about additional specific adverse events was reported by the vast majority of the psychological intervention trials. A few trials reported on hospitalizations (Appendix D), but with such a small proportion of trials reporting data, and those trials making different comparisons, evidence was insufficient to draw conclusions.

## **Detailed Synthesis: Pharmacological Treatments**

### **Characteristics of Trials**

The included trials are described in KQ 2 on efficacy and comparative effectiveness of pharmacological interventions.

### **Withdrawals Due to Adverse Events**

Of the included trials, all but four reported data on withdrawals due to adverse events—one of olanzapine compared with placebo,<sup>145</sup> two of fluoxetine compared with placebo,<sup>113,162</sup> and one of sertraline compared with citalopram and placebo.<sup>155</sup> Table 42 summarizes the results of our meta-analyses for withdrawals due to adverse events. When we included two rows in the table for any drug, the second row for the drug is a sensitivity analysis that included trials rated as high risk of bias. Additional details and forest plots are available in Appendix F. None of the differences between drug and placebo reached statistical significance for the main analyses or for the sensitivity analyses with the exception of paroxetine. Point estimates usually favored placebo (i.e., fewer withdrawals due to adverse events) or were on the line of no difference (i.e., equal proportion of withdrawals due to adverse events for those treated with drug or placebo).

**Table 42. Results of meta-analyses for withdrawals due to adverse events: risk difference between each medication and placebo**

| Medication class        | Drug        | N              | RD    | 95% CI      | Heterogeneity (I <sup>2</sup> ) |
|-------------------------|-------------|----------------|-------|-------------|---------------------------------|
| Alpha blockers          | Prazosin    | 2 <sup>a</sup> | 0.08  | -0.10, 0.26 | 0%                              |
| Anticonvulsants         | Divalproex  | 1 <sup>b</sup> | 0.04  | -0.04, 0.13 | NA                              |
| Anticonvulsants         | Divalproex  | 2 <sup>c</sup> | 0.04  | -0.04, 0.13 | 0%                              |
| Anticonvulsants         | Tiagabine   | 1 <sup>d</sup> | 0.00  | -0.07, 0.07 | NA                              |
| Anticonvulsants         | Topiramate  | 3 <sup>e</sup> | 0.01  | -0.08, 0.10 | 0%                              |
| Anticonvulsants         | Topiramate  | 4 <sup>f</sup> | 0.06  | -0.06, 0.18 | 44.6%                           |
| Atypical antipsychotics | Olanzapine  | 1 <sup>g</sup> | 0.08  | -0.32, 0.47 | NA                              |
| Atypical antipsychotics | Risperidone | 5 <sup>h</sup> | 0.00  | -0.02, 0.02 | 0%                              |
| Atypical antipsychotics | Risperidone | 7 <sup>i</sup> | 0.01  | -0.02, 0.05 | 9.4%                            |
| SSRIs                   | Fluoxetine  | 3 <sup>j</sup> | -0.01 | -0.04, 0.03 | 4.3%                            |
| SSRIs                   | Fluoxetine  | 4 <sup>k</sup> | -0.00 | -0.04, 0.03 | 0.3%                            |
| SSRIs                   | Paroxetine  | 3 <sup>l</sup> | 0.04  | 0.00, 0.07  | 0%                              |
| SSRIs                   | Paroxetine  | 4 <sup>m</sup> | 0.03  | -0.00, 0.06 | 0%                              |
| SSRIs                   | Setraline   | 7 <sup>n</sup> | 0.01  | -0.01, 0.04 | 0%                              |
| SNRI                    | Venlafaxine | 2 <sup>o</sup> | 0.02  | -0.03, 0.07 | 28.7%                           |
| Other SGAs              | Mirtazapine | 1 <sup>p</sup> | -0.16 | -0.51, 0.20 | NA                              |
| Other SGAs              | Nefazodone  | 1 <sup>q</sup> | 0.12  | -0.07, 0.31 | NA                              |

CI = confidence interval; N = number of trials included in analysis; RD = risk difference; SGA = second-generation antidepressant; SSRI = selective serotonin re-uptake inhibitor

<sup>a</sup>Studies included in analysis: Raskind et al., 2003,<sup>135</sup> Raskind et al., 2007.<sup>136</sup>

<sup>b</sup>Studies included in analysis: Davis et al., 2008.<sup>139</sup>

<sup>c</sup>Studies included in analysis: Davis et al., 2008,<sup>139</sup> Hamner, 2009.<sup>148</sup>

<sup>d</sup>Studies included in analysis: Davidson et al., 2001.<sup>167</sup>

<sup>e</sup>Studies included in analysis: Yeh et al., 2011,<sup>138</sup> Tucker et al., 2007,<sup>141</sup> Akuchekian, 2004.<sup>137</sup>

<sup>f</sup>Studies included in analysis: Yeh et al., 2011,<sup>138</sup> Lindley et al., 2007,<sup>144</sup> Tucker et al., 2007,<sup>141</sup> Akuchekian, 2004.<sup>137</sup>

<sup>g</sup>Studies included in analysis: Stein, 2002.<sup>146</sup>

<sup>h</sup>Studies included in analysis: Krystal, 2011,<sup>149</sup> Bartzokis, 2005,<sup>147</sup> Reich, 2005,<sup>151</sup> Hamner, 2003,<sup>148</sup> Monnelly, 2003.<sup>150</sup>

<sup>i</sup>Studies included in analysis: Krystal, 2011,<sup>149</sup> Bartzokis, 2005,<sup>147</sup> Reich, 2005,<sup>151</sup> Hamner, 2003,<sup>148</sup> Monnelly, 2003,<sup>150</sup> Rothbaum, 2008.<sup>152</sup>

<sup>j</sup>Studies included in analysis: Martenyi, 2007,<sup>161</sup> Martenyi, 2002,<sup>159</sup> Connor, 1999.<sup>157</sup>

<sup>k</sup>Studies included in analysis: Martenyi, 2007,<sup>161</sup> Martenyi, 2002,<sup>159</sup> Hertzberg, 2000,<sup>171</sup> Connor, 1999.<sup>157</sup>

<sup>l</sup>Studies included in analysis: Simon, 2008,<sup>164</sup> Marshall, 2001,<sup>163</sup> Tucker, 2001.<sup>134</sup>

<sup>m</sup>Studies included in analysis: Simon, 2008,<sup>164</sup> Marshall, 2001,<sup>163</sup> Tucker, 2001,<sup>134</sup> Marshall, 2007.<sup>172</sup>

<sup>n</sup>Studies included in analysis: Panahi, 2011,<sup>169</sup> Friedman, 2007,<sup>168</sup> Davidson, 2006,<sup>133</sup> Brady, 2005,<sup>166</sup> Zohar, 2002,<sup>170</sup> Davidson, 2001,<sup>167</sup> Brady, 2000.<sup>165</sup>

<sup>o</sup>Studies included in analysis: Davidson, 2006,<sup>133</sup> Davidson, 2006.<sup>173</sup>

<sup>p</sup>Studies included in analysis: Davidson, 2003.<sup>179</sup>

<sup>q</sup>Studies included in analysis: Davis, 2004.<sup>29</sup>

Note: Positive risk differences favor placebo.

Focusing on the medications with moderate SOE supporting efficacy (topiramate, fluoxetine, paroxetine, sertraline, and venlafaxine), all point estimates favored placebo except for the comparison between fluoxetine and placebo. Evidence was insufficient to determine whether withdrawals due to adverse events differ between topiramate and placebo, mainly because of imprecision. For fluoxetine, sertraline, and venlafaxine, evidence of low strength suggests similar rates (within 1% to 2%) of withdrawals due to adverse events for subjects treated with medication and those who received placebo. For paroxetine, evidence of moderate strength suggests a 4 percent higher rate of withdrawals due to adverse events with paroxetine than with placebo. Appendix G provides additional details for SOE grades.

## Mortality

Just two of the included medication trials reported any information about mortality—one 12-week trial (N=411) that compared fluoxetine 20mg, fluoxetine 40mg, and placebo<sup>161</sup> and one 12-

week trial (N=538) that compared venlafaxine, sertraline, and placebo.<sup>133</sup> One trial reported no deaths in any participants.<sup>161</sup> The trial that compared venlafaxine, sertraline, and placebo reported that one patient randomized to the venlafaxine ER group died, secondary to acute coronary insufficiency.<sup>133</sup> The investigators considered the death unrelated to study medication—the subject was an obese 62-year-old veteran who was a smoker with a history of treated type 2 diabetes, elevated cholesterol, and cardiac problems.<sup>133</sup>

### **Suicide, Suicidal Ideation, or Self-Harmful Behaviors**

Just two of the included medication trials reported any information about suicidality or self-harmful behaviors—one 12-week trial (N=411) that compared fluoxetine 20 mg, fluoxetine 40 mg, and placebo<sup>161</sup> and one 10-week trial (N=25) that compared paroxetine and placebo.<sup>164</sup>

The trial that compared fluoxetine 20 mg (n=163), fluoxetine 40 mg (n=160), and placebo (n=88) reported self-harm related events: one patient in the fluoxetine 40 mg group experience self-harmful behaviors; one patient in the 20 mg fluoxetine group experienced thoughts of self-mutilation, and four patients experienced suicidal ideation (one in the fluoxetine 20 mg group and three in the 40 mg group).<sup>161</sup> Study authors considered two of these to be serious adverse events: one patient with thoughts of self-mutilation in the fluoxetine 20 mg group and one with suicidal ideation in the fluoxetine 40 mg group.

The trial that compared paroxetine with placebo reported one inpatient psychiatric hospitalization for suicidal ideation for a patient (with a previous history of suicidal ideation) who was taking paroxetine.<sup>164</sup>

### **Other Specific Adverse Events, By Medication**

Limited information was reported for most of the medications to allow synthesis of any specific adverse events or to make definitive conclusions. We therefore focus here on the medications with moderate SOE supporting efficacy (see KQ 2)—topiramate, venlafaxine, fluoxetine, paroxetine, and sertraline—to conduct additional meta-analyses for specific adverse events. Additional details about the specific number of adverse events reported in each included trial are available in Appendix D.

### **Topiramate Compared With Placebo**

Of the three trials that compared topiramate with placebo, two reported data on rates of some specific adverse events.<sup>138,141</sup> The other only reported that the reason for the two dropouts in the topiramate group included drug side effects such as sexual dysfunction, light headedness, and dizziness.<sup>137</sup> Table 43 summarizes the results of our meta-analyses (when both trials reported an outcome) and our risk difference calculations (when just one trial reported the outcome). Forest plots are available in Appendix F. Additional details about the specific number of adverse events reported in each trial are available in Appendix D.

**Table 43. Results of meta-analyses and risk difference calculations for specific adverse events: topiramate compared with placebo**

| Outcome          | N Trials       | N Subjects | RD    | 95% CI      | Heterogeneity I <sup>2</sup> |
|------------------|----------------|------------|-------|-------------|------------------------------|
| Headache         | 2 <sup>a</sup> | 75         | -0.01 | -0.21, 0.18 | 12.9%                        |
| Insomnia         | 2 <sup>a</sup> | 75         | 0.12  | -0.05, 0.28 | 0%                           |
| Somnolence       | 1 <sup>b</sup> | 35         | -0.10 | -0.39, 0.20 | NA                           |
| Taste perversion | 1 <sup>c</sup> | 40         | 0.25  | 0.04, 0.46  | NA                           |
| Dyspepsia        | 1 <sup>c</sup> | 40         | 0.10  | -0.12, 0.32 | NA                           |
| Paresthesia      | 1 <sup>c</sup> | 40         | 0.15  | -0.05, 0.35 | NA                           |
| Nervousness      | 1 <sup>c</sup> | 40         | 0.15  | -0.05, 0.35 | NA                           |
| Fatigue          | 1 <sup>c</sup> | 40         | 0.20  | 0.00, 0.40  | NA                           |

CI = confidence interval; N = number of trials or subjects contributing data; RD = risk difference

<sup>a</sup>Studies included in meta-analysis: Yeh et al., 2011,<sup>138</sup> Tucker et al., 2007.<sup>141</sup>

<sup>b</sup>Studies included in risk difference calculation: Yeh et al., 2011.<sup>138</sup>

<sup>c</sup>Studies included in risk difference calculation: Tucker et al., 2007.<sup>141</sup>

Note: Positive risk differences favor placebo.

One trial also reported mean change in weight, finding a greater mean reduction in weight for the topiramate group than for the placebo group, but the difference was not statistically significant (-1.8±3.3 kg vs. -1.1±2.8 kg, p=0.43).<sup>141</sup>

Overall, findings for topiramate were insufficient to determine whether the risk of any of the specific adverse events is increased compared with placebo for adults with PTSD. Just two trials (total N=75) contributed data; with most specific adverse events only reported by one trial (with N of either 35 or 40 subjects). Risk of bias, unknown consistency (as data were often from just one study), and imprecision all contributed to our determination that evidence was insufficient to draw conclusions. Data suggest that the risk of insomnia, taste perversion, dyspepsia, paresthesias, nervousness, and fatigue may be increased with topiramate.

## SSRIs Compared With Placebo

### Fluoxetine Compared With Placebo

Of the five trials that compared fluoxetine with placebo, three reported data on rates of some specific adverse events.<sup>160-162</sup> Table 44 summarizes the results of our meta-analyses (when multiple trials reported an outcome) and our risk difference calculations (when just one trial reported the outcome). Forest plots are available in Appendix F. Additional details about the specific number of adverse events reported in each trial are available in Appendix D.

**Table 44. Results of meta-analyses and risk difference calculations for specific adverse events: fluoxetine compared with placebo**

| Outcome    | N Trials       | N Subjects | RD   | 95% CI      | Heterogeneity I <sup>2</sup> |
|------------|----------------|------------|------|-------------|------------------------------|
| Headache   | 3 <sup>a</sup> | 776        | 0.03 | -0.04, 0.09 | 28.2                         |
| Nausea     | 2 <sup>b</sup> | 712        | 0.05 | 0.00, 0.09  | 0                            |
| Insomnia   | 1 <sup>b</sup> | 301        | 0.03 | -0.06, 0.11 | NA                           |
| Diarrhea   | 1 <sup>c</sup> | 64         | 0.24 | 0.01, 0.47  | NA                           |
| Somnolence | 1 <sup>d</sup> | 411        | 0.05 | 0.00, 0.10  | 0                            |

CI = confidence interval; N = number of trials or subjects contributing data; RD = risk difference

<sup>a</sup>Studies included in meta-analysis: van der Kolk et al., 1994,<sup>162</sup> Martenyi et al., 2006,<sup>160</sup> Martenyi et al., 2007.<sup>161</sup>

<sup>b</sup>Studies included in meta-analysis: Martenyi et al., 2006,<sup>160</sup> Martenyi et al., 2007.<sup>161</sup>

<sup>c</sup>Studies included in risk difference calculation: van der Kolk et al., 1994.<sup>162</sup>

<sup>d</sup>Studies included in risk difference calculation: Martenyi et al., 2007.<sup>161</sup>

Note: Positive risk differences favor placebo.

The trial comparing fluoxetine 20mg (n=163), fluoxetine 40mg (n=160), and placebo (n=88) reported that no deaths occurred during 12 weeks of treatment.<sup>161</sup> It reported the following “serious adverse events”: one patient experienced thoughts of self-mutilation in the fluoxetine 20mg group; two patients had anxiety, one had chest pain, one had suicidal ideation, and one had gastritis in the fluoxetine 40mg group; and one patient reported palpitations and one thyroid carcinoma in the placebo group.

Overall, findings for fluoxetine were insufficient to determine whether the risk of most of the specific adverse events is increased compared with placebo for adults with PTSD. Three trials (total N=776) contributed data; with most specific adverse events only reported by one trial. Evidence suggests a small increase (~5%) in the risk of nausea (low SOE). The one trial reporting diarrhea found a 24 percent increase for those treated with fluoxetine compared with those who received placebo, but data were limited to one trial (N=64), thus consistency is unknown, and findings were imprecise (with confidence interval ranging from 1% to 47%, insufficient SOE). Risk of bias, inconsistency, and imprecision all contributed to our insufficient SOE determinations for most adverse effects. Appendix G provides additional details supporting our SOE grades.

### Paroxetine Compared With Placebo

Of the three trials that compared paroxetine with placebo, two reported specific data for a few adverse events.<sup>134,164</sup> The third provided some narrative description of which adverse events occurred with an incidence of at least 10 percent and twice that of placebo, but did not report the actual data.<sup>163</sup> Table 45 summarizes the results of our risk difference calculations. There were insufficient data to conduct meta-analyses—as none of the adverse events had data reported by more than one trial. Forest plots are available in Appendix F. Additional details about the specific number of adverse events reported in each trial are available in Appendix D.

**Table 45. Results of risk difference calculations for specific adverse events: paroxetine compared with placebo**

| Outcome    | N Trials       | N Subjects | RD    | 95% CI      | Heterogeneity I2 |
|------------|----------------|------------|-------|-------------|------------------|
| Nausea     | 1 <sup>a</sup> | 323        | 0.11  | 0.04, 0.18  | NA               |
| Dry Mouth  | 1 <sup>a</sup> | 323        | 0.10  | 0.04, 0.16  | NA               |
| Somnolence | 1 <sup>a</sup> | 323        | 0.13  | 0.07, 0.20  | NA               |
| Drowsiness | 1 <sup>b</sup> | 25         | -0.15 | -0.51, 0.21 | NA               |

CI = confidence interval; N = number of trials or subjects contributing data; RD = risk difference

<sup>a</sup>Studies included in risk difference calculation: Tucker et al., 2001.<sup>134</sup>

<sup>b</sup>Studies included in risk difference calculation: Simon et al., 2008.<sup>164</sup>

Note: Positive risk differences favor placebo.

The trial (N=563) that provided narrative description reported that the most commonly reported adverse events associated with paroxetine use (with an incidence of at least 10% and twice that of placebo) were asthenia, diarrhea, abnormal ejaculation, impotence, nausea, and somnolence.<sup>163</sup> The majority of the treatment-emergent adverse events were rated as mild to moderate in severity and most occurred at the beginning of treatment. There were no unexpected adverse events, and serious adverse experiences were infrequent (9 of the 365 patients treated with paroxetine). One patient experienced an onset of severe headaches on day 2 of paroxetine treatment and discontinued participation.

Overall, findings for paroxetine were insufficient to determine whether the risk of most specific adverse events is increased compared with placebo for adults with PTSD. Three trials



(total N=911) contributed information, but little data were reported. Evidence suggests an increase (of 10% to 13%) in the risk of nausea, dry mouth, and somnolence (low SOE). Risk of bias, lack of consistency, and imprecision all contributed to the insufficient SOE determinations for some adverse effects. Appendix G provides additional details supporting our SOE grades.

## Sertraline Compared With Placebo

Of the eight trials that compared sertraline with placebo, seven reported data for specific adverse events.<sup>133,155,165,167-170</sup> Table 46 summarizes the results of our meta-analyses (when multiple trials reported an outcome) and our risk difference calculations (when just one trial reported an outcome). Forest plots are available in Appendix F. Additional details about the specific number of adverse events reported in each trial are available in Appendix D.

**Table 46. Results of meta-analyses and risk difference calculations for specific adverse events: sertraline compared with placebo**

| Outcome            | N Trials       | N Subjects | RD    | 95% CI      | Heterogeneity I <sup>2</sup> |
|--------------------|----------------|------------|-------|-------------|------------------------------|
| Headaches          | 6 <sup>a</sup> | 1028       | 0.03  | -0.03, 0.08 | 0.0%                         |
| Nausea             | 7 <sup>b</sup> | 1061       | 0.09  | 0.04, 0.13  | 0.0%                         |
| Insomnia           | 6 <sup>c</sup> | 1019       | 0.05  | -0.02, 0.11 | 44.8%                        |
| Dry Mouth          | 5 <sup>d</sup> | 859        | 0.03  | -0.01, 0.07 | 0.0%                         |
| Diarrhea           | 5 <sup>e</sup> | 986        | 0.12  | 0.07, 0.17  | 0.0%                         |
| Dizziness          | 2 <sup>f</sup> | 385        | 0.04  | -0.02, 0.10 | 0.0%                         |
| Fatigue            | 4 <sup>g</sup> | 762        | 0.07  | 0.03, 0.11  | 0.0%                         |
| Somnolence         | 2 <sup>h</sup> | 521        | 0.01  | -0.08, 0.09 | 51.6%                        |
| Drowsiness         | 4 <sup>i</sup> | 507        | 0.05  | -0.00, 0.11 | 0.0%                         |
| Decreased Appetite | 5 <sup>j</sup> | 705        | 0.07  | 0.01, 0.13  | 43.7%                        |
| Increased Appetite | 2 <sup>k</sup> | 75         | -0.01 | -0.19, 0.16 | 0.0%                         |
| Constipation       | 2 <sup>l</sup> | 422        | 0.02  | -0.03, 0.07 | 0.0%                         |

CI = confidence interval; N = number of trials or subjects contributing data; RD = risk difference

<sup>a</sup>Studies included in analysis: Panahi et al., 2011,<sup>169</sup> Friedman et al., 2007,<sup>168</sup> Davidson et al., 2006,<sup>133</sup> Zohar et al., 2002,<sup>170</sup> Davidson et al., 2001,<sup>167</sup> Brady et al., 2000.<sup>165</sup>

<sup>b</sup>Studies included in analysis: Panahi et al., 2011,<sup>169</sup> Friedman et al., 2007,<sup>168</sup> Davidson et al., 2006,<sup>133</sup> Zohar et al., 2002,<sup>170</sup> Davidson et al., 2001,<sup>167</sup> Brady et al., 2000,<sup>165</sup> Tucker et al., 2003.<sup>155</sup>

<sup>c</sup>Studies included in analysis: Panahi et al., 2011,<sup>169</sup> Friedman et al., 2007,<sup>168</sup> Davidson et al., 2006,<sup>133</sup> Davidson, 2001,<sup>167</sup> Brady, 2000,<sup>165</sup> Tucker, 2003.<sup>155</sup>

<sup>d</sup>Studies included in analysis: Panahi et al., 2011,<sup>169</sup> Davidson et al., 2006,<sup>133</sup> Davidson et al., 2001,<sup>167</sup> Brady et al., 2000,<sup>165</sup> Zohar et al., 2002.<sup>170</sup>

<sup>e</sup>Studies included in analysis: Panahi et al., 2011,<sup>169</sup> Friedman et al., 2007,<sup>168</sup> Davidson et al., 2006,<sup>133</sup> Davidson et al., 2001,<sup>167</sup> Brady et al., 2000.<sup>165</sup>

<sup>f</sup>Studies included in analysis: Davidson et al., 2006,<sup>133</sup> Tucker et al., 2003.<sup>155</sup>

<sup>g</sup>Studies included in analysis: Davidson et al., 2006,<sup>133</sup> Davidson et al., 2001,<sup>167</sup> Tucker et al., 2003,<sup>155</sup> Friedman et al., 2007.<sup>168</sup>

<sup>h</sup>Studies included in analysis: Friedman et al., 2007,<sup>168</sup> Davidson et al., 2006.<sup>133</sup>

<sup>i</sup>Studies included in analysis: Panahi et al., 2011,<sup>169</sup> Zohar et al., 2002,<sup>170</sup> Davidson et al., 2001,<sup>167</sup> Brady et al., 2000.<sup>165</sup>

<sup>j</sup>Studies included in analysis: Panahi et al., 2011,<sup>169</sup> Zohar et al., 2002,<sup>170</sup> Davidson et al., 2001,<sup>167</sup> Davidson et al., 2006,<sup>133</sup> Tucker et al., 2003.<sup>155</sup>

<sup>k</sup>Studies included in analysis: Zohar et al., 2002,<sup>170</sup> Tucker et al., 2003.<sup>155</sup>

<sup>l</sup>Studies included in analysis: Panahi et al., 2011,<sup>169</sup> Davidson et al., 2006.<sup>133</sup>

Note: Positive risk differences favor placebo.

Overall, findings suggest increases in the risk of some specific adverse effects for people treated with sertraline. Evidence of moderate strength found between 7 percent and 12 percent increases in the risk of nausea, diarrhea, fatigue, and decreased appetite. Findings were insufficient to determine whether the risks of headache, insomnia, dry mouth, dizziness, somnolence, drowsiness, increased appetite, or constipation are increased for subjects treated with sertraline compared with those who received placebo. Risk of bias, inconsistency, and

imprecision all contributed to the insufficient SOE determinations. Appendix G provides additional details supporting our SOE grades.

## Venlafaxine Compared With Placebo

Of the two included trials that compared venlafaxine with placebo (total N=687), both reported data on rates of some specific adverse events.<sup>133,173</sup> Table 47 summarizes the results of our meta-analyses (when both trials reported an outcome) and our risk difference calculations (when just one trial reported the outcome). Forest plots are available in Appendix F. Additional details about the specific number of adverse events reported in each trial are available in Appendix D.

**Table 47. Results of meta-analyses and risk difference calculations for specific adverse events: venlafaxine compared with placebo**

| Outcome            | N trials       | N subjects | RD    | 95% CI      | Heterogeneity I <sup>2</sup> |
|--------------------|----------------|------------|-------|-------------|------------------------------|
| Headache           | 2 <sup>a</sup> | 687        | 0.01  | -0.06, 0.07 | 0.0%                         |
| Nausea             | 2 <sup>a</sup> | 687        | 0.10  | 0.05, 0.16  | 0.0%                         |
| Insomnia           | 2 <sup>a</sup> | 687        | 0.01  | -0.06, 0.08 | 59.3%                        |
| Dry Mouth          | 2 <sup>a</sup> | 687        | 0.07  | 0.02, 0.11  | 0.0%                         |
| Diarrhea           | 1 <sup>b</sup> | 358        | -0.02 | -0.09, 0.05 | NA                           |
| Dizziness          | 2 <sup>a</sup> | 687        | 0.06  | 0.01, 0.11  | 0.0%                         |
| Fatigue            | 2 <sup>a</sup> | 687        | 0.03  | -0.01, 0.07 | 0.0%                         |
| Somnolence         | 2 <sup>a</sup> | 687        | -0.00 | -0.04, 0.04 | 0.0%                         |
| Decreased Appetite | 1 <sup>b</sup> | 358        | 0.06  | -0.00, 0.11 | NA                           |
| Constipation       | 2 <sup>a</sup> | 687        | 0.06  | -0.02, 0.13 | 68.0%                        |

CI = confidence interval; N = number of trials or subjects contributing data; RD = risk difference

<sup>a</sup>Studies included in meta-analysis: Davidson, 2006,<sup>133</sup> Davidson, 2006.<sup>173</sup>

<sup>b</sup>Studies included in risk difference calculation: Davidson, 2006.<sup>133</sup>

Note: Positive risk differences favor placebo.

Overall, findings suggest small increases in the risk of some specific adverse effects for people treated with venlafaxine and no difference between venlafaxine and placebo for others. Evidence of moderate strength found a small increased risk (risk difference of 6% to 10%) of nausea, dry mouth, and dizziness for subjects treated with venlafaxine compared with those who received placebo. 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 insomnia, diarrhea, fatigue, decreased appetite, or constipation are increased for subjects treated with venlafaxine compared with those who received placebo. Risk of bias, inconsistency, and imprecision all contributed to the insufficient SOE determinations. Appendix G provides additional details supporting our SOE grades.

## Detailed Synthesis: Head-to-Head Studies of Psychological and Pharmacological Interventions

One included trial (N=88) compared a psychotherapy (EMDR) and a pharmacotherapy (fluoxetine).<sup>113</sup> It is described in KQ 3. The trial did not report any information about withdrawals due to adverse events, mortality, suicide, suicidal ideation, self-harmful behaviors, or other specific adverse events.

## **Detailed Synthesis: Combinations of Psychological Treatments and Pharmacological Treatments Compared With Either One Alone**

Two included trials compared combinations with a psychological or pharmacological treatment alone. Both are described in KQ 4. Neither trial reported any data about withdrawals due to adverse events, mortality, suicide, suicidal ideation, self-harmful behaviors, or other specific adverse events. One reported that treatment-emergent adverse events were numerically greater in the prolonged exposure plus paroxetine group but did not differ significantly from those of the prolonged exposure plus placebo group, but the trial did not report any data.<sup>183</sup>

## Discussion

We aimed to conduct a systematic review and meta-analysis of the comparative effectiveness and harms of psychological and pharmacological interventions for adults with posttraumatic stress disorder (PTSD). Given that there is some disagreement about whether various treatments are efficacious, we first assessed evidence for efficacy of the treatments of interest and then proceeded to assess comparative effectiveness. We also used this approach because our preliminary searches and input from experts during the topic refinement process suggested that we would find little head-to-head comparative evidence and that we might need to rely on indirect evidence to attempt to make conclusions about comparative effectiveness.

Below, we summarize the main findings and strength of evidence (SOE) by Key Question (KQ). We then discuss the findings in relation to what is already known, applicability of the findings, implications for decisionmaking, limitations, research gaps, and conclusions. When we have graded evidence as insufficient, it indicates that evidence is either unavailable, does not permit estimation of an effect, or does not permit us to draw a conclusion with at least a low level of confidence. It does not indicate that a treatment has been proven to lack efficacy.

### Key Findings and Strength of Evidence

Our results are based on studies we rated as low or medium for risk of bias. To determine whether this influenced our conclusions, we used studies rated as high risk of bias in sensitivity analyses. 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. The results did not change from statistically significant to nonsignificant or vice versa, with two exceptions: risperidone compared with placebo for PTSD symptom reduction and exposure therapy compared with stress inoculation training for loss of PTSD diagnosis. The main analysis found a statistically significant improvement in symptoms for risperidone (weighted mean difference [WMD] for change from baseline in the Clinician-Administered PTSD Scale [CAPS] of -4.6; 95% CI, -9.0 to -0.2), whereas the sensitivity analysis adding high risk of bias studies was nonsignificant (WMD, -4.0; 95% CI, -8.5 to 0.49). The main analysis found no statistically significant difference between exposure therapy and stress inoculation training for achieving loss of diagnosis (risk difference [RD], 0.18; 95% CI, -0.09 to 0.45; 1 trial, N=51), whereas the sensitivity analysis adding the only high risk of bias study found a significant difference favoring exposure therapy (RD, 0.26; 95% CI, 0.04 to 0.48; 2 trials, N=75).

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

### 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 cognitive processing therapy, 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 PTSD diagnosis. Evidence was insufficient to determine efficacy of relaxation, stress inoculation training, seeking safety, or

imagery rehearsal therapy. Of note, seeking safety was developed to target substance use disorders, and imagery rehearsal therapy was designed to focus specifically on nightmares rather than on PTSD.

Effect sizes were generally large for the 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 4 or less to achieve one loss of PTSD diagnosis for cognitive processing therapy, CT, exposure, CBT-mixed, and EMDR. Table 48 summarizes the main findings and SOE for the psychological treatments with evidence of efficacy. The outcomes included in the table are those most commonly reported: PTSD symptoms, loss of PTSD diagnosis, and depression symptoms. Evidence was insufficient to determine efficacy for achieving remission (no longer having symptoms) for all psychological treatments except for 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). We noted a few exceptions: 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 if 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 cognitive restructuring (CR) for achieving loss of PTSD diagnosis and (2) seeking safety and active controls (e.g., relapse prevention programs) for PTSD symptom reduction. Table 49 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). With few trials and few total subjects, most of our meta-analyses of head-to-head trials were underpowered to detect anything but medium to large differences between therapies. Evidence was insufficient to determine efficacy for achieving remission (no longer having symptoms) for all comparisons 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 insufficient for all comparisons (usually because no trials making the comparison reported those outcomes).

**Table 48. 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<br>Effect Size (95% CI) <sup>a</sup>  | Strength of Evidence |
|--------------------------------|---------------------|---|----------------------|
| Cognitive processing therapy   | PTSD symptoms       | SMD -1.40 (-1.95 to -0.85; 4 trials, N=299)<br>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             |
| Cognitive therapy <sup>b</sup> | 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)<br>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-M                          | PTSD symptoms       | SMD -1.09 (-1.4 to -0.78; 14 trials, N=825)<br>WMD -31.1 (-42.6 to -19.6; 8 trials, N=476)                                      | Moderate             |
|                                | Loss of diagnosis   | 0.26 (0.11, 0.41; 6 trials, N=290); NNT 4   | Moderate             |
|                                | Depression symptoms | WMD -10.4 (-14.4, -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, -0.74; 4 trials, N=117)   | Moderate             |
| NET                            | PTSD symptoms       | SMD -1.25 (-1.92 to -0.58; 3 trials, N=227)<br>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         |
| BEP                            | 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; BEP = brief eclectic psychotherapy; CAPS = Clinician-Administered PTSD Scale; CBT = cognitive behavior therapy; CBT-M = cognitive behavior therapy—mixed; CI = confidence interval; EMDR = eye movement desensitization and reprocessing; N = number of subjects; NET = narrative exposure therapy; NNT = number needed to treat; PDS = Posttraumatic Diagnostic Scale; PTSD = posttraumatic stress disorder; RD = risk difference; SMD = standardized mean difference; WMD = weighted mean difference

<sup>a</sup>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.<sup>43</sup> Baseline PTSD severity was generally in the severe (CAPS of 60 to 79) or extreme (CAPS ≥80) range across the included trials. Using CAPS, PTSD severity has been categorized as asymptomatic/few symptoms (0 to 19), mild PTSD/subthreshold (20 to 39), moderate PTSD/threshold (40 to 59), severe, and extreme.<sup>40</sup> 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*.

<sup>b</sup>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.

**Table 49. 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<br>Effect Size (95% CI) <sup>a</sup>  | 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) <sup>b</sup>  | 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         |

**Table 49. 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 (continued)**

| Comparison                                      | Outcome             | Results<br>Effect Size (95% CI) <sup>a</sup>  | Strength of Evidence |
|---|---------------------|---|----------------------|
| 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 treatment               | Insufficient         |
|   | Depression symptoms | 1 trial (N=140) reported more rapid improvement with EMDR but no difference after treatment               | Insufficient         |
| Seeking safety vs. active controls <sup>c</sup> | PTSD symptoms       | SMD 0.04 (-0.12 to 0.20; 4 trials, N=594)<br>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         |

CAPS = Clinician-Administered PTSD Scale; CBT-M = cognitive behavior therapy—mixed; CI = confidence interval; CR = cognitive restructuring; CT = cognitive therapy; EMDR = eye movement desensitization and reprocessing; N = number of subjects; PE = prolonged exposure; PTSD = posttraumatic stress disorder; RD = risk difference; SIT = stress inoculation training; SMD = standardized mean difference; WMD = weighted mean difference

<sup>a</sup>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 to 79) or extreme (CAPS ≥80) range across the included trials. Using CAPS, PTSD severity has been categorized as asymptomatic/few symptoms (0 to 19), mild PTSD/subthreshold (20 to 39), moderate PTSD/threshold (40 to 59), severe, and extreme.<sup>40</sup> For loss of diagnosis, data are risk difference (95% CI, number of trials and number of subjects contributing data) for the comparison between the two 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.

<sup>b</sup>Mean CAPS improvement: 38 (95% CI, 26 to 50) vs. 14 (95% CI, 4 to 25) in 1 trial;<sup>46</sup> between-group effect size was very large favoring CBT-M (Cohen’s d=1.6) in another.<sup>47</sup>

<sup>c</sup>Active controls were relapse prevention, psychoeducation, and treatment as usual in a VA substance use disorders clinic.

Note: Table only includes rows 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 the 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 50 summarizes the main findings and SOE for the pharmacological treatments with evidence of efficacy. The outcomes included in the table are those most commonly reported: PTSD symptoms, remission, and reduction of depression symptoms. Unlike the studies of psychological treatments, which often reported loss of PTSD diagnosis as an outcome, evidence was insufficient to determine efficacy for achieving loss of PTSD diagnosis for all of the pharmacological treatments because studies generally did not report it 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 usually insufficient (often with no trials reporting those outcomes). We noted a few exceptions: evidence supported 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).

**Table 50. 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<br>Effect Size (95% CI) <sup>a</sup>   | Strength of Evidence |
|------------------|----------------|---------------------|--|----------------------|
| Anticonvulsant   | Topiramate     | PTSD symptoms       | WMD -15.5 (-19.4 to -11.7; 3 trials, N=142)<br>SMD -0.96 (-1.89 to -0.03; 3 trials, 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)<br>HAMD -50.7% vs. -33.3, p=0.253 (1 trial, N=40)      | Insufficient         |
| Antipsychotic    | Risperidone    | PTSD symptoms       | WMD -4.60 (-9.0 to -0.2; 4 trials, N=419)<br>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)<br>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)<br>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)<br>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)<br>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 <sup>b</sup>   | Moderate             |
|                  |                | Depression symptoms | MADRS WMD -5.7 (-7.1 to -4.3; 2 trials, N=886)<br>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)<br>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)<br>SMD -0.13 (-0.32 to 0.06; 7 trials, N=1,085) | Low                  |

BDI = Beck Depression Inventory; CAPS = Clinician-Administered PTSD Scale; CI = confidence interval; ER= extended release; HAMD = Hamilton Rating Scale for Depression; 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 inhibitors; SSRI = selective serotonin reuptake inhibitors; WMD = weighted mean difference  
<sup>a</sup>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 to 79) or extreme (CAPS ≥80) range across the included trials. Using CAPS, PTSD severity has been categorized as asymptomatic/few symptoms (0 to 19), mild PTSD/subthreshold (20 to 39), moderate PTSD/threshold (40 to 59), severe, and extreme.<sup>40</sup> 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.<sup>43</sup> For depression symptoms, WMD data are between-group difference for mean change from baseline in BDI, HAMD, or MADRS score—whichever measure is specified.

<sup>b</sup>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 a significantly greater proportion of paroxetine-treated subjects achieved remission compared with placebo at week 12 (29.4% vs. 16.5%, p=0.008).<sup>134</sup> The other trial contributing data for this outcome found similar percentages of subjects achieving remission (33% vs. 14%).<sup>164</sup>

Little direct comparative evidence (i.e., head-to-head) was available to determine if pharmacological treatments differ in effectiveness. We identified just three medium-risk-of-bias

trials meeting inclusion criteria. Of those three, just one compared medications that have evidence supporting their efficacy—the trial compared 12 weeks of venlafaxine, sertraline, and placebo in 538 subjects with a variety of index trauma types.<sup>133</sup> It found no statistically significant difference for improvements in PTSD symptoms between venlafaxine and sertraline.

Our network meta-analysis of 28 trials (4,817 subjects) incorporating both direct and indirect evidence found paroxetine and topiramate to be more effective for reducing PTSD symptoms than most other medications included in the analysis. When compared with other medications with at least moderate SOE supporting efficacy, paroxetine was more effective than sertraline (WMD, -7.6; 95% CrI, -12 to -2.8) but was not significantly different from fluoxetine, topiramate, or venlafaxine. When compared with other 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. Of note, these findings have low SOE, because they are based primarily on indirect evidence. 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 there is moderate SOE supporting the efficacy of paroxetine and venlafaxine for achieving remission (with NNTs of ~8) but insufficient evidence to determine the efficacy of other medications for achieving remission.

### **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.<sup>113</sup> 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, because of medium risk of bias, unknown consistency (with data from just one study), and lack of precision (insufficient SOE).

### **Key Question 4: Combinations of Psychological Treatments and Pharmacological Treatments Compared With Either One Alone**

Our intention was to inform whether clinicians should start with combinations of treatments at the outset instead of a single treatment. Two trials provided limited information related to this KQ.<sup>183,184</sup> The most relevant trial (N=37) found greater improvement in PTSD symptoms (CAPS -51.1 versus -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.<sup>183</sup> 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. In addition, many other 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. We noted two exceptions: (1) subgroup analyses from one trial (N=88) that compared EMDR, fluoxetine, and placebo found that treatments were less effective for those with child-onset trauma and that EMDR was more effective than paroxetine at 6-month posttreatment followup for those with either child- or adult-onset trauma;<sup>113</sup> and (2) our subgroup analyses found a trend toward greater efficacy of EMDR for studies enrolling females with a history of sexual assault compared with those enrolling subjects with other trauma types—we found that EMDR was efficacious for both groups, but we noted a large effect size for females with a history of sexual assault (standardized mean difference [SMD], -1.68; 95% CI, -2.23 to -1.13; 2 trials, N=71) and a small to medium effect size (that did not reach a statistically significant benefit) for those with other trauma types (SMD, -0.44; 95% CI, -1.03 to 0.15; 2 trials, N=46).

## **Key Question 6: Adverse Effects of Treatments**

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 were often not reported. Focusing on the medications with moderate SOE supporting efficacy (see KQ 2)—topiramate, venlafaxine, fluoxetine, paroxetine, and sertraline—Table 51 summarizes the findings and SOE for selected specific adverse events. Most of the evidence for these events was insufficient to determine whether the risk was increased, often primarily because of lack of precision.

**Table 51. Risk difference and strength of evidence for selected adverse effects of pharmacological treatments compared with placebo<sup>a</sup>**

| Medication Class | Medication     | Outcome                | Results<br>Effect Size (95% CI) <sup>b</sup>                                       | Strength of Evidence |
|------------------|----------------|------------------------|--|----------------------|
| Anticonvulsant   | Topiramate     | W/D due to AE          | 0.01 (-0.08 to 0.10; 3 trials, N=142)  | Insufficient         |
|                  |                | Headache               | -0.01 (-0.21 to 0.18; 2 trials, N=75)  | Insufficient         |
|                  |                | Insomnia               | 0.12 (-0.05 to 0.28; 2 trials, N=75)   | Insufficient         |
|                  |                | Somnolence             | -0.10 (-0.39 to 0.20; 1 trial, N=35)   | Insufficient         |
|                  |                | Taste perversion       | 0.25 (0.04 to 0.46; 1 trial, N=40)   | Insufficient         |
|                  |                | Dyspepsia              | 0.10 (-0.12 to 0.32; 1 trial, N=40)  | Insufficient         |
|                  |                | Paresthesia            | 0.15 (-0.05 to 0.35; 1 trial, N=40)  | Insufficient         |
|                  |                | Nervousness            | 0.15 (-0.05 to 0.35; 1 trial, N=40)  | Insufficient         |
| SNRI             | Venlafaxine ER | Fatigue                | 0.20 (0.00 to 0.40; 1 trial, N=40)   | Insufficient         |
|                  |                | W/D due to AE          | 0.02 (-0.03 to 0.07; 2 trials, N=687)  | Low                  |
|                  |                | Headache               | 0.01 (-0.06 to 0.07; 2 trials, N=687)  | Low                  |
|                  |                | Nausea                 | 0.10 (0.05 to 0.16; 2 trials, N=687)   | Moderate             |
|                  |                | Insomnia               | 0.01 (-0.06 to 0.08; 2 trials, N=687)  | Insufficient         |
|                  |                | Dry mouth              | 0.07 (0.02 to 0.11; 2 trials, N=687)   | Moderate             |
|                  |                | Diarrhea               | -0.02 (-0.09 to 0.05; 1 trial, N=358)  | Insufficient         |
|                  |                | Dizziness              | 0.06 (0.01 to 0.11; 2 trials, N=687)   | Moderate             |
|                  |                | Fatigue                | 0.03 (-0.01 to 0.07; 2 trials, N=687)  | Insufficient         |
|                  |                | Somnolence             | -0.00 (-0.04 to 0.04; 2 trials, N=687)   | Low                  |
| SSRI             | Fluoxetine     | Decreased appetite     | 0.06 (-0.00 to 0.11; 1 trial, N=358)   | Insufficient         |
|                  |                | Constipation           | 0.06 (-0.02 to 0.13; 2 trials, N=687)  | Insufficient         |
|                  |                | W/D due to AE          | -0.01 (-0.04 to 0.03; 3 trials, N=766)   | Low                  |
|                  |                | Headache               | 0.03 (-0.04 to 0.09; 3 trials, N=776)  | Insufficient         |
|                  |                | Nausea                 | 0.05 (0.00 to 0.09; 2 trials, N=712)   | Low                  |
|                  |                | Insomnia               | 0.03 (-0.06 to 0.11; 1 trial, N=301)   | Insufficient         |
| SSRI             | Paroxetine     | Diarrhea               | 0.24 (0.01 to 0.47; 1 trial, N=64)   | Insufficient         |
|                  |                | Somnolence             | 0.05 (0.00 to 0.10; 1 trial, N=411)  | Insufficient         |
|                  |                | W/D due to AE          | 0.04 (0.00 to 0.07; 3 trials, N=911)   | Moderate             |
|                  |                | Nausea                 | 0.11 (0.04 to 0.18; 2 trials, N=886) <sup>c</sup>                                  | Low                  |
|                  |                | Dry mouth              | 0.10 (0.04 to 0.16; 1 trial, N=323)  | Low                  |
|                  |                | Diarrhea               | Incidence of at least 10% and twice that of placebo; 1 trial, N=563 <sup>163</sup> | Insufficient         |
|                  |                | Somnolence             | 0.13 (0.07 to 0.20; 2 trials, N=886) <sup>c</sup>                                  | Low                  |
| SSRI             | Sertraline     | Drowsiness             | -0.15 (-0.51 to 0.21; 1 trial, N=25)   | Insufficient         |
|                  |                | Sexual adverse effects | Incidence of at least 10% and twice that of placebo; 1 trial, N=563 <sup>163</sup> | Insufficient         |
|                  |                | W/D due to AE          | 0.01 (-0.01 to 0.04; 7 trials, N=1,122)  | Low                  |
|                  |                | Headache               | 0.03 (-0.03 to 0.08; 6 trials, N=1,028)  | Insufficient         |
|                  |                | Nausea                 | 0.09 (0.04 to 0.13; 7 trials, N=1,061)   | Moderate             |
|                  |                | Insomnia               | 0.05 (-0.02 to 0.11; 6 trials, N=1,019)  | Insufficient         |
|                  |                | Dry mouth              | 0.03 (-0.01 to 0.07; 5 trials, N=859)  | Insufficient         |
|                  |                | Diarrhea               | 0.12 (0.07 to 0.17; 5 trials, N=986)   | Moderate             |
|                  |                | Dizziness              | 0.04 (-0.02 to 0.10; 2 trials, N=385)  | Insufficient         |
|                  |                | Fatigue                | 0.07 (0.03 to 0.11; 4 trials, N=762)   | Moderate             |
|                  |                | Somnolence             | 0.01 (-0.08 to 0.09; 2 trials, N=521)  | Insufficient         |
|                  |                | Drowsiness             | 0.05 (-0.00 to 0.11; 4 trials, N=507)  | Insufficient         |
| SSRI             | Sertraline     | Decreased appetite     | 0.07 (0.01 to 0.13; 5 trials, N=705)   | Moderate             |
|                  |                | Increased appetite     | -0.01 (-0.19 to 0.16; 2 trials, N=75)  | Insufficient         |
|                  |                | Constipation           | 0.02 (-0.03 to 0.07; 2 trials, N=422)  | Insufficient         |

AE = adverse events; CI = confidence interval; ER = extended release; N = number; SNRI = serotonin and norepinephrine reuptake inhibitors; SSRI = selective serotonin reuptake inhibitors; W/D = withdrawals

<sup>a</sup>Table includes only those pharmacological treatments with moderate strength of evidence supporting their efficacy.

<sup>b</sup>Data reported are risk differences between medications and placebo (95% CI; number of trials, number of subjects). These data are results of our meta-analyses (if more than one trial reported data) or risk difference calculations (if one trial reported data). Positive risk differences favor placebo (more events in the medication group).

<sup>c</sup>Data are based on the only trial (N=323) reporting sufficient data to determine the risk difference.<sup>134</sup> One additional trial (N=563) that provided narrative description reported that the most commonly reported adverse events associated with paroxetine use (with an incidence of at least 10% and twice that of placebo) were asthenia, diarrhea, abnormal ejaculation, impotence, nausea, and somnolence.<sup>163</sup>

Note: We did not include rows for adverse events with no data (i.e., those with zero included trials reporting data). The adverse events included in the table are those reported by the included studies.

For withdrawals due to adverse events, we found similar rates (within 1% to 2%) 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%) in the risk of nausea for fluoxetine (low SOE); an increase (of 10% to 13%) 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% to 10%) 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.

Overall, evidence was insufficient to determine comparative rates of adverse events for various interventions.

However, other systematic reviews have summarized adverse event evidence for second-generation antidepressants, including selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs), from clinical trials that enroll subjects with depression or other conditions (not subjects with PTSD) and employ similar doses as those used in PTSD trials. Adverse events, including diarrhea, dizziness, dry mouth, fatigue, headache, nausea, sexual dysfunction, sweating, tremor, and weight gain, are commonly reported. Overall, second-generation antidepressants in clinical trials of patients with depression cause similar adverse events; however, the frequency of specific events differs among some antidepressants.<sup>186,187</sup> Evidence from multiple randomized controlled trials indicates that sertraline has a higher incidence of diarrhea than other SSRIs (and other second-generation antidepressants, including SNRIs and venlafaxine).<sup>186,187</sup> Further, of the SSRIs, paroxetine has the highest rate of discontinuation (and fluoxetine the lowest). It is less clear how SSRIs differ in frequency for other adverse events or that they differ in the severity of such events.<sup>186,187</sup>

Evidence from clinical trials enrolling patients with depression indicates that venlafaxine has a higher rate of nausea and vomiting than other second-generation antidepressants and that mirtazapine produces greater weight gain than the SSRIs.<sup>186,187</sup> Further, venlafaxine (like paroxetine) has a higher rate of discontinuation than the other second-generation antidepressants. Finally, venlafaxine has a higher rate of discontinuation due to adverse events than the SSRIs, but it has a lower rate of discontinuation due to lack of efficacy than the SSRIs.<sup>186,187</sup>

For topiramate, most of the evidence derives from trials of patients with epilepsy or trials for prevention of migraine headaches (its two U.S. Food and Drug Administration [FDA]-approved indications). The most common adverse event reported is paresthesias; other common side effects include fatigue, decreased appetite, nausea, diarrhea, and weight loss<sup>188,189</sup> (which is sometimes seen as a benefit).

For risperidone, the most relevant data come from its use in trials involving its FDA-approved indications for schizophrenia and bipolar disorder. Like the other available second-generation antipsychotics, its side effect profile involves sedation and orthostatic hypotension,<sup>190</sup> but the more concerning adverse events include prolactin elevation and extrapyramidal side effects (both greater with risperidone than with the other second-generation antipsychotics) and its high risk for weight gain and associated metabolic complications.<sup>191</sup>

## Findings in Relation to What Is Already Known

Existing guidelines and systematic reviews agree that some psychological therapies are effective treatments for adults with PTSD.<sup>2,13-17,192,193</sup> 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 Institute of Medicine [IOM] report<sup>2</sup>) 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.<sup>13-16</sup> We found insufficient direct evidence (from head-to-head trials) to support this approach. Indirect evidence would suggest that psychological treatments are more effective than pharmacological treatments (because effect sizes for reduction of PTSD symptoms are much larger in trials of the efficacious psychological treatments than in trials of the efficacious pharmacological treatments). However, conclusions based on naïve indirect comparisons can be flawed—primarily because it is difficult to determine how similar populations are across two somewhat different bodies of literature (i.e., studies of psychological treatments and 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 failed, 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.

We reached a few notably different conclusions than those presented in the IOM report.<sup>2</sup> First, we concluded that cognitive processing therapy has moderate evidence supporting efficacy for improving some outcomes for adults with PTSD, whereas the IOM report did not make a specific conclusion about cognitive processing therapy. We believe this difference was due to misclassification of three trials of cognitive processing therapy<sup>70-72</sup> that provided the bulk of the evidence supporting the efficacy of cognitive processing therapy. The IOM report classified these three trials as exposure therapy. Second, the authors concluded that evidence was inadequate to determine whether EMDR is efficacious, whereas we concluded that evidence supports its efficacy (low SOE for PTSD symptom reduction and moderate SOE for loss of diagnosis). They focused on four trials that they determined to have no major limitations<sup>44, 87, 111,</sup>

<sup>113</sup> but noted that only two showed a positive effect for EMDR (thus, with 2 out of 4 positive studies, they could not determine whether EMDR was efficacious). All four of those trials had point estimates favoring EMDR for reduction of PTSD symptoms; however, two of them lacked the power (i.e., they were imprecise) to detect a statistically significant difference between groups. We believe the main reason we reached a different conclusion is that we synthesized the data quantitatively (with meta-analysis) rather than qualitatively—increasing precision and ability to find a difference in these situations. Our meta-analysis for reduction of PTSD symptoms included four trials (3 of those mentioned above plus 1 more<sup>112</sup>); sensitivity analyses showed that removing any of those trials would not significantly change the findings. Finally, we found evidence supporting efficacy of some of the medications, whereas they concluded that evidence was inadequate to support the efficacy of any medications, including SSRIs. We believe that differences in approach to data synthesis (quantitative versus qualitative approach), similar to what we describe above for EMDR, are likely a main part of the explanation for the different conclusions. Of note, other recent systematic reviews, such as those from the Cochrane Collaboration,<sup>194</sup> have also concluded that evidence supports the efficacy of some medications.

Compared with some of the guidelines based on expert consensus and less structured literature reviews (e.g., APA, ISTSS), we reached different conclusions regarding the efficacy of stress inoculation training. For example, the APA guideline supports stress inoculation with moderate clinical confidence (Grade II in the APA system), while we concluded that there was insufficient evidence to determine its efficacy based on one medium risk of bias trial (N=41 total subjects in the stress inoculation training and waitlist arms, combined).<sup>49</sup> We also identified one study we rated as high risk of bias (N=27 total subjects in the stress inoculation training and waitlist arms, combined).<sup>85</sup> The APA used a different approach to data synthesis (qualitative rather than quantitative) and relied more on expert opinion to develop guidelines. The articles cited in the APA report regarding the efficacy of stress inoculation training are a narrative review,<sup>195</sup> the trial that we excluded due to high risk of bias,<sup>85</sup> and a nonrandomized trial<sup>196</sup> that enrolled subjects with rape-related fear and anxiety. We excluded the nonrandomized trial from our review because it did not require subjects to have a PTSD diagnosis (subjects were not assessed to determine if they met criteria for PTSD at any point in time) and because it did not meet our study design criteria for admissible evidence. Of note, the study did not report any outcome measures of PTSD symptoms.

## **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. The studies included 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. For example, 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),<sup>44</sup> CBT-mixed (N=45),<sup>65</sup> and topiramate (N=67).<sup>137</sup> For each of the following, two trials focused on combat-related trauma: cognitive processing therapy (total N=119),<sup>70,74</sup> exposure-based therapy (total N=370;<sup>92,93</sup> another study of exposure-based therapy enrolled those with combat- and terror-related PTSD<sup>90</sup>), and fluoxetine (total N=365).<sup>159,162</sup> Three trials assessing sertraline enrolled a majority of subjects with combat-related trauma (total N=281).<sup>168-170</sup>

Similarly, we did not find evidence to confirm or refute whether treatments are more or less efficacious for many other subgroups, including gender groups, racial or ethnic minorities, refugees, first responders, disaster victims, or for those with certain coexisting conditions, different PTSD symptoms, complex PTSD, exposure to childhood trauma, repeat victimization, or different levels of severity at presentation. Although many studies did not exclude subjects in these subgroups (e.g., those with a history of multiple past traumas, service-connected disability, or coexisting psychiatric conditions such as depression), studies generally did not report whether interventions were efficacious for such subjects either.

Providers may wonder about the applicability of the results to populations suffering from substance use disorders or from other psychiatric and medical comorbidities. In general, many studies excluded those with substance use disorders, cognitive disorders, and “serious” medical conditions. In the following paragraphs, we provide some information about how many studies set various exclusion criteria, first addressing substance use disorders for the trials of psychological treatments and then pharmacological treatments; then addressing other comorbidities.

For psychological treatments, 20 trials (35%) meeting our inclusion criteria excluded persons who had “substance dependence,” 18 trials (32%) excluded persons who had “current” or “active” substance abuse or dependence, and two trials (3.5%) excluded those who had active symptoms related to current substance use (withdrawal, intoxication, or other physical symptoms).<sup>57,121</sup> Four studies (7.0%) enrolled populations with substance use disorders and PTSD.<sup>33,117-119</sup> The remaining studies did not specify any inclusion or exclusion criteria based on substance use.

For the pharmacologic studies, 20 trials (59%) excluded persons who met criteria for alcohol or substance abuse or dependence within a specified time before the start of the study (3 or 6 months). Of the remaining studies, four (11.8%) excluded those with “current” or “active” substance abuse or dependence, five (15%) excluded those with substance dependence only (either implying or stating specifically that abuse was not an exclusion criteria), two (6%) enrolled a population with comorbid PTSD and alcohol dependence, five (15%) required a negative urine-drug screen in addition to other substance use exclusion criteria based on history, and three (9%) did not specify any exclusion criteria related to alcohol or substance use.

Regarding some of the other comorbidities, among the studies of psychological treatments, 47 (82%) excluded those with any psychosis (schizophrenia, current or past history of “psychosis”), 16 (28%) excluded those with bipolar I or II or history of mania, 2 (4%) excluded those with an anxiety disorder, 4 (7%) excluded those with depression, and 2 (4%) excluded those with an eating disorder. These data do not include studies that specified exclusion based only on severe comorbid disorders; for example, some included those with depression but



excluded those with “depression severe enough to require immediate treatment.” Thirty-two studies (56%) excluded participants determined to be at high risk of suicide or self-harm, whereas 13 studies (23%) excluded those with homicidal ideation or those at a “high risk of external violence.” Thirty studies (53%) excluded those with any cognitive disorder, including “organic mental disorder,” “organic mental dysfunction,” “cognitive dysfunction,” “traumatic brain injury,” or “mental retardation.”

In the pharmacologic studies, 24 (71%) excluded those with any history of bipolar disorder or mania; 25 (74%) excluded those with schizophrenia, “psychotic disorder,” or any “prior history of psychosis”; 10 excluded those with an anxiety disorder; and 9 excluded those with “depression.” As above, these counts do not include studies that specified exclusion criteria based on the severity of comorbid disease (e.g., this count does not include those who only excluded bipolar disorder if the person had “active, untreated bipolar disorder”). Nineteen studies (56%) excluded participants determined to be at high risk of suicide or self-harm, and 15 studies (44%) excluded those with homicidal ideation or those at “high risk of external violence.” Seventeen studies (50%) excluded persons with any cognitive disorder (“organic mental disorder or dysfunction,” “cognitive dysfunction,” or “traumatic brain injury”).

## Implications for Clinical and Policy Decisionmaking

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.<sup>17</sup> If numerous treatments are available and patients have no preference for a particular treatment, decisionmaking in the absence of direct evidence from head-to-head trials can be challenging. Nevertheless, choices must be made for patients needing treatments. Given the findings, the magnitude of benefit and SOE found for exposure therapy supports 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. 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 (i.e., no longer having symptoms), with NNTs ~8 to achieve one remission. In addition, paroxetine has evidence of efficacy for improving depression symptoms and functional impairment (moderate SOE), and venlafaxine has evidence of 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.

Evidence was insufficient to determine whether clinicians should begin with combinations of psychological and pharmacological therapies when initiating treatment. The only trial (N=37) that was very relevant for this issue (see KQ 4) found greater improvement in PTSD symptoms for adults treated with prolonged exposure plus an SSRI than for those treated with prolonged exposure alone.<sup>183</sup> The evidence was limited by unknown consistency (single trial), attrition, and lack of precision. Until further research is available to confirm or refute the findings, initial

treatment with combinations of psychological and pharmacological therapies does not seem to be supported by the evidence.

We found little evidence about which treatments are more or less effective for various subgroups of adults with PTSD—including those with different index trauma types. Further research may identify particular patient characteristics that clearly increase the chances of responding or not responding to certain treatments.

Access to and availability of treatments may vary for individuals and by geography. For example, among all the potential psychological treatments for PTSD, the U.S. Department of Veterans Affairs offers prolonged exposure therapy and cognitive processing therapy for its patients.<sup>197</sup> Many people with PTSD never seek or receive treatment—reasons may include symptoms of the disorder itself (e.g., avoidance, anxiety), particular patient characteristics that increase or decrease the likelihood of seeking treatment (e.g., age, marital status, race, comorbidities), lack of availability of treatments, stigma, costs, transportation, or unfamiliarity with accessing treatment.<sup>198-200</sup>

## **Limitations of the Comparative Effectiveness Review Process**

The scope of this review was limited to studies that enrolled adults with PTSD. The AHRQ has commissioned a separate report focused on children.<sup>201</sup> 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. Our review did not include an assessment of some factors important for clinical decision making, such as adherence or interactions with other therapies that could influence real world effectiveness of treatments. Further, we did not review literature on complementary and alternative medicine treatments.

For KQs 1 through 5, we included randomized controlled trials (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 criteria 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; and (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, useful information could possibly 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 the medications.

Our network meta-analysis used methods that do not rely solely on placebo-controlled trials; it allowed for the inclusion of data from head-to-head studies or those with active comparators. However, our network meta-analysis was limited primarily to indirect evidence. Very few head-to-head trials were identified for inclusion. Therefore, findings of the network meta-analysis

should be interpreted with caution. 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.

Finally, publication bias and selective reporting are potential limitations. Although we searched for unpublished studies and unpublished outcomes, and did not find direct evidence of either of these biases, many of the included trials were published prior to the availability of trial registries (e.g., [clinicaltrials.gov](http://clinicaltrials.gov)) that would allow for greater certainty in determining the potential for either type of bias.

## 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. As highlighted in the Key Findings and Strength of Evidence section, too few (and sometimes zero) studies with low- or medium-risk of bias were available to determine (1) whether some of the psychological and pharmacological treatments are efficacious; (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 introducing some risk of bias. We excluded 46 articles from our main data synthesis because of high risk of bias. The available evidence for many of the treatments of interest, especially many of the medications, was limited to few low- or medium-risk-of-bias trials. 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.<sup>186, 187, 202, 203</sup> 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 whether the attrition rates were related to the treatments (e.g., adverse effects, worsening of symptoms).

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 Applicability section).

Reporting of previous treatments and ongoing treatments (i.e., co-interventions) 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. In many cases, studies enrolled a heterogeneous group of subjects currently receiving various treatments that have potential benefits for PTSD.

Descriptions of usual care or treatment as usual were often limited for the included studies of psychological treatments. Interventions received by the groups were often not described in much (or any) detail, making it difficult to determine whether the people in those groups were receiving any care at all. In many studies, the groups seemed to be very similar to waitlist groups (except that the subjects were not on a waitlist to receive an intervention later). For analyses of the efficacy of psychological interventions, our main analyses included studies with both waitlist and usual care (or treatment as usual) control groups. We stratified our meta-analyses by

comparison group to show how the effect size and confidence interval would differ if we only included studies with a waitlist control, as opposed to including those with both waitlist and usual care controls. Of note, pooled effect sizes were very similar when combining studies with waitlist and usual care control groups and when only combining studies with waitlist control groups. Also, the effect sizes were sometimes slightly greater when combining studies with waitlist and usual care control groups than when only combining studies with waitlist control groups (e.g., PTSD symptoms for exposure therapy), and other times they were slightly lower (e.g., PTSD symptoms for cognitive processing therapy).

Heterogeneity of outcome measures used in the included studies also posed some challenges. For example, many different measures of PTSD symptoms were used (e.g., CAPS, Davidson Trauma Scale [DTS], Impact of Event Scale [IES]). In addition, some measures have several versions, such as the CAPS, which has evolved over the past decades into its current form.<sup>40</sup> It was sometimes unclear which version of a measure a study used.

Also, the definitions of loss of PTSD diagnosis and remission were somewhat heterogeneous. They were assessed using several different instruments across the studies. Complete explanations of the approach to assessing remission or loss of PTSD diagnosis were not always provided. For example, it was sometimes implied, but not explicitly stated, that loss of diagnosis was determined by assessment of DSM diagnostic criteria or by using a CAPS score (or another scale, such as the PSS) cutoff indicative of PTSD diagnosis. Further, many studies did not clearly report specific score cutoffs used to define loss of diagnosis or remission when reporting the results.

For many 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.

The timing of outcome assessment in the trials of psychological treatments was more heterogeneous than for the pharmacological trials. This was due in part to the differences in the duration of psychological treatments, as trials generally assessed outcomes after completion of treatment. For some psychological trials, post-treatment outcome measures were reported after a specified number of sessions, rather than a specific time period (see Appendix F for details). For such studies, if the study reported "posttreatment" as the timing of outcome assessment, we used the duration of treatment to indicate the timing (although we realize it may have been shortly thereafter, but such studies didn't always report the specific timing). It does not appear that the timing of post-treatment outcome measures has an influence on the overall conclusions, but the variation in timing of outcome assessment does contribute to the overall heterogeneity.

One criticism of psychological treatment trials has been the possibility of "allegiance bias"—the potential for contamination or distortion of results because of the investigators' theoretical perspective or treatment preferences.<sup>204</sup> One marker of allegiance to a treatment preference is when the developer of the method is a primary author in the study of that method. For some of the psychological therapy interventions, the developer of the methods seemed to be an author on the majority of studies, such as narrative exposure therapy<sup>125-127</sup> and brief eclectic psychotherapy.<sup>21,123</sup> For this report, we did not explore allegiance during our review of the included studies, and it is unclear what effect, if any, this issue has on the overall validity of the results.

## Research Gaps

We identified numerous gaps in the evidence that future research could address. Many of these gaps are highlighted in the Key Findings and Strength of Evidence section and the Limitations of the Evidence Base section. Of note, these gaps relate only to the key questions addressed by this report, and they should not eliminate a wide range of potentially important PTSD-related research that falls outside of the scope of our KQs. Table 52 summarizes the gaps and potential future research that could address the gaps.

In addition to the evidence gaps identified here, other 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.<sup>205</sup> 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).

**Table 52. Evidence gaps for future research, by Key Question**

| KQ | Evidence Gap  | Potential Future Research  |
|----|---|--|
| 1  | Most of the head-to-head evidence was insufficient to determine whether psychological treatments differ in effectiveness.   | Future studies could focus on comparisons between the psychological treatments with the best evidence of efficacy (e.g., exposure compared with cognitive processing therapy).   |
| 1  | Evidence was insufficient to determine efficacy of some psychological treatments.   | Future studies could 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).                       |
| 2  | Head-to-head comparative evidence was insufficient to determine whether pharmacological treatments differ in effectiveness.   | Future studies could focus on comparisons between the medications with moderate strength of evidence supporting their efficacy (fluoxetine, paroxetine, sertraline, topiramate, and venlafaxine).  |
| 2  | Evidence was insufficient to determine efficacy of many medications.  | Future studies could evaluate medications that have some evidence (often from 1 or 2 small trials) suggesting possible efficacy (e.g., prazosin, olanzapine, mirtazapine) or medications that have not yet been studied with some theoretical basis to support their potential efficacy. |
| 3  | Head-to-head evidence was insufficient to determine comparative effectiveness of psychological and pharmacological treatments.  | Future studies could focus on comparisons between the psychological and pharmacological treatments with the best evidence of efficacy (e.g., exposure therapy compared with paroxetine).   |
| 4  | Evidence was insufficient to determine comparative effectiveness of combinations of treatments (psychological plus pharmacological) compared with either one alone.                         | Future studies could focus on comparisons between 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).                                    |
| 5  | Evidence was insufficient to make definitive conclusions about whether any treatment approaches are more effective for victims of particular types of trauma.                               | Future trials could 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.                               |
| 6  | For psychological treatments, the vast majority of studies reported no information about adverse effects.   | Future studies could include validated measures of adverse effects, including assessment of mortality, suicide, suicidal ideation, self-harmful behaviors, and hospitalizations.   |
| 6  | For pharmacological treatments, few studies reported any information about mortality, suicide, suicidal ideation, self-harmful behaviors, or hospitalizations.                              | Future studies could include validated measures of adverse effects, including assessment of mortality, suicide, suicidal ideation, self-harmful behaviors, and hospitalizations.   |
| 6  | For pharmacologic treatments, most of the evidence for specific adverse effects was insufficient to determine whether the risk was increased, often primarily because of lack of precision. | Future studies could include validated measures of adverse effects to assess the risk of common adverse effects that might limit use of the medications (e.g., headache, gastrointestinal adverse effects, sexual adverse effects).  |

EMDR = eye movement desensitization and reprocessing

Note: Within the gaps highlighted above, future research could address how various treatments compare for initial treatment and for treatment-refractory populations.

## Conclusions

Several psychological and pharmacological treatments have at least moderate SOE supporting their efficacy for improving outcomes for adults with PTSD: exposure-based therapy, cognitive processing therapy, 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, cognitive processing therapy, CT, CBT-mixed therapies, and EMDR, effect sizes for improving PTSD symptoms were large (reduction in CAPS from 28.9 to 32.2; Cohen’s d from 1.08 to 1.40), 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; Cohen's d between 0.25 and 0.49 for fluoxetine, paroxetine, sertraline, and venlafaxine; Cohen's d 0.96 for topiramate, but with very wide confidence interval from -1.89 to -0.03). 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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# Appendix A. Outcome Measures and Instruments

Table A-1. Outcome measures and instruments

| Abbreviated Name | Complete Name                         | Description  | Range/Meaning of Possible Scores | Improvement Indicated by |
|------------------|---------------------------------------|--|----------------------------------|--------------------------|
| BDI              | Beck Depression Inventory             | 21-item measure used to assess depression. Self-report or verbally administered by a trained professional administrator. Administration time approximately 5 minutes.  | 0 to 63                          | Decrease                 |
| CAPS             | Clinician-Administered PTSD Scale     | Current version includes a 30-item structured interview administered by a trained professional. Corresponds to the DSM-IV criteria for PTSD symptoms, impact on functioning, response validity, lifetime diagnosis, and overall PTSD severity. Time frame for assessment includes past week, month, or worst month since trauma. Administration time approximately 45 to 60 minutes. In the past there were different versions corresponding to different time periods. CAPS-1 (later renamed CAPS-DX) assessed current and lifetime PTSD diagnosis. The CAPS-2 (later renamed CAPS-SX) assessed the severity of symptoms over the past one week. These two versions were later combined into the current version, which can be used to assess either symptoms or diagnoses. | 0 to 136                         | Decrease                 |
| DTS              | Davidson Trauma Scale                 | 17-item self-report measure that assesses the 17 DSM-IV symptoms of PTSD. Each item corresponds to a DSM-IV symptom of PTSD, and each symptom is rated in terms of frequency and severity. Scores can be calculated for each of the 3 PTSD symptom clusters (B,C, and D). Administration time approximately 10 minutes.  | 0 to 136                         | Decrease                 |
| GAF              | Global Assessment of Functioning      | Clinician administered scale used to assess the social, occupational, and psychological functioning of adults.   | 0 to 100                         | Increase                 |
| HADS             | Hospital Anxiety and Depression Scale | 14-item self-report measure developed to assess anxiety and depression in non-psychiatric populations. Meant to differentiate symptoms of depression with those of anxiety. Administration time 5 minutes.   | 0 to 42                          | Decrease                 |
| HAM-A or HAS     | Hamilton Anxiety Scale                | 14-item clinician administered measure used to assess the severity of anxiety symptoms. Administration time 10 to 15 minutes.  | 0 to 56                          | Decrease                 |
| HAM-D            | Hamilton Depression Scale             | 17 or 21 item (depending on version) clinician administered scale used to measure the severity of depressive   | 0 to 54 (17 item)                | Decrease                 |

| Abbreviated Name | Complete Name                             | Description   | Range/Meaning of Possible Scores           | Improvement Indicated by |
|------------------|---|---|--|--------------------------|
|                  |   | symptoms. Administration time 15 to 20 minutes.   |  |                          |
| IES              | Impact of Event Scale                     | 15-item self-reported measure used to assess the frequency with which experiences of "intrusions," "avoidance," and emotional numbing related to stressful events occurred in the last week. A total distress score is calculated by summing all 15 item responses.   | 0 to 75                                    | Decrease                 |
| IES-R            | Impact of Events Scale-Revised            | 22-item self-report measure that assesses subjective distress caused by traumatic events. Contains 7 items more than the IES regarding hyperarousal symptoms of PTSD. Items correspond directly to 14 of the 17 DSM-IV symptoms of PTSD. Subscales can be computed for Intrusion, Avoidance, and Hyperarousal.  | 0 to 88                                    | Decrease                 |
| MADRS            | Montgomery-Asberg Depression Rating Scale | 10-item clinician rated measure that assesses the severity of depression. Administration time approximately 15 minutes.   | 0 to 60                                    | Decrease                 |
| MISS or M-PTSD   | Mississippi Scale for Combat-related PTSD | 35-item self-report questionnaire used to assess DSM-III combat-related PTSD and related features (depression, suicidality, and substance abuse). Administration time approximately 10 to 15minutes.  | 35 to 175                                  | Decrease                 |
| MPSS-SR          | Modified PTSD Symptom Scale               | 17-item self-report measure that assesses the 17 DSM-III-R symptoms of PTSD. Measure is a modification of the PTSD Symptom Scale (PSS). Major modifications are that items are not keyed to any particular traumatic event and that the MPSS-SR includes severity ratings in addition to the original measure's frequency ratings for each item. It can be used to make a preliminary determination of the diagnosis of PTSD using either DSM-III-R criteria or a frequency, severity, or total score cutoff scores. It can be scored as a continuous measure of PTSD symptom severity. | 0 to 68 (intensity)<br>0 to 51 (frequency) | Decrease                 |
| PTDS or PDS      | Posttraumatic Diagnostic Scale            | 49- item self report measure for severity of PTSD symptoms related to a single identified traumatic event. Assesses all DSM-IV criteria (A-F) in the past month (time frame can be adjusted). Four sections include: trauma checklist, description of post traumatic event, assessment of 17 PTSD symptoms, and interference of symptoms. Total severity score  | 0 to 51                                    | Decrease                 |

| Abbreviated Name | Complete Name   | Description   | Range/Meaning of Possible Scores | Improvement Indicated by |
|------------------|---|---|----------------------------------|--------------------------|
|                  |   | reflecting frequency of 17 PTSD symptoms.   |                                  |                          |
| PCL              | PTSD Checklist  | 17-item self-report measure of the 17 DSM-IV symptoms of PTSD. Has been used to screen individuals for PTSD, diagnose PTSD, and monitor symptom change during and after treatment. There are three versions of the PCL: PCL-M (military), PCL-C (civilian), and PCL-S (specific). Administration time approximately 5 to 10 minutes.  | 17 to 85                         | Decrease                 |
| PTSD-I           | PTSD Interview  | Structured clinical interview. Patients given a copy of scale to read along with interviewer and asked to give subjective ratings for each symptom.   |                                  | Decrease                 |
| PSS-I            | PTSD Symptom Scale Interview  | 17-item semistructured interview that assesses the presence and severity of DSM-IV PTSD symptoms related to a single identified traumatic event in individuals with a known trauma history. Each item is assessed with a brief, single question. Interviewees are asked about symptoms they have experienced in the past 2 weeks. Administration time approximately 20 minutes. | 0 to 51                          | Decrease                 |
| PSS-SR           | PTSD Symptom Scale Self-report Version                              | 17-item self-report scale used to diagnose PTSD according to DSM-III-R criteria. Assesses the severity of PTSD symptoms (consists of the same 17 items as the PSS-I).   | 0 to 51                          | Decrease                 |
| Q-LES-Q-SF       | Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form | 16-item self-report questionnaire that assesses overall enjoyment and satisfaction with physical health, mood, work, household and leisure activities, social and family relationships, daily functioning, sexual life, economic status, overall well-being and medications.  | 14 to 70                         | Increase                 |
| SF-36            | 36-Item Short Form Health Survey                                    | 36-item scale of patient health status. Administration time less than 15 minutes  | 0 to 100 (mean)                  | Increase                 |
| SI-PTSD or SIP   | Structured Interview for PTSD                                       | Assesses the 17 PTSD symptoms as well as survival and behavioral guilt. For each item, the interviewer assigns a severity rating that reflects both frequency and intensity. Responses can be used to make a determination about whether client's symptoms meet DSM criteria B, C, and D for PTSD. Administration time approximately 20 to 30 minutes.                          | 0 to 68                          | Decrease                 |

| <b>Abbreviated Name</b> | <b>Complete Name</b>                                   | <b>Description</b>  | <b>Range/Meaning of Possible Scores</b> | <b>Improvement Indicated by</b> |
|-------------------------|--|---|---|---------------------------------|
| SCID                    | Structured Clinical Interview PTSD Module              | Semistructured interview used to assess the prevalence, absence, and subthreshold presence of PTSD used across trauma populations. Consists of separate modules corresponding to categories of diagnoses. Administration time 25 minutes. | Not quantitatively scored               | Decrease                        |
| SCL-90-R                | Symptom Checklist-90-Revised                           | 90-item self-report questionnaire used to assess a broad range of psychological problems, symptoms of psychopathology, patient progress, and treatment outcomes. Administration time approximately 12 to 15 minutes.                      | 0 to 360                                | Decrease                        |
| SDS                     | Sheehan Disability Scale                               | 5-item self-report measure developed to assess functional impairment in work/school, social and family life.  | 0 to 30                                 | Decrease                        |
| SF-12                   | Medical Outcome Study Self-Report Form                 | 12-item self-report measure of overall health status. Administration time less than 15 minutes.   | 0 to 100                                | Increase                        |
| SPRINT                  | Short PTSD Rating Interview                            | 8-item self-report measure that assesses the core symptoms of PTSD (intrusion, avoidance, numbing, arousal), somatic malaise, stress vulnerability, and role and social functional impairment.  | 0 to 32                                 | Decrease                        |
| STAI                    | State-Trait Anxiety Inventory                          | 20-item self-report measure that assesses state and trait anxiety. Administration time approximately 10 to 20 minutes.  | 20 to 80                                | Decrease                        |
| TOP-8                   | Treatment-outcome post-traumatic stress disorder scale | 8-item measure based on all three symptom clusters of post-traumatic stress disorder.   | 0 to 32                                 | Decrease                        |
| WAS                     | Work and Social Adjustment Scale                       | 5-item measure of general social impairment.  | 0 to 40                                 | Decrease                        |

## Appendix B. Search Strategy

**MEDLINE®:**

| Search | Most Recent Queries   | Result |
|--------|---|--------|
| #1     | Search "Stress Disorders, Post-Traumatic"[Mesh]   | 16684  |
| #2     | Search "post-traumatic stress disorder"[All Fields]   | 4090   |
| #3     | Search "post-traumatic stress disorders"[All Fields]  | 16739  |
| #4     | Search disorder* AND "post-traumatic"[tiab]   | 5983   |
| #5     | Search "Stress Disorders, Traumatic"[Mesh:NOE XP]   | 335    |
| #6     | Search "Combat Disorders"[Mesh]   | 2154   |
| #7     | Search "PTSD"   | 9226   |
| #8     | Search #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7   | 21449  |
| #9     | Search #8 Limits: Humans, English, All Adult: 19+ years, Young Adult: 19-24 years, Adult: 19-44 years, Middle Aged: 45-64 years, Middle Aged + Aged: 45+ years, Aged: 65+ years, 80 and over: 80+ years, Publication Date from 1980/01/01 to 2011/10/01   | 10509  |
| #10    | Search "implosive therapy"[MeSH Terms] OR "implosive therapy"[All Fields] OR ("exposure"[tiab] AND ("therapy"[tiab] OR "psychotherapy"[tiab])) OR "imaginal exposure"   | 22902  |
| #11    | Search "cognitive therapy"[MeSH] OR cognitive restructur*[tiab] OR cognitive processing therap*[tiab]   | 12055  |
| #12    | Search "Adaptation, Psychological"[Mesh] OR coping skill*[tiab]   | 88750  |
| #13    | Search "stress inoculation"   | 113    |
| #14    | Search "assertiveness training"   | 164    |
| #15    | Search psychodynamic[All Fields] AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields])   | 2221   |
| #16    | Search psychodynamic[All Fields] AND ("psychotherapy"[MeSH Terms] OR "psychotherapy"[All Fields])   | 2068   |
| #17    | Search ("psychoanalytic"[All Fields] AND "psychotherapy"[All Fields]) OR "psychoanalytic psychotherapy"[All Fields]   | 5012   |
| #18    | Search ("psycho-analytic"[All Fields] AND "psychotherapy"[All Fields]) OR "psycho-analytic psychotherapy"[All Fields]   | 14     |
| #19    | Search "psychoanalytic therapy"   | 13664  |
| #20    | Search "psycho-analytic therapy"  | 3      |
| #21    | Search "Eye Movement Desensitization Reprocessing"[MeSH] OR "EMDR"[tiab]  | 214    |
| #22    | Search "Psychotherapy"[Mesh]  | 134066 |
| #23    | Search "interpersonal therapy" OR "interpersonal psychotherapy"   | 626    |
| #24    | Search "family therapy"[tiab] OR "marital therapy"[tiab]  | 2591   |
| #25    | Search "group therapy" OR "group psychotherapy" OR "group psychological therapy"  | 12172  |
| #26    | Search "Hypnosis"[Mesh]   | 10183  |
| #27    | Search #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26  | 237601 |
| #28    | Search #9 AND #27   | 2601   |
| #29    | Search "Benzodiazepines"[Mesh]  | 54507  |
| #30    | Search "Antidepressive Agents, Tricyclic"[Pharmacological Action]   | 28037  |
| #31    | Search "Anticonvulsants"[Pharmacological Action]  | 120174 |
| #32    | Search "Adrenergic alpha-Antagonists"[Pharmacological Action]   | 47582  |
| #33    | Search "Antipsychotic Agents"[Pharmacological Action]   | 114583 |
| #34    | Search "Antidepressive Agents"[Pharmacological Action]  | 109682 |
| #35    | Search "citalopram" OR "escitalopram" OR "fluoxetine" OR "fluvoxamine" OR "paroxetine" OR "sertraline" OR "desvenlafaxine" OR "venlafaxine" OR "duloxetine" OR "imipramine" OR "amitriptyline" OR "desipramine" OR "bupropion" OR "mirtazapine" OR "nefazodone" OR "trazodone" OR "prazosin" OR "olanzapine" OR "risperidone" OR "benzodiazepines" [MeSH] OR "alprazolam" OR "diazepam" OR "lorazepam" OR "clonazepam" OR "topiramate" OR "tiagabine" OR "lamotrigine" OR "carbamazepine" OR "divalproex" | 136015 |
| #36    | Search #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35  | 400958 |
| #37    | Search #9 AND #36   | 510    |
| #38    | Search #28 OR #37   | 3023   |
| #39    | Search "Randomized Controlled Trial"[Publication Type] OR "Randomized Controlled Trials"  | 455950 |



| <b>Search</b> | <b>Most Recent Queries</b>  | <b>Result</b> |
|---------------|---|---------------|
|               | as Topic"[Mesh] OR "Single-Blind Method"[Mesh] OR "Double-Blind Method"[Mesh] OR "Random Allocation"[Mesh]  |               |
| #40           | Search "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[All Fields]   | 50159         |
| #41           | Search "Comparative Study"[Publication Type] OR "comparative study" OR case control stud* OR "Case-Control Studies"[Mesh]                                   | 1978917       |
| #42           | Search ("review"[Publication Type] AND "systematic"[tiab]) OR "systematic review"[All Fields] OR ("review literature as topic"[MeSH AND "systematic"[tiab]) | 42848         |
| #43           | Search "Cohort Studies"[Mesh] OR "cohort effect"[MeSH Term] OR cohort*[tiab]  | 1186051       |
| #44           | Search "trial"[tiab]  | 287417        |
| #45           | Search "Treatment Outcome"[Mesh]  | 500945        |
| #46           | Search #38 AND (#39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45)  | 1406          |

**Cochrane:**

| ID  | Search  | Hits   |
|-----|---|--------|
| #1  | "Stress Disorders, Post-Traumatic"[Mesh]  | 708    |
| #2  | "post-traumatic stress disorder"[All Fields]  | 357    |
| #3  | "post-traumatic stress disorders"[All Fields]   | 22     |
| #4  | disorder* AND "post-traumatic"[tiab]  | 987    |
| #5  | "Stress Disorders, Traumatic"[Mesh:NOEXP]   | 33     |
| #6  | "Combat Disorders"[Mesh]  | 58     |
| #7  | "PTSD"  | 826    |
| #8  | (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)  | 1278   |
| #9  | "Adult"[Mesh]   | 266836 |
| #10 | "Humans"[Mesh]  | 412719 |
| #11 | (#8 AND #9 AND #10), from 1980 to 2011  | 593    |
| #12 | "implosive therapy"[MeSH Terms] OR "implosive therapy"[All Fields] OR ("exposure"[tiab] AND ("therapy"[tiab] OR "psychotherapy"[tiab])) OR "imaginal exposure"  | 6045   |
| #13 | "cognitive therapy"[MeSH] OR cognitive restructur*[tiab] OR cognitive processing therap*[tiab]  | 6525   |
| #14 | "Adaptation, Psychological"[Mesh] OR coping skill*[tiab]  | 3207   |
| #15 | "stress inoculation"  | 109    |
| #16 | "assertiveness training"  | 82     |
| #17 | psychodynamic[All Fields] AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields])  | 347    |
| #18 | psychodynamic[All Fields] AND ("psychotherapy"[MeSH Terms] OR "psychotherapy"[All Fields])  | 318    |
| #19 | ("psychoanalytic"[All Fields] AND "psychotherapy"[All Fields]) OR "psychoanalytic psychotherapy"[All Fields]  | 181    |
| #20 | ("psycho-analytic"[All Fields] AND "psychotherapy"[All Fields]) OR "psycho-analytic psychotherapy"[All Fields]  | 0      |
| #21 | "psychoanalytic therapy"  | 138    |
| #22 | "psycho-analytic therapy"   | 0      |
| #23 | "Eye Movement Desensitization Reprocessing"[MeSH] OR "EMDR"[tiab]   | 87     |
| #24 | "Psychotherapy"[Mesh]   | 6282   |
| #25 | "interpersonal therapy" OR "interpersonal psychotherapy"  | 434    |
| #26 | "family therapy"[tiab] OR "marital therapy"[tiab]   | 1137   |
| #27 | "group therapy" OR "group psychotherapy" OR "group psychological therapy"   | 1269   |
| #28 | "Hypnosis"[Mesh]  | 939    |
| #29 | (#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28)   | 20386  |
| #30 | (#11 AND #29)   | 308    |
| #31 | "Benzodiazepines"[Mesh]   | 2830   |
| #32 | "Antidepressive Agents, Tricyclic"[Pharmacological Action]  | 999    |
| #33 | "Anticonvulsants"[Pharmacological Action]   | 2055   |
| #34 | "Adrenergic alpha-Antagonists"[Pharmacological Action]  | 948    |
| #35 | "Antipsychotic Agents"[Pharmacological Action]  | 3254   |
| #36 | "Antidepressive Agents"[Pharmacological Action]   | 4378   |
| #37 | "citalopram"[All Fields] OR "escitalopram"[All Fields] OR "fluoxetine"[All Fields] OR "fluvoxamine"[All Fields] OR "paroxetine"[All Fields] OR "sertraline"[All Fields] OR "desvenlafaxine"[All Fields] OR "venlafaxine"[All Fields] OR "duloxetine"[All Fields] OR "imipramine"[All Fields] OR "amitriptyline"[All Fields] OR "desipramine"[All Fields] OR "bupropion"[All Fields] OR "mirtazapine"[All Fields] OR "nefazodone"[All Fields] OR "trazodone"[All Fields] OR "prazosin"[All Fields] OR "olanzapine"[All Fields] OR "risperidone"[All Fields] OR "benzodiazepines"[MeSH] OR "alprazolam"[All Fields] OR "diazepam"[All Fields] OR "lorazepam"[All Fields] OR "clonazepam"[All Fields] OR "topiramate"[All Fields] OR "tiagabine"[All Fields] OR "lamotrigine"[All Fields] OR "carbamazepine"[All Fields] OR "divalproex"[All Fields] | 23631  |
| #38 | (#31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37)   | 28306  |
| #39 | (#11 AND #38)   | 107    |
| #40 | (#30 OR #39)  | 382    |

**IPA, CINAHL, PsycINFO:**

| #   | Query   | Results |
|-----|---|---------|
| S30 | S13 or S15 or S17 or S19 or S21 or S23 or S25 or S27 or S29   | 423     |
| S29 | S11 and S28   | 30      |
| S28 | DE "Best Practices" OR DE "Clinical Trials" OR DE "Evidence Based Practice"   | 84889   |
| S27 | S11 and S26   | 31      |
| S26 | Cohort  | 67610   |
| S25 | S11 and S24   | 1       |
| S24 | Case-Control  | 32466   |
| S23 | S11 and S22   | 16      |
| S22 | Comparative   | 151221  |
| S21 | S11 and S20   | 155     |
| S20 | review  | 546021  |
| S19 | S11 and S18   | 5       |
| S18 | meta-analysis   | 28744   |
| S17 | S11 and S16   | 2       |
| S16 | "Single Blind"  | 7068    |
| S15 | S11 and S14   | 73      |
| S14 | "double blind"  | 50926   |
| S13 | S11 and S12   | 205     |
| S12 | trial   | 185981  |
| S11 | S8 or S10   | 1433    |
| S10 | S6 and S9   | 482     |
| S9  | DE "Drug Therapy"   | 94759   |
| S8  | S6 and S7   | 1004    |
| S7  | DE "Treatment" OR DE "Adjunctive Treatment" OR DE "Aftercare" OR DE "Alternative Medicine" OR DE "Behavior Modification" OR DE "Bibliotherapy" OR DE "Cognitive Techniques" OR DE "Computer Assisted Therapy" OR DE "Creative Arts Therapy" OR DE "Crisis Intervention Services" OR DE "Cross Cultural Treatment" OR DE "Disease Management" OR DE "Health Care Services" OR DE "Interdisciplinary Treatment Approach" OR DE "Involuntary Treatment" OR DE "Language Therapy" OR DE "Life Sustaining Treatment" OR DE "Medical Treatment (General)" OR DE "Milieu Therapy" OR DE "Movement Therapy" OR DE "Multimodal Treatment Approach" OR DE "Online Therapy" OR DE "Outpatient Treatment" OR DE "Pain Management" OR DE "Partial Hospitalization" OR DE "Personal Therapy" OR DE "Physical Treatment Methods" OR DE "Preventive Medicine" OR DE "Psychotherapeutic Techniques" OR DE "Psychotherapy" OR DE "Rehabilitation" OR DE "Relaxation Therapy" OR DE "Sex Therapy" OR DE "Social Casework" OR DE "Sociotherapy" OR DE "Speech Therapy" OR DE "Treatment Guidelines" | 214922  |
| S6  | S5<br><br>Limiters - Published Date from: 19800101-20111031; Language: English; Articles about Human Studies; English Language; Exclude MEDLINE records; Human; Language: English; Age Groups: Adult: 19-44 years, Middle Aged: 45-64 years, Aged: 65+ years, Aged, 80 and over, All Adult; Publication Year from: 1980-2011; English; Language: English; Age Groups: Adulthood (18 yrs & older), Young Adulthood (18-29 yrs), Thirties (30-39 yrs), Middle Age (40-64 yrs), Aged (65 yrs & older), Very Old (85 yrs & older); Population Group: Human; Exclude Dissertations<br>Search modes - Boolean/Phrase  | 10945   |
| S5  | S1 or S2 or S3 or S4  | 26246   |
| S4  | "posttraumatic stress disorder"   | 21566   |
| S3  | "post-traumatic stress disorder"  | 5973    |
| S2  | PTSD  | 18581   |
| S1  | (DE "Posttraumatic Stress Disorder") OR (DE "Combat Experience")  | 17649   |

**Web of Science (ISI):**

| <b>Set</b> | <b>Results</b> | <b>Query</b>  |
|------------|----------------|---|
| # 1        | 11,499         | Topic=(PTSD)<br>Databases=SCI-EXPANDED, SSCI, A&HCI Timespan=All Years<br>Lemmatization=On                |
| # 2        | 27,258         | Topic=(posttraumatic)<br>Databases=SCI-EXPANDED, SSCI, A&HCI Timespan=All Years<br>Lemmatization=On       |
| # 3        | 12,587         | Topic=("post trauma*")<br>Databases=SCI-EXPANDED, SSCI, A&HCI Timespan=All Years<br>Lemmatization=On      |
| # 4        | 38,773         | #3 OR #2 OR #1<br>Databases=SCI-EXPANDED, SSCI, A&HCI Timespan=All Years<br>Lemmatization=On              |
| # 5        | 34,329         | (#4) AND Language=(English)<br>Databases=SCI-EXPANDED, SSCI, A&HCI Timespan=1980-2011<br>Lemmatization=On |
| # 6        | 33,425         | Topic=(Psychotherapy)<br>Databases=SCI-EXPANDED, SSCI, A&HCI Timespan=1980-2011<br>Lemmatization=On       |
| # 7        | 14,558         | Topic=(pharmacotherapy)<br>Databases=SCI-EXPANDED, SSCI, A&HCI Timespan=1980-2011<br>Lemmatization=On     |
| # 8        | 46,463         | #7 OR #6<br>Databases=SCI-EXPANDED, SSCI, A&HCI Timespan=1980-2011<br>Lemmatization=On                    |
| # 9        | 1,236          | #8 AND #5<br>Databases=SCI-EXPANDED, SSCI, A&HCI Timespan=1980-2011<br>Lemmatization=On                   |
| #          | 1,164          | #8 AND #5   |
| 1          |                | Refined by: Document Type=( ARTICLE OR REVIEW )   |
| 0          |                | Databases=SCI-EXPANDED, SSCI, A&HCI Timespan=1980-2011<br>Lemmatization=On                                |
| #          | 772,785        | Topic=(child)<br>Databases=SCI-EXPANDED, SSCI, A&HCI Timespan=1980-2011<br>Lemmatization=On               |
| 1          |                |   |
| 1          |                |   |
| #          | 918            | (#10 NOT #11) AND Language=(English)  |
| 1          |                | Databases=SCI-EXPANDED, SSCI, A&HCI Timespan=1980-2011  |
| 2          |                | Lemmatization=On  |

**EMBASE:**

| <b>No.</b> | <b>Query</b>  | <b>Results</b>   |
|------------|---|------------------|
| #1         | 'posttraumatic stress disorder'/exp   | 25,872           |
| #2         | 'psychotherapy'/exp   | <b>171,464</b>   |
| #3         | 'drug therapy'/exp  | <b>1,486,583</b> |
| #4         | #2 OR #3  | <b>1,645,726</b> |
| #5         | #1 AND #4   | 5,436            |
| #6         | 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'systematic review'/exp OR 'cohort analysis'/exp OR 'meta analysis'/exp OR 'comparative study'/exp OR 'case control study'/exp | 1,403,794        |
| #7         | #5 AND #6   | <b>692</b>       |
| #8         | #7 AND ('article'/it OR 'review'/it)  | <b>638</b>       |
| #9         | 'human'/exp   | 12,658,788       |
| #10        | 'adult'/exp OR 'middle aged'/exp OR 'aged'/exp  | <b>4,693,068</b> |
| #11        | #8 AND #9 AND #10   | <b>294</b>       |

**Total references identified by the main searches = 20649**

**Total references from main and handsearches, minus duplicates = 2609**

**The following update searches were conducted on May 24, 2012**

**MEDLINE®:**

| <b>Search</b> | <b>Most Recent Queries</b>  | <b>Result</b> |
|---------------|---|---------------|
| #1            | Search "Stress Disorders, Post-Traumatic"[Mesh]   | 17659         |
| #2            | Search "post-traumatic stress disorder"[All Fields]   | 4402          |
| #3            | Search "post-traumatic stress disorders"[All Fields]  | 17716         |
| #4            | Search disorder* AND "post-traumatic"[tiab]   | 6442          |
| #5            | Search "Stress Disorders, Traumatic"[Mesh:NOEXP]  | 369           |
| #6            | Search "Combat Disorders"[Mesh]   | 2260          |
| #7            | Search "PTSD"   | 9934          |
| #8            | Search #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7   | 22798         |
| #9            | Search #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 Filters: Humans   | 20950         |
| #10           | Search #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 Filters: Humans; English  | 19014         |
| #11           | Search #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 Filters: Humans; English; Adult: 19+ years  | 11362         |
| #12           | Search #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 Filters: Humans; English; Adult: 19+ years; Adult: 19-44 years  | 11362         |
| #13           | Search #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 Filters: Humans; English; Adult: 19+ years; Adult: 19-44 years; Aged: 65+ years   | 11362         |
| #14           | Search #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 Filters: Publication date from 2011/09/01 to 2012/12/31; Humans; English; Adult: 19+ years; Adult: 19-44 years; Aged: 65+ years | 412           |
| #15           | Search "implosive therapy"[MeSH Terms] OR "implosive therapy"[All Fields] OR ("exposure"[tiab] AND ("therapy"[tiab] OR "psychotherapy"[tiab])) OR "imaginal exposure"         | 24262         |
| #16           | Search "cognitive therapy"[MeSH] OR cognitive restructur*[tiab] OR cognitive processing therap*[tiab]   | 12901         |
| #17           | Search "Adaptation, Psychological"[Mesh] OR coping skill*[tiab]   | 91955         |
| #18           | Search "stress inoculation"   | 116           |
| #19           | Search "assertiveness training"   | 166           |
| #20           | Search psychodynamic[All Fields] AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields])                             | 2317          |
| #21           | Search psychodynamic[All Fields] AND ("psychotherapy"[MeSH Terms] OR "psychotherapy"[All Fields])   | 2168          |
| #22           | Search ("psychoanalytic"[All Fields] AND "psychotherapy"[All Fields]) OR "psychoanalytic psychotherapy"[All Fields]   | 5088          |
| #23           | Search ("psycho-analytic"[All Fields] AND "psychotherapy"[All Fields]) OR "psycho-analytic psychotherapy"[All Fields]   | 15            |
| #24           | Search "psychoanalytic therapy"   | 13832         |
| #25           | Search "psycho-analytic therapy"  | 3             |
| #26           | Search "Eye Movement Desensitization Reprocessing"[MeSH] OR "EMDR"[tiab]  | 230           |
| #27           | Search "Psychotherapy"[Mesh]  | 137632        |
| #28           | Search "interpersonal therapy" OR "interpersonal psychotherapy"   | 684           |
| #29           | Search "family therapy"[tiab] OR "marital therapy"[tiab]  | 2676          |
| #30           | Search "group therapy" OR "group psychotherapy" OR "group psychological therapy"  | 12408         |
| #31           | Search "Hypnosis"[Mesh]   | 10301         |
| #32           | Search #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31  | 245448        |
| #33           | Search #14 AND #32  | 77            |
| #34           | Search "Benzodiazepines"[Mesh]  | 55362         |
| #35           | Search "Antidepressive Agents, Tricyclic"[Pharmacological Action]   | 28334         |
| #36           | Search "Anticonvulsants"[Pharmacological Action]  | 122415        |
| #37           | Search "Adrenergic alpha-Antagonists"[Pharmacological Action]   | 47994         |
| #38           | Search "Antipsychotic Agents"[Pharmacological Action]   | 116441        |
| #39           | Search "Antidepressive Agents"[Pharmacological Action]  | 112131        |
| #40           | Search "citalopram" OR "escitalopram" OR "fluoxetine" OR "fluvoxamine" OR "paroxetine"  | 139350        |

| Search | Most Recent Queries   | Result  |
|--------|---|---------|
|        | OR "sertraline" OR "desvenlafaxine" OR "venlafaxine" OR "duloxetine" OR "imipramine"<br>OR "amitriptyline" OR "desipramine" OR "bupropion" OR "mirtazapine" OR<br>"nefazodone" OR "trazodone" OR "prazosin" OR "olanzapine" OR "risperidone" OR<br>"benzodiazepines" [MeSH] OR "alprazolam" OR "diazepam" OR "lorazepam" OR<br>"clonazepam" OR "topiramate" OR "tiagabine" OR "lamotrigine" OR "carbamazepine"<br>OR "divalproex" |         |
| #41    | Search #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40  | 408702  |
| #42    | Search #14 AND #41  | 8       |
| #43    | Search #33 OR #42   | 82      |
| #44    | Search "Randomized Controlled Trial"[Publication Type] OR "Randomized Controlled<br>Trials as Topic"[Mesh] OR "Single-Blind Method"[Mesh] OR "Double-Blind<br>Method"[Mesh] OR "Random Allocation"[Mesh]  | 476623  |
| #45    | Search "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR<br>"meta-analysis"[All Fields]  | 55455   |
| #46    | Search "Comparative Study"[Publication Type] OR "comparative study" OR case control<br>stud* OR "Case-Control Studies"[Mesh]  | 2043208 |
| #47    | Search ("review"[Publication Type] AND "systematic"[tiab]) OR "systematic review"[All<br>Fields] OR ("review literature as topic"[MeSH AND "systematic"[tiab])  | 48116   |
| #48    | Search "Cohort Studies"[Mesh] OR "cohort effect"[MeSH Term] OR cohort*[tiab]  | 1248320 |
| #49    | Search "trial"[tiab]  | 304105  |
| #50    | Search "Treatment Outcome"[Mesh]  | 535121  |
| #51    | Search #43 AND (#44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50)  | 40      |

**Cochrane:**

| <b>ID</b> | <b>Search</b>   | <b>Hits</b> |
|-----------|---|-------------|
| #1        | "Stress Disorders, Post-Traumatic"[Mesh]  | 791         |
| #2        | "post-traumatic stress disorder"[All Fields]  | 408         |
| #3        | "post-traumatic stress disorders"[All Fields]   | 29          |
| #4        | disorder* AND "post-traumatic"[tiab]  | 1153        |
| #5        | "Stress Disorders, Traumatic"[Mesh:NOEXP]   | 33          |
| #6        | "Combat Disorders"[Mesh]  | 66          |
| #7        | "PTSD"  | 912         |
| #8        | (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)  | 1465        |
| #9        | "Adult"[Mesh]   | 279247      |
| #10       | "Humans"[Mesh]  | 433254      |
| #11       | (#8 AND #9 AND #10), from 2011 to 2012  | 89          |
| #12       | "implosive therapy"[MeSH Terms] OR "implosive therapy"[All Fields] OR ("exposure"[tiab] AND ("therapy"[tiab] OR "psychotherapy"[tiab])) OR "imaginal exposure"  | 6877        |
| #13       | "cognitive therapy"[MeSH] OR cognitive restructur*[tiab] OR cognitive processing therap*[tiab]  | 7399        |
| #14       | "Adaptation, Psychological"[Mesh] OR coping skill*[tiab]  | 3550        |
| #15       | "stress inoculation"  | 122         |
| #16       | "assertiveness training"  | 101         |
| #17       | psychodynamic[All Fields] AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields])  | 390         |
| #18       | psychodynamic[All Fields] AND ("psychotherapy"[MeSH Terms] OR "psychotherapy"[All Fields])  | 360         |
| #19       | ("psychoanalytic"[All Fields] AND "psychotherapy"[All Fields]) OR "psychoanalytic psychotherapy"[All Fields]  | 198         |
| #20       | ("psycho-analytic"[All Fields] AND "psychotherapy"[All Fields]) OR "psycho-analytic psychotherapy"[All Fields]  | 0           |
| #21       | "psychoanalytic therapy"  | 155         |
| #22       | "psycho-analytic therapy"   | 0           |
| #23       | "Eye Movement Desensitization Reprocessing"[MeSH] OR "EMDR"[tiab]   | 97          |
| #24       | "Psychotherapy"[Mesh]   | 6781        |
| #25       | "interpersonal therapy" OR "interpersonal psychotherapy"  | 459         |
| #26       | "family therapy"[tiab] OR "marital therapy"[tiab]   | 1239        |
| #27       | "group therapy" OR "group psychotherapy" OR "group psychological therapy"   | 1453        |
| #28       | "Hypnosis"[Mesh]  | 1014        |
| #29       | (#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28)   | 22285       |
| #30       | (#11 AND #29)   | 56          |
| #31       | "Benzodiazepines"[Mesh]   | 3019        |
| #32       | "Antidepressive Agents, Tricyclic"[Pharmacological Action]  | 1020        |
| #33       | "Anticonvulsants"[Pharmacological Action]   | 2197        |
| #34       | "Adrenergic alpha-Antagonists"[Pharmacological Action]  | 968         |
| #35       | "Antipsychotic Agents"[Pharmacological Action]  | 3442        |
| #36       | "Antidepressive Agents"[Pharmacological Action]   | 4600        |
| #37       | "citalopram"[All Fields] OR "escitalopram"[All Fields] OR "fluoxetine"[All Fields] OR "fluvoxamine"[All Fields] OR "paroxetine"[All Fields] OR "sertraline"[All Fields] OR "desvenlafaxine"[All Fields] OR "venlafaxine"[All Fields] OR "duloxetine"[All Fields] OR "imipramine"[All Fields] OR "amitriptyline"[All Fields] OR "desipramine"[All Fields] OR "bupropion"[All Fields] OR "mirtazapine"[All Fields] OR "nefazodone"[All Fields] OR "trazodone"[All Fields] OR "prazosin"[All Fields] OR "olanzapine"[All Fields] OR "risperidone"[All Fields] OR "benzodiazepines"[MeSH] OR "alprazolam"[All Fields] OR "diazepam"[All Fields] OR "lorazepam"[All Fields] OR "clonazepam"[All Fields] OR "topiramate"[All Fields] OR "tiagabine"[All Fields] OR "lamotrigine"[All Fields] OR "carbamazepine"[All Fields] OR "divalproex"[All Fields] | 24418       |
| #38       | (#31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37)   | 29299       |
| #39       | (#11 AND #38)   | 14          |
| #40       | (#30 OR #39)  | 60          |



**IPA, CINAHL, PsycINFO:**

| #   | Query  | Results  | #      |
|-----|--|--|--------|
| S30 | S13 or S15 or S17 or S19 or S21 or S23 or S25 or S27 or S29  | Search modes - Boolean/Phrase  | 20     |
| S29 | S11 and S28  | Search modes - Boolean/Phrase  | 3      |
| S28 | DE "Best Practices" OR DE "Clinical Trials" OR DE "Evidence Based Practice"  | Search modes - Boolean/Phrase  | 89470  |
| S27 | S11 and S26  | Search modes - Boolean/Phrase  | 3      |
| S26 | Cohort   | Search modes - Boolean/Phrase  | 74332  |
| S25 | S11 and S24  | Search modes - Boolean/Phrase  | 0      |
| S24 | Case-Control   | Search modes - Boolean/Phrase  | 34711  |
| S23 | S11 and S22  | Search modes - Boolean/Phrase  | 1      |
| S22 | Comparative  | Search modes - Boolean/Phrase  | 157644 |
| S21 | S11 and S20  | Search modes - Boolean/Phrase  | 10     |
| S20 | review   | Search modes - Boolean/Phrase  | 576331 |
| S19 | S11 and S18  | Search modes - Boolean/Phrase  | 0      |
| S18 | meta-analysis  | Search modes - Boolean/Phrase  | 31266  |
| S17 | S11 and S16  | Search modes - Boolean/Phrase  | 0      |
| S16 | "Single Blind"   | Search modes - Boolean/Phrase  | 7534   |
| S15 | S11 and S14  | Search modes - Boolean/Phrase  | 3      |
| S14 | "double blind"   | Search modes - Boolean/Phrase  | 53132  |
| S13 | S11 and S12  | Search modes - Boolean/Phrase  | 8      |
| S12 | trial  | Search modes - Boolean/Phrase  | 197728 |
| S11 | S8 or S10  | Search modes - Boolean/Phrase  | 55     |
| S10 | S6 and S9  | Search modes - Boolean/Phrase  | 12     |
| S9  | DE "Drug Therapy"  | Search modes - Boolean/Phrase  | 99342  |
| S8  | S6 and S7  | Search modes - Boolean/Phrase  | 46     |
| S7  | DE "Treatment" OR DE "Adjunctive Treatment" OR DE "Aftercare" OR DE "Alternative Medicine" OR DE "Behavior Modification" OR DE "Bibliotherapy" OR DE "Cognitive Techniques" OR DE "Computer Assisted Therapy" OR DE "Creative Arts Therapy" OR DE "Crisis Intervention Services" OR DE "Cross Cultural Treatment" OR DE "Disease Management" OR DE "Health Care Services" OR DE "Interdisciplinary Treatment Approach" OR DE "Involuntary Treatment" OR DE | Limiters - Published Date from: 20110901-20121231; Language: English; Articles about Human Studies; English Language; Exclude MEDLINE records; Human; Language: English; Age Groups: Adult: 19-44 years, Middle Aged: 45-64 years, Aged: 65+ years, Aged, 80 and over, All Adult; Publication Year from: 2011-2012; English; Language: English; Age Groups: Adulthood (18 yrs & older), Young Adulthood (18-29 yrs), Thirties (30-39 yrs), Middle Age (40-64 yrs), Aged (65 yrs & older), Very Old (85 yrs & older); Population Group: Human; Exclude Dissertations<br>Search modes - Boolean/Phrase | 2017   |

| #  | Query  | Results  | #     |
|----|--|--|-------|
|    | "Language Therapy"<br>OR DE "Life<br>Sustaining Treatment"<br>OR D ... |  |       |
| S6 | S1 or S2 or S3 or S4   | Limiters - Published Date from: 20110901-20121231; Language: English; Articles about Human Studies; English Language; Exclude MEDLINE records; Human; Language: English; Age Groups: Adult: 19-44 years, Middle Aged: 45-64 years, Aged: 65+ years, Aged, 80 and over, All Adult; Publication Year from: 2011-2012; English; Language: English; Age Groups: Adulthood (18 yrs & older), Young Adulthood (18-29 yrs), Thirties (30-39 yrs), Middle Age (40-64 yrs), Aged (65 yrs & older), Very Old (85 yrs & older); Population Group: Human; Exclude Dissertations<br>Search modes - Boolean/Phrase | 632   |
| S5 | S1 or S2 or S3 or S4   | Search modes - Boolean/Phrase  | 28107 |
| S4 | "posttraumatic stress disorder"  | Search modes - Boolean/Phrase  | 23052 |
| S3 | "post-traumatic stress disorder"                                       | Search modes - Boolean/Phrase  | 6431  |
| S2 | PTSD   | Search modes - Boolean/Phrase  | 19921 |
| S1 | (DE "Posttraumatic Stress Disorder") OR<br>(DE "Combat Experience")    | Search modes - Boolean/Phrase  | 18878 |

**Web of Science (ISI):**

| <b>Set</b> | <b>Results</b>         | <b>Query</b>  |
|------------|------------------------|---|
| # 1        | <a href="#">12,501</a> | Topic=(PTSD)<br>Databases=SCI-EXPANDED, SSCI, A&HCI Timespan=All Years<br>Lemmatization=On  |
| # 2        | <a href="#">29,122</a> | Topic=(posttraumatic)<br>Databases=SCI-EXPANDED, SSCI, A&HCI Timespan=All Years<br>Lemmatization=On   |
| # 3        | <a href="#">13,375</a> | Topic=("post trauma*")<br>Databases=SCI-EXPANDED, SSCI, A&HCI Timespan=All Years<br>Lemmatization=On  |
| # 4        | <a href="#">41,367</a> | #3 OR #2 OR #1<br>Databases=SCI-EXPANDED, SSCI, A&HCI Timespan=All Years<br>Lemmatization=On  |
| # 5        | <a href="#">4,732</a>  | ((#4)) AND Language=(English)<br>Databases=SCI-EXPANDED, SSCI, A&HCI Timespan=2011-2012<br>Lemmatization=On   |
| # 6        | <a href="#">2,529</a>  | Topic=(Psychotherapy)<br>Databases=SCI-EXPANDED, SSCI, A&HCI Timespan=2011-2012<br>Lemmatization=On   |
| # 7        | <a href="#">1,760</a>  | Topic=(pharmacotherapy)<br>Databases=SCI-EXPANDED, SSCI, A&HCI Timespan=2011-2012<br>Lemmatization=On   |
| # 8        | <a href="#">4,146</a>  | #7 OR #6<br>Databases=SCI-EXPANDED, SSCI, A&HCI Timespan=2011-2012<br>Lemmatization=On  |
| # 9        | <a href="#">194</a>    | #8 AND #5<br>Databases=SCI-EXPANDED, SSCI, A&HCI Timespan=2011-2012<br>Lemmatization=On   |
| # 10       | <a href="#">184</a>    | (#9) AND Language=(English) AND Document Types=(Article OR Review)<br>Databases=SCI-EXPANDED, SSCI, A&HCI Timespan=2011-2012<br>Lemmatization=On          |
| # 11       | <a href="#">77,823</a> | Topic=(child)<br>Databases=SCI-EXPANDED, SSCI, A&HCI Timespan=2011-2012<br>Lemmatization=On   |
| # 12       | <a href="#">149</a>    | (#10 NOT #11) AND Language=(English) AND Document Types=(Article OR Review)<br>Databases=SCI-EXPANDED, SSCI, A&HCI Timespan=2011-2012<br>Lemmatization=On |

**EMBASE:**

| <b>No.</b> | <b>Query</b>  | <b>Results</b> |
|------------|---|----------------|
| #1         | 'posttraumatic stress disorder'/exp   | 28,109         |
| #2         | 'psychotherapy'/exp   | 178,445        |
| #3         | 'drug therapy'/exp  | 1,581,241      |
| #4         | #2 OR #3  | 1,746,450      |
| #5         | #1 AND #4   | 5,908          |
| #6         | 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'systematic review'/exp OR 'cohort analysis'/exp OR 'meta analysis'/exp OR 'comparative study'/exp OR 'case control study'/exp | 1,496,266      |
| #7         | #5 AND #6   | 783            |
| #8         | #7 AND ('article'/it OR 'review'/it)  | 716            |
| #9         | 'human'/exp   | 13,435,263     |
| #10        | 'adult'/exp OR 'middle aged'/exp OR 'aged'/exp  | 4,946,364      |
| #11        | #8 AND #9 AND #10 ((embase)/lim OR [embase classic]/lim) AND [2011-2012]/py   | 59             |

**PILOTS:**

| Query # | Search History  |
|---------|---|
| #1      | Search Query #1 DE="PTSD" ( <a href="#">Copy Query</a> )<br>26706 Published Works results found in PILOTS Database<br>Date Range: Earliest to 2012  |
| #3      | Search Query #3 "post-traumatic stress disorder" OR "post-traumatic stress disorders" ( <a href="#">Copy Query</a> )<br>3430 Published Works results found in PILOTS Database<br>Date Range: Earliest to 2012   |
| #4      | Search Query #4 disorder* AND "post-traumatic" ( <a href="#">Copy Query</a> )<br>4309 Published Works results found in PILOTS Database<br>Date Range: Earliest to 2012  |
| #5      | Search Query #5 "combat disorders" ( <a href="#">Copy Query</a> )<br>29 Published Works results found in PILOTS Database<br>Date Range: Earliest to 2012  |
| #6      | Search Query #6 PTSD ( <a href="#">Copy Query</a> )<br>28781 Published Works results found in PILOTS Database<br>Date Range: Earliest to 2012   |
| #7      | Search Query #7 (DE="PTSD") or("post-traumatic stress disorder" OR "post-traumatic stress disorders") or(disorder* AND "post-traumatic") or("combat disorders") or(PTSD) ( <a href="#">Copy Query</a> )<br>29010 Published Works results found in PILOTS Database<br>Date Range: Earliest to Current<br>Limited to:                     |
| #8      | Search Query #8 (DE="PTSD") or("post-traumatic stress disorder" OR "post-traumatic stress disorders") or(disorder* AND "post-traumatic") or("combat disorders") or(PTSD) ( <a href="#">Copy Query</a> )<br>28942 Published Works results found in PILOTS Database<br>Date Range: 1980 to 2012<br>Limited to:                            |
| #9      | Search Query #9 DE="adults" ( <a href="#">Copy Query</a> )<br>19683 Published Works results found in PILOTS Database<br>Date Range: 1980 to 2012<br>Limited to:   |
| #10     | Search Query #10 ((DE="PTSD") or("post-traumatic stress disorder" OR "post-traumatic stress disorders") or(disorder* AND "post-traumatic") or("combat disorders") or(PTSD)) and(DE="adults") ( <a href="#">Copy Query</a> )<br>13309 Published Works results found in PILOTS Database<br>Date Range: Earliest to Current<br>Limited to: |
| #11     | Search Query #11 DE="exposure therapy" ( <a href="#">Copy Query</a> )<br>579 Published Works results found in PILOTS Database<br>Date Range: Earliest to Current<br>Limited to:   |
| #12     | Search Query #12 "implosive therapy" OR (exposure AND (therapy OR psychotherapy)) OR "imaginal exposure" ( <a href="#">Copy Query</a> )<br>1478 Published Works results found in PILOTS Database<br>Date Range: Earliest to 2012  |
| #13     | Search Query #13 DE="cognitive therapy" ( <a href="#">Copy Query</a> )<br>1683 Published Works results found in PILOTS Database<br>Date Range: Earliest to 2012   |
| #14     | Search Query #14 cognitive restructur* OR cognitive processing therap* ( <a href="#">Copy Query</a> )<br>255 Published Works results found in PILOTS Database<br>Date Range: Earliest to 2012   |
| #15     | Search Query #15 "psychological adaptation" ( <a href="#">Copy Query</a> )<br>36 Published Works results found in PILOTS Database<br>Date Range: Earliest to 2012   |

| Query # | Search History   |
|---------|--|
| #16     | Search Query #16 DE="coping behavior" ( <a href="#">Copy Query</a> )<br>2281 Published Works results found in PILOTS Database<br>Date Range: Earliest to 2012  |
| #17     | Search Query #17 coping skill* ( <a href="#">Copy Query</a> )<br>202 Published Works results found in PILOTS Database<br>Date Range: Earliest to 2012  |
| #18     | Search Query #18 "stress inoculation" OR "assertiveness training" ( <a href="#">Copy Query</a> )<br>91 Published Works results found in PILOTS Database<br>Date Range: Earliest to 2012  |
| #19     | Search Query #19 psychodynamic AND (DE="psychotherapy" OR psychotherapy) ( <a href="#">Copy Query</a> )<br>246 Published Works results found in PILOTS Database<br>Date Range: Earliest to 2012  |
| #20     | Search Query #20 psychodynamic AND (therapy OR therapeutics) ( <a href="#">Copy Query</a> )<br>195 Published Works results found in PILOTS Database<br>Date Range: Earliest to 2012  |
| #21     | Search Query #21 psychoanalytic AND (psychotherapy OR "psychoanalytic psychotherapy") ( <a href="#">Copy Query</a> )<br>662 Published Works results found in PILOTS Database<br>Date Range: Earliest to 2012   |
| #22     | Search Query #22 psycho-analytic AND (psychotherapy OR "psychoanalytic psychotherapy") ( <a href="#">Copy Query</a> )<br>2 Published Works results found in PILOTS Database<br>Date Range: Earliest to 2012  |
| #23     | Search Query #23 "psychoanalytic therapy" ( <a href="#">Copy Query</a> )<br>17 Published Works results found in PILOTS Database<br>Date Range: Earliest to 2012  |
| #24     | Search Query #24 "psycho-analytic therapy" ( <a href="#">Copy Query</a> )<br>0 Published Works results found in PILOTS Database<br>Date Range: Earliest to 2012  |
| #26     | Search Query #26 DE="psychotherapy" ( <a href="#">Copy Query</a> )<br>3619 Published Works results found in PILOTS Database<br>Date Range: Earliest to 2012  |
| #28     | Search Query #28 "interpersonal therapy" OR "interpersonal psychotherapy" ( <a href="#">Copy Query</a> )<br>54 Published Works results found in PILOTS Database<br>Date Range: Earliest to 2012  |
| #29     | Search Query #29 "Eye Movement Desensitization Reprocessing" OR EMDR ( <a href="#">Copy Query</a> )<br>786 Published Works results found in PILOTS Database<br>Date Range: Earliest to 2012  |
| #30     | Search Query #30 "family therapy" OR "marital therapy" ( <a href="#">Copy Query</a> )<br>680 Published Works results found in PILOTS Database<br>Date Range: Earliest to 2012  |
| #31     | Search Query #31 "group therapy" OR "group psychotherapy" OR "group psychological therapy" ( <a href="#">Copy Query</a> )<br>1151 Published Works results found in PILOTS Database<br>Date Range: Earliest to 2012   |
| #32     | Search Query #32 DE="hypnotherapy" ( <a href="#">Copy Query</a> )<br>295 Published Works results found in PILOTS Database<br>Date Range: Earliest to 2012  |
| #33     | Search Query #33 (DE="exposure therapy") or("implosive therapy" OR (exposure AND (therapy OR psychotherapy)) OR "imaginal exposure") or(DE="cognitive therapy") or(cognitive restructur* OR cognitive processing therap*) or("psychological adaptation") or(DE="coping behavior") or(coping skill*) or("stress inoculation" OR "assertiveness training") or(psychodynamic AND (DE="psychotherapy" OR psychotherapy)) or(psychodynamic AND (therapy OR therapeutics)) or(psychoanalytic AND |

| Query # | Search History   |
|---------|--|
|         | <p>(psychotherapy OR "psychoanalytic psychotherapy")) or(psycho-analytic AND (psychotherapy OR "psychoanalytic psychotherapy")) or("psychoanalytic therapy") or(DE="psychotherapy") or("interpersonal therapy" OR "interpersonal psychotherapy") or("Eye Movement Desensitization Reprocessing" OR EMDR) or("family therapy" OR "marital therapy") or("group therapy" OR "group psychotherapy" OR "group psychological therapy") or(DE="hypnotherapy") (<a href="#">Copy Query</a>)</p> <p>9126 Published Works results found in PILOTS Database</p> <p>Date Range: Earliest to Current</p> <p>Limited to:</p>   |
| #34     | <p>Search Query #34 (((DE="PTSD") or("post-traumatic stress disorder" OR "post-traumatic stress disorders") or(disorder* AND "post-traumatic") or("combat disorders") or(PTSD)) and(DE="adults")) and((DE="exposure therapy") or("implosive therapy" OR (exposure AND (therapy OR psychotherapy)) OR "imaginal exposure") or(DE="cognitive therapy") or(cognitive restructur* OR cognitive processing therap*) or("psychological adaptation") or(DE="coping behavior") or(coping skill*) or("stress inoculation" OR "assertiveness training") or(psychodynamic AND (DE="psychotherapy" OR psychotherapy)) or(psychodynamic AND (therapy OR therapeutics)) or(psychoanalytic AND (psychotherapy OR "psychoanalytic psychotherapy")) or(psycho-analytic AND (psychotherapy OR "psychoanalytic psychotherapy")) or("psychoanalytic therapy") or(DE="psychotherapy") or("interpersonal therapy" OR "interpersonal psychotherapy") or("Eye Movement Desensitization Reprocessing" OR EMDR) or("family therapy" OR "marital therapy") or("group therapy" OR "group psychotherapy" OR "group psychological therapy") or(DE="hypnotherapy")) (<a href="#">Copy Query</a>)</p> <p>2589 Published Works results found in PILOTS Database</p> <p>Date Range: Earliest to Current</p> <p>Limited to:</p> |
| #35     | <p>Search Query #35 DE="benzodiazepine derivatives" (<a href="#">Copy Query</a>)</p> <p>94 Published Works results found in PILOTS Database</p> <p>Date Range: Earliest to Current</p> <p>Limited to:</p>  |
| #36     | <p>Search Query #36 DE="tricyclic derivatives" (<a href="#">Copy Query</a>)</p> <p>87 Published Works results found in PILOTS Database</p> <p>Date Range: Earliest to Current</p> <p>Limited to:</p>   |
| #37     | <p>Search Query #37 DE="antimanic drugs" (<a href="#">Copy Query</a>)</p> <p>104 Published Works results found in PILOTS Database</p> <p>Date Range: Earliest to Current</p> <p>Limited to:</p>  |
| #38     | <p>Search Query #38 anticonvulsant* OR "anticonvulsant drug" OR "anticonvulsant drugs" (<a href="#">Copy Query</a>)</p> <p>67 Published Works results found in PILOTS Database</p> <p>Date Range: Earliest to 2012</p>   |
| #39     | <p>Search Query #39 DE="antiadrenergic agents" (<a href="#">Copy Query</a>)</p> <p>109 Published Works results found in PILOTS Database</p> <p>Date Range: Earliest to 2012</p>  |
| #40     | <p>Search Query #40 DE=("antipsychotic drugs" or "antiadrenergic agents") (<a href="#">Copy Query</a>)</p> <p>246 Published Works results found in PILOTS Database</p> <p>Date Range: Earliest to 2012</p>   |
| #41     | <p>Search Query #41 DE=("antidepressant drugs" or "antiadrenergic agents") (<a href="#">Copy Query</a>)</p> <p>253 Published Works results found in PILOTS Database</p> <p>Date Range: Earliest to 2012</p>  |
| #42     | <p>Search Query #42 DE=("antidepressant drugs" or "antiadrenergic agents") (<a href="#">Copy Query</a>)</p> <p>253 Published Works results found in PILOTS Database</p> <p>Date Range: Earliest to 2012</p>  |
| #44     | <p>Search Query #44 "citalopram" OR "escitalopram" OR "fluoxetine" OR "fluvoxamine" OR "paroxetine" OR "sertraline" OR "desvenlafaxine" OR "venlafaxine" OR "duloxetine" OR "imipramine" OR "amitriptyline" OR "desipramine" OR "bupropion" OR "mirtazapine" OR "nefazodone" OR "trazodone" OR "prazosin" OR "olanzapine" OR "risperidone" OR "benzodiazepines" OR "alprazolam" OR "diazepam" OR "lorazepam"</p>   |

| Query # | Search History   |
|---------|--|
|         | <p>OR "clonazepam" OR "topiramate" OR "tiagabine" OR "lamotrigine" OR "carbamazepine" OR "divalproex" (<a href="#">Copy Query</a>)</p> <p>666 Published Works results found in PILOTS Database</p> <p>Date Range: Earliest to 2012</p>   |
| #46     | <p>Search Query #46 (DE="benzodiazepine derivatives") or(DE="tricyclic derivatives") or(DE="antimanic drugs") or(anticonvulsant* OR "anticonvulsant drug" OR "anticonvulsant drugs") or(DE="antiadrenergic agents") or(DE=("antipsychotic drugs" or "antiadrenergic agents")) or(DE="antidepressant drugs" or "antiadrenergic agents") or(DE=("antidepressant drugs" or "antiadrenergic agents")) or("citalopram" OR "escitalopram" OR "fluoxetine" OR "fluvoxamine" OR "paroxetine" OR "sertraline" OR "desvenlafaxine" OR "venlafaxine" OR "duloxetine" OR "imipramine" OR "amitriptyline" OR "desipramine" OR "bupropion" OR "mirtazapine" OR "nefazodone" OR "trazodone" OR "prazosin" OR "olanzapine" OR "risperidone" OR "benzodiazepines" OR "alprazolam" OR "diazepam" OR "lorazepam" OR "clonazepam" OR "topiramate" OR "tiagabine" OR "lamotrigine" OR "carbamazepine" OR "divalproex") (<a href="#">Copy Query</a>)</p> <p>1051 Published Works results found in PILOTS Database</p> <p>Date Range: Earliest to Current</p> <p>Limited to:</p>  |
| #47     | <p>Search Query #47 (((DE="PTSD") or("post-traumatic stress disorder" OR "post-traumatic stress disorders") or(disorder* AND "post-traumatic") or("combat disorders") or(PTSD)) and(DE="adults")) and((DE="benzodiazepine derivatives") or(DE="tricyclic derivatives") or(DE="antimanic drugs") or(anticonvulsant* OR "anticonvulsant drug" OR "anticonvulsant drugs") or(DE="antiadrenergic agents") or(DE=("antipsychotic drugs" or "antiadrenergic agents")) or(DE="antidepressant drugs" or "antiadrenergic agents")) or(DE=("antidepressant drugs" or "antiadrenergic agents")) or("citalopram" OR "escitalopram" OR "fluoxetine" OR "fluvoxamine" OR "paroxetine" OR "sertraline" OR "desvenlafaxine" OR "venlafaxine" OR "duloxetine" OR "imipramine" OR "amitriptyline" OR "desipramine" OR "bupropion" OR "mirtazapine" OR "nefazodone" OR "trazodone" OR "prazosin" OR "olanzapine" OR "risperidone" OR "benzodiazepines" OR "alprazolam" OR "diazepam" OR "lorazepam" OR "clonazepam" OR "topiramate" OR "tiagabine" OR "lamotrigine" OR "carbamazepine" OR "divalproex")) (<a href="#">Copy Query</a>)</p> <p>377 Published Works results found in PILOTS Database</p> <p>Date Range: Earliest to Current</p> <p>Limited to:</p>   |
| #48     | <p>Search Query #48 (((((DE="PTSD") or("post-traumatic stress disorder" OR "post-traumatic stress disorders") or(disorder* AND "post-traumatic") or("combat disorders") or(PTSD)) and(DE="adults")) and((DE="exposure therapy") or("implosive therapy" OR (exposure AND (therapy OR psychotherapy)) OR "imaginal exposure") or(DE="cognitive therapy") or(cognitive restructur* OR cognitive processing therap*) or("psychological adaptation") or(DE="coping behavior") or(coping skill*) or("stress inoculation" OR "assertiveness training") or(psychodynamic AND (DE="psychotherapy" OR psychotherapy)) or(psychodynamic AND (therapy OR therapeutics)) or(pschoanalytic AND (psychotherapy OR "psychoanalytic psychotherapy")) or(psycho-analytic AND (psychotherapy OR "psychoanalytic psychotherapy")) or("psychoanalytic therapy") or(DE="psychotherapy") or("interpersonal therapy" OR "interpersonal psychotherapy") or("Eye Movement Desensitization Reprocessing" OR EMDR) or("family therapy" OR "marital therapy") or("group therapy" OR "group psychotherapy" OR "group psychological therapy") or(DE="hypnotherapy"))) or(((DE="PTSD") or("post-traumatic stress disorder" OR "post-traumatic stress disorders") or(disorder* AND "post-traumatic") or("combat disorders") or(PTSD)) and(DE="adults")) and((DE="benzodiazepine derivatives") or(DE="tricyclic derivatives") or(DE="antimanic drugs") or(anticonvulsant* OR "anticonvulsant drug" OR "anticonvulsant drugs") or(DE="antiadrenergic agents") or(DE=("antipsychotic drugs" or "antiadrenergic agents")) or(DE="antidepressant drugs" or "antiadrenergic agents")) or(DE=("antidepressant drugs" or "antiadrenergic agents")) or("citalopram" OR "escitalopram" OR "fluoxetine" OR "fluvoxamine" OR "paroxetine" OR "sertraline" OR "desvenlafaxine" OR "venlafaxine" OR "duloxetine" OR "imipramine" OR "amitriptyline" OR "desipramine" OR "bupropion" OR "mirtazapine" OR "nefazodone" OR "trazodone" OR "prazosin" OR "olanzapine" OR "risperidone" OR "benzodiazepines" OR "alprazolam" OR "diazepam" OR "lorazepam" OR "clonazepam" OR "topiramate" OR "tiagabine" OR "lamotrigine" OR "carbamazepine" OR "divalproex")))) (<a href="#">Copy Query</a>)</p> <p>2920 Published Works results found in PILOTS Database</p> <p>Date Range: Earliest to Current</p> <p>Limited to:</p> |
| #50     | <p>Search Query #50 DE="randomized clinical trial" (<a href="#">Copy Query</a>)</p> <p>613 Published Works results found in PILOTS Database</p>  |



| Query # | Search History  |
|---------|---|
|         | Date Range: Earliest to Current<br>Limited to:  |
| #52     | Search Query #52 "single-blind" ( <a href="#">Copy Query</a> )<br>16 Published Works results found in PILOTS Database<br>Date Range: Earliest to 2012   |
| #53     | Search Query #53 "double-blind" ( <a href="#">Copy Query</a> )<br>187 Published Works results found in PILOTS Database<br>Date Range: Earliest to 2012  |
| #54     | Search Query #54 "random allocation" ( <a href="#">Copy Query</a> )<br>1 Published Works result found in PILOTS Database<br>Date Range: Earliest to 2012  |
| #55     | Search Query #55 DE="meta analysis" ( <a href="#">Copy Query</a> )<br>272 Published Works results found in PILOTS Database<br>Date Range: Earliest to 2012  |
| #56     | Search Query #56 "meta-analysis" ( <a href="#">Copy Query</a> )<br>316 Published Works results found in PILOTS Database<br>Date Range: Earliest to 2012   |
| #57     | Search Query #57 "comparative study" OR case control stud* ( <a href="#">Copy Query</a> )<br>179 Published Works results found in PILOTS Database<br>Date Range: Earliest to 2012   |
| #58     | Search Query #58 "systematic review" OR (review AND systematic) ( <a href="#">Copy Query</a> )<br>331 Published Works results found in PILOTS Database<br>Date Range: Earliest to 2012  |
| #59     | Search Query #59 "cohort studies" OR "cohort effect" OR cohort* ( <a href="#">Copy Query</a> )<br>841 Published Works results found in PILOTS Database<br>Date Range: Earliest to 2012  |
| #60     | Search Query #60 trial ( <a href="#">Copy Query</a> )<br>1361 Published Works results found in PILOTS Database<br>Date Range: Earliest to 2012  |
| #62     | Search Query #62 "treatment outcome" OR "treatment outcomes" ( <a href="#">Copy Query</a> )<br>652 Published Works results found in PILOTS Database<br>Date Range: Earliest to 2012   |
| #63     | Search Query #63 (DE="randomized clinical trial") or("single-blind") or("double-blind") or("random allocation") or(DE="meta analysis") or("meta-analysis") or("comparative study" OR case control stud*) or("systematic review" OR (review AND systematic)) or("cohort studies" OR "cohort effect" OR cohort*) or(trial) or("treatment outcome" OR "treatment outcomes") ( <a href="#">Copy Query</a> )<br>3432 Published Works results found in PILOTS Database<br>Date Range: Earliest to Current<br>Limited to:  |
| #64     | Search Query #64 (((((DE="PTSD") or("post-traumatic stress disorder" OR "post-traumatic stress disorders") or(disorder* AND "post-traumatic") or("combat disorders") or(PTSD)) and(DE="adults")) and((DE="exposure therapy") or("implosive therapy" OR (exposure AND (therapy OR psychotherapy)) OR "imaginal exposure") or(DE="cognitive therapy") or(cognitive restructur* OR cognitive processing therap*) or("psychological adaptation") or(DE="coping behavior") or(coping skill*) or("stress inoculation" OR "assertiveness training") or(psychodynamic AND (DE="psychotherapy" OR psychotherapy)) or(psychodynamic AND (therapy OR therapeutics)) or(pschoanalytic AND (psychotherapy OR "psychoanalytic psychotherapy")) or(psycho-analytic AND (psychotherapy OR "psychoanalytic psychotherapy")) or("psychoanalytic therapy") or(DE="psychotherapy") or("interpersonal therapy" OR "interpersonal psychotherapy") or("Eye Movement Desensitization Reprocessing" OR EMDR) or("family therapy" OR "marital therapy") or("group therapy" OR "group psychotherapy" OR "group psychological therapy") or(DE="hypnotherapy"))) or((((DE="PTSD") or("post-traumatic stress disorder" OR "post-traumatic stress disorders") or(disorder* AND "post-traumatic") or("combat disorders") or(PTSD)) and(DE="adults")) and((DE="benzodiazepine derivatives") or(DE="tricyclic derivatives") or(DE="antimanic drugs") or(anticonvulsant* OR "anticonvulsant drug" OR "anticonvulsant drugs") or(DE="antiadrenergic |

| Query # | Search History   |
|---------|--|
|         | <p>agents") or(DE=("antipsychotic drugs" or "antiadrenergic agents")) or(DE=("antidepressant drugs" or "antiadrenergic agents")) or(DE=("antidepressant drugs" or "antiadrenergic agents")) or("citalopram" OR "escitalopram" OR "fluoxetine" OR "fluvoxamine" OR "paroxetine" OR "sertraline" OR "desvenlafaxine" OR "venlafaxine" OR "duloxetine" OR "imipramine" OR "amitriptyline" OR "desipramine" OR "bupropion" OR "mirtazapine" OR "nefazodone" OR "trazodone" OR "prazosin" OR "olanzapine" OR "risperidone" OR "benzodiazepines" OR "alprazolam" OR "diazepam" OR "lorazepam" OR "clonazepam" OR "topiramate" OR "tiagabine" OR "lamotrigine" OR "carbamazepine" OR "divalproex")))) and((DE="randomized clinical trial") or("single-blind") or("double-blind") or("random allocation") or(DE="meta analysis") or("meta-analysis") or("comparative study" OR case control stud*) or("systematic review" OR (review AND systematic)) or("cohort studies" OR "cohort effect" OR cohort*) or(trial) or("treatment outcome" OR "treatment outcomes")) (<a href="#">Copy Query</a>)</p> |
|         | 670 Published Works results found in PILOTS Database   |
|         | Date Range: Earliest to Current  |
|         | Limited to:  |

**Total additional references identified by the update searches = 998; 362 remained after duplicates were removed.**

# Appendix C. Excluded Studies

## Excluded for No Original Data

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## Studies at High Risk of Bias

**(These studies were excluded from detailed analysis, and included in sensitivity analysis when possible.)**

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## Appendix D. Evidence Tables

**Table D-1. Characteristics of included randomized trials**

| Author, Year<br>Country                                 | Group Sample Sizes   | Setting<br>Study Duration   | Primary Outcome<br>& Timing of<br>Assessment   | Funding<br>Source                      |
|---|--|---|--|--|
| Akuchekian et al.,<br>2004 <sup>1</sup><br>Iran         | Randomized: 67<br>G1: 34<br>G2: 33<br>Analyzed:67<br>G1: 34<br>G2: 33  | Iranian Veterans<br>Administration medical<br>center<br>12 wks  | CAPS<br>Baseline & Posttreatment   | NR                                     |
| Asukai et al., 2010 <sup>2</sup><br>Japan               | Randomized: 24<br>G1: 12<br>G2: 12<br>Post-treatment Analyzed: 24<br>G1: 12<br>G2: 12                                      | Referred by psychiatric<br>clinics or victim-support<br>services; web recruitment<br>- Outpatient<br>8 to 15 weekly sessions <sup>a</sup> | CAPS<br>Baseline, Posttreatment, 3 mths,<br>6mths, 12 mths                                 | Government                             |
| Bartzokis et al.,<br>2005 <sup>3</sup><br>United States | Randomized:65<br>G1: 33<br>G2: 32<br>Analyzed: 48<br>G1: 22<br>G2: 26  | VA med center<br>16 wks   | CAPS<br>Baseline & Posttreatment (4 wks<br>residential phase & 16 wks<br>outpatient phase) | Foundation/non-profit &<br>Government  |
| Basoglu et al.,<br>2007 <sup>4</sup><br>Turkey          | Randomized: 31<br>G1: 16<br>G2: 15<br>Analyzed: Week 4: 30<br>G1: 15<br>G2: 15<br>Analyzed: Week 8: 31<br>G1: 16<br>G2: 15 | Outreach Mental Health<br>Care Delivery Program<br>Single session <sup>a</sup>  | CAPS<br>Baseline, 4 wks, 8 wks, 12 wks, 24<br>wks, 1yr                                     | Foundation/non-profit                  |
| Becker et al., 2007 <sup>5</sup><br>United States       | Randomized:30<br>G1: Unclear<br>G2: Unclear<br>Analyzed: 28<br>G1: 18<br>G2: 10  | VA med center<br>8 wks  | CAPS<br>Baseline & Posttreatment   | Pharmaceutical company &<br>Government |

**Table D-1. Characteristics of included randomized trials (continued)**

| <b>Author, Year<br/>Country</b>                         | <b>Group Sample Sizes</b>  | <b>Setting<br/>Study Duration</b>  | <b>Primary Outcome<br/>&amp; Timing of<br/>Assessment</b>             | <b>Funding<br/>Source</b> |
|---|--|--|---|---------------------------|
| Blanchard et al.,<br>2003 <sup>6</sup><br>United States | Randomized: 98<br>G1: 37<br>G2: 36<br>G3: 25<br>Analyzed: 98<br>G1: 37<br>G2: 36<br>G3: 25 | Outpatient special MH<br>8 to 12 wks   | CAPS<br>Baseline, Posttreatment, 3 mths                               | Government                |
| Boden et al., 2012 <sup>7</sup><br>United States        | Randomized: 117<br>G1: 59<br>G2: 58<br>Analyzed: 98<br>G1: 49<br>G2: 49                    | VA med center  | Addiction Severity Index (ASI)<br>Baseline, Posttreatment, 6 mths     | Government                |
| Brady et al., 2000 <sup>8</sup><br>United States        | Randomized: 187<br>G1: 94<br>G2: 93<br>Analyzed: 183<br>G1: 93<br>G2: 90                   | Outpatient Psychiatric clinics<br>in academic medical<br>centers and clinical<br>centers<br>12 wks | CAPS-2 & IES<br>Baseline & Posttreatment or at the<br>discontinuation | Pharmaceutical company    |
| Brady et al., 2005 <sup>9</sup><br>United States        | Randomized: 94<br>G1: 49<br>G2: 45<br>Analyzed: 94<br>G1: 49<br>G2: 45                     | Community and Outpatient<br>Substance Abuse<br>Treatment Programs<br>12 wks                        | CAPS<br>Baseline & Posttreatment                                      | Government                |
| Bryant et al., 2003 <sup>10</sup><br>Australia          | Randomized: 58<br>G1: 20<br>G2: 20<br>G3: 18<br>Analyzed: 58<br>G1: 20<br>G2: 20<br>G3: 18 | Outpatient special MH<br>8 wks   | CAPS<br>Baseline, Posttreatment, 6 mths                               | Government                |

**Table D-1. Characteristics of included randomized trials (continued)**

| Author, Year<br>Country                                    | Group Sample Sizes   | Setting<br>Study Duration      | Primary Outcome<br>& Timing of<br>Assessment                      | Funding<br>Source      |
|--|--|--------------------------------|---|------------------------|
| Bryant et al., 2008 <sup>11</sup><br>Australia             | Randomized: 118<br>G1: 31<br>G2: 28<br>G3: 31<br>G4: 28<br>Analyzed: 118<br>G1: 31<br>G2: 28<br>G3: 31<br>G4: 28 | Outpatient special MH<br>8 wks | CAPS<br>Baseline, Posttreatment, 6 mths                           | Government             |
| Butterfield et al.,<br>2001 <sup>12</sup><br>United States | Randomized: 15<br>G1: 10<br>G2: 5<br>Analyzed: 15<br>G1: 10<br>G2: 5   | Military<br>10 wks             | CAPS-2<br>Baseline & Posttreatment                                | Pharmaceutical company |
| Carlson et al.,<br>1998 <sup>13</sup><br>United States     | Randomized: 35<br>G1: 10<br>G2: 13<br>G3: 12<br>Analyzed: 34<br>G1:10<br>G2:12<br>G3:12                          | VA med center<br>6 wks         | CAPS<br>Baseline, posttreatment, 3 mths, 9<br>mths                | Government             |
| Chard et al., 2005 <sup>14</sup><br>United States          | Randomized: 71<br>G1: 36<br>G2: 35<br>Analyzed: 55<br>G1: 28<br>G2: 27   | Community<br>17 wks            | CAPS-SX<br>Baseline, Posttreatment, 3 mths, 1<br>yr               | Government             |
| Cloitre et al., 2002 <sup>15</sup><br>United States        | Randomized: 58<br>G1: 31<br>G2: 27<br>Analyzed:46<br>G1: 22<br>G2: 24  | Community<br>12 mths           | PTSD Sx improvement<br>Baseline, Posttreatment, 3 mths, 9<br>mths | Government             |

**Table D-1. Characteristics of included randomized trials (continued)**

| Author, Year | Group Sample Sizes | Setting | Primary Outcome | Funding |
|--------------|--------------------|---------|-----------------|---------|
|--------------|--------------------|---------|-----------------|---------|

| Country  |   | Study Duration                     | & Timing of Assessment  | Source                 |
|--|---|------------------------------------|---|------------------------|
| Cloitre et al., 2010 <sup>16</sup><br>United States  | Randomized: 104<br>G1: 33<br>G2: 38<br>G3: 33<br>Analyzed:104<br>G1: 33<br>G2: 38<br>G3: 33 | Outpatient special MH<br>16 wks    | CAPS & PSS-SR<br>Baseline, Posttreatment, 3 mths, 6 mths  | Government             |
| Connor et al., 1999 <sup>17</sup><br>Meltzer-Brody et al., 2000 <sup>18</sup><br>United States | Randomized: 54<br>G1: 27<br>G2: 27<br>Analyzed: 53<br>G1: 27<br>G2: 26                      | Community<br>12 wks                | Duke Global Rating for PTSD<br>Baseline, Posttreatment or at the discontinuation if prior to week 12                            | Government             |
| Cook et al., 2010 <sup>19</sup><br>United States   | Randomized: 124<br>G1: 61<br>G2: 63<br>Analyzed: 101<br>G1: 45<br>G2: 56                    | Outpatient special MH<br>6 wks     | CAPS<br>Baseline, Posttreatment, 1 month, 3 mths, 6 mths  | Government             |
| Cottraux, 2008 <sup>20</sup><br>France   | Randomized: 60<br>G1: 31<br>G2: 29<br>Analyzed:60<br>G1:31<br>G2:29                         | Outpatient special MH<br>16 wks    | General Criterion of Improvement (i.e., score <35 on the post-traumatic checklist scale)<br>Baseline, Posttreatment, 1yr, 2 yrs | Government             |
| Davidson et al., 2001 <sup>21</sup><br>United States   | Randomized: 208<br>G1: 100<br>G2: 108<br>Analyzed: 202<br>G1: 98<br>G2: 104                 | Study Centers–Outpatient<br>12 wks | CAPS-2 & IES<br>Baseline & Posttreatment or week of discontinuation if before week 12   | Pharmaceutical company |
| Davidson et al., 2003 <sup>22</sup><br>United States   | Randomized: 29<br>G1: Unclear<br>G2: Unclear<br>Analyzed:26<br>G1: 17<br>G2: 9              | Outpatient special MH<br>8 wks     | SPRINT<br>Baseline & Posttreatment  | Pharmaceutical company |

**Table D-1. Characteristics of included randomized trials (continued)**

| <b>Author, Year<br/>Country</b>   | <b>Group Sample Sizes</b>   | <b>Setting<br/>Study Duration</b>                             | <b>Primary Outcome<br/>&amp; Timing of<br/>Assessment</b>                                       | <b>Funding<br/>Source</b> |
|---|---|---|---|---------------------------|
| Davidson et al.,<br>2006 <sup>23</sup><br>United States   | Randomized: 538<br>G1: NR<br>G2: NR<br>G3: NR<br>Analyzed: 531<br>G1: 179<br>G2: 173<br>G3: 179 | Outpatient PC<br>12 wks                                       | CAPS<br>Baseline & Posttreatment  | Pharmaceutical company    |
| Davidson et al.,<br>2006 <sup>24</sup><br>Argentina, Chile,<br>Colombia,<br>Denmark,<br>Finland, Mexico,<br>Norway,<br>Portugal, South<br>Africa, Spain,<br>Sweden, and<br>United Kingdom | Randomized: 329<br>G1: 161<br>G2: 168<br>Analyzed: 329<br>G1: 161<br>G2: 168                    | Outpatient PC<br>24 wks                                       | CAPS-SX<br>Baseline and posttreatment or at<br>the time of discontinuation if<br>before week 24 | Pharmaceutical company    |
| Davidson et al.,<br>2007 <sup>25</sup><br>United States   | Randomized: 232<br>G1: 116<br>G2: 116<br>Analyzed: 202<br>G1: 105<br>G2: 97                     | Outpatient special MH<br>12 wks                               | CAPS, DTS & TOP-8<br>Baseline & Posttreatment   | Pharmaceutical company    |
| Davis et al., 2008 <sup>26</sup><br>United States   | Randomized: 85<br>G1: 44<br>G2: 41<br>Analyzed:<br>G1:41<br>G2:41                               | VA med center<br>8 wks  | CAPS<br>Baseline & Posttreatment  | Government                |
| Ehlers et al., 2003 <sup>27</sup><br>United Kingdom   | Randomized: 85<br>G1: 28<br>G2: 28<br>G3: 29<br>Analyzed:78<br>G1: 28<br>G2: 25<br>G3: 25       | Outpatient special MH<br>Mean: 9 wks; 0-3 booster<br>sessions | CAPS & PDS<br>Baseline, Posttreatment, 3 mths, 6<br>mths, 9 mths                                | Foundation/non-profit     |



**Table D-1. Characteristics of included randomized trials (continued)**

| <b>Author, Year<br/>Country</b>   | <b>Group Sample Sizes</b>  | <b>Setting<br/>Study Duration</b>   | <b>Primary Outcome<br/>&amp; Timing of<br/>Assessment</b>    | <b>Funding<br/>Source</b> |
|---|--|---|--|---------------------------|
| Ehlers et al., 2005 <sup>28</sup><br>United Kingdom                                       | Randomized: 28<br>G1: 14<br>G2: 14<br>Analyzed: 28<br>G1: 14<br>G2: 14   | Outpatient PC<br>4 to 12 wks and up to 3<br>monthly booster sessions                        | CAPS<br>Baseline, Posttreatment, 6 mths                      | Foundation/non-profit     |
| Fecteau et al.,<br>1999 <sup>29</sup><br>Canada   | Randomized: 23<br>G1: 12<br>G2: 11<br>Analyzed: 20<br>G1: 10<br>G2: 10   | Outpatient special MH<br>4 wks  | CAPS-2,<br>Baseline, Posttreatment, 3 mths, 6<br>mths        | Foundation/non-profit     |
| Foa et al., 1999 <sup>30</sup><br>Zoellner et al.,<br>1999 <sup>31</sup><br>United States | Randomized: 96<br>G1: 25<br>G2: 26<br>G3: 30<br>G4: 15<br>Analyzed: 79<br>G1: 23<br>G2: 19<br>G3: 22<br>G4: 15 | NR<br>9 wks   | PSS-I<br>Baseline, Posttreatment, 3 mths, 6<br>mths, 12 mths | Government                |
| Foa et al., 2005 <sup>32</sup><br>United States   | Randomized: 190<br>G1: NR<br>G2: NR<br>G3: NR<br>Analyzed: 179<br>G1: 79<br>G2: 74<br>G3: 26                   | Community and Academic<br>Specialty Clinic<br>12 wks (9-12 sessions, 1<br>session per week) | PSS-I<br>Baseline, Posttreatment, 3 mths, 6<br>mths, 12 mths | Government                |
| Forbes et al.,<br>2012 <sup>33</sup><br>Australia   | Randomized: 59<br>G1: 30<br>G2: 29<br>Analyzed: 59<br>G1: 30<br>G2: 29   | Veterans and Veterans<br>Families Counseling<br>Service<br>12 wks                           | CAPS<br>Baseline, Posttreatment, 3 mths                      | Government                |

**Table D-1. Characteristics of included randomized trials (continued)**

| <b>Author, Year<br/>Country</b>                         | <b>Group Sample Sizes</b>  | <b>Setting<br/>Study Duration</b>                                      | <b>Primary Outcome<br/>&amp; Timing of<br/>Assessment</b> | <b>Funding<br/>Source</b> |
|---|--|--|---|---------------------------|
| Ford et al., 2011 <sup>34</sup><br>United States        | Randomized: 146<br>G1: 48<br>G2: 53<br>G3: 45<br>Analyzed: 146<br>G1: 48<br>G2: 53<br>G3: 45 | Community<br>12 sessions <sup>a</sup>                                  | CAPS<br>Baseline, Posttreatment, 3 mths, 6<br>mths        | Government                |
| Friedman et al.,<br>2007 <sup>35</sup><br>United States | Randomized: 169<br>G1: 86<br>G2: 83<br>Analyzed: 166<br>G1: 84<br>G2: 82                     | VA med center<br>12 wks  | CAPS-2<br>Baseline & Posttreatment                        | Pharmaceutical company    |
| Gamito et al.,<br>2010 <sup>36</sup><br>Portugal        | Randomized: 10<br>G1: 5<br>G2: 2<br>G3: 3<br>Analyzed: 9<br>G1: 4<br>G2: 2<br>G3: 3          | Military<br>12 Sessions <sup>a</sup>                                   | CAPS<br>Baseline & Posttreatment                          | Government                |
| Gersons et al.,<br>2000 <sup>37</sup><br>Netherlands    | Randomized: 42<br>G1: 22<br>G2: 20<br>Analyzed: 42<br>G1: 22<br>G2: 20                       | Referred by occupational<br>physicians, police<br>department<br>16 wks | SI-PTSD & SCL-90<br>Baseline, Posttreatment, 3 mths       | Government                |
| Hamner et al.,<br>2003 <sup>38</sup><br>United States   | Randomized: 40<br>G1: 20<br>G2: 20<br>Analyzed: 37<br>G1: 19<br>G2: 18                       | Military<br>5 wks  | CAPS<br>Baseline & Posttreatment                          | Pharmaceutical company    |

**Table D-1. Characteristics of included randomized trials (continued)**

| <b>Author, Year<br/>Country</b>   | <b>Group Sample Sizes</b>   | <b>Setting<br/>Study Duration</b>  | <b>Primary Outcome<br/>&amp; Timing of<br/>Assessment</b>                  | <b>Funding<br/>Source</b>                                   |
|---|---|--|--|---|
| Hien et al., 2004 <sup>39</sup><br>United States                                    | Randomized: 128<br>G1: Unclear<br>G2: Unclear<br>G3: 32 (non-random)<br>Analyzed: 107<br>G1: 41<br>G2: 34<br>G3: 32 | Community<br>12 wks  | CAPS & IES<br>Baseline, Posttreatment, 6 mths, 9<br>mths follow-up         | Government  |
| Hien et al., 2009 <sup>40</sup><br>Hien et al., 2012 <sup>41</sup><br>United States | Randomized: 353<br>G1: 176<br>G2: 177<br>Analyzed: 289<br>G1: 140<br>G2: 149  | Community<br>6 wks   | CAPS<br>Baseline & Posttreatment   | Government  |
| Hinton et al., 2005 <sup>42</sup><br>United States                                  | Randomized: 40<br>G1: 20<br>G2: 20<br>Analyzed: 40<br>G1: 20<br>G2: 20  | Outpatient special MH<br>12 wks  | CAPS<br>Baseline, Posttreatment, 12 wks<br>after the completion of therapy | NR  |
| Hinton et al., 2009 <sup>43</sup><br>United States                                  | Randomized: 24<br>G1: 12<br>G2: 12<br>Analyzed: 24<br>G1: 12<br>G2: 12  | Community<br>12 wks  | CAPS<br>Baseline & Posttreatment   | NR, but at least 1 author has<br>pharmaceutical affiliation |
| Hinton et al., 2011 <sup>44</sup><br>United States                                  | Randomized: 24<br>G1: 12<br>G2: 12<br>Analyzed: 24<br>G1: 12<br>G2: 12  | Community<br>14 wks  | PTSD checklist<br>Baseline, Posttreatment, 12 wks                          | Government  |
| Hogberg et al.,<br>2007 <sup>45</sup><br>Sweden                                     | Randomized: 24<br>G1: 13<br>G2: 11<br>Analyzed: 21<br>G1: 12<br>G2: 9   | Employees of the public<br>transportation system -<br>Outpatient<br>2 mths | PTSD dx<br>Mean 10 days after treatment (last<br>month of study)           | Government  |

**Table D-1. Characteristics of included randomized trials (continued)**

| <b>Author, Year<br/>Country</b>                           | <b>Group Sample Sizes</b>   | <b>Setting<br/>Study Duration</b>  | <b>Primary Outcome<br/>&amp; Timing of<br/>Assessment</b>   | <b>Funding<br/>Source</b> |
|---|---|--|---|---------------------------|
| Hollifield et al.,<br>2007 <sup>46</sup><br>United States | Randomized: 84<br>G1: 29<br>G2: 28<br>G3: 27<br>Analyzed:73<br>G1: 24<br>G2: 25<br>G3: 24 | Outpatient special MH<br>12 wks  | PSS-SR<br><br>Baseline, Posttreatment, 3 mths               | Government                |
| Johnson et al.,<br>2011 <sup>47</sup><br>United States    | Randomized: 70<br>G1: 35<br>G2: 35<br>Analyzed: 70<br>G1: 35<br>G2: 35                    | Community<br>8 mths  | CAPS<br>Baseline & Posttreatment, 1 week,<br>3 mths, 6 mths | Government                |
| Krakow et al.,<br>2001 <sup>48</sup><br>United States     | Randomized: 186<br>G1: 88<br>G2: 80<br>Analyzed: 114<br>G1:54<br>G2:60                    | Community<br>5 wks   | PSS & CAPS<br>Baseline, Posttreatment, 3 mths, 6<br>mths    | Government                |
| Kruse et al., 2009 <sup>49</sup><br>Germany               | Randomized: 70<br>G1: 35<br>G2: 35<br>Analyzed:64<br>G1: 34<br>G2: 30                     | Yugoslavian Refugees<br>3 month weekly sessions;<br>after that once every 2<br>wks for a total of 25 hours<br>of therapy | HTQ<br>Baseline, Posttreatment, 12 mths                     | Academic                  |
| Krystal et al.,<br>2011 <sup>50</sup><br>United States    | Randomized: 296<br>G1: 147<br>G2: 149<br>Analyzed: 247<br>G1: 123<br>G2: 124              | VA med center<br>24 wks  | CAPS<br>Baseline & Posttreatment                            | Government                |
| Kubany et al.,<br>2003 <sup>51</sup><br>United States     | Randomized: 37<br>G1: 19<br>G2: 18<br>Analyzed: 32<br>G1:18<br>G2:14                      | NR<br>4.5 mths (7 to 10 sessions))   | PTSD remission<br>Baseline, Posttreatment, 3 mths           | Government                |

**Table D-1. Characteristics of included randomized trials (continued)**

| <b>Author, Year<br/>Country</b>  | <b>Group Sample Sizes</b>  | <b>Setting<br/>Study Duration</b>                         | <b>Primary Outcome<br/>&amp; Timing of<br/>Assessment</b>                               | <b>Funding<br/>Source</b> |
|--|--|---|---|---------------------------|
| Kubany et al.,<br>2004 <sup>52</sup><br>United States                            | Randomized:125<br>G1: 63<br>G2: 62<br>Analyzed:125<br>G1: 63<br>G2: 62   | Community<br>4 to 5.5 wks                                 | CAPS<br>Baseline, Posttreatment, 3 mths,<br>6mths                                       | Government                |
| Liedl et al., 2011 <sup>53</sup><br>Germany &<br>Switzerland                     | Randomized: 36<br>G1: 12<br>G2: 12<br>G3: 12<br>Analyzed:30<br>G1: 10<br>G2: 10<br>G3:10                       | Outpatient special MH<br>Average treatment of 4.8<br>mths | PDS<br>Baseline & Posttreatment   | NR                        |
| Lindauer et al.,<br>2005 <sup>54</sup><br>The Netherlands                        | Randomized: 24<br>G1: 12<br>G2: 12<br>Analyzed: 24<br>G1: 12<br>G2: 12   | Outpatient PC<br>16 wks                                   | SI-PTSD<br>Baseline & Posttreatment   | Government                |
| Litz et al., 2007 <sup>55</sup><br>United States                                 | Randomized: 45<br>G1: 24<br>G2: 21<br>Analyzed:<br>G1:23<br>G2:20  | Military<br>8 wks   | PTSD Symptom Scale - Interview<br>Version<br>Baseline, Posttreatment, 3 mths, 6<br>mths | Government                |
| Marks et al., 1998 <sup>56</sup><br>Lovell et al., 2001 <sup>57</sup><br>England | Randomized: 87<br>G1: 23<br>G2: 19<br>G3: 24<br>G4: 21<br>Analyzed: 77<br>G1: 20<br>G2: 18<br>G3: 19<br>G4: 20 | Community<br>10 wks                                       | CAPS-2, IES<br>Baseline, Posttreatment, 1 month,<br>3 mths, 6 mths                      | Foundation/non-profit     |

**Table D-1. Characteristics of included randomized trials (continued)**

| <b>Author, Year<br/>Country</b>   | <b>Group Sample Sizes</b>   | <b>Setting<br/>Study Duration</b>                              | <b>Primary Outcome<br/>&amp; Timing of<br/>Assessment</b> | <b>Funding<br/>Source</b>              |
|---|---|--|---|--|
| Marshall et al.,<br>2001 <sup>58</sup><br>United States   | Randomized: 563<br>G1: 188<br>G2: 187<br>G3: 188<br>Analyzed:551<br>G1: 183<br>G2: 182<br>G3: 186                             | NR–Outpatient<br>12 wks  | CAPS-2<br>Baseline & Posttreatment                        | Pharmaceutical company &<br>Government |
| Martenyi et al.,<br>2002 <sup>59</sup><br>Martenyi et al.,<br>2006 <sup>60</sup><br>Belgium, Bosnia,<br>Croatia,<br>Yugoslavia<br>Israel, & South<br>Africa | Randomized: 301<br>G1: 226<br>G2: 75<br>Analyzed: 301<br>G1: 226<br>G2: 75<br><br>Subgroup Analysis: 144<br>G1: 110<br>G2: 34 | Other - Study Centers<br>(Outpatient, but not clear)<br>12 wks | TOP-8<br>Baseline & Posttreatment                         | Pharmaceutical company                 |
| Martenyi et al.,<br>2007 <sup>61</sup><br>United States   | Randomized:411<br>G1: 163<br>G2: 160<br>G3: 88<br>Analyzed:298<br>G1:114<br>G2:120<br>G3: 64                                  | Study Centers -Outpatient<br>12 wks                            | TOP-8<br>Baseline & Posttreatment                         | Pharmaceutical company                 |
| McDonagh et al.,<br>2005 <sup>62</sup><br>United States   | Randomized: 74<br>G1: 29<br>G2: 22<br>G3: 23<br>Analyzed: 74<br>G1: 29<br>G2: 22<br>G3: 23                                    | NR<br>14 wks   | CAPS<br>Baseline, Posttreatment, 3 mths, 6<br>mths        | Government                             |
| Monnelly et al.,<br>2003 <sup>63</sup><br>United States   | Randomized: 16<br>G1: 8<br>G2: 8<br>Analyzed:15<br>G1:7<br>G2:8   | VA med center<br>6 wks   | PCL-M<br>Baseline & Posttreatment                         | Foundation/non-profit &<br>Government  |

**Table D-1. Characteristics of included randomized trials (continued)**

| <b>Author, Year<br/>Country</b>                        | <b>Group Sample Sizes</b>  | <b>Setting<br/>Study Duration</b>   | <b>Primary Outcome<br/>&amp; Timing of<br/>Assessment</b>                            | <b>Funding<br/>Source</b> |
|--|--|---|--|---------------------------|
| Monson et al.,<br>2006 <sup>64</sup><br>United States  | Randomized: 60<br>G1: 30<br>G2: 30<br>Analyzed: 60<br>G1: 30<br>G2: 30                           | VA med center<br>12 sessions (twice weekly) <sup>a</sup>                    | CAPS<br>Baseline, Posttreatment, 1 month   | Government                |
| Mueser et al.,<br>2008 <sup>65</sup><br>United States  | Randomized: 108<br>G1: 54<br>G2: 54<br>Analyzed: 59<br>G1: 32<br>G2: 27                          | Outpatient special MH<br>12 to 16 sessions <sup>a</sup>                     | CAPS-Total<br>Baseline, Posttreatment, 3 mths, 6<br>mths                             | Government                |
| Nacasch et al.,<br>2011 <sup>66</sup><br>Israel        | Randomized: 30<br>G1: 15<br>G2: 15<br>Analyzed: 30<br>G1: 15<br>G2: 15                           | VA med center<br>9 to 15 weeks  | PSS-I<br>Baseline, Posttreatment, 12 mths  | NR                        |
| Neuner et al.,<br>2004 <sup>67</sup><br>Uganda & Sudan | Randomized: 43<br>G1: 17<br>G2: 14<br>G3: 12<br>Analyzed: 43<br>G1: 17<br>G2: 14<br>G3: 12       | Sudanese Refugees in a<br>Ugandan refugee<br>settlement<br>3 to 4 wks       | Posttraumatic Stress Diagnostic<br>Scale<br>Baseline, Posttreatment, 4 mths, 1<br>yr | Foundation/non-profit     |
| Neuner et al.,<br>2008 <sup>68</sup><br>Uganda         | Randomized: 277<br>G1: 111<br>G2: 111<br>G3: 55<br>Analyzed: 277<br>G1: 111<br>G2: 111<br>G3: 55 | Rwandan and Somalian<br>refuges in a Ugandan<br>refugee settlement<br>3 wks | Posttraumatic Stress Diagnostic<br>Scale<br>Baseline, Posttreatment, 6 mths          | Foundation/non-profit     |

**Table D-1. Characteristics of included randomized trials (continued)**

| <b>Author, Year<br/>Country</b>                         | <b>Group Sample Sizes</b>   | <b>Setting<br/>Study Duration</b>   | <b>Primary Outcome<br/>&amp; Timing of<br/>Assessment</b>                | <b>Funding<br/>Source</b> |
|---|---|---|--|---------------------------|
| Neuner et al.,<br>2010 <sup>69</sup><br>Germany         | Randomized: 32<br>G1: 16<br>G2: 16<br>Analyzed:32<br>G1: 16<br>G2: 16   | Outpatient special MH<br>Sessions were scheduled on<br>a weekly or bi-weekly<br>basis, with a median of 9<br>treatment sessions.<br>Treatment was terminated<br>at the discretion of the<br>therapist, with a range of<br>5 to 17 sessions <sup>a</sup> | PDS<br>Baseline, Posttreatment, 6 mths                                   | Foundation/non-profit     |
| Nijdam et al.,<br>2012 <sup>70</sup><br>The Netherlands | Randomized:140<br>G1: 70<br>G2: 70<br>Analyzed: 140<br>G1:70<br>G2:70   | Outpat special MH<br>17 wks   | IES-R<br>Baseline & Posttreatment  | Academic                  |
| Panahi et al.,<br>2011 <sup>71</sup><br>Iran            | Randomized:70<br>G1: 35<br>G2: 35<br>Analyzed:<br>G1: 35<br>G2:35   | Outpat special MH<br>10 wks   | IES-R<br>Baseline & Posttreatment  | Academic                  |
| Petrakis et al.,<br>2011 <sup>72</sup><br>United States | Randomized:88<br>G1: 22<br>G2: 20<br>G3: 22<br>G4: 24<br>Analyzed: 88<br>G1: 22<br>G2: 20<br>G3: 22<br>G4: 24 | Veterans from outpatient<br>clinics and nonveterans<br>outpatients from the<br>community<br>12 wks  | CAPS<br>Baseline & Posttreatment   | Government                |
| Raskind et al.,<br>2003 <sup>73</sup><br>United States  | Randomized: 10<br>G1: 5<br>G2: 5<br>Analyzed:10<br>G1: 5<br>G2: 5   | VA med center<br>20 wks   | CAPS "Recurrent Distressing<br>Dreams Scale"<br>Baseline & Posttreatment | Government                |



**Table D-1. Characteristics of included randomized trials (continued)**

| <b>Author, Year<br/>Country</b>  | <b>Group Sample Sizes</b>   | <b>Setting<br/>Study Duration</b> | <b>Primary Outcome<br/>&amp; Timing of<br/>Assessment</b>  | <b>Funding<br/>Source</b> |
|--|---|-----------------------------------|--|---------------------------|
| Raskind et al.,<br>2007 <sup>74</sup><br>United States   | Randomized: 40<br>G1: 20<br>G2: 20<br>Analyzed: 34<br>G1: 17<br>G2: 17  | VA med center<br>8 wks            | CAPS "Recurrent Distressing<br>Dreams & PSQI<br>Baseline & Posttreatment   | Government                |
| Reich et al., 2004 <sup>75</sup><br>United States  | Randomized: 21<br>G1: 12<br>G2: 9<br>Analyzed: 21<br>G1: 12<br>G2: 9  | Community<br>8 wks                | CAPS-1 and CAPS-2<br><br>Both at baseline and at 1 wk, 2<br>wks, 4 wks, 8 wks; CAPS-1<br>readministered at 8 wks | Pharmaceutical company    |
| Resick et al., 2002 <sup>76</sup><br>Resick et al., 2003 <sup>77</sup><br>Resick et al., 2012 <sup>78</sup><br>United States | Randomized: 181<br>G1: NR<br>G2: NR<br>G3: NR<br>Analyzed: 171<br>G1: 62<br>G2: 62<br>G3: 47<br>Available for LTFU: 126<br>G1: 63<br>G2: 63 | NR<br>6 wks                       | CAPS<br>Baseline, posttreatment, 3 mths, 9<br>mths, 5 to 10 years  | Government                |
| Rothbaum et al.,<br>1997 <sup>79</sup><br>United States  | Randomized: 21<br>G1: Unclear<br>G2: Unclear<br>Analyzed: 18<br>G1: 10<br>G2: 8   | Outpatient special MH<br>4 wks    | PSS<br>Baseline & Posttreatment  | Academic                  |
| Rothbaum et al.,<br>2005 <sup>80</sup><br>United States  | Randomized: 72<br>G1: 24<br>G2: 26<br>G3: 24<br>Analyzed: 60<br>G1: 20<br>G2: 20<br>G3: 20  | Outpatient special MH<br>4.5 wks  | CAPS<br>Baseline, posttreatment, 6 mths  | Government                |

**Table D-1. Characteristics of included randomized trials (continued)**

| <b>Author, Year<br/>Country</b>                         | <b>Group Sample Sizes</b>  | <b>Setting<br/>Study Duration</b>   | <b>Primary Outcome<br/>&amp; Timing of<br/>Assessment</b>  | <b>Funding<br/>Source</b>           |
|---|--|---|--|-------------------------------------|
| Rothbaum et al.,<br>2006 <sup>81</sup><br>United States | Randomized: 65<br>G1: 34<br>G2: 31<br>Analyzed: 65<br>G1: 34<br>G2: 31       | Outpatient special MH<br>6 wks  | SI-PTSD<br>Baseline & Posttreatment  | Pharmaceutical company              |
| Schneier et al.,<br>2012 <sup>82</sup><br>United States | Randomized: 37<br>G1: 19<br>G2: 18<br>Analyzed: 37<br>G1: 19<br>G2: 18       | Outpatient special MH<br>10 wks   | CAPS<br>Baseline & Posttreatment   | Government                          |
| Schnurr et al.,<br>2003 <sup>83</sup><br>United States  | Randomized: 360<br>G1: 180<br>G2: 180<br>Analyzed: 325<br>G1: 162<br>G2: 163 | VA med center<br>30 wks active treatment and<br>5 subsequent monthly<br>booster sessions (12 mths<br>total) | CAPS<br>Baseline, posttreatment, at the end<br>of the booster sessions; 12 mths,<br>18 mths, 24 mths | Government                          |
| Schnurr et al.,<br>2007 <sup>84</sup><br>United States  | Randomized: 284<br>G1: 141<br>G2: 143<br>Analyzed: 284<br>G1: 141<br>G2: 143 | VA med center<br>10 wks   | CAPS<br>Baseline, posttreatment, 3 mths, 6<br>mths   | Government                          |
| Schnyder et al.,<br>2011 <sup>85</sup><br>Switzerland   | Randomized: 30<br>G1: 16<br>G2: 14<br>Analyzed: 30<br>G1: 16<br>G2: 14       | NR<br>16 wks  | CAPS<br>Baseline, posttreatment, 6 mths  | Foundation/non-profit &<br>Academic |
| Simon et al., 2008 <sup>86</sup><br>United States       | Randomized: 25<br>G1: 11<br>G2: 14<br>Analyzed: 23<br>G1: 9<br>G2: 14        | Outpatient PC<br>10 wks   | SPRINT<br>Baseline & posttreatment   | Pharmaceutical company              |

**Table D-1. Characteristics of included randomized trials (continued)**

| <b>Author, Year<br/>Country</b>   | <b>Group Sample Sizes</b>   | <b>Setting<br/>Study Duration</b>  | <b>Primary Outcome<br/>&amp; Timing of<br/>Assessment</b>                  | <b>Funding<br/>Source</b> |
|---|---|--|--|---------------------------|
| Spence et al.,<br>2011 <sup>87</sup><br>Australia   | Randomized: 44<br>G1: 23<br>G2: 21<br>Analyzed:42<br>G1: 23<br>G2:19                                      | Community<br>8 wks   | PCL-C<br>Baseline, posttreatment, 3mths                                    | Academic                  |
| Stein et al., 2002 <sup>88</sup><br>United States   | Randomized:19<br>G1: 10<br>G2: 9<br>Analyzed:19<br>G1: 10<br>G2: 9  | VA med center<br>8 wks   | CAPS<br>Baseline & Posttreatment   | Pharmaceutical company    |
| Tarrier et al., 1999 <sup>89</sup><br>Tarrier et al., 1999 <sup>90</sup><br>England           | Randomized: 72<br>G1: 35<br>G2: 37<br>Analyzed : 62<br>G1: 29<br>G2: 33                                   | Referred from primary,<br>secondary, & voluntary<br>health services -<br>Outpatient<br>16 sessions (over 112<br>days) <sup>a</sup> | CAPS, Penn Inventory, & IES<br>Baseline, Posttreatment, 6 mths,<br>12 mths | Foundation/non-profit     |
| Taylor et al., 2003 <sup>91</sup><br>Canada   | Randomized:60<br>G1: 19<br>G2: 22<br>G3: 19<br>Analyzed:45<br>G1: 15<br>G2: 15<br>G3: 15                  | Outpatient special MH<br>8 wks   | CAPS<br>Baseline, Posttreatment, 1 month,<br>3 mths                        | Foundation/non-profit     |
| Tucker et al.,<br>2001 <sup>92</sup><br>United States and<br>Canada                           | Randomized: 323<br>G1: 163<br>G2: 160<br>Analyzed: 307<br>G1: 151<br>G2: 156                              | Other–Outpatient<br>12 wks   | CAPS-2<br>Baseline & Posttreatment   | Pharmaceutical company    |
| Tucker et al.,<br>2003 <sup>93</sup><br>Tucker et al.,<br>2004 <sup>94</sup><br>United States | Randomized: 59<br>G1: 25<br>G2: 23<br>G3: 10<br>Analyzed: 58<br>G1: unclear<br>G2: unclear<br>G3: unclear | Outpatient special MH<br>10 wks  | CAPS<br>Baseline & Posttreatment   | Pharmaceutical company    |

**Table D-1. Characteristics of included randomized trials (continued)**

| <b>Author, Year<br/>Country</b>                             | <b>Group Sample Sizes</b>  | <b>Setting<br/>Study Duration</b>  | <b>Primary Outcome<br/>&amp; Timing of<br/>Assessment</b> | <b>Funding<br/>Source</b> |
|---|--|--|---|---------------------------|
| Tucker et al.,<br>2007 <sup>95</sup><br>United States       | Randomized: 40<br>G1: 20<br>G2: 20<br>Analyzed:38<br>G1: 19<br>G2: 19                      | Outpatient special MH<br>12 wks  | CAPS<br>Baseline & Posttreatment                          | Pharmaceutical company    |
| van der Kolk et al.,<br>1994 <sup>96</sup><br>United States | Randomized: 64<br>G1: 33<br>G2: 31<br>Analyzed: 47<br>G1: 21<br>G2: 27                     | Hospital Trauma Clinic & VA<br>Outpatient Clinic<br>5 wks                      | CAPS<br>Baseline & Posttreatment                          | Pharmaceutical company    |
| van der Kolk et al.,<br>2007 <sup>97</sup><br>United States | Randomized: 88<br>G1: 29<br>G2: 30<br>G3: 29<br>Analyzed: 88<br>G1: 29<br>G2: 30<br>G3: 29 | Outpatient special MH<br>8 wks   | CAPS<br>Baseline, Posttreatment, 6 mths                   | Government                |
| van Emmerik et al.,<br>2008 <sup>98</sup><br>Netherlands    | Randomized:125<br>G1: 41<br>G2: 44<br>G3:40<br>Analyzed:125<br>G1:41<br>G2:44<br>G3:40     | Outpatient special MH<br>5 sessions (Overall Mean<br>119.49 days) <sup>a</sup> | IES<br>Baseline, Posttreatment, follow-up<br>time varied  | Government                |
| Yeh et al., 2011 <sup>99</sup><br>Brazil                    | Randomized:35<br>G1: 17<br>G2: 18<br>Analyzed: 31<br>G1: 17<br>G2: 14                      | Outpatient special MH<br>12 wks  | CAPS<br>Baseline & Posttreatment                          | Foundation/non-profit     |

**Table D-1. Characteristics of included randomized trials (continued)**

| Author, Year<br>Country                                  | Group Sample Sizes  | Setting<br>Study Duration | Primary Outcome<br>& Timing of<br>Assessment       | Funding<br>Source      |
|--|---|---------------------------|--|------------------------|
| Zlotnick et al.,<br>2009 <sup>100</sup><br>United States | Randomized: 49<br>G1: 27<br>G2: 22<br>Analyzed: 44<br>G1: 23<br>G2: 21      | Prison<br>6 to 8 wks      | CAPS<br>Baseline, Posttreatment, 3 mths, 6<br>mths | Government             |
| Zohar et al., 2002 <sup>101</sup><br>Israel              | Randomized: Unclear<br>G1: NR<br>G2: NR<br>Analyzed: 42<br>G1: 23<br>G2: 19 | Military<br>10 wks        | CAPS-2<br>Baseline & Posttreatment                 | Pharmaceutical company |

<sup>a</sup>Number of treatment sessions reported when duration of treatment not specified

Abbreviations: CAPS = Clinician-Administered PTSD Scale; CAPS-1 = Clinician-Administered PTSD Scale, Version 1; CAPS-2 = Clinician-Administered PTSD Scale, Version 2; CAPS-SX = Clinician-Administered PTSD Scale; DTS = Davidson Trauma Scale; Dx = diagnosis; G = group; HTQ = Harvard Trauma Questionnaire; IES = Impact of Event Scale; MH = mental health; mths = months; NR = not reported; PC = patient center; PCL-C = Posttraumatic stress disorder checklist-civilian version; PCL-M = Posttraumatic stress disorder checklist-military version; PDS = Posttraumatic Stress Diagnostic Scale; PSQI = Pittsburgh Sleep Quality Index; PSS = PTSD Symptom Scale; PSS-I = PTSD Symptom Scale Interview; PSS-SR = PTSD Symptom Scale Self-report Version; Psych = psychiatric; PTSD = Posttraumatic Stress Disorder; SCL-90 = 90 item symptoms checklist; SI-PTSD = Structured Interview for PTSD; SPRINT = Short PTSD Rating Interview; Sx = serious; TOP-8 = Treatment-outcome posttraumatic; stress disorder scale (8 item); VA = Veterans Administration; wks = weeks; Yr = year.

**Table D-2. Characteristics of samples from included randomized trials**

| Author, Year                         | Population Trauma Type               | Baseline PTSD   | % Without PTSD Diagnosis                        | Mean Age                                  | % Female  | % Nonwhite                                      |
|--------------------------------------|--------------------------------------|---|---|---|---|---|
| Akuchekian et al., 2004 <sup>1</sup> | Male<br>Combat                       | CAPS<br>Overall: NR<br>G1: 50.7<br>G2: 48.9             | NA  | Overall: 40<br>G1: NR<br>G2: NR           | NA  | Overall: 100<br>G1: 100<br>G2: 100              |
| Asukai et al., 2010 <sup>2</sup>     | Male & Female<br>Mixed               | CAPS<br>Overall: NR<br>G1: 84.6<br>G2: 84.3             | NA  | Overall: 29<br>G1: 27<br>G2: 31           | Overall: 87.5<br>G1: 91.6<br>G2: 83.3             | Overall: 100<br>G1: 100<br>G2: 100              |
| Bartzokis et al., 2005 <sup>3</sup>  | Male<br>Combat                       | CAPS<br>Overall: NR<br>G1: 102.2<br>G2: 98.6            | NA  | Overall: 52<br>G1: NR<br>G2: NR           | NA  | Overall: 32.3<br>G1: NR<br>G2: NR               |
| Basoglu et al., 2007 <sup>4</sup>    | Male & Female<br>Natural<br>disaster | CAPS<br>Overall: NR<br>G1: 63.1<br>G2: 62.3             | NA  | Overall: 34<br>G1: NR<br>G2: NR           | Overall: 87.0<br>G1: NR<br>G2: NR                 | NR  |
| Becker et al., 2007 <sup>5</sup>     | Male & Female<br>Mixed               | NR  | NA  | Overall: 50<br>G1: NR<br>G2: NR           | Overall: 21.0<br>G1: NR<br>G2: NR                 | Overall: 71.4<br>G1: NR<br>G2: NR               |
| Blanchard et al., 2003 <sup>6</sup>  | Male & Female<br>MVA                 | CAPS<br>Overall: NR<br>G1: 68.2<br>G2: 65.0<br>G3: 65.8 | Overall: NR<br>G1: 22.2<br>G2: 22.2<br>G3: 12.5 | Overall: 41<br>G1: 41<br>G2: 41<br>G3: 42 | Overall: 73.0<br>G1: 77.8<br>G2: 77.8<br>G3: 62.5 | Overall: 10.2<br>G1: 3.7<br>G2: 7.4<br>G3: 12.5 |
| Boden et al., 2012 <sup>7</sup>      | Male<br>Combat                       | IES-R<br>Overall: NR<br>G1: 46.8<br>G2: 47.7            | Overall: 7.69<br>G1: Unclear<br>G2: Unclear     | Overall: 54<br>G1: 55<br>G2: 53           | NA  | Overall:<br>G1: 81.7<br>G2: 67.3                |
| Brady et al., 2000 <sup>8</sup>      | Male & Female<br>Mixed               | CAPS-2<br>Overall: NR<br>G1: 76.6<br>G2: 75.1           | NA  | Overall: 40<br>G1: 40<br>G2: 40           | Overall: 73.3<br>G1: 75.5<br>G2: 71.0             | Overall: 16.0<br>G1: 19.2<br>G2: 11.8           |
| Brady et al., 2005 <sup>9</sup>      | Male & Female<br>Mixed               | CAPS<br>Overall: NR<br>G1: 60.1<br>G2: 57.6             | NA  | Overall: 37<br>G1: 37<br>G2: 37           | Overall: 45.9<br>G1: 43.0<br>G2: 49.0             | NR  |

**Table D-2. Characteristics of samples from included randomized trials (continued)**

| Author, Year                           | Population Trauma Type        | Baseline PTSD  | % Without PTSD Diagnosis | Mean Age  | % Female                                    | % Nonwhite  |
|--|-------------------------------|--|--------------------------|---|---|---|
| Bryant et al., 2003 <sup>10</sup>      | Male & Female Mixed           | CAPS-I<br>Overall: NR<br>G1: 32.5<br>G2: 32.7<br>G3: 32.8<br><br>CAPS-F<br>Overall: NR<br>G1: 36.8<br>G2: 36.0<br>G3: 38.3 | NA                       | Overall: 35<br>G1: 37<br>G2: 32<br>G3: 36           | Overall: 51.7<br>G1: NR<br>G2: NR<br>G3: NR | NR  |
| Bryant et al., 2008 <sup>11</sup>      | Male & Female Mixed           | CAPS<br>Overall: NR<br>G1: 73.3<br>G2: 76.8<br>G3: 76.1<br>G4: 71.4  | NA                       | Overall: 37<br>G1: 39<br>G2: 41<br>G3: 36<br>G4: 34 | NR  | Overall: 8.5<br>G1: 9.7<br>G2: 7.1<br>G3: 6.5<br>G4: 10.7 |
| Butterfield et al., 2001 <sup>12</sup> | Male & Female Mixed           | SIP<br>Overall: NR<br>G1: 39.7<br>G2: 45.9   | NA                       | Overall: 43<br>G1: 45<br>G2: 40                     | Overall: 93.3<br>G1: 90.0<br>G2: 100        | Overall: 46.7<br>G1: 40.0<br>G2: 60.0                     |
| Carlson et al., 1998 <sup>13</sup>     | Male Combat                   | IES<br>G1: 52.5<br>G1: 52.9<br>G3: 52.8  | NA                       | Overall: 48<br>G1: 53<br>G2: 47<br>G3: 45           | NA  | Overall: 45.7<br>G1: 40.0<br>G2: 46.2<br>G3: 50.0         |
| Chard et al., 2005 <sup>14</sup>       | Female Childhood sexual abuse | CAPS-SX<br>Overall: NR<br>G1: 65.5<br>G2: 68.3   | NA                       | Overall: 33<br>G1: NR<br>G2: NR                     | Overall: 100<br>G1: 100<br>G2: 100          | Overall: 18.5<br>G1: NR<br>G2: NR                         |
| Cloitre et al., 2002 <sup>15</sup>     | Female Childhood Abuse        | CAPS<br>Overall: NR<br>G1: 69.0<br>G2: 69.0  | NA                       | Overall: 34<br>G1: NR<br>G2: NR                     | Overall: 100<br>G1: 100<br>G2: 100          | Overall: 54.0<br>G1: NR<br>G2: NR                         |

**Table D-2. Characteristics of samples from included randomized trials (continued)**

| Author, Year  | Population Trauma Type       | Baseline PTSD  | % Without PTSD Diagnosis | Mean Age                                  | % Female                              | % Nonwhite  |
|---|------------------------------|--|--------------------------|---|---------------------------------------|---|
| Cloitre et al., 2010 <sup>16</sup>  | Female<br>Childhood<br>Abuse | CAPS<br>Overall: NR<br>G1: 63.1<br>G2: 64.3<br>G3: 64.5  | NA                       | Overall: 36<br>G1: 33<br>G2: 37<br>G3: 39 | Overall: 100<br>G1: 100<br>G2: 100    | Overall: 64.0<br>G1: 63.0<br>G2: 63.0<br>G3: 67.0 |
| Connor et al., 1999 <sup>17</sup><br>Meltzer-Brody et al., 2000 <sup>18</sup> | Male & Female<br>Mixed       | Duke Global<br>Severity Rating<br>for PTSD (Duke)<br>Overall: NR<br>G1: 4.2<br>G2: 4.6<br><br>SIP<br>Overall: NR<br>G1: 34.0<br>G2: 34.5<br><br>DTS<br>Overall: NR<br>G1: 73.7<br>G2: 79.4 | NA                       | Overall: 37<br>G1: 36<br>G2: 38           | Overall: 91.0<br>G1: 89.0<br>G2: 93.0 | Overall: 7.0<br>G1: 0.0<br>G2: 15.0               |
| Cook et al., 2010 <sup>19</sup>   | Male<br>Combat               | CAPS<br>Overall: NR<br>G1: 81.3<br>G2: 79.5  | NA                       | Overall: 59<br>G1: 60<br>G2: 59           | NA                                    | Overall: 58.1<br>G1: 55.8<br>G2: 60.4             |
| Cottraux, 2008 <sup>20</sup>  | Male & Female<br>Mixed       | PCLS<br>Overall: 60.8<br>G1: NR<br>G2: NR  | NA                       | Overall: 39<br>G1: NR<br>G2: NR           | Overall: 70.0<br>G1: NR<br>G2: NR     | NR  |
| Davidson et al., 2001 <sup>21</sup>   | Male & Female<br>Mixed       | CAPS-2<br>Overall: NR<br>G1: 73.9<br>G2: 73.5  | NA                       | Overall: 37<br>G1: 37<br>G2: 36           | Overall: 77.8<br>G1: 84.0<br>G2: 72.0 | Overall: 16.5<br>G1: 17.0<br>G2: 16.0             |



**Table D-2. Characteristics of samples from included randomized trials (continued)**

| Author, Year                        | Population Trauma Type | Baseline PTSD                                  | % Without PTSD Diagnosis | Mean Age                        | % Female                              | % Nonwhite |
|-------------------------------------|------------------------|--|--------------------------|---------------------------------|---------------------------------------|------------|
| Davidson et al., 2003 <sup>22</sup> | Male & Female Mixed    | SPRINT<br>Overall: NR<br>G1: 21.7<br>G2: 25.0  | NA                       | Overall: 46<br>G1: 48<br>G2: 43 | NR                                    | NR         |
| Davidson et al., 2006 <sup>23</sup> | Male & Female Mixed    | NR   | NA                       | NR                              | NR                                    | NR         |
| Davidson et al., 2006 <sup>24</sup> | Male & Female Mixed    | CAPS-SX<br>Overall: NR<br>G1: 81.0<br>G2: 82.9 | NA                       | Overall: 41<br>G1: 42<br>G2: 41 | Overall: 54.1<br>G1: 55.3<br>G2: 53.0 | NR         |
| Davidson et al., 2007 <sup>25</sup> | NR Mixed               | CAPS<br>Overall: NR<br>G1: 82.4<br>G2: 82.7    | NA                       | Overall: 43<br>G1: NR<br>G2: NR | Overall: 66.0<br>G1: NR<br>G2: NR     | NR         |
| Davis et al., 2008 <sup>26</sup>    | Male & Female Combat   | CAPS<br>Overall: NR<br>G1: 75.2<br>G2: 77.3    | NA                       | Overall: 55<br>G1: NR<br>G2: NR | Overall: 2.0<br>G1: NR<br>G2: NR      | NR         |

**Table D-2. Characteristics of samples from included randomized trials (continued)**

| Author, Year  | Population Trauma Type | Baseline PTSD   | % Without PTSD Diagnosis | Mean Age  | % Female   | % Nonwhite  |
|---|------------------------|---|--------------------------|---|--|---|
| Ehlers et al., 2003 <sup>27</sup>                                     | NR<br>MVA              | CAPS Frequency<br>Overall: NR<br>G1: 31.7<br>G2: 32.6<br>G3: 32.8<br>CAPS Intensity<br>Overall: NR<br>G1: 26.7<br>G2: 26.7<br>G3: 25.9<br>PDS Frequency<br>Overall: NR<br>G1: 26.2<br>G2: 27.9<br>G3: 27.0<br>PDS Distress<br>Overall: NR<br>G1: 25.8<br>G2: 27.3<br>G3: 26.2 | NA                       | Overall: 39<br>G1: NR<br>G2: NR                     | NR   | NR  |
| Ehlers et al., 2005 <sup>28</sup>                                     | Male & Female<br>Mixed | CAPS (frequency)<br>Overall: NR<br>G1: 42.0<br>G2: 31.6<br><br>CAPS (intensity)<br>Overall: NR<br>G1: 36.5<br>G2: 29.0  | NA                       | Overall: 37<br>G1: 35<br>G2: 38                     | Overall: 53.6<br>G1: 57.0<br>G2: 50.0                    | Overall: 3.6<br>G1: 7.1<br>G2: 0.0                    |
| Fecteau et al., 1999 <sup>29</sup>                                    | Male & Female<br>MVA   | CAPS-2<br>Overall: NR<br>G1: 70.9<br>G2: 77.3   | NA                       | Overall: 41<br>G1: NR<br>G2: NR                     | Overall: 70.0<br>G1: NR<br>G2: NR                        | NR  |
| Foa et al., 1999 <sup>30</sup><br>Zoellner et al., 1999 <sup>31</sup> | Female<br>Assault      | PSS-I<br>Overall: NR<br>G1: 29.5<br>G2: 29.4<br>G3: 30.0<br>G4: 32.9  | NA                       | Overall: 35<br>G1: NR<br>G2: NR<br>G3: NR<br>G4: NR | Overall: 100<br>G1: 100<br>G2: 100<br>G3: 100<br>G4: 100 | Overall: 36.0<br>G1: NR<br>G2: NR<br>G3: NR<br>G4: NR |

**Table D-2. Characteristics of samples from included randomized trials (continued)**

| Author, Year   | Population Trauma Type                | Baseline PTSD  | % Without PTSD Diagnosis                                  | Mean Age                                    | % Female                                      | % Nonwhite   |
|--|---------------------------------------|--|---|---|---|--|
| Foa et al., 2005 <sup>32</sup>                                     | Female Assault                        | PSS-I<br>Overall: NR<br>G1: 34.0<br>G2: 31.1<br>G3: 33.3 | NA  | Overall: 31<br>G1: NR<br>G2: NR<br>G3: NR   | Overall: 100<br>G1: 100<br>G2: 100<br>G3: 100 | Overall: 50.8<br>G1: NR<br>G2: NR<br>G3: NR  |
| Forbes et al., 2012 <sup>33</sup>                                  | Male & Female Combat/Military Related | CAPS<br>Overall: NR<br>G1: 75.53<br>G2: 65.75            | NA  | Overall: 54<br>G1: 53.13<br>G2: 53.62       | Overall: 3.39<br>G1: 7<br>G2: 0               | Overall: 0<br>G1: 0<br>G2: 0   |
| Ford et al., 2011 <sup>34</sup>                                    | Female Victimization or incarceration | CAPS<br>Overall: NR<br>G1: 62.3<br>G2: 61.9<br>G3: 68.7  | Overall: NR<br>G1: 20.0<br>G2: 26.0<br>G3: 13.0           | Overall: 30.7<br>G1: NR<br>G2: NR<br>G3: NR | Overall: 100<br>G1: 100<br>G2: 100<br>G3: 100 | Overall: 59<br>African American: 40.0<br>Latina: 1.8<br>Other: 1.0<br>G1: NR<br>G2: NR<br>G3: NR |
| Friedman et al., 2007 <sup>35</sup>                                | Male & Female Veterans Mixed          | CAPS-2<br>Overall: NR<br>G1: 72.1<br>G2: 73.8            | NA  | Overall: 45<br>G1: 45<br>G2: 46             | Overall: 20.1<br>G1: 20.9<br>G2: 19.3         | Overall: 71.0<br>G1: 32.6<br>G2: 25.3  |
| Gamito et al., 2010 <sup>36</sup>                                  | Male Combat                           | NR   | NA  | Overall: 64<br>G1: NR<br>G2: NR<br>G3: NR   | NA  | NR   |
| Gersons et al., 2000 <sup>37</sup>                                 | Male & Female Other                   | NR   | NA  | Overall: 37<br>G1: 35<br>G2: 38             | Overall: 11.9<br>G1: 18.2<br>G2: 5.0          | NR   |
| Hamner et al., 2003 <sup>38</sup>                                  | Male Combat                           | CAPS<br>Overall: NR<br>G1: 90.3<br>G2: 89.1              | NA  | Overall: 52<br>G1: 51<br>G2: 54             | NA  | Overall: 54.1<br>G1: 47.4<br>G2: 61.1  |
| Hien et al., 2004 <sup>39</sup>                                    | Female Mixed                          | CAPS<br>Overall: NR<br>G1: 72.2<br>G2: 70.4<br>G3: 73.9  | Overall: 12% (subthreshold)<br>G1: NR<br>G2: NR<br>G3: NR | Overall: 37<br>G1: 38<br>G2: 34<br>G3: 40   | Overall: 100<br>G1: 100<br>G2: 100<br>G3: 100 | Overall: 62.6<br>G1: 75.6<br>G2: 50.0<br>G3: 59.4  |
| Hien et al., 2009 <sup>40</sup><br>Hien et al., 2012 <sup>41</sup> | Female Mixed                          | CAPS<br>Overall: 62.9<br>G1: 61.6<br>G2: 64.2            | Overall: 19.6<br>G1: 23.3<br>G2: 15.8                     | Overall: 39<br>G1: 39<br>G2: 39             | Overall: 100<br>G1: 100<br>G2: 100<br>G3: 100 | Overall: 54.4<br>G1: 52.8<br>G2: 55.9  |

**Table D-2. Characteristics of samples from included randomized trials (continued)**

| Author, Year                          | Population Trauma Type               | Baseline PTSD  | % Without PTSD Diagnosis              | Mean Age                                  | % Female  | % Nonwhite                                       |
|---------------------------------------|--------------------------------------|--|---------------------------------------|---|---|--|
| Hinton et al., 2005 <sup>42</sup>     | Male & Female<br>Witness<br>Genocide | CAPS<br>Overall: NR<br>G1: 74.9<br>G2: 75.9                                  | NA                                    | Overall: 52<br>G1: 51<br>G2: 53           | Overall: 60.0<br>G1: 60.0<br>G2: 60.0             | Overall: 100<br>G1: 100<br>G2: 100               |
| Hinton et al., 2009 <sup>43</sup>     | Male & Female<br>Witness<br>Genocide | CAPS<br>Overall: NR<br>G1: 75.4<br>G2: 77.3                                  | NA                                    | Overall: 50<br>G1: 50<br>G2: 49           | Overall: 60.0<br>G1: 60.0<br>G2: 60.0             | Overall: 100<br>G1: 100<br>G2: 100               |
| Hinton et al., 2011 <sup>44</sup>     | Female<br>Other                      | PTSD checklist<br>Overall: NR<br>G1: 69.8<br>G2: 71.1                        | NA                                    | Overall: 50<br>G1: 48<br>G2: 51           | Overall: 100<br>G1: 100<br>G2: 100                | Overall: 100<br>G1: 100<br>G2: 100               |
| Hogberg et al., 2007 <sup>45</sup>    | Male & Female<br>Chronic PTSD        | IES<br>Overall: NR<br>G1: 39.3<br>G2: 39.1                                   | NA                                    | Overall: 43<br>G1: 43<br>G2: 43           | Overall: 21.0<br>G1: 23.0<br>G2: 18.0             | NR   |
| Hollifield et al., 2007 <sup>46</sup> | Male & Female<br>Mixed               | PSS-SR 2 week<br>version<br>Overall: NR<br>G1: 31.3<br>G2: 32.52<br>G3: 30.8 | NA                                    | Overall: 42<br>G1: 42<br>G2: 41<br>G3: 43 | Overall: 47.9<br>G1: 62.1<br>G2: 78.6<br>G3: 63.0 | Overall: 23.5<br>G1: 13.8<br>G2: 0.0<br>G3: 11.1 |
| Johnson et al., 2011 <sup>47</sup>    | Female<br>Interpersonal<br>Violence  | CAPS<br>Overall: NR<br>G1: 53.3<br>G2: 62.7                                  | Overall: 12.9<br>G1: 11.4<br>G2: 14.3 | Overall: 33<br>G1: 32<br>G2: 33           | Overall: 100<br>G1: 100<br>G2: 100                | Overall: 57.1<br>G1: 51.4<br>G2: 62.9            |
| Krakov et al., 2001 <sup>48</sup>     | Female<br>Sexual Abuse<br>Assault    | CAPS<br>Overall: NR<br>G1: 81.9<br>G2: 79.6                                  | NA                                    | Overall: 38<br>G1: 40<br>G2: 36           | Overall: 100<br>G1: 100<br>G2: 100                | Overall: 37.5<br>G1: 45.2<br>G2: 30.8            |
| Kruse et al., 2009 <sup>49</sup>      | Male & Female<br>Other               | SCID<br>Overall: NR<br>G1: NR<br>G2: NR                                      | NA                                    | Overall: 45<br>G1: 45<br>G2: 44           | Overall: 67.2<br>G1: 64.7<br>G2: 70.0             | NR   |
| Krystal et al., 2011 <sup>50</sup>    | Male & Female<br>Combat              | CAPS<br>Overall: 78.2<br>G1: 78.2<br>G2: 78.2                                | NA                                    | Overall: 54<br>G1: 54<br>G2: 55           | Overall: 3.4<br>G1: 3.8<br>G2: 3.0                | Overall: 33.7<br>G1: 36.8<br>G2: 30.6            |

**Table D-2. Characteristics of samples from included randomized trials (continued)**

| Author, Year  | Population Trauma Type        | Baseline PTSD  | % Without PTSD Diagnosis                    | Mean Age  | % Female  | % Nonwhite  |
|---|-------------------------------|--|---|---|---|---|
| Kubany et al., 2003 <sup>51</sup>                                     | Female Interpersonal Violence | CAPS<br>Overall: NR<br>G1: 82.0<br>G2: 79.1                              | NA  | Overall: 36<br>G1: NR<br>G2: NR                     | Overall: 100<br>G1: 100<br>G2: 100                            | Overall: 51.4<br>G1: NR<br>G2: NR   |
| Kubany et al., 2004 <sup>52</sup><br>United States                    | Female Interpersonal violence | CAPS<br>Overall: NR<br>G1: 74.4<br>G2: 78.0                              | NA  | Overall: 42<br>G1: NR<br>G2: NR                     | Overall: 100<br>G1: 100<br>G2: 100                            | Overall: 47.2<br>Native Hawaiian: 8.8<br>Filipino: 7.2<br>Japanese: 6.4<br>Black: 4.8<br>Samoan: 4.8<br>American Indian: 1.6<br>Other: 13.6<br>G1: NR<br>G2: NR |
| Liedl et al., 2011 <sup>53</sup>                                      | Male & Female Mixed           | PDS<br>Overall: NR<br>G1: 31.2<br>G2: 27.0<br>G3: 25.6                   | Overall: 13.0<br>G1: NR<br>G2: NR<br>G3: NR | Overall: 42<br>G1: 42<br>G2: 42<br>G3: 41           | Overall: 43.3<br>G1: 40.0<br>G2: 50.0<br>G3: 40.0             | NR  |
| Lindauer et al., 2005 <sup>54</sup>                                   | Male & Female Mixed           | NR   | NA  | Overall: 39<br>G1: 38<br>G2: 40                     | Overall: 54.2<br>G1: 41.7<br>G2: 66.7                         | NR  |
| Litz et al., 2007 <sup>55</sup>                                       | Male & Female Combat          | PSS-I<br>Overall: NR<br>G1: 26.7<br>G2: 29.2                             | NA  | Overall: 39<br>G1: 39<br>G2: 40                     | Overall: 22.0<br>G1: 25.0<br>G2: 19.0                         | Overall: 29.5<br>G1: 25.0<br>G2: 35.0   |
| Marks et al., 1998 <sup>56</sup><br>Lovell et al., 2001 <sup>57</sup> | Male & Female Mixed           | CAPS Severity<br>Overall: NR<br>G1: 2.6<br>G2: 3.2<br>G3: 3.1<br>G4: 2.7 | NA  | Overall: 38<br>G1: 39<br>G2: 39<br>G3: 38<br>G4: 36 | Overall: 35.8<br>G1: 39.2<br>G2: 31.6<br>G3: 25.0<br>G4: 47.6 | NR  |
| Marshall et al., 2001 <sup>58</sup>                                   | Male & Female Chronic PTSD    | CAPS-2<br>Overall: NR<br>G1: 75.3<br>G2: 74.3<br>G3: 74.4                | NA  | Overall: 42<br>G1: NR<br>G2: NR<br>G3: NR           | NR  | Overall: <10%<br>G1: NR<br>G2: NR<br>G3: NR   |

**Table D-2. Characteristics of samples from included randomized trials (continued)**

| Author, Year                        | Population Trauma Type                    | Baseline PTSD   | % Without PTSD Diagnosis | Mean Age  | % Female   | % Nonwhite  |
|-------------------------------------|---|---|--------------------------|---|--|---|
| Martenyi et al., 2002 <sup>59</sup> | Male & Female Mixed                       | CAPS-2<br>Overall: NR   | NA                       | Overall: 38<br>G1: 38<br>G2: 37                       | Overall: 19.0<br>G1: 20.0<br>G2: 15.0                    | Overall: 9.0<br>G1: 11.0<br>G2: 5.0               |
| Martenyi et al., 2006 <sup>60</sup> |   | G1: 80.5<br>G2: 81.3<br><br>Subgroup Analysis:<br>Overall: NR<br>G1: 78.7<br>G2: 77.7 |                          | Subgroup Analysis:<br>Overall: 36<br>G1: 36<br>G2: 37 | Subgroup Analysis:<br>Overall: 0.7<br>G1: 0.9<br>G2: 0.0 | Subgroup Analysis:<br>NR                          |
| Martenyi et al., 2007 <sup>60</sup> | Male & Female Mixed                       | CAPS<br>Overall: NR<br>G1: 78.9<br>G2: 78.2<br>G3: 75.4                               | NA                       | Overall: 41<br>G1: 41<br>G2: 40<br>G3: 41             | Overall: 71.5<br>G1: 71.2<br>G2: 71.9<br>G3: 71.6        | Overall: 23.1<br>G1: 23.9<br>G2: 26.2<br>G3: 15.9 |
| McDonagh et al., 2005 <sup>62</sup> | Female Childhood Sexual Abuse             | CAPS<br>Overall: NR<br>G1: 69.9<br>G2: 67.7<br>G3: 72.0                               | NA                       | Overall: 41<br>G1: 40<br>G2: 40<br>G3: 42             | Overall: 100<br>G1: 100<br>G2: 100<br>G3: 100            | Overall: 6.6<br>G1: 10.0<br>G2: 5.0<br>G3: 4.0    |
| Monnelly et al., 2003 <sup>63</sup> | Male Combat                               | PCL-M<br>Overall: NR<br>G1: 73.0<br>G2: 72.0  | NA                       | Overall: 51<br>G1: 49<br>G2: 54                       | NA   | Overall: 20.0<br>G1: NR<br>G2: NR                 |
| Monson et al., 2006 <sup>64</sup>   | Male & Female Combat                      | CAPS<br>Overall: NR<br>G1: 76.7<br>G2: 79.1   | NA                       | Overall: 54<br>G1: 55<br>G2: 53                       | Overall: 10.0<br>G1: 6.7<br>G2: 13.3                     | Overall: 6.7<br>G1: 6.7<br>G2: 6.7                |
| Mueser et al., 2008 <sup>65</sup>   | Male & Female Mixed                       | CAPS<br>Overall: NR<br>G1: 74.5<br>G2: 76.2   | NA                       | Overall: 44<br>G1: 45<br>G2: 43                       | Overall: 78.7<br>G1: 75.9<br>G2: 81.5                    | Overall: 15.7<br>G1: 14.8<br>G2: 16.7             |
| Nacasch et al., 2011 <sup>66</sup>  | Male & Female Combat or Terror            | PSS-I<br>Overall: NR<br>G1: 37.1<br>G2: 36.8  | NA                       | Overall:<br>G1: 34.8<br>G2: 33.7                      | Overall: NR<br>G1: NR<br>G2: NR                          | Overall: 100<br>G1: 100<br>G2: 100                |
| Neuner et al., 2004 <sup>67</sup>   | Male & Female Rwandan & Somalian Refugees | PTDS<br>Overall: NR<br>G1: 25.2<br>G2: 22.0<br>G3: 19.5                               | NA                       | Overall: 33<br>G1: 32<br>G2: 34<br>G3: 34             | Overall: 60.5<br>G1: 53.3<br>G2: 57.1<br>G3: 75.0        | Overall: 100<br>G1: 100<br>G2: 100<br>G3: 100     |

**Table D-2. Characteristics of samples from included randomized trials (continued)**

| Author, Year                        | Population Trauma Type                    | Baseline PTSD   | % Without PTSD Diagnosis | Mean Age  | % Female   | % Nonwhite  |
|-------------------------------------|---|---|--------------------------|---|--|---|
| Neuner et al., 2008 <sup>68</sup>   | Male & Female Rwandan & Somalian Refugees | PTSD<br>Overall: NR<br>G1: 25.9<br>G2: 26.7<br>G3: 21.3   | NA                       | Overall: 35<br>G1: 34<br>G2: 35<br>G3: 36           | Overall: 51.3<br>G1: 50.5<br>G2: 53.2<br>G3: 49.1          | Overall: 100<br>G1: 100<br>G2: 100<br>G3: 100                 |
| Neuner et al., 2010 <sup>69</sup>   | Male & Female Asylum-seekers/Refugees     | PTSD<br>Overall: NR<br>G1: 38.9<br>G2: 36.9   | NA                       | Overall: 31<br>G1: 31<br>G2: 32                     | Overall: 31.2<br>G1: 31.2<br>G2: 31.2                      | NR  |
| Nijdam et al., 2012 <sup>70</sup>   | Male & Female Mixed                       | IES-R<br>Overall: NR<br>G1: 79.9<br>G2: 72.8  | NA                       | Overall: NR<br>G1: 37.3<br>G2: 38.3                 | Overall: 56.43<br>G1: 61.4<br>G2: 51.4                     | Overall: 100.0<br>G1: 100.0<br>G2: 100.0                      |
| Panahi et al., 2011 <sup>71</sup>   | Male Combat                               | IES-R<br>Overall: NR<br>G1: 65.4<br>G2: 65.1  | NA                       | Overall:<br>G1: 46.5<br>G2: 44.6                    | Overall: 0<br>G1: 0<br>G2: 0                               | Overall: 100.0<br>G1: 100.0<br>G2: 100.0                      |
| Petrakis et al., 2011 <sup>72</sup> | Male & Female Mixed                       | CAPS<br>Overall: NR<br>G1: 73.5<br>G2: 69.8<br>G3: 62.5<br>G4: 77.8   | NA                       | Overall: 47<br>G1: 45<br>G2: 49<br>G3: 47<br>G4: 47 | Overall: 9.1<br>G1: 0.0<br>G2: 5.0<br>G3: 18.2<br>G4: 12.5 | Overall: 25.0<br>G1: 27.2<br>G2: 30.0<br>G3: 13.7<br>G4: 41.7 |
| Raskind et al., 2003 <sup>73</sup>  | Male Combat                               | CAPS "Recurrent distressing dreams; CAPS difficulty falling/staying asleep<br>Overall: NR<br>G1: 79.1<br>G2: 83.6 | NA                       | Overall: 53<br>G1: NR<br>G2: NR                     | NA   | NR  |
| Raskind et al., 2007 <sup>74</sup>  | Male & Female Combat                      | CAPS<br>Overall: 70.0<br>G1: NR<br>G2: NR   | NA                       | Overall: 56<br>G1: NR<br>G2: NR                     | Overall: 5.0<br>G1: NR<br>G2: NR                           | Overall: 35.0<br>G1: NR<br>G2: NR                             |

**Table D-2. Characteristics of samples from included randomized trials (continued)**

| Author, Year  | Population Trauma Type                           | Baseline PTSD  | % Without PTSD Diagnosis | Mean Age                                  | % Female                                      | % Nonwhite                                  |
|---|--|--|--------------------------|---|---|---|
| Reich et al., 2004 <sup>75</sup>  | Female<br>Childhood<br>Sexual<br>Abuse           | CAPS-1<br>Overall: NR<br>G1: 65.5<br>G2: 73.9<br><br>CAPS-2 Total<br>Overall: NR<br>G1: 63.5<br>G2: 65.6 | NA                       | Overall: 28<br>G1: 31<br>G2: 24           | Overall: 100<br>G1: 100<br>G2: 100            | Overall: 14.3<br>G1: 25.0<br>G2: 0.0        |
| Resick et al., 2002 <sup>76</sup><br>Resick et al., 2003 <sup>77</sup><br>Resick et al., 2012 <sup>78</sup> | Female<br>Sexual Assault                         | CAPS<br>Overall: NR<br>G1: 74.8<br>G2: 76.6<br>G3: 69.9  | NA                       | Overall: 32<br>G1: NR<br>G2: NR<br>G3: NR | Overall: 100<br>G1: 100<br>G2: 100<br>G3: 100 | Overall: 29.0<br>G1: NR<br>G2: NR<br>G3: NR |
| Rothbaum et al., 1997 <sup>79</sup>   | Female<br>Sexual Abuse,<br>Assault               | PSS-I<br>Overall: NR<br>G1: 33.3<br>G2: 39.0   | NA                       | Overall: 35<br>G1: 32<br>G2: 39           | Overall: 100<br>G1: 100<br>G2: 100            | NR  |
| Rothbaum et al., 2005 <sup>80</sup>   | Female<br>Sexual Abuse,<br>Assault               | CAPS<br>Data reported in<br>graphs only  | NA                       | Overall: 34<br>G1: NR<br>G2: NR<br>G3: NR | Overall: 100<br>G1: 100<br>G2: 100<br>G3: 100 | Overall: 31.7<br>G1: NR<br>G2: NR<br>G3: NR |
| Rothbaum et al., 2006 <sup>81</sup>   | Male & Female<br>Mixed                           | SIP<br>Overall: 35.9<br>G1: 36.0<br>G2: 35.9   | NA                       | Overall: 39<br>G1: 37<br>G2: 42           | Overall: 64.6<br>G1: NR<br>G2: NR             | Overall: 20.0<br>G1: NR<br>G2: NR           |
| Schneier et al., 2012 <sup>82</sup>   | Male & Female<br>World Trade<br>Center<br>Attack | CAPS<br>Overall: 69.1<br>G1: 72.6<br>G2: 65.4  | NA                       | Overall: 50<br>G1: 49<br>G2: 52           | Overall: 54.0<br>G1: 42.1<br>G2: 66.7         | Overall: 32.4<br>G1: 31.6<br>G2: 33.3       |
| Schnurr et al., 2003 <sup>83</sup>  | Male<br>Combat                                   | CAPS Severity<br>Overall: 81.2<br>G1: 80.4<br>G2: 82.0   | NA                       | Overall: 51<br>G1: 51<br>G2: 51           | NA  | Overall: 33.8<br>G1: 32.7<br>G2: 35.0       |
| Schnurr et al., 2007 <sup>84</sup>  | Female<br>Mixed                                  | CAPS<br>Overall: NR<br>G1: 77.6<br>G2: 77.9  | NA                       | Overall: 45<br>G1: 45<br>G2: 45           | Overall: 100<br>G1: 100<br>G2: 100            | Overall: 45.5<br>G1: 44.0<br>G2: 46.9       |



**Table D-2. Characteristics of samples from included randomized trials (continued)**

| Author, Year   | Population Trauma Type     | Baseline PTSD                                 | % Without PTSD Diagnosis                                | Mean Age   | % Female   | % Nonwhite                            |
|--|----------------------------|---|---|--|--|---------------------------------------|
| Schnyder et al., 2011 <sup>85</sup>                                      | Male & Female Mixed        | CAPS<br>Overall: NR<br>G1: 78.6<br>G2: 73.4   | Subsyndromal PTSD<br>Overall: 4.0<br>G1: 2.0<br>G2: 2.0 | Overall: 40<br>G1: NR<br>G2: NR  | Overall: 46.7<br>G1: NR<br>G2: NR  | NR                                    |
| Simon et al., 2008 <sup>86</sup>   | Male & Female Mixed        | SPRINT<br>Overall: NR<br>G1: 16.1<br>G2: 17.0 | NA  | Overall: 46<br>G1: 48<br>G2: 44  | Overall: 56.0<br>G1: 44.0<br>G2: 64.0  | Overall: 26.0<br>G1: 29.0<br>G2: 22.0 |
| Spence et al., 2011 <sup>87</sup>  | Male & Female Mixed        | PCL-C<br>Overall: NR<br>G1: 60.8<br>G2: 57.0  | NA  | Overall: 43<br>G1: 43<br>G2: 42  | Overall: 81.0<br>G1: 74.0<br>G2: 89.0  | NR                                    |
| Stein et al., 2002 <sup>88</sup>   | Male Combat                | CAPS<br>Overall: NR<br>G1: 86.1<br>G2: 84.0   | NA  | Overall: 53<br>G1: 55<br>G2: 51  | NA   | NR                                    |
| Tarrier et al., 1999 <sup>89</sup><br>Tarrier et al., 1999 <sup>90</sup> | Male & Female Mixed        | CAPS<br>Overall: NR<br>G1: 71.1<br>G2: 77.6   | NA  | Overall: 39<br>G1: NR<br>G2: NR<br><br>Tarrier et al., 1999 - 12 month:<br>Overall: 38<br>G1: NR<br>G2: NR | Overall: 42.0<br>G1: NR<br>G2: NR<br><br>Tarrier et al., 1999 - 12 month:<br>Overall: 41.0<br>G1: NR<br>G2: NR | NR                                    |
| Taylor et al., 2003 <sup>91</sup>  | Male & Female Mixed        | NR  | NA  | Overall: 37<br>G1: NR<br>G2: NR  | Overall: 75.0<br>G1: NR<br>G2: NR  | Overall: 23.0<br>G1: NR<br>G2: NR     |
| Tucker et al., 2001 <sup>92</sup>  | Male & Female Chronic PTSD | CAPS-2<br>Overall: NR<br>G1: 74.3<br>G2: 73.2 | NA  | Overall: 41<br>G1: 42<br>G2: 40  | Overall: 65.8<br>G1: 66.2<br>G2: 65.4  | Overall: 27.8<br>G1: 31.1<br>G2: 24.4 |

**Table D-2. Characteristics of samples from included randomized trials (continued)**

| Author, Year                            | Population Trauma Type | Baseline PTSD  | % Without PTSD Diagnosis                   | Mean Age                                  | % Female  | % Nonwhite  |
|---|------------------------|--|--|---|---|---|
| Tucker et al., 2003 <sup>93</sup>       | Male & Female          | Tucker et al., 2003<br>CAPS  | NA   | Overall: 39<br>G1: 39                     | Overall: 74.1<br>G1: 68.0                         | Overall: 13.7<br>G1: 24                           |
| Tucker et al., 2004 <sup>94</sup>       |                        | Overall: NR<br>G1: 91.0<br>G2: 83.9<br>G3: 94.2                                  |  | G2: 39<br>G3: 37                          | G2: 78.0<br>G3: 80.0                              | G2: 8.7<br>G3: 0.0                                |
|   |                        | Tucker et al., 2004<br>CAPS<br>Overall: 88.7<br>G1: 88.5<br>G2: 83.1<br>G3: 95.0 |  |   |   |   |
| Tucker et al., 2007 <sup>95</sup>       | Male & Female<br>Mixed | CAPS<br>Overall: NR<br>G1: 88.3<br>G2: 91.1                                      | NA   | Overall: 42<br>G1: 42<br>G2: 41           | Overall: 78.9<br>G1: 78.9<br>G2: 78.9             | Overall: 10.5<br>G1: 5.2<br>G2: 15.8              |
| van der Kolk et al., 1994 <sup>96</sup> | Male & Female<br>Mixed | CAPS<br>Overall: NR<br>G1: NR<br>G2: NR  | NA   | Overall: 40<br>G1: 41<br>G2: 40           | Overall: 34.4<br>G1: NR<br>G2: NR                 | NR  |
| van der Kolk et al., 2007 <sup>97</sup> | Male & Female<br>Mixed | CAPS 1 week<br>Overall: 71.2<br>G1: 69.4<br>G2: 73.7<br>G3: 70.3                 | NA   | Overall: 36<br>G1: 39<br>G2: 34<br>G3: 36 | Overall: 83.0<br>G1: 75.9<br>G2: 86.7<br>G3: 86.2 | Overall: 32.9<br>G1: 31.0<br>G2: 36.7<br>G3: 31.0 |
| van Emmerik et al., 2008 <sup>98</sup>  | Male & Female<br>Mixed | IES<br>Overall: NR<br>G1: 46.4<br>G2: 47.9<br>G3: 49.1                           | Overall: 3.2<br>G1: NR<br>G2: NR<br>G3: NR | Overall: 40<br>G1: 39<br>G2: 43<br>G3: 39 | Overall: 67.2<br>G1: 63.4<br>G2: 65.9<br>G3: 72.5 | NR  |
| Yeh et al., 2011 <sup>99</sup>          | Male & Female<br>Mixed | CAPS<br>Overall: NR<br>G1: 78.8<br>G2: 66.1                                      | NA   | Overall: 40<br>G1: 44<br>G2: 37           | Overall: 67.7<br>G1: 70.6<br>G2: 64.3             | NR  |

**Table D-2. Characteristics of samples from included randomized trials (continued)**

| Author, Year                         | Population Trauma Type  | Baseline PTSD                                 | % Without PTSD Diagnosis              | Mean Age                        | % Female                             | % Nonwhite                        |
|--------------------------------------|-------------------------|---|---------------------------------------|---------------------------------|--------------------------------------|-----------------------------------|
| Zlotnick et al., 2009 <sup>100</sup> | Female<br>Mixed         | CAPS<br>Overall: NR<br>G1: 69.4<br>G2: 64.4   | Overall: 16.5<br>G1: 15.0<br>G2: 18.0 | Overall: 35<br>G1: 37<br>G2: 32 | Overall: 100<br>G1: 100<br>G2: 100   | Overall: 53.0<br>G1: NR<br>G2: NR |
| Zohar et al., 2002 <sup>101</sup>    | Male & Female<br>Combat | CAPS-2<br>Overall: NR<br>G1: 91.2<br>G2: 93.3 | NA                                    | Overall: 40<br>G1: 41<br>G2: 38 | Overall: 11.6<br>G1: 17.0<br>G2: 5.0 | NR                                |

Abbreviations: CAPS = Clinician-Administered PTSD Scale; CAPS-1 = Clinician-Administered PTSD Scale, Version 1; CAPS-2 = Clinician-Administered PTSD Scale, Version 2; CAPS-F = Clinician-Administered PTSD Scale-Female; CAPS-I = Clinician-Administered PTSD Scale-Interview; CAPS-SX = Clinician-Administered PTSD Scale; DTS = Davidson Trauma Scale; G = group; IES = Impact of Event Scale; MVA = motor vehicle accident; NA = not applicable; NR = not reported; PCL-C = Posttraumatic stress disorder checklist-civilian Version; PCL-M = Posttraumatic stress disorder checklist-military version; PDS = Posttraumatic Stress Diagnostic Scale; PSS-I = PTSD Symptom Scale Interview; PSS-SR = PTSD Symptom Scale Self-report Version; PTDS = Posttraumatic Diagnostic Scale; PTSD = Post-Traumatic Stress Disorder; SCID = Structured Clinical Interview PTSD Module; SIP = Structured Interview for PTSD; SPRINT = Short PTSD Rating Interview; TOP-8 = Treatment-outcome posttraumatic; stress disorder scale (8 item).

**Table D-3. Intervention and control components from randomized controlled trials**

| Author, Year                         | Arm 1   | Arm 2      | Arm 3 | Arm 4 | Co-Interventions Allowed | Description of Co-Interventions   |
|--------------------------------------|---|------------|-------|-------|--------------------------|---|
| Akuchekian et al., 2004 <sup>1</sup> | Topiramate<br>25 to 500 mg/day (sensitive patients started at 12.5mg/day) | Placebo    | NA    | NA    | Yes                      | Topiramate was added to other psychotropic regimens. Participants had to be on other psychotropic medications for at least 6 months, with that medication failing.  |
| Asukai et al., 2010 <sup>2</sup>     | CBT, exposure-based therapy<br>8 to 15 weekly sessions of 90 minutes      | Usual care | NA    | NA    | Yes                      | Both groups allowed to continue treatment as usual and allowed to be on stable dosages of medications (no change at least 8 weeks prior to treatment).<br>Treatment as Usual:<br>G1: 83.3%<br>G2: 100%<br><br>Supportive counseling<br>Overall: 91.6 %<br><br>SSRI<br>Overall: 54%<br><br>Other antidepressants:<br>Overall: 33%<br><br>Day-time minor tranquilizers, sleeping pills or both:<br>overall: 79% |

**Table D-3. Intervention and control components from randomized controlled trials (continued)**

| Author, Year                        | Arm 1  | Arm 2     | Arm 3 | Arm 4 | Co-Interventions Allowed | Description of Co-Interventions   |
|-------------------------------------|--|-----------|-------|-------|--------------------------|---|
| Bartzokis et al., 2005 <sup>3</sup> | Risperidone<br>1 to 3 mg/day                                   | Placebo   | NA    | NA    | Yes                      | Intervention added to ongoing psychotropic medication regimen.<br><br>Stable psychotropic medications: 92%<br><br>Antidepressants: 88%<br><br>Anxiolytics: 32%<br><br>Hypnotics: 28%<br><br>Anxiolytics & Hypnotics: 9%<br><br>Anxiolytics or Hyponitics: 51% |
| Basoglu et al., 2007 <sup>4</sup>   | CBT, exposure-based therapy<br>1 single sessions of 60 minutes | Wait list | NA    | NA    | Unclear                  | NA  |
| Becker et al., 2007 <sup>5</sup>    | Bupropion<br>100 to 300 mg/day                                 | Placebo   | NA    | NA    | Yes                      | Allowed to maintain previous medications. Exclusions were medications that contraindicate bupropion.<br><br>Antidepressants<br>G1: 12<br>G2: 6<br><br>SSRIs<br>G1: 7<br>G2: 5<br><br>Trazodone<br>G1: 1<br>G2: 1<br><br>Neuroleptics<br>G1: 4<br>G2: 0        |

**Table D-3. Intervention and control components from randomized controlled trials (continued)**

| Author, Year                        | Arm 1   | Arm 2  | Arm 3              | Arm 4 | Co-Interventions Allowed | Description of Co-Interventions               |
|-------------------------------------|---|--|--------------------|-------|--------------------------|---|
| Blanchard et al., 2003 <sup>6</sup> | CBT-mixed<br>Focus on normalizing the patient's view, relaxation training, patient asked to write a description of the MVA and its immediate aftermath, including their thoughts and sensory perception<br>8 to 12 weekly sessions as deemed necessary by therapist | Supportive psychotherapy<br>8 to 12 weekly sessions as deemed necessary by therapist   | Wait list          | NA    | Unclear                  | NA  |
| Boden et al., 2012 <sup>7</sup>     | Seeking Safety and Treatment as Usual, Bi-weekly sessions over 12 weeks.  | Treatment as Usual   | NA                 | NA    | No                       | NA  |
| Brady et al., 2000 <sup>8</sup>     | Sertraline<br>25 to 200 mg/day  | Placebo  | NA                 | NA    | Yes                      | Chloral hydrate taken as needed for insomnia. |
| Brady et al., 2005 <sup>9</sup>     | Sertraline<br>150 mg/day  | Placebo  | NA                 | NA    | No                       | NA  |
| Bryant et al., 2003 <sup>10</sup>   | CBT, exposure based therapy(Prolonged Imaginal Exposure)<br>8 weekly sessions of 90 minutes with structured homework  | CBT-Mixed Prolonged Imaginal Exposure plus Cognitive Restructuring<br>8 weekly sessions of 90 minutes with structured homework | Supportive Control | NA    | Unclear                  | NA  |

**Table D-3. Intervention and control components from randomized controlled trials (continued)**

| Author, Year                           | Arm 1  | Arm 2   | Arm 3   | Arm 4   | Co-Interventions Allowed | Description of Co-Interventions                                  |
|--|--|---|---|---|--------------------------|--|
| Bryant et al., 2008 <sup>11</sup>      | CBT, exposure based (Imaginal Exposure)<br>8 weekly sessions of 100 minutes with structured daily homework                                     | CBT, exposure-based therapy (In vivo exposure)<br>8 weekly sessions of 100 minutes with structured daily homework         | CBT, exposure-based therapy (Imaginal Exposure/ In vivo Exposure)<br>8 weekly sessions of 100 minutes with structured daily homework activities | CBT-mixed Imaginal Exposure/ In vivo Exposure/ cognitive restructuring<br>8 weekly sessions of 100 minutes with structured daily homework | Unclear                  | NA   |
| Butterfield et al., 2001 <sup>12</sup> | Olanzapine<br>5 to 20mg/day  | Placebo   | NA  | NA  | Unclear                  | NR   |
| Carlson et al., 1998 <sup>13</sup>     | EMDR<br>12 sessions of 60 to 75 minutes, twice a week  | CBT, coping skills therapy<br>Biofeedback and general relaxation skills for 12 sessions for 40 plus minutes, twice a week | Wait list   | NA  | Unclear                  | NA   |
| Chard et al., 2005 <sup>14</sup>       | CBT, cognitive processing therapy<br>CPT-SA<br>17 weeks of a combination of 90 minute group sessions and 60-minute individual therapy sessions | Wait list<br>5 to 10 minute phone call once a week  | NA  | NA  | Yes                      | Prescription medications allowed if stable for at least 3 months |

**Table D-3. Intervention and control components from randomized controlled trials (continued)**

| Author, Year  | Arm 1  | Arm 2   | Arm 3  | Arm 4 | Co-Interventions Allowed | Description of Co-Interventions   |
|---|--|---|--|-------|--------------------------|---|
| Cloitre et al., 2002 <sup>15</sup>  | CBT, exposure-based therapy<br>16 sessions over 12 weeks (STAIR)   | Waitlist  | NA   | NA    | Unclear                  | NA  |
| Cloitre et al., 2010 <sup>16</sup>  | CBT-Mixed (STAIR) + Prolonged Exposure<br>16 weekly sessions (over 12 weeks), with 8 sessions for skills training and 8 for exposure | CBT-Mixed (STAIR) + Support (Skills Training)<br>16 weekly sessions (over 12 weeks) | Support (Skills Training) + Prolonged Exposure<br>16 weekly sessions (over 12 weeks) | NA    | Yes                      | Allowed to maintain psychotherapy or psychopharmacological treatment if it had been ongoing $\geq$ 3 months prior to study entry and if psychotherapy was not PTSD-focused. |
| Connor et al., 1999 <sup>17</sup><br>Meltzer-Brody et al., 2000 <sup>18</sup> | Fluoxetine<br>10 to 60mg/day   | Placebo   | NA   | NA    | Unclear                  | NA  |
| Cook et al., 2010 <sup>19</sup>   | CBT, exposure-based therapy<br>6 weekly sessions of 90 minute group sessions   | Psychoeducation<br>6 weekly sessions of 90 minute group sessions                    | NA   | NA    | Yes                      | Patients permitted to continue treatment as usual; able to continue medications if on stable dose but could change doses during study.                                      |
| Cottraux, 2008 <sup>20</sup>  | CBT-mixed<br>Exposure in imagination or in vivo and cognitive therapy<br>10 to 16 sessions of 60 to 120 minutes over 16 weeks        | Supportive Control  | NA   | NA    | Yes                      | Psychotropic medications not allowed during intervention.<br>Benzodiazepines and hypnotics were allowed.  |
| Davidson et al., 2001 <sup>21</sup>   | Sertraline<br>50 to 200 mg/day   | Placebo   | NA   | NA    | Yes                      | Occasional use of chloral hydrate for insomnia.   |



**Table D-3. Intervention and control components from randomized controlled trials (continued)**

| Author, Year                        | Arm 1   | Arm 2  | Arm 3                | Arm 4 | Co-Interventions Allowed | Description of Co-Interventions          |
|-------------------------------------|---|--|----------------------|-------|--------------------------|--|
| Davidson et al., 2003 <sup>22</sup> | Mirtazapine<br>15 to 45 mg/day  | Placebo                                      | NA                   | NA    | No                       | NA                                       |
| Davidson et al., 2006 <sup>23</sup> | Venlafaxine<br>75 to 300mg/day  | Sertraline<br>50 to 200mg/day                | Placebo              | NA    | No                       | NA                                       |
| Davidson et al., 2006 <sup>24</sup> | Venlafaxine<br>37.5 to 300 mg/day   | Placebo                                      | NA                   | NA    | No                       | NA                                       |
| Davidson et al., 2007 <sup>25</sup> | Tiagabine<br>4 to16mg/day   | Placebo                                      | NA                   | NA    | Unclear                  | NA                                       |
| Davis et al., 2008 <sup>26</sup>    | Divalproex<br>1000 to 3000 mg/day   | Placebo                                      | NA                   | NA    | Yes                      | Low dose trazodone for insomnia allowed. |
| Ehlers et al., 2003 <sup>27</sup>   | Cognitive Therapy<br>Mean of 9 weekly sessions of 60 minutes during first 3 months, mean of 2.4 booster sessions (duration unspecified)   | Self-help booklet based on principles of CBT | Repeated assessments | NA    | No                       | NA                                       |
| Ehlers et al., 2005 <sup>28</sup>   | CBT-mixed<br>Cognitive therapy including restructuring and exposure<br>Up to 12 weekly sessions of 90 minutes for the initial sessions, 60 minutes thereafter, and 3 monthly boosters | Wait list                                    | NA                   | NA    | Unclear                  | NA                                       |
| Fecteau et al., 1999 <sup>29</sup>  | CBT-mixed<br>Coping skills, exposure-therapy, and cognitive restructuring<br>4 weekly sessions of 120 minutes   | Wait list                                    | NA                   | NA    | Unclear                  | NA                                       |

**Table D-3. Intervention and control components from randomized controlled trials (continued)**

| Author, Year  | Arm 1  | Arm 2  | Arm 3   | Arm 4     | Co-Interventions Allowed | Description of Co-Interventions  |
|---|--|--|---|-----------|--------------------------|--|
| Foa et al., 1999 <sup>30</sup><br>Zoellner et al., 1999 <sup>31</sup> | CBT, exposure-based therapy(Prolonged Exposure)<br>9 twice-weekly sessions, two sessions of 120 minutes followed by 7 sessions of 90 minutes | CBT, coping skills therapy<br>Stress Inoculation Training<br>9 twice-weekly sessions, two sessions of 120 min followed by 7 sessions of 90 minutes | CBT-mixed Combined treatment (Prolonged exposure and Stress Inoculation Training)<br>9 twice-weekly sessions, two sessions of 120 min followed by 7 sessions of 90 min) | Wait list | Unclear                  | NA   |
| Foa et al., 2005 <sup>32</sup>  | CBT, exposure-based therapy(Prolonged Exposure)<br>9 to 12 weekly sessions of 90 to 120 minutes  | CBT-mixed Prolonged Exposure plus Cognitive Restructuring<br>9 to 12 weekly sessions of 90 to 120 minutes.   | Wait list   | NA        | Yes                      | Psychiatric medications allowed if stable for at least 3 months  |
| Forbes et al., 2012 <sup>33</sup>                                     | CBT, cognitive processing therapy<br>12 bi-weekly sessions; session 1 90 minutes, all other session 60 minutes                               | Treatment as Usual   | NA  | NA        | Yes                      | Stable use of psychotropic medications (period of 4 weeks) and concurrent interventions for issues other than PTSD were allowed as long as they did not alter course of study. |
| Ford et al., 2011 <sup>34</sup>                                       | Trauma Affect Regulation: Guide for Education and Therapy (TARGET),<br>12 sessions of 50 minutes   | Present centered therapy, 12 sessions.   | Waitlist  | NA        | NA                       | 35% of sample under mental health treatment; 28% of sample undergoing pharmacotherapy  |
| Friedman et al., 2007 <sup>35</sup>                                   | Sertraline<br>25 to 200 mg/day   | Placebo  | NA  | NA        | No                       | NA   |

|                                       |  |  |           |    |         |   |
|---------------------------------------|--|--|-----------|----|---------|---|
| Gamito et al.,<br>2010 <sup>36</sup>  | Virtual reality exposure<br>therapy "VRET"<br>12 sessions                            | CBT, exposure-<br>based therapy<br>(Imaginal<br>exposure)<br>12 sessions | Wait list | NA | Yes     | Stable medical regimens maintained<br>by participants' psychiatrists. |
| Gersons et al.,<br>2000 <sup>37</sup> | Eclectic psychotherapy(Brief<br>Eclectic Psychotherapy)<br>16 sessions of 60 minutes | Wait list  | NA        | NA | Unclear | NA  |

**Table D-3. Intervention and control components from randomized controlled trials (continued)**

| Author, Year   | Arm 1   | Arm 2   | Arm 3   | Arm 4 | Co-Interventions Allowed | Description of Co-Interventions   |
|--|---|---|---|-------|--------------------------|---|
| Hamner et al., 2003 <sup>38</sup>                                  | Risperidone<br>1 to 6 mg/day  | Placebo   | NA  | NA    | Yes                      | <p>Patients stable for at least 1 month on antidepressants, benzodiazepines, and PRN sleep medications were included.</p> <p>Antidepressant use:<br/>G1: 15<br/>G2: 15</p> <p>Benzodiazepine use:<br/>G1: 4<br/>G2: 2</p> <p>Receiving "other" psychotropics:<br/>G1: 10<br/>G2: 10</p> |
| Hien et al., 2004 <sup>39</sup>                                    | Seeking Safety<br>Addresses PTSD and Substance Abuse<br>2 times a week, 60 minute sessions for 12 consecutive weeks | Relapse prevention condition<br>Addresses only substance abuse<br>Twice-weekly 60 minute individual sessions for 12 consecutive weeks | Usual care<br>Non-randomized<br>Standard community Care | NA    | Yes                      | <p>Pharmacotherapy:<br/>G1 &amp; G2 combined: 19%<br/>G3: 22.58%</p>  |
| Hien et al., 2009 <sup>40</sup><br>Hien et al., 2012 <sup>41</sup> | Seeking Safety<br>2 sessions per week, 75 to 90 minutes over 6 weeks  | Psychoeducation<br>2 sessions per week, 75 to 90 minutes over 6 weeks   | NA  | NA    | Yes                      | <p>Mean mental health visits per week separate from study (SD):<br/>G1: 1.3 (1.6)<br/>G2: 1.5 (2.7)</p> <p>Mean visits to 12-step substance abuse meetings (SD):<br/>G1: 3.4 (4.1)<br/>G2: 2.8 (3.7)</p>  |

**Table D-3. Intervention and control components from randomized controlled trials (continued)**

| Author, Year                       | Arm 1   | Arm 2   | Arm 3 | Arm 4 | Co-Interventions Allowed | Description of Co-Interventions  |
|------------------------------------|---|---|-------|-------|--------------------------|--|
| Hinton et al., 2005 <sup>42</sup>  | CBT-mixed<br>Information on PTSD and Panic Disorder, relaxation techniques, culturally appropriate visualization, cognitive restructuring, exposure to anxiety-related sensations and trauma related memories, emotional-processing protocol, and cognitive flexibility.<br>12 sessions across 12 weeks                 | Wait list   | NA    | NA    | Yes                      | All patients continued supportive psychotherapy and medications (combination of SSRI and clonazepam).          |
| Hinton et al., 2009 <sup>43</sup>  | CBT-Mixed<br>Information on PTSD and Panic Disorder, muscle relaxation, guided imagery, mindfulness training, yoga-like stretching, cognitive restructuring, various exercises to teach emotional distancing and switching, and interoceptive exposure.<br>12 weekly individual sessions (no duration of time provided) | Waitlist  | NA    | NA    | Yes                      | All patients continued supportive psychotherapy<br>All patients used psychoactive medications including SSRIs. |
| Hinton et al., 2011 <sup>44</sup>  | CBT-mixed<br>Culturally Adapted CBT: Has components of coping skills, cognitive "modification", mentions exposure<br>14 weekly sessions of 60 minutes   | Applied Muscle Relaxation<br>14 weekly sessions of 60 minutes | NA    | NA    | Yes                      | Participants continued to receive pharmacotherapy and supportive therapy.                                      |
| Hogberg et al., 2007 <sup>45</sup> | EMDR<br>Five 90 minute sessions over 2 months   | Wait list   | NA    | NA    | Yes                      | One wait-list patient (G2) on SSRI   |

**Table D-3. Intervention and control components from randomized controlled trials (continued)**

| Author, Year                          | Arm 1   | Arm 2  | Arm 3     | Arm 4 | Co-Interventions Allowed | Description of Co-Interventions   |
|---------------------------------------|---|--|-----------|-------|--------------------------|---|
| Hollifield et al., 2007 <sup>46</sup> | Acupuncture<br>2 times a week, 60 minute sessions   | CBT-mixed<br>Cognitive restructuring, behavior activation, and coping skills<br>12 weekly sessions for 120 minutes | Wait list | NA    | Yes                      | Allowed to be on stable medications (for at least 3 months) and received supportive therapy at same time but "no active treatment specifically for PTSD".             |
| Johnson et al., 2011 <sup>47</sup>    | CBT-mixed<br>Psychoeducation and CBT restructuring<br>Up to 12 60 to 90 minute sessions over 8 weeks  | Usual care   | NA        | NA    | Yes                      | Psychotropic Medications<br>Overall: 21.4<br>G1: 20<br>G2: 22.9   |
| Krakov et al., 2001 <sup>48</sup>     | IRT<br>Two 180 minute sessions spaced 1 week apart with a 60 minute follow-up 3 weeks later           | Wait list  | NA        | NA    | Yes                      | 79% of participants were concurrently receiving psychotherapy and/or psychotropic medications   |
| Kruse et al., 2009 <sup>49</sup>      | CBT-Mixed<br>25 hours of total therapy, first 3 months weekly; after 3 months. once every other week. | Usual care   | NA        | NA    | Unclear                  | Unclear   |
| Krystal et al., 2011 <sup>50</sup>    | Risperidone<br>1 to 4 mg/day  | Placebo  | NA        | NA    | Yes                      | Entry criteria for study specified that patients had to be on a SRI medication or have had at least two prior trials of SRIs.<br><br>Ongoing pharmacotherapy allowed. |
| Kubany et al., 2003 <sup>51</sup>     | CBT, cognitive restructuring<br>8 to 11 90 minute sessions  | Wait list  | NA        | NA    | Yes                      | Continuation of prior treatment   |

**Table D-3. Intervention and control components from randomized controlled trials (continued)**

| Author, Year  | Arm 1  | Arm 2   | Arm 3   | Arm 4      | Co-Interventions Allowed | Description of Co-Interventions   |
|---|--|---|---|------------|--------------------------|---|
| Kubany et al., 2004(Kubany, 2004 #806)                                | CBT-Mixed (Cognitive Trauma Therapy-Battered Women), 8 to 11, 90 minute sessions biweekly  | Wait list   | NA  | NA         | Yes                      | Participants not required to discontinue other services or prescription medication.   |
| Liedl et al., 2011 <sup>53</sup>                                      | CBT-Mixed<br><br>Coping skill (Biofeedback) 10 weekly 90 minute sessions, to be completed in 3-6 months (average treatment lasting 4.8 months) | CBT-Mixed Coping skills (biofeedback) + physical activity 10 weekly 90 minute sessions, to be completed in 3 to 6 months (average treatment lasting 4.8 months)+ daily designated physical activity, 20 minutes a day | Wait list   |            | Unclear                  | NR  |
| Lindauer et al., 2005 <sup>54</sup>                                   | Eclectic psychotherapy Brief Eclectic Psychotherapy 16 weekly sessions of 45 to 60 minutes   | Wait list   | NA  | NA         | No                       | NA  |
| Litz et al., 2007 <sup>55</sup>                                       | CBT-mixed Stress management skills, in vivo exposure, and relapse prevention<br><br>Mean number days spent in treatment = 46.76                | Internet-delivered supportive counseling<br>Mean days spent in treatment= 36.92   | NA  | NA         | No                       | NA  |
| Marks et al., 1998 <sup>56</sup><br>Lovell et al., 2001 <sup>57</sup> | CBT, exposure-based therapy(Prolonged Exposure) 10, 90 minute sessions   | CBT, cognitive restructuring 10,90 minute sessions  | CBT-mixed Exposure Combined with Cognitive Restructuring 10, 105 minutes sessions | Relaxation | Yes                      | Currently on Antidepressants Overall: 28%<br>G1: 17%<br>G2: 26%<br>G3: 42%<br>G4: 24% |
| Marshall et al.,  | Paroxetine   | Paroxetine  | Placebo   | NA         | No                       | NA  |

|                    |           |           |
|--------------------|-----------|-----------|
| 2001 <sup>58</sup> | 20 mg/day | 40 mg/day |
|--------------------|-----------|-----------|

**Table D-3. Intervention and control components from randomized controlled trials (continued)**

| Author, Year   | Arm 1   | Arm 2  | Arm 3     | Arm 4 | Co-Interventions Allowed | Description of Co-Interventions  |
|--|---|--|-----------|-------|--------------------------|--|
| Martenyi et al., 2002 <sup>59</sup><br>Martenyi et al., 2006 <sup>60</sup> | Fluoxetine<br>20 to 80 mg/day   | Placebo  | NA        | NA    | Unclear                  | NA   |
| Martenyi et al., 2007 <sup>61</sup>  | Fluoxetine<br>20 mg/day   | Fluoxetine<br>40 mg/day  | Placebo   | NA    | Unclear                  | NA   |
| McDonagh et al., 2005 <sup>62</sup>  | CBT-mixed<br>Exposure and cognitive restructuring therapy<br>14 sessions, sessions 1 to 7 were 120 minutes, final 7 were 90 minutes.<br>Average time to completion = 17.5 weeks.            | Present-Centered<br>Therapy<br>14 sessions, sessions 1 to 7 were 120 minutes, final 7 were 90 minutes.<br>Average time to completion = 19.5 weeks. | Wait list | NA    | Unclear                  | NA   |
| Monnelly et al., 2003 <sup>63</sup>  | Risperidone<br>0.5 to 2.0mg/day   | Placebo  | NA        | NA    | Yes                      | Psychotropic medication or individual or group therapy that was ongoing at the beginning of the study continued unchanged.   |
| Monson et al., 2006 <sup>64</sup>  | CBT, cognitive processing therapy<br>12-sessions conducted twice a week whenever possible, over 6 weeks   | Wait list  | NA        | NA    | Yes                      | Allowed to maintain their psychopharmacological treatment, but they had to be on a stable regimen for at least 2 months prior to study entry. Allowed to continue in psychotherapeutic interventions not specifically focused on PTSD.   |
| Mueser et al., 2008 <sup>65</sup>  | CBT-mixed<br>CBT for PTSD Program included crisis plan review, psychoeducation, breathing retraining, cognitive restructuring, and generalization training.<br>12 to 16 sessions(unclear on | Usual care   | NA        | NA    | Yes                      | Received comprehensive treatment for psychiatric illness throughout the study period (i.e., pharmacological treatment, monitoring, case management, supportive counseling, and access to psychiatric rehabilitation). No efforts were made to control or modify any of these services. |



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time period), delivered  
over a 4- to 6-months

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**Table D-3. Intervention and control components from randomized controlled trials (continued)**

| Author, Year                       | Arm 1  | Arm 2  | Arm 3   | Arm 4 | Co-Interventions Allowed | Description of Co-Interventions   |
|------------------------------------|--|--|---|-------|--------------------------|---|
| Nacasch et al., 2011 <sup>66</sup> | CBT, exposure-based therapy (Prolonged exposure therapy), 9 to 15 weekly sessions lasting 90 to 120 minutes                    | Treatment as Usual   | NA  | NA    | Yes                      | Taking psychotropic medications at baseline:<br>Overall: 22 (73.3%)<br>G1: 10 (66.7%)<br>G2: 12 (80.0%)   |
| Neuner et al., 2004 <sup>67</sup>  | CBT, exposure-based therapy (Narrative Exposure Therapy) 4 sessions, 90 to 120 minutes.  | Supportive Counseling 4 sessions, 90 to 120 minutes  | Psycho-education About the nature and prevalence of PTSD 1 session, 90 to 120 minutes | NA    | Unclear                  | NA  |
| Neuner et al., 2008 <sup>68</sup>  | CBT, exposure based (Narrative Exposure Therapy) 6 sessions (usually 2 sessions per week), between 60 to 120 minutes           | Flexible Trauma Counseling 6 sessions (usually 2 sessions per week), between 60 to 120 minutes       | No-treatment monitoring group   | NA    | Unclear                  | NA  |
| Neuner et al., 2010 <sup>69</sup>  | CBT, exposure based (Narrative Exposure Therapy) 5 to 17 weekly or biweekly sessions (M=8.79), average duration of 120 minutes | Usual care   | NA  | NA    | Yes                      | % of patients using concurrent antidepressant medications:<br>G1: 62.50%<br>G2: 43.8%   |
| Nijdam et al., 2012 <sup>70</sup>  | Eclectic psychotherapy 16 weekly sessions of 45 to 60 minutes.   | EMDR Weekly sessions of 90 minutes. Unclear of how many sessions or weeks- entire trial was 17 weeks | NA  | NA    | Yes                      | Pharmacological treatments were allowed if stable for at least 4 weeks. Participants not allowed to attend any other trauma-focused intervention during the trial.<br><br>% on psychoactive medication<br>G1: 42.9%<br>G2: 41.4 |
| Panahi et al., 2011 <sup>71</sup>  | Sertraline 50 to 200 mg/day  | Placebo  | NA  | NA    | Yes                      | Chloral hydrate or diazepam was allowed to be taken as needed.  |

**Table D-3. Intervention and control components from randomized controlled trials (continued)**

| Author, Year                        | Arm 1   | Arm 2  | Arm 3  | Arm 4  | Co-Interventions Allowed | Description of Co-Interventions  |
|-------------------------------------|---|--|--|--|--------------------------|--|
| Petrakis et al., 2011 <sup>72</sup> | Paroxetine (40 mg/day)+ Naltrexone (50 mg/day)<br>Participants who could not tolerate the highest dose in either condition were brought to lower doses. | Paroxetine (40 mg/day) +Placebo<br>Participants who could not tolerate the highest dose in either condition were brought to lower doses. | Desipramine (200 mg/day) + Naltrexone (50 mg/day)<br>Participants who could not tolerate the highest dose in either condition were brought to lower doses. | Desipramine (200 mg/day + Placebo<br>Participants who could not tolerate the highest dose in either condition were brought to lower doses. | Yes                      | Participants were not on any psychiatric medications before starting the study.<br>Sleep medications were taken as needed (n=6).<br>All subjects received Clinical Management/Compliance Enhancement therapy.  |
| Raskind et al., 2003 <sup>73</sup>  | Prazosin 2 to 10 mg/day   | Placebo  | Other  | NA   | Yes                      | Medications and psychotherapy allowed.   |
| Raskind et al., 2007 <sup>74</sup>  | Prazosin 2 to 15 mg at bedtime  | Placebo  | NA   | NA   | Yes                      | Received group/individual psychotherapy for at least 2 months prior to entering study. They maintained unaltered through the study. No new therapies were started after the trial.<br><br>Overall: 27<br>G1: 14<br>G2: 13                            |
| Reich et al., 2004 <sup>75</sup>    | Risperidone 0.5 to 8 mg/day   | Placebo  | NA   | NA   | Yes                      | Subjects were instructed to maintain all other psychotropic medications at constant dosages during the study (1 antidepressant and/or 1 hypnotic at bedtime allowed at study entry).<br><br>Subjects who experienced extrapyramidal effects could be |

|                                   |   |   |           |    |     |                           |  |
|-----------------------------------|---|---|-----------|----|-----|---------------------------|--|
|                                   |   |   |           |    |     | Stabilized medication use | treated with benztropine at dosages of up to 2 mg b.i.d. |
| Resick et al., 2002 <sup>76</sup> | CBT, cognitive processing therapy   | CBT, exposure-based therapy (Prolonged Exposure)                              | Wait list | NA | Yes |                           |  |
| Resick et al., 2003 <sup>77</sup> | 2 times a week for over 6 weeks; 60 to 90 minute sessions (total of 13 hours) |   |           |    |     |                           |  |
| Resick et al., 2012 <sup>78</sup> |   | 2 times a week for over 6 weeks; 60 to 90 minute sessions (total of 13 hours) |           |    |     |                           |  |

**Table D-3. Intervention and control components from randomized controlled trials (continued)**

| Author, Year                        | Arm 1   | Arm 2   | Arm 3     | Arm 4 | Co-Interventions Allowed | Description of Co-Interventions   |
|-------------------------------------|---|---|-----------|-------|--------------------------|---|
| Rothbaum et al., 1997 <sup>79</sup> | EMDR<br>3 weekly 90 minute sessions   | Wait list   | NA        | NA    | Yes                      | Overall: 5<br>G1: 3<br>G2: 2<br>Concurrent therapy information is not reported                              |
| Rothbaum et al., 2005 <sup>80</sup> | CBT, exposure-based therapy (Prolonged Exposure)<br>9, 90 minute sessions, twice a week   | EMDR<br>9, 90-minute sessions, twice a week   | Wait list | NA    | Yes                      | Psychotropic medication allowed if dosage stable for 30 days, and not allowed to change for study duration. |
| Rothbaum et al., 2006 <sup>81</sup> | CBT, exposure based (Prolonged Exposure) plus Sertraline<br>25 to 200mg per day<br>2 times a week for 10 weeks,<br>45 to 60 minute sessions   | Sertraline<br>25 to 200mg/day per   | NA        | NA    | Unclear                  | NA  |
| Schneier et al., 2012 <sup>82</sup> | CBT, exposure based (Prolonged Exposure) + Paroxetine (12.5 to 50 mg/day)<br>Prolonged exposure therapy, 10 weekly 90 minute sessions<br>Paroxetine administered by psychiatrists (visits were 30 mins weekly for 6 | CBT, exposure based (Prolonged Exposure) + placebo<br>Prolonged exposure therapy, 10 weekly 90 minute sessions<br>Placebo administered by | NA        | NA    | Yes                      | Zolpidem allowed for insomnia   |

|                                    |   |  |    |    |     |   |
|------------------------------------|---|--|----|----|-----|---|
|                                    | weeks, every 2 weeks for 4 weeks, and then every 4 weeks)   | psychiatrists (visits were 30 mins weekly for 6 weeks, every 2 weeks for 4 weeks, and then every 4 weeks)  |    |    |     |   |
| Schnurr et al., 2003 <sup>83</sup> | Exposure-based, trauma-focused group therapy (psychoeducation, cognitive restructuring, relapse prevention, and coping skills training) 30 weekly sessions of 90 to 120 minutes; then 5 monthly 15-minute phone calls | Present-centered group Therapy(avoided trauma-focused references, cognitive restructuring, and other trauma-focused group therapy components) 30 weekly sessions of 90 minutes | NA | NA | Yes | Individuals taking psychoactive medications had to have a stable regimen for at least 2 months before study entry; medication changes were allowed during study if clinically justified; no other psychotherapeutic treatment for PTSD allowed, other than 12-step programs |

**Table D-3. Intervention and control components from randomized controlled trials (continued)**

| Author, Year                        | Arm 1   | Arm 2  | Arm 3 | Arm 4 | Co-Interventions Allowed | Description of Co-Interventions  |
|-------------------------------------|---|--|-------|-------|--------------------------|--|
| Schnurr et al., 2007 <sup>84</sup>  | CBT, exposure-based therapy (Prolonged Exposure)<br>10 weekly sessions of 90 minutes  | Present-centered therapy<br>10 weekly sessions of 90 minutes       | NA    | NA    | Yes                      | Psychoactive medication allowed if on stable dose for at least 2 months prior to start.<br>Receiving Psychotropic medication<br>G1: 76.3%<br>G2: 73.4%<br>Psychotherapy for other problems, brief visits with an existing therapist and self-help groups also allowed.<br>Receiving Psychotherapy:<br>G1: 67.4%<br>G2: 57.3% |
| Schnyder et al., 2011 <sup>85</sup> | Eclectic psychotherapy<br>BEP<br>16 sessions of 50 minutes  | Wait list<br>Minimal attention control                             | NA    | NA    | No                       | No other psychotherapy for PTSD allowed but if taking psychoactive medication had to be on a stable regimen for at least 2 months prior to entering trial.<br><br>40% taking psychotropic medication (mostly antidepressants), 16.75% taking analgesic medication.   |
| Simon et al., 2008 <sup>86</sup>    | Paroxetine<br>12.5 to 62.5 mg/day   | Placebo<br>Placebo and 5 additional sessions of prolonged exposure | NA    | NA    | Yes                      | Sleep aids were allowed if stable before randomization.  |
| Spence et al., 2011 <sup>87</sup>   | CBT-mixed<br>Imaginal exposure, Coping skills, Cognitive processing<br>8 weeks of 7 internet based lessons plus assignments and email or telephone conversations with therapist | Wait list  | NA    | NA    | Yes                      | Medications for depression or anxiety allowed.<br><br>Overall: 57% of the total randomized sample<br>G1: 65%<br>G2: 48%  |

**Table D-3. Intervention and control components from randomized controlled trials (continued)**

| Author, Year   | Arm 1   | Arm 2  | Arm 3  | Arm 4 | Co-Interventions Allowed | Description of Co-Interventions   |
|--|---|--|--|-------|--------------------------|---|
| Stein et al., 2002 <sup>88</sup>   | Olanzapine<br>10 to 20 mg   | Placebo  | NA   | NA    | Yes                      | Current stable regimen allowed.<br>Fluoxetine, N = 5 (mean dose 40 mg/day)<br><br>Paroxetine, N = 7 (mean dose = 40 mg/day)<br><br>Sertraline, N = 7 (mean dose = 200 mg/day) |
| Tarrier et al., 1999 <sup>89</sup><br>Tarrier et al., 1999 <sup>90</sup> | CBT, exposure-based therapy<br>Imaginal Exposure Therapy<br>16 sessions of 60 minutes   | CBT, cognitive restructuring<br>Cognitive Therapy<br>16 sessions of 60 minutes | NA   | NA    | No                       | NA  |
| Taylor et al., 2003 <sup>91</sup>  | CBT, exposure-based therapy<br>Four 90 minute sessions of imaginal exposure, then four 90 minute sessions of in-vivo exposure | EMDR<br>8 weekly sessions of 90 minutes  | Relaxation Training<br>8 weekly sessions of 90 minutes | NA    | Yes                      | Current regimen of psychotropic medications allowed.  |
| Tucker et al., 2001 <sup>92</sup>  | Paroxetine<br>20 to 50mg/day  | Placebo  | NA   | NA    | Yes                      | Chloral hydrate was permitted in doses up to 1000 mg for a maximum of 3 nights per week during the first week of double-blind treatment.                                      |
| Tucker et al., 2003 <sup>93</sup><br>Tucker et al., 2004 <sup>94</sup>   | Citalopram<br>20 to 50 mg/day   | Sertraline<br>50 to 200 mg/day   | Placebo  | NA    | Yes                      | Not on any medications affecting autonomic functioning. Occasional diphenhydramine for sleep was allowed.   |
| Tucker et al., 2007 <sup>95</sup>  | Topiramate<br>25 to 400mg/day; given 2 times a day  | Placebo  | NA   | NA    | No                       | NA  |

**Table D-3. Intervention and control components from randomized controlled trials (continued)**

| Author, Year                            | Arm 1  | Arm 2  | Arm 3     | Arm 4 | Co-Interventions Allowed | Description of Co-Interventions   |
|---|--|--|-----------|-------|--------------------------|---|
| van der Kolk et al., 1994 <sup>96</sup> | Fluoxetine<br>20 to 60mg/day   | Placebo  | NA        | NA    | Yes                      | No other psychotropic agents. Lorazepam permitted for severe insomnia<br>Overall: 3 subjects used (average dose of 0.7 mg)<br>Subjects allowed were to continue current psychotherapeutic regimen. None received intensive, trauma-specific psychotherapy at the time of the trial. |
| van der Kolk et al., 2007 <sup>97</sup> | EMDR<br>8 weekly sessions of 90 min  | Fluoxetine<br>10 to 60 mg/day  | Placebo   | NA    | Yes                      | Ongoing supportive psychotherapy allowed, provided that it had been ongoing at least 3 months and did not involve exposure to or processing of traumatic memories   |
| van Emmerik et al., 2008 <sup>98</sup>  | CBT-Mixed<br>Psychoeducation, prolonged exposure, imaginal exposure, exposure in vivo, cognitive exposure<br>Participants with Acute PTSD (n=62) Received 5 weekly sessions of 90 minutes<br>Participants with Chronic PTSD (n=58) received 10 weekly sessions of 90 minutes | Structured writing therapy<br>Acute PTSD (n=62) patients received 5 weekly sessions of 90 minutes<br>Chronic PTSD (n=58) received 10 weekly sessions of 90 minutes | Wait list | NA    | Yes                      | Overall: 19.2% receiving psychotropic medications<br>G1: NR<br>G2: NR<br>G3: NR<br>Co-therapies were not allowed.   |
| Yeh et al., 2011 <sup>99</sup>          | Topiramate<br>25 to 200mg/day  | Placebo  | NA        | NA    | Yes                      | Zolpidem (10 mg/day) was allowed for insomnia   |
| Zlotnick et al., 2009 <sup>100</sup>    | Seeking Safety<br>Present focused, abstinence-oriented, and emphasized an empowering compassionate approach<br>3 times a week for 6 to 8 weeks; 90 minute sessions; booster sessions were weekly for 12 weeks  | Usual care<br>Psychoeducational group and individual case management and drug counseling (followed 12-step model)<br>Weekly sessions for 3 to 6 months             | NA        | NA    | Unclear                  | Unclear   |



**Table D-3. Intervention and control components from randomized controlled trials (continued)**

| <b>Author, Year</b>               | <b>Arm 1</b>                   | <b>Arm 2</b> | <b>Arm 3</b> | <b>Arm 4</b> | <b>Co-Interventions Allowed</b> | <b>Description of Co-Interventions</b> |
|-----------------------------------|--------------------------------|--------------|--------------|--------------|---------------------------------|--|
| Zohar et al., 2002 <sup>101</sup> | Sertraline<br>50 to 200 mg/day | Placebo      | NA           | NA           | Unclear                         | NR                                     |

Abbreviations: b.i.d. = 2 x daily; BEp=brief eclectic psychotherapy; CBT = Cognitive behavioral therapy; CPT-SA = Cognitive Processing Therapy for Sexual Abuse Survivors; EMDR = Eye movement desensitization and reprocessing; G = group; IRT = imagery rehearsal therapy; mg = milligram; min = minutes; MVA = motor vehicle accident; NA = not applicable; NR = not reported; PTSD = post-traumatic stress disorder; SD = standard deviation; SSRIs = Selective serotonin re-uptake inhibitors or serotonin-specific reuptake inhibitor; STAIR = Skills Training in Affect and Interpersonal Regulations; VRET = virtual reality exposure therapy.

**Table D-4. Clinician administered PTSD scales**

| Author, Year                         | Clinician Administered CAPS or CAPS 2  | Clinician Administered PSS-I | Clinician Administered SI-PTSD | Clinician Administered Other |
|--------------------------------------|--|------------------------------|--------------------------------|------------------------------|
| Akuchekian et al., 2004 <sup>1</sup> | <p>CAPS</p> <p>Mean (SD)</p> <p>G1 Pre-tx: 50.70 (7.7)</p> <p>G1 Post-tx: 32.75 (8.2)</p> <p>G2 Pre-tx: 48.9 (9.13)</p> <p>G2 Post-tx: 46.62 (8.8)</p> <p>G1 vs. G2, p=0.00 (based on t-test)</p>  | NR                           | NR                             | NR                           |
| Asukai et al., 2010 <sup>2</sup>     | <p>CAPS</p> <p>Adjusted Mean (SE)</p> <p>G1 Pre-tx: 84.58 (7.78)</p> <p>G1 Post-tx: 43.76 (8.43)</p> <p>G2 Pre-tx: 84.33 (7.78)</p> <p>G2 Post-tx: 84.81 (7.96)</p> <p>At post: G1 vs. G2=</p> <p>p&lt;0.01 (based on t-test)</p>  | NR                           | NR                             | NR                           |
| Bartzokis et al., 2005 <sup>3</sup>  | <p>CAPS</p> <p>Unadjusted Change from baseline (SD)</p> <p>G1: -14.3 (16.7)</p> <p>G2: -4.6 (13.2)</p> <p>G1 vs. G2, p&lt;0.05</p>   | NR                           | NR                             | NR                           |
| Basoglu et al., 2007 <sup>4</sup>    | <p>CAPS</p> <p>Mean (SD)</p> <p>G1 Pre-tx: 63.1 (10.1)</p> <p>G1 Week 4: 38.7 (18.7)</p> <p>G1 Week 8: 30.2 (20.3)</p> <p>G2 Pre-tx: 62.3 (14.5)</p> <p>G2 Week 4: 54.5 (16.9)</p> <p>G2 Week 8: 49.1 (20.3)</p> <p>G1 vs. G2 at Week 4, p&lt;0.01</p> <p>G1 vs. G2 at Week 8, p&lt;0.01</p> | NR                           | NR                             | NR                           |

**Table D-4. Clinician administered PTSD scales (continued)**

| Author, Year                           | Clinician Administered<br>CAPS or CAPS 2   | Clinician Administered<br>PSS-I | Clinician Administered<br>SI-PTSD | Clinician Administered<br>Other |
|--|--|---------------------------------|-----------------------------------|---------------------------------|
| Becker et al.,<br>2007 <sup>5</sup>    | CAPS<br>Within Group Mean Change<br>(SD)(Baseline-Endpoint)<br>G1: 12.33 (24.12)<br>G2: 16.99 (11.26)<br><br>Group effect , p<0.01   | NR                              | NR                                | NR                              |
| Blanchard et al.,<br>2003 <sup>6</sup> | CAPS<br>Mean (SD)<br>G1 Pre-tx: 68.2 (22.7)<br>G1 Post-tx: 23.7 (26.2)<br><br>G2 Pre-tx: 65.0 (25.9)<br>G2 Post-tx:40.1 (25.7)<br><br>G3 Baseline: 65.8 (26.6)<br>G3 Post-tx: 54.0 (25.9)<br><br>Group X Time at post-tx, p<0.001<br>G1 vs. G2, p=0.002<br>G1 vs. G3, p<0.001<br>G2 vs. G3, p=0.012<br><br>Including Dropouts<br>Group X Time at post-tx, p<0.001<br>G1 vs. G2, p=0.013<br>G1 vs. G3, p<0.001<br>G2 vs. G3, p=0.052<br><br>Group X Time, 3 mth FU<br>p=0.048<br>G1 continued to have lower scores<br>than G2, p=0.003<br>Decreases from post-tx to the 3<br>mth fu, NS | NR                              | NR                                | NR                              |
| Boden et al.,<br>2012 <sup>7</sup>     | NR   | NR                              | NR                                | NR                              |

**Table D-4. Clinician administered PTSD scales (continued)**

| Author, Year                      | Clinician Administered CAPS or CAPS 2   | Clinician Administered PSS-I | Clinician Administered SI-PTSD | Clinician Administered Other |
|-----------------------------------|---|------------------------------|--------------------------------|------------------------------|
| Brady et al., 2000 <sup>8</sup>   | CAPS-2<br>Mean change (SEM)<br>G1: -33.0 (2.8)<br>G2: -23.2 (2.9)<br>Difference Between Mean Change (95% CI): 9.8 (1.8 to 17.7), p=0.02   | NR                           | NR                             | NR                           |
| Brady et al., 2005 <sup>9</sup>   | CAPS ANCOVA<br>F (2, 68) = 2.68, p=0.08   | NR                           | NR                             | NR                           |
| Bryant et al., 2003 <sup>10</sup> | CAPS-Intensity<br>Mean (SD)<br>G1 Pre-tx: 32.50 (8.71)<br>G1 Post-tx: 19.15 (11.15)<br>G1 6 mth FU: -20.70 (12.00)<br><br>G2 Pre-tx: 32.70 (7.51)<br>G2 Post-tx: 15.90 (13.36)<br>G2 6 mth FU: 15.70 (14.79)<br><br>G3 Pre-tx: 32.83 (8.01)<br>G3 Post-tx: 28.00 (15.31)<br>G3 6 mth FU: 30.28 (12.89)<br><br>Post-tx, p<0.01 (main effects)<br>FU, p<0.05 (main effects) | NR                           | NR                             | NR                           |

**Table D-4. Clinician administered PTSD scales (continued)**

| Author, Year                                | Clinician Administered<br>CAPS or CAPS 2  | Clinician Administered<br>PSS-I | Clinician Administered<br>SI-PTSD | Clinician Administered<br>Other |
|---|---|---------------------------------|-----------------------------------|---------------------------------|
| Bryant et al.,<br>2003 <sup>10</sup> cont'd | CAPS-Frequency (CAPS-F)<br>Mean (SD)<br>G1 Pre-tx: 36.80 (9.82)<br>G2 Post-tx: 20.55 (12.73)<br>G1 6 mth FU: 23.25 (12.90)<br><br>G2 Pre-tx: 36.00 (8.69)<br>G2 Post-tx: 17.20 (15.62)<br>G2 6 mth FU: 17.00 (15.22)<br><br>G3 Pre-tx: 38.33 (9.64)<br>G3 Post-tx: 30.00 (16.42)<br>G3 6 mth FU: 32.44 (13.57)<br><br>Post-tx, $p < 0.01$ (main effects)<br>FU, $p < 0.05$ (main effects)   |                                 |                                   |                                 |
| Bryant et al.,<br>2008 <sup>11</sup>        | CAPS<br>Mean (SD)<br>G1 Pre-tx: 73.29 (18.82)<br>G1 Post-tx: 55.50 (33.83)<br>G1 6 mth FU: 59.94 (32.36)<br><br>G2 Pre-tx: 76.79 (15.53)<br>G2 Post-tx: 55.96 (24.56)<br>G2 6 mth FU: 59.32 (29.62)<br><br>G3 Pre-tx: 76.06 (19.19)<br>G3 Post-tx: 55.39 (37.45)<br>G3 6 mth FU: 56.39 (35.87)<br><br>G4 Pre-tx: 71.35 (17.28)<br>G4 Post-tx: 29.86 (27.11)<br>G4 6 mth FU: 32.86 (27.44)<br><br>Post-tx, $p < 0.01$ (main effect)<br>6 mth FU, $p < 0.005$ (main effect) | NR                              | NR                                | NR                              |

**Table D-4. Clinician administered PTSD scales (continued)**

| Author, Year                              | Clinician Administered<br>CAPS or CAPS 2 | Clinician Administered<br>PSS-I | Clinician Administered<br>SI-PTSD   | Clinician Administered<br>Other  |
|---|--|---------------------------------|---|--|
| Butterfield et al.,<br>2001 <sup>12</sup> | NR                                       | NR                              | SIP<br>Mean (SD)<br>G1 Pre-tx: 39.7 (9.7)<br>G1 Post-tx: 19.2 (8.7)<br><br>G2 Pre-tx: 45.9 (8.2)<br>G2 Post-tx: 17.0 (17.5) | TOP-8<br>Mean (SD)<br>G1 Pre-tx: 19.3 (4.2)<br>G1 Post-tx: 12.6 (6.4)<br><br>G2Baseline: 21.8 (3.3)<br>G2 Post-tx: 10.5 (8.7)<br><br>SPRINT - Mean (SD)<br>G1 Pre-tx: 31.5 (5.7)<br>G2 Post-tx: 17.9 (7.8)<br><br>G2 Pre-tx: 34.8 (2.1)<br>G2 Post-tx: 20.5 (11.1) |

**Table D-4. Clinician administered PTSD scales (continued)**

| Author, Year                          | Clinician Administered<br>CAPS or CAPS 2   | Clinician Administered<br>PSS-I | Clinician Administered<br>SI-PTSD | Clinician Administered<br>Other |
|---------------------------------------|--|---------------------------------|-----------------------------------|---------------------------------|
| Carlson et al.,<br>1998 <sup>13</sup> | <p>CAPS - Frequency<br/>Mean (SD)<br/>G1 Pre-tx: 2.5 (0.5)<br/>G1 3 mth FU: 0.7 (0.6)</p> <p>G2 Pre-tx: 2.6 (0.5)<br/>G2 3 mth FU: 2.0 (0.7)</p> <p>G3 Pre-tx: 2.4 (0.6)<br/>NR<br/>Group X Time, p&lt;0.0004</p> <p>CAPS Total - Intensity:<br/>Mean(SD)<br/>G1 Pre-tx: 2.4 (0.7)<br/>G1 3 mth FU: 0.8 (0.7)</p> <p>G2 Pre-tx: 2.4 (0.5)<br/>G2 3 mth FU: 2.0 (0.5)</p> <p>G3 Pre-tx: 2.5 (0.6)<br/>NR</p> <p>Group X Time, p&lt;0.002</p> <p>CAPS Total - Overall<br/>Mean Change (SD) at 9 months<br/>G1: 36.9 (28.6)<br/>G2: 67.8 (24.7)<br/>p&lt;0.05</p> | NR                              | NR                                | NR                              |

**Table D-4. Clinician administered PTSD scales (continued)**

| Author, Year                          | Clinician Administered<br>CAPS or CAPS 2   | Clinician Administered<br>PSS-I | Clinician Administered<br>SI-PTSD | Clinician Administered<br>Other |
|---------------------------------------|--|---------------------------------|-----------------------------------|---------------------------------|
| Chard et al.,<br>2005 <sup>14</sup>   | CAPS-SX<br>G1 Pre-tx: 65.46 (26.39)<br>G1 Post-tx: 9.00 (11.04)<br><br>G2 Pre-tx 68.30 (23.67)<br>G2 Post-tx: 62.96 (30.68)<br><br>p<0.001 (interaction)   | NR                              | NR                                | NR                              |
| Cloitre et al.,<br>2002 <sup>15</sup> | CAPS<br>Mean (SD)<br>G1 Pre-tx:69 (16.3)<br>G1 Post-tx: 31 (25.2)<br><br>G2 Pre-tx:69 (16.6)<br>G2 Post-tx:62 (22.7)<br><br>p<.01 (interaction)  | NR                              | NR                                | NR                              |
| Cloitre et al.,<br>2010 <sup>16</sup> | CAPS<br>Mean (SD)<br>G1 Pre-tx:63.08 (18.29)<br>G1 Post-tx: 32.70 (19.37)<br>G1 3 mth FU:24.66 (18.47)<br>G1 6 mth FU:20.44 (19.01)<br><br>G2 Pre-tx: 64.34 (21.15)<br>G2 Post-tx: 32.32 (23.04)<br>G2 3 mth FU:31.88 (22.98)<br>G2 6 mth FU:32.51 (22.69)<br><br>G3 Pre-tx: 64.50 (15.86)<br>G3 Post-tx: 39.72 (18.34)<br>G3 3 mth FU: 39.71 (17.59)<br>G3 6 mth FU: 28.56 (21.00)<br><br>Group X Time<br>G1 vs. G3 at 3 mths, p=0.01<br>No other contrasts significant | NR                              | NR                                | NR                              |



**Table D-4. Clinician administered PTSD scales (continued)**

| Author, Year  | Clinician Administered CAPS or CAPS 2   | Clinician Administered PSS-I | Clinician Administered SI-PTSD  | Clinician Administered Other   |
|---|---|------------------------------|---|--|
| Connor et al., 1999 <sup>17</sup><br>Meltzer-Brody et al., 2000 <sup>18</sup> | NR  | NR                           | SIP<br>Week 12 difference (Baseline - Endpoint) (95% CI)<br>G1 vs. G2 Difference: 10.3 (3.7 to 16.9), p<0.005<br><br>According to Meltzer-Brody paper, effect was significant for all 4 cluster scores (p<0.02) (intrusion, avoidance, numbing, hyperarousal) | Duke Global Severity Rating for PTSD (Duke)<br>Week 12 difference (Baseline - Endpoint) (95% CI)<br>G1 vs. G2 Difference: 1.1 (0.6 to 1.6), p<0.0001   |
| Cook et al., 2010 <sup>19</sup>   | CAPS<br>Mean (SD)<br>G1 Pre-tx: 81.34 (14.00)<br>G1 Post-tx: 74.04 (20.36)<br><br>G2 Pre-tx: 79.48 (15.27)<br>G2 Post-tx: 74.85 (19.52)<br><br>p<0.001 (treatment effect, Wald) | NR                           | NR  | NR   |
| Cottraux, 2008 <sup>20</sup>  | NR  | NR                           | NR  | NR   |
| Davidson et al., 2001 <sup>21</sup>   | CAPS-2<br>Change from Baseline to Endpoint (SD)<br>G1: -33.0 (2.4)<br>G2: -26.2 (2.3)<br>p=0.04 (t-test)  | NR                           | NR  | NR   |
| Davidson et al., 2003 <sup>22</sup>   | NR  | NR                           | SIP<br>Mean (SD)<br>G1 Pre-tx: 34.7 (7.0)<br>G1 Post-tx: 17.4 (4.0)<br><br>G2 Pre-tx: 38.4 (6.7)<br>G2 Post-tx: 32.9 (12.7)<br><br>Between Tx effect size 1.06<br>p=0.04<br>Treatment effect F=5.0; p=.04)  | SPRINT<br>Mean (SD)<br>G1 Pre-tx: 21.7 (6.0)<br>G1 Post-tx: 12.4 (8.8)<br><br>G2 Pre-tx: 25.0 (4.2)<br>G2 Post-tx: 19.4 (8.2)<br>Between Tx effect size<br>0.49<br>p=NS<br><br>Treatment effect, F=1.7;<br>p=.20 |

**Table D-4. Clinician administered PTSD scales (continued)**

| Author, Year                           | Clinician Administered<br>CAPS or CAPS 2  | Clinician Administered<br>PSS-I | Clinician Administered<br>SI-PTSD | Clinician Administered<br>Other |
|--|---|---------------------------------|-----------------------------------|---------------------------------|
| Davidson et al.,<br>2006 <sup>23</sup> | CAPS-SX17<br>Mean Within-group difference<br>(95% CI):<br>G1: -41.51 (-45.66 to -37.36)<br>G2: -39.44 (-43.67 to -35.21)<br>G3: -34.17 (-38.33 to -30.01)<br><br>Between group p-values based<br>on pairwise comparisons from<br>the analysis of covariance model<br>using baseline adjusted values<br>G1 vs. G3: 0.015<br>G2 vs. G3: 0.081<br>G1 vs. G2: 0.494 | NR                              | NR                                | NR                              |
| Davidson et al.,<br>2006 <sup>24</sup> | CAPS-SX<br>Mean (SD)<br>G1 Pre-tx: 81.0 (14.62)<br>G1 Post-tx: 29.2 (26.09)<br><br>G2 Pre-tx: 82.9 (15.50)<br>G2 Post-tx: 38.1 (29.11)<br><br>Between Group Mean Difference<br>-8.9, p=0.006  | NR                              | NR                                | NR                              |
| Davidson et al.,<br>2007 <sup>25</sup> | CAPS<br>Change from baseline (SD)<br>G1: 30.7 (25.1)<br>G2: 30.2 (26.3)<br>p=0.85   | NR                              | NR                                | DTS & TOP-8 NR, both NS         |

**Table D-4. Clinician administered PTSD scales (continued)**

| <b>Author, Year</b>                 | <b>Clinician Administered<br/>CAPS or CAPS 2</b>  | <b>Clinician Administered<br/>PSS-I</b> | <b>Clinician Administered<br/>SI-PTSD</b> | <b>Clinician Administered<br/>Other</b>  |
|-------------------------------------|---|---|---|--|
| Davis et al.,<br>2008 <sup>26</sup> | CAPS<br>Mean(SD)<br>G1 Pre-tx: 75.2 (19.1)<br>G1 Post-tx: 60.1 (24.1)<br><br>G2 Pre-tx: 77.3 (15.3)<br>G2 Post-tx: 60.8 (26.6)<br><br>30% reduction in PTSD scores:<br>G1: NR<br>G2: NR<br>Diff b/t groups, p>0.45<br><br>G1 vs. G2, diff over time, p=NS | NR                                      | NR  | TOP-8<br>Mean(SD)<br>G1 Pre-tx: 19.4 (5.3)<br>G1 Post-tx: 15.4 (6.6)<br><br>G2 Pre-tx: 19.7 (4.3)<br>G2 Post-tx: 15.8 (6.5)<br><br>G1 vs. G2, NS |

**Table D-4. Clinician administered PTSD scales (continued)**

| <b>Author, Year</b>                  | <b>Clinician Administered<br/>CAPS or CAPS 2</b>  | <b>Clinician Administered<br/>PSS-I</b> | <b>Clinician Administered<br/>SI-PTSD</b> | <b>Clinician Administered<br/>Other</b> |
|--------------------------------------|---|---|---|---|
| Ehlers et al.,<br>2003 <sup>27</sup> | CAPS Frequency<br>Mean (SD)<br>G1 Pre-tx: 31.7 (9.5)<br>G1 3 mth FU: 11.2(10.3)<br>G1 9 mth FU: 10.2 (9.9)<br><br>G2 Pre-tx: 32.6 (8.6)<br>G2 3 mth FU: 22.9 (12.9)<br>G2 9 mth FU: 21.4 (11.4)<br><br>G3 Pre-tx: 32.8 (11.5)<br>G3 3 mth FU: 25.6 (12.9)<br>G3 9 mth FU: 21.1 (15.2)<br><br>3 mth FU<br>Overall: p<0.001<br>G1 vs. G2, p<0.001<br>G1 vs. G3, p<0.001<br><br>9 mth FU<br>Overall: p<0.001<br>G1 vs. G2: p<0.001<br>G1 vs. G3: p=0.001<br><br>CAPS Intensity<br>Mean (SD)<br>G1 Pre-tx: 26.7 (7.4)<br>G1 3 mth FU: 10.2 (9.4)<br>G1 9 mth FU: 9.7 (9.5)<br><br>G2 Pre-tx: 26.7 (7.4)<br>G2 3 mth FU: 19.6 (9.0)<br>18.6 (10.1)<br>G2 9 mth FU: G3: 22.4 (11.9) | NR                                      | NR  | NR                                      |

**Table D-4. Clinician administered PTSD scales (continued)**

| <b>Author, Year</b>                                 | <b>Clinician Administered<br/>CAPS or CAPS 2</b>  | <b>Clinician Administered<br/>PSS-I</b> | <b>Clinician Administered<br/>SI-PTSD</b> | <b>Clinician Administered<br/>Other</b> |
|---|---|---|---|---|
| Ehlers et al.,<br>2003 <sup>27</sup><br>(continued) | G3 Pre-tx: 25.9 (10.4)<br>G3 3 mth FU: 22.4 (11.9)<br>G3 9 mth FU: 17.0 (13.8)<br><br>3 mth FU<br>Overall: p <0.001<br>G1 vs.G2: p<0.001<br>G1 vs. G3: p<0.001<br><br>9 mth FU<br>Overall, p=0.002<br>G1 vs.G2, p=0.001<br>G1 vs. G3, p=0.004 |   |   |   |

**Table D-4. Clinician administered PTSD scales (continued)**

| Author, Year                         | Clinician Administered<br>CAPS or CAPS 2  | Clinician Administered<br>PSS-I | Clinician Administered<br>SI-PTSD | Clinician Administered<br>Other |
|--------------------------------------|---|---------------------------------|-----------------------------------|---------------------------------|
| Ehlers et al.,<br>2005 <sup>28</sup> | <p>CAPS-Intensity<br/>Mean (SD)</p> <p>G1 Pre-tx: 36.5 (9.4)<br/>G1 Post-tx: 13.7 (13.4)<br/>G1 Post-tx FU adjusted: 10.4<br/>G1 6 mth FU: 15.5 (14.8)</p> <p>G2 Pre-tx: 29.0 (8.5)<br/>G2 Post-tx: 30.9 (9.6)<br/>G2 Post-tx adjusted: 34.2</p> <p>G1 vs. G2, <math>p &lt; 0.005</math><br/>Changes in G1, <math>p &lt; 0.005</math><br/>Changes in G2, NS</p> <p>CAPS-Frequency<br/>Mean (SD)</p> <p>G1 Pre-tx: 42.0 (8.5)<br/>G1 Post-tx: 16.0 (15.3)<br/>G1 Post-tx adjusted: 11.4<br/>G1 6 mth FU: 16.0 (14.4)</p> <p>G2 Pre-tx: 31.6 (8.4)<br/>G2 Post-tx: 35.5 (11.4)<br/>G2 Post-tx adjusted: 40.2</p> <p>G1 vs. G2, <math>p &lt; 0.005</math><br/>Changes in G1, <math>p &lt; 0.005</math><br/>Changes in G2, NS</p> | NR                              | NR                                | NR                              |

**Table D-4. Clinician administered PTSD scales (continued)**

| Author, Year   | Clinician Administered<br>CAPS or CAPS 2   | Clinician Administered<br>PSS-I  | Clinician Administered<br>SI-PTSD | Clinician Administered<br>Other |
|--|--|--|-----------------------------------|---------------------------------|
| Fecteau et al.,<br>1999 <sup>29</sup>                                    | CAPS-2<br>Mean (SD)<br>G1 Pre-tx: 70.9 (16.2)<br>G1 Post-tx: 37.5 (30.4)<br><br>G2 Pre-tx: 77.3 (22.7)<br>G2 Post-tx: 74.6 (24.7)<br><br>Group effects, p<0.01 | NR   | NR                                | NR                              |
| Foa et al., 1999 <sup>30</sup><br>Zoellner et al.,<br>1999 <sup>31</sup> | NR   | PSS-I<br>Mean (SD)<br>G1 Pre-tx: 29.48 (9.94)<br>G1 Post-tx: 11.70 (7.32)<br>G1 3 mth FU: 11.84 (9.01)<br>G1 6 mth FU: 11.16 (7.38)<br>G1 12 mth FU: 10.69 (8.96)<br><br>G2 Pre-tx: 29.42 (8.69)<br>G2 Post-tx: 12.89 (8.96)<br>G2 3 mth FU: 15.06 (13.33)<br>G2 6 mth FU: 11.24 (11.86)<br>G2 12 mth FU: 12.64 (14.71)<br><br>G3 Pre-tx: 29.95 (6.97)<br>G3 Post-tx: 13.55 (9.35)<br>G3 3 mth FU: 11.45 (9.03)<br>G3 6 mth FU: 13.17 (10.98)<br>G3 12 mth FU: 12.56 (12.25)<br><br>G4 Pre-tx 32.93 (5.89)<br>G4 Post-tx: 26.93 (8.47)<br><br>Main Effects, p<0.01<br>G1 vs. G4, p<0.001<br>G2 vs. G4, p<0.05<br>G3 vs. G4, p<0.05<br><br>G1 vs. G2, p=0.14<br>G1 vs. G3, p=0.11 | NR                                | NR                              |

**Table D-4. Clinician administered PTSD scales (continued)**

| Author, Year                         | Clinician Administered<br>CAPS or CAPS 2  | Clinician Administered<br>PSS-I  | Clinician Administered<br>SI-PTSD | Clinician Administered<br>Other |
|--------------------------------------|---|--|-----------------------------------|---------------------------------|
| Foa et al., 2005 <sup>32</sup>       | NR  | PSS-I<br>Mean (SD)<br>G1 Pre-tx: 34.0 (5.9)<br>G1 Post-tx: 17.9 (14.5)<br><br>G2 Pre-tx: 31.1 (8.1)<br>G2 Post-tx: 16.8 (13.2)<br><br>G3 Pre-tx: 33.3 (6.2)<br>G3 Post-tx: 26.8 (9.6)<br><br>Group X Time interaction, p<0.01<br>G1 vs. G3 t-test, p<0.001 | NR                                | NR                              |
| Forbes et al.,<br>2012 <sup>33</sup> | CAPS<br>Mean (SD)<br>G1 Pre-tx: 75.53 (16.35)<br>G1 Post-tx: 48.03 (27.89)<br>G1 3 month FU: 45.30 (28.15)<br><br>G2 Pre-tx: 64.55 (19.46)<br>G2 Post-tx: 57.73 (20.01)<br>G2 3 month FU: 52.55 (18.93)<br><br>Change over time<br>Post-tx, p=0.002<br>Post vs. 3 month FU, p=0.649 | NR   | NR                                | NR                              |
| Ford et al., 2011 <sup>34</sup>      | CAPS<br>Mean (SD)<br>G1 Pre-tx: 62.3 (18.1)<br>G1 Post-tx: 38.7 (25.6)<br><br>G2 Pre-tx: 61.9 (21.3)<br>G2 Post-tx: 39.7 (21.4)<br><br>G3 Pre-tx: 68.7 (17.0)<br>G3 Post-tx: 62.5 (23.3)<br><br>Group X Time Effect, p<0.001  | NR   | NR                                | NR                              |



**Table D-4. Clinician administered PTSD scales (continued)**

| <b>Author, Year</b>                    | <b>Clinician Administered<br/>CAPS or CAPS 2</b>   | <b>Clinician Administered<br/>PSS-I</b> | <b>Clinician Administered<br/>SI-PTSD</b> | <b>Clinician Administered<br/>Other</b> |
|--|--|---|---|---|
| Friedman et al.,<br>2007 <sup>35</sup> | CAPS-2<br>Change at Endpoint (SE)<br>G1: -13.1(3.0)<br>G2: -15.4(3.1)<br>Between Group Differences, NS   | NR                                      | NR  | NR                                      |
| Gamito et al.,<br>2010 <sup>36</sup>   | CAPS<br>G1 Percentage variation: -8<br>G2 Percentage variation: -1<br>G3 Percentage variation: -6<br>Effects, NS   | NR                                      | NR  | NR                                      |
| Gersons et al.,<br>2000 <sup>37</sup>  | NR   | NR                                      | NR  | NR                                      |
| Hamner et al.,<br>2003 <sup>38</sup>   | CAPS<br>Mean (SD)<br>G1 Pre-tx: 90.3 (23.0)<br>G1 Post-tx: 81.3 (24.3)<br><br>G2 Pre-tx: 89.1 (12.2)<br>G2 Post-tx: 79.0 (21.0)<br><br>Between-treatment changes, NS | NR                                      | NR  | NR                                      |

**Table D-4. Clinician administered PTSD scales (continued)**

| <b>Author, Year</b>             | <b>Clinician Administered<br/>CAPS or CAPS 2</b>  | <b>Clinician Administered<br/>PSS-I</b> | <b>Clinician Administered<br/>SI-PTSD</b> | <b>Clinician Administered<br/>Other</b> |
|---------------------------------|---|---|---|---|
| Hien et al., 2004 <sup>39</sup> | CAPS Frequency and Intensity<br>Mean (SD)<br>G1 Pre-tx: 72.17 (19.70)<br>G1 Post-tx: 57.15 (22.33)<br>G1 6 mth FU: 59.85 (21.12)<br>G1 9 mth FU: 55.34 (20.85)<br><br>G2 Pre-tx: 70.38 (16.84)<br>G2 Post-tx: 51.21 (25.21)<br>G2 6 mth FU: 52.65 (24.08)<br>G2 9 mth FU: 47.82 (27.73)<br><br>G3 Pre-tx: 73.88 (19.16)<br>G3 Post-tx:68.00 (24.20)<br>G3 6 mth FU:64.79 (23.81)<br>G3 9 mth FU: 66.00 (23.99)<br><br>CAPS Global Severity<br>Mean (SD)<br>G1 Pre-tx: 2.73 (0.63)<br>G1 Post-tx: 2.14 (1.53)<br>G1 6 mth FU:<br>G1 9 mth FU: 1.79 (0.63)<br><br>G2 Pre-tx: 2.41 (0.70)<br>G2 Post-tx:1.75 (0.79)<br>G2 6 mth FU: 1.62 (0.65)<br>G2 9 mth FU: 1.40 (1.12)<br><br>G3 Pre-tx: 2.82 (1.16)<br>G3 Post-tx: 2.43 (1.09)<br>G3 6 mth FU: 2.35 (0.70)<br>G3 9 mth FU: 2.14 (1.07)<br><br>Significance NR for CAPS | NR                                      | NR  | NR                                      |

**Table D-4. Clinician administered PTSD scales (continued)**

| Author, Year   | Clinician Administered CAPS or CAPS 2   | Clinician Administered PSS-I | Clinician Administered SI-PTSD | Clinician Administered Other |
|--|---|------------------------------|--------------------------------|------------------------------|
| Hien et al., 2009 <sup>40</sup><br>Hien et al., 2012 <sup>41</sup> | CAPS, ITT Analysis Data<br>Mean (SD)<br>G1 Pre-tx: 61.6 (19.4)<br>G1 Post-tx: 31.7 (23.4)<br>G1 Average of FU: 24.3 (22.1)<br><br>G2 Pre-tx: 64.2 (19.4)<br>G2 Post-tx.: 32.7 (23.4)<br>G2 Average of FU: 27.1 (23.4)<br><br>Post-tx<br>G1 vs. G2, p<0.001  | NR                           | NR                             | NR                           |
| Hinton et al., 2005 <sup>42</sup>                                  | CAPS<br>Mean (SD)<br>G1 Pre-tx: 74.85 (14.67)<br>G1 2 <sup>nd</sup> Assessment: 39.25 (19.92)<br>G1 3 <sup>rd</sup> Assessment: 41.30 (13.95)<br>G1 FU Assessment: 44.56 (14.58)<br><br>G2 Pre-tx: 75.91 (11.5)<br>G2 2 <sup>nd</sup> Assessment: 73.05 (99.43)<br>G2 3 <sup>rd</sup> Assessment: 45.05 (8.72)<br>G2 FU Assessment: 43.56 (10.22)<br><br>Group Differences at 2 <sup>nd</sup> Assessment, p<0.001<br>Group Differences at 1 <sup>st</sup> , 3 <sup>rd</sup> , & 4 <sup>th</sup> assessments, NS | NR                           | NR                             | NR                           |

**Table D-4. Clinician administered PTSD scales (continued)**

| Author, Year                             | Clinician Administered<br>CAPS or CAPS 2  | Clinician Administered<br>PSS-I | Clinician Administered<br>SI-PTSD | Clinician Administered<br>Other |
|--|---|---------------------------------|-----------------------------------|---------------------------------|
| Hinton et al.,<br>2009 <sup>43</sup>     | <p>CAPS<br/>Mean (SD)<br/>G1 Pre-tx: 75.41 (13.47)<br/>G1 2<sup>nd</sup> Assessment: 46.83<br/>(17.17)<br/>G1 3<sup>rd</sup> Assessment: 44.75<br/>(14.85)</p> <p>G2 Pre-tx: 77.25 (11.47)<br/>G2 2<sup>nd</sup> Assessment: 74.25 (9.43)<br/>G2 3<sup>rd</sup> Assessment: 45.83 (8.45)</p> <p>Between group difference at 2nd<br/>assessment , <math>p &lt; 0.01</math></p> <p>Between group differences at 3<sup>rd</sup><br/>assessment, NS</p> | NR                              | NR                                | NR                              |
| Hinton et al.,<br>2011 <sup>44</sup>     | NR  | NR                              | NR                                | NR                              |
| Hogberg et al.,<br>2007 <sup>45</sup>    | NR  | NR                              | NR                                | NR                              |
| Hollifield et al.,<br>2007 <sup>46</sup> | NR  | NR                              | NR                                | NR                              |
| Johnson et al.,<br>2011 <sup>47</sup>    | <p>CAPS<br/>Mean (SD)<br/>G1 Pre-tx: 53.34 (24.29)<br/>G1 Post-tx: 24.76 (18.47)<br/>G1 3 mth FU: 21.15 (24.79)<br/>G1 6 mth FU: 18.62 (18.84)</p> <p>G2 Pre-tx: 62.69 (25.38)<br/>G2 Post-tx: 42.38 (29.33)<br/>G2 3 mth FU: 31.27 (22.01)<br/>G2 6 mth FU: 26.56 (25.83)</p> <p>Time effect, <math>p &lt; 0.0001</math><br/>Treatment effect, <math>p &gt; 0.05</math></p>  | NR                              | NR                                | NR                              |

**Table D-4. Clinician administered PTSD scales (continued)**

| Author, Year                          | Clinician Administered<br>CAPS or CAPS 2   | Clinician Administered<br>PSS-I   | Clinician Administered<br>SI-PTSD | Clinician Administered<br>Other  |
|---------------------------------------|--|---|-----------------------------------|--|
| Krakow et al.,<br>2001 <sup>48</sup>  | CAPS<br>Mean (SD)<br>G1 Pre-tx: 81.88 (16.96)<br>G1 Post-tx: 49.58 (23.96)<br>Change: 32.3 (21.40)<br><br>G1 Pre-tx: 79.62 (24.37)<br>G2 Post-tx: 68.37 (27.26)<br>Change: 11.25 (21.65)<br><br>G1 vs. G2, p<0.001 | PSS<br>Mean (SD)<br>G1 Pre-tx: 28.29 (10.37)<br>G1 Post-tx: 17.19 (10.39)<br>Change: 11.1 (11.06)<br><br>G1 Pre-tx: 28.48 (11.73)<br>G2 Post-tx: 25.26 (11.78)<br>Change: 3.22 (9.02)<br><br>G1 vs. G2, p<0.001 | NR                                | NR   |
| Kruse et al.,<br>2009 <sup>49</sup>   | NR   | NR  | NR                                | HTQ<br>Mean (SD)<br>G1 Pre-tx: 3.5 (0.4)<br>G1 Post-tx: 2.2 (0.7)<br><br>G2 Pre-tx: 3.5 (0.4)<br>G2 Post-tx: 3.6 (0.3)<br><br>Group X Time Interaction,<br>p<0.001<br><br>Within Group Change<br>G1: p<0.001<br>G2: p<0.05 |
| Krystal et al.,<br>2011 <sup>50</sup> | CAPS<br>Mean Difference (95 % CI)<br>2.73 (-0.74 to 6.20)<br>p=0.12  | NR  | NR                                | NR   |

**Table D-4. Clinician administered PTSD scales (continued)**

| Author, Year                                 | Clinician Administered<br>CAPS or CAPS 2   | Clinician Administered<br>PSS-I | Clinician Administered<br>SI-PTSD | Clinician Administered<br>Other |
|--|--|---------------------------------|-----------------------------------|---------------------------------|
| Kubany et al.,<br>2003 <sup>51</sup>         | CAPS<br>Mean (SD)<br>G1 Pre-tx: 80.9 (20.7)<br>G1 Post-tx: 10.1 (19.3)<br>G1 3 mth FU: 7.9 (9.3)<br><br>G2 Pre-tx: 79.1 (22.1)<br>G2 Post-tx: 76.1 (25.2)<br>G2 Post-therapy: 11.6 (13.6)<br>G2 3 mth FU: 12.4 (13.8)<br><br>G1 Post-tx change, p<0.05<br>G2 Post-tx change, NS<br><br>G1 3 mth change, NS<br>G2 Post-therapy, p<0.05<br>G2 3 mth change, NS | NR                              | NR                                | NR                              |
| Kubany et al.,<br>2004(Kubany,<br>2004 #806) | CAPS (ITT Sample)<br>Mean (SD)<br>G1 Pre-tx: 74.4 (19.9)<br>G1 Post-tx: 33.3 (32.8)<br><br>G2 Pre-tx: 78.0 (20.5)<br>G2 Post-tx: 74.1 (21.9)<br><br>Between group significance, NR   | NR                              | NR                                | NR                              |
| Liedl et al., 2011 <sup>53</sup>             | NR   | NR                              | NR                                | NR                              |

**Table D-4. Clinician administered PTSD scales (continued)**

| Author, Year                           | Clinician Administered<br>CAPS or CAPS 2 | Clinician Administered<br>PSS-I | Clinician Administered<br>SI-PTSD   | Clinician Administered<br>Other |
|--|--|---------------------------------|---|---------------------------------|
| Lindauer et al.,<br>2005 <sup>54</sup> | NR                                       | NR                              | <p>SI-PTSD Reexperiencing Score<br/>Mean (SD)<br/>G1 Pre-tx: 3.4 (0.9)<br/>G1 Post-tx: 1.2 (1.5)</p> <p>G2 Pre-tx: 3.9 (0.8)<br/>G2 Post-tx: 3.1 (1.8)</p> <p>G1 vs. G2, p&lt;0.05</p> <p>SI-PTSD Avoidance Score<br/>Mean (SD)<br/>G1 Pre-tx: 3.9 (1.1.)<br/>G1 Post-tx: 1.6 (2.2)</p> <p>G2 Pre-tx: 3.5 (0.7)<br/>G2 Post-tx: 3.2 (1.7)</p> <p>G1 vs. G2, NS</p> <p>SI-PTSD Hyperarousal<br/>Mean (SD)<br/>G1 Pre-tx: 3.8 (0.9)<br/>G2 Post-tx: 1.3 (1.8)</p> <p>G2 Pre-tx: 3.8 (1.0)<br/>G2 Post-tx: 2.7 (1.5)</p> <p>G1 vs. G2, p&lt;0.05</p> | NR                              |

**Table D-4. Clinician administered PTSD scales (continued)**

| Author, Year                    | Clinician Administered CAPS or CAPS 2 | Clinician Administered PSS-I  | Clinician Administered SI-PTSD | Clinician Administered Other |
|---------------------------------|---------------------------------------|---|--------------------------------|------------------------------|
| Litz et al., 2007 <sup>55</sup> | NR                                    | PSS-I<br>Mean (SD) (Completer Group)<br>G1 Pre-tx: 26.71 (9.02)<br>G1 Post-tx: 14.86 (13.35)<br>G1 3 mth FU: 13.20 (8.63)<br>G1 6 mth FU: 8.67 (7.98)<br><br>G2 Pre-tx: 29.16 (9.93)<br>G2 Post-tx: 20.00 (11.50)<br>G2 3 mth FU: 13.96 (8.63)<br>G2 6 mth FU: 17.50 (10.40)<br><br>ITT Analysis<br>Post-tx<br>Time effect, $p < 0.001$<br><br>3 mth FU<br>G1 v.s G2, NS<br><br>Completer Analysis<br>3 mth FU<br>G1 vs. G2, NS<br>6 mth FU<br>Group Effect, $p = 0.06$ | NR                             | NR                           |



**Table D-4. Clinician administered PTSD scales (continued)**

| Author, Year                         | Clinician Administered<br>CAPS or CAPS 2  | Clinician Administered<br>PSS-I | Clinician Administered<br>SI-PTSD | Clinician Administered<br>Other |
|--------------------------------------|---|---------------------------------|-----------------------------------|---------------------------------|
| Marks et al.,<br>1998 <sup>56</sup>  | Marks et al., 1998 <sup>56</sup><br>CAPS-2  | NR                              | NR                                | NR                              |
| Lovell et al.,<br>2001 <sup>57</sup> | <p>Mean Change Score at Post-tx<br/>(95% CI)<br/>G1: 30 (19 to 42)<br/>G2: 36 (26 to 45)<br/>G3: 38 (26 to 50)<br/>G4: 14 (4 to 25)</p> <p>Additional results presented in<br/>graphs<br/>CAPS<br/>Mean change in G1 + G2 + G3 vs.<br/>G4<br/>Post, p=0.005<br/>1 mth FU, p=0.01<br/>3 mth FU, p=0.005</p> <p>Lovell et al., 2001<sup>57</sup><br/>CAPS, Re-experiencing subscale<br/>Mean (SD)<br/>G1 Pre-tx: 13.3 (3.9)<br/>G1 Post-tx: 6.8 (7.5)</p> <p>G2 Pre-tx: 14.9 (5.0)<br/>G2 Post-tx: 7.8 (4.9)</p> <p>G3 Pre-tx: 15.1 (6.4)<br/>G3 Post-tx: 6.8 (7.2)</p> <p>G4 Pre-tx: 11.6 (6.1)<br/>G4 Post-tx: 9.7 (7.4)</p> <p>Post-tx<br/>G1 + G2 + G3 vs. G4, p&lt;0.02</p> <p>Followups<br/>G1 + G2 + G3 vs. G4, NS</p> |                                 |                                   |                                 |

**Table D-4. Clinician administered PTSD scales (continued)**

| Author, Year                                | Clinician Administered<br>CAPS or CAPS 2   | Clinician Administered<br>PSS-I | Clinician Administered<br>SI-PTSD | Clinician Administered<br>Other |
|---|--|---------------------------------|-----------------------------------|---------------------------------|
| Marks et al.,<br>1998 <sup>56</sup>         | CAPS, Avoidance/numbing<br>subscale  |                                 |                                   |                                 |
| Lovell et al.,<br>2001 <sup>57</sup> cont'd | Mean (SD)<br>G1 Pre-tx: 23.4 (8.3)<br>G1 Post-tx: 11.5 (13.1)<br><br>G2 Pre-tx: 30.7 (7.6)<br>G2 Post-tx: 15.2 (11.0)<br><br>G3 Pre-tx: 29.8 (9.3)<br>G3 Post-tx: 11.9 (11.9)<br><br>G4 Pre-tx: 23.0 (9.1)<br>G4 Post-tx: 17.1 (8.9)<br><br>Post-tx<br>G1 + G2 +G3 vs. G4, p<0.004<br><br>1 month FU<br>G1 + G2 +G3 vs. G4, p<0.02<br><br>3 month FU<br>G1 + G2 +G3 vs. G4, p<0.01<br><br>CAPS, Increased arousal subscale<br>Mean (SD)<br>G1 Pre-tx: 25.2 (8.5)<br>G1 Post-tx: 13.2 (11.1)<br><br>G2 Pre-tx: 29.1 (8.8)<br>G2 Post-tx: 16.5 (10.0)<br><br>G3 Pre-tx: 28.6 (7.7)<br>G3 Post-tx: 16.6 (11.7)<br><br>G4 Pre-tx: 23.7 (7.6)<br>G4 Post-tx: 17.0 (10.5)<br>Post-tx<br>G1 + G2 +G3 vs. G4, NS |                                 |                                   |                                 |

**Table D-4. Clinician administered PTSD scales (continued)**

| Author, Year   | Clinician Administered<br>CAPS or CAPS 2   | Clinician Administered<br>PSS-I | Clinician Administered<br>SI-PTSD | Clinician Administered<br>Other  |
|--|--|---------------------------------|-----------------------------------|--|
| Marks et al.,<br>1998 <sup>56</sup><br>Lovell et al.,<br>2001 <sup>57</sup> cont'd | <p>Followups<br/>G1 + G2 +G3 vs. G4, NS</p> <p>CAPS, Associated features<br/>subscale</p> <p>Mean (SD)</p> <p>G1 Pre-tx: 16.7 (9.0)<br/>G1 Post-tx: 8.1 (9.7)</p> <p>G2 Pre-tx: 22.6 (10.2)<br/>G2 Post-tx: 10.3 (8.8)</p> <p>G3 Pre-tx: 20.8 (10.8)<br/>G3 Post-tx: 11.0 (11.0)</p> <p>G4 Pre-tx: 15.2 (8.0)<br/>G4 Post-tx: 12.0 (11.0)</p> <p>Post-tx<br/>G1 + G2 +G3 vs. G4, p&lt;0.04</p> <p>Followups<br/>G1 + G2 +G3 vs. G4, NS</p> |                                 |                                   |  |
| Marshall et al.,<br>2001 <sup>58</sup>   | <p>CAPS-2</p> <p>Adjusted Mean Differences (95%<br/>CI)</p> <p>G1 vs. G3<br/>-14.3 (-19.7 to -8.8)<br/>p&lt;0.001</p> <p>G2 vs. G3<br/>-12.2 (-17.7 to -6.6)<br/>p&lt;0.001</p>  | NR                              | NR                                | <p>TOP-8</p> <p>Adjusted Mean<br/>Differences (95% CI)</p> <p>G1 vs. G3<br/>-3.4 (-5.1 to -1.8)<br/>p&lt;0.001</p> <p>G2 vs. G3<br/>-2.9 (-4.5 to -1.3)<br/>p&lt;0.001</p> |
| Martenyi et al.,<br>2002 <sup>59</sup><br>Martenyi et al.,<br>2006 <sup>60</sup>   | <p>CAPS</p> <p>Changes from Pre-tx to Post-tx<br/>Least Square Means (SD), p-<br/>value</p> <p>G1: -34.6 (28.1)<br/>G2: -26.8 (26.1)<br/>p=0.021</p>   | NR                              | NR                                | <p>TOP-8</p> <p>Changes from Pre-tx to<br/>Post-tx<br/>Least Square Means, p-<br/>value</p> <p>G1: -10.3<br/>G2: -8.0<br/>p=0.006</p>                                      |

**Table D-4. Clinician administered PTSD scales (continued)**

| Author, Year                           | Clinician Administered<br>CAPS or CAPS 2   | Clinician Administered<br>PSS-I | Clinician Administered<br>SI-PTSD | Clinician Administered<br>Other   |
|--|--|---------------------------------|-----------------------------------|---|
| Martenyi et al.,<br>2007 <sup>61</sup> | CAPS<br>Mean change from baseline (SD)<br>ITT Analysis<br>G1: -42.9 (23.1)<br>G2: -42.8 (27.9)<br>G3: -36.6 (25.7)<br>Overall p-value= 0.15  | NR                              | NR                                | TOP-8<br>Mean change from baseline<br>(SE)<br>Completer analysis<br>G1: -10.59 (0.58)<br>G2: -10.25 (0.60)<br>G3: -10.59 (0.81)<br>Overall p-value= 0.907 |
| McDonagh et al.,<br>2005 <sup>62</sup> | CAPS<br>Mean (SD)<br>G1 Pre-tx: 69.9 (16.8)<br>G1 Post-tx: 53.1 (28.8)<br><br>G2 Pre-tx: 67.7 (14.6)<br>G2 Post-tx: 47.2 (22.4)<br><br>G3 Pre-tx: 72.0 (17.6)<br>G3 Post-tx: 65.5 (18.6)<br><br>Group X Time, p<0.10 | NR                              | NR                                | NR  |
| Monnelly et al.,<br>2003 <sup>63</sup> | NR   | NR                              | NR                                | NR  |
| Monson et al.,<br>2006 <sup>64</sup>   | CAPS<br>Mean (SE)<br>G1 Pre-tx: 76.73 (2.6)<br>G1 Post-tx: 52.14 (3.9)<br>G1 1 mth FU: 58.13 (4.5)<br><br>G2 Pre-tx: 79.10 (3.5)<br>G2 Post-tx: 76.03 (3.7)<br>G1 1 mth FU: 74.37 (4.3)<br><br>Group X Time, p<0.01  | NR                              | NR                                | NR  |

**Table D-4. Clinician administered PTSD scales (continued)**

| Author, Year                          | Clinician Administered<br>CAPS or CAPS 2  | Clinician Administered<br>PSS-I  | Clinician Administered<br>SI-PTSD | Clinician Administered<br>Other |
|---------------------------------------|---|--|-----------------------------------|---------------------------------|
| Mueser et al.,<br>2008 <sup>65</sup>  | <p>CAPS</p> <p>Mean (SD)</p> <p>G1 Pre-tx: 74.46 (17.56)</p> <p>G1 Post-tx: 55.53 (27.92)</p> <p>G1 3 mth FU: 55.10 (25.96)</p> <p>G1 6 mth FU: 57.48 (25.34)</p><br><p>G2 Pre-tx: 76.15 (17.07)</p> <p>G2 Post-tx: 67.78 (26.84)</p> <p>G2 3 mth FU: 64.80 (28.25)</p> <p>G2 6 mth FU: 70.90 (24.15)</p><br><p>Group effect, p=0.005</p> | NR   | NR                                | NR                              |
| Nacasch et al.,<br>2011 <sup>66</sup> | NR  | <p>PSS-I</p> <p>Mean (SD)</p> <p>G1 Pre-tx: 37.1 (3.8)</p> <p>G1 Post-tx: 18.9 (9.1)</p> <p>G1 FU: 16.3 (10.4)</p><br><p>G2 Pre-tx: 36.8 (6.2)</p> <p>G2 Post-tx: 35.0 (8.9)</p> <p>G2 FU: 35.4 (7.6)</p><br><p>Post-tx</p> <p>Treatment X Time, p&lt;0.001</p><br><p>12 month FU</p> <p>Treatment X Time (Pre to FU),<br/>p&lt;0.001</p> <p>Treatment X Time (Post to FU),<br/>NS</p> | NR                                | NR                              |

**Table D-4. Clinician administered PTSD scales (continued)**

| Author, Year                         | Clinician Administered<br>CAPS or CAPS 2 | Clinician Administered<br>PSS-I | Clinician Administered<br>SI-PTSD | Clinician Administered<br>Other   |
|--------------------------------------|--|---------------------------------|-----------------------------------|---|
| Neuner et al.,<br>2004 <sup>67</sup> | NR                                       | NR                              | NR                                | Composite International<br>Diagnostic Interview-<br>PTSD<br>Mean (SD)<br>G1 Pre-tx: 13.4 (2.1)<br>G1 1 year FU: 8.9 (2.7)<br><br>G2 Pre-tx: 13.9 (2.3)<br>G2 1 year FU: 12.6 (3.2)<br><br>G3 Pre-tx: 14.2 (2.9)<br>G3 1 year FU: 13.4 (3.3)<br><br>1 year Group X Time<br>G1 vs. G2, p=0.01<br>G1 vs. G3, p=0.01  |
| Neuner et al.,<br>2008 <sup>68</sup> | NR                                       | NR                              | NR                                | PDS<br>Mean (SD)<br>G1 Pre-tx: 25.9 (13.2)<br>G1 Post-tx: 5.4 (6.6)<br>G1 6 mth FU: 6.1 (6.8)<br><br>G2 Pre-tx: 26.7 (12.5)<br>G2 Post-tx: 5.3 (5.7)<br>G2 6 mth FU: 5.0 (6.6)<br><br>G3 Pre-tx: 21.3 (10.6)<br>G3 Post-tx: NR<br>G3 6 mth FU: 10.1 (8.1)<br><br>G1 vs. G2 Comparisons<br>Group X Time at Post-tx,<br>p=0.87<br>Treatment Groups vs.<br>Control<br>Treatment X Time, p=0.01 |

**Table D-4. Clinician administered PTSD scales (continued)**

| Author, Year                        | Clinician Administered CAPS or CAPS 2  | Clinician Administered PSS-I | Clinician Administered SI-PTSD  | Clinician Administered Other  |
|-------------------------------------|--|------------------------------|---|---|
| Neuner et al., 2010 <sup>69</sup>   | NR   | NR                           | NR  | PDS<br>Mean(SD)<br>G1 Pre-tx: 38.9 (6.4)<br>G1 Post-tx: 26.0 (9.2)<br><br>G2 Pre-tx: 36.9 (8.0)<br>G2 Post-tx: 34.1 (6.1)<br><br>Group X Time, p=0.01 |
| Nijdam et al., 2012 <sup>70</sup>   | NR   | NR                           | SI-PTSD<br>Mean Difference at 1 <sup>st</sup> Post (95% CI)<br>10.80 (6.37 to 15.23)<br>p<0.001<br><br>Mean Difference at 2 <sup>nd</sup> Post (95% CI)<br>2.41 (-2.10 to 6.92)<br>p=0.29 | NR  |
| Panahi et al., 2011 <sup>71</sup>   | NR   | NR                           | NR  | NR  |
| Petrakis et al., 2011 <sup>72</sup> | CAPS<br>Mean( SE)<br>G1 Pre-tx: 73.54 (5.007)<br>G1 Post-tx: 40.024 (5.53)<br><br>G2 Pre-tx: 69.810 (5.166)<br>G2 Post-tx: 36.591 (5.570)<br><br>G3 Pre-tx: 62.500 (5.047)<br>G3 Post-tx: 26.751 (5.353)<br><br>G4 Pre-tx: 77.833 (4.832)<br>G4 Post-tx: 41.392 (4.949)<br><br>Time effect, p<0.00<br>Group X Time, NS | NR                           | NR  | NR  |

**Table D-4. Clinician administered PTSD scales (continued)**

| Author, Year                       | Clinician Administered CAPS or CAPS 2  | Clinician Administered PSS-I | Clinician Administered SI-PTSD | Clinician Administered Other |
|------------------------------------|--|------------------------------|--------------------------------|------------------------------|
| Raskind et al., 2003 <sup>73</sup> | CAPS<br>G1 Pre-tx: 79.1 (17.0)<br>G1 Post-tx: 57.3 (32.3)<br><br>G2 Pre-tx: 83.6 (17.6)<br>G2 Post-tx: 86.5 (30.0)<br><br>G1 vs. G2 Change, p<0.01         | NR                           | NR                             | NR                           |
| Raskind et al., 2007 <sup>74</sup> | CAPS<br>Means (SD)<br>G1 Pre-tx: 76.0 (22)<br>G1 Post-tx: 63.0 (20.0)<br><br>G2 Pre-tx: 78.0 (18.0)<br>G2 Post-tx: 71.0 (22.0)<br><br>G1 vs. G2 Change, NS | NR                           | NR                             | NR                           |
| Reich et al., 2004 <sup>75</sup>   | CAPS-2<br>Mean Changes from Baseline<br>Score (SD)<br>G1: -29.6 (31.5)<br>G2: -18.6 (12.3)<br>p=0.015  | NR                           | NR                             | NR                           |



**Table D-4. Clinician administered PTSD scales (continued)**

| Author, Year                        | Clinician Administered CAPS or CAPS 2  | Clinician Administered PSS-I  | Clinician Administered SI-PTSD | Clinician Administered Other |
|-------------------------------------|--|---|--------------------------------|------------------------------|
| Resick et al., 2002 <sup>76</sup>   | CAPS<br>Mean (SD)  | NR  | NR                             | NR                           |
| Resick et al., 2003 <sup>77</sup>   | G1 Pre-tx: 74.76 (18.77)<br>G1 Post-tx: 39.08 (31.12)  |   |                                |                              |
| Resick et al., 2012 <sup>78</sup>   | G1 3 mth FU: 42.21 (30.13)<br>G1 9 mth FU: 42.87 (31.06)<br>G1 LTFU: 26.00 (23.35)<br><br>G2 Pre-tx: 76.60 (19.72)<br>G2 Post-tx: 44.89 (33.52)<br>G2 3 mth FU: 49.16 (32.86)<br>G2 9 mth FU: 46.98 (33.68)<br>G2 LTFU: 25.90 (26.05) G3 Pre-tx: 69.85 (19.57)<br>G3 Post-tx: 69.26 (18.55)<br>G3 3 mth FU: 69.26 (18.55)<br>G3 9 mth FU: 69.26 (18.55) Posttreatment differences, p<.0001<br>3 mth FU differences, p<0.0001<br>9 mth FU differences, p<0.0001<br>LTFU differences, NS |   |                                |                              |
| Rothbaum et al., 1997 <sup>79</sup> | NR   | PSS<br>Mean (SD)<br>G1 Pre-tx: 33.3 (8.7)<br>G1 Post-tx: 14.3 (8.4)<br>G1 3 mth FU: 9.8 (8.7)<br><br>G2 Pre-tx: 39.0 (8.2)<br>G2 Post-tx: 35.0 (5.9)<br><br>Posttreatment G1 vs. G2, p<0.05 | NR                             | NR                           |
| Rothbaum et al., 2005 <sup>80</sup> | Data reported in graphs  | NR  | NR                             | NR                           |

**Table D-4. Clinician administered PTSD scales (continued)**

| Author, Year                        | Clinician Administered CAPS or CAPS 2  | Clinician Administered PSS-I | Clinician Administered SI-PTSD  | Clinician Administered Other   |
|-------------------------------------|--|------------------------------|---|--|
| Rothbaum et al., 2006 <sup>81</sup> | NR   | NR                           | SIP<br>Mean Change from Baseline (SD)<br>G1: -0.3 (7.60)<br>p=ns<br><br>G2: 5.9 (7.82)<br>p<0.001<br><br>G1 vs. G2, ns (t-test) | NR   |
| Schneier et al., 2012 <sup>82</sup> | CAPS<br>Mean (SD)<br>G1 Pre-tx: 72.6 (12.9)<br>G1 Post-tx: 21.5 (19.9)<br><br>G2 Pre-tx: 65.4 (12.8)<br>G2 Post-tx: 35.6 (31.3)<br><br>Treatment Group Effect, p=0.01<br>Time Effect, p<0.001  | NR                           | NR  | NR   |
| Schnurr et al., 2003 <sup>83</sup>  | CAPS<br>Mean (SE)<br>G1 Pre-tx: 80.41 (1.45)<br>G1 7 mth FU: 74.00 (1.32)<br>G1 12 mth FU: 72.79 (1.51)<br>Change at 7 mths, p<0.001<br>Change at 12 mths, p<0.001<br><br>G2 Pre-tx: 82.01 (1.44)<br>G2 7 mth FU: 76.03 (1.32)<br>G2 12 mth: 74.82 (1.49)<br>Change at 7 mths, p<0.001<br>Change at 12 mths, p<0.001<br><br>Treatment Effect, p=0.29<br>Cohort Effect, p=0.01<br>Treatment X Cohort Effect, p=0.04 | NR                           | NR  | PTSD Checklist<br>Mean (SD)<br>G1 Pre-tx: 61.84 (0.91)<br>G1 7 mth FU: 59.70 (0.84)<br>G1 12 mth FU: 58.78 (0.89)<br>Change at 7 mths, p<0.01<br>Change at 12 mths, p<0.01<br><br>G2 Pre-tx: 62.60 (0.94)<br>G2 7 mth FU: 61.03 (0.84)<br>G2 12 mth FU: 60.00 (0.88)<br>Change at 7 mths, p>0.05<br>Change at 12 mths, p<0.05<br><br>Treatment Effect, NS<br>Treatment X Cohort Effect, p=0.05 |

**Table D-4. Clinician administered PTSD scales (continued)**

| Author, Year                          | Clinician Administered<br>CAPS or CAPS 2   | Clinician Administered<br>PSS-I | Clinician Administered<br>SI-PTSD | Clinician Administered<br>Other |
|---------------------------------------|--|---------------------------------|-----------------------------------|---------------------------------|
| Schnurr et al.,<br>2007 <sup>84</sup> | CAPS<br>Baseline<br>Mean (95% CI)<br>G1: 77.6 (74.8 to 80.4)<br>G2: 77.9 (75.1 to 80.6)<br><br>Least Means (95% CI)<br>Immediate posttreatment<br>G1: 52.9 (47.7 to 58.0)<br>G2: 60.1 (55.3 to 64.8)<br>G1 vs. G2, $P=.01$<br><br>3 mth FU<br>G1: 49.7 (44.7 to 54.7)<br>G2: 56.0 (50.5 to 61.5)<br>G1 vs. G2, $P=.047$<br><br>6-month<br>G1: 50.4 (45.0 to 55.8)<br>G2: 54.5 (49.3 to 59.7)<br>G1 vs. G2, $p=.21$<br><br>Treatment Effect, $p=0.03$<br>Treatment X Time, $p=0.37$ | NR                              | NR                                | NR                              |

**Table D-4. Clinician administered PTSD scales (continued)**

| Author, Year                        | Clinician Administered CAPS or CAPS 2   | Clinician Administered PSS-I | Clinician Administered SI-PTSD | Clinician Administered Other  |
|-------------------------------------|---|------------------------------|--------------------------------|---|
| Schnyder et al., 2011 <sup>85</sup> | CAPS<br>Mean (SD)<br>G1 Pre-tx: 78.6 (16.0)<br>G1 Post-tx: 60.8 (32.8)<br>G1 6 mth FU: 58.1 (30.5)<br><br>G2 Pre-tx: 73.4 (19.2)<br>G2 Post-tx: 66.4 (20.0)<br><br>Group Effect, p<0.01 | NR                           | NR                             | NR  |
| Simon et al., 2008 <sup>86</sup>    | NR  | NR                           | NR                             | SPRINT<br>Mean (SD)<br>G1 Pre-tx: 16.11 (8.99)<br>G1 Improvement Post-tx: 2.33 (5.24)<br><br>G2 Pre-tx: 17.00 (7.65)<br>G2 Improvement Post-tx: 4.57 (7.24)<br><br>p=NS |
| Spence et al., 2011 <sup>87</sup>   | NR  | NR                           | NR                             | NR  |
| Stein et al., 2002 <sup>88</sup>    | CAPS<br>Mean Change from Baseline (95% CI)<br>G1: -14.8 (SD=14.16)<br>p<.05<br>G2 : -2.67 (SD=10.55)<br>p<0.05  | NR                           | NR                             | NR  |

**Table D-4. Clinician administered PTSD scales (continued)**

| Author, Year                          | Clinician Administered<br>CAPS or CAPS 2   | Clinician Administered<br>PSS-I | Clinician Administered<br>SI-PTSD | Clinician Administered<br>Other   |
|---------------------------------------|--|---------------------------------|-----------------------------------|---|
| Tarrier et al.,<br>1999 <sup>89</sup> | CAPS Global Severity<br>Mean (SD)  | NR                              | NR                                | NR  |
| Tarrier et al.,<br>1999 <sup>90</sup> | G1 Pre-tx: 71.14 (18.98)<br>G1 Post-tx: 48.24 (30.25)<br>G1 6 mth FU: 52.11 (23.78)<br><br>G2 Pre-tx: 77.76 (14.95)<br>G2 Post-tx: 50.82 (23.99)<br>G2 6 mth FU: 50.21 (24.37)<br><br>G1 vs. G2 differences, NS<br><br>12-Month Follow-up<br>G1 Pre-tx: 71.76 (19.59)<br>G1 12 mth FU: 45.16 (28.26)<br><br>G2 Pre-tx: 76.93 (15.40)<br>G2 12 mth FU: 52.48 (24.09)<br><br>G1 vs. G2 differences, NS |                                 |                                   |   |
| Taylor et al.,<br>2003 <sup>91</sup>  | CAPS<br>Data only reported in graphs<br>Completers<br>G1 Pre-Post changes, p<0.005<br>G2 Pre-Post changes, p<.001<br>G3 Pre-Post changes, p<0.005<br><br>Intent to Treat<br>No significant differences   | NR                              | NR                                | NR  |
| Tucker et al.,<br>2001 <sup>92</sup>  | CAPS-2<br>Adjusted Mean Differences (95%<br>CI), G1 vs. G2<br>-10.6 (-16.2 to -5.0)  | NR                              | NR                                | TOP-8<br>Adjusted Mean<br>Differences (95% CI), G1<br>vs. G2<br>-3.8 (-5.6 to -1.9) |

**Table D-4. Clinician administered PTSD scales (continued)**

| Author, Year                            | Clinician Administered CAPS or CAPS 2  | Clinician Administered PSS-I | Clinician Administered SI-PTSD | Clinician Administered Other   |
|---|--|------------------------------|--------------------------------|--|
| Tucker et al., 2003 <sup>93</sup>       | Tucker et al., 2004<br>CAPS  | NR                           | NR                             | NR   |
| Tucker et al., 2004 <sup>94</sup>       | Mean (SD)<br>G1 Pre-tx: 91.0 (10.58)<br>G1 Post-tx: 60.28 (26.15)<br><br>G2 Pre-tx: 83.91 (17.28)<br>G2 Post-tx: 42.09 (29.09)<br><br>G3 Pre-tx: 94.20 (11.9)<br>G3 Post-tx: 55.5 (29.07)<br><br>Between group differences, NS |                              |                                |  |
| Tucker et al., 2007 <sup>95</sup>       | CAPS<br>Mean Percentage Change (SD)<br>G1: -59.5 (35.9)<br>G2: -45.5 (34.3)<br>p=0.227   | NR                           | NR                             | TOP-8<br>Mean Percentage Change (SD)<br>G1: -67.9 (30.0)<br>G2: -41.6 (37.8)<br>p= 0.023 |
| van der Kolk et al., 1994 <sup>96</sup> | CAPS<br>Difference in Improvement G1 vs. G2= 12.59<br><br>ANCOVA Results<br>F = -12.59, t = -2.67, p=0.0106  | NR                           | NR                             | NR   |

**Table D-4. Clinician administered PTSD scales (continued)**

| Author, Year                            | Clinician Administered<br>CAPS or CAPS 2   | Clinician Administered<br>PSS-I | Clinician Administered<br>SI-PTSD | Clinician Administered<br>Other |
|---|--|---------------------------------|-----------------------------------|---------------------------------|
| van der Kolk et al., 2007 <sup>97</sup> | <p>CAPS</p> <p>Mean (SD) ( Post-tx &amp; FU - ITT)</p> <p>G1 Pre-tx (1 mth CAPS): 71.7 (11.9)</p> <p>G1 Pre-tx (1 wk CAPS): 69.4 (12.7)</p> <p>G1 Post-tx: 32.55 (22.5)</p> <p>G1 FU: 25.79 (21.61)</p><br><p>G2 Pre-tx (1 mth CAPS): 75.9 (15.6)</p> <p>G2 Pre-tx (1 wk CAPS): 73.7 (13.4)</p> <p>G2 Post-tx: 42.67 (22.11)</p> <p>G2 FU: 42.12 (15.83)</p><br><p>G3 Pre-tx (1 mth CAPS): 74.5 (12.5)</p> <p>G3 Pre-tx (1 wk CAPS): 70.3 (13.0)</p> <p>G3 Post-tx: 43.55 (22.6)</p> <p>G3 FU: NA</p><br><p>Posttreatment</p> <p>Treatment effect, NS</p> <p>G1 vs. G3, NS</p> <p>G2 vs G3, NS</p> <p>G1 vs. G2, NS</p><br><p>Followup</p> <p>G1 vs. G2, p=0.005</p> |                                 |                                   |                                 |
| van Emmerik et al., 2008 <sup>98</sup>  | NR   | NR                              | NR                                | NR                              |
| Yeh et al., 2011 <sup>99</sup>          | <p>CAPS</p> <p>Mean( SD)</p> <p>G1 Pre-tx: 78.76 (12.64)</p> <p>G1 Post-tx: 30.41 (30.90)</p><br><p>G2 Pre-tx: 66.14 (22.63)</p> <p>G2 Post-tx: 35.78 (33.76)</p><br><p>Between Group Change, p=0.49</p>   | NR                              | NR                                | NR                              |

**Table D-4. Clinician administered PTSD scales (continued)**

| Author, Year                         | Clinician Administered CAPS or CAPS 2  | Clinician Administered PSS-I | Clinician Administered SI-PTSD | Clinician Administered Other |
|--------------------------------------|--|------------------------------|--------------------------------|------------------------------|
| Zlotnick et al., 2009 <sup>100</sup> | CAPS<br>Mean difference (95% CI)<br>-2.30 (-13.81, 9.21)   | NR                           | NR                             | NR                           |
| Zohar et al., 2002 <sup>101</sup>    | CAPS-2<br>Mean Change from Baseline (SD)<br>G1: -18.7 (6.7)<br>G2: -13.5 (6.6)<br>Between Group Change,<br>p=0.530 | NR                           | NR                             | NR                           |

Abbreviations: ANOVA = analysis of variance; ANCOVA = analysis of covariance; CAPS = Clinician-administered PTSD Scale; CI = confidence interval; FU = follow-up; NR= not reported; NS = not significant; PSS= PTSD Symptom Scale; PSS-I= PTSD Symptom Scale Interview; Pre-tx = pretreatment; Post-tx = Posttreatment; PTSD= Post-Traumatic Stress Disorder; SD = standard deviation; SE = standard error; SI-PTSD or SIP= Structured Interview for PTSD; SPRINT= Short PTSD Rating Interview; TOP-8 = Treatment Outcome PTSD Scale; SD = standard deviation; SE = standard error.



**Table D-5. Self-administered PTSD scales, remission, and loss of diagnosis**

| Author, Year                         | Self-Administered IES or IES-R   | Self-Administered PCL  | Self-Administered Other (e.g., MPSS, PSS-SR)   | Remission (No Longer Having Symptoms) | Loss of PTSD Diagnosis   |
|--------------------------------------|--|--|--|---------------------------------------|--|
| Akuchekian et al., 2004 <sup>1</sup> | NR   | NR   | NR   | NR                                    | NR   |
| Asukai et al., 2010 <sup>2</sup>     | IES-R<br>Adjusted Means (SE)<br>G1 Pre-tx: 59.67 (5.06)<br>G1 Post-tx: 21.15 (5.53)<br><br>G2 Pre-tx: 59.75 (5.06)<br>G2 Post-tx: 53.75 (5.20)<br><br>At post: G1 vs. G2 =<br>p<0.001(based on t-test)   | NR   | NR   | NR                                    | NR   |
| Bartzokis et al., 2005 <sup>3</sup>  | NR   | NR   | NR   | NR                                    | NR   |
| Basoglu et al., 2007 <sup>4</sup>    | NR   | NR   | NR   | NR                                    | NR   |
| Becker et al., 2007 <sup>5</sup>     | NR   | NR   | DTS<br>Within Group Mean<br>Change<br>(SD)(Baseline-<br>Endpoint)<br>G1: 13.22 (21.62)<br>G2: 10.6 (29.20)<br><br>Group effect, p<0.05 | NR                                    | NR   |
| Blanchard et al., 2003 <sup>6</sup>  | IES<br>Mean (SD)<br>G1 Baseline: 40.4 (13.8)<br>G1 Post-tx: 12.1 (14.9)<br>G1 FU: 12.2 (13.6)<br><br>G2 Baseline: 38.7 (20.9)<br>G2 Post-tx: 27.4 (19.1)<br>G2 FU: 24.0 (20.1)<br><br>G3 Baseline:40.2 (15.9)<br>G3 Post-tx: 36.6 (17.2)<br><br>Post-tx<br>G1 vs. G2 & G3, p<0.01<br>G2 vs. G3, NS | PCL<br>Mean (SD)<br>G1 Baseline: 54.4 (12.2)<br>G1 Post-tx: 31.3 (14.1)<br>G1 FU: 31.1 (14.2)<br><br>G2 Baseline: 55.0 (14.7)<br>G2 Post-tx: 43.8 (14.6)<br>G2 FU: 40.8 (14.4)<br><br>G3 Baseline: 55.9 (13.3)<br>G3 Post-tx: 53.9 (14.1)<br><br>Post-tx<br>G1 vs. G2 & G3, p<0.01<br>G2 vs. G3, significantly<br>greater change | NR   | NR                                    | Improved from PTSD<br>to sub-syndromal<br>PTSD or non-PTSD<br>G1: 76.2%<br>G2: 47.6<br>G3: 23.8%<br><br>3 month FU<br>G1: 81%<br>G2: 42.9% |

**Table D-5. Self-administered PTSD scales, remission, and loss of diagnosis (continued)**

| Author, Year                    | Self-Administered IES or IES-R  | Self-Administered PCL | Self-Administered Other (e.g., MPSS, PSS-SR)  | Remission (No Longer Having Symptoms) | Loss of PTSD Diagnosis |
|---------------------------------|---|-----------------------|---|---------------------------------------|------------------------|
| Boden et al., 2012 <sup>7</sup> | <p>IES-R</p> <p>Mean (SD)</p> <p>G1 Pre-tx: 46.8 (19.5)</p> <p>G1 Post-tx: 40.8 (20.9)</p> <p>G1 6 mth FU: 38.9 (16.7)</p><br><p>G2 Pre-tx: 47.4 (16.3)</p> <p>G2 Post-tx: 42.4 (21.3)</p> <p>G2 6 mth FU: 36.5 (16.9)</p><br><p>Between Group Differences, NS</p><br><p>G1 Within Group Differences</p> <p>Pre-tx vs. 6mth FU, <math>p &lt; 0.05</math></p><br><p>G2 Within Group Differences</p> <p>Pre-tx vs. 6mth, <math>p &lt; 0.05</math></p><br><p>G2 Within Group Differences</p> <p>Post-tx vs. 6 mth FU, <math>p &lt; 0.05</math></p> | NR                    | NR  | NR                                    | NR                     |
| Brady et al., 2000 <sup>8</sup> | <p>IES</p> <p>Mean Change (SEM)</p> <p>G1: -16.2 (1.6)</p> <p>G2: -12.1 (1.6)</p> <p>Difference Between Mean Change (95% CI): 4.1 (-0.4 to 8.7), <math>p = 0.07</math></p>  | NR                    | <p>DTS</p> <p>Mean Change (SEM)</p> <p>G1: -28.1 (2.8)</p> <p>G2: -16.1 (2.8)</p> <p>G1 vs. G2 <math>p = 0.003</math></p> | NR                                    | NR                     |
| Brady et al., 2005 <sup>9</sup> | <p>IES</p> <p>Authors reported 'no significant difference between groups' (data NR)</p>   | NR                    | NR  | NR                                    | NR                     |

**Table D-5. Self-administered PTSD scales, remission, and loss of diagnosis (continued)**

| Author, Year                      | Self-Administered IES or IES-R  | Self-Administered PCL | Self-Administered Other (e.g., MPSS, PSS-SR) | Remission (No Longer Having Symptoms) | Loss of PTSD Diagnosis  |
|-----------------------------------|---|-----------------------|--|---------------------------------------|---|
| Bryant et al., 2003 <sup>10</sup> | <p>IES-Intrusions<br/>Mean (SD)<br/>G1 Pre-tx: 23.85 (7.07)<br/>G1 Post-tx: 17.65 (7.34)<br/>G1 6 mth FU: 17.60 (9.88)</p> <p>G2 Pre-tx: 26.60 (7.02)<br/>G2 Post-tx: 15.10 (12.86)<br/>G2 6 mth FU: 15.95 (12.18)</p> <p>G3 Pre-tx: 28.44 (6.60)<br/>G3 Post-tx: 15.10 (12.86)<br/>G3 6 mth FU: 25.44 (7.79)</p> <p>Post-tx, <math>p &lt; 0.01</math> (main effects)<br/>FU, <math>p &lt; 0.05</math> (main effects)</p> <p>IES-Avoidance<br/>Mean (SD)<br/>G1 Pre-tx: 26.40 (6.65)<br/>G1 Post-tx: 19.45 (13.48)<br/>G1 6 mth FU: 20.75 (12.66)</p> <p>G2 Pre-tx: 26.40 (6.65)<br/>G2 Post-tx: 16.15 (13.49)<br/>G2 6 mth FU: 14.95 (12.32)</p> <p>G3 Pre-tx: 26.17 (8.95)<br/>G3 Post-tx: 25.50 (9.54)<br/>G3 6 mth FU: 24.78 (9.55)</p> <p>Post-tx, <math>p &lt; 0.01</math> (main effect)<br/>FU, <math>p &lt; 0.05</math> (main effect)</p> | NR                    | NR   | NR                                    | <p>No longer met criteria for PTSD at Posttreatment<br/>G1: 50.0%<br/>G2: 65.0%<br/>G3: 33.0%<br/><math>p(G2/G3) &lt; 0.05</math></p> <p>No longer met criteria for PTSD at 6 month follow-up<br/>G1: 50.0%<br/>G2: 60.0%<br/>G3: 22.0%<br/><math>p(G1/G3) &lt; 0.07</math><br/><math>p(G2/G3) &lt; 0.05</math></p> |

**Table D-5. Self-administered PTSD scales, remission, and loss of diagnosis (continued)**

| Author, Year                      | Self-Administered IES or IES-R   | Self-Administered PCL | Self-Administered Other (e.g., MPSS, PSS-SR) | Remission (No Longer Having Symptoms) | Loss of PTSD Diagnosis  |
|-----------------------------------|--|-----------------------|--|---------------------------------------|---|
| Bryant et al., 2008 <sup>11</sup> | <p>IES-Intrusions<br/>Mean (SD)<br/>G1 Pre-tx: 24.48 (7.56)<br/>G1 Post-tx: 19.94 (8.62)<br/>G1 6 mth FU: 20.87 (10.40)</p> <p>G2 Pre-tx: 24.21 (10.55)<br/>G2 Post-tx: 17.25 (11.83)<br/>G2 6 mth FU: 19.21 (12.58)</p> <p>G3 Pre-tx: 27.58 (8.72)<br/>G3 Post-tx: 20.81 (13.17)<br/>G3 6 mth FU: 23.05 (12.14)</p> <p>G4 Pre-tx: 24.89 (8.01)<br/>G4 Post-tx: 14.07 (10.58)<br/>G4 6 mth FU: 13.35 (11.01)</p> <p>Post-tx, NS (main effect)<br/>6 month FU, p&lt;0.05 (main effect)</p> <p>IES-Avoidance<br/>Mean (SD)<br/>G1 Pre-tx: 29.10 (6.03)<br/>G1 Post-tx: 20.58 (11.52)<br/>G1 6 mth FU: 21.13 (10.56)</p> <p>G2 Pre-tx: 22.68 (10.52)<br/>G2 Post-tx: 17.54 (12.29)<br/>G2 6 mth FU: 17.57 (10.85)</p> <p>G3 Pre-tx: 27.61 (8.50)<br/>G3 Post-tx: 21.81 (14.31)<br/>G3 6 mth FU: 25.16 (15.14)</p> | NR                    | NR   | NR                                    | <p>No PTSD at Posttreatment (Based on CAPS)<br/>G1: 37.0%<br/>G2: 35.0%<br/>G3: 41.0%<br/>G4: 65.0%<br/>p&lt;0.10</p> <p>No PTSD at 6 month follow-up (Based on CAPS)<br/>G1: 25.0%<br/>G2: 31.0%<br/>G3: 37.0%<br/>G4: 69.0%<br/>p&lt;0.01</p> |

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G4 Pre-tx: 23.71 (8.63)  
G4 Post-tx:13.14 (11.00)  
G4 6 mth FU: 13.18  
(12.58)

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**Table D-5. Self-administered PTSD scales, remission, and loss of diagnosis (continued)**

| Author, Year                                     | Self-Administered IES or IES-R  | Self-Administered PCL | Self-Administered Other (e.g., MPSS, PSS-SR)   | Remission (No Longer Having Symptoms) | Loss of PTSD Diagnosis  |
|--|---|-----------------------|--|---------------------------------------|---|
| Bryant et al., 2008 <sup>11</sup><br>(continued) | Post-tx, NS (main effect)<br>6 month FU, p<0.05 (main effect)   |                       |  |                                       |   |
| Butterfield et al., 2001 <sup>12</sup>           | NR  | NR                    | DTS<br>Mean (SD)<br>G1 Pre-tx: 91.6 (25.4)<br>G1 Post-tx: 57.4 (35.6)<br><br>G2 Pre-tx: 95.8 (16.7)<br>G2 Post-tx: 56.0 (36.6)<br><br>G1 vs. G2, no group X<br>time differences found  | NR                                    | NR  |
| Carlson et al., 1998 <sup>13</sup>               | IES Total<br>Mean (SD)<br>G1 Pre-tx: 52.5 (9.0)<br>G1 Post-tx: 35.2 (22.0)<br>G1 3 mth: 29.1 (22.0)<br>G1 9 mth: 34.8 (28.0)<br><br>G2 Pre-tx: 52.9 (9.3)<br>G2 Post-tx: 44.5 (17.4)<br>G2 3 mth: 45.7 (15.0)<br>G2 9 mth: 47.0 (23.0)<br><br>G3 Pre-tx: 52.8 (11.5)<br>G3 Post-tx: 38.7 (16.2)<br><br>Post-tx & 3 mth FU,<br>Group X Time, p=NS<br><br>9 month FU, p<0.24 (t-<br>test) | NR                    | MISS<br>Mean (SD)<br>G1 Pre-tx: 117.5 (14.3)<br>G1 Post-tx: 92.8 (20.8)<br>G1 3 mth: 92.4 (17.2)<br>G1 9 mth: 97.8 (29.8)<br><br>G2 Pre-tx: 119.4 (18.3)<br>G2 Post-tx: 114.2 (17.5)<br>G2 3 mth: 110.6 (18.6)<br>G1 9 mth: 127.0 (12.4)<br><br>G3 Pre-tx: 117.9 (17.6)<br>G3 Post-tx: 112.9 (21.7)<br><br>Group X Treatment,<br>p<0.006<br>G1 vs. G3, p<0.05<br>(post-tx)<br>G1 vs. G2, p<0.05<br>(post-tx & follow-up)<br><br>3 month FU,<br>p<0.05 (t-test) | NR                                    | PTSD diagnosis by<br>CAPS at 3 months<br>follow-up:<br>G1: 77.8% (7 of 9)<br>G2: 22.2% (2 of 9) |

9 month FU, p<0.05 (t-test)

**Table D-5. Self-administered PTSD scales, remission, and loss of diagnosis (continued)**

| Author, Year                       | Self-Administered IES or IES-R | Self-Administered PCL | Self-Administered Other (e.g., MPSS, PSS-SR)  | Remission (No Longer Having Symptoms)   | Loss of PTSD Diagnosis  |
|------------------------------------|--------------------------------|-----------------------|---|---|---|
| Chard et al., 2005 <sup>14</sup>   | NR                             | NR                    | MPSS<br>Mean (SD)<br>G1 Pre-tx: 57.57 (22.85)<br>G1 Post-tx: 7.54 (9.51)<br><br>G2 Pre-tx: 57.52 (24.74)<br>G2 Post-tx: 57.70 (27.47)<br>p<0.001 (interaction)  | NR  | No longer met PTSD criteria based on CAPS-SX at Posttreatment<br>G1: 93%<br>G2: 26%<br>p<0.001  |
| Cloitre et al., 2002 <sup>15</sup> | NR                             | NR                    | MPSS-SR<br>Mean (SD)<br>G1 Pre-tx: 69 (16.6)<br>G1 Post-tx: 29 (27.6)<br><br>G2 Pre-tx: 73 (18.6)<br>G2 Post-tx: 58 (28.6)<br>p<0.01 (interaction)  | NR  | NR  |
| Cloitre et al., 2010 <sup>16</sup> | NR                             | NR                    | PSS-SR<br>Mean (SD)<br>G1 Pre-tx e: 36.7 (12.87)<br>G1 Post-tx: 14.0 (11.46)<br>G1 3 mth FU: 12.5 (11.41)<br>G1 6 mth FU: 8.9 (9.83)<br><br>G2 Pre-tx: 39.9 (12.65)<br>G2 Post-tx: 14.5 (12.79)<br>G2 3 mth FU: 17.3 (10.10)<br>G2 6 mth FU: 13.7 (13.64)<br><br>G3 Pre-tx: 38.2 (11.14)<br>G3 Post-tx: 19.0 (9.83) | PTSD-negative @ posttreatment<br>G1: 61%<br>G2: 47%<br>G3: 33%<br>p=0.11<br><br>Persistence of PTSD-negative status (maintained their status through the 3-month and 6-months assessments)<br>G1: 55%<br>G2: 37%<br>G3: 21%<br>p=0.03 | CAPS score <20 at posttreatment<br>G1: 27%<br>G2: 24%<br>G3: 6%<br>p=0.04<br><br>Remission Rate: (Pairwise analyses)<br>G1 vs. G3: p=0.04<br>OR (95% CI): 5.67 (1.11–28.81).<br><br>The rate of sustained PTSD full remission differed among the three groups |

G3 3 mth FU:21.4  
(11.54)  
G3 6 mth FU: 20.5  
(13.56)

G1 vs G3: p=0.01  
OR (95% CI):4.23  
(1.42–12.59)

G1: 24%,  
G2: 13%  
G3: 0%  
p=0.002

p=0.03(interaction)  
G1 pre vs. G1 post:  
p<0.001  
G1 pre vs. G1 3 mon:  
p<0.001  
G1 post to G1 6 mon:  
p<0.001

**Table D-5. Self-administered PTSD scales, remission, and loss of diagnosis (continued)**

| Author, Year  | Self-Administered IES or IES-R | Self-Administered PCL   | Self-Administered Other (e.g., MPSS, PSS-SR)  | Remission (No Longer Having Symptoms) | Loss of PTSD Diagnosis |
|---|--------------------------------|---|---|---------------------------------------|------------------------|
| Connor et al., 1999 <sup>17</sup><br>Meltzer-Brody et al., 2000 <sup>18</sup> | NR                             | NR  | DTS<br>Week 12 difference<br>(Baseline -<br>Endpoint)(95% CI)<br>G1 vs. G2 Difference:<br>27.4 (11.2 to 43.5),<br>p<0.005<br><br>According to Meltzer-<br>Brody paper, effect<br>was significant<br>(p<0.02) for all 4<br>cluster scores<br>(intrusion, avoidance,<br>numbing,<br>hyperarousal) | NR                                    | NR                     |
| Cook et al., 2010 <sup>19</sup>   | NR                             | PTSD Military Checklist<br>Mean (SD)<br>G1 Pre-tx: 62.73 (10.18)<br>G1 1 mth:58.83 (13.56)<br>G1 3 mth FU: 60.13<br>(12.16)<br>G1 6 mth FU: 59.05<br>(11.78)<br><br>G2 Baseline:65.06<br>(9.48) | NR  | NR                                    | NR                     |



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G2 1 mth:60.96 (11.43)  
G2 3 mth FU:61.13  
(12.00)  
G2 6 mth FU: 59.64  
(12.30)  
Interactions, NS

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**Table D-5. Self-administered PTSD scales, remission, and loss of diagnosis (continued)**

| Author, Year                        | Self-Administered IES or IES-R   | Self-Administered PCL   | Self-Administered Other (e.g., MPSS, PSS-SR)  | Remission (No Longer Having Symptoms) | Loss of PTSD Diagnosis  |
|-------------------------------------|--|---|---|---------------------------------------|---|
| Cottraux, 2008 <sup>20</sup>        | NR   | <p>PCLS &lt;44 (criteria for loss of PTSD diagnosis)<br/>(Post-tx):<br/>G1: 33%<br/>G2: 14%<br/>Fisher's exact, p=0.12</p> <p>PCLS &lt;35 (Post-tx)<br/>G1: 20%<br/>G2: 7%<br/>Fisher's exact, p=0.25</p> <p>PCLS, mean change (SD):<br/>Mean change in G1: -13.5 (13.2)<br/>Mean change in G2: -6.3 (12.9)<br/>Group Effect, p=0.044<br/>Interaction, NS</p> | NR  | NR                                    | Proportion without PTSD at posttest: G1+G2 > G3, chi-sq = 10.58, df = 2, p=0.01 |
| Davidson et al., 2001 <sup>21</sup> | <p>IES<br/>Change from Baseline to Endpoint (SD)<br/>G1: -19.2 (1.5)<br/>G2: -14.1 (1.5)<br/>p=0.02 (t-test)</p> | NR  | <p>DTS<br/>Change from Baseline to Endpoint (SD)<br/>G1: -32.3 (2.8)<br/>G2: -20.0 (2.7)<br/>p=0.002 (t-test)</p>   | NR                                    | NR  |
| Davidson et al., 2003 <sup>22</sup> | NR   | NR  | <p>DTS<br/>Mean (SD)<br/>G1 Pre-tx: 74.8 (36.5)<br/>G1 Post-tx: 54.1 (40.0)<br/>Change: 20.7</p> <p>G2 Pre-tx: 93.8 (29.4)<br/>G2 Post-tx: 82.6 (27.7)<br/>Change: 11.2</p> <p>Treatment effect, p=0.20</p> | NR                                    | NR  |

**Table D-5. Self-administered PTSD scales, remission, and loss of diagnosis (continued)**

| Author, Year                        | Self-Administered IES or IES-R | Self-Administered PCL | Self-Administered Other (e.g., MPSS, PSS-SR)  | Remission (No Longer Having Symptoms)   | Loss of PTSD Diagnosis |
|-------------------------------------|--------------------------------|-----------------------|---|---|------------------------|
| Davidson et al., 2006 <sup>23</sup> | NR                             | NR                    | DTS<br>Mean Within-group difference (95% CI):<br>G1: -42.86 (-47.56 to -38.17)<br>G2: -38.92 (-43.69 to -34.16)<br>G3: -34.59 (-39.27 to -29.91)<br><br>Between group p-values based on pairwise comparisons from the analysis of covariance model using baseline adjusted values<br>G1 v G3: 0.015<br>G2 v G3: 0.203<br>G1 v G2: 0.248 | CAPS-SX17 total ≤ 20<br>Scores reported in figure<br><br>G1 vs. G3: p<0.05 at week 4 & 12<br>G1 vs. G2: p<0.01 at week 4, <0.05 at week 6<br>G1 vs. G3: p<0.001 at week 6   | NR                     |
| Davidson et al., 2006 <sup>24</sup> | NR                             | NR                    | NR  | Remission Rates at 12 weeks (score ≤ 20 on CAPS-SX)<br>G1: 42.9% (n=69/161)<br>G2: 28.0% (n=47/168)<br>p=0.005<br><br>Remission Rates at 24 weeks (score ≤ 20 on CAPS-SX)<br>G1: 50.9% (n=82/161)<br>G2: 37.5% (n=63/168)<br>p=0.01 | NR                     |
| Davidson et al., 2007 <sup>25</sup> | NR                             | NR                    | NR  | G1: 16%<br>G2: 14%<br>p=0.88  | NR                     |

|                                  |    |    |  |    |    |
|----------------------------------|----|----|--|----|----|
| Davis et al., 2008 <sup>26</sup> | NR | NR | DTS<br>Data Not Presented<br>G1 vs. G2, NS | NR | NR |
|----------------------------------|----|----|--|----|----|

**Table D-5. Self-administered PTSD scales, remission, and loss of diagnosis (continued)**

| Author, Year                      | Self-Administered IES or IES-R | Self-Administered PCL | Self-Administered Other (e.g., MPSS, PSS-SR)  | Remission (No Longer Having Symptoms) | Loss of PTSD Diagnosis |
|-----------------------------------|--------------------------------|-----------------------|---|---------------------------------------|------------------------|
| Ehlers et al., 2003 <sup>27</sup> | NR                             | NR                    | <p>PDS Frequency<br/>Mean (SD)<br/>G1 Pre-tx: 30.2 (7.9)<br/>G1 3 mth FU: 8.3 (9.8)<br/>G1 9 mth FU: 8.7 (8.1)</p> <p>G2 Pre-tx: 30.9 (7.5)<br/>G2 3 mth FU: 19.9 (7.8)<br/>G2 9 mth FU: 20.0 (7.8)</p> <p>G3 Pre-tx: 31.1 (7.5)<br/>G3 3 mth FU: 22.6 (11.6)<br/>G3 9 mth FU: 19.4 (12.5)</p> <p>3 mth FU<br/>Overall: p&lt;0.001<br/>G1 vs. G2, p&lt;0.001<br/>G1 vs. G3, p&lt;0.001</p> <p>9 mth FU<br/>Overall: p &lt;0.001<br/>G1 vs. G2, p&lt;0.001<br/>G1 vs. G3, p&lt;0.001</p> <p>PDS Distress<br/>Mean (SD)<br/>G1 Pre-tx: 31.6 (9.1)<br/>G1 3mth FU: 7.1 (10.3)<br/>G1 9 mth FU : 7.3 (8.6)</p> <p>G2 Pre-tx: 32.0 (7.2)<br/>G2 3 mth FU: 20.3 (8.2)<br/>G2 9 mth FU: 19.0 (8.8)</p> | NR                                    | NR                     |

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G3 Pre-tx: 31.4 (8.4)  
G3 3 mth FU: 22.3 (12.2)  
G3 9 mth FU: 20.0 (14.1)

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**Table D-5. Self-administered PTSD scales, remission, and loss of diagnosis (continued)**

| Author, Year                                     | Self-Administered IES or IES-R   | Self-Administered PCL | Self-Administered Other (e.g., MPSS, PSS-SR)   | Remission (No Longer Having Symptoms) | Loss of PTSD Diagnosis |
|--|--|-----------------------|--|---------------------------------------|------------------------|
| Ehlers et al., 2003 <sup>27</sup><br>(continued) |  |                       | 3mth FU<br>Overall: p<0.001<br>G1 vs. G2: p<0.001<br>G1 vs. G3: p<0.001<br><br>9 mth FU<br>Overall: p <0.001<br>G1 vs. G2, <0.001<br>G1 vs. G3, <0.001   |                                       |                        |
| Ehlers et al., 2005 <sup>28</sup>                | NR   | NR                    | PDS<br>Mean (SD)<br>G1 Pre-tx: 32.4 (6.5)<br>G1 Post-tx: 10.3 (8.9)<br>G1 6 mth FU: 12.4 (9.9)<br><br>G2 Pre-tx: 31.2 (6.3)<br>G2 Post-tx: 29.8 (8.4)<br><br>G1 vs. G2, p<0.0005<br>Changes in G1, p<0.0005<br>Changes in G1, NS | NR                                    | NR                     |
| Fecteau et al., 1999 <sup>29</sup>               | IES-I<br>Mean (SD)<br>G1 Pre-tx: 20.4 (8.7)<br>G1 Post-tx: 8.3 (8.9)<br><br>G2 Pre-tx: 24.8 (8.0)<br>G2 Post-tx: 24.4 (8.4)<br><br>Group Effects, p<0.01 | NR                    | NR   | NR                                    | NR                     |

**Table D-5. Self-administered PTSD scales, remission, and loss of diagnosis (continued)**

| Author, Year                                      | Self-Administered IES or IES-R  | Self-Administered PCL  | Self-Administered Other (e.g., MPSS, PSS-SR) | Remission (No Longer Having Symptoms) | Loss of PTSD Diagnosis |
|---|---|--|--|---------------------------------------|------------------------|
| Fecteau et al., 1999 <sup>29</sup><br>(continued) | <p>IES-A<br/>Mean (SD)<br/>G1 Pre-tx: 24.7 (8.2)<br/>G1 Post-tx: 7.2 (11.4)</p> <p>G2 Pre-tx: 26.5 (10.5)<br/>G2 Post-tx: 24.4 (6.3)</p> <p>Group Effects, <math>p &lt; 0.001</math></p> <p>Follow up for G1 Only<br/>IES<br/>Mean (SD)<br/>G1 Pre-tx: 46.1 (14.7)<br/>G1 Post-tx: 15.5 (19.6)<br/>G1 3 mth FU: 13.0 (14.9)<br/>G1 6 mth FU: 8.3 (7.0)<br/>3 mth change, <math>p &lt; 0.001</math> (n = 10)<br/>6 mth change, <math>p &lt; 0.001</math> (n = 8)</p> |  |  |                                       |                        |
| Foa et al., 1999 <sup>30</sup>                    | NR  | NR   | NR   | NR                                    | NR                     |
| Zoellner et al., 1999 <sup>31</sup>               |   |  |  |                                       |                        |
| Foa et al., 2005 <sup>32</sup>                    | NR  | NR   | NR   | NR                                    | NR                     |
| Forbes et al., 2012 <sup>33</sup>                 | NR  | <p>PCL<br/>Mean (SD)<br/>G1 Pre-tx: 61.63 (11.50)<br/>G1 Post-tx: 45.67 (16.66)<br/>G1 FU: 41.13 (17.51)</p> <p>G2 Pre-tx: 57.45 (12.55)<br/>G2 Post-tx: 53.84 (11.11)<br/>G2 FU: 49.11 (11.00)</p> <p>Change over time<br/>Post-tx, <math>p = 0.007</math><br/>FU, <math>p = 0.943</math></p> | NR   | NR                                    | NR                     |

**Table D-5. Self-administered PTSD scales, remission, and loss of diagnosis (continued)**

| Author, Year                        | Self-Administered IES or IES-R  | Self-Administered PCL | Self-Administered Other (e.g., MPSS, PSS-SR)   | Remission (No Longer Having Symptoms)  | Loss of PTSD Diagnosis  |
|-------------------------------------|---|-----------------------|--|--|---|
| Ford et al., 2011 <sup>34</sup>     | NR  | NR                    | NR   | <p>Met Criteria for full remission at Posttreatment</p> <p>G1: 21%<br/>G2: 15%<br/>G3: 0</p> <p>G1 vs. G2, p=0.45<br/>G1 vs. G3, p&lt;0.001<br/>G2 vs. G3, p=0.007</p> <p>Met Criteria for full remission at 3 month FU</p> <p>G1:29%<br/>G2:19%</p> <p>Met Criteria for full remission at 6 month FU</p> <p>G1: 33%<br/>G2: 24.5%</p> <p>Approximately 60% in each group were in partial remission.</p> | <p>Lost of PTSD diagnosis</p> <p>Baseline to Post-tx</p> <p>G1 :35%<br/>G2: 29%<br/>G3: 11%</p> |
| Friedman et al., 2007 <sup>35</sup> | <p>IES</p> <p>Change at Endpoint (SE)</p> <p>G1: -8.7(1.8)<br/>G2: -8.1(1.9)</p> <p>Between Group Differences, NS</p> |                       | <p>DTS</p> <p>Change at Endpoint (SE)</p> <p>G1: -11.4 (3.5)<br/>G2: -10.5 (3.5)</p> <p>Between Group Differences, NS</p> <p>MISS-Civilian Trauma Version</p> <p>Change at Endpoint (SE)</p> <p>G1: -4.3 (1.7)<br/>G2: -2.8 (1.7)</p> <p>Between Group Differences, NS</p> | NR   | NR  |



**Table D-5. Self-administered PTSD scales, remission, and loss of diagnosis (continued)**

| Author, Year                       | Self-Administered IES or IES-R  | Self-Administered PCL | Self-Administered Other (e.g., MPSS, PSS-SR) | Remission (No Longer Having Symptoms)   | Loss of PTSD Diagnosis |
|------------------------------------|---|-----------------------|--|---|------------------------|
| Gamito et al., 2010 <sup>36</sup>  | IES-R<br>G1 Percentage variation: -1<br>G2 Percentage variation: 1<br>G3 Percentage variation: 7  | NR                    | NR   | NR  | NR                     |
| Gersons et al., 2000 <sup>37</sup> | NR  | NR                    | NR   | Proportions by Treatment (%<br>p values)<br><br>No PTSD Posttest<br>G1: 91%<br>G2: 50%<br>p<0.01<br><br>3-month Follow-up<br>G1: 96%<br>G2: 35%<br>p<0.01 | NR                     |
| Hamner et al., 2003 <sup>38</sup>  | NR  | NR                    | NR   | NR  | NR                     |
| Hien et al., 2004 <sup>39</sup>    | IES-R<br>Mean (SD)<br>G1 Pre-tx: 47.49 (14.50)<br>G1 Post-tx: 33.57 (14.92)<br>G1 6 mth FU: 39.12 (17.23)<br>G1 9 mth FU: 35.11 (16.82)<br><br>G2 Pre-tx: 46.12 (10.57)<br>G2 Post-tx: 28.90 (19.94)<br>G2 6 mth FU: 36.38 (20.16)<br>G2 9 mth FU: 29.67 (18.84)<br><br>G3 Pre-tx: 51.52 (12.76)<br>G3 Post-tx: 40.64 (20.43)<br>G3 6 mth FU: 40.06 (17.62)<br>G3 9 mth FU: 47.57 (13.21) | NR                    | NR   | NR  | NR                     |

**Table D-5. Self-administered PTSD scales, remission, and loss of diagnosis (continued)**

| Author, Year   | Self-Administered IES or IES-R | Self-Administered PCL  | Self-Administered Other (e.g., MPSS, PSS-SR)  | Remission (No Longer Having Symptoms) | Loss of PTSD Diagnosis   |
|--|--------------------------------|--|---|---------------------------------------|--|
| Hien et al., 2009 <sup>40</sup><br>Hien et al., 2012 <sup>41</sup> | NR                             | NR   | PSS-SR, ITT Analysis<br>Data<br>Mean (SD)<br>G1 Pre-tx: 45.4 (15.3)<br>G1 Post-tx: 32.7 (13.9)<br>G1 Average Over FU:<br>30.0 (13.0)<br><br>G2 Pre-tx: 45.6 (15.3)<br>G2 Post-tx.: 33.8<br>(15.1)<br>G2 Average Over FU:<br>32.0 (15.0)<br><br>Post-tx<br>G1 vs. G2, p=0.59<br><br>12-mth FU (Average<br>Over)<br>G1 vs. G2, p=0.97 | NR                                    | NR   |
| Hinton et al., 2005 <sup>42</sup>                                  | NR                             | NR   | NR  | NR                                    | Percentage who no longer met PTSD criteria at assessment 2<br>G1: 60% (n= 12)<br>G2: 0%<br>p<0.001 |
| Hinton et al., 2009 <sup>43</sup>                                  | NR                             | NR   | NR  | NR                                    | NR   |
| Hinton et al., 2011 <sup>44</sup>                                  | NR                             | PTSD Checklist<br>Mean (SD)<br>G1 Pre-tx: 69.8 (6.5)<br>G1 Post-tx: 39.1 (15.1)<br>G1 FU: 36.4 (12.7)<br><br>G2 Pre-tx: 71.1 (7.9)<br>G2 Post-tx: 61.6 (13.2)<br>G2 FU: 58.9 (14.7)<br><br>Post-tx<br>G1 vs. G2, p<0.05 (t-test) | NR  | NR                                    | NR   |

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FU  
G1 vs. G2,  $p < 0.05$  (t-test)

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**Table D-5. Self-administered PTSD scales, remission, and loss of diagnosis (continued)**

| Author, Year                          | Self-Administered IES or IES-R   | Self-Administered PCL | Self-Administered Other (e.g., MPSS, PSS-SR)  | Remission (No Longer Having Symptoms) | Loss of PTSD Diagnosis  |
|---------------------------------------|--|-----------------------|---|---------------------------------------|---|
| Hogberg et al., 2007 <sup>45</sup>    | <p>IES</p> <p>Mean (SD)</p> <p>Pre-tx</p> <p>G1 Pre-tx: 39.3 (17.2)</p> <p>G1 Post-tx: 23.2 (17.4)</p> <p>G2 Pre-tx: 39.1 (12.6)</p> <p>G2 Post-tx: 34 (16.2)</p> <p>Within-group effect over time:</p> <p>G1: p&lt;0.05</p> <p>G2: p&lt;0.05</p> <p>Between group differences, NS</p> | NR                    | NR  | NR                                    | <p>6 EMDR patients retained PTSD diagnosis, but denominator not given</p> <p>G1: 67% (8 of 12)</p> <p>G2: 11% (1 of 11)</p> <p>p=0.02</p>       |
| Hollifield et al., 2007 <sup>46</sup> | NR   | NR                    | <p>PSS-SR</p> <p>Mean (SD)</p> <p>G1 Pre-tx: 31.33 (10.10)</p> <p>G1 Post-tx: 15.65 (13.95)</p> <p>G1 3 mth FU: 15.42 (12.54)</p> <p>G2 Pre-tx: 32.52 (6.63)</p> <p>G2 Post-tx: 20.02 (10.56)</p> <p>G2 3 mth FU: 16.68 (12.20)</p> <p>G3 Pre-tx: 30.79 (9.54)</p> <p>G3 Post-tx: 27.92 (12.33)</p> <p>G3 3 mth FU: 27.92 (12.33)</p> <p>RMANOVA</p> <p>G1 vs. G2, p=0.29</p> <p>G1 vs. G3, p&lt;0.01</p> <p>G2 vs. G3, p&lt;0.01</p> | NR                                    | <p>PSS-SR &lt;16 at end of tx:</p> <p>G1: 68%</p> <p>G2: 43%</p> <p>G3: 19%</p> <p>PSS-SR &lt;16 at 3-months:</p> <p>G1: 68%</p> <p>G2: 62%</p> |

**Table D-5. Self-administered PTSD scales, remission, and loss of diagnosis (continued)**

| Author, Year                       | Self-Administered IES or IES-R | Self-Administered PCL | Self-Administered Other (e.g., MPSS, PSS-SR) | Remission (No Longer Having Symptoms)   | Loss of PTSD Diagnosis   |
|------------------------------------|--------------------------------|-----------------------|--|---|--|
| Johnson et al., 2011 <sup>47</sup> | NR                             | NR                    | NR   | NR  | NR   |
| Krakow et al., 2001 <sup>48</sup>  | NR                             | NR                    | NR   | NR  | NR   |
| Kruse et al., 2009 <sup>49</sup>   | NR                             | NR                    | NR   | According to the PTSD scale of the HTQ<br>G1: 82.4%<br>G2: 0%   | NR   |
| Krystal et al., 2011 <sup>50</sup> | NR                             | NR                    | NR   | Fisher's exact test, p<.001<br>% of veterans remitted based on CAPS at 24 weeks †<br>G1: 4.9<br>G2: 4.0 | % of veterans with mild symptoms/ subdiagnostic based on CAPS at 24 weeks †<br>G1: 14.6<br>G2: 6.5 |
| Kubany et al., 2003 <sup>51</sup>  | NR                             | NR                    | NR   | NR  | No longer met diagnostic criteria for PTSD Based on CAPS<br>G1: 94.0%<br>G1: 0.0%                  |
| Kubany et al., 2004 <sup>52</sup>  | NR                             | NR                    | NR   | NR  | Lost of PTSD diagnosis based on completers<br>G1: 91%<br>G2: NR                                    |

**Table D-5. Self-administered PTSD scales, remission, and loss of diagnosis (continued)**

| Author, Year                        | Self-Administered IES or IES-R | Self-Administered PCL | Self-Administered Other (e.g., MPSS, PSS-SR)  | Remission (No Longer Having Symptoms) | Loss of PTSD Diagnosis  |
|-------------------------------------|--------------------------------|-----------------------|---|---------------------------------------|---|
| Liedl et al., 2011 <sup>53</sup>    | NR                             | NR                    | <p>PDS Part I</p> <p>G1 Pre-tx: 31.2 (12.6)<br/>G1 Post-tx: 28.7 (13.2)<br/>G1 3 mth FU: 28.7 (13.2)</p> <p>G2 Pre-tx: 27.0 (7.6)<br/>G2 Post-tx: 21.9(12.9)<br/>G2 3 mth FU: 21.9 (12.9)</p> <p>G3 Pre-tx: 25.6(11.7)<br/>G3 Post-tx: 26.8 (13.1)</p> <p>G2 showed larger pre-tx to post-tx effect sizes than G1 group for PTSD (<math>d = 0.48</math> vs <math>d = 0.19</math>)</p> <p>G2 scored more favorably than G3 on all post-tx measures</p> <p>No within group differences at Post-tx or 3 mth FU</p> | NR                                    | NR  |
| Lindauer et al., 2005 <sup>54</sup> | NR                             | NR                    | NR  | NR                                    | <p>SI-PTSD scale used to diagnose PTSD, % improved at Post-tx</p> <p>G1: 83.3%</p> <p>G2: 25%</p> <p><math>p &lt; 0.05</math></p> |

**Table D-5. Self-administered PTSD scales, remission, and loss of diagnosis (continued)**

| Author, Year  | Self-Administered IES or IES-R  | Self-Administered PCL | Self-Administered Other (e.g., MPSS, PSS-SR) | Remission (No Longer Having Symptoms) | Loss of PTSD Diagnosis  |
|---|---|-----------------------|--|---------------------------------------|---|
| Litz et al., 2007 <sup>55</sup>                                       | NR  | NR                    | NR   | NR                                    | % no longer meeting criteria for PTSD based on PSS-I $\leq 6$<br>ITT Analysis<br>Post-tx:<br>G1: 25%<br>G2: 5%<br>Likelihood ratio=3.89, p<0.05<br><br>3-mth F/U, p=NR<br><br>6 mth F/U<br>G1: 25%<br>G2: 3%<br>Likelihood ratio=8.35, p<0.01 |
| Marks et al., 1998 <sup>56</sup><br>Lovell et al., 2001 <sup>57</sup> | IES (first 11 weeks)<br>Mean Change Score (95% CI)<br>G1: 28 (19 to 37)<br>G2: 25 (15 to 34)<br>G3: 35 (24 to 49)<br>G4: 13 (5 to 19)<br><br>Additional results presented in graphs<br>IES<br>Mean change in G1 + G2 + G3 vs. G4<br>Post, p=0.008<br>1 mth FU, p=0.08<br>3 mth FU, p=0.05 | NR                    | NR   | NR                                    | PTSD Criteria not meet by CAPS<br>G1: 75%<br>G2: 65%<br>G3: 63%<br>G4: 55%  |

**Table D-5. Self-administered PTSD scales, remission, and loss of diagnosis (continued)**

| Author, Year   | Self-Administered IES or IES-R | Self-Administered PCL  | Self-Administered Other (e.g., MPSS, PSS-SR)   | Remission (No Longer Having Symptoms) | Loss of PTSD Diagnosis   |
|--|--------------------------------|--|--|---------------------------------------|--|
| Marshall et al., 2001 <sup>58</sup>  | NR                             | NR   | DTS<br>Adjusted Mean<br>Differences (95% CI)<br>G1 vs. G3<br>-12.2 (-18.1 to -6.3)<br>p<0.001<br><br>G2 vs. G3<br>-10.9 (-16.9 to -4.9)<br>p<0.001 | NR                                    | NR   |
| Martenyi et al., 2002 <sup>59</sup><br>Martenyi et al., 2006 <sup>60</sup> | NR                             | NR   | DTS<br>Changes from Pre-tx<br>to Post-tx<br>Least Square Means<br>(SE), p-value<br>G1: -33.8 (2.25)<br>G2: -27.3 (3.66)<br>p=0.117                 | NR                                    | NR   |
| Martenyi et al., 2007 <sup>61</sup>  | NR                             | NR   | NR   | NR                                    | G1: 40.5%<br>G2: 38.8%<br>G3: 37.5   |
| McDonagh et al., 2005 <sup>62</sup>  | NR                             | NR   | NR   | NR                                    | No longer met criteria<br>for PTSD (CAPS)<br>G1: 27.6%<br>G2: 31.8%<br>G3: 17.4% |
| Monnelly et al., 2003 <sup>63</sup>  | NR                             | PCL-M<br>Median Change Scores<br>G1: -10.0<br>G2: -0.5<br>p=0.02 | NR   | NR                                    | NR   |



**Table D-5. Self-administered PTSD scales, remission, and loss of diagnosis (continued)**

| Author, Year                      | Self-Administered IES or IES-R | Self-Administered PCL | Self-Administered Other (e.g., MPSS, PSS-SR) | Remission (No Longer Having Symptoms) | Loss of PTSD Diagnosis  |
|-----------------------------------|--------------------------------|-----------------------|--|---------------------------------------|---|
| Monson et al., 2006 <sup>64</sup> | NR                             | NR                    | NR   | NR                                    | <p>Did Not Meet Diagnostic Criteria for PTSD at Post-treatment<br/>                     G1: 40% (n=12)<br/>                     G2: 3% (n=1)<br/>                     p&lt;0.001</p> <p>Did Not Meet Diagnostic Criteria for PTSD at 1-month<br/>                     G1: 30% (n= 9)<br/>                     G2: 3% (n=1)<br/>                     p=0.01</p>  |
| Mueser et al., 2008 <sup>65</sup> | NR                             | NR                    | NR   | NR                                    | <p>CAPS Dx, n(%)<br/>                     G1 Pre-tx: 54 (100.0)<br/>                     G1 Post-tx: 21 (67.7)<br/>                     G1 3 mth FU: 19 (63.3)<br/>                     G1 6 mth FU: 24 (72.7)</p> <p>G2 Pre-tx: 54 (100.0)<br/>                     G2 Post-tx: 21 (77.8)<br/>                     G2 3 mth: 27 (77.1)<br/>                     G2 6 mth: 17 (85.0)</p> <p>Group effect, p=0.63,</p> |

**Table D-5. Self-administered PTSD scales, remission, and loss of diagnosis (continued)**

| Author, Year                        | Self-Administered IES or IES-R | Self-Administered PCL | Self-Administered Other (e.g., MPSS, PSS-SR)   | Remission (No Longer Having Symptoms) | Loss of PTSD Diagnosis  |
|-------------------------------------|--------------------------------|-----------------------|--|---------------------------------------|---|
| Nacasch et al., 2011 <sup>66</sup>  | NR                             | NR                    | NR   | NR                                    | NR  |
| Neuner et al., 2004 <sup>67</sup>   | NR                             | NR                    | <p>PDS</p> <p>Mean (SD)</p> <p>G1 Pre-tx: 25.2 (7.4)</p> <p>G1 Post-tx: 19.1 (11.7)</p> <p>G1 4 mth FU: 24.5 (7.8)</p> <p>G1 1 year FU: 16.0 (5.1)</p> <p>G2 Pre-tx: 22.0 (8.0)</p> <p>G2 Post-tx: 19.8 (10.9)</p> <p>G2 4 mth FU: 22.8 (23.1)</p> <p>G2 1 year FU: 23.1 (7.7)</p> <p>G3 Pre-tx: 19.5 (8.0)</p> <p>G3 Post-tx: 21.2 (9.4)</p> <p>G4 Post-tx: 27.7 (6.6)</p> <p>G3 1 year FU: 23.9 (7.0)</p> <p>1 year Group X Time</p> <p>G1 vs. G2, p=0.01</p> <p>G1 vs. G3, p=0.01</p> | NR                                    | <p>Percentage of Patients Without a PTSD Diagnosis at 1 year follow-up</p> <p>G1: 71.0%</p> <p>G2: 21.0%</p> <p>G3: 20.0%</p> |
| Neuner et al., 2008 <sup>68</sup>   | NR                             | NR                    | NR   | NR                                    | <p>No longer fulfilled criteria for PTSD at 9 months.</p> <p>G1: 69.85%</p> <p>G2: 65.2%</p> <p>G3: 36.8%</p>                 |
| Neuner et al., 2010 <sup>69</sup>   | NR                             | NR                    | NR   | NR                                    | <p>G1: 6.25%</p> <p>G2: 0%</p>  |
| Petrakis et al., 2011 <sup>72</sup> | NR                             | NR                    | NR   | NR                                    | NR  |
| Raskind et al., 2003 <sup>73</sup>  | NR                             | NR                    | NR   | NR                                    | NR  |
| Raskind et al., 2007 <sup>74</sup>  | NR                             | NR                    | NR   | NR                                    | NR  |

**Table D-5. Self-administered PTSD scales, remission, and loss of diagnosis (continued)**

| Author, Year                        | Self-Administered IES or IES-R   | Self-Administered PCL | Self-Administered Other (e.g., MPSS, PSS-SR) | Remission (No Longer Having Symptoms) | Loss of PTSD Diagnosis           |
|-------------------------------------|--|-----------------------|--|---------------------------------------|----------------------------------|
| Reich et al., 2004 <sup>75</sup>    | NR   | NR                    | NR   | NR                                    | NR                               |
| Resick et al., 2002 <sup>76</sup>   | NR   | NR                    | PSS  | NR                                    | Lost of PTSD Dx at Posttreatment |
| Resick et al., 2003 <sup>77</sup>   |  |                       | Mean (SD)                                    |                                       | G1: 53%                          |
| Resick et al., 2012 <sup>78</sup>   |  |                       | G1 Pre-tx: 29.55 (8.62)                      |                                       | G2: 53%                          |
|                                     |  |                       | G1 Post-tx: 13.66 (11.05)                    |                                       | G3: 2.2%                         |
|                                     |  |                       | G1 3 mth FU: 14.67 (11.79)                   |                                       | G1 vs. G2 Overtime, NS           |
|                                     |  |                       | G1 9 mth FU: 15.13 (12.03)                   |                                       | LTFU                             |
|                                     |  |                       | G1 LTFU: 9.68 (10.38)                        |                                       | G1: 81.6                         |
|                                     |  |                       | G2 Pre-tx: 30.09 (9.18)                      |                                       | G2: 58.7                         |
|                                     |  |                       | G2 Post-tx: 17.99 (13.17)                    |                                       | G1 vs. G2, NS                    |
|                                     |  |                       | G2 3 mth FU: 18.05 (13.78)                   |                                       |                                  |
|                                     |  |                       | G2 9 mth FU: 18.40 (13.98)                   |                                       |                                  |
|                                     |  |                       | G2 LTFU: 9.89 (10.52)                        |                                       |                                  |
|                                     |  |                       | G3 Pre-tx: 28.70 (7.33)                      |                                       |                                  |
|                                     |  |                       | G3 Post-tx: 27.77 (8.12)                     |                                       |                                  |
|                                     |  |                       | G3 3 mth FU: 27.77 (8.12)                    |                                       |                                  |
|                                     |  |                       | G3 9 mth FU: 27.77 (8.12)                    |                                       |                                  |
|                                     |  |                       | Only G1 vs. G2 Posttreatment differences, NS |                                       |                                  |
|                                     |  |                       | 3 mth FU differences, NS                     |                                       |                                  |
|                                     |  |                       | 9 mth FU differences, NS                     |                                       |                                  |
|                                     |  |                       | LTFU differences, p=0.06                     |                                       |                                  |
| Rothbaum et al., 1997 <sup>79</sup> | IES<br>Mean (SD)<br>G1 Pre-tx: 47.4 (15.0)<br>G1 Post-tx: 12.4 (11.2)<br>G1 3 mth FU: 5.7 (5.8)<br><br>G2 Pre-tx: 48.9 (8.9) | NR                    | NR   | NR                                    | NR                               |

G2 Post-tx: 45.4 (6.4)

Posttreatment G1 vs. G2,  
p<0.01

**Table D-5. Self-administered PTSD scales, remission, and loss of diagnosis (continued)**

| Author, Year                        | Self-Administered IES or IES-R | Self-Administered PCL | Self-Administered Other (e.g., MPSS, PSS-SR) | Remission (No Longer Having Symptoms)   | Loss of PTSD Diagnosis  |
|-------------------------------------|--------------------------------|-----------------------|--|---|---|
| Rothbaum et al., 2005 <sup>80</sup> | Data only presented in graphs  | NR                    | NR   | NR  | Loss of PTSD Dx at Posttreatment:<br>G1: 95%<br>G2: 75%<br>G3: 10%<br>G1&G2 vs. G3<br>p<0.001<br>G1 vs. G2 p=0.108<br><br>Loss of PTSD Dx at 6 months f/u:<br>G1: 94.4%<br>G2: 73.7%<br>p=0.185 |
| Rothbaum et al., 2006 <sup>81</sup> | NR                             | NR                    | NR   | NR  | NR  |
| Schneier et al., 2012 <sup>82</sup> | NR                             | NR                    | NR   | CAPS ≤20<br>Remission, n (%)<br>G1 @ wk 10 (N=13) 8 (61.5)<br>G2 @ wk 10 (N=13) 3 (23.1)<br><br>Treatment Group Effect, p=0.03<br><br>Change over time, p=0.007 | NR  |

**Table D-5. Self-administered PTSD scales, remission, and loss of diagnosis (continued)**

| Author, Year                        | Self-Administered IES or IES-R | Self-Administered PCL   | Self-Administered Other (e.g., MPSS, PSS-SR) | Remission (No Longer Having Symptoms)  | Loss of PTSD Diagnosis   |
|-------------------------------------|--------------------------------|---|--|--|--|
| Schnurr et al., 2003 <sup>83</sup>  | NR                             | NR  | NR   | NR   | NR   |
| Schnurr et al., 2007 <sup>84</sup>  | NR                             | <p>PCL</p> <p>Baseline</p> <p>Mean (95% CI)</p> <p>G1: 58.2 (56.0 to 60.3)</p> <p>G2: 57.1 (55.0 to 59.2)</p> <p>Least Square Means (95% CI)</p> <p>Immediate posttreatment</p> <p>G1: 41.6 (38.4 to 44.9)</p> <p>G2: 48.9 (45.8 to 52.0)</p> <p>G2</p> <p>G1 vs. G2, <math>p &lt; 0.001</math></p> <p>3-month</p> <p>G1: 43.5 (40.2 to 46.7)</p> <p>G2: 48.8 (45.3 to 52.4)</p> <p>at posttreatment</p> <p>G1 vs. G2, <math>p &lt; 0.008</math></p> <p>6-month</p> <p>G1: 44.6 (41.2 to 48.1)</p> <p>G2: 48.5 (45.2 to 51.8)</p> <p>G1 vs. G2, <math>p = 0.049</math></p> <p>Treatment X Time, <math>p = 0.18</math></p> | NR   | <p>Total remission, CAPS score <math>&lt; 20</math></p> <p>G1: 15.2%</p> <p>G2: 6.9%</p> <p>OR (95% CI): 2.43 (1.10-5.37)</p>  | <p>Loss of diagnosis based on CAPS</p> <p>G1: 41.0%</p> <p>G2: 27.9%</p> <p>OR (95% CI): 1.80 (1.10-2.96)</p>                              |
| Schnyder et al., 2011 <sup>85</sup> | NR                             | NR  | NR   | <p>Remission Rates (CAPS score <math>&lt; 20</math>)</p> <p>Posttreatment</p> <p>G1: 12.5% (n=2)</p> <p>G2: 0.0% (n= 0)</p> <p>6-month Follow-up</p> <p>G1: 18.8% (n=3)</p> <p>G2: 0.0% (n= 0)</p> | <p>Lost of PTSD Diagnosis (CAPS Total Score of <math>&lt; 50</math>)</p> <p>Posttreatment</p> <p>G1: 12.5% (n=2)</p> <p>G2: 0.0% (n=0)</p> |

**Table D-5. Self-administered PTSD scales, remission, and loss of diagnosis (continued)**

| Author, Year                      | Self-Administered IES or IES-R | Self-Administered PCL   | Self-Administered Other (e.g., MPSS, PSS-SR) | Remission (No Longer Having Symptoms)  | Loss of PTSD Diagnosis  |
|-----------------------------------|--------------------------------|---|--|--|---|
| Simon et al., 2008 <sup>86</sup>  | NR                             | NR  | NR   | Remission based on having a SPRINT score less than 6 at end point<br>G1: 33%<br>G2: 14%    | NR  |
| Spence et al., 2011 <sup>87</sup> | NR                             | PCL-C<br>Mean (SD)<br>G1 Pre-tx: 60.78 (10.03)<br>G1 Post-tx: 44.78 (17.29)<br>G1 3 mth FU: 43.17 (17.89)<br><br>G2 Pre-tx: 57.00 (9.69)<br>G2 Post-tx: 51.79 (12.51)<br>G2 3 mth FU: NR<br><br>Treatment effect at 8 weeks, $p < 0.03$ | NR   | Significant difference between groups at posttreatment for remission on PCL ( $p < 0.01$ ) | Loss of diagnosis based on PCL at 3 months<br>G1: 61%<br>G2: NR |
| Stein et al., 2002 <sup>88</sup>  | NR                             | NR  | NR   | NR   | NR  |

**Table D-5. Self-administered PTSD scales, remission, and loss of diagnosis (continued)**

| Author, Year   | Self-Administered IES or IES-R   | Self-Administered PCL | Self-Administered Other (e.g., MPSS, PSS-SR)  | Remission (No Longer Having Symptoms) | Loss of PTSD Diagnosis   |
|--|--|-----------------------|---|---------------------------------------|--|
| Tarrier et al., 1999 <sup>89</sup><br>Tarrier et al., 1999 <sup>90</sup> | IES-I<br>Mean (SD)<br>G1 Pre-tx: 23.86 (8.24)<br>G1 Post-tx: 16.39 (10.04)<br>G1 6 mth FU: 15.85 (9.26)<br><br>G2 Pre-tx: 26.73 (7.80)<br>G1 Post-tx: 17.91 (10.29)<br>G2 6 mth FU: 17.72 (10.40)<br><br>G1 vs. G2 differences, NS<br><br>12 Month Follow-up<br>G1 Pre-tx: 24.68 (7.47)<br>G1 12 mth FU: 15.67 (9.16)<br><br>G2 Baseline: 26.55 (7.78)<br>G2 12 mth FU: 18.68 (9.24)<br><br>G1 vs. G2 differences, NS<br><br>IES-A<br>Mean (SD)<br>G1 Pre-tx: 22.69 (9.24)<br>G1 Post-tx: 14.89 (9.09)<br>G1 6 mth FU: 17.70 (10.74)<br><br>G2 Pre-tx: 26.21 (7.55)<br>G2 Post-tx: 19.61 (10.09)<br>G2 6 mth FU: 18.31 (9.66)<br><br>G1 vs. G2 differences, NS<br><br>IES-A<br>12 Month Follow-up<br>G1 Pre-tx: 23.00 (9.36) | NR                    | Penn Inventory<br>Mean (SD)<br>G1 Pre-tx: 47.28 (10.96)<br>G1 Post-tx: 34.43 (14.69)<br>G1 6 mth FU: 41.78 (12.50)<br><br>G2 Pre-tx: 46.52 (12.98)<br>G2 Post-tx: 36.09 (15.46)<br>G2 6 mth FU: 37.24 (15.76)<br><br>G1 vs. G2 differences, NS<br><br>12 Follow-up<br>G1 Pre-tx: 47.52 (10.79)<br>G1 12 mth FU: 41.04 (14.08)<br><br>G2 Pre-tx: 47.03 (13.45)<br>G2 12 mth FU: 38.39 (15.12)<br><br>G1 vs. G2 differences, NS | NR                                    | Percent of Patients who were no longer PTSD cases<br><br>Posttreatment Overall: 50%<br>G1: 59%<br>G2: 42%<br><br>6-Months Overall: 52%<br>G1: 52%<br>G2: 52%<br><br>12-Months Overall: 61% |

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G1 12 mth FU: 18.00  
(11.36)

G2 Pre-tx: 26.21 (7.93)

G2 12 mth FU: 20.68  
(10.97)

G1 vs. G2 differences, NS

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**Table D-5. Self-administered PTSD scales, remission, and loss of diagnosis (continued)**

| Author, Year   | Self-Administered IES or IES-R   | Self-Administered PCL | Self-Administered Other (e.g., MPSS, PSS-SR)  | Remission (No Longer Having Symptoms)   | Loss of PTSD Diagnosis |
|--|--|-----------------------|---|---|------------------------|
| Taylor et al., 2003 <sup>91</sup>                                      | NR   | NR                    | PTSD Symptom Severity Scale (part of PTSDS)<br>Intent to Treat Sample<br>3 treatments did not differ (p>0.05) | NR  | NR                     |
| Tucker et al., 2001 <sup>92</sup>                                      | NR   | NR                    | DTS<br>Adjusted Mean Differences (95% CI)<br><br>G1 vs. G2<br>-12.6 (-18.8 to -6.4)<br>p<0.001                | CAPS-2 total score <20<br><br>29.4% vs. 16.5% achieved remission; OR, 2.29; 95% CI, 1.24 to 4.23; p=0.008 | NR                     |
| Tucker et al., 2003 <sup>93</sup><br>Tucker et al., 2004 <sup>94</sup> | Tucker et al., 2003<br>IES<br>G1 Pre-tx: 50.04<br>G1 Post-tx: 24.65<br><br>G2 Pre-tx: 46.26<br>G2 Post-tx: 17.16<br><br>G3 Pre-tx: 53.8<br>G3 Post-tx: 20.57<br><br>Between group differences,<br>p value NR | NR                    | NR  | NR  | NR                     |
| Tucker et al., 2007 <sup>95</sup>                                      | NR   | NR                    | DTS<br>Mean Percentage Change (SD)<br>G1: -54.1(35.8)<br>G2: -32.3(34.8)<br>p=0.065                           | CAPS score <20, N<br>G1: 8<br>G2: 4<br>p=0.295  | NR                     |

**Table D-5. Self-administered PTSD scales, remission, and loss of diagnosis (continued)**

| Author, Year                            | Self-Administered IES or IES-R   | Self-Administered PCL | Self-Administered Other (e.g., MPSS, PSS-SR) | Remission (No Longer Having Symptoms)   | Loss of PTSD Diagnosis  |
|---|--|-----------------------|--|---|---|
| van der Kolk et al., 1994 <sup>96</sup> | NR   | NR                    | NR   | NR  | NR  |
| van der Kolk et al., 2007 <sup>97</sup> | NR   | NR                    | NR   | % asymptomatic, defined as CAPS <20<br>G1: 28<br>G2: 13<br>G3: 10<br>G1 vs. G2, p=0.17<br>G1 vs. G3, p=0.09<br>G2 vs. G3, p=0.72<br>6-month post-treatment f/u (intent-to-follow)<br>G1: 58%<br>G2: 0%<br>G3: NA<br>p<0.001 | Lost of PTSD Diagnosis, %<br>G1: 76<br>G2: 73<br>G3: 59<br>G1 vs. G2, p=0.82<br>G1 vs. G3, 0.16<br>G2 vs. G3, 0.23 (G2/3)<br>6-month post-treatment f/u (intent-to-follow)<br>G1: 88%<br>G2: 73%<br>G3: NA<br>p= 0.20 |
| van Emmerik et al., 2008 <sup>98</sup>  | IES<br>Mean (SD)<br>G1 Pre-tx: 46.40 (12.32)<br>G1 Post: 32.00 (20.32)<br>G1 FU: 33.68 (22.18)<br><br>G2 Pre-tx: 47.87 (13.82)<br>G2 Post-tx: 34.32 (22.58)<br>G2 FU: 33.68 (24.63)<br><br>G3 Pre-tx: 49.14 (14.66)<br>G3 Post-tx: 45.66 (13.65)<br>G3 FU: 46.63 (13.17)<br><br>Group X Time Effect<br>G1 vs G2, p=0.62<br>G1+G2 vs G3, p<0.01 | NR                    | NR   | NR  | NR  |

**Table D-5. Self-administered PTSD scales, remission, and loss of diagnosis (continued)**

| Author, Year                         | Self-Administered IES or IES-R | Self-Administered PCL | Self-Administered Other (e.g., MPSS, PSS-SR) | Remission (No Longer Having Symptoms) | Loss of PTSD Diagnosis   |
|--------------------------------------|--------------------------------|-----------------------|--|---------------------------------------|--|
| Yeh et al., 2011 <sup>99</sup>       | NR                             | NR                    | NR   | NR                                    | NR   |
| Zlotnick et al., 2009 <sup>100</sup> | NR                             | NR                    | NR   | NR                                    | Percentage that Loss PTSD Diagnosis based on CAPS<br><br>Post-tx<br>G1: 52<br>G2: 45<br><br>3 mth FU<br>G1: 61<br>G2: 57<br><br>6 mth FU<br>G1: 57<br>G2: 62 |
| Zohar et al., 2002 <sup>101</sup>    | NR                             | NR                    | NR   | NR                                    | NR   |

Abbreviations: ANOVA = analysis of variance; ANCOVA = analysis of covariance; CI = confidence interval; DTS = Davidson Trauma Scale; FU = Follow-up; IES = Impact of Event Scale; NR= not reported; NS = not significant; PCL-C =Posttraumatic Stress Disorder Checklist-Civilian; PCL-M = Posttraumatic Stress Disorder Checklist-Military; PCLS = Posttraumatic Stress Disorder Checklist Scale; PDS = Posttraumatic Diagnostic Scale; Pre-tx = pretreatment; Post-tx = Posttreatment; PSS= PTSD Symptom Scale; PSS-SR= PTSD Symptom Scale-Self-report; PTSD= Post-Traumatic Stress Disorder; RMANOVA, repeated measures analysis of variance; SD = standard deviation; SE = standard error.

**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work**

| Author, Year                         | Comorbid Medical Condition | Comorbid Psychiatric Condition   | QOL  | Disability/Functional Impairment | Return to Work/Active Duty OR Ability to Work |
|--------------------------------------|----------------------------|--|--|----------------------------------|---|
| Akuchekian et al., 2004 <sup>1</sup> | NR                         | NR   | NR   | NR                               | NR  |
| Asukai et al., 2010 <sup>2</sup>     | NR                         | <p>CES-D<br/>Adjusted Means (SE)<br/>G1 Pre-tx:39.58 (3.53)<br/>G1 Post-tx: 20.30 (3.97)</p> <p>G2 Pre-tx:39.50 (3.52)<br/>G2 Pre-tx: 34.81 (3.65)</p> <p>At post: G1 vs. G2=<br/>p&lt;0.05(based on t-test)</p>   | <p>GHQ-28<br/>Adjusted Means (SE)<br/>G1 Pre-tx:21.58 (1.89)<br/>G1 Post-tx: 10.04 (2.15)</p> <p>G2 Pre-tx:20.50 (1.89)<br/>G2 Post-tx: 17.65 (1.97)</p> <p>At post: G1 vs. G2=<br/>p&lt;0.05(based on t-test)</p> | NR                               | NR  |
| Bartzokis et al., 2005 <sup>3</sup>  | NR                         | <p>HAM-A<br/>Unadjusted Change from baseline (SD)<br/>G1: -7.4 (5.7)<br/>G2:-2.0 (7.0)<br/>p&lt;0.001<br/>G1 vs. G2, p&lt;0.001</p> <p>HAM-D<br/>Unadjusted Change from baseline (SD)<br/>G1: -3.7 (8.0)<br/>G2: -1.4 (8.7)<br/>G1 vs. G2, p&gt;0.05</p> | NR   | NR                               | NR  |

**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year                        | Comorbid Medical Condition | Comorbid Psychiatric Condition  | QOL | Disability/Functional Impairment  | Return to Work/Active Duty OR Ability to Work |
|-------------------------------------|----------------------------|---|-----|---|---|
| Basoglu et al., 2007 <sup>4</sup>   | NR                         | BDI<br>Mean (SD)<br>G1 Pre-tx:23.4 (5.9)<br>G1 4 weeks:13.1 (6.2)<br>G1 8 weeks: 13.3 (9.2)<br><br>G2 Pre-tx:21.9 (3.5)<br>G2 4 weeks: 20.5 (7.4)<br>G2 8 weeks:18.4 (11.0)<br><br>G1 vs. G2 at Week 4,<br>p<0.01<br>G1 vs. G2 at Week 8,<br>p<0.007  | NR  | Work and Social Adjustment<br>Mean (SD)<br>G1 Pre-tx: 4.1 (0.8)<br>G1 4 weeks: 2.2 (1.4)<br>G1 8 weeks: 1.7 (1.9)<br><br>G2 Pre-tx: 4.1 (0.9)<br>G2 4 weeks:3.3 (1.4)<br>G2 8 weeks:2.7 (1.6)<br><br>G1 vs. G2 at Week 4,<br>p<0.01<br>G1 vs. G2 at Week 8,<br>p<0.007  | NR  |
| Becker et al., 2007 <sup>5</sup>    | NR                         | BDI<br>Within Group Mean Change (SD) (Baseline-Endpoint)<br>G1: 3.22 (4.77)<br>G2: 3.61 (10.44)<br><br>Group effect, p<0.05   | NR  | NR  | NR  |
| Blanchard et al., 2003 <sup>6</sup> | NR                         | BDI<br>Mean (SD)<br>G1 Pre-tx: 24.3 (10.8)<br>G1 Post-tx: 11.6 (12.3)<br>G1 FU: 12.6 (13.5)<br><br>G2 Pre-tx: 17.8 (13.0)<br>G2 Post-tx: 56.3 (12.2)<br>G2 FU: 17.8 (13.0)<br><br>G3 Pre-tx: 25.2 (11.9)<br>G3 Post-tx: 24.0 (12.1)<br><br>Group X Time, Post-Tx<br>G1 vs. G2 & G3 (Post-tx) (Group X Time), p<0.001<br>G2 vs G3 (Post-tx) (Group X Time), NS | NR  | GAF<br>Mean (SD)<br>G1 Pre-tx: 53.9 (11.4)<br>G1 Post-tx: 75.8 (12.2)<br>G1 FU: 74.7 (12.8)<br><br>G2 Pre-tx: 56.0 (9.7)<br>G2 Post-tx: 64.3 (13.4)<br>G2 FU: 66.3 (15.1)<br><br>G3 Pre-tx: 56.0 (13.1)<br>G3 Post-tx: 60.4 (9.6)<br><br>Group X Time, Post-Tx<br>G1 vs. G2, p=0.001<br>G1 vs G3, p=0.001<br>G2 vs & G3, NS | NR  |

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No changes at 3 mths

No changes at 3 months

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**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year  | Comorbid Medical Condition | Comorbid Psychiatric Condition   | QOL | Disability/Functional Impairment | Return to Work/Active Duty OR Ability to Work |
|---|----------------------------|--|-----|----------------------------------|---|
| Blanchard et al.,<br>2003 <sup>6</sup><br>(continued) |                            | <p>State-Anxiety<br/>Mean (SD)<br/>G1 Pre-tx: 55.3 (14.1)<br/>G1 Post-tx: 38.9 (14.0)<br/>G1 FU: 42.6 (15.4)</p> <p>G2 Pre-tx: 56.3 (12.2)<br/>G2 Post-tx: 50.7 (12.6)<br/>G2 FU: 49.1 (14.5)</p> <p>G3 Pre-tx: 58.5 (10.9)<br/>G3 Post-tx: 58.8 (12.3)</p> <p>Group X Time, Post-tx<br/>G1 vs. G2 &amp; G3, p&lt;0.001<br/>G2 vs. G3, significantly<br/>greater change for G2<br/>Changes at 3 mths, NS</p> |     |                                  |   |
|   |                            | <p>Trait-Anxiety<br/>Mean (SD)<br/>G1 Pre-tx: 55.7 (14.0)<br/>G1 Post-tx: 41.0 (16.5)<br/>G1 FU: 40.6 (15.3)</p> <p>G2 Pre-tx: 56.7 (10.4)<br/>G2 Post-tx: 52.4 (12.3)<br/>G2 FU: 52.3 (12.6)</p> <p>G3 Pre-tx: 58.9 (10.1)<br/>G3 Post-tx: 57.7 (9.9)</p>   |     |                                  |   |
|   |                            | <p>Group X Time, Post-Tx<br/>G1 vs. G2 &amp; G3, p&lt;0.001<br/>G2 vs. G3, NS<br/>Changes at 3 mths</p>  |     |                                  |   |

**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year                                       | Comorbid Medical Condition | Comorbid Psychiatric Condition  | QOL | Disability/Functional Impairment | Return to Work/Active Duty OR Ability to Work |
|--|----------------------------|---|-----|----------------------------------|---|
| Blanchard et al., 2003 <sup>6</sup><br>(continued) |                            | Global Severity Index<br>Mean (SD)<br>G1 Pre-tx: 70.1 (9.3)<br>G1 Post-tx: 57.3 (12.6)<br>G1 FU: 58.4 (14.3)<br><br>G2 Pre-tx: 73.2 (6.4)<br>G2 Post-tx: 67.6 (9.0)<br>G2 FU: 65.3 (13.1)<br><br>Group X Time, Post-tx<br>G1 vs. G2 & G3, p<0.001<br>G2 vs. G3, significantly<br>greater change for G2  |     |                                  |   |
| Boden et al., 2012 <sup>7</sup>                    | NR                         | ASI<br>Drug Use<br>Mean (SD)<br>G1 Pre-tx: 0.09 (0.08)<br>G1 Post-tx: 0.06 (0.06)<br>G1 6 mth FU: 0.05 (0.06)<br><br>G2 Pre-tx: 0.11 (0.08)<br>G2 Post-tx: 0.10 (0.09)<br>G2 6 mth FU: 0.09 (0.09)<br><br>Between Group Differences<br>at Post-tx, p<0.05<br><br>Between Group Differences<br>at 6 month FU, p<0.05<br><br>G1 Within Group<br>Differences<br>Pre-tx vs. Post-tx, p<0.05<br><br>G1 Within Group<br>Differences<br>Pre-tx vs. 6mth FU, p<0.05 | NR  | NR                               | NR  |



**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year                       | Comorbid Medical Condition | Comorbid Psychiatric Condition  | QOL | Disability/Functional Impairment | Return to Work/Active Duty OR Ability to Work |
|------------------------------------|----------------------------|---|-----|----------------------------------|---|
| Boden et al., 2012'<br>(continued) |                            | Alcohol Use<br>Mean (SD)<br>G1 Pre-tx: 0.29 (0.26)<br>G1 Post-tx: 0.17 (0.19)<br>G1 6 mth FU: 0.14 (0.17)<br><br>G2 Pre-tx: 0.23 (0.24)<br>G2 Post-tx: 0.15 (0.13)<br>G2 6 mth FU: 0.14 (0.15)<br><br>Between Group<br>Differences, NS<br><br>G1 Within Group<br>Differences<br>Pre-tx vs. Post-tx, p<0.05<br><br>G1 Within Group<br>Differences<br>Pre-tx vs. 6 month FU,<br>p<0.05<br><br>G2 Within Group<br>Differences<br>Pre-tx vs. Post-tx, p<0.05<br><br>G2 Within Group<br>Differences<br>Post-tx vs. 6 month FU,<br>p<0.05 |     |                                  |   |

**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year                    | Comorbid Medical Condition | Comorbid Psychiatric Condition  | QOL  | Disability/Functional Impairment  | Return to Work/Active Duty OR Ability to Work |
|---------------------------------|----------------------------|---|--|---|---|
| Brady et al., 2000 <sup>8</sup> | NR                         | HAM-D<br>Mean Change (SEM)<br>G1: -8.6 (1.3)<br>G2: -5.0 (1.2)<br>G1 vs. G2, p=0.04 | Q-LES-Q<br>Mean Change (SEM)<br>G1: 11.7 (2.1)<br>G2: 3.3 (16.7)<br>G1 vs. G2, p=0.004 | CAPS social functioning subscale<br>Mean Change (SEM)<br>G1 :-1.2 (0.11)<br>G2: -0.7 (0.11)<br>G1 vs. G2, p=0.001<br><br>CAPS occupational functioning subscale<br>Mean change(Endpoint – Baseline) (SEM)<br>G1 :-0.7 (0.10)<br>G2: -0.4 (0.10)<br>G1 vs. G2, p=0.001 | NR  |
| Brady et al., 2005 <sup>9</sup> | NR                         | HAM-D<br>ANOVA<br>No significant between-group differences (p>0.05)                 | NR   | NR  | NR  |

**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year                      | Comorbid Medical Condition | Comorbid Psychiatric Condition  | QOL | Disability/Functional Impairment   | Return to Work/Active Duty OR Ability to Work |
|-----------------------------------|----------------------------|---|-----|--|---|
| Bryant et al., 2003 <sup>10</sup> | NR                         | <p>STAI-State<br/>Mean (SD)<br/>G1 Pre-tx: 56.80 (11.22)<br/>G1 Post-tx: 43.10 (13.52)<br/>G1 6 mth FU: 42.85 (14.90)</p> <p>G2 Pre-tx: 54.60 (8.20)<br/>G2 Post-tx: 41.45 (14.77)<br/>G2 6 mth FU: 43.45 (11.85)</p> <p>G3 Pre-tx: 56.28 (11.12)<br/>G3 Post-tx: 51.50 (12.00)<br/>G3 6 mth FU: 53.33 (9.70)</p> <p>Post-tx, p&lt;0.01 (main effects)<br/>FU, p&lt;0.05 (main effect)</p> <p>BDI<br/>Mean (SD)<br/>G1 Pre-tx: 21.65 (11.18)<br/>G1 Post-tx: 17.45 (12.82)<br/>G1 6 mth FU: 16.15 (12.19)</p> <p>G2 Pre-tx: 23.15 (10.05)<br/>G2 Post-tx: 13.85 (14.31)<br/>G2 6 mth FU: 14.95 (13.99)</p> <p>G3 Pre-tx: 26.56 (11.15)<br/>G3 Post-tx: 23.78 (12.10)<br/>G3 6 mth FU: 25.33 (12.05)</p> <p>Post-tx, p&lt;0.01 (main</p> | NR  | <p>Good End State Functioning at Follow-up ( Being below specific cut-off scores for both PTSD and depression)<br/>G1: 15.0%<br/>G2: 40.0%<br/>G3: 0.0%</p> <p>G1 vs. G3, p&lt;0.01<br/>G1 vs. G2, p&lt;0.07</p> | NR  |

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effect)  
FU,  $p < 0.05$  (main effect)

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**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year                      | Comorbid Medical Condition | Comorbid Psychiatric Condition  | QOL | Disability/Functional Impairment | Return to Work/Active Duty OR Ability to Work |
|-----------------------------------|----------------------------|---|-----|----------------------------------|---|
| Bryant et al., 2008 <sup>11</sup> | NR                         | <p>STAI</p> <p>Mean (SD)</p> <p>G1 Pre-tx: 59.10 (15.08)</p> <p>G1 Post-tx: 50.71 (16.36)</p> <p>G1 6 mth FU: 56.19 (16.03)</p> <p>G2 Pre-tx: 58.25 (15.62)</p> <p>G2 Post-tx: 50.36 (18.68)</p> <p>G2 6 mth FU: 51.14 (17.88)</p> <p>G3 Pre-tx: 59.32 (12.75)</p> <p>G3 Post-tx: 48.87 (16.74)</p> <p>G3 6 mth FU: 54.84 (15.44)</p> <p>G4 Pre-tx: 56.93 (12.75)</p> <p>G4 Post-tx: 46.46 (17.21)</p> <p>G4 6 mth FU: 46.89 (24.54)</p> <p>Post-tx, NS (main effect)</p> <p>6 month FU, NS (main effect)</p> <p>BDI</p> <p>Mean (SD)</p> <p>G1 Pre-tx: 24.03 (10.81)</p> <p>G1 Post-tx: 21.31 (13.23)</p> <p>G1 6 mth FU: 20.58 (12.83)</p> <p>G2 Pre-tx: 25.38 (12.82)</p> <p>G2 Post-tx: 19.36 (11.28)</p> <p>G2 6 mth FU: 19.79 (12.43)</p> <p>G3 Pre-tx: 24.23 (11.38)</p> | NR  | NR                               | NR  |

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G3 Post-tx: 22.16 (15.44)  
G3 6 mth FU: 24.81  
(14.90)

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**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year                                     | Comorbid Medical Condition | Comorbid Psychiatric Condition  | QOL | Disability/Functional Impairment   | Return to Work/Active Duty OR Ability to Work |
|--|----------------------------|---|-----|--|---|
| Bryant et al., 2008 <sup>11</sup><br>(continued) |                            | G4 Pre-tx: 21.79 (10.25)<br>G4 Post-tx: 13.96 (12.05)<br>G4 6 mth FU: 13.54 (11.85) |     |  |   |
|  |                            | Post-tx, NS (main effect)<br>6 month FU, p<0.05 (main effect)                       |     |  |   |
| Butterfield et al., 2001 <sup>12</sup>           | NR                         | NR  | NR  | SDS<br>Mean (SD)<br>G1 Pre-tx: 19.8 (7.9)<br>G2 Post-tx: 12.1 (7.8)<br>Change: -7.7<br><br>G2 Pre-tx: 21.6 (7.2)<br>G2 Post-tx: 13.6 (8.7)<br>Change: -8.0 | NR  |
|  |                            |   |     | G1 vs. G2, no group X time differences found   |   |

**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year                       | Comorbid Medical Condition | Comorbid Psychiatric Condition  | QOL | Disability/Functional Impairment | Return to Work/Active Duty OR Ability to Work |
|------------------------------------|----------------------------|---|-----|----------------------------------|---|
| Carlson et al., 1998 <sup>13</sup> | NR                         | <p>BDI</p> <p>Mean (SD)</p> <p>G1 Pre-tx: 20.1 (7.5)</p> <p>G1 Post-tx: 6.9 (5.9)</p> <p>G1 3 mth FU: 8.6 (9.4)</p> <p>G1 9 mth FU:6.6 (5.9)</p> <p>G2 Pre-tx: 23.6 (10.8)</p> <p>G2 Post-tx: 15.8 (12.5)</p> <p>G2 3 mth FU: 18.3 (11.7)</p> <p>G2 9 mth FU:22.5 (12.1)</p> <p>G3 Pre-tx: 24.0 (9.9)</p> <p>G3 Post-tx: 23.5 (12.8)</p> <p>Post &amp; 3 mths</p> <p>Group X Time, <math>p &lt; 0.004</math></p> <p>G1 vs. G3, <math>p &lt; 0.01</math> (post)</p> <p>G1 vs. G2, NS (3 months)</p> <p>9 month FU</p> <p><math>p &lt; 0.00</math> (t-test)</p> <p>STAI-State</p> <p>G1 Pre-tx: 47.2 (9.4)</p> <p>G1 Post-tx: 34.9 (9.0)</p> <p>G1 3 mth FU:40.6 (4.9)</p> <p>G2 Pre-tx: 58.2 (12.2)</p> <p>G2 Post-tx: 46.3 (13.3)</p> <p>G2 3 mth FU:47.7</p> | NR  | NR                               | NR  |



**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year                                      | Comorbid Medical Condition | Comorbid Psychiatric Condition  | QOL | Disability/Functional Impairment | Return to Work/Active Duty OR Ability to Work |
|---|----------------------------|---|-----|----------------------------------|---|
| Carlson et al., 1998 <sup>13</sup><br>(continued) |                            | G3 Pre-tx: 58.2 (10.5)<br>G3 Post-tx: 51.4 (17.8)   |     |                                  |   |
|   |                            | Post-tx & 3 mths<br>Group X Time, NS<br>9 mo FU: DataNR   |     |                                  |   |
|   |                            | STAI-Trait<br>Mean (SD)<br>G1 Pre-tx: 54.0 (9.9)<br>G1 Post-tx: 38.6 (9.7)<br>G1 3 mth FU: 41.9 (6.9) |     |                                  |   |
|   |                            | G2 Pre-tx: 58.0 (9.1)<br>G2 Post-tx: 50.8 (10.7)<br>G2 3 mth FU: 51.8 (7.4)                           |     |                                  |   |
|   |                            | G3 Pre-tx: 61.7 (10.6)<br>G3 Post-tx: 55.8 (11.2)   |     |                                  |   |
|   |                            | Group X Time, p<0.06  |     |                                  |   |
|   |                            | Post-tx<br>G1 vs. G3, p<0.001<br>G1 vs G2, p<0.01   |     |                                  |   |
|   |                            | 3 month FU<br>G1 vs. G2, p<0.01   |     |                                  |   |

**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year                       | Comorbid Medical Condition | Comorbid Psychiatric Condition   | QOL | Disability/Functional Impairment  | Return to Work/Active Duty OR Ability to Work |
|------------------------------------|----------------------------|--|-----|---|---|
| Chard et al., 2005 <sup>14</sup>   | NR                         | BDI-II<br>Mean (SD)<br>G1 Pre-tx: 24.43 (10.81)<br>G1 Post-tx: 3.26 (4.75)<br><br>G2 Pre-tx: 24.52 (11.55)<br>G2 Post-tx: 22.41 (12.57)  | NR  | NR  | NR  |
| Cloitre et al., 2002 <sup>15</sup> | NR                         | p<0.001<br>BDI<br>Mean (SD)<br>G1 Pre-tx:25 (10.6)<br>G1 Post-tx: 8 (7.8)<br><br>G2 Pre-tx:23 (9.0)<br>G2 Post-tx: 22 (11.4)<br><br>p<0.01 (interaction)<br><br>STAI-S<br>Mean (SD)<br>G1 Pre-tx:57 (9.6)<br>G1 Post-tx: 36 (8.6)<br><br>G2 Pre-tx: 53 (15.6)<br>G2 Post-tx: 55 (14.9)<br><br>p<0.01 (interaction) | NR  | SAS-SR<br>Mean (SD)<br>G1 Per-tx:2.44(0.29)<br>G1 Post-tx:2.06 (0.40)<br><br>G2 Pre-tx:2.57 (0.42)<br>G2 Post-tx: 2.47 (0.53)<br><br>p=0.02 (interaction) | NR  |

**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year               | Comorbid Medical Condition | Comorbid Psychiatric Condition  | QOL | Disability/Functional Impairment | Return to Work/Active Duty OR Ability to Work |
|----------------------------|----------------------------|---|-----|----------------------------------|---|
| Cloitre et al., 2010<br>16 | NR                         | <p>STAI</p> <p>Mean (SD)</p> <p>G1 Pre-tx:50.4 (9.41)</p> <p>G1 Post-tx:39.2 (9.92)</p> <p>G1 3 mth FU:38.8 (9.90)</p> <p>G1 6 mth FU:37.4 (10.72)</p> <p>G2 Pre-tx: 48.2 (12.45)</p> <p>G2 Post-tx: 42.9 (12.34)</p> <p>G2 3 mth FU: 41.8 (13.53)</p> <p>G2 6 mth FU:42.4 (12.66)</p> <p>G3 Pre-tx: 50.2 (10.85)</p> <p>G3 Post-tx:41.1 (12.13)</p> <p>G3 3 mth FU:51.8 (11.16)</p> <p>G3 6 mth FU: 47.5 (12.66)</p> <p>p&lt;0.003 (interaction)</p> <p>3 mth FU</p> <p>G1 vs. G3, p&lt;0.001</p> <p>6 mth FU</p> <p>G1 vs. G3, p&lt;0.003</p> <p>BDI</p> <p>Mean (SD)</p> <p>G1 Pre-tx: 18.8 (10.01)</p> <p>G1 Post-tx: 8.9 (7.64)</p> <p>G1 3 mth FU: 9.8 (9.96)</p> <p>G1 6 mth FU: 7.9 (10.77)</p> <p>G2 Pre-tx: 21.1 (8.80)</p> <p>G2 Post-tx: 11.9 (8.54)</p> <p>G2 3 mth FU: 12.0 (8.75)</p> <p>G2 6 mth FU: 13.4 (8.84)</p> <p>G3 Pre-tx: 22.1 (10.60)</p> <p>G3 Post-tx: 12.9 (9.41)</p> <p>G3 3 mth FU: 14.2 (10.09)</p> <p>G3 6 mth FU: 13.6 (9.12)</p> | NR  | NR                               | NR  |

**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year  | Comorbid Medical Condition | Comorbid Psychiatric Condition  | QOL   | Disability/Functional Impairment   | Return to Work/Active Duty OR Ability to Work |
|---|----------------------------|---|---|--|---|
| Cloitre et al., 2010 <sup>16</sup><br>(continued)                             |                            | No treatment or interaction effects obtained for BDI  |   |  |   |
| Connor et al., 1999 <sup>17</sup><br>Meltzer-Brody et al., 2000 <sup>18</sup> | NR                         | NR  | NR  | SDS<br>Week 12 difference (Baseline - Endpoint)(95% CI)<br>G1 vs. G2 Difference: 6.2 (1.4 to 11.0), p<0.05<br><br>CHEF criterion of response<br>Week 12 difference (Baseline - Endpoint)(95% CI)<br>G1 vs. G2 Difference: 0.37 (0.17 to 0.57), p<0.001 | NR  |
| Cook et al., 2010 <sup>19</sup>   | NR                         | BDI<br>Mean (SD)<br>G1 Pre-tx: 26.85 (11.82)<br>G1 at 1 mth: 24.16 (13.35)<br>G1 at 3 mths: 24.80 (13.14)<br>G1 at 6 mths: 25.02 (13.30)<br><br>G2 Pre-tx: 23.51 (11.92)<br>G2 at 1 month: 22.31 (12.76)<br>G2 at 3 mths:23.76 (12.76)<br>G2 at 6 mths: 23.37 (12.34)<br>Interactions, NS | SF-36 Mental<br>Mean (SD)<br>G1 Pre-tx:29.69 (9.08)<br>G1 at 1 mth:32.33 (10.63)<br>G1 at 3 mths: 30.98 (9.33)<br>G1 at 6 mths:32.15 (8.99)<br><br>G2 Pre-tx:34.52 (12.06)<br>G2 at 1 mth:32.84 (9.75)<br>G2 at 3mths: 34.00 (10.35)<br>G2 at 6 mths: 34.78 (10.87)<br>Interactions, NS |  | NR  |

**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year                                   | Comorbid Medical Condition | Comorbid Psychiatric Condition   | QOL  | Disability/Functional Impairment  | Return to Work/Active Duty OR Ability to Work |
|--|----------------------------|--|--|---|---|
| Cook et al., 2010 <sup>19</sup><br>(continued) |                            |  | SF-36 Physical Component<br>Mean (SD)<br>G1 Pre-tx: 37.17 (9.21)<br>G1 1 mth:39.48 (10.19)<br>G1 at 3 mths: 37.72 (9.57)<br>G1 at 6mths: 35.80 (9.64)<br><br>G2 Pre-tx: 38.53 (9.64)<br>G2 Post-tx:36.84 (10.34)<br>G2 at 3 mths: 35.96 (11.97)<br>G2 at 6 mths: 37.21 (11.23)<br>Interactions, NS |   |   |
| Cotraux, 2008 <sup>20</sup>                    | NR                         | HAM-A<br>Post-tx (ITT analysis)<br>G1 Mean Change from Baseline (SD): -11 (9)<br>G2 Mean Change from Baseline (SD): -5.7 (8)<br>Group effect, p=0.028<br>Interaction, p=NS | Marks' Quality of Life Scale<br>ITT analysis = NR<br><br>Post-tx (completer analysis)<br>G1 Mean Change from Baseline (SD): -6.66 (8.13)<br>G2 Mean Change from Baseline (SD): -9.60 (7.98)<br>p=0.26  | Fear Questionnaire, Global Phobic Disability Subscale:<br>ITT analysis = NR<br><br>Post-tx (completer analysis) POST-TREATMENT<br>G1 Mean Change from Baseline (SD): -2.14 (2.75)<br>G2 Mean Change from Baseline (SDI): -2.00 (2.69)<br>p=0.86 | NR  |

**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year                                | Comorbid Medical Condition | Comorbid Psychiatric Condition  | QOL  | Disability/Functional Impairment   | Return to Work/Active Duty OR Ability to Work |
|---|----------------------------|---|--|--|---|
| Cottraux, 2008 <sup>20</sup><br>(continued) |                            | <p>52 Weeks<br/>G1 Mean Change from Baseline (sd): -10.04 (11.18),<br/>G2 Mean Change from Baseline (sd): -8.79 (10.15),<br/>Interaction, p=0.73</p> <p>104 Weeks<br/>G1 Mean Change from Baseline (sd): -12.56 (11.29), p=NR<br/>G2 Mean Change from Baseline (sd): -17.00 (7.19), p=NR<br/>Interaction, p=0.30</p> <p>Depression, BDI short form<br/>ITT = NR</p> <p>Completer Analysis (Post-tx):<br/>G1 Mean Change from Baseline (sd): -5.44 (6.15)</p> <p>G2 Mean Change from Baseline (sd): -4.66 (6.95),<br/>Interaction, p=0.70</p> <p>52 WEEKS<br/>G1 Mean Change from Baseline (sd): -4.33(5.65),<br/>G2 Mean Change from Baseline (sd): -4.07</p> | <p>52 Weeks<br/>G1 Mean Change from Baseline (SD): -9.42 (9.36), p=NR<br/>G2 Mean Change from Baseline (SD): -7.64 (9.12), p=NR<br/>Interaction, p=0.57</p> <p>104 Weeks<br/>G1 Mean Change from Baseline (SD): -10.00 (7.65), p=NR<br/>G2 Mean Change from Baseline (SD): -12.66 (8.23), p=NR<br/>Interaction, p=0.42</p> | <p>52 Weeks<br/>G1 Mean Change from Baseline (SD): -2.54 (2.90), p=NR<br/>G2 Mean Change from Baseline (SDI): -1.00 (2.48), p=NR<br/>Interaction, p=0.11</p> <p>104 Weeks<br/>G1 Mean Change from Baseline (SD): -3.52 (2.79), p=NR<br/>G2 Mean Change from Baseline (SDI): -2.33 (2.82), p=NR<br/>Interaction, p=0.44</p> |   |

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(5.80),  
Interaction,  $p=0.89$

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**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year                                | Comorbid Medical Condition | Comorbid Psychiatric Condition  | QOL | Disability/Functional Impairment | Return to Work/Active Duty OR Ability to Work |
|---|----------------------------|---|-----|----------------------------------|---|
| Cottraux, 2008 <sup>20</sup><br>(continued) |                            | 104 WEEKS:<br>G1 Mean Change from Baseline (sd): -5.87 (6.66), p=NR<br>G2 Mean Change from Baseline: -6.22 (5.84), p=NR<br>Interaction, p=0.89  |     |                                  |   |
| Davidson et al., 2001 <sup>21</sup>         | NR                         | HAM-D<br>Change from Baseline to Endpoint (SD)<br>G1: -7.7 (1.0)<br>G2: -6.3 (1.0)<br>p=0.33 (t-test)<br><br>HAM-A<br>Change from Baseline to Endpoint (SD)<br>G1: -7.8 (0.8)<br>G2: -6.4 (0.9)<br>p=0.26 (t-test)  | NR  | NR                               | NR  |
| Davidson et al., 2003 <sup>22</sup>         | NR                         | HADS-D<br>Mean (SD)<br>G1 Pre-tx: 10.2 (6.1)<br>G1 Post-tx: 8.0 (6.0)<br><br>G2 Pre-tx: 13.5 (4.3)<br>G2 Post-tx: 13.0 (3.7)<br><br>Treatment effect, p=0.08<br><br>HADS-A<br>G1 Pre-tx: 11.8 (5.0)<br>G1 Post-tx: 9.0 (5.8)<br><br>G2 Pre-tx: 15.0 (3.3)<br>G2 Post-tx: 13.8 (3.7)<br><br>Treatment effect, p<0.05 | NR  | NR                               | NR  |



**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year                        | Comorbid Medical Condition | Comorbid Psychiatric Condition  | QOL  | Disability/Functional Impairment  | Return to Work/Active Duty OR Ability to Work |
|-------------------------------------|----------------------------|---|--|---|---|
| Davidson et al., 2006 <sup>23</sup> | NR                         | HAM-D<br>Mean Within-group difference (95% CI)<br>G1: -7.09(-8.13 to -6.05)<br>G2: -6.42 (-7.48 to - 5.37)<br>G3: -5.54 (-6.58 to -4.50)<br><br>Between group p-values based on pairwise comparisons from the analysis of variance model using baseline adjusted values<br>G1 vs. G3: 0.039<br>G2 vs. G3: 0.244<br>G1 vs. G2: 0.379 | Q-LES-Q-SF<br>Mean Within-group difference (95% CI)<br>G1: 11.54 (9.73 to 13.35)<br>G2: 11.17 (9.30 to 13.04)<br>G3: 8.75 (6.94 to 10.56)<br><br>Between group p-values based on pairwise comparisons from the analysis of covariance model using baseline adjusted values<br>G1 vs. G3: 0.033<br>G2 vs. G3: 0.068<br>G1 vs. G2: 0.782 | GAF<br>Mean Within-group difference (95% CI)<br>G1: 14.16(12.16 to 16.16)<br>G2: 13.63 (11.57 to 15.70)<br>G3: 11.41 (9.32 to 13.49)<br><br>Between group p-values based on pairwise comparisons from the analysis of covariance model using baseline adjusted values<br>G1 vs. G3: 0.062<br>G2 vs. G3: 0.136<br>G1 vs. G2: 0.720<br><br>SDS<br>Mean Within-group difference (95% CI)<br>G1: -8.54 (-9.78 to -7.29)<br>G2:-8.17 (-9.43 to -6.90)<br>G3: -6.52 (-7.76 to -5.29)<br><br>Between group p-values based on pairwise comparisons from the analysis of covariance model using baseline adjusted values<br>G1 vs. G3: 0.025<br>G2 vs. G3: 0.068<br>G1 vs. G2: 0.683 | NR  |

**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year                        | Comorbid Medical Condition | Comorbid Psychiatric Condition  | QOL   | Disability/Functional Impairment  | Return to Work/Active Duty OR Ability to Work |
|-------------------------------------|----------------------------|---|---|---|---|
| Davidson et al., 2006 <sup>24</sup> |                            | HAM-D<br>Between Group Mean Difference<br>-1.4, p=0.007   | Q-LES-Q-SF<br>Between Group Mean Difference<br>3.7, p=0.007 | SDS<br>Between Group Mean Difference<br>-2.0, p=0.03<br><br>GAF<br>Between Group Mean Difference<br>3.3, p=0.03 |   |
| Davidson et al., 2007 <sup>25</sup> | NR                         | NR  | NR  | SDS<br>Change from baseline (SD)<br>G1: -5.5 (7.0)<br>G2: -5.9 (7.7)<br>p=0.74                                  | NR  |
| Davis et al., 2008 <sup>26</sup>    | NR                         | MADRS<br>Mean (SD)<br>G1 Pre-tx: 27.3 (8.5)<br>G1 Post-tx :22.2 (10.6)<br><br>G2 Pre-tx: 28.5 (7.1)<br>G2 Post-tx: 24.0 (10.3)<br><br>Diff b/t groups, p=NS<br><br>HAM-A<br>Mean (SD)<br>G1 Pre-tx:24.1 (10.1)<br>G1 Post-tx:19.4 (9.1)<br><br>G2 Pre-tx: 22.8 (8.5)<br>G2 Post-tx: :20.1 (10.7)<br><br>Diff b/t groups, p=NS | NR  | NR  | NR  |

**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year                      | Comorbid Medical Condition | Comorbid Psychiatric Condition  | QOL | Disability/Functional Impairment  | Return to Work/Active Duty OR Ability to Work |
|-----------------------------------|----------------------------|---|-----|---|---|
| Ehlers et al., 2003 <sup>27</sup> | NR                         | <p>BDI</p> <p>Mean (SD)</p> <p>G1 Pre-tx: 18.8 (6.7)</p> <p>G1 3 mth FU: 7.3 (6.3)</p> <p>G1 9 mth FU: 6.5(7.0)</p><br><p>G2 Pre-tx: 22.9 (9.2)</p> <p>G2 3 mth FU: 16.1 (6.6)</p> <p>G2 9 mth FU : 15.2 (6.9)</p><br><p>G3 Pre-tx: 22.7 (8.9)</p> <p>G3 3 mth FU: 17.1 (9.6)</p> <p>G3 9 mth FU : 12.0 (10.0)</p><br><p>3 mth FU</p> <p>Overall: p&lt;0.001</p> <p>G1 vs. G2, p&lt;0.001</p> <p>G1 vs. G3, p&lt;0.001</p><br><p>9 mth FU</p> <p>Overall: p&lt;0.001</p> <p>G1 vs. G2, p&lt;0.001</p> <p>G1 vs. G3, p=0.02</p><br><p>BAI</p> <p>Mean (SD)</p> <p>G1 Pre-tx: 21.6 (7.9)</p> <p>G1 3 mth FU: 6.0 (5.8)</p> <p>G1 9 mth FU: 5.8 (4.9)</p><br><p>G2 Pre-tx: 22.2 (9.9)</p> <p>G2 3 mth FU: 14.2 (8.9)</p> <p>G2 9 mth FU: 14.0 (8.6)</p><br><p>G3 Pre-tx: 24.4 (7.4)</p> <p>G3 3 mth FU: 15.7 (10.4)</p> <p>G3 9 mth FU: 12.6 (8.6)</p> | NR  | <p>SDS</p> <p>Mean (SD)</p> <p>G1 Pre-tx: 5.9 (2.4)</p> <p>G1 3 mth FU: 2.3 (2.8)</p> <p>G1 9 mth FU: 1.8 (2.5)</p><br><p>G2 Pre-tx: 6.3 (2.0)</p> <p>G2 3 mth FU: 4.3 (2.5)</p> <p>G2 9 mth FU: 3.7 (2.2)</p><br><p>G3 Pre-tx: 6.1 (1.9)</p> <p>G3 3 mth FU: 4.2 (1.9)</p> <p>G3 9 mth FU: 3.2 (2.7)</p><br><p>3 mth FU</p> <p>Overall: p&lt;0.001</p> <p>G1 vs.G2, p=0.001</p> <p>G1 vs. G3, p&lt;0.001</p><br><p>9 mth FU</p> <p>Overall: p=0.003</p> <p>G1 vs. G2, p=0.001</p> <p>G1 vs. G3, p= 0.007</p> | NR  |

**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year                                     | Comorbid Medical Condition | Comorbid Psychiatric Condition  | QOL | Disability/Functional Impairment  | Return to Work/Active Duty OR Ability to Work |
|--|----------------------------|---|-----|---|---|
| Ehlers et al., 2003 <sup>27</sup><br>(continued) |                            | 3 mth FU<br>Overall: p<0.001<br>G1 v.s G2: p<0.001<br>G1 vs. G3: p<0.001<br><br>9 mth FU<br>Overall: p<0.001<br>G1 vs. G2, p<0.001<br>G1 vs. G3, p<0.001  |     |   |   |
| Ehlers et al., 2005 <sup>28</sup>                | NR                         | BDI<br>Mean (SD)<br>G1 Pre-tx: 23.7 (9.0)<br>G1 Post-tx: 10.6 (8.6)<br>G1 6 mth FU: 11.2 (9.6)<br><br>G2 Pre-tx: 23.2 (8.0)<br>G2 Post-tx: 19.3 (7.2)<br><br>G1 vs. G2, p=0.003<br>G1 Changes, p<0.0005<br>G2 Changes, p=0.025<br><br>BAI<br>Mean (SD)<br>G1 Pre-tx: 24.1 (11.1)<br>G1 Post-tx: 8.2 (10.8)<br>G1 6 mth FU: 7.5 (9.7)<br><br>G2 Pre-tx: 19.2 (7.2)<br>G2 Post-tx: 21.2 (11.2)<br><br>G1 vs. G2, p<0.0005<br>G1 Changes, p<0.0005<br>G2 Changes, NS | NR  | SDS<br>Mean (SD)<br>G1 Pre-tx: 7.6 (1.9)<br>G1 Post-tx: 3.0 (2.6)<br>G1 6 mth FU: 3.0 (2.6)<br><br>G2 Pre-tx: 6.7 (1.9)<br>G2 Post-tx: 6.3 (1.8)<br><br>G1 vs. G2, p<0.0005<br>G1 Changes, p<0.0005<br>G2 Changes, NS | NR  |

**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year                       | Comorbid Medical Condition | Comorbid Psychiatric Condition  | QOL | Disability/Functional Impairment | Return to Work/Active Duty OR Ability to Work |
|------------------------------------|----------------------------|---|-----|----------------------------------|---|
| Fecteau et al., 1999 <sup>29</sup> | NR                         | <p>BAI</p> <p>Mean (SD)</p> <p>G1 Pre-tx: 30.6 (7.4)</p> <p>G1 Post-tx: 15.8 (13.8)</p><br><p>G2 Pre-tx: 34.8 (15.8)</p> <p>G2 Post-tx: 32.0 (13.3)</p><br><p>Group effect, p-value &lt;0.05</p><br><p>Follow up for G1 Only</p> <p>BAI</p> <p>G1 Pre-tx: 30.6 (7.4)</p> <p>G1 Post-tx: 15.8 (13.8)</p> <p>G1 3 mth FU: 16.9 (13.8)</p> <p>G1 6 mth FU: 16.8 (11.8)</p><br><p>Change at 3 mths, p&lt;0.05 (n = 10)</p> <p>Change at 6 mths, p&lt;0.01 (n = 8)</p><br><p>BDI</p> <p>Mean (SD)</p> <p>G1 Pre-tx: 26.3 (9.8)</p> <p>G1 Post-tx: 20.1 (17.1)</p><br><p>G2 Pre-tx: 27.9 (10.5)</p> <p>G2 Post-tx: 24.7 (8.1)</p><br><p>Group effect, NS</p><br><p>Follow up for G1 Only</p> <p>BDI</p> | NR  | NR                               | NR  |

**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year  | Comorbid Medical Condition | Comorbid Psychiatric Condition   | QOL | Disability/Functional Impairment   | Return to Work/Active Duty OR Ability to Work |
|---|----------------------------|--|-----|--|---|
| Fecteau et al., 1999 <sup>29</sup><br>(continued)                     |                            | G1 Pre-tx: 26.3 (9.8)<br>G1 Post-tx: 20.1 (17.1)<br>G1 3 mth FU: 19.6 (15.6)<br>G1 6 mth FU: 15.9 (11.0)**<br>Change at 3 mths, NS (n = 10)<br>Change at 6 mths, NS (n = 8)  |     |  |   |
| Foa et al., 1999 <sup>30</sup><br>Zoellner et al., 1999 <sup>31</sup> | NR                         | BDI<br>Mean (SD)<br>G1 Pre-tx: 17.58 (11.29)<br>G1 Post-tx: 5.75 (4.77)<br>G1 3 mth FU: 8.02 (6.77)<br>G1 6 mth FU: 6.85 (5.61)<br>G1 12 mth FU: 6.15 (7.73)<br><br>G2 Pre-tx: 21.73 (11.02)<br>G2 Post-tx: 10.05 (8.06)<br>G2 3 mth FU: 14.58 (12.16)<br>G2 6 mth FU: 13.54 (12.51)<br>G2 12 mth FU: 11.92 (14.48)<br><br>G3 Pre-tx: 21.36 (10.51)<br>G3 Post-tx: 10.49 (9.90)<br>G3 3 mth FU: 13.65 (10.53)<br>G3 6 mth FU: 10.00 (9.46)<br>G3 12 mth FU: 11.88 (9.92)<br><br>G4 Pre-tx: 25.21 (11.20)<br>G4 Post-tx: 22.10 (14.97)<br><br>Main Effect, p<0.01 | NR  | Social Adjustment Scale - Global<br>Mean (SD)<br>G1 Pre-tx: 3.73 (0.83)<br>G1 Post-tx: 2.45 (0.60)<br>G1 3 mth FU: 2.58 (0.69)<br>G1 6 mth FU: 2.33 (0.84)<br>G1 12 mth FU: 2.69 (0.87)<br><br>G2 Pre-tx: 3.79 (1.23)<br>G2 Post-tx: 2.68 (1.00)<br>G2 3 mth FU: 3.00 (1.37)<br>G2 6 mth FU: 2.83 (1.10)<br>G2 12 mth FU: 3.00 (1.30)<br><br>G3 Pre-tx: 4.00 (1.11)<br>G3 Post-tx: 2.95 (1.33)<br>G3 3 mth FU: 3.37 (1.46)<br>G3 6 mth FU: 2.94 (1.55)<br>G3 12 mth FU: 3.13 (2.03)<br><br>G4 Pre-tx: 3.93 (1.16)<br>G4 Post-tx: 3.73 (1.10)<br><br>Treatment Effect, p<0.05<br>G1 vs. G4, p<0.01<br>G2 vs. G4, p=0.08<br>G3 vs. G4, p=0.09<br>Active treatments did not differ from one another, p=0.14 | NR  |

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G1 vs. G4,  $p < 0.001$

G2 vs. G4,  $p < 0.05$

G3 vs. G4,  $p < 0.05$

G1 vs. G3,  $p < 0.025$

G1 vs. G2,  $p = 0.06$

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**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year  | Comorbid Medical Condition | Comorbid Psychiatric Condition  | QOL | Disability/Functional Impairment | Return to Work/Active Duty OR Ability to Work |
|---|----------------------------|---|-----|----------------------------------|---|
| Foa et al., 1999 <sup>30</sup><br>Zoellner et al.,<br>1999 <sup>31</sup><br>(continued) |                            | STAI-State<br>Mean (SD)<br>G1 Pre-tx: 49.95 (13.70)<br>G1 Post-tx: 32.43 (10.93)<br>G1 3 mth FU: 37.16<br>(11.80)<br>G1 6 mth FU: 34.95<br>(11.45)<br>G1 12 mth FU: 34.84<br>(12.43)<br><br>G2 Pre-tx: 51.50 (13.37)<br>G2 Post-tx: 39.07 (11.55)<br>G2 3 mth FU: 41.26<br>(14.02)<br>G2 6 mth FU: 43.33<br>(17.01)<br>G2 12 mth FU: 42.46<br>(16.98)<br><br>G3 Pre-tx: 50.66 (15.37)<br>G3 Post-tx: 40.55 (15.41)<br>G3 3 mth FU: 43.74<br>(15.27)<br>G3 6 mth FU: 41.12<br>(14.77)<br>G3 12 mth FU: 38.75<br>(13.29)<br><br>G4 Pre-tx: 51.44 (12.60)<br>G4 Post-tx: 50.40 (13.80)<br><br>Main Effect, p<0.01<br>G1 vs. G4, p<0.001<br>G2 vs. G4, p=0.11<br>G3 vs. G4, p=0.14<br><br>G2 vs. G3, NS<br>G1 vs. G2, p<0.025 |     |                                  |   |



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G1 vs. G3,  $p < 0.01$

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**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year                   | Comorbid Medical Condition | Comorbid Psychiatric Condition   | QOL | Disability/Functional Impairment   | Return to Work/Active Duty OR Ability to Work |
|--------------------------------|----------------------------|--|-----|--|---|
| Foa et al., 2005 <sup>32</sup> | NR                         | BDI<br>Mean (SD)<br>G1 Pre-tx: 26.1 (9.9)<br>G1 Post-tx: 14.6 (13.8)<br><br>G2 Pre-tx: 23.4 (9.3)<br>G2 Post-tx: 13.8 (12.9)<br><br>G3 Pre-tx: 23.6 (10.3)<br>G3 Post-tx: 21.0 (10.7)<br><br>Group X Time interaction,<br>p<0.001<br>G1 vs. G3, p<0.05<br>G2 vs. G3, p<0.05<br>G1 vs. G2, ns | NR  | Social Adjustment Scale - Work<br>Mean (SD)<br>G1 Pre-tx: 3.4 (1.2)<br>G1 Post-tx: 2.8 (1.4)<br><br>G2 Pre-tx: 3.2 (1.2)<br>G2 Post-tx: 2.7 (1.4)<br><br>G3 Pre-tx: 3.4 (1.5)<br>G3 Post-tx: 3.5 (1.3)<br><br>Group X Time interaction,<br>p=0.059<br><br>Social Adjustment Scale-Social<br>Mean (SD)<br>G1 Pre-tx: 4.1 (1.0)<br>G1 Post-tx: 3.5 (1.3)<br><br>G2 Pre-tx: 4.0 (1.0)<br>G2 Post-tx: 3.3 (1.2)<br><br>G3 Pre-tx: 4.0 (1.2)<br>G3 Post-tx: 3.8 (1.1)<br><br>Group X Time interaction, ns | NR  |

**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year                      | Comorbid Medical Condition | Comorbid Psychiatric Condition   | QOL   | Disability/Functional Impairment | Return to Work/Active Duty OR Ability to Work |
|-----------------------------------|----------------------------|--|---|----------------------------------|---|
| Forbes et al., 2012 <sup>33</sup> | NR                         | BDI-II<br>Mean (SD)<br>G1 Pre-tx: 26.33 (11.38)<br>G1 Post-tx:15.91 (11.97)<br>G1 FU: 14.77 (12.86)<br><br>G2 Pre-tx: 24.78 (11.99)<br>G2 Post-tx: 20.83 (11.83)<br>G2 FU: 19.11 (10.15)<br><br>Change over time<br>Post-tx, p=0.054<br>FU, p=0.785<br><br>STAI-Trait<br>Mean (SD)<br>G1 Pre-tx: 59.97 (13.52)<br>G1 Post-tx: 44.59 (13.12)<br>G1 FU: 43.59 (11.49)<br><br>G2 Pre-tx: 50.29 (9.94)<br>G2 Post-tx: 48.31 (12.75)<br>G2 FU: 47.26 (16.17)<br><br>Change over time<br>Post-tx, p=0.018<br>FU, p=0.917 | Abbreviated Dyadic Adjustment Scale (ADAS)<br>Mean (SD)<br>G1 Pre-tx: 25.84 (6.95)<br>G1 Post-tx:27.41 (7.72)<br>G1 FU: 25.81 (6.80)<br><br>G2 Pre-tx: 28.73 (5.13)<br>G2 Post-tx:26.15 (6.34)<br>G2 FU: 27.98 (6.98)<br><br>Change over time<br>Post-tx, p=0.014<br>FU, p=0.025<br><br>World Health Organization Quality of Life Scale (WHO-QOL)<br>WHOQOL-Physical<br>Mean (SD)<br>G1 Pre-tx: 19.68 (5.23)<br>G1 Post-tx:21.23 (5.00)<br>G1 FU:19.81 (5.38)<br><br>G2 Pre-tx: 20.73 (4.69)<br>G2 Post-tx:22.20 (4.90)<br>G2 FU:20.39 (4.70) | NR                               | NR  |

**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year                                     | Comorbid Medical Condition | Comorbid Psychiatric Condition | QOL  | Disability/Functional Impairment | Return to Work/Active Duty OR Ability to Work |
|--|----------------------------|--------------------------------|--|----------------------------------|---|
| Forbes et al., 2012 <sup>33</sup><br>(continued) |                            |                                | Change over time<br>Post-tx, p=0.911<br>FU, p=0.453  |                                  |   |
|  |                            |                                | WHOQOL-<br>Psychological<br>Mean (SD)<br>G1 Pre-tx: 15.70<br>(4.34)<br>G1 Post-tx:18.22<br>(4.59)<br>G1 FU: 18.40 (4.66) |                                  |   |
|  |                            |                                | G2 Pre-tx: 15.54<br>(3.56)<br>G2 Post-tx: 16.23<br>(4.27)  |                                  |   |
|  |                            |                                | G2 FU: 16.35 (4.88)  |                                  |   |
|  |                            |                                | Change over time<br>Post-tx, p=0.093<br>FU, p=0.955  |                                  |   |
|  |                            |                                | WHOQOL-Social<br>Mean (SD)<br>G1 Pre-tx: 7.77<br>(2.78)<br>G1 Post-tx: 8.43<br>(3.36)<br>G1 FU: 8.97 (3.12)              |                                  |   |
|  |                            |                                | G2 Pre-tx: 8.46<br>(2.83)<br>G2 Post-tx: 8.29<br>(2.20)  |                                  |   |
|  |                            |                                | G2 FU: 8.00 (2.38)   |                                  |   |

**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year                                     | Comorbid Medical Condition | Comorbid Psychiatric Condition | QOL   | Disability/Functional Impairment | Return to Work/Active Duty OR Ability to Work |
|--|----------------------------|--------------------------------|---|----------------------------------|---|
| Forbes et al., 2012 <sup>33</sup><br>(continued) |                            |                                | Change over time<br>Post-tx, p=0.152<br>FU, p=0.197                 |                                  |   |
|  |                            |                                | WHOQOL-<br>Environmental<br>Mean (SD)<br>G1 Pre-tx: 27.50<br>(4.53) |                                  |   |
|  |                            |                                | G1 Post-tx: 28.73<br>(3.97)   |                                  |   |
|  |                            |                                | G1 FU: 28.16 (4.29)<br>G2 Pre-tx: 29.07<br>(4.80)                   |                                  |   |
|  |                            |                                | G2 Post-tx:28.40<br>(4.89)  |                                  |   |
|  |                            |                                | G2 FU: 28.14 (5.51)   |                                  |   |
|  |                            |                                | Change over time<br>Post-tx, p=0.016<br>FU, p=0.738                 |                                  |   |

**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year                        | Comorbid Medical Condition | Comorbid Psychiatric Condition  | QOL | Disability/Functional Impairment | Return to Work/Active Duty OR Ability to Work |
|-------------------------------------|----------------------------|---|-----|----------------------------------|---|
| Ford et al., 2011 <sup>34</sup>     | NR                         | BDI<br>Mean (SD)<br>G1 Pre-tx: 16.0 (10.8)<br>G1 Post-tx: 11.6 (10.9)<br><br>G2 Pre-tx: 17.8 (10.2)<br>G2 Post-tx: 11.9 (10.1)<br><br>G3 Pre-tx: 17.8 (10.2)<br>G3 Post-tx: 11.9 (10.1)<br><br>Group X Time Effect,<br>p<0.01<br><br>STAI<br>Mean (SD)<br>G1 Pre-tx: 38.1 (13.0)<br>G1 Post-tx: 31.4 (11.3)<br><br>G2 Pre-tx: 41.6 (13.0)<br>G2 Post-tx: 37.4 (13.3)<br><br>G3 Pre-tx: 43.0 (10.9)<br>G3 Post-tx: 42.6 (12.9)<br><br>Group X Time Effect,<br>p=0.19 | NR  | NR                               | NR  |
| Friedman et al., 2007 <sup>35</sup> | NR                         | HAM-A<br>Change at Endpoint (SE)<br>G1: -4.1 (1.0)<br>G2: -6.1 (1.1)<br>Between Group Differences, NS<br><br>HAM-D<br>Change at Endpoint (SE)<br>G1: -2.7 (1.1)<br>G2: -4.2 (1.1)<br>Between Group  | NR  | NR                               | NR  |

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Differences, NS

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**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year                       | Comorbid Medical Condition | Comorbid Psychiatric Condition  | QOL | Disability/Functional Impairment | Return to Work/Active Duty OR Ability to Work  |
|------------------------------------|----------------------------|---|-----|----------------------------------|--|
| Gamito et al., 2010 <sup>36</sup>  | NR                         | BDI<br>Mean (SD)<br>G1 Pre-tx: 24.25 (9.46)<br>G1 Post-tx.: 14.25 (7.67)<br>p=0.003<br><br>SCL-90-R<br>(Psychopathology)<br>Depression<br>G1 Change, p=0.011<br><br>Somatization<br>G1 Change, p<0.01<br><br>Anxiety<br>G1 Change, p<0.05   | NR  | NR                               | NR   |
| Gersons et al., 2000 <sup>37</sup> | NR                         | Symptom Checklist-90-<br>Phobic Anxiety Subscale<br>Mean (SD)<br>G1 Pre-tx: 21.1 (7.3)<br>G1 Post-tx: 13.4 (5.6)<br>G1 3 mth FU: 13.8 (4.6)<br><br>G2 Pre-tx: 22.1 (11.0)<br>G2 Post-tx: 17.8 (7.4)<br>G2 3 mth FU: 21.1 (7.6)<br><br>Post-tx G1 vs. G2,<br>p<0.01<br>3-mth FU G1 vs. G2,<br>p<0.05<br><br>Symptom Checklist-90-<br>Anxiety Subscale<br>Mean (SD)<br>G1 Pre-tx: 10.1 (3.1)<br>G1 Post-tx: 7.7 (1.6)<br>G1 3 mth FU: 7.6 (0.9) | NR  | NR                               | Proportions by<br>Treatment (% , p<br>values)<br><br>Resumption of<br>Polic work<br>Pre-tx<br>G1: 18%<br>G2: 25%<br>NS<br>Post-tx<br>G1: 77%<br>G2: 70%<br>NS<br>3-month Follow-<br>up<br>G1: 86%<br>G2: 60%<br>p<0.05 |



**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year                                      | Comorbid Medical Condition | Comorbid Psychiatric Condition   | QOL | Disability/Functional Impairment | Return to Work/Active Duty OR Ability to Work |
|---|----------------------------|--|-----|----------------------------------|---|
| Gersons et al., 2000 <sup>37</sup><br>(continued) |                            | <p>G2 Pre-tx: 14.4 (4.7)<br/>G2 Post-tx: 9.8 (3.7)<br/>G2 3 mth FU: 9.8 (3.7)</p> <p>Post-tx G1 vs. G2,<br/>p&lt;0.01<br/>3 mth FU G1 vs. G2,<br/>p&lt;0.05</p> <p>Symptom Checklist-90-<br/>Depression Subscale<br/>Mean (SD)<br/>G1 Pre-tx: 35.1 (14.6)<br/>G1 Post-tx: 21.0 (7.4)<br/>G1 3 mth FU: 21.6 (8.5)</p> <p>G2 Pre-tx: 34.9 (13.0)<br/>G2 Post-tx: 28.5 (9.6)<br/>G2 3 mth FU: 30.5 (10.5)</p> <p>Post-tx G1 vs. G2,<br/>p&lt;0.01<br/>3 mth FU G1 vs. G2,<br/>p&lt;0.05</p> |     |                                  |   |
| Hamner et al., 2003 <sup>38</sup>                 | NR                         | NR   | NR  | NR                               | NR  |
| Hien et al., 2004 <sup>39</sup>                   | NR                         | NR   | NR  | NR                               | NR  |

**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year   | Comorbid Medical Condition | Comorbid Psychiatric Condition  | QOL | Disability/Functional Impairment | Return to Work/Active Duty OR Ability to Work |
|--|----------------------------|---|-----|----------------------------------|---|
| Hien et al., 2009 <sup>40</sup><br>Hien et al., 2012 <sup>41</sup> | NR                         | Addiction Severity Index<br>Alcohol Use (Completer)<br>Mean (SD)<br>G1 Pre-tx: 0.46 (0.50)<br>G1 1 week: 0.23 (0.42)<br>G1 3 mth FU: 0.32 (0.47)<br>G1 6 mth FU: 0.34 (0.48)<br>G1 12 mth FU: 0.43 (0.50)<br><br>G2 Pre-tx: 0.41 (0.49)<br>G2 1 week: 0.20 (0.41)<br>G2 3 mth FU: 0.20 (0.41)<br>G2 6 mth FU: 0.31 (0.46)<br>G2 12 mth FU: 0.19 (0.39)<br><br>Addiction Severity Index<br>Cocaine Use (Completer)<br>Mean (SD)<br>G1 Pre-tx: 0.39 (0.49)<br>G1 1 week: 0.16 (0.37)<br>G1 3 mth FU: 0.21 (0.41)<br>G1 6 mth FU: 0.19 (0.40)<br>G1 12 mth FU: 0.27 (0.45)<br><br>G2 Pre-tx: 0.36 (0.48)<br>G2 1 week: 0.23 (0.42)<br>G2 3 mth FU: 0.24 (0.43)<br>G2 6 mth FU: 0.20 (0.40)<br>G2 12 mth FU: 0.21 (0.41)<br><br>Between Group Post-tx<br>slopes, p=0.09 | NR  | NR                               | NR  |

**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year                      | Comorbid Medical Condition | Comorbid Psychiatric Condition   | QOL | Disability/Functional Impairment | Return to Work/Active Duty OR Ability to Work |
|-----------------------------------|----------------------------|--|-----|----------------------------------|---|
| Hinton et al., 2005 <sup>42</sup> | NR                         | <p>Anxiety Sensitivity Index (ASI)<br/> Mean (SD)<br/> G1 Pre-tx: 3.08 (0.61)<br/> G1 2<sup>nd</sup> Assessment: 1.65 (0.45)<br/> G1 3<sup>rd</sup> Assessment: 1.86 (1.98)<br/> G1 FU Assessment: 1.98 (0.40)</p> <p>G2 Pre-tx: 3.27 (0.53)<br/> G2 2<sup>nd</sup> Assessment: 3.19 (0.36)<br/> G2 3<sup>rd</sup> Assessment 1.84 (0.42)<br/> G2 FU Assessment: 1.91 (0.49)</p> <p>Group Differences at 2<sup>nd</sup> Assessment, p&lt;0.001<br/> Group Differences at 1<sup>st</sup>, 3<sup>rd</sup>, &amp; 4<sup>th</sup> assessments, NS</p> <p>Average of the Symptom Checklist-90-R's Anxiety and Depression subscale (SCL)<br/> Mean (SD)<br/> G1 Pre-tx: 2.92 (0.61)<br/> G1 2<sup>nd</sup> Assessment: 1.72 (0.43)<br/> G1 3<sup>rd</sup> Assessment: 1.77 (0.30)<br/> G1 FU Assessment: 2.02 (0.78)</p> | NR  | NR                               | NR  |

**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year                                     | Comorbid Medical Condition | Comorbid Psychiatric Condition  | QOL | Disability/Functional Impairment | Return to Work/Active Duty OR Ability to Work |
|--|----------------------------|---|-----|----------------------------------|---|
| Hinton et al., 2005 <sup>42</sup><br>(continued) |                            | G2 Pre-tx: 3.02 (0.51)<br>G2 2 <sup>nd</sup> Assessment: 2.94 (0.45)<br>G2 3 <sup>rd</sup> Assessment: 2.03 (0.41)<br>G2 FU Assessment: 1.96 (0.89)<br><br>Group Differences at 2 <sup>nd</sup> Assessment, p<0.001<br><br>Group Differences at 1 <sup>st</sup> , 3 <sup>rd</sup> , & 4 <sup>th</sup> assessments, NS |     |                                  |   |
| Hinton et al., 2009 <sup>43</sup>                | NR                         | NR  | NR  | NR                               | NR  |
| Hinton et al., 2011 <sup>44</sup>                | NR                         | SCL Anxiety Scale<br>Mean (SD)<br>G1 Pre-tx: 2.5 (0.5)<br>G1 Post-tx: 1.5 (0.7)<br>G1 FU: 1.4 (0.6)<br><br>G2 Pre-tx: 2.6 (0.6)<br>G2 Post-tx: 2.2 (0.7)<br>G2 FU: 2.1 (0.8)<br><br>Post-tx<br>G1 vs. G2, p<0.05 (t-test)<br><br>FU<br>G1 vs. G2, p<0.05 (t-test)   | NR  | NR                               | NR  |

**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year                       | Comorbid Medical Condition | Comorbid Psychiatric Condition   | QOL | Disability/Functional Impairment   | Return to Work/Active Duty OR Ability to Work |
|------------------------------------|----------------------------|--|-----|--|---|
| Hogberg et al., 2007 <sup>45</sup> | NR                         | <p>BAI</p> <p>Mean (SD)</p> <p>Pre-tx</p> <p>G1 Pre-tx: 16.7 (10.0)</p> <p>G1 Post-tx: 9.5 (14.0)</p><br><p>G2 Pre-tx: 13.1 (9.3)</p> <p>G2 Post-tx: 11.4 (4.9)</p><br><p>Within group change</p> <p>G1: p&lt;0.05</p> <p>G2: NS</p><br><p>Between group change,</p> <p>NS</p><br><p>HAM-A</p> <p>Mean (SD)</p> <p>G1 Pre-tx: 16.0 (6.5)</p> <p>G1 Post-tx: 9.8 (7.2)</p><br><p>G2 Pre-tx: 18.2 (6.6)</p> <p>G2 Post-tx: 16.1 (5.1)</p><br><p>Within group change</p> <p>G1: p&lt;0.05</p> <p>G2: NS</p><br><p>Between group change,</p> <p>NS</p> |     | <p>GAF</p> <p>Mean (SD)</p> <p>G1 Pre-tx: 64.0 (3.6)</p> <p>G1 Post-tx: 78.9 (12.5)</p><br><p>G2 Pre-tx: 64.9 (3.9)</p> <p>G2 Post-tx: 66.8 (6.0)</p><br><p>Within group change</p> <p>G1: p&lt;0.05</p> <p>G2: NS</p><br><p>Between group change,</p> <p>p&lt;0.05</p><br><p>SDI</p> <p>Mean (SD)</p> <p>G1 Pre-tx: 4.5 (2.3)</p> <p>G1 Post-tx: 4.2 (3.3)</p><br><p>G2 Pre-tx: 5.9 (4.5)</p> <p>G2 Post-tx: 5.4 (3.4)</p><br><p>Within group change</p> <p>G1: NS</p> <p>G2: NS</p><br><p>Between group change, NS</p> | NR  |

**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year                                      | Comorbid Medical Condition | Comorbid Psychiatric Condition   | QOL | Disability/Functional Impairment  | Return to Work/Active Duty OR Ability to Work |
|---|----------------------------|--|-----|---|---|
| Hogberg et al., 2007 <sup>45</sup><br>(continued) |                            | HAM-D<br>Mean (SD)<br>G1 Pre-tx: 29.5 (3.5)<br>G1 Post-tx: 26.8 (5.0)<br><br>G2 Pre-tx: 30.0 (3.4)<br>G2 Post-tx: 31.3 (4.5)<br><br>Within group change<br>G1: NS<br>G2: NS<br><br>Between group change,<br>p<0.05   |     |   |   |
| Hollifield et al., 2007 <sup>46</sup>             | NR                         | Depression (HSCL-25)<br>Mean (SD)<br>G1 Pre-tx: 2.50 (0.70)<br>G1 Post-tx: 1.89 (0.76)<br>G1 3 mth FU: 1.88 (0.75)<br><br>G2 Pre-tx: 2.63 (0.53)<br>G2 Post-tx: 2.00 (0.63)<br>G2 3 mth FU: 1.91 (0.69)<br><br>G3 Pre-tx: 2.61 (0.65)<br>G3 Post-tx: 2.53 (0.67)<br>G3 3 mth FU: 2.53 (0.67)<br><br>RMANOVA<br>G1 vs. G2, p=0.77<br>G1 vs. G3, p<0.01<br>G2 vs. G3, p<0.01 | NR  | SDI<br>Mean (SD)<br>G1 Pre-tx: 3.78 (0.83)<br>G1 Post-tx: 2.98 (1.26)<br>G1 3 mth FU: 2.79 (1.32)<br><br>G2 Pre-tx: 4.09 (0.81)<br>G2 Post-tx: 3.30 (1.22)<br>G2 3 mth FU: 3.00 (1.29)<br><br>G3 Pre-tx: 4.00 (1.02)<br>G3 Post-tx: 3.96 (1.04)<br>G3 3 mth FU: 3.96 (1.04)<br><br>RMANOVA<br>G1 vs. G2, p=0.83<br>G1 vs. G3, p<0.01<br>G2 vs. G3, p<0.01 | NR  |

**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year  | Comorbid Medical Condition | Comorbid Psychiatric Condition   | QOL | Disability/Functional Impairment | Return to Work/Active Duty OR Ability to Work |
|---|----------------------------|--|-----|----------------------------------|---|
| Hollifield et al.,<br>2007 <sup>46</sup><br>(continued) |                            | Anxiety (HSCL-25)<br>Mean (SD)<br>G1 Pre-tx: 2.45 (0.57)<br>G1 Post-tx: 1.67 (0.72)<br>G1 3mth FU: 1.66 (0.56)<br><br>G2 Pre-tx: 2.40 (0.42)<br>G2 Post-tx: 1.78 (0.54)<br>G2 3 mth FU: 1.81 (0.61)<br><br>G3 Pre-tx: 2.26 (0.67)<br>G3 Post-tx: 2.14 (0.61)<br>G3 3 mth FU: 2.14 (0.61)<br><br>RMANOVA<br>G1 vs. G2, p=0.30<br>G1 vs. G3, p<0.01<br>G2 vs. G3, p<0.01 |     |                                  |   |

**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year                       | Comorbid Medical Condition | Comorbid Psychiatric Condition  | QOL   | Disability/Functional Impairment | Return to Work/Active Duty OR Ability to Work |
|------------------------------------|----------------------------|---|---|----------------------------------|---|
| Johnson et al., 2011 <sup>47</sup> | NR                         | BDI<br>Mean (SD)<br>G1 Pre-tx: 24.17 (9.10)<br>G1 Post-tx: 10.68 (8.80)<br>G1 3 mth FU: 11.61 (10.69)<br>G1 6 mth FU: 8.16 (8.62)<br><br>G2 Pre-tx: 21.89 (11.54)<br>G2 Post-tx: 18.53 (12.12)<br>G2 3 mth FU: 15.73 (10.90)<br>G2 6 mth FU: 12.85 (11.87)<br><br>Time effect, $p < 0.0001$<br>Treatment effect, $p < 0.01$ | SF-36: no significant changes for either group (results not provided) | NR                               | NR  |
| Krakow et al., 2001 <sup>48</sup>  | NR                         | NR  | SF-36: no significant changes for either group (results not provided) | NR                               | NR  |



**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year                     | Comorbid Medical Condition | Comorbid Psychiatric Condition   | QOL  | Disability/Functional Impairment | Return to Work/Active Duty OR Ability to Work |
|----------------------------------|----------------------------|--|--|----------------------------------|---|
| Kruse et al., 2009 <sup>49</sup> | NR                         | SCL-90-R's Global Severity Index<br>Mean (SD)<br>G1 Pre-tx: 2.0 (0.7)<br>G1 Post-tx: 1.0 (0.9)<br><br>G2 Pre-tx: 2.0 (0.9)<br>G2 Post-tx: 2.2 (0.8)<br><br>Group X Time, p<0.001 | SF-36- Physical Mean (SD)<br>G1 Pre-tx: 59.9 (12.5)<br>G1 Post-tx: 77.7 (18.1)<br><br>G2 Pre-tx: 55.1 (13.5)<br>G2 Post-tx: 53.1 (13.5)<br><br>SF-36-Mental Mean (SD)<br>G1 Pre-tx: 43.6 (12.4)<br>G1 Post-tx: 77.7 (18.1)<br><br>G2 Pre-tx: 55.1 (13.5)<br>G2 Post-tx: 53.1 (13.5)<br><br>Group X Time, p<0.001 | NR                               | NR  |

**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year                       | Comorbid Medical Condition | Comorbid Psychiatric Condition  | QOL   | Disability/Functional Impairment | Return to Work/Active Duty OR Ability to Work |
|------------------------------------|----------------------------|---|---|----------------------------------|---|
| Krystal et al., 2011 <sup>50</sup> | NR                         | <p>HAMA<br/>Mean Difference (95% CI)<br/>1.16 (-0.18 to 2.51)<br/>p=0.9</p> <p>MADRS<br/>Mean Difference (95% CI)<br/>1.19<br/>(-.029 to 2.68)<br/>p=0.09</p> <p>PANNSS<br/>Mean Difference (95% CI)<br/>-0.21 (-2.37 to 1.96)<br/>p=0.85</p> | <p>BLSI<br/>Mean Difference<br/>(95% CI)<br/>-0.32 (-4.04 to 3.40)<br/>p=0.87</p> <p>SF-36V PCS<br/>Mean Difference<br/>(95% CI)<br/>-1.13 (-2.58 to 0.32)<br/>p=0.13</p> <p>SF-36V MCS<br/>Mean Difference<br/>(95% CI)<br/>-0.26 (-2.13 to 1.61)<br/>p=0.79</p> | NR                               | NR  |
| Kubany et al., 2003 <sup>51</sup>  | NR                         | <p>BDI<br/>G1 Mean Change from<br/>Baseline (95% CI): 70.8<br/>p&lt;.05<br/>G2 Mean Change from<br/>Baseline (95% CI): 67.5<br/>(pretherapy 1); 64.5<br/>(pretherapy 2)<br/>p&lt;.05</p>  | NR  | NR                               | NR  |
| Kubany et al., 2004 <sup>52</sup>  | NR                         | <p>BDI (ITT Sample)<br/>Mean (SD)<br/>G1 Pre-tx: 26.9 (10.1)<br/>G1 Post-tx: 12.0 (14.2)</p> <p>G2 Pre-tx: 27.4 (11.0)<br/>G2 Post-tx: 28.7 (10.5)</p> <p>Between group<br/>significance, NR</p>  | NR  | NR                               | NR  |

**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year                     | Comorbid Medical Condition | Comorbid Psychiatric Condition   | QOL | Disability/Functional Impairment | Return to Work/Active Duty OR Ability to Work |
|----------------------------------|----------------------------|--|-----|----------------------------------|---|
| Liedl et al., 2011 <sup>53</sup> | NR                         | <p>HSCL List-25 – Anxiety</p> <p>G1 Pre-tx: 2.9 (0.8)<br/>           G1 Post-tx: 2.3 (0.7)<br/>           G1 3 mth FU: 2.5 (0.5)<br/>           Change at post-tx,<br/>           p&lt;0.05<br/>           Change at 3 mth FU, NS</p> <p>G2 Pre-tx: 2.6 (0.5)<br/>           G2 Post-tx: 2.2 (0.6)<br/>           G2 3 mth FU: 2.2 (0.6)<br/>           Change at post-tx,<br/>           p&lt;0.05<br/>           Change at 3mth FU, NS</p> <p>G3 Pre-tx: 2.9 (0.6)<br/>           G3 Post-tx: 2.8 (0.8)<br/>           Change at post-tx, NS</p> <p>G2 scored more favorably than G3 on all posttreatment outcome measures</p> | NR  | NR                               | NR  |

**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year                        | Comorbid Medical Condition | Comorbid Psychiatric Condition   | QOL | Disability/Functional Impairment | Return to Work/Active Duty OR Ability to Work   |
|-------------------------------------|----------------------------|--|-----|----------------------------------|---|
| Lindauer et al., 2005 <sup>54</sup> | NR                         | <p>HADS-Depressive Subscore<br/>Mean (SD)<br/>G1 Pre-tx: 11.8 (4.3)<br/>G1 Post-tx: 8.0 (6.7)</p> <p>G2 Pre-tx: 9.0 (3.5)<br/>G2 Post-tx: 9.1 (5.7)</p> <p>G1 vs. G2, <math>p &gt; 0.05</math></p> <p>HADS-Anxiety Subscore<br/>Mean (SD)<br/>G1 Pre-tx: 13.1 (3.2)<br/>G1 Post-tx: 8.1 (4.8)</p> <p>G2 Pre-tx: 11.3 (3.3)<br/>G2 Post-tx: 12.0 (4.7)</p> <p>G1 vs. G2, <math>p &lt; 0.05</math></p> | NR  | NR                               | <p>Patients on Sick Leave (%)<br/>G1 Pre-tx: 66.7%<br/>G1 Post-tx: 33.3%</p> <p>G2 Pre-tx: 50%<br/>G2 Post-tx: 50%</p> <p>G1 vs. G2, NS</p> |

**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year                    | Comorbid Medical Condition | Comorbid Psychiatric Condition   | QOL | Disability/Functional Impairment | Return to Work/Active Duty OR Ability to Work |
|---------------------------------|----------------------------|--|-----|----------------------------------|---|
| Litz et al., 2007 <sup>55</sup> | NR                         | <p data-bbox="753 334 789 362">BAI</p> <p data-bbox="753 367 1045 475">G1 Pre-tx: 18.70 (10.60)<br/>G1 Post-tx: 8.43 (5.93)<br/>G1 3mth FU: 6.11 (5.69)<br/>G1 6 mth FU: 6.38 (5.21)</p> <p data-bbox="753 505 1045 638">G2 Pre-tx: 20.92 (15.00)<br/>G2 Post-tx: 12.59 (13.45)<br/>G2 3 mth FU: 9.92 (8.19)<br/>G2 6 mth FU: 14.43 (9.96)</p> <p data-bbox="753 667 972 748">ITT Analysis<br/>Post-tx<br/>Time effect, <math>p &lt; 0.001</math></p> <p data-bbox="753 777 984 911">Completer Analysis<br/>3 mth FU<br/>G1 vs. G2, NS<br/>6 mth FU<br/>G1 vs. G2, <math>p = 0.06</math></p> <p data-bbox="753 940 1045 1073">BDI<br/>G1 Pre-tx: 18.87 (9.52)<br/>G1 Post-tx: 12.14 (9.56)<br/>G1 3 mth FU: 12.51 (6.53)<br/>G1 6 mth FU: 8.50 (7.54)</p> <p data-bbox="753 1102 1045 1269">G2 Pre-tx: 24.43 (12.08)<br/>G2 Post-tx: 17.47 (11.19)<br/>G2 3 mth FU: 13.23 (9.08)<br/>G2 6 mth FU: 16.84 (8.66)</p> | NR  | NR                               | NR  |

**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year                                   | Comorbid Medical Condition | Comorbid Psychiatric Condition  | QOL | Disability/Functional Impairment | Return to Work/Active Duty OR Ability to Work |
|--|----------------------------|---|-----|----------------------------------|---|
| Litz et al., 2007 <sup>55</sup><br>(continued) |                            | ITT Analysis<br>Post-tx<br>Time effect, $p < 0.001$<br><br>Completer Analysis<br>3 mth FU<br>G1 vs. G2, NS<br>6 mth FU<br>G1 vs. G2, $p < 0.05$ |     |                                  |   |

**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year  | Comorbid Medical Condition | Comorbid Psychiatric Condition   | QOL | Disability/Functional Impairment   | Return to Work/Active Duty OR Ability to Work |
|---|----------------------------|--|-----|--|---|
| Marks et al., 1998 <sup>56</sup><br>Lovell et al., 2001 <sup>57</sup> | NR                         | BDI (11 weeks)<br>Mean Change Score<br>(95% CI)<br>G1: 13 (8 to 18)<br>G2: 17 (11 to 22)<br>G3: 18 (13 to 23)<br>G4: 7 (3 to 11)<br><br>Additional results presented<br>in graphs<br>BDI<br>Mean change in G1 + G2 +<br>G3 vs. G4<br>Post, p=0.004<br>1 mth FU, p=0.08 | NR  | Work/Social Adjustment (Self<br>Report) (Completer data)<br>Mean (SD)<br>G1 Pre-tx: 21.5 (8.9)<br>G1 Post-tx: 11.8 (12.3)<br>G1 1 mth FU: 9.5 (12.1)<br>G1 3 mth FU: 5.2 (8.3)<br>G1 6 mth FU: 4.1 (7.8)<br><br>G2 Pre-tx: 26.9 (8.8)<br>G2 Post-tx: 14.3 (10.0)<br>G2 1 mth FU: 13.9 (10.9)<br>G2 3 mth FU: 14.7 (12.1)<br>G2 6 mth FU: 13.4 (11.7)<br><br>G3 Pre-tx: 29.4 (7.9)<br>G3 Post-tx: 13.2 (12.1)<br>G3 1 mth FU: 13.2 (12.2)<br>G3 3 mth FU: 10.3 (9.3)<br>G3 6 mth FU: 4.5 (6.9)<br><br>G4 Pre-tx: 22.1 (9.5)<br>G4 Post-tx: 17.5 (11.6)<br>G4 1 mth FU: 15.0 (11.3)<br>G4 3 mth FU: 14.9 (12.3)<br><br>Additional results presented in<br>graphs<br>Work/Social Adjustment Mean<br>change in G1 + G2 + G3<br>vs. G4<br>Post, p=0.002<br>1 mth FU, p=0.006<br>3 mth FU, p=0.005 | NR  |

**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year   | Comorbid Medical Condition | Comorbid Psychiatric Condition  | QOL | Disability/Functional Impairment   | Return to Work/Active Duty OR Ability to Work |
|--|----------------------------|---|-----|--|---|
| Marshall et al., 2001 <sup>58</sup>  | NR                         | MADRS<br>Adjusted Mean Differences (95% CI)<br>G1 vs. G3<br>-5.6 (-8.0 to -3.3)<br>p<0.001<br><br>G2 vs. G3<br>-5.1 (-7.4 to -2.8)<br>p<0.001   | NR  | SDS<br>Adjusted Mean Differences (95% CI) G1 vs. G3<br>-2.4 (-4.1 to -0.8)<br>p<0.005<br><br>G2 vs. G3<br>-2.0 (-3.7 to -0.3)<br>p<0.001 | NR  |
| Martenyi et al., 2002 <sup>59</sup><br>Martenyi et al., 2006 <sup>60</sup> | NR                         | MADRS<br>Changes from Pre-tx to Post-tx<br>Least Square Means (SE), p-value<br>G1: -6.5 (0.45)<br>G2: -3.5 (0.75)<br>p<0.001<br><br>HAM-A<br>Changes from Pre-tx to Post-tx<br>Least Square Means (SE), p-value<br>G1: -8.7 (0.48)<br>G2: -5.7 (0.79)<br>p=0.001<br><br>Hopkins 90-Item Symptom Checklist-Revised (SCL-90-R)<br>Changes from Pre-tx to Post-tx<br>Least Square Means (SE), p-value<br>G1: -51.8 (4.40)<br>G2: -36.4 (7.20)<br>p=0.058 | NR  | NR   | NR  |



**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year                        | Comorbid Medical Condition | Comorbid Psychiatric Condition   | QOL | Disability/Functional Impairment | Return to Work/Active Duty OR Ability to Work |
|-------------------------------------|----------------------------|--|-----|----------------------------------|---|
| Martenyi et al., 2007 <sup>61</sup> |                            | MADRS<br>Mean change from baseline<br>(SE) (Completer analysis)<br>G1: -5.05 (0.82)<br>G2: -5.04 (0.84)<br>G3: -3.45 (1.14)<br>p=0.463 |     |                                  |   |
|                                     |                            | HAMA<br>Mean change from baseline<br>(SE) (Completer analysis)<br>G1: -9.12 (0.61)<br>G2: -9.16 (0.62)<br>G3: -7.67 (0.84)<br>p=.296   |     |                                  |   |

**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year                        | Comorbid Medical Condition | Comorbid Psychiatric Condition   | QOL  | Disability/Functional Impairment | Return to Work/Active Duty OR Ability to Work |
|-------------------------------------|----------------------------|--|--|----------------------------------|---|
| McDonagh et al., 2005 <sup>62</sup> | NR                         | BDI<br>Mean (SD)<br>G1 Pre-tx: 18.9 (9.6)<br>G1 Post-tx: 12.9 (12.5)<br><br>G2 Pre-tx: 17.0 (7.7)<br>G2 Post-tx: 10.8 (9.5)<br><br>G3 Pre-tx: 20.9 (7.8)<br>G3 Post-tx: 19.0 (11.3)<br><br>Group X Time, p>0.10<br><br>STAI<br>Mean (SD)<br>G1 Pre-tx: 53.5 (10.4)<br>G1 Post-tx: 46.2 (13.9)<br><br>G2 Pre-tx: 54.5 (9.2)<br>G2 Post-tx: 46.4 (12.2)<br><br>G3 Pre-tx: 54.6 (9.6)<br>G3 Post-tx: 51.5 (9.7) | QOLI<br>Mean (SD)<br>G1 Pre-tx: 36.1 (15.9)<br>G1 Post-tx: 39.5 (17.0)<br><br>G2 Pre-tx: 35.2 (15.3)<br>G2 Post-tx: 39.0 (12.6)<br><br>G3 Pre-tx: 36.8 (13.2)<br>G3 Post-tx: 37.2 (14.7)<br><br>Group X Time, p>0.10 | NR                               | NR  |

**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year                        | Comorbid Medical Condition | Comorbid Psychiatric Condition  | QOL | Disability/Functional Impairment | Return to Work/Active Duty OR Ability to Work |
|-------------------------------------|----------------------------|---|-----|----------------------------------|---|
| Monnelly et al., 2003 <sup>63</sup> | NR                         | NR  | NR  | NR                               | NR  |
| Monson et al., 2006 <sup>64</sup>   | NR                         | BDI<br>Mean (SE)<br>G1 Pre-tx: 25.39 (1.8)<br>G1 Post-tx: 17.42 (1.6)<br>G1 1 mth FU: 18.75 (1.9)<br><br>G2 Pre-tx: 28.53 (1.6)<br>G2 Post-tx: 27.06 (1.4)<br>G2 1 mth FU: 23.92 (1.8)<br><br>Group X Time, NS<br><br>STAI<br>Mean (SE)<br>G1 Pre-tx: 54.38 (2.1)<br>G1 Post-tx: 46.92 (2.1)<br>G1 1 mth FU: 47.51 (2.4)<br><br>G2 Baseline: 55.62 (1.8)<br>G2 Postassessment:<br>58.16 (2.0)<br>G2 1-month follow-up:<br>56.98 (2.3)<br><br>Group X Time, p<0.01 | NR  | NR                               | NR  |

**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year                      | Comorbid Medical Condition | Comorbid Psychiatric Condition  | QOL  | Disability/Functional Impairment | Return to Work/Active Duty OR Ability to Work |
|-----------------------------------|----------------------------|---|--|----------------------------------|---|
| Mueser et al., 2008 <sup>65</sup> | NR                         | BDI-II<br>Mean (SD)<br>G1 Pre-tx: 31.48 (13.24)<br>G1 Post-tx: 21.91 (11.52)<br>G1 3 mth FU: 21.67 (13.32)<br>G1 6 mth FU: 25.02 (12.85)<br><br>G2 Pre-tx: 31.76 (13.76)<br>G2 Post-tx: 27.70 (14.75)<br>G2 3 mth FU: 30.66 (15.26)<br>G2 6 mth FU: 31.30 (13.50)<br><br>Group effect, p<0.001<br><br>BAI<br>Mean (SD)<br>G1 Pre-tx: 48.29 (13.04)<br>G1 Post-tx: 42.59 (12.95)<br>G1 3 mth FU: 41.10 (14.29)<br>G1 6 mth FU: 43.58 (12.03)<br><br>G2 Pre-tx: 49.68 (13.26)<br>G2 Post-tx: 45.81 (14.16)<br>G2 3 mth FU: 48.04 (15.62)<br>G2 6 mth FU: 47.84 (13.73)<br><br>Group effect, p =0.03 | SF-12 - Physical<br>Mean (SD)<br>G1 Pre-tx: 39.81 (11.63)<br>G1 Post-tx: 39.23 (11.26)<br>G1 3 mth FU: 39.17 (13.61)<br>G1 6 mth FU: 38.89 (13.44)<br><br>Group effect, p=.002<br><br>G2 Pre-tx: 40.74 (11.54)<br>G2 Post-tx: 39.34 (12.98)<br>G2 3 mth FU: 38.14 (11.59)<br>G2 6 mth FU: 35.81 (10.72)<br><br>Group effect, p=0.002 | NR                               | NR  |

**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year                                     | Comorbid Medical Condition | Comorbid Psychiatric Condition  | QOL  | Disability/Functional Impairment | Return to Work/Active Duty OR Ability to Work |
|--|----------------------------|---|--|----------------------------------|---|
| Mueser et al., 2008 <sup>65</sup><br>(continued) |                            | Brief Psychiatric Rating Scale<br>Mean (SD)<br>G1 Pre-tx: 43.92 (7.69)<br>G1 Post-tx: 39.63 (10.00)<br>G1 3 mth FU: 40.57 (7.33)<br>G1 6 mth FU: 41.78 (6.81)<br><br>G2 Pre-tx: 43.77 (7.42)<br>G2 Post-tx: 42.25 (7.59)<br>G2 3 mth FU: 43.97 (10.37)<br>G2 6 mth FU: 46.60 (11.56)<br><br>Group effect, p =0.02 | SF-12-Mental Mean (SD)<br>G1 Pre-tx:: 29.35 (9.57)<br>G1 Post-tx: 33.81 (11.02)<br>G1 3 mth FU: 33.92 (11.03)<br>G1 6 mth FU: 31.19 (9.12)<br><br>G2 Pre-tx: 29.37 (9.05)<br>G2 Post-tx: 33.75 (10.93)<br>G2 3 mth FU: 29.99 (11.44)<br>G2 6 mth FU: 26.66 (10.01)<br><br>Group effect, p=0.13 |                                  |   |

**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year                       | Comorbid Medical Condition | Comorbid Psychiatric Condition  | QOL | Disability/Functional Impairment | Return to Work/Active Duty OR Ability to Work |
|------------------------------------|----------------------------|---|-----|----------------------------------|---|
| Nacasch et al., 2011 <sup>66</sup> | NR                         | <p>BDI<br/>Mean (SD)<br/>G1 Pre-tx: 26.0 (7.9)<br/>G1 Post-tx: 13.2 (7.6)</p> <p>G2 Pre-tx: 31.4 (8.8)<br/>G2 Post-tx: 26.8 (10.7)</p> <p>Post-tx<br/>Treatment X Time, NS<br/>G1 vs. G2, p=0.007</p> <p>STAI - State<br/>Mean (SD)<br/>G1 Pre-tx: 59.5 (11.6)<br/>G1 Post-tx: 44.3 (11.0)</p> <p>G2 Pre-tx: 60.9 (13.3)<br/>G2 Post-tx: 62.0 (12.3)</p> <p>Post-tx<br/>Treatment X Time, p=0.007<br/>G1 vs. G2, p&lt;0.001</p> <p>STAI - Trait<br/>Mean (SD)<br/>G1 Pre-tx: 59.5 (8.3)<br/>G1 Post-tx: 47.7 (12.6)</p> <p>G2 Pre-tx: 61.0 (10.9)<br/>G2 Post-tx: 61.7 (12.5)</p> <p>Post-tx<br/>Treatment X Time, p=0.016<br/>G1 vs. G2, p=0.017</p> | NR  | NR                               | NR  |

**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year                      | Comorbid Medical Condition | Comorbid Psychiatric Condition   | QOL   | Disability/Functional Impairment | Return to Work/Active Duty OR Ability to Work |
|-----------------------------------|----------------------------|--|---|----------------------------------|---|
| Neuner et al., 2004 <sup>67</sup> | NR                         | Self-Reporting<br>Questionnaire 20 (SRQ-20)<br>Mean (SD)<br>G1 Pre-tx: 15.6 (2.9)<br>G1 Post-tx: 13.1 (5.1)<br>G1 4 mth FU: 11.9 (4.9)<br>G1 1 year FU: 11.0 (5.1)<br><br>G2 Pre-tx: 16.5 (2.7)<br>G2 Post-tx: 14.3 (5.0)<br>G2 4 mth FU: 12.8 (3.9)<br>G2 1 year FU: 12.4 (4.8)<br><br>G3 Pre-tx: 18.6 (2.0)<br>G3 Post-tx: 15.3 (3.2)<br>G3 4 mth FU: 15.1 (2.6)<br>G3 1 year FU: 14.4 (4.1)<br><br>Group X Time, NS<br>G1 vs. G2, p<0.01<br>G1 vs. G3, NS | SF-12,<br>Psychological health Scale<br>Mean (SD)<br>G1 Pre-tx: 0.27 (0.12)<br>G1 Post-tx: 0.36 (0.19)<br>G1 4 mth FU: 0.38 (0.12)<br>G1 1 year FU: 0.44 (0.19)<br><br>G2 Pre-tx: 0.34 (0.11)<br>G2 Post-tx: 0.33 (0.21)<br>G2 4 mth FU: 0.33 (0.14)<br>G2 1 year FU: 0.36 (0.14)<br><br>G3 Pre-tx: 0.23 (0.15)<br>G3 Post-tx: 0.33 (0.19)<br>G3 4 mth FU: 0.37 (0.14)<br>G3 1 year FU: 0.35 (0.17)<br><br>Group X Time, NS<br>G1 vs. G2, NS<br>G1 vs. G3, NS |                                  | NR  |
| Neuner et al., 2008 <sup>68</sup> | NR                         | NR   | NR  | NR                               | NR  |

**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year                      | Comorbid Medical Condition | Comorbid Psychiatric Condition  | QOL | Disability/Functional Impairment | Return to Work/Active Duty OR Ability to Work |
|-----------------------------------|----------------------------|---|-----|----------------------------------|---|
| Neuner et al., 2010 <sup>69</sup> | NR                         | Hopkins Symptom Checklist - 25 Depression Scale<br>Mean (SD)<br>G1 Pre-tx: 3.0 (0.4)<br>G1 Post-tx: 2.6 (0.6)<br><br>G2 Pre-tx: 3.0 (0.5)<br>G2 Post-tx: 2.9 (0.5)  | NR  | NR                               | NR  |
| Nijdam et al., 2012 <sup>70</sup> | NR                         | Group X Time, NS<br>HADS - Depression<br>Mean Estimated Differences @ first f/u:<br>3.58 (1.68 to 5.49)<br>p<0.001<br><br>Mean Estimated Differences @ 2nd f/u:<br>1.47 (-0.44 to 3.39)<br>p= 0.13<br><br>HADS-Anxiety<br>Mean Estimated Differences @ 2nd f/u:<br>3.74 (2.03 to 5.46)<br>p<0.001<br><br>HADS-Anxiety<br>Mean Estimated Differences @ 2nd f/u:<br>0.80 (-0.93 to 2.50)<br>p=0.36<br><br>MDD in G1<br>% @ baseline: 67.1<br>% @ 1st f/u: 36.4<br>% @ 2nd f/u: 19 | NR  | NR                               | NR  |



**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year                                     | Comorbid Medical Condition | Comorbid Psychiatric Condition   | QOL | Disability/Functional Impairment | Return to Work/Active Duty OR Ability to Work |
|--|----------------------------|--|-----|----------------------------------|---|
| Nijdam et al., 2012 <sup>70</sup><br>(continued) |                            | <p>MDD in G2<br/>% @ baseline: 52.9<br/>% @ 1st f/u: 13.7<br/>% @ 2nd f/u: 14.6</p> <p>MDD between group difference @ 1st f/u: p&lt;0.05<br/>MDD between group difference @ 2nd f/u: p=0.57</p> <p>Anxiety in G1<br/>% @ baseline: 20<br/>% @ 1st f/u: 9.1<br/>% @ 2nd f/u: 11.9</p> <p>Anxiety in G2<br/>% @ baseline: 11.4<br/>% @ 1st f/u: 9.8<br/>% @ 2nd f/u: 10.4</p> <p>MDD between group difference @ 1st f/u: p=0.91<br/>MDD between group difference @ 2nd f/u: p=0.82</p> |     |                                  |   |
| Panahi et al., 2011 <sup>71</sup>                | NR                         | NR   | NR  | NR                               | NR  |

**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year                        | Comorbid Medical Condition | Comorbid Psychiatric Condition  | QOL | Disability/Functional Impairment | Return to Work/Active Duty OR Ability to Work |
|-------------------------------------|----------------------------|---|-----|----------------------------------|---|
| Petrakis et al., 2011 <sup>72</sup> | NR                         | HAM-D<br>Mean( SE)<br>G1 Pre-tx: 13.273 (1.112)<br>G1 Post-tx:9.328 (1.256)<br><br>G2 Pre-tx: 10.950 (1.167)<br>G2 Post-tx:8.238 (1.299)<br><br>G3 Pre-tx: 11.195 (1.132)<br>G3 Post-tx: 8.563 (1.201)<br><br>G4 Pre-tx: 13.167 (1.065)<br>G4 Post-tx: 8.943 (1.117)<br><br>Time effect, p<0.00<br>Group X Time, NS | NR  | NR                               | NR  |
| Raskind et al., 2003 <sup>73</sup>  | NR                         | NR  | NR  | NR                               | NR  |
| Raskind et al., 2007 <sup>74</sup>  | NR                         | HAM-D<br>Mean (SD)<br>G1 Pre-tx: 18.3 (8.8)<br>G1 Post-tx: 12.7 (7.7)<br><br>G2 Pre-tx: 15.3 (7.8)<br>G2 Post-tx: 14.7 (7.1)<br>G1 vs. G2 Change,<br>p=0.08   | NR  | NR                               | NR  |
| Reich et al., 2004 <sup>75</sup>    | NR                         | NR  | NR  | NR                               | NR  |

**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year  | Comorbid Medical Condition | Comorbid Psychiatric Condition  | QOL | Disability/Functional Impairment | Return to Work/Active Duty OR Ability to Work |
|---|----------------------------|---|-----|----------------------------------|---|
| Resick et al., 2002 <sup>76</sup><br>Resick et al., 2003 <sup>77</sup><br>Resick et al., 2012 <sup>78</sup> | NR                         | BDI<br>Mean (SD)<br>G1 Pre-tx: 23.70 (10.39)<br>G1 Post-tx: 12.73 (11.17)<br>G1 3 mth FU: 13.22 (11.64)<br>G1 9 mth FU: 14.17 (11.85)<br>G1 LTFU: 9.41 (11.13)<br><br>G2 Pre-tx: 24.03 (8.88)<br>G2 Post-tx: 16.00 (11.06)<br>G2 3 mth FU: 16.49 (11.62)<br>G2 9 mth FU: 16.41 (11.37)<br>G1 LTFU: 12.06 (12.68)<br>G3 Pre-tx: 23.33 (8.07)<br>G3 Post-tx: 22.62 (8.59)<br>G3 3 mth FU: 22.62 (8.59)<br>G3 9 mth FU: 22.62 (8.59)<br>Posttreatment differences,<br>p<0.0001<br>3 mth FU differences,<br>p<0.0001<br>9 mth FU differences,<br>p<0.0001<br>LTFU differences, NS | NR  | NR                               | NR  |

**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year                        | Comorbid Medical Condition | Comorbid Psychiatric Condition   | QOL | Disability/Functional Impairment | Return to Work/Active Duty OR Ability to Work |
|-------------------------------------|----------------------------|--|-----|----------------------------------|---|
| Rothbaum et al., 1997 <sup>79</sup> | NR                         | <p>BDI</p> <p>Mean (SD)</p> <p>G1 Pre-tx: 21.4 (9.6)</p> <p>G1 Post-tx: 7.3 (5.5)</p> <p>G1 3 mth FU: 7.9 (5.3)</p><br><p>G2 Pre-tx: 34.8 (13.8)</p> <p>G2 Post-tx: 30.4 (15.7)</p><br><p>G1 vs. G2, p&lt;0.05</p><br><p>STAI-State</p> <p>Mean (SD)</p> <p>G1 Pre-tx: 50.4 (10.6)</p> <p>G1 Post-tx: 31.8 (14.7)</p> <p>G1 3 mth FU: 37.3 (14.3)</p><br><p>G2 Pre-tx: 63.1 (21.0)</p> <p>G2 Post-tx: 48.5 (15.5)</p><br><p>STAI-Trait</p> <p>Mean (SD)</p> <p>G1 Pre-tx: 53.5 (10.9)</p> <p>G1 Post-tx: 35.0 (14.3)</p> <p>G1 3 mth FU: 37.3 (14.3)</p><br><p>G2 Pre-tx: 64.9 (11.1)</p> <p>G2 Post-tx 58.8 (11.1)</p><br><p>Post treatment G1 vs. G2, NS</p> | NR  | NR                               | NR  |

**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year                        | Comorbid Medical Condition | Comorbid Psychiatric Condition   | QOL | Disability/Functional Impairment | Return to Work/Active Duty OR Ability to Work |
|-------------------------------------|----------------------------|--|-----|----------------------------------|---|
| Rothbaum et al., 2005 <sup>80</sup> | NR                         | <p>BDI</p> <p>Mean (SD)</p> <p>G1 Pre-tx: 16.70 (8.18)</p> <p>G1 Post-tx: 4.65 (4.99)</p> <p>G1 6 mth FU: 4.44 (5.07)</p><br><p>G2 Pre-tx: 25.95 (7.11)</p> <p>G2 Post-tx: 10.70 (11.45)</p> <p>G2 6 mth FU: 10.53 (10.92)</p><br><p>G3 Pre-tx: 24.05 (10.50)</p> <p>G3 Post-tx: 22.20 (10.55)</p><br><p>Posttreatment G1 &amp; G2 vs. G3, p&lt;0.001</p> <p>Posttreatment G1 vs G2, p=NS</p> <p>6 mth FU G1 vs G2, p=NS</p><br><p>STAI-State</p> <p>Mean (SD)</p> <p>G1 Pre-tx: 43.33 (12.59)</p> <p>G1 Post-tx: 30.00 (10.44)</p> <p>G1 6 mth FU: 29.19 (8.79)</p><br><p>G2 Pre-tx: 51.10 (11.05)</p> <p>G2 Post-tx: 32.60 (11.62)</p> <p>G2 6 mth FU: 38.89 (14.54)</p> | NR  | NR                               | NR  |

**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year  | Comorbid Medical Condition | Comorbid Psychiatric Condition  | QOL | Disability/Functional Impairment | Return to Work/Active Duty OR Ability to Work |
|---|----------------------------|---|-----|----------------------------------|---|
| Rothbaum et al.,<br>2005 <sup>80</sup><br>(continued) |                            | G3 Pre-tx: 46.58 (13.48)<br>G3 Post-tx: 49.00 (13.73)<br><br>Posttreatment G1 & G2<br>vs. G3, p<0.001<br>Posttreatment G1 vs G2,<br>p=NS<br>6 mth FU G1 vs G2, p=NS |     |                                  |   |
|   |                            | STAI-Trait<br>G1 Pre-tx: 48.72 (8.62)<br>G1 Post-tx: 35.56 (9.88)<br>G1 6 mth FU: 34.19<br>(7.52)   |     |                                  |   |
|   |                            | G2 Pre-tx: 56.80 (10.95)<br>G2 Post-tx: 41.10 (14.48)<br>G2 6 mth FU: 41.44<br>(13.26)  |     |                                  |   |
|   |                            | G3 Pre-tx: 53.42 (13.07)<br>G3 Post-tx: 53.95 (13.01)   |     |                                  |   |
|   |                            | Posttreatment G1 & G2<br>vs. G3, p<0.001<br>Posttreatment G1 vs G2,<br>p=NR<br>6 mth FU G1 vs. G2, NR   |     |                                  |   |

**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year                        | Comorbid Medical Condition | Comorbid Psychiatric Condition  | QOL   | Disability/Functional Impairment | Return to Work/Active Duty OR Ability to Work |
|-------------------------------------|----------------------------|---|---|----------------------------------|---|
| Rothbaum et al., 2006 <sup>81</sup> | NR                         | BDI<br>Combined reduction: 1.6 (7.52), ns<br><br>STAI-S<br>Combined reduction: 2.0 (10.40), ns  | NR  | NR                               | NR  |
| Schneier et al., 2012 <sup>82</sup> | NR                         | HAM-D<br>Mean (SD)<br>G1 Pre-tx: 16.9 (4.9)<br>G1 Post-tx: 7.7 (3.7)<br><br>G2 Pre-tx: 16.6 (4.9)<br>G2 Post-tx: 11.4 (6.7)<br><br>Treatment Group Effect, p=0.14<br><br>Change over time, p=0.02 | Quality of Life<br>Enjoyment and Satisfaction, Mean (SD)<br>G1 Pre-tx: 47.1 (11.0)<br>G1 Post-tx: 67.9 (12.7)<br><br>G2 Pre-tx: 45.4 (18.5)<br>G2 Post-tx: 54.8 (22.3)<br><br>Treatment Group Effect, p= 0.02<br><br>Change over time, p=0.08<br><br>** higher scores represent better QOL; analyses revealed a significant 2-way time x treatment interaction p=0.06 | NR                               | NR  |

**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year                       | Comorbid Medical Condition | Comorbid Psychiatric Condition | QOL   | Disability/Functional Impairment  | Return to Work/Active Duty OR Ability to Work |
|------------------------------------|----------------------------|--------------------------------|---|---|---|
| Schnurr et al., 2003 <sup>83</sup> | NR                         | NR                             | <p>Only reported that there was no change on the Quality of Life Inventory.</p> <p>SF-36 – Mental Mean (SE)<br/>           G1: Pre-tx: 30.72 (0.86)<br/>           G1 7 mth FU: 31.84 (0.73)<br/>           G1 12 mth FU: 30.92 (0.81)<br/>           Change at 7 mths, p&gt;0.05<br/>           Change at 12 mths, p&gt;0.05</p> <p>G2 Pre-tx: 30.54 (0.85)<br/>           G2 7 mth FU: 30.75 (0.73)<br/>           G2 12 mth FU: 31.83 (0.79)<br/>           Change at 7 mths, p&gt;0.05<br/>           Change at 12 mths, p&gt;0.05</p> <p>SF-36- Physical<br/>           G1 Pre-tx: 41.78 (0.94)<br/>           G1 7 mth FU: 40.35 (0.68)<br/>           G1 12 mth FU: 40.24 (0.73)</p> | <p>General Health Questionnaire Mean (SE)<br/>           G1 Pre-tx: 32.69 (0.55)<br/>           G1 7 mth FU: 31.16 (0.49)<br/>           G1 12 mth FU: 31.88 (0.53)<br/>           Change at 7 mths, p&lt;0.001<br/>           Change at 12 mths, p&lt;0.05</p> <p>G2 Pre-tx: 33.45 (0.54)<br/>           G2 7 mth FU: 31.62 (0.49)<br/>           G2 12 mth FU: 31.19 (0.53)<br/>           Change at 7 mths, p&lt;0.01<br/>           Change at 12 mths, p&lt;0.001</p> <p>Treatment Effect, NS<br/>           Treatment X Cohort, NS</p> | NR  |



**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year                                      | Comorbid Medical Condition | Comorbid Psychiatric Condition   | QOL  | Disability/Functional Impairment | Return to Work/Active Duty OR Ability to Work |
|---|----------------------------|--|--|----------------------------------|---|
| Schnurr et al., 2003 <sup>83</sup><br>(continued) |                            |  | Change at 7 mths, p>0.05<br>Change at 12 mths, p>0.05<br><br>G2 Pre-tx: 40.06 (0.95)<br>G2 7 mth FU: 39.96 (0.68)<br>G2 12 mth FU: 38.93 (0.71)<br>Change at 7 mths, p>0.05<br>Change at 12 mths, p<0.01<br><br>Treatment Effect, NS<br>Treatment X Cohort, NS |                                  |   |
| Schnurr et al., 2007 <sup>84</sup>                | NR                         | BDI<br>Baseline<br>Mean (95% CI)<br>G1: 25.3 (23.8 to 26.9)<br>G2: 23.9 (22.4 to 25.5)<br><br>Least Means (95% CI)<br>Immediate posttreatment<br>G1: 17.4 (15.3 to 19.5)<br>G2: 19.9 (18.0 to 21.9)<br>p=0.04<br><br>3-month follow-up<br>G1: 18.5 (16.3 to 20.7)<br>G2: 21.1 (19.1 to 23.1)<br>p=0.04 | QOL Inventory<br>Baseline<br>Mean (95 % CI)<br>G1: 0.06 (-0.24 to 0.35)<br>G2: 0.09 (-0.26 to 0.44)<br><br>Least Means (95% CI)<br>Immediate posttreatment<br>G1: 0.56 (0.19 to 0.93)<br>G2: 0.24 (-0.12 to 0.60)<br>NS  | NR                               | NR  |

**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year   | Comorbid Medical Condition | Comorbid Psychiatric Condition  | QOL   | Disability/Functional Impairment | Return to Work/Active Duty OR Ability to Work |
|--|----------------------------|---|---|----------------------------------|---|
| Schnurr et al.,<br>2007 <sup>84</sup><br>(continued) |                            | 6-month follow-up<br>G1: 19.2 (17.1 to 21.3)<br>G2: 20.4 (18.2 to 22.7)<br>NS                                   | 3-month follow-up<br>G1: 0.35 (-0.05 to 0.75)<br>G2: 0.22 (-0.14 to 0.60)<br>NS                                 |                                  |   |
|  |                            | Treatment effect, NS<br>Treatment X Time, NS  | NS  |                                  |   |
|  |                            | STAI<br>Baseline<br>Mean (95% CI)<br>G1: 52.1 (49.9 to 54.4)<br>G2: 52.4 (50.2 to 54.7)                         | 6-month follow-up<br>G1: 0.23 (-0.12 to 0.58)<br>G2: 0.14 (-0.26 to 0.53)<br>NS                                 |                                  |   |
|  |                            | Least Means (95% CI)<br>Immediate posttreatment<br>G1: 45.7 (42.6 to 48.7)<br>G2: 50.3 (47.4 to 53.3)<br>p=0.01 | Treatment effect,<br>NS<br>Treatment X Time,<br>NS  |                                  |   |
|  |                            | 3-month follow-up<br>G1: 48.8 (45.9 to 51.8)<br>G2: 50.5 (47.7 to 53.3)<br>NS                                   | SF-36-Mental<br>Baseline<br>Mean (95% CI)<br>G1: 30.1 (28.4 to 31.7)<br>G2: 30.6 (28.7 to 32.6)                 |                                  |   |
|  |                            | 6-month follow-up<br>G1: 50.4 (47.3 to 53.6)<br>G2: 50.8 (48.0 to 53.6)<br>NS                                   | Least Means (95% CI)<br>Immediate posttreatment<br>G1: 37.5 (35.0 to 40.0)<br>G2: 33.4 (30.9 to 35.8)<br>p<0.01 |                                  |   |
|  |                            | Treatment effect, NS<br>Treatment X Time, p<0.05  |   |                                  |   |

**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year   | Comorbid Medical Condition | Comorbid Psychiatric Condition | QOL   | Disability/Functional Impairment | Return to Work/Active Duty OR Ability to Work |
|--|----------------------------|--------------------------------|---|----------------------------------|---|
| Schnurr et al.,<br>2007 <sup>84</sup><br>(continued) |                            |                                | 3-month follow-up<br>G1: 35.6 (33.2 to 38.1)<br>G2: 33.8 (31.1 to 36.4)<br>NS                                     |                                  |   |
|  |                            |                                | 6-month follow-up<br>G1: 35.3 (33.0 to 37.7)<br>G2: 33.4 (30.9 to 35.9)<br>NS                                     |                                  |   |
|  |                            |                                | Treatment effect,<br>NS<br>Treatment X Time,<br>NS  |                                  |   |
|  |                            |                                | SF-36-Physical<br>Baseline<br>Mean (95% CI)<br>G1: 38.3 (36.4 to 40.2)<br>G2: 39.7 (37.5 to 41.8)                 |                                  |   |
|  |                            |                                | Least Means<br>(95% CI)<br>Immediate<br>posttreatment<br>G1: 38.1 (36.1 to 40.2)<br>G2: 39.5 (37.5 to 41.4)<br>NS |                                  |   |

**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year                                      | Comorbid Medical Condition | Comorbid Psychiatric Condition   | QOL  | Disability/Functional Impairment | Return to Work/Active Duty OR Ability to Work |
|---|----------------------------|--|--|----------------------------------|---|
| Schnurr et al., 2007 <sup>84</sup><br>(continued) |                            |  | 3-month follow-up<br>G1: 39.1 (37.1 to 41.1)<br>G2: 38.8 (36.7 to 40.9)<br>NS<br><br>6-month follow-up<br>G1: 38.8 (36.7 to 40.8)<br>G2: 38.3 (36.2 to 40.5)<br>NS<br><br>Treatment effect,<br>NS<br>Treatment X Time,<br>NS |                                  |   |
| Schnyder et al., 2011 <sup>85</sup>               | NR                         | HADS - Anxiety<br>Mean (SD)<br>G1 Pre-tx:14.4 (2.6)<br>G1 Post-tx:12.2 (4.2)<br>G1 6 mth FU: 11.8 (5.4)<br><br>G2 Pre-tx:13.8 (2.5)<br>G2 Post-tx:13.5 (3.1)<br><br>Group Effect, p<0.05<br><br>HADS - Depression<br>G1 Pre-tx:13.4 (4.8)<br>G1 Post-tx:10.8 (5.8)<br>G1 6 mth FU: 11.4 (5.6)<br><br>G2 Pre-tx: 10.7 (3.5)<br>G2 Post-tx: 11.4 (4.2)<br><br>Group Effect, p<0.05 | NR   | NR                               | NR  |
| Simon et al., 2008 <sup>86</sup>                  | NR                         | NR   | NR   | NR                               | NR  |

**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year                      | Comorbid Medical Condition | Comorbid Psychiatric Condition   | QOL | Disability/Functional Impairment   | Return to Work/Active Duty OR Ability to Work |
|-----------------------------------|----------------------------|--|-----|--|---|
| Spence et al., 2011 <sup>87</sup> | NR                         | <p data-bbox="751 337 905 357">Patient Health</p> <p data-bbox="751 363 1024 472">Questionnaire-9 item<br/>G1 Pre-tx: 15.61 (4.38)<br/>G1 Post-tx: 10.17 (5.65)<br/>G1 3 mth FU: 9.91 (6.12)</p> <p data-bbox="751 505 1031 581">G2 Pre-tx: 15.05 (4.90)<br/>G2 Post-tx: 13.84 (4.95)<br/>G2 3 mth FU: NR</p> <p data-bbox="751 613 974 634">G1 vs. G2, p&lt;0.01</p> <p data-bbox="751 667 1024 797">Generalized Anxiety Disorder Scale<br/>G1 Pre-tx: 12.91 (4.57)<br/>G1 Post-tx: 7.91 (5.98)<br/>G1 3 mth FU: 7.26 (5.94)</p> <p data-bbox="751 829 1024 906">G2 Pre-tx: 11.11 (3.89)<br/>G2 Post-tx: 10.63 (3.53)<br/>G2 3 mth FU: NR</p> <p data-bbox="751 938 995 993">G1 vs. G2 @ 8 weeks:<br/>p&lt;0.04**</p> | NR  | <p data-bbox="1325 337 1381 357">SDS</p> <p data-bbox="1325 363 1604 440">G1 Pre-tx: 18.17 (6.96)<br/>G1 Post-tx: 13.22 (9.42)<br/>G1 3 mth FU: 11.30 (9.64)</p> <p data-bbox="1325 472 1604 548">G2 Pre-tx: 19.42 (8.03)<br/>G2 Post-tx: 18.11 (6.67)<br/>G2 3 mth FU: NR</p> <p data-bbox="1325 581 1541 602">G1 vs G2, p=0.07</p> | NR  |

**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year   | Comorbid Medical Condition | Comorbid Psychiatric Condition   | QOL | Disability/Functional Impairment | Return to Work/Active Duty OR Ability to Work                                      |
|--|----------------------------|--|-----|----------------------------------|--|
| Stein et al., 2002 <sup>88</sup>   | NR                         | CES -D<br>G1: -5.25 (SD=6.27)<br>G2: 4.88 (SD=9.66)<br>p<.03   | NR  | NR                               | NR   |
| Tarrier et al., 1999 <sup>89</sup><br>Tarrier et al., 1999 <sup>90</sup> | NR                         | BDI<br>Mean (SD)<br>G1 Pre-tx: 23.93 (10.95)<br>G1 Post-tx: 17.43 (11.88)<br>G1 6-mth FU: 20.41 (10.60)<br><br>G2 Pre-tx: 27.45 (12.39)<br>G2 Post-tx: 19.03 (13.20)<br>G2 6 mth FU: 20.83 (12.79)<br><br>G1 vs. G2 differences, NS<br><br>12-Month Follow-up<br>G1 Pre-tx: 23.52 (10.87)<br>G1 12 mth FU: 20.33 (11.40)<br><br>G2 Pre-tx: 26.90 (12.34)<br>G2 12 mth FU: 20.93 (13.55)<br><br>G1 vs. G2 differences, NS<br><br>BAI<br>Mean (SD)<br>G1 Pre-tx: 26.86 (10.75)<br>G1 6 mth FU: 23.04 (12.18)<br><br>G2 Pre-tx: 26.39 (12.05)<br>G2 6 mth FU: 20.66 (12.97) | NR  | NR                               | Percentage Back at Work<br>6 Month Follow-up<br>Overall: 40%<br>G1: 44%<br>G2: 37% |

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G1 vs. G2 differences, NS

12-Month Follow-up  
G1 Pre-tx: 26.76 (10.23)  
G1 12 mth FU: 20.58  
(13.01)

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**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year  | Comorbid Medical Condition | Comorbid Psychiatric Condition  | QOL | Disability/Functional Impairment  | Return to Work/Active Duty OR Ability to Work |
|---|----------------------------|---|-----|---|---|
| Tarrier et al., 1999 <sup>89</sup><br>Tarrier et al., 1999 <sup>90</sup><br>(continued) |                            | G2 Pre-tx: 26.34 (12.32)<br>G2 12 mth FU: 21.54 (14.13)   |     |   |   |
|   |                            | G1 vs. G2 differences, NS   |     |   |   |
| Taylor et al., 2003 <sup>91</sup>   | NR                         | BDI<br>Mean (SD)<br>G1 Pre-tx: 26.4 (10.0)<br>G1 Post-tx: 16.04 (9.1)<br>G1 FU: 14.4 (11.0)<br><br>G2 Pre-tx: 23.2 (7.8)<br>G2 Post-tx: 13.0 (10.6)<br>G2 FU: 12.7 (8.9)<br><br>G3 Pre-tx: 26.3 (11.1)<br>G3 Post-tx: 21.0 (13.8)<br>G3 FU: 16.7 (8.9)<br><br>Treatment Effects, NS<br>Treatment X Time, NS<br>Time Effect from Post-tx to FU, p 0.01 | NR  | NR  | NR  |
| Tucker et al., 2001 <sup>92</sup>   | NR                         | MADRS<br>Adjusted Mean Differences (95% CI), G1 vs. G2<br>-3.9 (-6.4 to -1.2)   | NR  | SDS<br>Adjusted Mean Differences (95% CI), G1 vs. G2<br>-2.6 (-4.4 to -0.7) | NR  |



**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year                      | Comorbid Medical Condition  | Comorbid Psychiatric Condition   | QOL | Disability/Functional Impairment | Return to Work/Active Duty OR Ability to Work |
|-----------------------------------|---|--|-----|----------------------------------|---|
| Tucker et al., 2003 <sup>93</sup> | RefId 824   | BDI  | NR  | NR                               | NR  |
| Tucker et al., 2004 <sup>94</sup> | Systolic BP difference<br>G1 Pre-tx: 6.66<br>G1 Post-tx: 0.70<br><br>G2 Pre-tx: 4.20<br>G2 Post-tx: -0.11<br><br>G3 Pre-tx: 7.25<br>G3 Post-tx: 1.00<br><br>Between group differences, NS<br><br>Diastolic BP<br>G1 Pre-tx: 2.28<br>G1 Post-tx: -1.65<br><br>G2 Pre-tx: 2.22<br>G2 Post-tx: 0.47<br><br>G3 Pre-tx: 5.60<br>G3 Post-tx: -2.93<br><br>Between group differences, NS | G1 Pre-tx: 29.72(13.93)<br>G1 Post-tx: 13.65 (11.06)<br><br>G2 Pre-tx: 27.09 (12.25)<br>G2 Post-tx: 13.67 (14.56)<br><br>G3 Pre-tx: 31.60 (9.38)<br>G3 Post-tx: 16.00 (17.21)<br><br>Between group differences, p value NR |     |                                  |   |

**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year  | Comorbid Medical Condition  | Comorbid Psychiatric Condition   | QOL   | Disability/Functional Impairment  | Return to Work/Active Duty OR Ability to Work |
|---|---|--|---|---|---|
| Tucker et al., 2003 <sup>93</sup><br>Tucker et al., 2004 <sup>94</sup><br>(continued) | Heart rate difference<br>Mean (SD)<br>G1 Pre-tx: 3.22 (5.16)<br>G1 Post-tx: 1.65 (3.00)<br><br>G2 Pre-tx: 2.20 (3.56)<br>G2 Post-tx: 1.69 (3.75)<br><br>G3 Pre-tx: 0.85 (1.00)<br>G3 Post-tx: 0.57 (2.75)<br><br>Between group differences,<br>NS |  |   |   |   |
| Tucker et al., 2007 <sup>95</sup>   | NR  | HAM-A<br>Mean Percentage Change (SD)<br>G1: -53.9 (42.8)<br>G2: -40.0 (44.2)<br>p= 0.331<br><br>HAM-D<br>Mean Percentage Change (SD)<br>G1 -50.7 (45.6)<br>G2 -33.3 (46.8)<br>p= 0.253 | Sexual Functioning Scale<br>Mean Percentage Change (SD)<br>G1: 2.58 (31.2)<br>G2: 16.2 (20.4)<br>p= 0.120 | SDS<br>Mean Percentage Change (SD)<br>G1: -30.6 (56.4)<br>G2: -35.4 (61.9)<br>p=0.804 | NR  |
| van der Kolk et al., 1994 <sup>96</sup>   | NR  | HAM-D<br>Difference in Improvement G1 vs. G2 = 7.11<br><br>ANCOVA Results<br>F = -7.11, t = -3.72,<br>p=0.0006   | NR  | NR  | NR  |

**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year                            | Comorbid Medical Condition | Comorbid Psychiatric Condition  | QOL | Disability/Functional Impairment | Return to Work/Active Duty OR Ability to Work |
|---|----------------------------|---|-----|----------------------------------|---|
| van der Kolk et al., 2007 <sup>97</sup> | NR                         | BDI-II<br>Mean (SD)<br>G1 Pre-tx:<br>G1 Post-tx: 9.10 (6.02)<br>G1 6 mth FU: 5.25 (5.23)<br><br>G2 Pre-tx:<br>G2 Post-tx: 13.00 (8.66)<br>G2 6 mth FU: 14.00 (7.71)<br><br>G3 Pre-tx:<br>G3 Post-tx: 14.38 (9.74)<br>G3: NA<br><br>Treatment effect, NS<br><br>Posttreatment<br>G1 vs. G2, p= 0.08<br>G1 vs. G3, p=0.07<br>G2 vs. G3, p=0.94<br><br>Followup<br>G1 vs. G2, p<.001 | NR  | NR                               | NR  |

**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year                           | Comorbid Medical Condition | Comorbid Psychiatric Condition  | QOL | Disability/Functional Impairment | Return to Work/Active Duty OR Ability to Work |
|--|----------------------------|---|-----|----------------------------------|---|
| van Emmerik et al., 2008 <sup>98</sup> | NR                         | <p>BDI</p> <p>Mean (SD)</p> <p>G1 Pre-tx: 20.52 (9.43)</p> <p>G1 Post-tx: 15.31 (9.44)</p> <p>G1 FU: 14.79 (9.48)</p><br><p>G2 Pre-tx: 22.55 (10.63)</p> <p>G2 Post-tx: 19.39 (13.38)</p> <p>G2 FU: 18.65 (13.56)</p><br><p>G3 Pre-tx: 21.24 (8.88)</p> <p>G3 Post-tx: 20.66 (10.77)</p> <p>G3 FU: 21.17 (11.13)</p><br><p>Group X Time Effect</p> <p>G1 vs G2, p=0.51</p> <p>G1+G2 vs G3, p&lt;0.04</p><br><p>STAI-State</p> <p>Mean (SD)</p> <p>G1 Pre-tx: 55.44 (11.22)</p> <p>G1 Post-tx: 46.51 (14.32)</p> <p>G1 FU: 46.90 (15.02)</p><br><p>G2 Pre-tx: 54.22 (11.90)</p> <p>G2 Post-tx: 47.49 (15.75)</p> <p>G2 FU: 46.70 (15.09)</p><br><p>G3 Pre-tx: 57.14 (11.60)</p> <p>G3 Post-tx: 54.06 (12.18)</p> <p>G3 FU: 55.08 (12.83)</p><br><p>Group X Time Effect</p> <p>G1 vs. G2, p=0.81</p> <p>G1+G2 vs G3, p=0.05</p> | NR  | NR                               | NR  |

**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year  | Comorbid Medical Condition | Comorbid Psychiatric Condition   | QOL | Disability/Functional Impairment | Return to Work/Active Duty OR Ability to Work |
|---|----------------------------|--|-----|----------------------------------|---|
| van Emmerik et al., 2008 <sup>98</sup><br>(continued) |                            | STAI-Trait<br>G1 Pre-tx: 50.54 (8.49)<br>G1 Post-tx: 46.23 (9.80)<br>G1 FU: 48.15 (9.00)<br><br>G2 Pre-tx: 50.35 (7.33)<br>G2 Post-tx: 47.62 (8.81)<br>G2 FU: 47.19 (8.76)<br><br>G3 Pre-tx: 53.20 (8.70)<br>G3 Post-tx: 52.23 (7.31)<br>G3: 52.06 (7.28)<br><br>Group X Time<br>G1 vs G2, p=0.37<br>G1+G2 vs G3, p=0.20 |     |                                  |   |
| Yeh et al., 2011 <sup>99</sup>                        | NR                         | BDI<br>Mean( SD)<br>G1 Pre-tx: 22.29 (9.47)<br>G1 Post-tx 13.81 (10.29)<br><br>G2 Pre-tx: 22.0 (11.80)<br>G2 Post-tx:18.14 (14.77)<br><br>Between Group Change,<br>p=0.72  | NR  | NR                               | NR  |
| Zlotnick et al., 2009 <sup>100</sup>                  | NR                         | Addiction Severity Index<br>Mean difference (95% CI)<br>0.01 (-0.06 to -0.08)  | NR  | NR                               | NR  |

**Table D-6. Comorbid conditions, quality of life, impairment, and ability to return to work (continued)**

| Author, Year                     | Comorbid Medical Condition | Comorbid Psychiatric Condition  | QOL | Disability/Functional Impairment | Return to Work/Active Duty OR Ability to Work |
|----------------------------------|----------------------------|---|-----|----------------------------------|---|
| Zohar et al., 2002 <sup>01</sup> | NR                         | MADRS<br>Mean Change from Baseline (SD)<br>G1: -9.17 (3.13)<br>G2: -5.96 (3.33)<br>NS | NR  | NR                               | NR  |

Abbreviations: ANOVA = analysis of variance; ANCOVA = analysis of covariance; BDI = Beck Depression Inventory; CES-D = Center for Epidemiologic Studies Depression Scale; CI = confidence interval; FU = Follow-up; GAF = Global Assessment of Functioning; GHQ-28 = General Health Questionnaire (28 item); HADS-A = Hospital Anxiety Scale; HADS-D = Hospital Depression Scale; HAM-A = Hamilton Rating Scale for Anxiety; HAM-D = Hamilton Rating Scale for Depression; MADRS = Montgomery-Åsberg Depression Rating Scale; NR = not reported; NS = not significant; PHQ = The Patient Health Questionnaire; Pre-tx = pretreatment; Post-tx = Posttreatment; PTSD = Post-Traumatic Stress Disorder; Q-LES-Q-SF = Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form; QOL = quality of life; RMANOVA, repeated measures analysis of variance; SD = standard deviation; SDS = Sheehan Disability Scale; SE = standard error; SF-36 = Short Form (36) Health Survey; SF-36V = Veterans Short Form 36 Questionnaire; STAI = State-Trait Anxiety Inventory.

**Table D-7. Subgroup analysis of included randomized trials: reduction, remission, and loss of diagnosis**

| <b>Author Year</b>  | <b>Subgroup Analyzed</b>                | <b>PTSD Symptom Reduction</b>  | <b>Remission</b> | <b>Loss of Diagnosis</b> |
|---|---|--|------------------|--------------------------|
| Akuchekian et al., 2004 <sup>1</sup>  | NA                                      | NA   | NA               | NA                       |
| Asukai et al., 2010 <sup>2</sup>  | NA                                      | NA   | NA               | NA                       |
| Bartzokis et al., 2005 <sup>3</sup>   | NA                                      | NA   | NA               | NA                       |
| Basoglu et al., 2007 <sup>4</sup>   | NA                                      | NA   | NA               | NA                       |
| Becker et al., 2007 <sup>5</sup>  | NA                                      | NA   | NA               | NA                       |
| Blanchard et al., 2003 <sup>6</sup>   | NA                                      | NA   | NA               | NA                       |
| Boden et al., 2012 <sup>7</sup>   | NA                                      | NA   | NA               | NA                       |
| Brady et al., 2000 <sup>8</sup>   | NA                                      | NA   | NA               | NA                       |
| Brady et al., 2005 <sup>9</sup>   | NA                                      | NA   | NA               | NA                       |
| Bryant et al., 2003 <sup>10</sup>   | NA                                      | NA   | NA               | NA                       |
| Bryant et al., 2008 <sup>11</sup>   | NA                                      | NA   | NA               | NA                       |
| Butterfield et al., 2001 <sup>12</sup>  | NA                                      | NA   | NA               | NA                       |
| Carlson et al., 1998 <sup>13</sup>  | NA                                      | NA   | NA               | NA                       |
| Chard et al., 2005 <sup>14</sup>  | NA                                      | NA   | NA               | NA                       |
| Cloitre et al., 2002 <sup>15</sup>  | NA                                      | NA   | NA               | NA                       |
| Cloitre et al., 2010 <sup>16</sup>  | NA                                      | NA   | NA               | NA                       |
| Connor et al., 1999 <sup>17</sup><br>Meltzer-Brody et al., 2000 <sup>18</sup> | Individuals with specific PTSD symptoms | Meltzer-Brody et al., 2000 <sup>18</sup><br>Symptom-Specific Effects-DTS<br>Mean (SD)<br>Within Group Mean Change (Endpoint-Baseline)<br><br>Intrusion | NR               | NR                       |

Baseline  
 G1 Baseline: 17.7  
 G1 Post-tx: 6.7  
 Change: -11.0  
 G2 Baseline: 21.5  
 G2 Post-tx: 13.5  
 Change: -8.0  
 p=0.0082

**Table D-7. Subgroup analysis of included randomized trials: reduction, remission, and loss of diagnosis (continued)**

| Author<br>Year   | Subgroup<br>Analyzed | PTSD Symptom<br>Reduction   | Remission | Loss of Diagnosis |
|--|----------------------|---|-----------|-------------------|
| Connor et al.,<br>1999 <sup>17</sup>                       |                      | Avoidance<br>Baseline:<br>G1 Baseline: 9.2<br>G1 Post-tx: G1: 3.0<br>Change: -6.2<br>G2 Baseline: 9.3<br>G2 Post-tx: 6.3<br>Change: -3.0<br>p=0.0153    |           |                   |
| Meltzer-Brody et<br>al., 2000 <sup>18</sup><br>(continued) |                      | Numbing<br>Baseline:<br>G1 Baseline: 22.3<br>G1 Post-tx: 6.2<br>Change: -16.1<br>G2 Baseline: 22.6<br>G2 Post-tx: 15.1<br>Change: -7.5<br>p=0.0017      |           |                   |
|  |                      | Hyperarousal<br>Baseline:<br>G1 Baseline: 24.7<br>G1 Post-tx: 9.0<br>Change: -15.7<br>G2 Baseline: 26.0<br>G2 Post-tx: 17.3<br>Change: -8.7<br>p=0.0029 |           |                   |
|  |                      | SIP<br>Intrusion<br>Baseline  |           |                   |



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G1 Baseline: 10.1  
G1 Post-tx: 2.9  
Change: 7.2  
G2 Baseline: 9.6  
G2 Post-tx: 5.5  
Change: 4.1  
p=0.0108

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**Table D-7. Subgroup analysis of included randomized trials: reduction, remission, and loss of diagnosis (continued)**

| Author Year  | Subgroup Analyzed | PTSD Symptom Reduction  | Remission | Loss of Diagnosis |
|--|-------------------|---|-----------|-------------------|
| Connor et al., 1999 <sup>17</sup><br>Meltzer-Brody et al., 2000 <sup>18</sup><br>(continued) |                   | <p>Avoidance<br/>Baseline:<br/>G1 Baseline: 3.9<br/>G1 Post-tx: 1.1<br/>Change: 2.8<br/>G2 Baseline: 4.1<br/>G2 Post-tx: 2.5<br/>Change: 1.6<br/>p=0.0189</p> <p>Numbing<br/>G1 Baseline: 9.6<br/>G2 Baseline: 10.2<br/>Change: 7.1<br/>G1 Post-tx: 2.5<br/>G2 Post-tx: 5.8<br/>Change: 4.4<br/>p=0.0028</p> <p>Hyperarousal<br/>G1 Baseline: 10.5<br/>G1 Post-tx: 3.6<br/>Change: 6.9<br/>G2 Baseline: 10.8<br/>G2 Post-tx: 6.6<br/>Change: 4.2<br/>p=0.0118</p> |           |                   |
| Cook et al., 2010 <sup>19</sup>  | NA                | NA  | NA        | NA                |
| Cottraux, 2008 <sup>20</sup>   | NA                | NA  | NA        | NA                |
| Davidson et al., 2001 <sup>21</sup>  | Gender            | <p>CAPS-2<br/>Treatment X Sex analysis was performed but was found to be not significant.</p>   | NR        | NR                |
| Davidson et al., 2003 <sup>22</sup>  | NA                | NA  | NA        | NA                |
| Davidson et al., 2006 <sup>23</sup>  | NA                | NA  | NA        | NA                |
| Davidson et al., 2006 <sup>24</sup>  | NA                | NA  | NA        | NA                |

**Table D-7. Subgroup analysis of included randomized trials: reduction, remission, and loss of diagnosis (continued)**

| Author Year   | Subgroup Analyzed      | PTSD Symptom Reduction   | Remission | Loss of Diagnosis |
|---|------------------------|--|-----------|-------------------|
| Davidson et al., 2007 <sup>25</sup>                                   | Gender                 | CAPS<br>For those with PTSD, 3 yrs:<br>Mean Change from Baseline:<br>G1: 39.3 (25.9), p=NR<br>G2: 31.2 (27.9), p=NR<br>For Women:<br>Mean Change from Baseline:<br>G1: 35.0 (24.8), p=NR<br>G2: 22.4 (33.4), p=NR  | NR        | NR                |
| Davis et al., 2008 <sup>26</sup>                                      | NA                     | NA   | NA        | NA                |
| Ehlers et al., 2003 <sup>27</sup>                                     | NA                     | NA   | NA        | NA                |
| Ehlers et al., 2005 <sup>28</sup>                                     | NA                     | NA   | NA        | NA                |
| Fecteau et al., 1999 <sup>29</sup>                                    | NA                     | NA   | NA        | NA                |
| Foa et al., 1999 <sup>30</sup><br>Zoellner et al., 1999 <sup>31</sup> | Racial/ethnic minority | PSS-I, Mean (SD)<br>African American<br>G1 Pre-tx: 28.48 (7.82)<br>G1 Post- tx: 14.35 (8.78)<br>G1 12 mth FU: 13.43 (11.00)<br><br>G2 Pre-tx: 35.00 (8.69)<br>G2 Post-tx: 29.20 (8.61)<br>G2 12 mth FU: NR<br><br>Caucasian<br>G1 Pre-tx: 30.27 (8.90)<br>G1 Post-tx: 11.76 (8.23)<br>G1 12 mth FU: 18.99 (12.30)<br><br>G2 Pre-tx: 31.90 (4.09)<br>G2 Post-tx: 25.80 (8.63)<br>G2 12 mth FU: NR<br><br>Main effects of treatment, p<0.001 | NR        | NR                |

**Table D-7. Subgroup analysis of included randomized trials: reduction, remission, and loss of diagnosis (continued)**

| Author Year                         | Subgroup Analyzed       | PTSD Symptom Reduction   | Remission | Loss of Diagnosis |
|-------------------------------------|-------------------------|--|-----------|-------------------|
| Foa et al., 2005 <sup>32</sup>      | NA                      | NA   | NA        | NA                |
| Forbes et al., 2012 <sup>33</sup>   | NA                      | NA   | NA        | NA                |
| Ford et al., 2011 <sup>34</sup>     | NA                      | NA   | NA        | NA                |
| Friedman et al., 2007 <sup>35</sup> | Gender                  | CAPS-2<br>Trauma type<br>Adjusted mean Change at Endpoint<br>(SE)<br>Noncombat : -22.2 (4.4)<br>Combat : -11.7 (2.4)<br>Main Effects, p=0.039  | NR        | NR                |
|                                     | Substance Abuse History | IES<br>Trauma Type<br>Adjusted mean Change at Endpoint<br>(SE)<br>Group 1<br>Noncombat: -7.1 (3.7)<br>Combat: -9.2 (2.0)<br>Group 2<br>Noncombat: -18.7 (3.7)<br>Combat: -4.4 (2.1)                          |           |                   |
|                                     | Severity Level          | Gender<br>Adjusted mean Change at Endpoint<br>(SE)<br>Male<br>G1:-9.6 (2.0)<br>G2: -6.5 (2.0)<br>Female<br>G1: -4.2 (4.3)<br>G2: -16.5 (4.6)<br>TX X Gender interaction, p<0.027<br>Pairwise comparisons, NS |           |                   |
|                                     |                         | Illness severity<br>Adjusted mean Change at Endpoint<br>(SE): Data NR  |           |                   |

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Greater change in more severely ill  
Main Effects,  $p=0.17$

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**Table D-7. Subgroup analysis of included randomized trials: reduction, remission, and loss of diagnosis (continued)**

| <b>Author<br/>Year</b>                   | <b>Subgroup<br/>Analyzed</b> | <b>PTSD Symptom<br/>Reduction</b> | <b>Remission</b> | <b>Loss of Diagnosis</b> |
|--|------------------------------|-----------------------------------|------------------|--------------------------|
| Gamito et al.,<br>2010 <sup>36</sup>     | NA                           | NA                                | NA               | NA                       |
| Gersons et al.<br>2000 <sup>37</sup>     | NA                           | NA                                | NA               | NA                       |
| Hamner et al.,<br>2003 <sup>38</sup>     | NA                           | NA                                | NA               | NA                       |
| Hien et al., 2004 <sup>39</sup>          | NA                           | NA                                | NA               | NA                       |
| Hien et al., 2009 <sup>40</sup>          | NA                           | NA                                | NA               | NA                       |
| Hien et al., 2012 <sup>41</sup>          | NA                           | NA                                | NA               | NA                       |
| Hinton et al.,<br>2005 <sup>42</sup>     | NA                           | NA                                | NA               | NA                       |
| Hinton et al.,<br>2009 <sup>43</sup>     | NA                           | NA                                | NA               | NA                       |
| Hinton et al.,<br>2011 <sup>44</sup>     | NA                           | NA                                | NA               | NA                       |
| Hogberg et al.,<br>2007 <sup>45</sup>    | NA                           | NA                                | NA               | NA                       |
| Hollifield et al.,<br>2007 <sup>46</sup> | NA                           | NA                                | NA               | NA                       |
| Johnson et al.,<br>2011 <sup>47</sup>    | NA                           | NA                                | NA               | NA                       |
| Krakov et al.,<br>2001 <sup>48</sup>     | NA                           | NA                                | NA               | NA                       |
| Kruse et al.,<br>2009 <sup>49</sup>      | NA                           | NA                                | NA               | NA                       |
| Krystal et al.,<br>2011 <sup>50</sup>    | NA                           | NA                                | NA               | NA                       |
| Kubany et al.,<br>2003 <sup>51</sup>     | NA                           | NA                                | NA               | NA                       |
| Kubany et al.,<br>2004 <sup>52</sup>     | NA                           | NA                                | NA               | NA                       |
| Liedl et al., 2011 <sup>53</sup>         | NA                           | NA                                | NA               | NA                       |
| Lindauer et al.,<br>2005 <sup>54</sup>   | NA                           | NA                                | NA               | NA                       |
| Litz et al., 2007 <sup>55</sup>          | NA                           | NA                                | NA               | NA                       |
| Marks et al.,<br>1998 <sup>56</sup>      | NA                           | NA                                | NA               | NA                       |
| Lovell et al.,<br>2001 <sup>57</sup>     | NA                           | NA                                | NA               | NA                       |

**Table D-7. Subgroup analysis of included randomized trials: reduction, remission, and loss of diagnosis (continued)**

| Author Year                         | Subgroup Analyzed          | PTSD Symptom Reduction  | Remission | Loss of Diagnosis |
|-------------------------------------|----------------------------|---|-----------|-------------------|
| Marshall et al., 2001 <sup>58</sup> | Gender                     | CAPS-2<br>Adjusted Mean Differences (95% CI)  | NR        | NR                |
|                                     | Depressed vs. Nondepressed | Men<br>G1 vs. G3: -11.7 (-23.3 to -0.1),<br>p<0.05<br>G2 vs. G3: -13.4 (-24.6 to -2.2),<br>p=0.02<br>Women<br>G1 vs. G3: -13.7 (-20.4 to -6.9),<br>p<0.001<br>G2 vs. G3: -11.2 (-18.0 to -4.3),<br>p=0.002<br>Nondepressed<br>G1 vs. G3: -16.8 (-23.7 to -9.8),<br>p<0.001<br>G2 vs. G3: -12.7 (-19.8 to -5.6),<br>p<0.001<br>Depressed<br>G1 vs. G3: -11.0 (-20.4 to -1.7),<br>p<0.03<br>G2 vs. G3: -11.8 (-20.9 to -2.7),<br>p<0.02 |           |                   |

**Table D-7. Subgroup analysis of included randomized trials: reduction, remission, and loss of diagnosis (continued)**

| Author Year                         | Subgroup Analyzed      | PTSD Symptom Reduction   | Remission | Loss of Diagnosis |
|-------------------------------------|------------------------|--|-----------|-------------------|
| Martenyi et al., 2002 <sup>59</sup> | Gender                 | Martenyi et al., 2002 <sup>59</sup><br>TOP-8   | NR        | NR                |
| Martenyi et al., 2006 <sup>60</sup> | Racial/ethnic minority | Changes from Pre-tx to Post-tx<br>Least Square Mean, (SE), p - value                         |           |                   |
|                                     | Trauma Type            | Male<br>G1: -9.8 (0.49)<br>G2: -7.8 (0.77), p=0.026  |           |                   |
|                                     | Number of Traumas      | Female<br>G1: -10.8 (1.25)<br>G2: -6.9 (2.54), p=0.169                                       |           |                   |
|                                     | Different Symptoms     | White<br>G1: -9.8 (0.47)<br>G2: -7.4 (0.76)  |           |                   |
|                                     | Military Veterans      | Nonwhite<br>G1: -14.4 (1.09)<br>G2: -18.2 (2.53), p=0.156                                    |           |                   |
|                                     |                        | Combat Related Yes<br>G1: -9.4 (0.72)<br>G2: -5.0 (1.10), p<0.001                            |           |                   |
|                                     |                        | Combat Related No<br>G1: -10.3 (0.65)<br>G2: -9.6 (1.05), p=0.543                            |           |                   |
|                                     |                        | Number of Traumas, One Trauma Only<br>G1: -9.9 (0.61)<br>G2: -9.7 (1.00), p=0.847            |           |                   |
|                                     |                        | Number of Traumas, ≥ 2 traumas<br>G1: -9.9 (0.74)<br>G2: -5.1 (1.16), p<.001                 |           |                   |
|                                     |                        | Dissociative Symptoms<br>DES total score = 0<br>G1: -9.9 (0.69)<br>G2: -4.4 (1.17), p<0.001  |           |                   |
|                                     |                        | Dissociative Symptoms<br>DES total score > 0<br>G1: -10.7 (0.55)<br>G2: -9.8 (0.89), p=0.383 |           |                   |



**Table D-7. Subgroup analysis of included randomized trials: reduction, remission, and loss of diagnosis (continued)**

| Author Year   | Subgroup Analyzed   | PTSD Symptom Reduction  | Remission | Loss of Diagnosis  |
|---|---------------------|---|-----------|--|
| Martenyi et al., 2002 <sup>59</sup><br>Martenyi et al., 2006 <sup>60</sup><br>(continued) |                     | Martenyi et al., 2006 <sup>60</sup><br>TOP-8<br>Mean Difference, 95% CI<br>-3.86 (-6.12 to -1.60), p=0.001<br>CAPS<br>Mean Difference, 95% CI<br>-15.05 (-23.80 to -6.30), p<0.001<br>DTS<br>Mean Difference, 95% CI<br>-12.88 (-23.97 to -1.79), p=0.023 |           |  |
| Martenyi et al., 2007 <sup>61</sup>   | NA                  | NA  | NA        | NA   |
| McDonagh et al., 2005 <sup>62</sup>   | NA                  | NA  | NA        | NA   |
| Monnelly et al., 2003 <sup>63</sup>   | NA                  | NA  | NA        | NA   |
| Monson et al., 2006 <sup>64</sup>   | Comorbid conditions | NR  | NR        | Loss of PTSD Diagnosis:<br>Endpoint:<br>Disabled: 33%<br>Non-disabled: 47%<br>1 month f/u:<br>Disabled: 33%<br>Non-disabled: 27% |

**Table D-7. Subgroup analysis of included randomized trials: reduction, remission, and loss of diagnosis (continued)**

| Author Year                        | Subgroup Analyzed | PTSD Symptom Reduction  | Remission | Loss of Diagnosis |
|------------------------------------|-------------------|---|-----------|-------------------|
| Mueser et al., 2008 <sup>65</sup>  | Severity Level    | <p>CAPS<br/>Mean (SD)</p> <p>Severe, CAPS &gt; 65<br/>G1 Pre-tx: 82.05 (14.46)<br/>G1 Post-tx: 59.68 (29.12)<br/>G1 3 mth FU: 57.23 (26.92)<br/>G1 6mth FU: 62.78 (25.01)</p> <p>G2 Pre-tx: 83.87 (12.45)<br/>G2 Post-tx: 79.65 (18.41)<br/>G2 3 mth FU: 74.50 (22.17)<br/>G2 6 mth FU: 74.24 (23.54)</p> <p>Group effect, p=0.004</p> <p>Mild/Moderate, CAPS &lt;65<br/>G1 Pre-tx: 54.73 (4.74)<br/>G1 Post-tx: 40.71 (17.56)<br/>G1 3mth FU: 49.25 (23.77)<br/>G1 6 mth FU: 45.30 (22.73)</p> <p>G2 Pre-tx:56.07 (9.16)<br/>G2 Post-tx: 33.86 (15.40)<br/>G2 3 mth FU: 36.78 (25.83)<br/>G2 6 mth FU: 52.00 (21.93)</p> <p>Group Effect, p =.77</p> | NR        | NR                |
| Nacasch et al., 2011 <sup>66</sup> | NA                | NA  | NA        | NA                |
| Neuner et al., 2004 <sup>67</sup>  | NA                | NA  | NA        | NA                |
| Neuner et al., 2008 <sup>68</sup>  | NA                | NA  | NA        | NA                |
| Neuner et al., 2010 <sup>69</sup>  | NA                | NA  | NA        | NA                |
| Nijdam et al., 2012 <sup>70</sup>  | NA                | NA  | NA        | NA                |
| Panahi et al., 2011 <sup>71</sup>  | NA                | NA  | NA        | NA                |

**Table D-7. Subgroup analysis of included randomized trials: reduction, remission, and loss of diagnosis (continued)**

| Author Year                         | Subgroup Analyzed       | PTSD Symptom Reduction   | Remission | Loss of Diagnosis |
|-------------------------------------|-------------------------|--|-----------|-------------------|
| Petrakis et al., 2011 <sup>72</sup> | NA                      | NA   | NA        | NA                |
| Raskind et al., 2003 <sup>73</sup>  | NA                      | NA   | NA        | NA                |
| Raskind et al., 2007 <sup>74</sup>  | NA                      | NA   | NA        | NA                |
| Reich et al., 2004 <sup>75</sup>    | NA                      | NA   | NA        | NA                |
| Resick et al., 2002 <sup>76</sup>   | Exposed to Child Trauma | CAPS   | NR        | NR                |
| Resick et al., 2003 <sup>77</sup>   |                         | Mean (SD)  |           |                   |
| Resick et al., 2012 <sup>78</sup>   |                         | No Childhood Sexual Abuse<br>Pre-tx: 70.6 (18.9)<br>Post-tx: 28.0 (20.7)<br>9 mth FU: 10.9 (9.1) |           |                   |
|                                     |                         | Childhood Sexual Abuse<br>Pre-tx: 76.8 (18.4)<br>Post-tx: 28.4 (27.1)<br>9 mth FU: 33.3 (29.6)   |           |                   |
|                                     |                         | Time effect, p=0.000<br>Group effect, NS<br>Group X Time, NS                                     |           |                   |
| Rothbaum et al., 1997 <sup>79</sup> | NA                      | NA   | NA        | NA                |
| Rothbaum et al., 2005 <sup>80</sup> | NA                      | NA   | NA        | NA                |
| Rothbaum et al., 2006 <sup>81</sup> | NA                      | NA   | NA        | NA                |
| Schneier et al., 2012 <sup>82</sup> | NA                      | NA   | NA        | NA                |
| Schnurr et al., 2003 <sup>83</sup>  | NA                      | NA   | NA        | NA                |
| Schnurr et al., 2007 <sup>84</sup>  | NA                      | NA   | NA        | NA                |
| Schnyder et al., 2011 <sup>85</sup> | NA                      | NA   | NA        | NA                |
| Simon et al., 2008 <sup>86</sup>    | NA                      | NA   | NA        | NA                |
| Spence et al.,                      | NA                      | NA   | NA        | NA                |

2011<sup>87</sup>**Table D-7. Subgroup analysis of included randomized trials: reduction, remission, and loss of diagnosis (continued)**

| Author Year                             | Subgroup Analyzed | PTSD Symptom Reduction   | Remission | Loss of Diagnosis |
|---|-------------------|--|-----------|-------------------|
| Stein et al., 2002 <sup>88</sup>        | NA                | NA   | NA        | NA                |
| Tarrier et al., 1999 <sup>89</sup>      | NA                | NA   | NA        | NA                |
| Tarrier et al., 1999 <sup>90</sup>      | NA                | NA   | NA        | NA                |
| Taylor et al., 2003 <sup>91</sup>       | NA                | NA   | NA        | NA                |
| Tucker et al., 2001 <sup>92</sup>       | Gender            | CAPS-2<br>Adjusted Mean Differences (95% CI),<br>G1 vs. G2<br>Men: -15.15 (-24.31 to -5.98)<br>Women: -10.00 (-18.68 to -3.30) | NR        | NR                |
| Tucker et al., 2003 <sup>93</sup>       | NA                | NA   | NA        | NA                |
| Tucker et al., 2004 <sup>94</sup>       | NA                | NA   | NA        | NA                |
| Tucker et al., 2007 <sup>95</sup>       | NA                | NA   | NA        | NA                |
| van der Kolk et al., 1994 <sup>96</sup> | NA                | NA   | NA        | NA                |

**Table D-7. Subgroup analysis of included randomized trials: reduction, remission, and loss of diagnosis (continued)**

| Author Year                             | Subgroup Analyzed        | PTSD Symptom Reduction  | Remission   | Loss of Diagnosis  |
|---|--------------------------|---|---|--|
| van der Kolk et al., 2007 <sup>97</sup> | Exposure to Child Trauma | CAPS<br>Mean (SD)<br>Child-onset<br>G1 Post-tx: 38.36 (20.73)<br>G1 6 mth FU: 33.00 (22.34)<br><br>G2 Post-tx: 40.20 (14.33)<br>G2 6 mth FU: 50.43 (8.24)<br><br>G3 Post-tx: 46.57 (20.18)<br>G3 6 mth FU: NR<br><br>Adult-onset:<br>G1 Post-tx: 19.92 (14.64)<br>G1 6 mth FU: 20.17 (19.36)<br><br>G2 Post-tx: 37.75 (23.69)<br>G2 6 mth FU: 35.36 (16.76)<br><br>G3 Post-tx: 31.92(13.87)<br>G3 6 mth FU: NR<br><br>Onset X Treatment Effect, NS<br><br>Patients with adult-onset had greater reductions in PTSD symptoms than those with child-onset at post-tx & 6 mth; p<0.005 (ITT), p=0.02 (Completer) | Asymptomatic at Posttreatment, %<br>Child-onset<br>G1: 9.1<br>G2: 10.0<br>G3: 7.1<br><br>Adult-onset<br>G1: 46.2<br>G2: 18.8<br>G3: 16.7<br><br>Asymptomatic at Followup, %<br>Child-onset<br>G1: 33.3<br>G2: 0.0<br>G3: NR<br><br>Adult-onset<br>G1: 75.0<br>G2: 0.0<br>G3: NR<br><br>Adult-onset more likely to achieve asymptomatic end-state function in G1 only (Chi-square, ITT) Posttreatment, p=0.037 Followup, p=0.045 | Lost of PTSD Diagnosis at Posttreatment, %<br>Child-onset<br>G1: 72.7<br>G2: 90.0<br>G3: 57.1<br><br>Adult-onset<br>G1: 100.0<br>G2: 75.0<br>G3: 75.0<br><br>Lost of PTSD Diagnosis at Followup, %<br>Child-onset<br>G1: 88.9<br>G2: 42.9<br>G3: NR<br><br>Adult-onset<br>G1: 91.7<br>G2: 90.9<br>G3: NR<br><br>Adult-onset more likely to lose diagnosis in G1 only (Chi-square, ITT) Posttreatment, p=0.052 Followup, p=0.045<br><br>G2, adult-onset more likely to lose diagnosis than child-onset, p=0.036 |
| van Emmerik et al., 2008 <sup>98</sup>  | NA                       | NA  | NA  | NA   |
| Yeh et al., 2011 <sup>99</sup>          | NA                       | NA  | NA  | NA   |
| Zlotnick et al., 2009 <sup>100</sup>    | NA                       | NA  | NA  | NA   |
| Zohar et al., 2002 <sup>101</sup>       | NA                       | NA  | NA  | NA   |

Abbreviations: CAPS = Clinician-administered PTSD Scale; CI = confidence interval; DTS = Davidson Trauma Scale; IES = Impact of Events Scale; NA = not applicable; NR= not reported; PSS-I= PTSD Symptom Scale Interview; PTSD= Post-Traumatic Stress Disorder; SD = standard deviation; SE = standard error; TOP-8 = Treatment Outcome PTSD Scale.

**Table D-8. Subgroup analysis of included randomized trials: comorbidities, quality of life, and disability**

| Author Year                              | Subgroup Analyzed                        | Comorbid Medical Condition | Comorbid Psychiatric Condition | QOL | Disability/Functional Impairment | Return to Work/Duty |
|--|--|----------------------------|--------------------------------|-----|----------------------------------|---------------------|
| Akuchekian et al., 2004 <sup>1</sup>     | NA                                       | NA                         | NA                             | NA  | NA                               | NA                  |
| Asukai et al., 2010 <sup>2</sup>         | NA                                       | NA                         | NA                             | NA  | NA                               | NA                  |
| Bartzokis et al., 2005 <sup>3</sup>      | NA                                       | NA                         | NA                             | NA  | NA                               | NA                  |
| Basoglu et al., 2007 <sup>4</sup>        | NA                                       | NA                         | NA                             | NA  | NA                               | NA                  |
| Becker et al., 2007 <sup>5</sup>         | NA                                       | NA                         | NA                             | NA  | NA                               | NA                  |
| Blanchard et al., 2003 <sup>6</sup>      | NA                                       | NA                         | NA                             | NA  | NA                               | NA                  |
| Brady et al., 2000 <sup>8</sup>          | NA                                       | NA                         | NA                             | NA  | NA                               | NA                  |
| Brady et al., 2005 <sup>9</sup>          | NA                                       | NA                         | NA                             | NA  | NA                               | NA                  |
| Bryant et al., 2003 <sup>10</sup>        | NA                                       | NA                         | NA                             | NA  | NA                               | NA                  |
| Bryant et al., 2008 <sup>11</sup>        | NA                                       | NA                         | NA                             | NA  | NA                               | NA                  |
| Butterfield et al., 2001 <sup>12</sup>   | NA                                       | NA                         | NA                             | NA  | NA                               | NA                  |
| Carlson et al., 1998 <sup>13</sup>       | NA                                       | NA                         | NA                             | NA  | NA                               | NA                  |
| Chard et al., 2005 <sup>14</sup>         | NA                                       | NA                         | NA                             | NA  | NA                               | NA                  |
| Cloitre et al., 2002 <sup>15</sup>       | NA                                       | NA                         | NA                             | NA  | NA                               | NA                  |
| Cloitre et al., 2010 <sup>16</sup>       | NA                                       | NA                         | NA                             | NA  | NA                               | NA                  |
| Connor et al., 1999 <sup>17</sup>        | Individuals with different PTSD symptoms | NR                         | NR                             | NR  | NR                               | NR                  |
| Meltzer-Brody et al., 2000 <sup>18</sup> |  |                            |                                |     |                                  |                     |
| Cook et al., 2010 <sup>19</sup>          | NA                                       | NA                         | NA                             | NA  | NA                               | NA                  |
| Cottraux, 2008 <sup>20</sup>             | NA                                       | NA                         | NA                             | NA  | NA                               | NA                  |
| Davidson et al.,                         | Gender                                   | NR                         | NR                             | NR  | NR                               | NR                  |

|  |                                    |    |    |    |    |    |
|--|------------------------------------|----|----|----|----|----|
| 2001 <sup>21</sup>                     |                                    |    |    |    |    |    |
| Davidson et al.,<br>2003 <sup>22</sup> | NA                                 | NA | NA | NA | NA | NA |
| Davidson et al.,<br>2006 <sup>23</sup> | NA                                 | NA | NA | NA | NA | NA |
| Davidson et al.,<br>2006 <sup>24</sup> | NA                                 | NA | NA | NA | NA | NA |
| Davidson et al.,<br>2007 <sup>25</sup> | Gender                             | NR | NR | NR | NR | NR |
|  | Length of<br>PTSD<br>Diagnosi<br>s |    |    |    |    |    |

**Table D-8. Subgroup analysis of included randomized trials: comorbidities, quality of life, and disability (continued)**

| Author Year   | Subgroup Analyzed      | Comorbid Medical Condition | Comorbid Psychiatric Condition   | QOL | Disability/Functional Impairment   | Return to Work/Duty |
|---|------------------------|----------------------------|--|-----|--|---------------------|
| Davis et al., 2008 <sup>26</sup>                                      | NA                     | NA                         | NA   | NA  | NA   | NA                  |
| Ehlers et al., 2003 <sup>27</sup>                                     | NA                     | NA                         | NA   | NA  | NA   | NA                  |
| Ehlers et al., 2005 <sup>28</sup>                                     | NA                     | NA                         | NA   | NA  | NA   | NA                  |
| Fecteau et al., 1999 <sup>29</sup>                                    | NA                     | NA                         | NA   | NA  | NA   | NA                  |
| Foa et al., 1999 <sup>30</sup><br>Zoellner et al., 1999 <sup>31</sup> | Racial/ethnic minority | NR                         | BDI, Mean (SD)<br>African American<br>G1 Pre-tx: 18.76 (9.66)<br>G1 Post-tx: 7.97 (7.21)<br>G1 12 mth FU: 9.77 (9.83)<br><br>G2 Pre-tx: 29.20 (8.61)<br>G2 Post-tx: 26.96 (16.29)<br>G2 12 mth FU: NR<br><br>Caucasian<br>G1 Pre-tx: 20.87 (11.64)<br>G1 Post-tx: 9.01 (8.43)<br>G1 12 mth FU: 9.73 (11.61)<br><br>G2 Pre-tx: 21.41 (10.35)<br>G2 Post-tx: 19.40 (14.44)<br>G2 12 mth FU: NR<br><br>Main effects of treatment, p<0.001 | NA  | SAS-Global Mean (SD)<br>African American<br>G1 Pre-tx: 3.91 (1.00)<br>G2 Pre-tx: 4.60 (1.14)<br>G1 12 mth FU: 3.07 (1.22)<br><br>G1 Post-tx: 2.74 (1.18)<br>G2 Post-tx: 4.40 (0.89)<br>G2 12 mth FU: NR<br><br>Caucasian<br>G1 Pre-tx: 3.80 (1.09)<br>G1 Post-tx: 2.68 (0.94)<br>G1 12 mth FU: 2.98 (1.47)<br><br>G2 Pret-tx: 3.60 (1.07)<br>G2 Post-tx: 3.40 (1.07)<br>G2 12 mth FU: NR<br><br>Main effects of treatment, p<0.01<br><br>No main effect for ethnicity or treatment X ethnicity | NA                  |



**Table D-8. Subgroup analysis of included randomized trials: comorbidities, quality of life, and disability (continued)**

| Author Year  | Subgroup Analyzed | Comorbid Medical Condition | Comorbid Psychiatric Condition  | QOL | Disability/Functional Impairment | Return to Work/Duty |
|--|-------------------|----------------------------|---|-----|----------------------------------|---------------------|
| Foa et al., 1999 <sup>30</sup><br>Zoellner et al., 1999 <sup>31</sup><br>(continued) |                   |                            | STAI-State<br>Mean (SD)<br>African American<br>G1 Pre-tx: 49.49<br>(13.41)<br>G1 Post-tx: 33.33<br>(12.11)<br>G1 12 mth FU: 35.86<br>(13.34)<br><br>G2 Pre-tx: 62.00<br>(7.68)<br>G2 Post-tx: 54.00<br>(14.14)<br>G2 12 mth FU: NR<br><br>Caucasian<br>G1 Pre-tx: 51.31<br>(14.43)<br>G1 Post-tx: 39.33<br>(13.25)<br>G1 12 mth FU: 39.72<br>(14.76)<br><br>G2 Pre-tx: 45.57<br>(10.94)<br>G2 Post-tx: 48.60<br>(14.02)<br>G2 12 mth FU: NR<br><br>Main effects of<br>treatment, p<0.05 |     |                                  |                     |

**Table D-8. Subgroup analysis of included randomized trials: comorbidities, quality of life, and disability (continued)**

| Author Year  | Subgroup Analyzed | Comorbid Medical Condition | Comorbid Psychiatric Condition | QOL | Disability/Functional Impairment | Return to Work/Duty |
|--|-------------------|----------------------------|--------------------------------|-----|----------------------------------|---------------------|
| Foa et al., 1999 <sup>30</sup><br>Zoellner et al., 1999 <sup>31</sup><br>(continued) |                   |                            |                                |     |                                  |                     |
| Foa et al., 2005 <sup>32</sup>   | NA                | NA                         | NA                             | NA  | NA                               | NA                  |
| Forbes et al., 2012 <sup>33</sup>  | NA                | NA                         | NA                             | NA  | NA                               | NA                  |
| Ford et al., 2011 <sup>34</sup>  | NA                | NA                         | NA                             | NA  | NA                               | NA                  |
| Friedman et al., 2007 <sup>35</sup>  | Gender            | NR                         | NR                             | NR  | NR                               | NR                  |
| Gamito et al., 2010 <sup>36</sup>  | NA                | NA                         | NA                             | NA  | NA                               | NA                  |
| Gersons et al., 2000 <sup>37</sup>   | NA                | NA                         | NA                             | NA  | NA                               | NA                  |
| Hamner et al., 2003 <sup>38</sup>  | NA                | NA                         | NA                             | NA  | NA                               | NA                  |
| Hien et al., 2004 <sup>39</sup>  | NA                | NA                         | NA                             | NA  | NA                               | NA                  |
| Hien et al., 2009 <sup>40</sup>  | NA                | NA                         | NA                             | NA  | NA                               | NA                  |
| Hien et al., 2012 <sup>41</sup>  | NA                | NA                         | NA                             | NA  | NA                               | NA                  |
| Hinton et al., 2005 <sup>42</sup>  | NA                | NA                         | NA                             | NA  | NA                               | NA                  |
| Hinton et al., 2009 <sup>43</sup>  | NA                | NA                         | NA                             | NA  | NA                               | NA                  |
| Hinton et al., 2011 <sup>44</sup>  | NA                | NA                         | NA                             | NA  | NA                               | NA                  |
| Hogberg et al., 2007 <sup>45</sup>   | NA                | NA                         | NA                             | NA  | NA                               | NA                  |
| Hollifield et al., 2007 <sup>46</sup>  | NA                | NA                         | NA                             | NA  | NA                               | NA                  |
| Johnson et al., 2011 <sup>47</sup>   | NA                | NA                         | NA                             | NA  | NA                               | NA                  |
| Krakow et al., 2001 <sup>48</sup>  | NA                | NA                         | NA                             | NA  | NA                               | NA                  |
| Kruse et al., 2009 <sup>49</sup>   | NA                | NA                         | NA                             | NA  | NA                               | NA                  |
| Krystal et al.,  | NA                | NA                         | NA                             | NA  | NA                               | NA                  |

|                                     |    |    |    |    |    |    |
|-------------------------------------|----|----|----|----|----|----|
| 2011 <sup>50</sup>                  |    |    |    |    |    |    |
| Kubany et al., 2003 <sup>51</sup>   | NA | NA | NA | NA | NA | NA |
| Kubany et al., 2004 <sup>52</sup>   | NA | NA | NA | NA | NA | NA |
| Liedl et al., 2011 <sup>53</sup>    | NA | NA | NA | NA | NA | NA |
| Lindauer et al., 2005 <sup>54</sup> | NA | NA | NA | NA | NA | NA |

**Table D-8. Subgroup analysis of included randomized trials: comorbidities, quality of life, and disability (continued)**

| Author Year                         | Subgroup Analyzed   | Comorbid Medical Condition | Comorbid Psychiatric Condition  | QOL   | Disability/Functional Impairment | Return to Work/Duty |
|-------------------------------------|---------------------|----------------------------|---|---|----------------------------------|---------------------|
| Litz et al., 2007 <sup>55</sup>     | NA                  | NA                         | NA  | NA  | NA                               | NA                  |
| Marks et al., 1998 <sup>56</sup>    | NA                  | NA                         | NA  | NA  | NA                               | NA                  |
| Lovell et al., 2001 <sup>57</sup>   |                     |                            |   |   |                                  |                     |
| Marshall et al., 2001 <sup>58</sup> | Gender              | NR                         | NR  | NR  | NR                               | NR                  |
| Martenyi et al., 2002 <sup>59</sup> | Military/Veterans   | NR                         | Martenyi et al., 2006 <sup>60</sup>   | Martenyi et al., 2006 <sup>60</sup>   | NR                               | NR                  |
| Martenyi et al., 2006 <sup>60</sup> |                     |                            | MADR<br>Mean Difference, 95% CI, -5.03 (-7.53 to -2.53), p<0.001<br><br>HAMA<br>Mean Difference, 95% CI -4.70 (-7.13 to -2.27), p<0.001 | SF-36 Mental Health<br>Mean Difference, 95% CI, 15.20 (8.52 to 21.87), p<0.001<br><br>SF-36 Physical Functioning<br>Mean Difference, 95% CI 0.56 (-7.43 to 8.54), p=0.891 |                                  |                     |
| Martenyi et al., 2007 <sup>61</sup> | NA                  | NA                         | NA  | NA  | NA                               | NA                  |
| McDonagh et al., 2005 <sup>62</sup> | NA                  | NA                         | NA  | NA  | NA                               | NA                  |
| Monnelly et al., 2003 <sup>63</sup> | NA                  | NA                         | NA  | NA  | NA                               | NA                  |
| Monson et al., 2006 <sup>64</sup>   | Comorbid conditions | NR                         | NR  | NR  | NR                               | NR                  |
| Mueser et al.,                      | Severity            | NR                         | NR  | NR  | NR                               | NR                  |

| 2008 <sup>65</sup>                    | Level |    |    |    |    |    |
|---------------------------------------|-------|----|----|----|----|----|
| Nacasch et al.,<br>2011 <sup>66</sup> | NA    | NA | NA | NA | NA | NA |
| Neuner et al.,<br>2004 <sup>67</sup>  | NA    | NA | NA | NA | NA | NA |
| Neuner et al.,<br>2008 <sup>68</sup>  | NA    | NA | NA | NA | NA | NA |
| Neuner et al.,<br>2010 <sup>69</sup>  | NA    | NA | NA | NA | NA | NA |
| Nijdam et al.,<br>2012 <sup>70</sup>  | NA    | NA | NA | NA | NA | NA |
| Panahi et al.,<br>2011 <sup>71</sup>  | NA    | NA | NA | NA | NA | NA |

**Table D-8. Subgroup analysis of included randomized trials: comorbidities, quality of life, and disability (continued)**

| Author Year   | Subgroup Analyzed        | Comorbid Medical Condition | Comorbid Psychiatric Condition  | QOL | Disability/Functional Impairment | Return to Work/Duty |
|---|--------------------------|----------------------------|---|-----|----------------------------------|---------------------|
| Petrakis et al., 2011 <sup>72</sup>   | NA                       | NA                         | NA  | NA  | NA                               | NA                  |
| Raskind et al., 2003 <sup>73</sup>  | NA                       | NA                         | NA  | NA  | NA                               | NA                  |
| Raskind et al., 2007 <sup>74</sup>  | NA                       | NA                         | NA  | NA  | NA                               | NA                  |
| Reich et al., 2004 <sup>75</sup>  | NA                       | NA                         | NA  | NA  | NA                               | NA                  |
| Resick et al., 2002 <sup>76</sup><br>Resick et al., 2003 <sup>77</sup><br>Resick et al., 2012 <sup>78</sup> | Exposure to Child Trauma | NR                         | BDI<br>Mean (SD)<br>No Childhood Sexual Abuse<br>Pre-tx: 22.4 (9.5)<br>Post-tx: 10.0 (8.3)<br>9 mth FU: 10.9 (9.1)<br><br>Childhood Sexual Abuse<br>Pre-tx: 24.9 (9.1)<br>Post-tx: 11.4 (10.4)<br>9 mth FU: 12.9 (12.7)<br><br>Time effect, p=0.000<br>Group effect, NS<br>Group X Time, NS | NR  | NR                               | NR                  |
| Rothbaum et al., 1997 <sup>79</sup>   | NA                       | NA                         | NA  | NA  | NA                               | NA                  |
| Rothbaum et al., 2005 <sup>80</sup>   | NA                       | NA                         | NA  | NA  | NA                               | NA                  |
| Rothbaum et al., 2006 <sup>81</sup>   | NA                       | NA                         | NA  | NA  | NA                               | NA                  |
| Schneier et al., 2012 <sup>82</sup>   | NA                       | NA                         | NA  | NA  | NA                               | NA                  |
| Schnurr et al., 2003 <sup>83</sup>  | NA                       | NA                         | NA  | NA  | NA                               | NA                  |
| Schnurr et al., 2007 <sup>84</sup>  | NA                       | NA                         | NA  | NA  | NA                               | NA                  |
| Schnyder et al.,  | NA                       | NA                         | NA  | NA  | NA                               | NA                  |

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|                                      |    |    |    |    |    |    |
|--------------------------------------|----|----|----|----|----|----|
| 2011 <sup>85</sup>                   |    |    |    |    |    |    |
| Simon et al.,<br>2008 <sup>86</sup>  | NA | NA | NA | NA | NA | NA |
| Spence et al.,<br>2011 <sup>87</sup> | NA | NA | NA | NA | NA | NA |

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**Table D-8. Subgroup analysis of included randomized trials: comorbidities, quality of life, and disability (continued)**

| Author Year                             | Subgroup Analyzed        | Comorbid Medical Condition | Comorbid Psychiatric Condition | QOL | Disability/Functional Impairment | Return to Work/Duty |
|---|--------------------------|----------------------------|--------------------------------|-----|----------------------------------|---------------------|
| Stein et al., 2002 <sup>88</sup>        | NA                       | NA                         | NA                             | NA  | NA                               | NA                  |
| Tarrier et al., 1999 <sup>89</sup>      | NA                       | NA                         | NA                             | NA  | NA                               | NA                  |
| Tarrier et al., 1999 <sup>90</sup>      |                          |                            |                                |     |                                  |                     |
| Taylor et al., 2003 <sup>91</sup>       | NA                       | NA                         | NA                             | NA  | NA                               | NA                  |
| Tucker et al., 2001 <sup>92</sup>       | Gender                   | NR                         | NR                             | NR  | NR                               | NR                  |
| Tucker et al., 2003 <sup>93</sup>       | NA                       | NA                         | NA                             | NA  | NA                               | NA                  |
| Tucker et al., 2004 <sup>94</sup>       |                          |                            |                                |     |                                  |                     |
| Tucker et al., 2007 <sup>95</sup>       | NA                       | NA                         | NA                             | NA  | NA                               | NA                  |
| van der Kolk et al., 1994 <sup>96</sup> | NA                       | NA                         | NA                             | NA  | NA                               | NA                  |
| van der Kolk et al., 2007 <sup>97</sup> | Exposure to Child Trauma | NR                         | NR                             | NR  | NR                               | NR                  |
| van Emmerik et al., 2008 <sup>98</sup>  | NA                       | NA                         | NA                             | NA  | NA                               | NA                  |
| Yeh et al., 2011 <sup>99</sup>          | NA                       | NA                         | NA                             | NA  | NA                               | NA                  |
| Zlotnick et al., 2009 <sup>100</sup>    | NA                       | NA                         | NA                             | NA  | NA                               | NA                  |
| Zohar et al., 2002 <sup>101</sup>       | NA                       | NA                         | NA                             | NA  | NA                               | NA                  |

Abbreviations: BDI = Beck Depression Inventory; HAM-A = Hamilton Rating Scale for Anxiety; MADRS = Montgomery–Åsberg Depression Rating Scale; NA = not applicable; NR= not reported; PTSD= Post-Traumatic Stress Disorder; QOL = quality of life; SAS = Social Adjustment Scale; SD = standard deviation; SE = standard error; SF-36 = Short Form (36) Health Survey; STAI = State-Trait Anxiety Inventory.

**Table D-9. Adverse events/harms reported by included randomized controlled trials**

| Author Year                          | Overall AE | Withdrawal Due to AE | Mortality | Suicidality | Disturbed Sleep | Agitation | Sedation | Weight Gain       | Other Adverse Effects   |
|--------------------------------------|------------|----------------------|-----------|-------------|-----------------|-----------|----------|-------------------|---|
| Akuchekian et al., 2004 <sup>1</sup> | NR         | G1: 2<br>G2: 3       | NR        | NR          | NR              | NR        | NR       | NR                | NR  |
| Asukai et al., 2010 <sup>2</sup>     | NR         | NR                   | NR        | NR          | NR              | NR        | NR       | NR                | NR  |
| Bartzokis et al., 2005 <sup>3</sup>  | NR         | G1: 3<br>G2: 2       | NR        | NR          | NR              | NR        | NR       | NS between groups | NS differences on Barnes Akathisia Scale, Columbia Scale, or Abnormal Involuntary Movement Scale  |
| Basoglu et al., 2007 <sup>4</sup>    | NR         | NR                   | NR        | NR          | NR              | NR        | NR       | NR                | NR  |
| Becker et al., 2007 <sup>5</sup>     | NR         | G1: 1<br>G2: NR      | NR        | NR          | NR              | NR        | NR       | NR                | G1 & G2 <sup>a</sup> : Heart pounding, concentration problems, problem achieving orgasm, & erectile dysfunction<br><br>G1: ability to achieve orgasm (positive & negative direction) & 1 reported rash<br>G2: 30% reported increased appetite |
| Blanchard et al., 2003 <sup>6</sup>  | NR         | NR                   | NR        | NR          | NR              | NR        | NR       | NR                | NR  |
| Boden et al., 2012 <sup>7</sup>      | NR         | NR                   | NR        | NR          | NR              | NR        | NR       | NR                | NR  |



**Table D-9. Adverse events/harms reported by included randomized controlled trials (continued)**

| Author Year                            | Overall AE      | Withdrawal Due to AE | Mortality | Suicidality | Disturbed Sleep  | Agitation | Sedation | Weight Gain                                       | Other Adverse Effects  |
|--|-----------------|----------------------|-----------|-------------|--|-----------|----------|---|--|
| Brady et al., 2000 <sup>8</sup>        | NR              | G1: 5<br>G2: 5       | NR        | NR          | Insomnia <sup>a</sup><br>G1: 16.0%<br>G2: 4.3%<br>p=0.01 | NR        | NR       | Change, Mean kg<br>G1: -1.3<br>G2: -0.3<br>p=0.01 | Headache <sup>a</sup><br>G1: 20.2%<br>G2: 28.3%<br>Diarrhea <sup>a</sup><br>G1: 23.4%<br>G2: 19.6%<br>Malaise <sup>a</sup><br>G1: 17.0%<br>G2: 15.2%<br>Nausea <sup>a</sup><br>G1: 16.0%<br>G2: 12.0%<br>Drowsiness <sup>a</sup><br>G1: 12.8%<br>G2: 9.8%<br>Dry Mouth <sup>a</sup><br>G1: 11.7%<br>G2: 4.3% |
| Brady et al., 2005 <sup>9</sup>        | NR              | G1: 0<br>G2: 0       | NR        | NR          | NR   | NR        | NR       | NR  | NR   |
| Bryant et al., 2003 <sup>10</sup>      | NR              | NR                   | NR        | NR          | NR   | NR        | NR       | NR  | NR   |
| Bryant et al., 2008 <sup>11</sup>      | NR              | NR                   | NR        | NR          | NR   | NR        | NR       | NR  | NR   |
| Butterfield et al., 2001 <sup>12</sup> | G1: 45<br>G2: 3 | NR                   | NR        | NR          | NR   | NR        | NR       | G1: 6<br>G2: 0                                    | Dry mouth<br>G1: 3<br>G2: 0<br>Drowsiness<br>G1: 3<br>G2: 1<br>Constipation<br>G1: 3<br>G2: 1<br>Increased appetite<br>G1: 3<br>G2: 0<br>Diarrhea<br>G1: 2<br>G2: 0  |

**Table D-9. Adverse events/harms reported by included randomized controlled trials (continued)**

| Author Year   | Overall AE | Withdrawal Due to AE | Mortality | Suicidality | Disturbed Sleep | Agitation | Sedation | Weight Gain | Other Adverse Effects  |
|---|------------|----------------------|-----------|-------------|-----------------|-----------|----------|-------------|--|
| Butterfield et al., 2001 <sup>12</sup><br>(continued) |            |                      |           |             |                 |           |          |             | Tingling<br>G1: 2<br>G2: 0<br>Unsteadiness<br>G1: 2<br>G2: 0<br>Forgetfulness<br>G1: 3<br>G2: 0<br>Frequent urination<br>G1: 4<br>G2: 1<br>Uncomfortable to move<br>G1: 4<br>G2: 0<br>Thirst<br>G1: 6<br>G2: 0<br>Swelling<br>G1: 4<br>G2: 0 |
| Carlson et al., 1998 <sup>13</sup>                    | NR         | NR                   | NR        | NR          | NR              | NR        | NR       | NR          | NR   |
| Chard et al., 2005 <sup>14</sup>                      | NR         | NR                   | NR        | NR          | NR              | NR        | NR       | NR          | NR   |
| Cloitre et al., 2002 <sup>15</sup>                    | NR         | NR                   | NR        | NR          | NR              | NR        | NR       | NR          | NR   |
| Cloitre et al., 2010 <sup>16</sup>                    | NR         | NR                   | NR        | NR          | NR              | NR        | NR       | NR          | CAPS, Symptom worsening posttreatment:<br>G1: 1 (3.6)<br>G2: 3 (7.4)<br>G3: 5 (15)<br>p=NS<br>posttreatment to 6-mth fu<br>G1: 0 (0)<br>G2: 5 (22.7)<br>G3: 5 (31.3)<br>G1 vs. G2, p=0.02<br>G1 vs. G3, p=0.006                              |

**Table D-9. Adverse events/harms reported by included randomized controlled trials (continued)**

| Author Year  | Overall AE     | Withdrawal Due to AE         | Mortality | Suicidality | Disturbed Sleep   | Agitation | Sedation | Weight Gain    | Other Adverse Effects   |
|--|----------------|------------------------------|-----------|-------------|---|-----------|----------|----------------|---|
| Connor et al., 1999 <sup>17</sup> Meltzer-Brody et al., 2000 <sup>18</sup> | NR             | NR                           | NR        | NR          | NR  | NR        | NR       | NR             | NR  |
| Cook et al., 2010 <sup>19</sup>  | NR             | NR                           | NR        | NR          | NR  | NR        | NR       | NR             | NR  |
| Cottraux, 2008 <sup>20</sup>   | NR             | G1: 0<br>G2: 5               | NR        | NR          | NR  | NR        | NR       | NR             | Worsening of symptoms<br>G1: 0<br>G2: 5   |
| Davidson et al., 2001 <sup>21</sup>  | NR             | G1: 32 (30%)<br>G2: 35 (27%) | NR        | NR          | Insomnia<br>G1: 35%<br>G2: 22%<br>p=0.04<br><br>Vivid Dreams<br>G1: 10%<br>G2: 4%<br>p=0.10 | NR        | NR       | NR             | Headache<br>G1: 33%<br>G2: 24%, p=0.17<br>Diarrhea<br>G1: 28%<br>G2: 11%, p=0.003<br>Nausea<br>G1: 23%<br>G2: 11%, p=0.03<br>Drowsiness<br>G1: 17%<br>G2: 11%, p=0.24<br>Nervousness<br>G1: 14%<br>G2: 8%, p=0.27<br>Fatigue<br>G1: 13%<br>G2: 5%, p=0.05<br>Decreased Appetite<br>G1: 12%<br>G2: 1%, p=0.001<br>Dry Mouth<br>G1: 10%<br>G2: 7%, p=0.45 |
| Davidson et al., 2003 <sup>22</sup>  | G1: 3<br>G2: 3 | G1: 3<br>G2: 3               | NR        | NR          | NR  | NR        | NR       | G1: 3<br>G2: 1 | Palpitations<br>G1: 0<br>G2: 3 (33.3%)<br>Increased appetite:<br>G1: 6 (35.3%)<br>G2: 1 (11.1%)   |

**Table D-9. Adverse events/harms reported by included randomized controlled trials (continued)**

| Author Year                         | Overall AE | Withdrawal Due to AE                           | Mortality                 | Suicidality | Disturbed Sleep   | Agitation | Sedation   | Weight Gain   | Other Adverse Effects  |
|-------------------------------------|------------|--|---------------------------|-------------|---|-----------|--|---|--|
| Davidson et al., 2006 <sup>23</sup> | NR         | G1: 17, 9.5%<br>G2: 22, 12.7%<br>G3: 19, 10.6% | None related to study med | NR          | Insomnia <sup>a</sup><br>G1: 24, 13%<br>G2: 18, 10%<br>G3: 16, 9% | NR        | Fatigue <sup>a</sup><br>G1: 19, 11%<br>G2: 24, 14%<br>G3: 17, 9%<br><br>Somnolence <sup>a</sup><br>G1: 21, 12%<br>G2: 18, 10%<br>G3: 24, 13% | Kg <sup>a</sup><br>G1 -.5<br>G2: -.3<br>G3: +.9<br>G1 vs G3:<br>p=0.0006<br>4<br>G2 vs<br>G3:<br>p=0.0242 | Headache <sup>a</sup><br>G1: 53, 29%<br>G2: 57, 32%<br>G3: 55, 29%<br><br>Nausea <sup>a</sup><br>G1 45, 24%<br>G2: 39, 23%<br>G3: 27, 14%<br><br>Diarrhea <sup>a</sup><br>G1: 22, 12%<br>G2: 47, 26%<br>G3: 25, 13%<br><br>Dry Mouth <sup>a</sup><br>G1: 34, 18%<br>G2: 26, 15%<br>G3: 27, 15%<br><br>Dizziness <sup>a</sup><br>G1: 24, 13%<br>G2: 21, 10%<br>G3: 14, 8%<br><br>Constipation <sup>a</sup><br>G1: 21, 12%<br>G2: 12, 7%<br>G3: 18, 10%<br><br>Appetite Decrease <sup>a</sup><br>G1: 21, 12%<br>G2: 13, 8%<br>G3: 11, 6% |

**Table D-9. Adverse events/harms reported by included randomized controlled trials (continued)**

| Author Year                         | Overall AE | Withdrawal Due to AE | Mortality | Suicidality | Disturbed Sleep  | Agitation | Sedation                     | Weight Gain  | Other Adverse Effects  |
|-------------------------------------|------------|----------------------|-----------|-------------|------------------|-----------|------------------------------|--|--|
| Davidson et al., 2006 <sup>24</sup> | NR         | G1: 15<br>G2: 9      | NR        | NR          | G1: 12<br>G2: 17 | NR        | Somnolence<br>G1: 9<br>G2: 9 | Weight Change of 7% or greater<br>G1: 20<br>G2: 12 | Reported by at Least 5% of patients<br>Headache<br>G1: 46<br>G2: 44<br>Nausea<br>G1: 35<br>G2: 19<br>Dizziness<br>G1: 29<br>G2: 19<br>Dry Mouth<br>G1: 21<br>G2: 8<br>Constipation<br>G1: 20<br>G2: 5<br>Fatigue<br>G1: 13<br>G2: 6<br>Insomnia<br>G1: 12<br>G2: 17<br>Decreased libido<br>G1: 8<br>G2: 6<br>Nasopharyngitis<br>G1: 8<br>G2: 11<br>Increased Sweating<br>G1: 21<br>G2: 6 |

**Table D-9. Adverse events/harms reported by included randomized controlled trials (continued)**

| Author Year                         | Overall AE       | Withdrawal Due to AE | Mortality | Suicidality | Disturbed Sleep | Agitation | Sedation                         | Weight Gain | Other Adverse Effects   |
|-------------------------------------|------------------|----------------------|-----------|-------------|-----------------|-----------|----------------------------------|-------------|---|
| Davidson et al., 2007 <sup>25</sup> | G1: NR<br>G2: NR | G1: 8%<br>G2: 8%     | NR        | NR          | NR              | NR        | Somnolence<br>G1: 20%<br>G2: 10% | NR          | Vomiting<br>G1: 11<br>G2: 4<br><br>Tremor<br>G1: 10<br>G2: 6<br><br>Dizziness<br>G1: 32%<br>G2: 13%<br><br>Headache<br>G1: 25%<br>G2: 27%<br><br>Nausea<br>G1: 18%<br>G2: 20%<br><br>Serious Adverse Event<br>G1:1<br>G2:0<br><br>One individual experienced dizziness, loss of consciousness, and nausea |

**Table D-9. Adverse events/harms reported by included randomized controlled trials (continued)**

| Author Year                      | Overall AE   | Withdrawal Due to AE | Mortality | Suicidality | Disturbed Sleep | Agitation | Sedation         | Weight Gain | Other Adverse Effects   |
|----------------------------------|--|----------------------|-----------|-------------|-----------------|-----------|------------------|-------------|---|
| Davis et al., 2008 <sup>26</sup> | NR<br>(reported AEs greater than 6% in each group) | G1: 3<br>G2: 1       | NR        | NR          | NR              | NR        | G1: 12<br>G2: <6 | NR          | SAE unrelated to study<br>G1: 1<br>G2: 0<br><br>Lack of Efficacy:<br>G1:0<br>G2:1<br><br>Dizziness:<br>G1: 24<br>G2: <6<br><br>Nausea:<br>G1: 14<br>G2: <6<br><br>GI tract upset:<br>G1: 12<br>G2: <6<br><br>Diarrhea:<br>G1: 12<br>G2: <6<br><br>Increased urinary frequency:<br>G1: 10<br>G2: <6<br><br>Headache:<br>G1: 10<br>G2: <6<br><br>Memory Deficit:<br>G1: 10<br>G2: <6<br><br>Abnormal vision:<br>G1: 7<br>G2: <6 |

**Table D-9. Adverse events/harms reported by included randomized controlled trials (continued)**

| Author Year   | Overall AE | Withdrawal Due to AE | Mortality  | Suicidality | Disturbed Sleep | Agitation | Sedation | Weight Gain | Other Adverse Effects   |
|---|------------|----------------------|------------|-------------|-----------------|-----------|----------|-------------|---|
| Davis et al., 2008 <sup>26</sup><br>(continued)                       |            |                      |            |             |                 |           |          |             | Muscle weakness/myalgia:<br>G1: <6<br>G2: 7   |
| Ehlers et al., 2003 <sup>27</sup>                                     | NR         | NR                   | NR         | NR          | NR              | NR        | NR       | NR          | NR  |
| Ehlers et al., 2005 <sup>28</sup>                                     | NR         | NR                   | NR         | NR          | NR              | NR        | NR       | NR          | NR  |
| Fecteau et al., 1999 <sup>29</sup>                                    | NR         | NR                   | NR         | NR          | NR              | NR        | NR       | NR          | NR  |
| Foa et al., 1999 <sup>30</sup><br>Zoellner et al., 1999 <sup>31</sup> | NR         | NR                   | NR         | NR          | NR              | NR        | NR       | NR          | NR  |
| Foa et al., 2005 <sup>32</sup>  | NR         | Overall: 12          | Overall: 1 | Overall: 4  | NR              | NR        | NR       | NR          | NR  |
| Forbes et al., 2012 <sup>33</sup>                                     | NA         | NA                   | NA         | NA          | NA              | NA        | NA       | NA          | NA  |
| Ford et al., 2011 <sup>34</sup>                                       | NA         | NA                   | NA         | NA          | NA              | NA        | NA       | NA          | Worsening of symptoms:<br>3 of G1 and 1 of G2 showed evidence of symptom worsening at post-tx; by 6 months all improved from baseline.<br><br>From post-tx to 3 month FU:<br>4 G1 and 3 G1 reported worsened PTSD symptoms; all but two improved at 6-months.<br><br>From post-tx to 6 month FU<br>0 G2 and 3 G1 reported worsened PTSD symptoms. |



**Table D-9. Adverse events/harms reported by included randomized controlled trials (continued)**

| Author Year  | Overall AE       | Withdrawal Due to AE | Mortality | Suicidality | Disturbed Sleep                          | Agitation | Sedation   | Weight Gain | Other Adverse Effects  |
|--|------------------|----------------------|-----------|-------------|--|-----------|--|-------------|--|
| Friedman et al., 2007 <sup>35</sup>                                | G1: NR<br>G2: NR | G1: 11<br>G2: 5      | NR        | NR          | Insomnia <sup>a</sup><br>G1: 12<br>G2: 8 | NR        | Fatigue <sup>a</sup><br>G1: 9<br>G2: 1<br>Somnolence <sup>a</sup><br>G1: 12<br>G2: 7 | NR          | Diarrhea <sup>a</sup><br>G1: 27<br>G2: 15<br>Headache <sup>a</sup><br>G1: 23<br>G2: 20<br>Nausea <sup>a</sup><br>G1: 18<br>G2: 8 |
| Gamito et al., 2010 <sup>36</sup>                                  | NR               | NR                   | NR        | NR          | NR                                       | NR        | NR   | NR          | NR   |
| Gersons et al., 2000 <sup>37</sup>                                 | NR               | NR                   | NR        | NR          | NR                                       | NR        | NR   | NR          | NR   |
| Hamner et al., 2003 <sup>38</sup>                                  | NR               | G1: 0<br>G2: 0       | NR        | NR          | NR                                       | NR        | NR   | NR          | Akathisia, n<br>G1: 1<br>G2: 0<br>Nausea and vomiting, n<br>G1: 1<br>G2: 0   |
| Hien et al., 2004 <sup>39</sup>                                    | NR               | NR                   | NR        | NR          | NR                                       | NR        | NR   | NR          | Psychiatric Hospitalization<br>G1: 5%<br>G2: 5%<br>G3: 6%  |
| Hien et al., 2009 <sup>40</sup><br>Hien et al., 2012 <sup>41</sup> | NR               | NR                   | NR        | NR          | NR                                       | NR        | NR   | NR          | NR   |
| Hinton et al., 2005 <sup>42</sup>                                  | NR               | NR                   | NR        | NR          | NR                                       | NR        | NR   | NR          | NR   |
| Hinton et al., 2009 <sup>43</sup>                                  | NR               | NR                   | NR        | NR          | NR                                       | NR        | NR   | NR          | NR   |
| Hinton et al., 2011 <sup>44</sup>                                  | NR               | NR                   | NR        | NR          | NR                                       | NR        | NR   | NR          | NR   |

**Table D-9. Adverse events/harms reported by included randomized controlled trials (continued)**

| Author Year                           | Overall AE   | Withdrawal Due to AE        | Mortality | Suicidality | Disturbed Sleep | Agitation | Sedation   | Weight Gain                               | Other Adverse Effects   |
|---------------------------------------|--|-----------------------------|-----------|-------------|-----------------|-----------|--|---|---|
| Hogberg et al., 2007 <sup>45</sup>    | NR   | G1: 1 <sup>b</sup><br>G2: 0 | NR        | NR          | NR              | NR        | NR   | NR  | NR  |
| Hollifield et al., 2007 <sup>46</sup> | NR   | G1: 1<br>G2: 0<br>G3: NR    | NR        | NR          | NR              | NR        | NR   | NR  | Perceived kidney pain<br>G1: 1<br>G2: 0<br>G3: 0  |
| Johnson et al., 2011 <sup>47</sup>    | NR   | NR                          | NR        | NR          | NR              | NR        | NR   | NR  | NR  |
| Krakov et al., 2001 <sup>48</sup>     | NR   | NR                          | NR        | NR          | NR              | NR        | NR   | NR  | NR  |
| Kruse et al., 2009 <sup>49</sup>      | NR   | NR                          | NR        | NR          | NR              | NR        | NR   | NR  | NR  |
| Krystal et al., 2011 <sup>50</sup>    | Overall: 206<br>G1: 109<br>G2: 97<br>p= 0.08<br>(Coded using Medical Dictionary for Regulatory Activities) | G1: 1<br>G2: 1              | NR        | NR          | NR              | NR        | Somnolence<br>Overall: 15<br>G1: 13<br>G2: 2<br>p= 0.00<br><br>Fatigue<br>Overall: 18<br>G1: 18<br>G2: 0<br>p=0.00 | Overall: 23<br>G1: 20<br>G2: 3<br>p= 0.00 | Disturbance in attention<br>Overall: 11<br>G1: 9<br>G2: 2<br>p=0.03<br><br>Gastrointestinal disorders<br>Overall: 78<br>G1: 41<br>G2: 37<br>p=0.59<br><br>Salivary hypersecretion<br>Overall: 14<br>G1: 13<br>G2: 1<br>p=0.00 |

**Table D-9. Adverse events/harms reported by included randomized controlled trials (continued)**

| Author Year                                       | Overall AE | Withdrawal Due to AE | Mortality | Suicidality | Disturbed Sleep | Agitation | Sedation | Weight Gain | Other Adverse Effects   |
|---|------------|----------------------|-----------|-------------|-----------------|-----------|----------|-------------|---|
| Krystal et al., 2011 <sup>50</sup><br>(continued) |            |                      |           |             |                 |           |          |             | Psychiatric disorders<br>Overall:65<br>G1: 42<br>G2: 23<br>p=0.01<br><br>Decreased Libido<br>Overall: 8<br>G1:8<br>G2:0<br>p=0.00<br><br>General disorders and administration site conditions:<br>Overall: 49<br>G1: 31<br>G2: 18<br>p=0.04<br><br>Respiratory, thoracic and mediastinal disorders<br>Overall:24<br>G1: 20<br>G2: 4<br>p=0.00<br><br>Dyspnea<br>Overall<br>G1: 8<br>G2: 0<br>p=0.00<br><br>Nasal congestion<br>G1: 6<br>G2: 0<br>p=0.01 |
| Kubany et al., 2003 <sup>51</sup>                 | NR         | NR                   | NR        | NR          | NR              | NR        | NR       | NR          | NR  |
| Kubany et al., 2004 <sup>52</sup>                 | NR         | NR                   | NR        | NR          | NR              | NR        | NR       | NR          | NR  |

**Table D-9. Adverse events/harms reported by included randomized controlled trials (continued)**

| Author Year                         | Overall AE | Withdrawal Due to AE       | Mortality | Suicidality | Disturbed Sleep | Agitation | Sedation | Weight Gain | Other Adverse Effects   |
|-------------------------------------|------------|----------------------------|-----------|-------------|-----------------|-----------|----------|-------------|---|
| Liedl et al., 2011 <sup>53</sup>    | NR         | NR                         | NR        | NR          | NR              | NR        | NR       | NR          | NR  |
| Lindauer et al., 2005 <sup>54</sup> | NR         | NR                         | NR        | NR          | NR              | NR        | NR       | NR          | NR  |
| Litz et al., 2007 <sup>55</sup>     | NR         | NR                         | NR        | NR          | NR              | NR        | NR       | NR          | NR  |
| Marks et al., 1998 <sup>56</sup>    | NR         | NR                         | NR        | NR          | NR              | NR        | NR       | NR          | NR  |
| Lovell et al., 2001 <sup>57</sup>   | NR         | NR                         | NR        | NR          | NR              | NR        | NR       | NR          | NR  |
| Marshall et al., 2001 <sup>58</sup> | NR         | G1: 21<br>G2: 28<br>G3: 18 | NR        | NR          | NR              | NR        | NR       | NR          | Serious Adverse Events<br>G1 & G2: 9 combined<br>G3: 0<br>The study reports that the most commonly reported AEs associated with paroxetine use (with an incidence of at least 10% and twice that of placebo) were asthenia, diarrhea, abnormal ejaculation, impotence, nausea, and somnolence (data NR)." |

**Table D-9. Adverse events/harms reported by included randomized controlled trials (continued)**

| Author Year                         | Overall AE  | Withdrawal Due to AE  | Mortality | Suicidality | Disturbed Sleep   | Agitation | Sedation | Weight Gain | Other Adverse Effects   |
|-------------------------------------|---|---|-----------|-------------|---|-----------|----------|-------------|---|
| Martenyi et al., 2002 <sup>59</sup> | Martenyi et al., 2002 <sup>59</sup>   | Martenyi et al., 2002 <sup>59</sup>   | NR        | NR          | Martenyi et al., 2002 <sup>59</sup>   | NR        | NR       | NR          | Martenyi et al., 2002 <sup>59</sup>   |
| Martenyi et al., 2006 <sup>60</sup> | G1: 53%<br>G2: 55%<br>Martenyi et al., 2006 <sup>60</sup><br>G1: 55.5%<br>G2: 55.9% | G1: 2.7%<br>G2: 4.0%<br>Martenyi et al., 2006 <sup>60</sup><br>G1: 3<br>G2: 1 |           |             | Insomnia<br>G1: 12%<br>G2: 12%<br>Martenyi et al., 2006 <sup>60</sup><br>Insomnia<br>G1: 14.5%<br>G2: 11.8% |           |          |             | Most Commonly Reported<br>Headache<br>G1: 16%<br>G2: 15%<br>Nausea<br>G1: 14%<br>G2: 7%<br>Dry Mouth<br>G1: 7%<br>G2: 7%<br>Anxiety<br>G1:<br>G2: 7%<br>Martenyi et al., 2006 <sup>60</sup><br>Most Commonly Reported (> 5%)<br>Headache<br>G1: 15.5%<br>G2: 11.8%<br>Nausea<br>G1: 12.7%<br>G2: 5.9%<br>Vomiting<br>G1: 6.4%<br>G2: 2.9%<br>Dry Mouth:<br>G1: 7.3%<br>G2: 11.8%<br>Abdominal Pain<br>G1: 7.3%<br>G2: 2.9%<br>Diarrhea<br>G1: 5.5%<br>G2: 2.9 %<br>Nervousness:<br>G1: 5.5%<br>G2: 0.0% |

**Table D-9. Adverse events/harms reported by included randomized controlled trials (continued)**

| Author Year                         | Overall AE                    | Withdrawal Due to AE   | Mortality               | Suicidality                         | Disturbed Sleep | Agitation | Sedation | Weight Gain | Other Adverse Effects  |
|-------------------------------------|-------------------------------|--|-------------------------|-------------------------------------|-----------------|-----------|----------|-------------|--|
| Martenyi et al., 2007 <sup>61</sup> | G1: 68%<br>G2: 78%<br>G3: 65% | G1: 4.3%<br>G2:<br>13.1%<br>G3: 8.0%                               | G1: 0<br>G2: 0<br>G3: 0 | G1: n = 1<br>G2: n = 3<br>G3: n = 0 | NR              | NR        | NR       | NR          | Serious Adverse Events, n<br>G1: 1 (thoughts of self-mutilation)<br>G2: 5 (2 patients anxiety; 1 patient, chest pain; 1 patient, suicidal ideation; and 1 patient, gastritis)<br>G3: 2 (palpitation, thyroid carcinoma). |
| McDonagh et al., 2005 <sup>62</sup> | NR                            | NR   | NR                      | NR                                  | NR              | NR        | NR       | NR          | NR   |
| Monnelly et al., 2003 <sup>63</sup> | G1: 4<br>G2: 3                | G1: 1<br>G2: 0   | NR                      | NR                                  | NR              | NR        | NR       | NR          | Urinary retention<br>G1: 1<br>G2: 0<br>Mild Adverse Events<br>G1: 4<br>G2: 2.  |
| Monson et al., 2006 <sup>64</sup>   | NR                            | NR   | NR                      | NR                                  | NR              | NR        | NR       | NR          | NR   |
| Mueser et al., 2008 <sup>65</sup>   | NR                            | G1: 2<br>withdrawals due to "other psychiatric symptoms"<br>G2: NR | NR                      | NR                                  | NR              | NR        | NR       | NR          | NR   |
| Nacasch et al., 2011 <sup>66</sup>  | NR                            | NR   | NR                      | NR                                  | NR              | NR        | NR       | NR          | NR   |
| Neuner et al., 2004 <sup>67</sup>   | NR                            | NR   | NR                      | NR                                  | NR              | NR        | NR       | NR          | NR   |
| Neuner et al., 2008 <sup>68</sup>   | NR                            | NR   | NR                      | NR                                  | NR              | NR        | NR       | NR          | NR   |
| Neuner et al., 2010 <sup>69</sup>   | NR                            | NR   | NR                      | G1: 2<br>G2: 0                      | NR              | NR        | NR       | NR          | NR   |
| Nijdam et al., 2012 <sup>70</sup>   | NR                            | NR   | NR                      | NR                                  | NR              | NR        | NR       | NR          | NR   |

**Table D-9. Adverse events/harms reported by included randomized controlled trials (continued)**

| Author Year                       | Overall AE | Withdrawal Due to AE | Mortality | Suicidality | Disturbed Sleep             | Agitation | Sedation                     | Weight Gain | Other Adverse Effects  |
|-----------------------------------|------------|----------------------|-----------|-------------|-----------------------------|-----------|------------------------------|-------------|--|
| Panahi et al., 2011 <sup>71</sup> | NR         | NR                   | NR        | NR          | Insomnia<br>G1: 10<br>G2: 4 | NR        | Drowsiness<br>G1: 5<br>G2: 2 | NR          | AE reported by at least 10%<br>Headache<br>G1: 10<br>G2: 6<br>Nausea<br>G1: 10<br>G2: 5<br>Restlessness<br>G1: 8<br>G2: 5<br>Diarrhea<br>G1: 7<br>G2: 4<br>Dry Mouth<br>G1: 6<br>G2: 5<br>Asthenia<br>G1: 5<br>G2: 2<br>Decreased appetite<br>G1: 5<br>G2: 3<br>Constipation<br>G1: 5<br>G2: 3<br>Decreased libido<br>G1: 4<br>G2: 2 |

**Table D-9. Adverse events/harms reported by included randomized controlled trials (continued)**

| Author Year                         | Overall AE                       | Withdrawal Due to AE             | Mortality | Suicidality | Disturbed Sleep | Agitation | Sedation | Weight Gain | Other Adverse Effects   |
|-------------------------------------|----------------------------------|----------------------------------|-----------|-------------|-----------------|-----------|----------|-------------|---|
| Petrakis et al., 2011 <sup>72</sup> | G1: 2<br>G2: 3<br>G3: 1<br>G4: 3 | G1: 0<br>G2: 0<br>G3: 2<br>G4: 0 | NR        | NR          | NR              | NR        | NR       | NR          | Adverse Effects of Desipramine (G3 or G4)<br>Dizziness or lightheaded: 2<br><br>Tachycardia: 1<br><br>Adverse Effects of Paroxetine (G2 only)<br>Experienced a Seizure: 1<br><br>Side Effects of Desipramine: reported significantly more gastrointestinal symptoms (abdominal pain, nausea, vomiting, loss of appetite, constipation, diarrhea, dry mouth, coughing up blood, vomiting, black/blood/light stool, yellow eyes, weight gain, and increased thirst than paroxetine treated subjects (F = 7.67, p=0.007) |
| Raskind et al., 2003 <sup>73</sup>  | none serious                     | NR                               | NR        | NR          | NR              | NR        | NR       | NR          | Serious Adverse Events<br>G1: 0<br>G2: 0<br>Mild Orthostatic Hypotension, n<br>G1: 2 (resolved upon dose increase)<br>G2: 0   |



**Table D-9. Adverse events/harms reported by included randomized controlled trials (continued)**

| Author Year                        | Overall AE     | Withdrawal Due to AE | Mortality | Suicidality | Disturbed Sleep            | Agitation | Sedation | Weight Gain                                      | Other Adverse Effects   |
|------------------------------------|----------------|----------------------|-----------|-------------|----------------------------|-----------|----------|--|---|
| Raskind et al., 2007 <sup>74</sup> | NR             | G1: 3<br>G2: 1       | NR        | NR          | Insomnia<br>G1: 1<br>G2: 1 | NR        | NR       | NR   | Dizziness<br>G1: 9<br>G2: 6<br>Nasal or sinus Congestion<br>G1: 6<br>G2: 1<br>Headache<br>G1: 3<br>G2: 1<br>Dry Mouth<br>G1: 2<br>G2: 0<br>Sweating<br>G1: 0<br>G2: 1<br>Depression<br>G1: 0<br>G2: 1<br>Lower extremity edema<br>G1: 0<br>G2: 1<br>Blood Pressure: No significant difference |
| Reich et al., 2004 <sup>75</sup>   | G1: 4<br>G2: 1 | G1: 1<br>G2: 0       | NR        | NR          | NR                         | NR        | NR       | Mean Increase in Weight<br>G1: 2.5 lb<br>G2: 3lb | Reported by Each Group<br>G1: Sedation, dry mouth, tremor, apathy, and poor concentration<br>G2: Sedation<br># or % not reported for specific adverse events  |

**Table D-9. Adverse events/harms reported by included randomized controlled trials (continued)**

| Author Year                         | Overall AE   | Withdrawal Due to AE | Mortality  | Suicidality    | Disturbed Sleep    | Agitation | Sedation | Weight Gain | Other Adverse Effects   |
|-------------------------------------|--|----------------------|--|----------------|--------------------|-----------|----------|-------------|---|
| Resick et al., 2002 <sup>76</sup>   | NR   | NR                   | NR   | NR             | NR                 | NR        | NR       | NR          | NR  |
| Resick et al., 2003 <sup>77</sup>   |  |                      |  |                |                    |           |          |             |   |
| Resick et al., 2012 <sup>78</sup>   |  |                      |  |                |                    |           |          |             |   |
| Rothbaum et al., 1997 <sup>79</sup> | NR   | NR                   | NR   | NR             | NR                 | NR        | NR       | NR          | NR  |
| Rothbaum et al., 2005 <sup>80</sup> | NR   | NR                   | NR   | NR             | NR                 | NR        | NR       | NR          | NR  |
| Rothbaum et al., 2006 <sup>81</sup> | NR   | NR                   | NR   | NR             | NR                 | NR        | NR       | NR          | NR  |
| Schneier et al., 2012 <sup>82</sup> | NR   | NR                   | NR   | NR             | NR                 | NR        | NR       | NR          | NR  |
| Schnurr et al., 2003 <sup>83</sup>  | NR   | NR                   | G1: 0<br>G2: 4<br>One death in G2 was suicide. The other 3 deaths in the G2 group were of "natural causes" | NR             | NR                 | NR        | NR       | NR          | NR  |
| Schnurr et al., 2007 <sup>84</sup>  | G1: 5<br>G2: 14  | G1: NR<br>G2: NR     | G1: 0<br>G2: 2 (non-suicide)   | G1: 1<br>G2: 3 | NR                 | NR        | NR       | NR          | Psychiatric hospitalization<br>G1: 4<br>G2: 9   |
| Schnyder et al., 2011 <sup>85</sup> | NR   | NR                   | NR   | NR             | NR                 | NR        | NR       | NR          | NR  |
| Simon et al., 2008 <sup>86</sup>    | G1: All reported at least 1<br>G2: All reported at least 1 | G1: 1<br>G2: 1       | NR   | G1: 1<br>G2: 0 | G1: 89%<br>G2: 85% | NR        | NR       | NR          | Concentration and Memory Difficulties<br>G1: 89%<br>G2: 85%<br>Drowsiness<br>G1: 67%<br>G2: 77% |

|                                   |    |    |    |    |    |    |    |    |    |
|-----------------------------------|----|----|----|----|----|----|----|----|----|
| Spence et al., 2011 <sup>87</sup> | NR | NR | NR | NR | NR | NR | NR | NR | NR |
|-----------------------------------|----|----|----|----|----|----|----|----|----|

**Table D-9. Adverse events/harms reported by included randomized controlled trials (continued)**

| Author Year  | Overall AE     | Withdrawal Due to AE                     | Mortality      | Suicidality    | Disturbed Sleep | Agitation      | Sedation                               | Weight Gain                                     | Other Adverse Effects   |
|--|----------------|--|----------------|----------------|-----------------|----------------|--|---|---|
| Stein et al., 2002 <sup>88</sup>   | G1: 3<br>G2: 2 | G1: 3<br>G2: 2                           | G1: 0<br>G2: 0 | G1: 0<br>G2: 0 | G1: 0<br>G2: 0  | G1: 0<br>G2: 0 | G1: 2<br>G2: 0                         | G1: 13 lbs.<br>mean<br>weight<br>gain<br>G2: NR | G1: 0<br>G2: 0  |
| Tarrier et al., 1999 <sup>89</sup><br>Tarrier et al., 1999 <sup>90</sup> | NR             | NR                                       | NR             | NR             | NR              | NR             | NR                                     | NR  | NR  |
| Taylor et al., 2003 <sup>91</sup>  | NR             | NR                                       | NR             | NR             | NR              | NR             | NR                                     | NR  | NR  |
| Tucker et al., 2001 <sup>92</sup>  | NR             | G1: 17.97<br>(11.9%)<br>G2: 10<br>(6.4%) | NR             | NR             | NR              | NR             | Somnolence<br>G1:<br>17.2%<br>G2: 3.8% | NR  | Nausea<br>G1: 19.2%<br>G2: 8.3%<br>Dry Mouth<br>G1: 13.9%<br>G2: 4.5%<br>Asthenia<br>G1: 13.2%<br>G2: 5.8%<br>Abnormal-ejaculation<br>G1: 11.8%<br>G2: 3.7%<br>Incidence of non-<br>ejaculation-related sexual<br>adverse events<br>(decreased libido,<br>impotence, female<br>genital disorders)<br>G1: 7.3%<br>G2: 2.6% |

**Table D-9. Adverse events/harms reported by included randomized controlled trials (continued)**

| Author Year                       | Overall AE                 | Withdrawal Due to AE           | Mortality | Suicidality | Disturbed Sleep          | Agitation | Sedation                | Weight Gain | Other Adverse Effects  |
|-----------------------------------|----------------------------|--------------------------------|-----------|-------------|--------------------------|-----------|-------------------------|-------------|--|
| Tucker et al., 2003 <sup>93</sup> | Overall NR (just specific) | 2 overall; group not specified | NR        | NR          | Insomnia                 | NR        | Fatigue                 | NR          | Jitteriness  |
| Tucker et al., 2004 <sup>94</sup> |                            |                                |           |             | G1: 13<br>G2: 6<br>G3: 6 |           | G1: 8<br>G2: 6<br>G3: 3 |             | G1: 6<br>G2: 6<br>G3: 2<br>GI distress<br>G1: 3<br>G2: 6<br>G3: 2<br>Nausea<br>G1: 5<br>G2: 8<br>G3: 3<br>Vomiting<br>G1: 1<br>G2: 1<br>G3: 0<br>Decreased appetite<br>G1: 9<br>G2: 8<br>G3: 1<br>Increased appetite<br>G1: 7<br>G2: 8<br>G3: 5<br>Decreased sexual function<br>G1: 4<br>G2: 1<br>G3: 0<br>Dizziness<br>G1: 4<br>G2: 4<br>G3: 2<br>Sweating, chills<br>G1: 3<br>G2: 4<br>G3: 0 |

**Table D-9. Adverse events/harms reported by included randomized controlled trials (continued)**

| Author Year                             | Overall AE                                 | Withdrawal Due to AE | Mortality | Suicidality | Disturbed Sleep | Agitation                     | Sedation                  | Weight Gain  | Other Adverse Effects   |
|---|--|----------------------|-----------|-------------|-----------------|-------------------------------|---------------------------|--|---|
| Tucker et al., 2007 <sup>95</sup>       | G1: 45 <sup>c</sup><br>G2: 25 <sup>c</sup> | G1: 4<br>G2: 3       | NR        | NR          | G1: 4<br>G2: 3  | Nervousness<br>G1: 4<br>G2: 1 | Fatigue<br>G1: 4<br>G2: 0 | Weight gain in each condition<br>G1: -1.8 (3.3)<br>G2: -1.1 (2.6) kgs<br>p=0.434 | Headache<br>G1: 7<br>G2: 5<br>Sinusitis<br>G1: 5<br>G2: 2<br>Taste Perversion<br>G1: 5<br>G2: 0<br>Language problems<br>G1: 4<br>G2: 3<br>Dyspepsia<br>G1: 4<br>G2: 2<br>Paresthesia<br>G1: 4<br>G2: 1<br>Hypertension<br>G1: 2<br>G2: 4<br>Difficulty with concentration/attention<br>G1: 2<br>G2: 4 |
| van der Kolk et al., 1994 <sup>96</sup> | NR   | NR                   | NR        | NR          | NR              | NR                            | NR                        | NR   | Side Effects Reported at p<0.05 level<br>Diarrhea, n<br>G1: 25<br>G2: 16<br>Sweating, n<br>G1: 20<br>G2: 10<br>Headaches, n<br>G1: 10<br>G2: 3  |

**Table D-9. Adverse events/harms reported by included randomized controlled trials (continued)**

| Author Year                             | Overall AE   | Withdrawal Due to AE | Mortality | Suicidality | Disturbed Sleep | Agitation | Sedation                         | Weight Gain | Other Adverse Effects   |
|---|--------------|----------------------|-----------|-------------|-----------------|-----------|----------------------------------|-------------|---|
| van der Kolk et al., 2007 <sup>97</sup> | NR           | NR                   | NR        | NR          | NR              | NR        | NR                               | NR          | NR  |
| van Emmerik et al., 2008 <sup>98</sup>  | NR           | NR                   | NR        | NR          | NR              | NR        | NR                               | NR          | NR  |
| Yeh et al., 2011 <sup>99</sup>          | NR           | G1: 1<br>G2: 0       | NR        | NR          | NR              | NR        | Somnolence<br>G1: 23%<br>G2: 35% | NR          | Insomnia<br>G1: 23%<br>G2: 7%<br>Paresthia<br>G1: 17%<br>Headache<br>G1: 11%<br>G2: 21%<br>Irritability<br>G1: 11%<br>Dyspepsia<br>G1: 17%<br>Difficulty with Concentration<br>G1: 11%      |
| Zlotnick et al., 2009 <sup>100</sup>    | NR           | NR                   | NR        | NR          | NR              | NR        | NR                               | NR          | NR  |
| Zohar et al., 2002 <sup>101</sup>       | >10% overall | G1: 3<br>G2: 1       | NR        | NR          | NR              | NR        | NR                               | NR          | Nausea<br>G1: 8<br>G2: 4<br>Headache<br>G1: 6<br>G2: 3<br>Drowsiness<br>G1: 6<br>G2: 3<br>Asthenia<br>G1: 4<br>G2: 1<br>Increased appetite<br>G1: 3<br>G2: 2<br>Dry mouth<br>G1: 3<br>G2: 2 |

**Table D-9. Adverse events/harms reported by included randomized controlled trials (continued)**

| Author Year                       | Overall AE | Withdrawal Due to AE | Mortality | Suicidality | Disturbed Sleep | Agitation | Sedation | Weight Gain | Other Adverse Effects                |
|-----------------------------------|------------|----------------------|-----------|-------------|-----------------|-----------|----------|-------------|--------------------------------------|
| Zohar et al., 2002 <sup>101</sup> |            |                      |           |             |                 |           |          |             | Decreased appetite<br>G1: 3<br>G2: 1 |

<sup>a</sup> Reported by at least 10 percent of patients

<sup>b</sup> Adverse event was an adverse reaction during the provocation and somatic investigation using SPECT.

<sup>c</sup> Number of adverse events occurring in > 20 percent of subjects.

Abbreviations: AE = adverse events; kg = kilogram; NA = not applicable; NR= not reported; NS = not significant; SAE = serious adverse events.

## References for Evidence Tables

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## Appendix E. Risk of Bias Assessment

In general terms, a “low” risk of bias study has the least risk of bias and its results are considered to be valid. A “medium” risk of bias study is susceptible to some bias but probably not sufficient to invalidate its results. A “high” risk of bias study has significant risk of bias (e.g., stemming from serious errors in design, conduct, or analysis) that may invalidate its results. Two independent reviewers assigned risk of bias ratings for each study. For each article, one of the two reviewers was always an experienced investigator (DJ, JS, BG, KC, or CF). Disagreements between the two reviewers were resolved by discussion and consensus or by consulting a third member of the team. We gave high risk of bias ratings to studies that had a fatal flaw (defined as a methodological shortcoming that leads to a very high risk of bias) in one or more categories. The most common methodologic shortcomings contributing to high risk of bias ratings were high rates of attrition or differential attrition, inadequate methods used to handle missing data, and lack of intention-to-treat analysis. Below we list the 12 questions used to assess risk of bias. Then, Table E-1 provides the answers to these questions for each study. Following the table is a description of our rationale for all high risk of bias ratings.

### Randomized Controlled Trials

#### Criteria

Was randomization adequate?

Was allocation concealment adequate?

Were groups similar at baseline?

Were outcome assessors masked?

Were care providers masked?

Were patients masked?

Was overall attrition 20% or higher?

Was differential attrition 15% or higher?

Did the study use intention-to-treat analysis?

Did the study use adequate methods for handling missing data?

Were outcome measures equal, valid, and reliable?

Did study report adequate treatment fidelity (therapist adherence) based on measurement by independent raters?

**Table E-1. Quality ratings for efficacy/effectiveness trials**

| Author, Year                         | RADQ    | ACA     | Similar at BS | AMsk    | ProvMsk | PatMsk | % Comp Overall<br>I<br>G1<br>G2<br>G3<br>G4 | Overall Attrition ≥20% | Diff. Attrition ≥15% | ITT | MFD   | Meas. Equal, Valid and Reliable | Fid   | ROB  |
|--------------------------------------|---------|---------|---------------|---------|---------|--------|---|------------------------|----------------------|-----|-------|---------------------------------|-------|------|
| Akuchekian et al., 2004 <sup>1</sup> | Unclear | Unclear | Unclear       | Unclear | Unclear | Yes    | 93<br>94<br>91                              | No                     | No                   | No  | CA    | Yes                             | NA    | Med  |
| Arntz et al., 2007 <sup>2</sup>      | Unclear | Unclear | Yes           | Unclear | No      | No     | 45<br>72                                    | Yes                    | Yes                  | Yes | LOCF  | Yes                             | No    | High |
| Asukai et al., 2010 <sup>3</sup>     | Yes     | Unclear | Yes           | Yes     | No      | No     | 75<br>92                                    | No                     | Yes                  | Yes | MI    | Yes                             | Mixed | Med  |
| Bartzokis et al., 2005 <sup>4</sup>  | Unclear | Unclear | Unclear       | Yes     | Yes     | Yes    | 74<br>67<br>81                              | Yes                    | No                   | No  | Other | Yes                             | NA    | Med  |
| Basoglu et al., 2007 <sup>5</sup>    | Yes     | Yes     | Yes           | No      | No      | No     | 100<br>100<br>100                           | No                     | No                   | No  | NA    | Yes                             | No    | Med  |
| Beck et al., 2009 <sup>6</sup>       | Unclear | Unclear | Unclear       | Unclear | No      | No     | 75<br>65<br>89                              | Yes                    | Yes                  | No  | CA    | Yes                             | Yes   | High |
| Becker et al., 2007 <sup>7</sup>     | Unclear | Unclear | Unclear       | Yes     | Unclear | Yes    | 90 to<br>100<br>83 to<br>100                | No                     | No                   | Yes | LOCF  | Yes                             | NA    | Med  |
| Beidel et al., 2011 <sup>8</sup>     | Unclear | Unclear | Unclear       | Unclear | No      | No     | 86<br>78<br>94                              | No                     | Yes                  | No  | CA    | Yes                             | Yes   | High |
| Bichescu et al., 2007 <sup>9</sup>   | Unclear | Unclear | Yes           | No      | No      | No     | 100<br>100<br>100                           | No                     | No                   | NA  | NA    | Yes                             | No    | High |
| Blanchard et al., 2003 <sup>10</sup> | Unclear | Unclear | Yes           | Yes     | No      | No     | 80<br>73<br>75<br>96                        | Yes                    | Yes                  | Yes | LOCF  | Yes                             | Yes   | Med  |
| Boden et                             | Yes     | Unclear | No            | Yes     | No      | No     | 84  | Yes                    | No                   | Yes | Uncle | Yes                             | Yes   | Med  |



|  |         |         |    |         |         |     |    |     |    |     |      |     |    |     |
|--|---------|---------|----|---------|---------|-----|----|-----|----|-----|------|-----|----|-----|
| al.,<br>2012 <sup>11</sup>             |         |         |    |         |         |     | 83 |     |    |     |      | ar  |    |     |
|  |         |         |    |         |         |     | 85 |     |    |     |      |     |    |     |
| Brady et<br>al.,<br>2000 <sup>12</sup> | Unclear | Unclear | No | Unclear | Unclear | Yes | 69 | Yes | No | Yes | LOCF | Yes | NA | Med |
|  |         |         |    |         |         |     | 68 |     |    |     |      |     |    |     |
|  |         |         |    |         |         |     | 70 |     |    |     |      |     |    |     |

**Table E-1. Quality ratings for efficacy/effectiveness trials (continued)**

| Author, Year                           | RADQ    | ACA     | Similar at BS | AMsk    | Pro vMs k | PatMsk | % Comp Overall<br>G1<br>G2<br>G3<br>G4 | Overall Attrition<br>n<br>≥20% | Diff. Attrition<br>n<br>≥15% | ITT | MFD     | Meas. Equal, Valid and Reliable | Fid | ROB   |
|--|---------|---------|---------------|---------|-----------|--------|--|--------------------------------|------------------------------|-----|---------|---------------------------------|-----|---|
| Brady et al., 2005 <sup>13</sup>       | Yes     | Unclear | Yes           | Unclear | Yes       | Yes    | 63<br>69                               | Yes                            | No                           | Yes | Other   | Yes                             | NA  | Med   |
| Braun et al., 1990 <sup>14</sup>       | Unclear | Unclear | Unclear       | Yes     | Unclear   | Yes    | 63<br>57<br>67                         | Yes                            | No                           | No  | CA      | No                              | NA  | High  |
| Brom et al., 1989 <sup>15</sup>        | Unclear | Unclear | Unclear       | Unclear | No        | No     | 89<br>90<br>90<br>87                   | No                             | No                           | No  | CA      | Mixed                           | No  | High  |
| Bryant, et al., 2003 <sup>16</sup>     | Unclear | Unclear | Yes           | Yes     | No        | No     | 78<br>75<br>75<br>83                   | Yes                            | No                           | Yes | LOCF    | Yes                             | Yes | Med   |
| Bryant et al., 2008 <sup>17</sup>      | Yes     | Yes     | Yes           | Yes     | No        | No     | 76<br>74<br>79<br>68<br>86             | Yes                            | No                           | Yes | LOCF    | Yes                             | Yes | Med   |
| Butterfield et al., 2001 <sup>18</sup> | Unclear | Unclear | Unclear       | Unclear | Unclear   | Yes    | 73<br>70<br>80                         | Yes                            | No                           | Yes | CA      | Yes                             | NA  | Med   |
| Carlson et al., 1998 <sup>19</sup>     | Unclear | Unclear | No            | No      | No        | No     | 97<br>92<br>100<br>100                 | No                             | No                           | No  | Unclear | Yes                             | No  | Med (post-treatment)<br><br>High (3- & 9-mth) |
| Chard et al., 2005 <sup>20</sup>       | Unclear | Unclear | Yes           | Yes     | No        | No     | 82<br>83<br>80                         | No                             | No                           | Yes | LOCF    | Yes                             | Yes | Med   |
| Cloitre et al., 2002 <sup>21</sup>     | Unclear | Unclear | Unclear       | Yes     | No        | No     | 79<br>71<br>89                         | Yes                            | Yes                          | Yes | LOCF    | Yes                             | Yes | Med   |

**Table E-1. Quality ratings for efficacy/effectiveness trials (continued)**

| Author, Year                             | RADQ    | ACA     | Similar at BS | AMsk    | Prov Msk | PatMsk  | % Comp Overall<br>G1<br>G2<br>G3<br>G4 | Overall Attrition<br>≥20% | Diff. Attrition<br>≥15% | ITT | MFD   | Meas. Equal, Valid and Reliable | Fid | ROB  |
|--|---------|---------|---------------|---------|----------|---------|--|---------------------------|-------------------------|-----|-------|---------------------------------|-----|------|
| Cloitre et al., 2010 <sup>22</sup>       | Unclear | No      | Yes           | Yes     | No       | Unclear | 73                                     | Yes                       | Yes                     | Yes | MI    | Yes                             | Yes | Med  |
|  |         |         |               |         |          |         | 85                                     |                           |                         |     |       |                                 |     |      |
|  |         |         |               |         |          |         | 74                                     |                           |                         |     |       |                                 |     |      |
|  |         |         |               |         |          |         | 61                                     |                           |                         |     |       |                                 |     |      |
|  |         |         |               |         |          |         | 3 Month                                |                           |                         |     |       |                                 |     |      |
|  |         |         |               |         |          |         | 68                                     |                           |                         |     |       |                                 |     |      |
| 76                                       |         |         |               |         |          |         |  |                           |                         |     |       |                                 |     |      |
| 68                                       |         |         |               |         |          |         |  |                           |                         |     |       |                                 |     |      |
| 61                                       |         |         |               |         |          |         |  |                           |                         |     |       |                                 |     |      |
| 6 Month                                  |         |         |               |         |          |         |  |                           |                         |     |       |                                 |     |      |
| 63                                       |         |         |               |         |          |         |  |                           |                         |     |       |                                 |     |      |
| 70                                       |         |         |               |         |          |         |  |                           |                         |     |       |                                 |     |      |
| 61                                       |         |         |               |         |          |         |  |                           |                         |     |       |                                 |     |      |
| 61                                       |         |         |               |         |          |         |  |                           |                         |     |       |                                 |     |      |
| Connor et al., 1999 <sup>23</sup>        | Yes     | Yes     | No            | Yes     | Yes      | Yes     | 67                                     | Yes                       | Yes                     | Yes | LOCF  | Mixed                           | NA  | Med  |
| Meltzer-Brody et al., 2000 <sup>24</sup> |         |         |               |         |          |         | 78                                     |                           |                         |     |       |                                 |     |      |
|  |         |         |               |         |          |         | 59                                     |                           |                         |     |       |                                 |     |      |
| Cook et al., 2010 <sup>25</sup>          | Yes     | Unclear | Yes           | Yes     | No       | Unclear | 73                                     | Yes                       | Yes                     | Yes | MI    | Yes                             | Yes | Med  |
| Cottraux, 2008 <sup>26</sup>             | Yes     | Yes     | Yes           | Yes     | No       | No      | 81                                     | Yes                       | Yes                     | Yes | LOCF  | Yes                             | No  | Med  |
|  |         |         |               |         |          |         | 64                                     |                           |                         |     |       |                                 |     |      |
|  |         |         |               |         |          |         | 70                                     |                           |                         |     |       |                                 |     |      |
| 87                                       |         |         |               |         |          |         |  |                           |                         |     |       |                                 |     |      |
| 52                                       |         |         |               |         |          |         |  |                           |                         |     |       |                                 |     |      |
| Davidson et al., 1990 <sup>27</sup>      | Unclear | Unclear | Yes           | Yes     | Yes      | Yes     | 72                                     | Yes                       | No                      | No  | CA    | Yes                             | NA  | High |
| Davidson, et al., 1993 <sup>28</sup>     |         |         |               |         |          |         | 68                                     |                           |                         |     |       |                                 |     |      |
|  |         |         |               |         |          |         | 76                                     |                           |                         |     |       |                                 |     |      |
| Davidson et al.,                         | Yes     | Unclear | Yes           | Unclear | Unclear  | Yes     | 66                                     | Yes                       | No                      | Yes | Other | Yes                             | NA  | Med  |
|  |         |         |               |         |          |         | 67                                     |                           |                         |     |       |                                 |     |      |



**Table E-1. Quality ratings for efficacy/effectiveness trials (continued)**

| Author, Year                          | RADQ    | ACA     | Similar at BS | AMsk    | Pro vMs k | PatMsk | % Comp Overall<br>G1<br>G2<br>G3<br>G4 | Overall Attrition<br>≥20% | Diff. Attrition<br>≥15% | ITT | MFD  | Meas. Equal, Valid and Reliable | Fid   | ROB  |
|---------------------------------------|---------|---------|---------------|---------|-----------|--------|--|---------------------------|-------------------------|-----|------|---------------------------------|-------|------|
| Davidson et al., 2003 <sup>30</sup>   | Unclear | Unclear | Yes           | Unclear | Yes       | Yes    | 82<br>67                               | Yes                       | Yes                     | Yes | LOCF | Yes                             | NA    | Med  |
| Davidson et al., 2006 <sup>31</sup>   | Unclear | Unclear | Unclear       | Unclear | Yes       | Yes    | 65<br>NR<br>NR                         | Yes                       | No                      | Yes | LOCF | Yes                             | NA    | Med  |
| Davidson et al., 2006 <sup>32</sup>   | Yes     | Unclear | Yes           | Unclear | Yes       | Yes    | 68<br>70<br>67                         | Yes                       | No                      | Yes | LOCF | Yes                             | NA    | Med  |
| Davidson et al., 2007 <sup>33</sup>   | Unclear | Unclear | Unclear       | Yes     | Yes       | Yes    | 61<br>66<br>55                         | Yes                       | No                      | No  | LOCF | Yes                             | NA    | Med  |
| Davis et al., 2004 <sup>34</sup>      | Unclear | Yes     | No            | Yes     | Yes       | Yes    | 55<br>52<br>60                         | Yes                       | No                      | Yes | LOCF | Yes                             | NA    | High |
| Davis et al., 2008 <sup>35</sup>      | Yes     | Yes     | Yes           | Yes     | Yes       | Yes    | 77<br>83                               | Yes                       | No                      | Yes | LOCF | Yes                             | NA    | Low  |
| Devilly et al., 1999 <sup>36</sup>    | No      | No      | No            | Unclear | No        | No     | 72<br>80<br>64                         | Yes                       | Yes                     | No  | NA   | Yes                             | Yes   | High |
| Difede et al., 2007 <sup>37</sup>     | No      | No      | No            | Yes     | No        | No     | 86<br>77<br>100                        | No                        | Yes                     | No  | CA   | Yes                             | Mixed | High |
| Difede et al., 2007 <sup>38</sup>     | Unclear | Yes     | Yes           | Yes     | No        | No     | 68<br>47<br>88                         | Yes                       | Yes                     | Yes | LOCF | Yes                             | Yes   | High |
| Echeburu a et al., 1996 <sup>39</sup> | Unclear | Unclear | Unclear       | No      | No        | No     | 100<br>100<br>100                      | No                        | No                      | Yes | NA   | No                              | No    | High |
| Echeburu a et al., 1997 <sup>40</sup> | No      | No      | Unclear       | Unclear | No        | No     | 100<br>100<br>100                      | No                        | No                      | Yes | NA   | Yes                             | No    | High |

**Table E-1. Quality ratings for efficacy/effectiveness trials (continued)**

| Author, Year  | RADQ    | ACA     | Similar at BS | AMsk    | Pro vMs k | PatMsk | % Comp Overall<br>G1<br>G2<br>G3<br>G4 | Overall Attrition<br>≥20% | Diff. Attrition<br>≥15% | ITT | MFD                    | Meas. Equal, Valid and Reliable | Fid   | ROB  |
|---|---------|---------|---------------|---------|-----------|--------|--|---------------------------|-------------------------|-----|------------------------|---------------------------------|-------|------|
| Ehlers et al., 2003 <sup>41</sup>                                     | Yes     | Yes     | Unclear       | Yes     | No        | No     | 100<br>89<br>90                        | No                        | No                      | Yes | Unclear                | Yes                             | No    | Med  |
| Ehlers et al., 2005 <sup>42</sup>                                     | Unclear | Unclear | Yes           | Yes     | No        | No     | 100<br>100<br>100                      | No                        | No                      | No  | NA                     | Yes                             | Mixed | Med  |
| Fecteau et al., 1999 <sup>43</sup>                                    | Unclear | Unclear | No            | No      | No        | No     | 83<br>91                               | No                        | No                      | No  | CA                     | Yes                             | Yes   | Med  |
| Feske et al., 2008 <sup>44</sup>                                      | Unclear | Unclear | Yes           | Unclear | No        | No     | 78<br>69<br>86                         | Yes                       | Yes                     | No  | CA                     | Yes                             | No    | High |
| Foa et al., 1991 <sup>45</sup>  | Unclear | Unclear | No            | Yes     | No        | No     | 82<br>82<br>71<br>79<br>100            | No                        | Yes                     | No  | CA                     | Yes                             | No    | High |
| Foa et al., 2005 <sup>46</sup>  | No      | Yes     | No            | Yes     | No        | No     | 64<br>66<br>59<br>96                   | Yes                       | Yes                     | Yes | LOCF                   | Yes                             | Yes   | Med  |
| Foa et al., 1999 <sup>47</sup><br>Zoellner et al., 1999 <sup>48</sup> | Unclear | Unclear | Unclear       | Yes     | No        | No     | 82<br>92<br>73<br>73<br>100            | No                        | Yes                     | Yes | LOCF                   | Yes                             | Yes   | Med  |
| Forbes et al., 2012 <sup>49</sup>                                     | Yes     | Yes     | Yes           | Yes     | No        | No     | 78<br>80<br>79                         | Yes                       | No                      | Yes | LOCF                   | Yes                             | Yes   | Med  |
| Ford et al., 2011 <sup>50</sup>                                       | Yes     | Yes     | Unclear       | No      | No        | No     | 71<br>71<br>66<br>78                   | Yes                       | No                      | Yes | Mixed model regression | Yes                             | Yes   | Med  |

| Author, Year                        | RADQ | ACA     | Similar at BS | AMsk | Pro vMsk | PatMsk | % Comp Overall<br>G1<br>G2<br>G3<br>G4 | Overall Attrition ≥20% | Diff. Attrition ≥15% | ITT | MFD  | Meas. Equal, Valid and Reliable | Fid | ROB |
|-------------------------------------|------|---------|---------------|------|----------|--------|--|------------------------|----------------------|-----|------|---------------------------------|-----|-----|
| Friedman et al., 2007 <sup>31</sup> | Yes  | Unclear | Yes           | Yes  | Unclear  | Yes    | 70<br>83                               | Yes                    | No                   | Yes | LOCF | Yes                             | NA  | Med |

**Table E-1. Quality ratings for efficacy/effectiveness trials (continued)**

| Author, Year                              | RADQ    | ACA     | Similar at BS | AMsk    | Pro vMs k | PatMsk  | % Comp Overall<br>G1<br>G2<br>G3<br>G4 | Overall Attrition<br>≥20% | Diff. Attrition<br>≥15% | ITT | MFD                  | Meas. Equal, Valid and Reliable | Fid | ROB  |
|---|---------|---------|---------------|---------|-----------|---------|--|---------------------------|-------------------------|-----|----------------------|---------------------------------|-----|------|
| Frommberger et al., 2004 <sup>52</sup>    | Unclear | Unclear | Unclear       | Unclear | Unclear   | No      | 76<br>80<br>73                         | Yes                       | No                      | No  | CA                   | Yes                             | No  | High |
| Gamito et al., 2010 <sup>53</sup>         | Unclear | Unclear | Unclear       | No      | No        | No      | 90<br>80<br>100<br>100                 | No                        | No                      | No  | CA                   | Yes                             | No  | Med  |
| Gersons et al., 2000 <sup>54</sup>        | Unclear | Unclear | No            | Yes     | No        | No      | 98<br>100<br>95                        | No                        | No                      | NR  | Unclear              | Yes                             | Yes | Med  |
| Hamner et al., 2003 <sup>55</sup>         | Unclear | Unclear | Yes           | Yes     | Yes       | Yes     | 53<br>67                               | Yes                       | No                      | Yes | LOCF                 | Yes                             | Yes | Med  |
| Hamner et al., 2009 <sup>56</sup>         | Unclear | Unclear | Yes           | Yes     | No        | Unclear | 56<br>46                               | Yes                       | No                      | Yes | Other                | Yes                             | NA  | High |
| Hensel-Dittman et al., 2011 <sup>57</sup> | Yes     | Yes     | No            | No      | No        | No      | 75<br>73<br>77                         | Yes                       | No                      | Yes | Mixed effects models | Yes                             | No  | High |
| Hertzberg et al., 1999 <sup>58</sup>      | Unclear | Unclear | Unclear       | Unclear | Unclear   | Yes     | 93<br>91<br>100                        | No                        | No                      | No  | CA                   | Mixed                           | NA  | High |
| Hertzberg et al., 2000 <sup>59</sup>      | Unclear | Unclear | Unclear       | Unclear | Unclear   | Yes     | 92<br>100<br>83                        | No                        | Yes                     | No  | Other                | Mixed                           | NA  | High |
| Hien et al., 2004 <sup>60</sup>           | Unclear | Unclear | Yes           | Unclear | No        | No      | 76<br>61<br>71<br>100                  | Yes                       | No                      | Yes | LOCF                 | Yes                             | Yes | Med  |



**Table E-1. Quality ratings for efficacy/effectiveness trials (continued)**

| Author, Year                          | RADQ    | ACA     | Similar at BS | AMsk    | Pro vM sk | PatMsk  | % Comp Overall<br>G1<br>G2<br>G3<br>G4                   | Overall Attrition<br>n<br>≥20% | Diff. Attrition<br>n<br>≥15% | ITT | MFD   | Meas. Equal, Valid and Reliable | Fid | ROB  |
|---------------------------------------|---------|---------|---------------|---------|-----------|---------|--|--------------------------------|------------------------------|-----|-------|---------------------------------|-----|------|
| Hien et al., 2009 <sup>61</sup>       | Yes     | Yes     | Yes           | Yes     | No        | No      | 1 week<br>63   | Yes                            | No                           | Yes | Other | Yes                             | Yes | Med  |
| Hien et al., 2012 <sup>62</sup>       |         |         |               |         |           |         | 61<br>64<br>3 mos.<br>63<br>58<br>12<br>mos.<br>63<br>59 |                                |                              |     |       |                                 |     |      |
| Hinton et al., 2005 <sup>63</sup>     | Unclear | Unclear | Yes           | Yes     | No        | No      | 100<br>100<br>100  | No                             | No                           | No  | NA    | Yes                             | No  | Med  |
| Hinton et al., 2009 <sup>64</sup>     | Yes     | Unclear | Yes           | Yes     | No        | No      | 100<br>100<br>100  | No                             | No                           | No  | NA    | Yes                             | No  | Med  |
| Hinton et al., 2011 <sup>65</sup>     | Unclear | Unclear | Yes           | Unclear | No        | Unclear | 100<br>100<br>100  | No                             | No                           | No  | NA    | Yes                             | No  | Med  |
| Hogberg et al., 2007 <sup>66</sup>    | Yes     | Yes     | Yes           | Yes     | No        | No      | 88<br>92<br>82   | No                             | No                           | No  | CA    | Yes                             | Yes | Med  |
| Hollifield et al., 2007 <sup>67</sup> | Yes     | Yes     | Yes           | Yes     | No        | No      | 78<br>66<br>75   | Yes                            | No                           | Yes | LOCF  | Yes                             | No  | Med  |
| Ironson et al., 2002 <sup>68</sup>    | No      | Unclear | No            | No      | No        | No      | 73<br>50<br>100  | Yes                            | Yes                          | No  | CA    | Yes                             | No  | High |
| Johnson et al., 2006 <sup>69</sup>    | Unclear | Unclear | No            | Yes     | No        | No      | 75<br>73<br>79   | Yes                            | No                           | No  | CA    | Yes                             | No  | High |
| Johnson et al., 2011 <sup>70</sup>    | Yes     | Unclear | No            | No      | No        | No      | 91<br>97   | No                             | No                           | Yes | Other | Yes                             | Yes | Med  |

**Table E-1. Quality ratings for efficacy/effectiveness trials (continued)**

| Author, Year                         | RADQ    | ACA     | Similar at BS | AMsk    | Pro vM sk | PatMsk | % Comp Overall<br>G1<br>G2<br>G3<br>G4      | Overall Attrition<br>n<br>≥20% | Diff. Attrition<br>n<br>≥15% | ITT | MFD   | Meas. Equal, Valid and Reliable | Fid   | ROB  |
|--------------------------------------|---------|---------|---------------|---------|-----------|--------|---|--------------------------------|------------------------------|-----|-------|---------------------------------|-------|------|
| Karatzias et al., 2011 <sup>71</sup> | Unclear | Unclear | Yes           | Yes     | No        | No     | 59<br>57<br>61<br><br>F/U<br>50<br>48<br>52 | Yes                            | No                           | Yes | Other | Yes                             | Mixed | High |
| Keane et al., 1989 <sup>72</sup>     | Unclear | Unclear | No            | No      | No        | No     | NR<br>NR<br>NR                              | NR                             | NR                           | NR  | NR    | No                              | No    | High |
| Kosten et al., 1991 <sup>73</sup>    | Unclear | Unclear | No            | Yes     | Yes       | Yes    | 52<br>39<br>79<br>33                        | Yes                            | Yes                          | Yes | LOCF  | Yes                             | NA    | High |
| Krakov et al., 2000 <sup>74</sup>    | Unclear | Unclear | Yes           | Unclear | No        | No     | 54<br>49<br>59                              | Yes                            | No                           | No  | CA    | Yes                             | No    | High |
| Krakov et al., 2001 <sup>75</sup>    | Yes     | Unclear | Yes           | Yes     | No        | No     | 68<br>61<br>75                              | Yes                            | No                           | Yes | LOCF  | Yes                             | No    | Med  |
| Krupnick et al., 2008 <sup>76</sup>  | Unclear | Unclear | Unclear       | Unclear | No        | No     | 63<br>44                                    | Yes                            | Yes                          | Yes | Other | Yes                             | No    | High |
| Kruse et al., 2009 <sup>77</sup>     | NA      | NA      | No            | Unclear | No        | No     | 91<br>97<br>86                              | No                             | No                           | No  | CA    | Yes                             | No    | Med  |
| Krystal et al., 2011 <sup>78</sup>   | Yes     | Yes     | Yes           | Unclear | Yes       | Yes    | 83<br>84<br>83                              | No                             | No                           | Yes | MI    | Yes                             | NA    | Low  |
| Kubany et al., 2003 <sup>79</sup>    | Unclear | Unclear | Yes           | Yes     | No        | No     | 86<br>95<br>78                              | No                             | Yes                          | Yes | LOCF  | Yes                             | No    | Med  |

**Table E-1. Quality ratings for efficacy/effectiveness trials (continued)**

| Author, Year                        | RADQ    | ACA     | Similar at BS | AMsk    | Pro v M s k | PatMsk  | % Comp Overall<br>G1<br>G2<br>G3<br>G4                       | Overall Attrition<br>≥20% | Diff. Attrition<br>≥15% | ITT | MFD  | Meas. Equal, Valid and Reliable | Fid | ROB  |
|-------------------------------------|---------|---------|---------------|---------|-------------|---------|--|---------------------------|-------------------------|-----|--|---------------------------------|-----|------|
| Kubany et al., 2004 <sup>80</sup>   | Unclear | Unclear | Unclear       | Yes     | No          | No      | 65<br>73<br>56   | Yes                       | Yes                     | Yes | Main analysis: CA<br>Some from ITT analysis: LO CF | Yes                             | No  | Med  |
| Lee et al., 2002 <sup>81</sup>      | No      | No      | Unclear       | No      | No          | No      | 89<br>NR<br>NR   | No                        | No                      | NR  | Unclear  | Yes                             | Yes | High |
| Liedl et al., 2011 <sup>82</sup>    | Unclear | Unclear | Yes           | Unclear | No          | Unclear | 94<br>92<br>92<br>100<br><br>3 Month<br>83<br>83<br>83<br>83 | No                        | No                      | No  | NA   | Yes                             | No  | Med  |
| Lindauer et al., 2005 <sup>83</sup> | Yes     | Yes     | Yes           | Yes     | No          | No      | 75<br>58<br>92   | Yes                       | Yes                     | Yes | LOCF   | Yes                             | Yes | Med  |
| Lindley et al., 2007 <sup>84</sup>  | Unclear | Unclear | Yes           | Yes     | Yes         | Yes     | 45<br>75   | Yes                       | Yes                     | No  | Unclear  | Yes                             | NA  | High |
| Litz et al., 2007 <sup>85</sup>     | Unclear | Unclear | Yes           | Yes     | No          | No      | 73<br>Unclear<br>Unclear                                     | Yes                       | No                      | Yes | Other  | Yes                             | No  | Med  |

**Table E-1. Quality ratings for efficacy/effectiveness trials (continued)**

| Author, Year                        | RADQ    | ACA     | Similar at BS | AMsk    | ProvMsk | Pat Msk | % Comp Overall<br>G1<br>G2<br>G3<br>G4 | Overall Attrition<br>≥20% | Diff. Attrition<br>≥15% | ITT | MFD   | Meas. Equal, Valid and Reliable | Fid | ROB  |
|-------------------------------------|---------|---------|---------------|---------|---------|---------|--|---------------------------|-------------------------|-----|-------|---------------------------------|-----|------|
| Marcus et al., 1997 <sup>86</sup>   | Yes     | Unclear | NR            | No      | No      | No      | NR                                     | NR                        | NR                      | No  | Other | Yes                             | No  | High |
| Marks et al., 1998 <sup>87</sup>    | Yes     | Unclear | No            | Yes     | No      | No      | 89                                     | No                        | Yes                     | Yes | LOCF  | Yes                             | Yes | Med  |
| Lovell et al., 2001 <sup>88</sup>   |         |         |               |         |         |         | 87<br>95<br>79<br>95                   |                           |                         |     |       |                                 |     |      |
| Marshall et al., 2001 <sup>89</sup> | Unclear | Unclear | Unclear       | Unclear | Yes     | Yes     | 63<br>65<br>61<br>64                   | Yes                       | No                      | Yes | LOCF  | Yes                             | NA  | Med  |
| Marshall et al., 2007 <sup>90</sup> | Unclear | Unclear | Unclear       | Yes     | Yes     | Yes     | 47<br>Unclear<br>Unclear               | Yes                       | Yes                     | Yes | Other | Yes                             | NA  | High |
| Martenyi et al., 2002 <sup>91</sup> | Yes     | Unclear | Yes           | Unclear | Unclear | Yes     | NR                                     | NR                        | NR                      | Yes | LOCF  | Yes                             | NA  | Med  |
| Martenyi et al., 2006 <sup>92</sup> |         |         |               |         |         |         |  |                           |                         |     |       |                                 |     |      |
| Martenyi et al., 2007 <sup>93</sup> | Unclear | Unclear | Yes           | Yes     | Unclear | Yes     | 86<br>90<br>88                         | No                        | No                      | Yes | LOCF  | Yes                             | NA  | Med  |
| McDonagh et al., 2005 <sup>94</sup> | Unclear | Unclear | Yes           | Yes     | No      | No      | 67<br>59<br>91<br>91<br>77             | Yes                       | Yes                     | Yes | LOCF  | Yes                             | Yes | Med  |
| McLay et al., 2011 <sup>95</sup>    | Unclear | Unclear | Unclear       | Unclear | No      | No      | 95<br>100<br>90                        | No                        | No                      | No  | CA    | Mixed                           | No  | High |
| McRae et al.,                       | Unclear | Unclear | Unclear       | Unclear | Yes     | Yes     | 70<br>68                               | Yes                       | No                      | No  | None  | Yes                             | NA  | High |

| Author, Year                        | RADQ    | ACA     | Similar at BS | AMsk | ProvMsk | Pat Msk | % Comp Overall<br>G1<br>G2<br>G3<br>G4 | Overall Attrition ≥20% | Diff. Attrition ≥15% | ITT | MFD | Meas. Equal, Valid and Reliable | Fid | ROB |
|-------------------------------------|---------|---------|---------------|------|---------|---------|--|------------------------|----------------------|-----|-----|---------------------------------|-----|-----|
| 2004 <sup>96</sup>                  |         |         |               |      |         |         | 72                                     |                        |                      |     |     |                                 |     |     |
| Monnelly et al., 2003 <sup>97</sup> | Unclear | Unclear | Unclear       | Yes  | Yes     | Yes     | 88<br>100                              | No                     | No                   | No  | CA  | Yes                             | NA  | Med |

**Table E-1. Quality ratings for efficacy/effectiveness trials (continued)**

| Author, Year                             | RADQ    | ACA     | Similar at BS | AMsk    | ProvMsk | PatMsk | % Comp Overall<br>G1<br>G2<br>G3<br>G4 | Overall Attrition ≥20% | Diff. Attrition ≥15% | ITT     | MFD                 | Meas. Equal, Valid and Reliable | Fid   | ROB  |
|--|---------|---------|---------------|---------|---------|--------|--|------------------------|----------------------|---------|---------------------|---------------------------------|-------|------|
| Monson et al., 2006 <sup>98</sup>        | Unclear | Unclear | Yes           | Yes     | No      | No     | 83<br>80<br>87                         | No                     | No                   | Yes     | Other               | Yes                             | Yes   | Med  |
| Mueser et al., 2008 <sup>99</sup><br>391 | Yes     | Yes     | Yes           | Yes     | No      | Yes    | 68<br>70<br>65                         | Yes                    | Yes                  | Yes     | MI                  | Yes                             | NR    | Med  |
| Nacasch et al., 2011 <sup>100</sup>      | Unclear | Yes     | Yes           | Yes     | No      | No     | 87<br>87<br>87                         | No                     | No                   | Yes     | Unclear             | Yes                             | No    | Med  |
| Neuner et al., 2004 <sup>101</sup>       | Yes     | Yes     | Yes           | Yes     | No      | No     | 93<br>88<br>93<br>100                  | No                     | No                   | Yes     | Other               | Yes                             | Mixed | Med  |
| Neuner et al., 2008 <sup>102</sup>       | No      | Yes     | Yes           | Yes     | No      | No     | 91<br>96<br>80<br>100                  | Yes                    | Yes                  | Yes     | Other               | Yes                             | Yes   | Med  |
| Neuner et al., 2010 <sup>103</sup>       | Unclear | Unclear | Yes           | Yes     | No      | No     | 94<br>88<br>100                        | No                     | No                   | Yes     | Other               | Yes                             | No    | Med  |
| Nijdam et al., 2012 <sup>104</sup>       | Yes     | Yes     | Yes           | Yes     | No      | No     | 64<br>60<br>69                         | Yes                    | No                   | Yes     | Mixed linear models | Yes                             | Yes   | Med  |
| Panahi et al., 2011 <sup>105</sup>       | Yes     | Unclear | Yes           | Yes     | Yes     | Yes    | 89<br>91<br>86                         | No                     | No                   | Yes     | LOCF & MI           | Yes                             | NA    | Low  |
| Otto et al., 2003 <sup>106</sup>         | Unclear | Unclear | No            | Unclear | No      | No     | NR<br>NR<br>NR                         | No                     | No                   | Unclear | Other               | Yes                             | No    | High |
| Padala et al., 2006 <sup>107</sup>       | Unclear | Unclear | No            | Unclear | Yes     | Yes    | 75<br>82<br>67                         | Yes                    | Yes                  | No      | CA                  | Yes                             | NA    | High |

|  |         |         |         |    |    |    |    |     |     |    |         |     |    |      |
|--|---------|---------|---------|----|----|----|----|-----|-----|----|---------|-----|----|------|
| Paunovic<br>et al.,<br>2001 <sup>108</sup> | Unclear | Unclear | Unclear | No | No | No | 80 | Yes | Yes | NR | Unclear | Yes | No | High |
|  |         |         |         |    |    |    | 89 |     |     |    |         |     |    |      |
|  |         |         |         |    |    |    | 73 |     |     |    |         |     |    |      |

**Table E-1. Quality ratings for efficacy/effectiveness trials (continued)**

| Author, Year                           | RADQ    | ACA     | Similar at BS | AMsk    | Pro vMsk k | PatMsk  | % Comp Overall<br>G1<br>G2<br>G3<br>G4                           | Overall Attrition<br>n<br>≥20% | Diff. Attrition<br>n<br>≥15% | ITT | MFD   | Meas. Equal, Valid and Reliable | Fid | ROB  |
|--|---------|---------|---------------|---------|------------|---------|--|--------------------------------|------------------------------|-----|-------|---------------------------------|-----|------|
| Petrakis et al., 2011 <sup>109</sup>   | Unclear | Yes     | No            | Yes     | Yes        | Yes     | 64<br>80<br>73<br>67   | Yes                            | Yes                          | Yes | Other | Yes                             | Yes | Med  |
| Power et al., 2002 <sup>110</sup>      | Yes     | Yes     | Yes           | Yes     | No         | No      | 69<br>69<br>57<br>83   | Yes                            | Yes                          | No  | CA    | Yes                             | No  | High |
| Raskind et al., 2003 <sup>111</sup>    | Unclear | Unclear | Unclear       | Yes     | Yes        | Yes     | 100<br>60 (only 20% of those who received placebo 2nd completed) | Yes                            | Yes                          | No  | LOCF  | Yes                             | NA  | Med  |
| Raskind et al., 2007 <sup>112</sup>    | Yes     | Unclear | Unclear       | Yes     | Yes        | Yes     | 85<br>80<br>85   | No                             | No                           | Yes | LOCF  | Yes                             | Yes | Med  |
| Rauch et al., 2009 <sup>113</sup>      | Unclear | Unclear | No            | Yes     | No         | No      | 68<br>66<br>60<br>96   | Yes                            | Yes                          | No  | CA    | Yes                             | No  | High |
| Ready et al., 2010 <sup>114</sup>      | Unclear | Unclear | No            | Yes     | No         | No      | 82<br>83<br>80   | No                             | No                           | No  | CA    | Yes                             | No  | High |
| Reich, 2005 <sup>115</sup>             | Unclear | Unclear | Yes           | Unclear | Yes        | Yes     | 76<br>75<br>78   | Yes                            | No                           | Yes | LOCF  | Yes                             | NA  | Med  |
| Reist, 1989 <sup>116</sup>             | Unclear | Unclear | Unclear       | Unclear | Unclear    | Unclear | 67<br>NR<br>NR   | Yes                            | NR                           | No  | CA    | No                              | NA  | High |
| Resick, 2002 <sup>117</sup><br>Resick, | Unclear | Unclear | Yes           | Yes     | No         | No      | 67<br>66<br>65   | Yes                            | Yes                          | Yes | LOCF  | Yes                             | Yes | Med  |



| Author, Year  | RADQ | ACA | Similar at BS | AMsk | ProvMsk | PatMsk | % Comp Overall<br>G1<br>G2<br>G3<br>G4 | Overall Attrition<br>≥20% | Diff. Attrition<br>≥15% | ITT | MFD | Meas. Equal, Valid and Reliable | Fid | ROB |
|---|------|-----|---------------|------|---------|--------|--|---------------------------|-------------------------|-----|-----|---------------------------------|-----|-----|
| 2003 <sup>118</sup><br>Resick et al., 2012 <sup>119</sup> |      |     |               |      |         |        | 85                                     |                           |                         |     |     |                                 |     |     |

**Table E-1. Quality ratings for efficacy/effectiveness trials (continued)**

| Author, Year                  | RADQ    | ACA     | Similar at BS | AMsk    | ProvMsk | PatMsk | % Comp Overall<br>G1<br>G2<br>G3<br>G4                    | Overall Attrition<br>≥20% | Diff. Attrition<br>≥15% | ITT | MFD     | Meas. Equal, Valid and Reliable | Fid | ROB  |
|-------------------------------|---------|---------|---------------|---------|---------|--------|---|---------------------------|-------------------------|-----|---------|---------------------------------|-----|------|
| Rothbaum, 1997 <sup>120</sup> | Unclear | Unclear | No            | Yes     | No      | No     | 86<br>NR<br>NR  | No                        | Unclear                 | No  | Unclear | Yes                             | Yes | Med  |
| Rothbaum, 2005 <sup>121</sup> | Unclear | Unclear | No            | Yes     | No      | No     | 81<br>NR<br>NR<br>NR                                      | No                        | No                      | No  | CA      | Yes                             | Yes | Med  |
| Rothbaum, 2006 <sup>122</sup> | Unclear | Unclear | Yes           | Yes     | No      | No     | 89<br>97<br>82  | No                        | No                      | Yes | LOCF    | Yes                             | No  | Med  |
| Rothbaum, 2008 <sup>123</sup> | Unclear | Unclear | Yes           | Unclear | Unclear | Yes    | 64<br>100   | Yes                       | Yes                     | No  | CA      | Yes                             | NA  | High |
| Schneier, 2012 <sup>124</sup> | Yes     | Yes     | Yes           | Yes     | No      | No     | 70<br>68<br>72  | Yes                       | No                      | Yes | CA      | Yes                             | Yes | Med  |
| Schnurr, 2003 <sup>125</sup>  | Yes     | Yes     | Yes           | Yes     | No      | No     | 84<br>77<br>91<br><br>Booster treatment<br>92<br>96<br>91 | No                        | No                      | Yes | Other   | Yes                             | Yes | Low  |

| Author, Year                  | RADQ    | ACA     | Similar at BS | AMsk | Pro vMsk | PatMsk | % Comp Overall<br>G1<br>G2<br>G3<br>G4 | Overall Attrition ≥20% | Diff. Attrition ≥15% | ITT | MFD  | Meas. Equal, Valid and Reliable | Fid | ROB |
|-------------------------------|---------|---------|---------------|------|----------|--------|--|------------------------|----------------------|-----|------|---------------------------------|-----|-----|
| Schnurr, 2007 <sup>126</sup>  | Yes     | Yes     | Yes           | Yes  | No       | No     | 71<br>62<br>79                         | Yes                    | Yes                  | Yes | MI   | Yes                             | Yes | Med |
| Schnyder, 2011 <sup>127</sup> | Unclear | Unclear | No            | Yes  | No       | No     | 93<br>94<br>93                         | Yes                    | No                   | Yes | LOCF | Yes                             | Yes | Med |
| Simon, 2008 <sup>128</sup>    | Unclear | Unclear | Yes           | Yes  | Yes      | Yes    | 80<br>73<br>86                         | Yes                    | No                   | Yes | LOCF | Yes                             | No  | Med |

**Table E-1. Quality ratings for efficacy/effectiveness trials (continued)**

| Author, Year                      | RADQ    | ACA     | Similar at BS | AMsk    | Pro vMs k | PatMsk  | % Comp Overall<br>G1<br>G2<br>G3<br>G4 | Overall Attrition<br>≥20% | Diff. Attrition<br>≥15% | ITT | MFD   | Meas. Equal, Valid and Reliable | Fid | ROB  |
|-----------------------------------|---------|---------|---------------|---------|-----------|---------|--|---------------------------|-------------------------|-----|-------|---------------------------------|-----|------|
| Spence, 2011 <sup>129</sup>       | Yes     | Unclear | No            | No      | Unclear   | No      | 81<br>78<br>86                         | No                        | No                      | Yes | Other | Yes                             | No  | Med  |
| Spivak, 2006 <sup>130</sup>       | Yes     | Unclear | Yes           | Yes     | Yes       | Yes     | 70<br>55<br>85                         | Yes                       | Yes                     | No  | CA    | Yes                             | NA  | High |
| Stein, 2002 <sup>131</sup>        | Unclear | Unclear | Yes           | Yes     | Yes       | Yes     | 70<br>78                               | Yes                       | No                      | Yes | LOCF  | Yes                             | NA  | Med  |
| Tarrier, 1999 <sup>132</sup>      | Yes     | Yes     | No            | Yes     | No        | No      | 86<br>83<br>89                         | No                        | No                      | No  | CA    | Yes                             | Yes | Med  |
| Tarrier, 1999 <sup>133</sup>      |         |         |               |         |           |         |  |                           |                         |     |       |                                 |     |      |
| Taylor, 2003 <sup>134</sup>       | Unclear | Unclear | Yes           | Yes     | Yes       | No      | 75<br>68<br>79<br>79                   | Yes                       | No                      | No  | CA    | Yes                             | Yes | Med  |
| Tucker, 2001 <sup>135</sup>       | Unclear | Unclear | Yes           | Unclear | Unclear   | Yes     | 61<br>62<br>60                         | Yes                       | No                      | Yes | LOCF  | Yes                             | NA  | Med  |
| Tucker, 2003 <sup>136</sup>       | Unclear | Unclear | Yes           | Yes     | Yes       | Yes     | 76<br>80<br>74<br>70                   | Yes                       | No                      | No  | LOCF  | Yes                             | NA  | Med  |
| Tucker, 2004 <sup>137</sup>       |         |         |               |         |           |         |  |                           |                         |     |       |                                 |     |      |
| Tucker, 2007 <sup>138</sup>       | Yes     | Yes     | Yes           | Yes     | Unclear   | Yes     | 74<br>84                               | Yes                       | No                      | Yes | LOCF  | Yes                             | NA  | Med  |
| Ulmer, 2011 <sup>139</sup>        | Unclear | Unclear | Yes           | No      | No        | Unclear | 82<br>67<br>100                        | No                        | Yes                     | Yes | Other | Yes                             | No  | High |
| van der Kolk, 1994 <sup>140</sup> | Unclear | Unclear | Unclear       | Unclear | Unclear   | Yes     | 73<br>64<br>87                         | Yes                       | Yes                     | No  | CA    | Yes                             | NA  | Med  |
| van der Kolk, 2007 <sup>141</sup> | Unclear | Unclear | Yes           | Yes     | Yes       | Yes     | 83<br>87<br>90                         | No                        | No                      | Yes | LOCF  | Yes                             | NA  | Med  |

**Table E-1. Quality ratings for efficacy/effectiveness trials (continued)**

| Author, Year                     | RADQ    | ACA     | Similar at BS | AMsk | Prov Msk | PatMsk | % Comp Overall<br>G1<br>G2<br>G3<br>G4 | Overall Attrition<br>≥20% | Diff. Attrition<br>≥15% | ITT | MFD     | Meas. Equal, Valid and Reliable | Fid | ROB  |
|----------------------------------|---------|---------|---------------|------|----------|--------|--|---------------------------|-------------------------|-----|---------|---------------------------------|-----|------|
| van Emmerik, 2008 <sup>142</sup> | Yes     | Yes     | Yes           | Yes  | No       | No     | 68<br>NR<br>NR                         | Yes                       | No                      | Yes | LOCF    | Yes                             | No  | Med  |
| Wagner, 2007 <sup>143</sup>      | Unclear | Unclear | No            | Yes  | No       | No     | 88<br>75<br>100                        | No                        | No                      | Yes | LOCF    | Yes                             | No  | High |
| Yeh, 2011 <sup>144</sup>         | Yes     | Yes     | No            | Yes  | Yes      | Yes    | 74<br>82<br>67                         | Yes                       | Yes                     | No  | LOCF    | Yes                             | NA  | Med  |
| Zlotnick, 1997 <sup>145</sup>    | Unclear | Unclear | No            | No   | No       | No     | 69<br>71<br>67                         | Yes                       | No                      | No  | CA      | Mixed                           | No  | High |
| Zlotnick, 2009 <sup>146</sup>    | Unclear | Unclear | No            | No   | No       | No     | 90<br>85<br>95                         | No                        | No                      | No  | CA      | Yes                             | No  | Med  |
| Zohar, 2002 <sup>147</sup>       | Unclear | Unclear | No            | Yes  | Yes      | Yes    | 74<br>79                               | Yes                       | No                      | Yes | Unclear | Yes                             | Yes | Med  |

Abbreviations: ACA = allocation concealment adequate; AMsk = assessor masked; BS = baseline; CA = Completer Analyses; Diff = differential; Fid = Reported adequate treatment fidelity; ITT = intent-to-treat; LOCF = Last Observation Carried Forward = Med = Medium; MFD = Method of handling dropouts; MI = Multiple Imputation; NA = not applicable; NR = not reported; PatMsk = patient masked; Prov Msk = provider masked; RADQ = Randomization adequate; ROB = Risk of Bias.

## Additional Comments on Trials Rated High Risk of Bias

Arntz et al., 2007:<sup>2</sup> Very high attrition and high differential attrition (just 45% completed in one group, 72% in the other); outcome assessor and randomization procedures unclear; outcome assessors not described as masked; no description of treatment fidelity.

Beck et al., 2009.<sup>6</sup> High risk of attrition bias, due to the overall and the differential attrition (24% difference between groups). Unclear whether groups were similar at baseline for demographics and most potential confounders (as the information is not provided). In addition, inadequate handling of missing data (used completers analysis). No description of randomization method or allocation concealment.

Beidel et al., 2011:<sup>8</sup> High risk of selection bias; completers analysis in a small trial (N=35) with high differential dropout; and risk of bias from no masking.

Bichescu et al., 2007:<sup>9</sup> No attempt to create similar groups, this subsequently affected assessor blinding. Few details of randomization process beyond "were randomized".

Braun et al., 1990:<sup>14</sup> High attrition, non-standard outcome measures, baseline data not reported to allow determination of similarity or differences between groups.

Brom et al., 1989:<sup>15</sup> Appears to be completers analysis with no approach to handling missing data reported; no data reported to allow comparison of groups at baseline; no masking of outcome assessors reported; no information on treatment fidelity; methods of randomization and allocation concealment not reported; potential measurement bias due to differences in timing of assessments across groups.

Davidson et al., 1993;<sup>28</sup> Davidson, 1990:<sup>27</sup> Completer analysis for all subjects completing minimum of 4 weeks (40/46 subjects did so and were included in the analyses, 87%); and separately for the 33/46 (71.1%) that completed 8 weeks; no treatment of missing data; with high attrition. It was also unclear whether randomization or allocation concealment were adequate.

Davis et al., 2004:<sup>34</sup> Very high attrition (close to 50% overall); groups mostly similar at baseline but differed in prior treatments (with just 1 subject in the placebo group previously treated with an antidepressant vs. 15 to 27% of subjects with previous treatment with antidepressants, benzodiazepines, or other medication in the nefazodone group); ITT analysis with LOCF (with exception of 1 patient).

Devilly et al., 1999:<sup>36</sup> High risk of selection bias, attrition bias; inadequate handling of missing data; inadequate randomization procedure (alternating for much of the assignment); inadequate allocation concealments; baseline differences between groups for several of the reported characteristics (age, psychotropic medications, marital status, living partners, IES); high overall and differential attrition (over 15%) in a head to head study with already small N (32 randomized); completers analysis for the 23 that completed.

Difede et al., 2007:<sup>37</sup> High attrition and differential attrition (% completing were 68% vs. 47% vs. 88%); differences in baseline PTSD severity between groups (scores on CAPS).

Difede et al., 2007:<sup>38</sup> Very high attrition, and high differential attrition; over 1/2 for the CBT group did not complete treatment.

Echeburua et al., 1996:<sup>39</sup> Inadequate randomization; similar description to the other study by the same author where subjects were actually assigned by alternating, rather than at random;

delivered by a single therapist and no mention of assuring treatment fidelity/therapist adherence; no masking of outcome assessors reported and not using validated measure--thus high risk of measurement bias; high risk of selection bias in this very small (N=20) head to head study due to inadequate randomization, inadequate information reported to determine if groups were comparable at baseline; no mention of co-interventions (e.g., medications) that could confound the findings.

Echeburua et al., 1997:<sup>40</sup> Study was not actually an RCT, it used alternating to assign subjects to groups (personal communication with author on 2/7/2012, email); high risk of selection bias and confounding with small sample size, method of group assignment, and no data reported to determine if groups similar at baseline; single therapist used and unclear whether there was a separate masked outcome assessor.

Feske et al., 2008:<sup>44</sup> High risk of selection bias and confounding; already small sample size and the high overall and differential attrition with completer analysis; attrition bias; 4 of 13 randomized subjects in the prolonged exposure group (31%) dropped out, 2 were withdrawn due to medication changes and 2 for unknown reasons; 2/14 treatment as usual clients withdrawn.

Foa et al., 1991:<sup>45</sup> High attrition for some groups and high differential attrition; completer analysis only; study did not report adequate treatment fidelity; some baseline differences between groups for income, assault characteristics; high risk of selection bias and confounding.

Frommberger et al., 2004:<sup>52</sup> High risk of selection bias and confounding; attrition bias; no reporting of adequate fidelity; Small sample size with no data shown on baseline covariates across groups; outcome assessment not masked; over 20% attrition and nothing done for missing data (completer analysis).

Hamner et al., 2009:<sup>56</sup> Substantial dropout, limited description of randomization; study reported as double blind, but write up suggests VPA folks got a lot more blood draws/monitoring; also, study physician told by pharmacist to adjust doses, so not blind to treatment arm.

Hensel-Dittman et al., 2011.<sup>57</sup> High risk of selection bias and confounding. First, no data were reported to allow baseline comparison of groups for most variables, and this is a fairly small sample size, making baseline differences more likely. The authors only report baseline data for a few of the outcome measures, and there was an 11-point difference between groups for baseline CAPS score. They did some matching during the randomization, but it is unclear if that worked to produce comparable groups at baseline. Next, the study did not report adequate treatment fidelity based on measurement by independent raters; no information was reported about treatment fidelity. They report that they videotaped all sessions, but there is no information reported to confirm to support adequate treatment fidelity, which would be very important since all of the same therapists delivered both interventions and it would be fairly easy to have some of the components of one therapy introduced into the other therapy. Next, lack of masking; the authors report that they attempted to keep outcome assessors blind, but that treatment condition was occasionally revealed to them, but it is unclear how frequently this occurred.

Hertzberg et al., 1999:<sup>58</sup> Baseline characteristics not reported for important potential confounders in this small study (n=15) to allow for determination of potential selection bias; in addition, unclear whether randomization or allocation concealment were adequate; unclear whether outcome assessors were masked. Completers analysis.

Hertzberg et al., 2000:<sup>59</sup> Baseline characteristics not reported for important potential confounders in this small study (n=12) to allow for determination of potential selection bias (described as "non-significant difference", but given small sample size, almost any difference will be non-significant). In addition, unclear whether randomization or allocation concealment were adequate; unclear whether outcome assessors were masked. Instruments of uncertain validity used to assess outcomes.

Ironson et al., 2002:<sup>68</sup> High risk of selection bias; randomization compromised by adding more participants to PE group to achieve equal group numbers; high overall and differential attrition (and 50% dropouts from the PE group); marked differences in baseline severity of PTSD and depression between groups (otherwise, minimal baseline data reported to allow comparison of groups); completer analysis; no handling of missing data.

Johnson et al., 2006:<sup>69</sup> Inadequate methods of handling missing data, completers analysis; did not report adequate treatment fidelity based on measurement by independent raters; high potential for selection bias with small numbers in each treatment arm and no reporting of baseline demographics (only reported in aggregate for the three intervention groups) and potential confounders for comparison, and there were differences in the baseline values for the measures of PTSD symptoms (e.g., baseline CAPS scores were 82 for Counting and 61.7 for EMDR, 64.2 for waitlist). The authors describe the study as a randomized trial. However, from their description of the design, it appears that the participants for the waitlist control group were recruited separately from the group recruited to the active treatments. In other words, participants recruited to the active condition were randomized to one of three active treatments, but the persons recruited to the control condition were not assigned to that group randomly. Accordingly, it's not really a randomized trial for the comparisons with the control condition.

Karatzias et al., 2011:<sup>71</sup> Very high attrition rate (over 40%); unclear whether randomization or allocation concealment were adequate.

Keane et al., 1989.<sup>72</sup> High risk of selection bias: Baseline differences between groups included race (for Intervention vs. waitlist: 0% vs. 31% Black), and service connection (36% vs. 69%) possibly biasing control group toward reporting greater severity of symptoms; difference between group in co-interventions/medications administered over the course of the study (42.9% [6/14] in intervention group received anxiolytic, sleep, or pain meds at some point during the study vs. 76.9% [10/13] in the control group received anxiolytic medications at some point during waiting; and some evidence suggests worse outcomes for those with PTSD treated with anxiolytics). The PTSD ratings were completed by therapists who were administering the therapy and thus were not blinded. Of note, the study found no difference between active intervention and control group in self-reported PTSD symptoms but a substantial differences in PTSD ratings completed by the non-blinded therapists. Potential measurement bias with no masking or independence of outcome assessors and outcomes assessed at different timepoints for the two groups. Unclear whether randomization, allocation concealment, and masking were adequate. Attrition information not reported, nor was approach to handling missing data. No description of methods to ensure treatment fidelity.

Kosten et al., 1991:<sup>73</sup> High attrition, almost 50%; and high differential attrition (% completers by group: 52 vs. 39 vs. 79 vs. 33).

Krakow et al., 2000:<sup>74</sup> Very high attrition, around 50%; did not report adequate treatment fidelity.

Krupnick et al., 2008:<sup>76</sup> High risk of selection bias due to attrition. Very high attrition and high differential attrition (% completers by group: 63 vs. 44). Regarding "other" method of handling dropouts: imputed missing scores as the application of the observed group mean change.

Lee et al., 2002:<sup>81</sup> Inadequate randomization procedure (alternating); no allocation concealment, no blinding of outcome assessors; unclear whether groups were similar at baseline for several characteristics; details of analysis and missing data were NR; differential attrition data unclear.

Lindley et al., 2007:<sup>84</sup> High attrition and high differential attrition (30%), method of handling dropouts/missing data was unclear.

Marcus et al., 1997:<sup>86</sup> No data reported to allow assessment of how groups compare at baseline, how many patients dropped out after randomization, or how many people are in the 2 groups. Attrition information not reported; does not describe use of ITT analysis; Outcome assessors were not masked, increasing potential for measurement bias; did not report adequate treatment fidelity.

Marshall et al., 2007:<sup>90</sup> High risk of selection bias due to high rate of attrition. Also, not clear if groups were similar at baseline (article does not show the data--it just has a sentence that says that patient demographics did not differ significantly between groups; although later Tables do show similar baseline PTSD severity for CAPS and some other measures).

McLay et al., 2011:<sup>95</sup> Unclear adequacy of randomization or allocation concealment; unclear whether or not outcome assessors were masked; small sample with possible significant differences in prior deployments between treatment groups, raising risk of selection bias. The measures themselves were reliable but post assessments were reported to be given sporadically over a 36 week period. Study did not report adequate treatment fidelity.

McRae et al., 2004.<sup>96</sup> Completers analysis with inadequate handling of missing data in this head-to-head study that found no difference between treatments; high risk of selection bias; unable to determine if randomized groups were similar at baseline (data only reported for completers; 26/37 subjects); unclear whether randomization and allocation concealment were adequate.

Otto et al., 2003:<sup>106</sup> No masking; no reporting of handling of missing data; no reporting of attrition data; not sure if ITT or completers analysis.

Padala et al., 2006:<sup>107</sup> High risk of selection bias and confounding; differential attrition along with small sample size (N=20); completer analysis; only reports age, race, mean TOP-8, and mean CAPS at baseline---the race characteristics were quite different (55% Caucasian in Risperidone group vs. 89% in the Placebo group).

Paunovic et al., 2001:<sup>108</sup> High risk of selection bias and confounding; high differential attrition in this small (N=20) head to head study comparing two types of psychotherapy that found no difference between the two, and was not powered to find a small to moderate difference between treatments; no assessor masking; did not reported whether ITT; handling of missing data NR.

Power et al., 2002:<sup>110</sup> High overall and differential attrition; completers analysis; no approach to handling missing data; no assessment of treatment fidelity; in the two active treatment groups, about 31% and 43% did not complete treatment, respectively.

Rauch et al., 2009:<sup>113</sup> High risk of selection bias and confounding; completers analysis, using just the set of subjects that completed an RCT (Foa et al 2005, J Consul Clin Psychol); baseline differences in race and income.



Ready et al., 2010:<sup>114</sup> High risk of selection bias and confounding. This small study (N = 11) did not report differences in many baseline covariates across intervention groups. However, there were large differences in some of the few that they did report (CAPS, BDI), which strongly suggests that there were important differences in baseline covariates.

Reist et al., 1989:<sup>116</sup> Non-standard outcome measures, high attrition, only overall attrition not group-specific attrition reported, completer analysis.

Rothbaum et al., 2008:<sup>123</sup> Randomization unclear, high differential attrition (36% differential), completer's analysis; unclear whether outcome assessors were masked.

Spivak et al., 2006:<sup>130</sup> Completers analysis; and high overall and differential attrition with already small sample size (40 randomized, 11/20 completed in the reboxetine group vs. 17/20 in the fluvoxamine group).

Ulmer et al., 2011:<sup>139</sup> High risk of selection bias and confounding in this small study (N=22); differential attrition (% completers: 82 vs. 67 vs. 100); no description of treatment fidelity; unclear adequacy of randomization and allocation concealment; no masking of outcome assessors. Also, participants received a range of treatments outside of the study varying in intensity and type.

Wagner et al., 2007:<sup>143</sup> High risk of selection bias and confounding in this small study (N=8) with randomization method unclear, and groups different at baseline (younger in treatment group: mean age 28 vs. 39; more males 75% vs. 0%; more prior trauma and greater injury severity); no description of treatment fidelity; single therapist.

Zlotnick et al., 1997:<sup>145</sup> High attrition (31%) with completers analysis; no masking of outcome assessors; baseline data not reported to allow comparison of groups for many things (they did run statistical tests for some demographic variables, and report no statistically significant differences); higher baseline scores for DTS, CR-PTSD, and DES for the wait list group.

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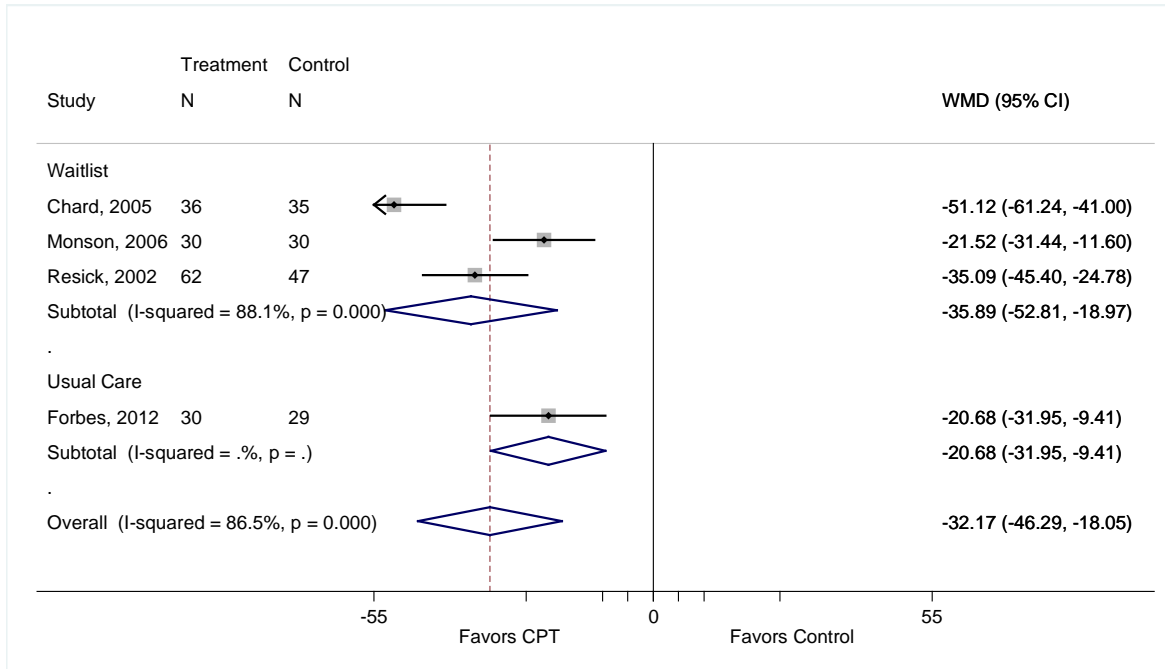
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# Appendix F. Meta-Analysis

## Key Question 1

### Cognitive Processing Therapy: Meta-Analysis Results

Figure F-1. Change in CAPS for cognitive processing therapy compared with control, by type of comparator



Timing of outcome assessment: 17 weeks (Chard, 2005), 10 weeks (Monson, 2006), 6 weeks (Resick, 2002), 12 weeks (Forbes, 2012).

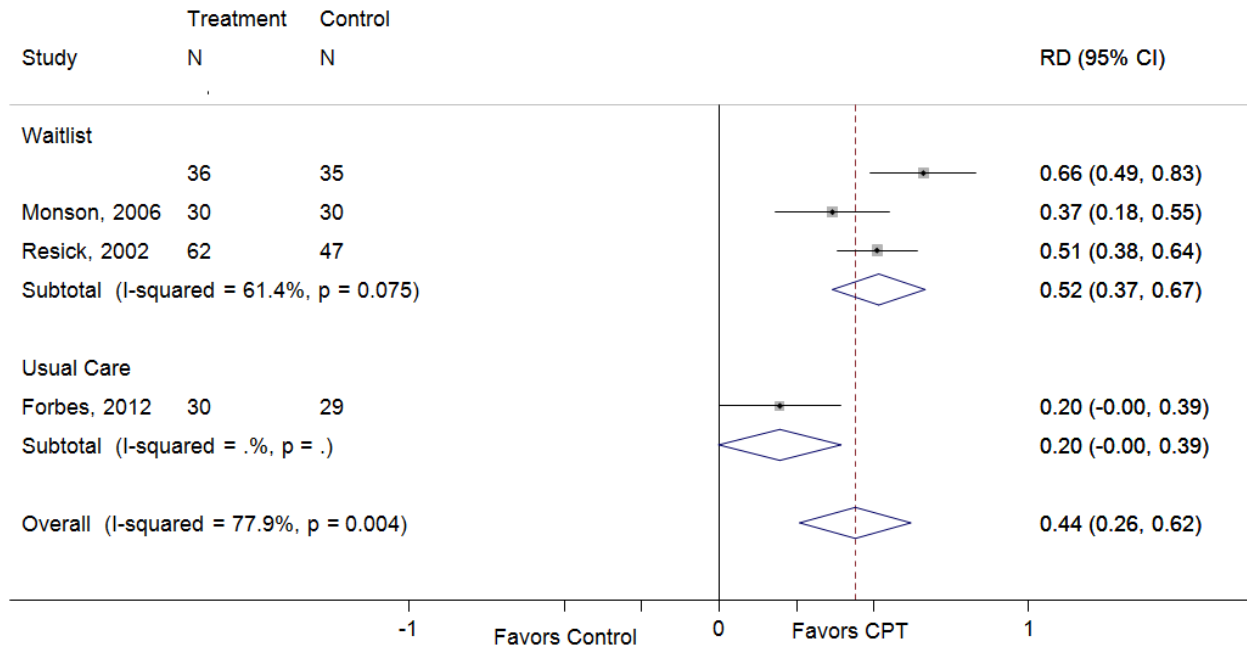
Table F-1. Change in CAPS for cognitive processing therapy compared with control: Statistics with one study removed

| Study Omitted | Overall Estimate | 95% Confidence Interval |
|---------------|------------------|-------------------------|
| Chard, 2005   | -25.85           | (-35.06 to -16.64)      |
| Forbes, 2012  | -35.89           | (-52.81 to -18.97)      |
| Monson, 2006  | -35.77           | (-52.82 to -18.72)      |
| Resick, 2002  | -31.17           | (-51.06 to -11.27)      |
| Combined      | -32.17           | (-46.29 to -18.05)      |

Table F-2. Change in CAPS for cognitive processing therapy compared with control: Statistics with one study removed, by type of comparator

| Study Omitted     | Overall Estimate | 95% Confidence Interval |
|-------------------|------------------|-------------------------|
| <b>Waitlist</b>   |                  |                         |
| Chard, 2005       | -28.23           | (-41.53 to -14.93)      |
| Monson, 2006      | -43.14           | (-58.85 to -27.43)      |
| Resick, 2002      | -36.30           | (-65.31 to -7.30)       |
| Combined          | -35.89           | (-52.81 to -18.97)      |
| <b>Usual Care</b> |                  |                         |
| NA                | NA               | NA                      |

**Figure F-2. Loss of PTSD diagnosis for cognitive processing therapy compared with control, by type of comparator**



Timing of outcome assessment: 17 weeks (Chard, 2005), 10 weeks (Monson, 2006), 6 weeks (Resick, 2002), 12 weeks (Forbes, 2012).

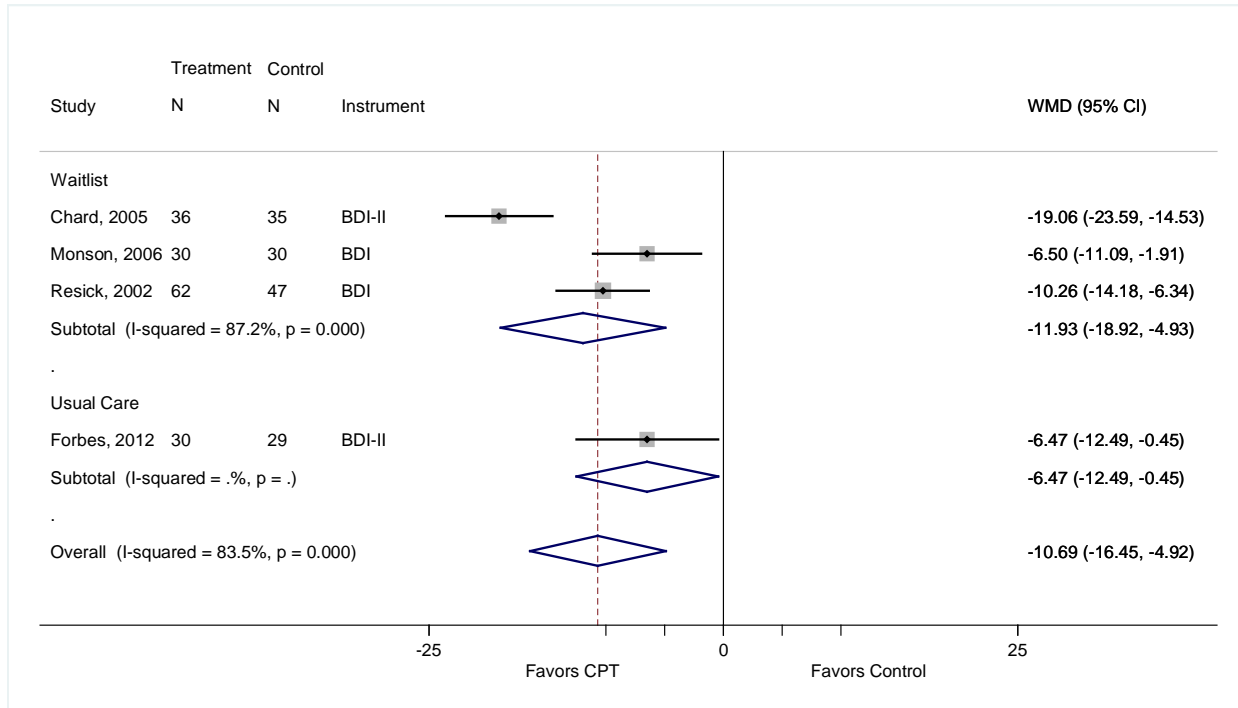
**Table F-3. Loss of PTSD diagnosis for cognitive processing therapy compared with control: Statistics with one study removed**

| Study Omitted | Overall Estimate | 95% Confidence Interval |
|---------------|------------------|-------------------------|
| Chard, 2005   | 0.37             | (0.19 to 0.55)          |
| Forbes, 2012  | 0.52             | (0.37 to 0.67)          |
| Monson, 2006  | 0.46             | (0.23 to 0.70)          |
| Resick, 2002  | 0.41             | (0.14 to 0.68)          |
| Combined      | 0.44             | (0.26 to 0.62)          |

**Table F-4. Loss of PTSD diagnosis for cognitive processing therapy compared with control: Statistics with one study removed, by type of comparator**

| Study Omitted     | Overall Estimate | 95% Confidence Interval |
|-------------------|------------------|-------------------------|
| <b>Waitlist</b>   |                  |                         |
| Chard, 2005       | 0.45             | (0.32 to 0.59)          |
| Monson, 2006      | 0.57             | (0.43 to 0.72)          |
| Resick, 2002      | 0.52             | (0.23 to 0.80)          |
| Combined          | 0.52             | (0.37 to 0.67)          |
| <b>Usual Care</b> |                  |                         |
| NA                | NA               | NA                      |

**Figure F-3. Change in BDI for cognitive processing therapy compared with control, by type of comparator**



Timing of outcome assessment: 17 weeks (Chard, 2005), 10 weeks (Monson, 2006), 6 weeks (Resick, 2002), 12 weeks (Forbes, 2012).

**Table F-5. Change in BDI for cognitive processing therapy compared with control: Statistics with one study removed**

| Study Omitted | Overall Estimate | 95% Confidence Interval |
|---------------|------------------|-------------------------|
| Chard, 2005   | -8.24            | (-10.91 to -5.57)       |
| Forbes, 2012  | -11.93           | (-18.92 to -4.93)       |
| Monson, 2006  | -12.09           | (-19.13 to -5.05)       |
| Resick, 2002  | -10.78           | (-19.43 to -2.13)       |
| Combined      | -10.69           | (-16.45 to -4.92)       |

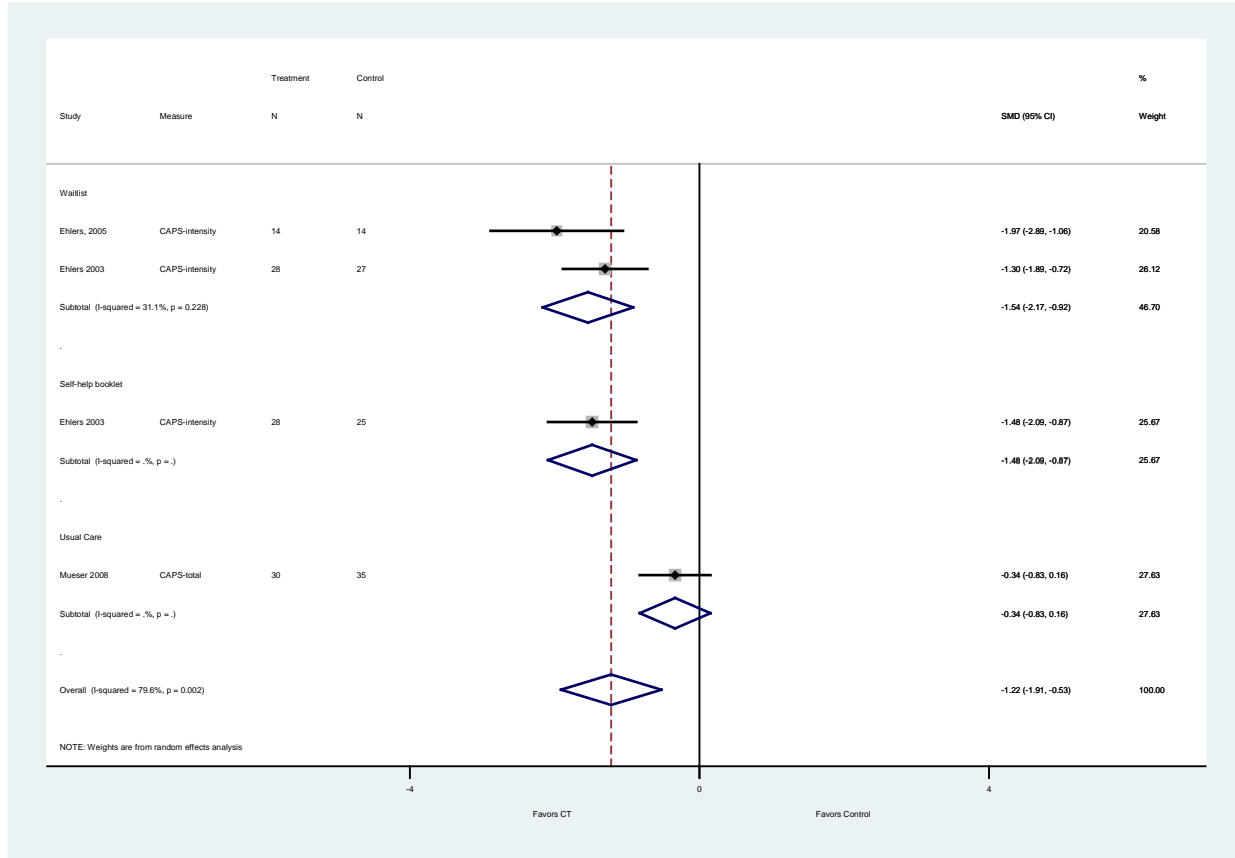
**Table F-6. Change in BDI for cognitive processing therapy compared with control: Statistics with one study removed, by type of comparator**

| Study Omitted     | Overall Estimate | 95% Confidence Interval |
|-------------------|------------------|-------------------------|
| <b>Waitlist</b>   |                  |                         |
| Chard, 2005       | -8.58            | (-12.24 to -4.91)       |
| Monson, 2006      | -14.58           | (-23.21 to -5.96)       |
| Resick, 2002      | -12.79           | (-25.09 to -0.48)       |
| Combined          | -11.93           | (-18.92 to -4.93)       |
| <b>Usual Care</b> |                  |                         |
| NA                | NA               | NA                      |

# Cognitive Therapy: Meta-Analysis Results

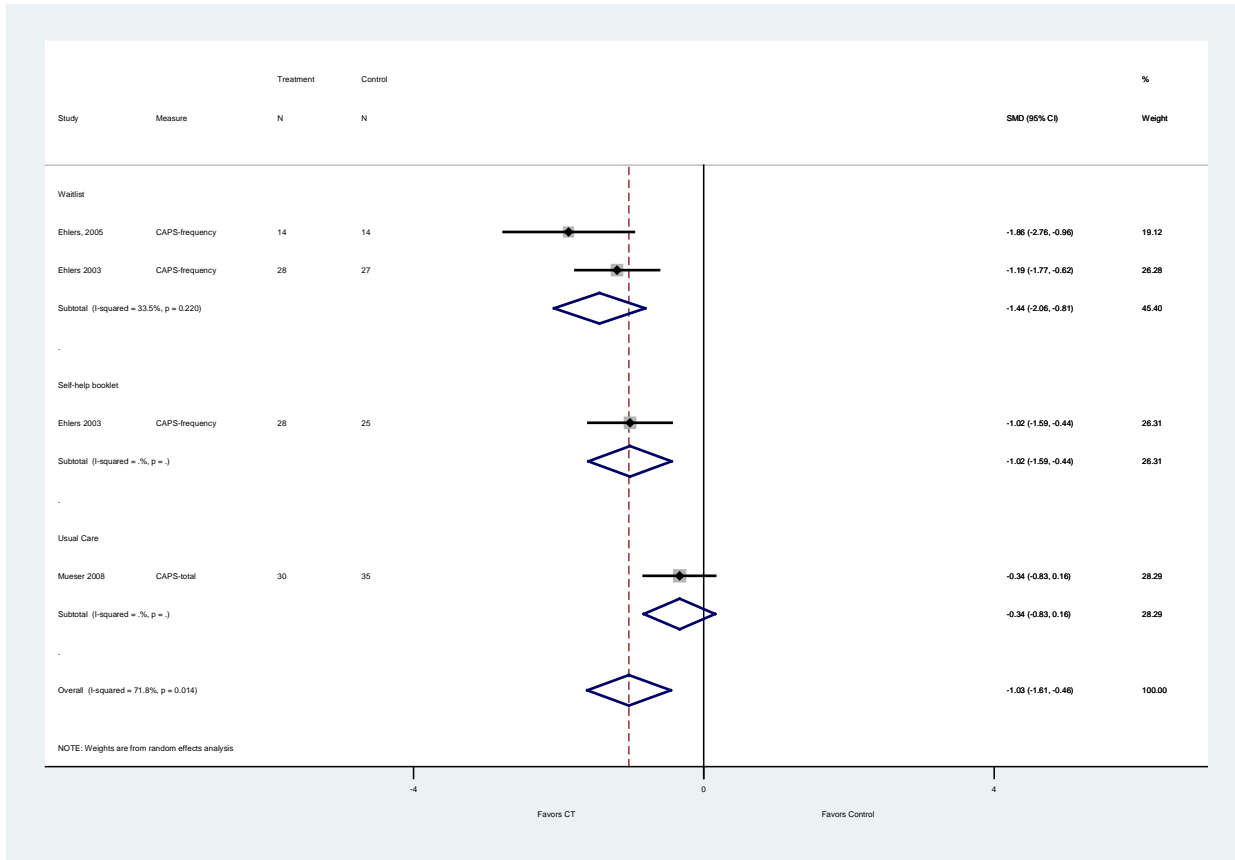
**Note:** These are the cognitive therapy studies that were not specified as cognitive processing therapy

**Figure F-4.** Change in PTSD symptoms for cognitive therapy compared with control, by type of comparator



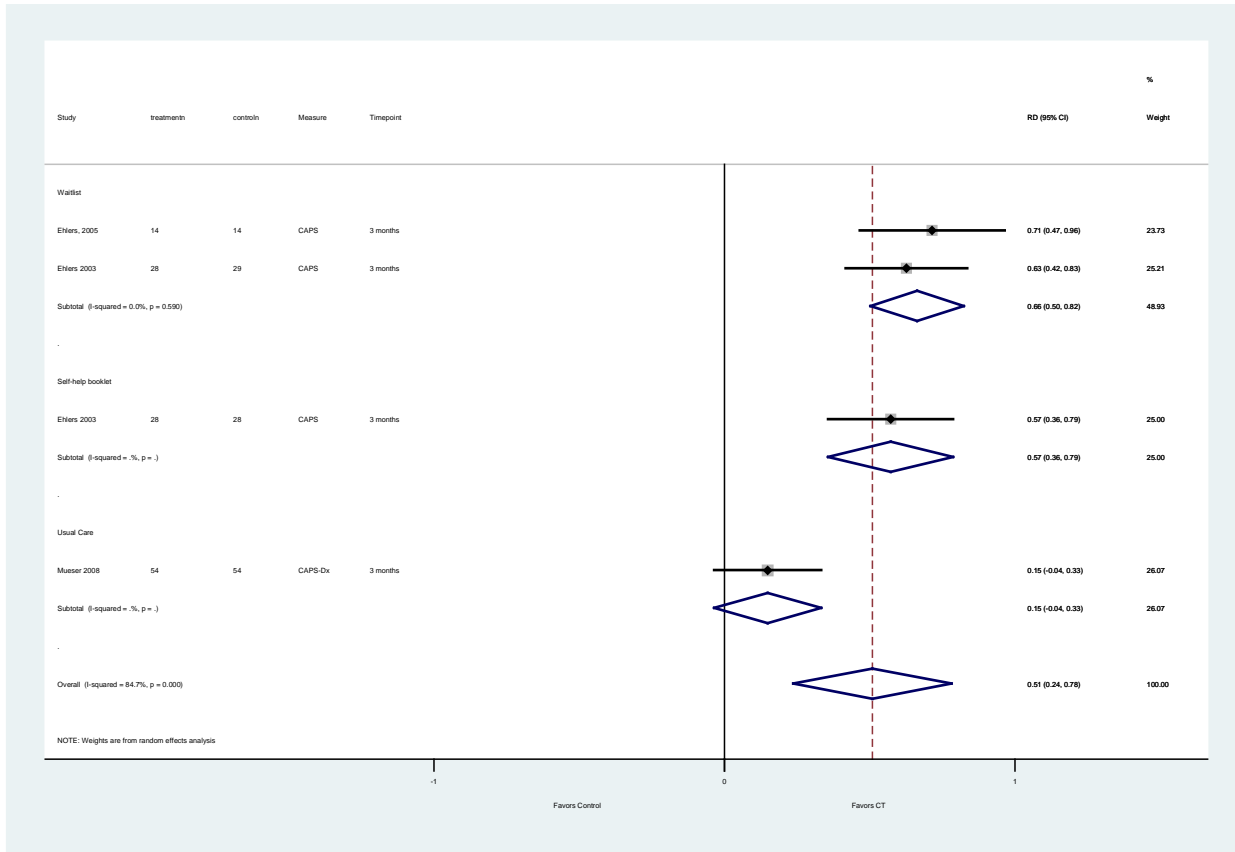
Timing of outcome assessment: 3 months for all studies.

**Figure F-5. Change in PTSD symptoms for cognitive therapy compared with control, by type of comparator**



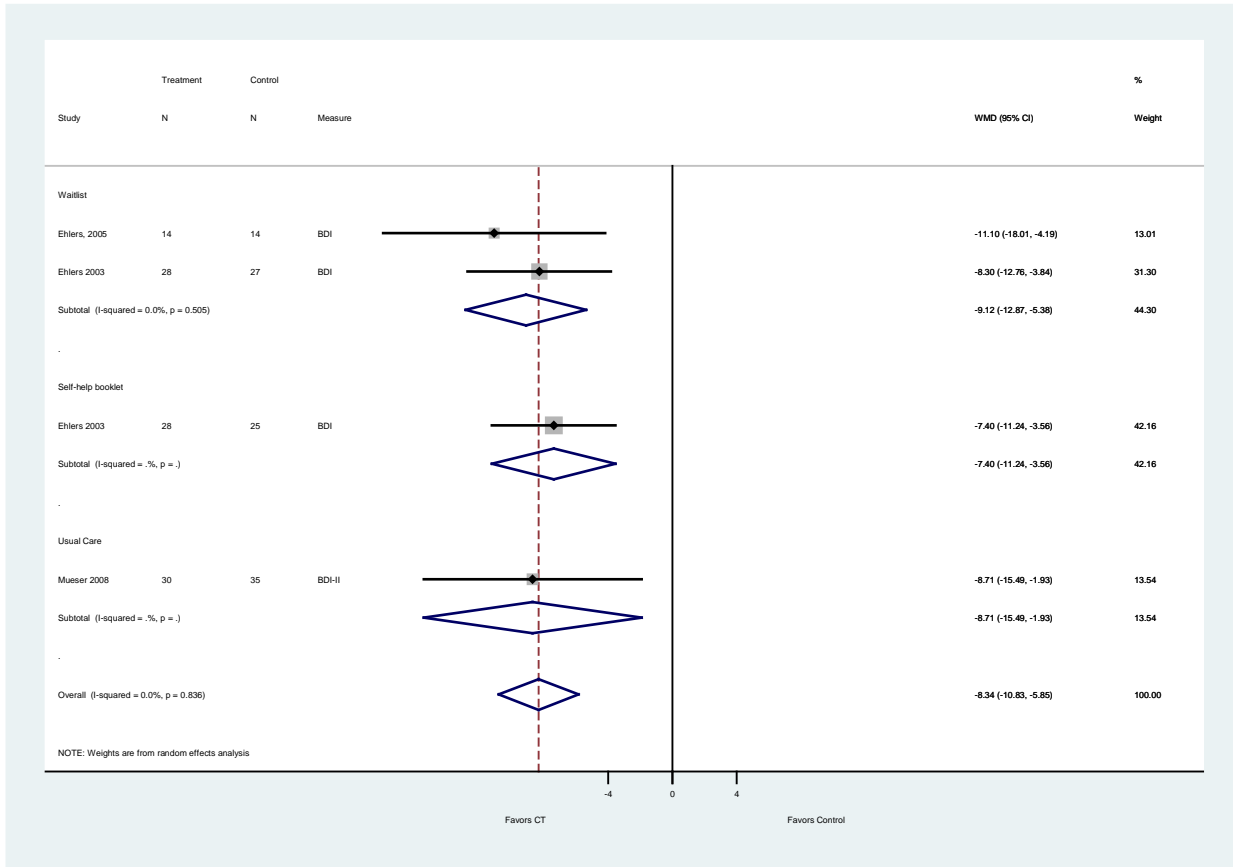
Timing of outcome assessment: 3 months for all studies.

**Figure F-6. Loss of PTSD diagnosis for cognitive therapy compared with control, by type of comparator**



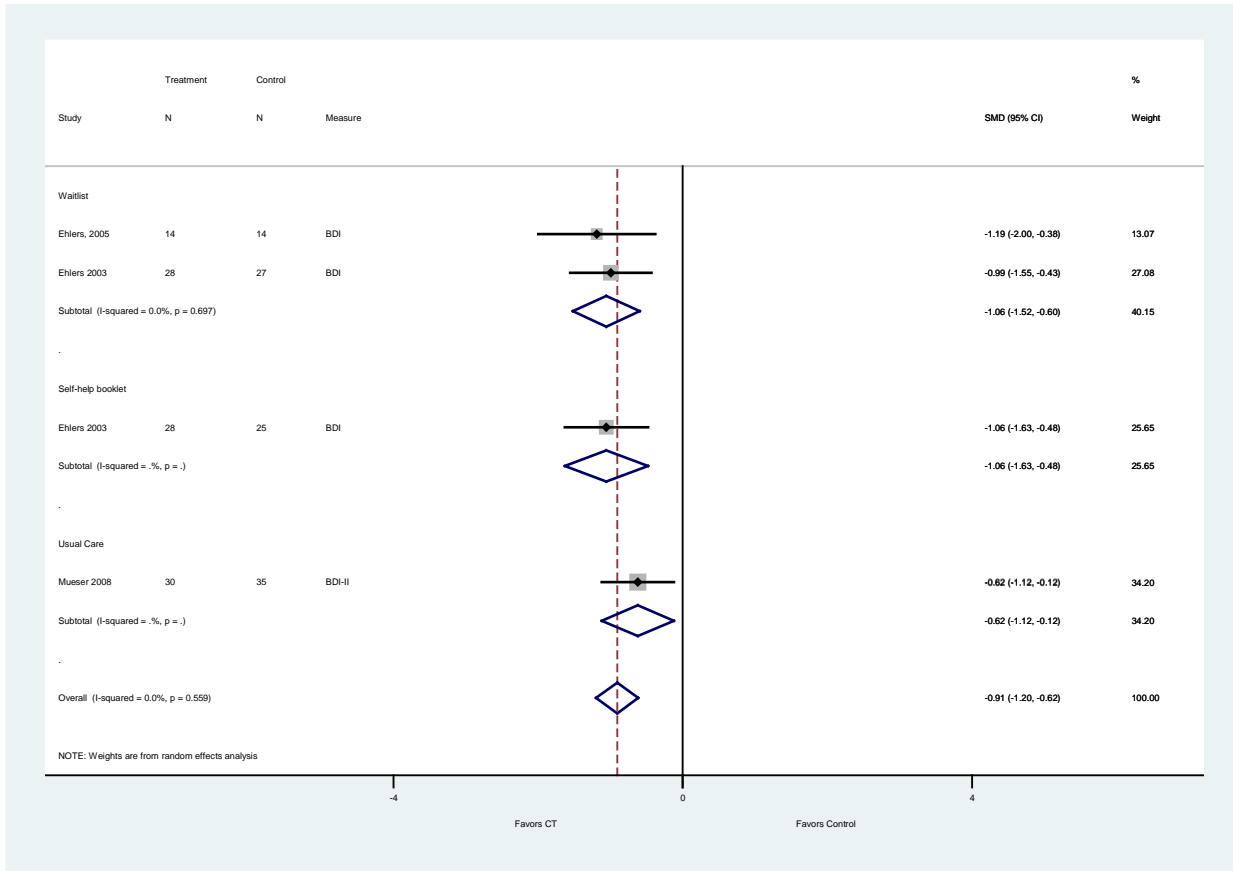


**Figure F-7. Change in BDI for cognitive therapy compared with control, by type of comparator, weighted mean difference**



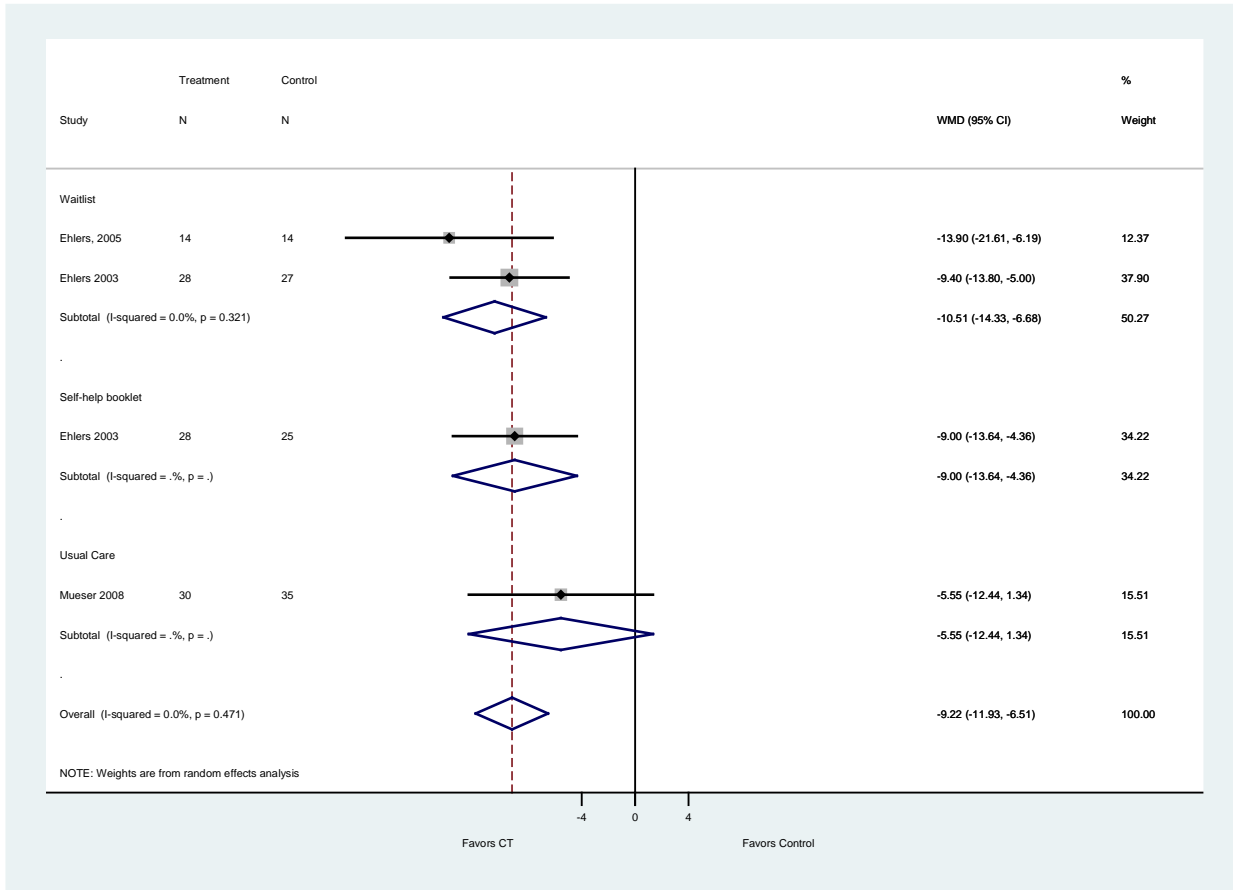
Timing of outcome assessment: 3 months for all studies.

**Figure F-8. Change in BDI for cognitive therapy compared with control, by type of comparator, Cohen's d**



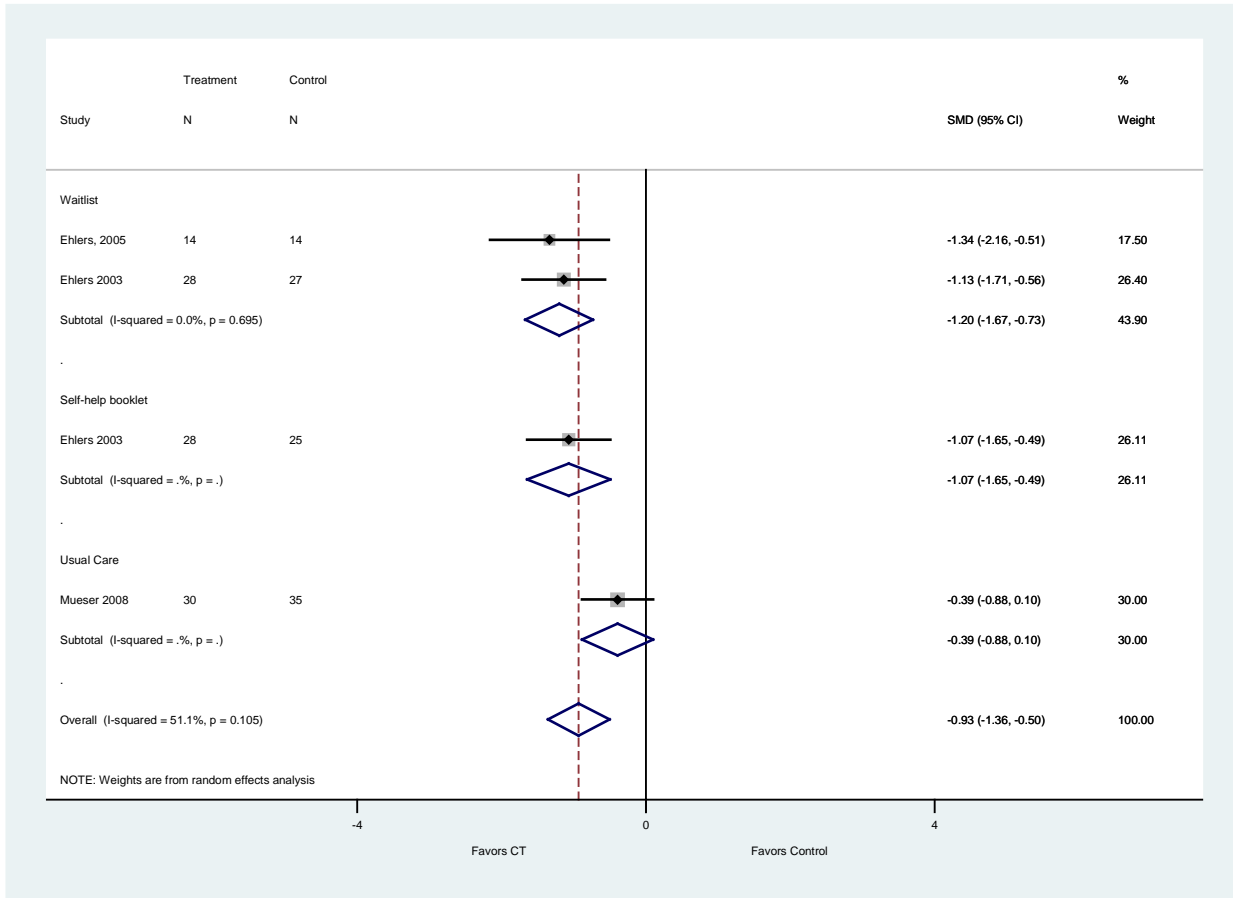
Timing of outcome assessment: 3 months for all studies.

**Figure F-9. Change in BAI for cognitive therapy compared with control, by type of comparator, weighted mean difference**



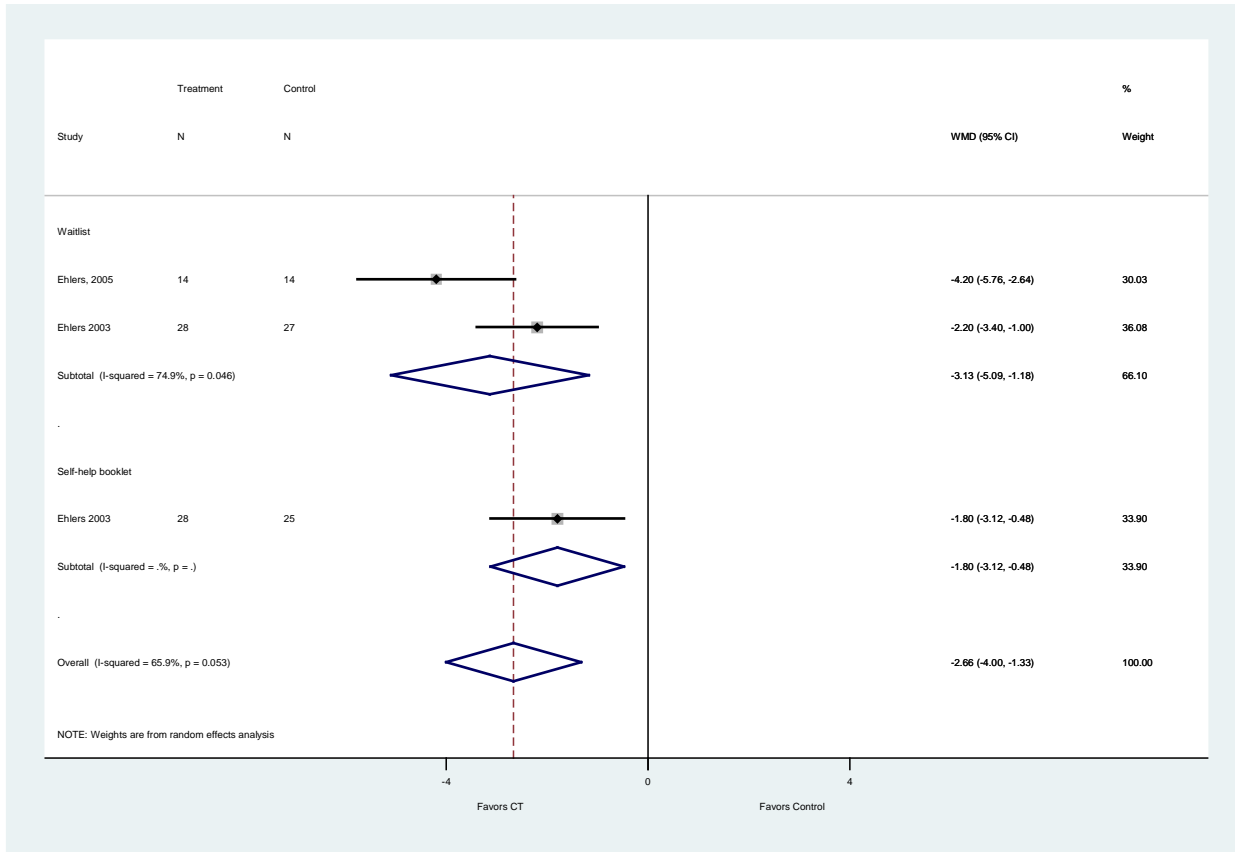
Timing of outcome assessment: 3 months for all studies.

**Figure F-10. Change in BAI for cognitive therapy compared with control, by type of comparator, Cohen's d**



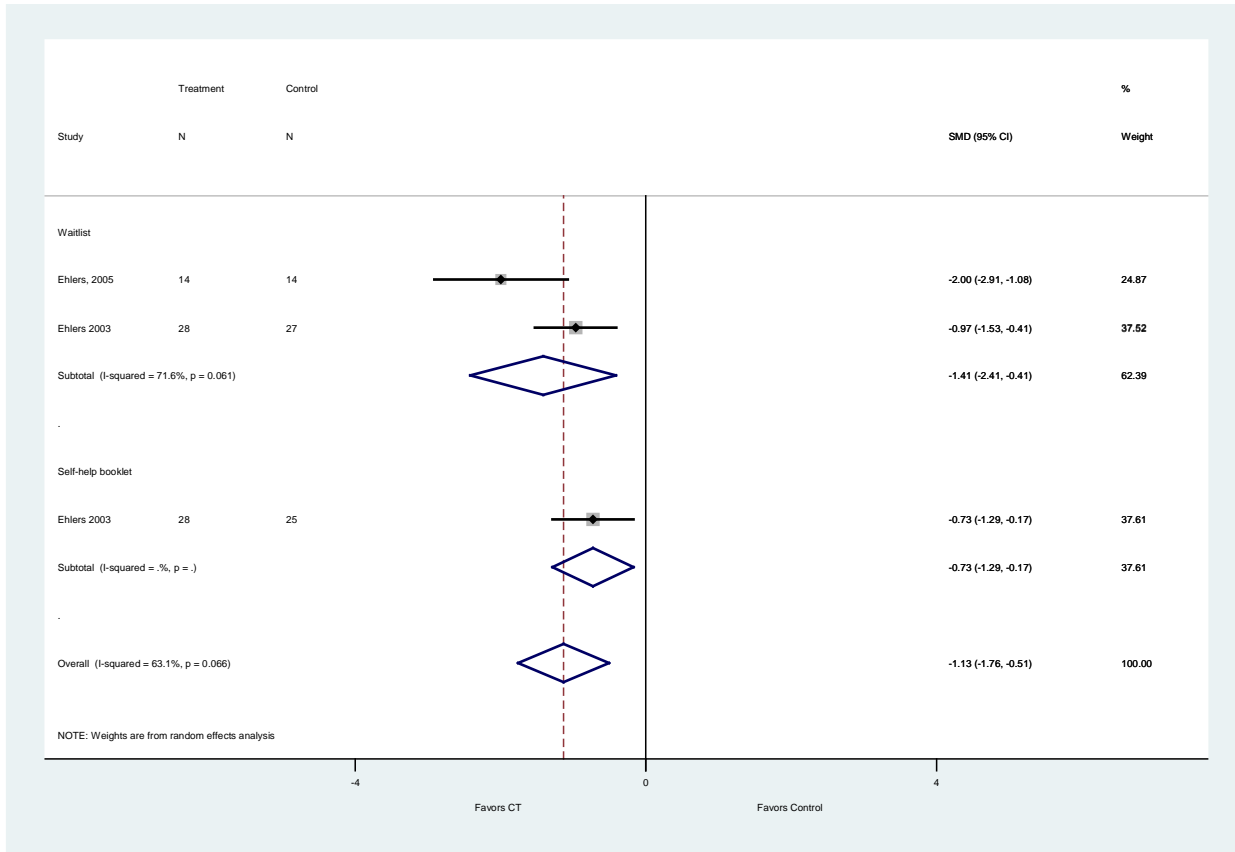
Timing of outcome assessment: 3 months for all studies.

**Figure F-11. Change in Sheehan's Disability Score for cognitive therapy compared with control, by type of comparator, weighted mean difference**



Timing of outcome assessment: 3 months for all studies.

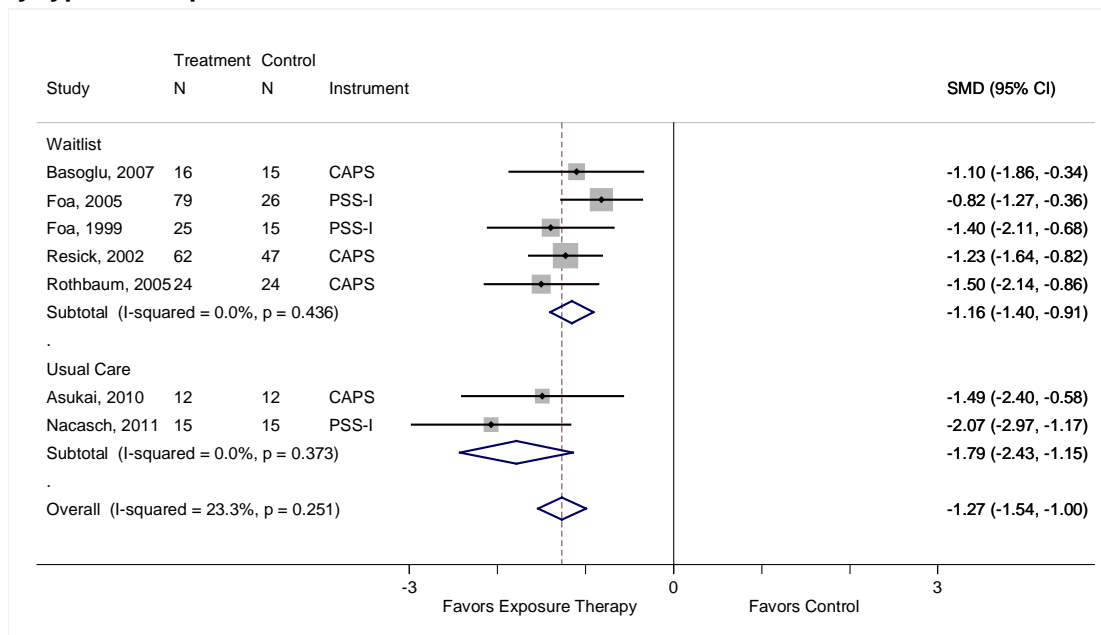
**Figure F-12. Change in Sheehan's Disability Score for cognitive therapy compared with control, by type of comparator, Cohen's d**



Timing of outcome assessment: 3 months for all studies.

## CBT Exposure-Based Therapy: Meta-Analysis Results

**Figure F-13. PTSD symptom reduction (any measure) for exposure therapy compared with control, by type of comparator**



Timing of outcome assessment: 8 weeks (Basoglu, 2007), 12 weeks (Foa, 2005), 9 weeks (Foa, 1999), 6 weeks (Resick, 2002), 4.5 weeks (Rothbaum, 2005), 9 to 15 weeks (Nacasch), “post-treatment” or 8 to 15 weeks (Asukai, 2010).

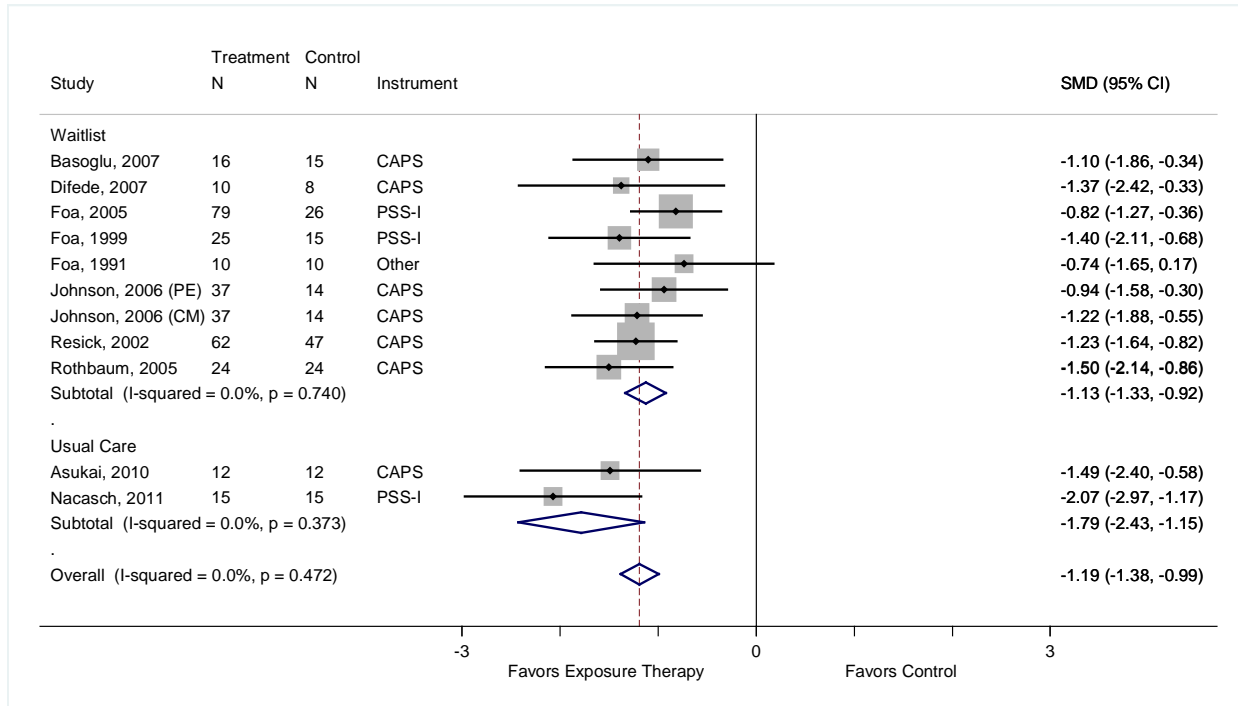
**Table F-7. PTSD symptom reduction (any measure) for exposure therapy compared with control, by type of comparator: Statistics with one study removed**

| Study Omitted  | Overall Estimate | 95% Confidence Interval |
|----------------|------------------|-------------------------|
| Basoglu, 2007  | -1.30            | (-1.62 to -0.99)        |
| Foa, 2005      | -1.38            | (-1.64 to -1.11)        |
| Foa, 1999      | -1.26            | (-1.58 to -0.95)        |
| Resick, 2002   | -1.31            | (-1.67 to -0.95)        |
| Rothbaum, 2005 | -1.24            | (-1.55 to -0.93)        |
| Asukai, 2010   | -1.26            | (-1.56 to -0.96)        |
| Nacasch, 2011  | -1.18            | (-1.42 to -0.94)        |
| Combined       | -1.27            | (-1.54 to -1.00)        |

**Table F-8. PTSD symptom reduction (any measure) for exposure therapy compared with control, by type of comparator: Statistics with one study removed, by type of comparator**

| Study Omitted     | Overall Estimate | 95% Confidence Interval |
|-------------------|------------------|-------------------------|
| <b>Waitlist</b>   |                  |                         |
| Basoglu, 2007     | -1.17            | (-1.47 to -0.88)        |
| Foa, 2005         | -1.29            | (-1.58 to -1.00)        |
| Foa, 1999         | -1.13            | (-1.40 to -0.85)        |
| Resick, 2002      | -1.14            | (-1.48 to -0.80)        |
| Rothbaum, 2005    | -1.10            | (-1.36 to -0.84)        |
| Combined          | -1.16            | (-1.40 to -0.91)        |
| <b>Usual Care</b> |                  |                         |
| Asukai, 2010      | -2.07            | (-2.97 to -1.17)        |
| Nacasch, 2011     | -1.49            | (-2.40 to -0.58)        |
| Combined          | -1.79            | (-2.43 to -1.15)        |

**Figure F-14. PTSD symptom reduction (any measure) for exposure therapy compared with control, by type of comparator: Sensitivity analysis including high risk of bias studies**

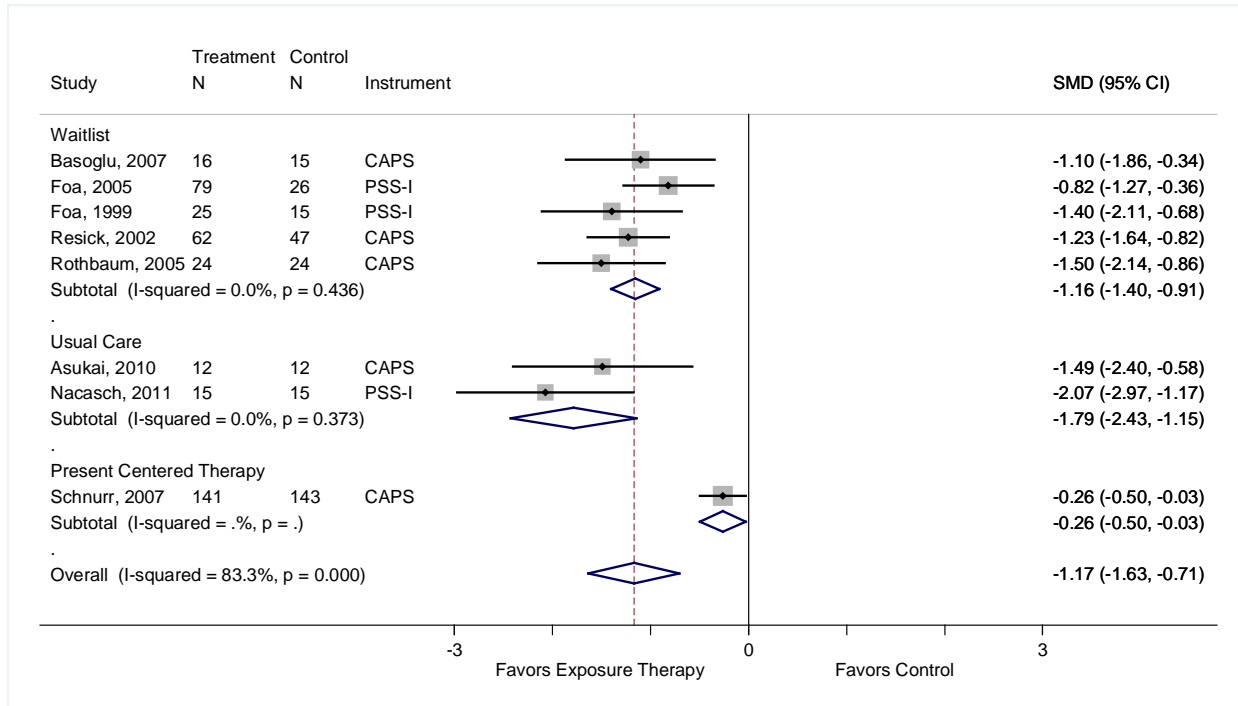


Note: Difede et al., 2007, Johnson et al., 2006, and Foa et al., 1991 were rated as having a high risk of bias.

Timing of outcome assessment: 8 weeks (Basoglu, 2007), 24 weeks (Difede 2007), 12 weeks (Foa, 2005), 9 weeks (Foa, 1999 and Foa, 1991), 6 to 9 sessions (Johnson, 2006), 6 weeks (Resick, 2002), 4.5 weeks (Rothbaum, 2005) “post-treatment” or 8 to 15 weeks (Asukai, 2010), 9 to 15 weeks (Nacasch).



**Figure F-15. PTSD symptom reduction (any measure) for exposure therapy compared with control, by type of comparator: Sensitivity analysis including present centered therapy**

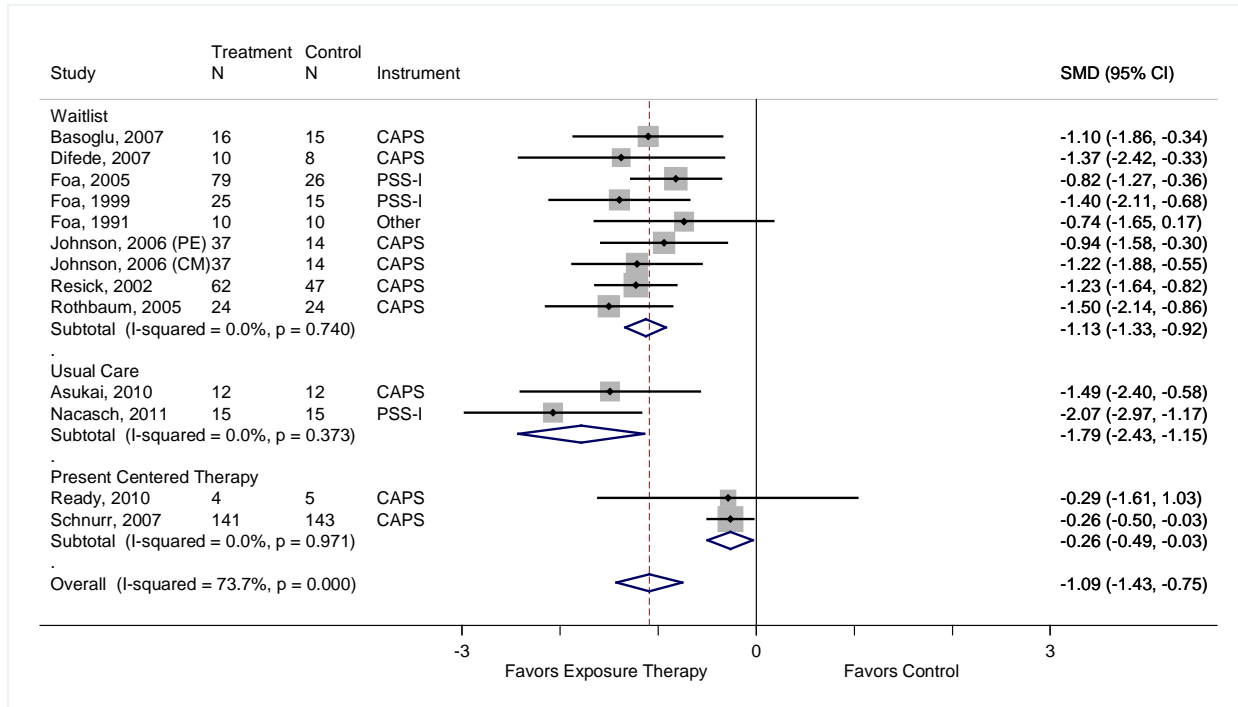


Timing of outcome assessment: 8 weeks (Basoglu, 2007), 12 weeks (Foa, 2005), 9 weeks (Foa, 1999), 6 weeks (Resick, 2002), 4.5 weeks (Rothbaum, 2005), “post-treatment” or 8 to 15 weeks (Asukai, 2010), 9 to 15 weeks (Nacasch), 10 weeks (Schnurr 2007).

**Table F-9. PTSD symptom reduction (any measure) for exposure therapy compared with control: Sensitivity analysis including present centered therapy, statistics with one study removed**

| Study Omitted  | Overall Estimate | 95% Confidence Interval |
|----------------|------------------|-------------------------|
| Basoglu, 2007  | -1.18            | (-1.69 to -0.67)        |
| Foa, 2005      | -1.24            | (-1.80 to -0.69)        |
| Foa, 1999      | -1.14            | (-1.64 to -0.64)        |
| Resick, 2002   | -1.17            | (-1.70 to -0.64)        |
| Rothbaum, 2005 | -1.12            | (-1.61 to -0.63)        |
| Asukai, 2010   | -1.14            | (-1.63 to -0.64)        |
| Nacasch, 2011  | -1.06            | (-1.52 to -0.61)        |
| Combined       | -1.17            | (-1.63 to -0.71)        |

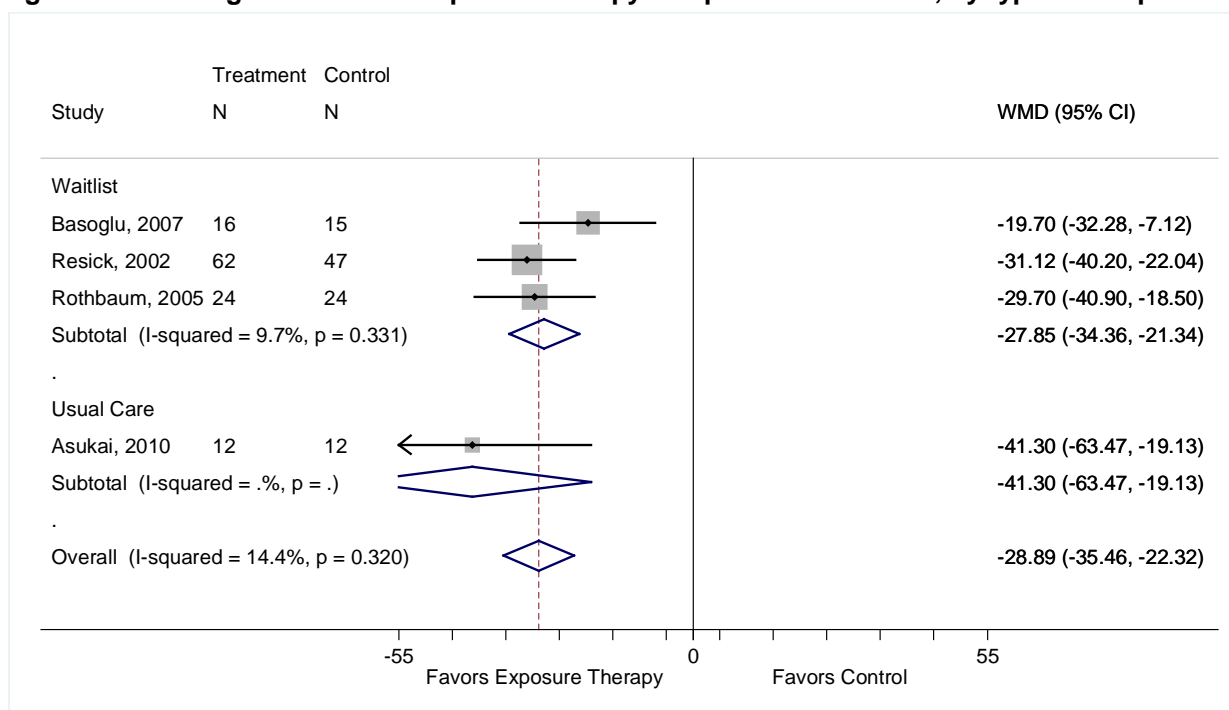
**Figure F-16. PTSD symptom reduction (any measure) for exposure therapy compared with control, by type of comparator: Sensitivity analysis including present centered therapy and high risk of bias studies**



Note: Ready et al., 2010, Difede et al., 2007, Johnson et al., 2006, and Foa et al., 1991 were rated as having a high risk of bias.

Timing of outcome assessment: 8 weeks (Basoglu, 2007), 24 weeks (Difede 2007), 12 weeks (Foa, 2005), 9 weeks (Foa, 1999 and Foa, 1991), 6 to 9 sessions (Johnson, 2006), 4.5 weeks (Resick, 2002), 4.5 weeks (Rothbaum, 2005), “post-treatment” or 8 to 15 weeks (Asukai, 2010), 9 to 15 weeks (Nacasch), 10 sessions (Ready, 2010), 10 weeks (Schnurr 2007).

**Figure F-17. Change in CAPS for exposure therapy compared with control, by type of comparator**



Timing of outcome assessment: 8 weeks (Basoglu, 2007), 12 weeks, 6 weeks (Resick, 2002), 4.5 weeks (Rothbaum, 2005), “post-treatment” or 8 to 15 weeks (Asukai, 2010).

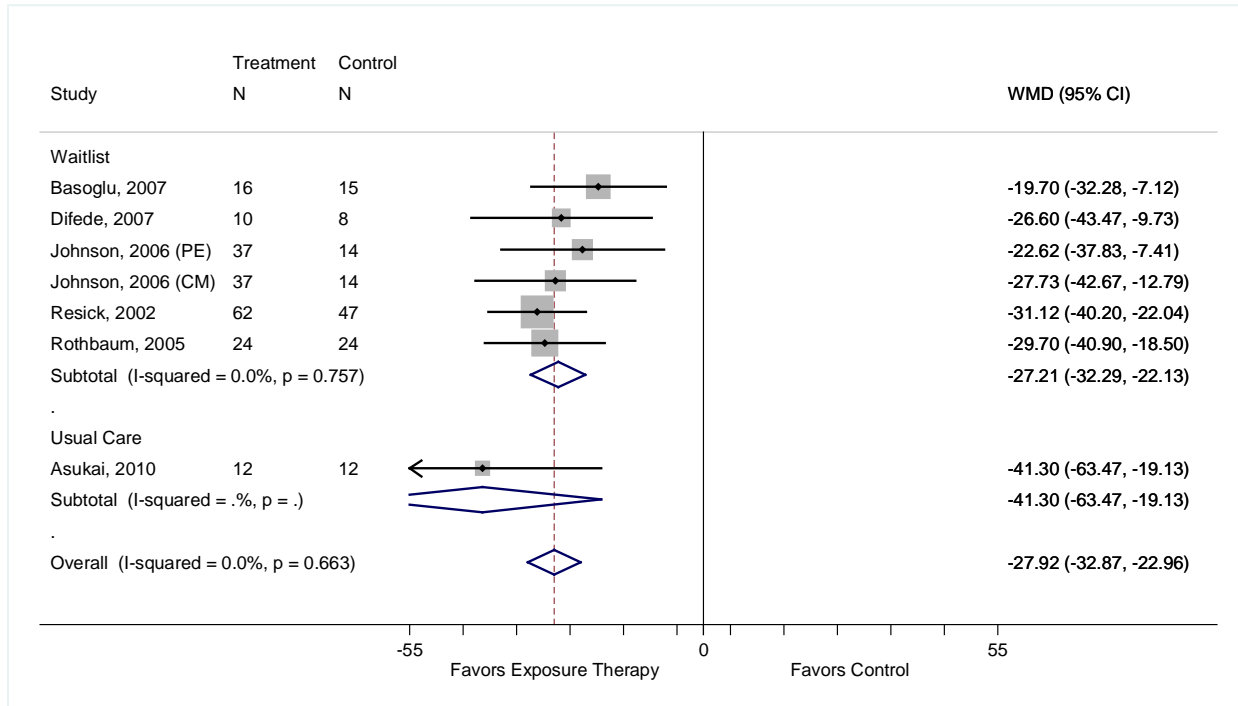
**Table F-10. Change in CAPS for exposure therapy compared with control, by type of comparator: Statistics with one study removed**

| Study Omitted  | Overall Estimate | 95% Confidence Interval |
|----------------|------------------|-------------------------|
| Basoglu, 2007  | -31.54           | (-38.27 to -24.82)      |
| Resick, 2002   | -27.85           | (-38.11 to -17.59)      |
| Rothbaum, 2005 | -28.75           | (-38.91 to -18.59)      |
| Asukai, 2010   | -27.85           | (-34.36 to -21.34)      |
| Combined       | -28.89           | (-35.46 to -22.32)      |

**Table F-11. Change in CAPS for exposure therapy compared with control, by type of comparator: Statistics with one study removed, by type of comparator**

| Study Omitted     | Overall Estimate | 95% Confidence Interval |
|-------------------|------------------|-------------------------|
| <b>Waitlist</b>   |                  |                         |
| Basoglu, 2007     | -30.56           | (-37.61 to -23.50)      |
| Resick, 2002      | -25.13           | (-34.89 to -15.36)      |
| Rothbaum, 2005    | -26.27           | (-37.34 to -15.21)      |
| Combined          | -27.85           | (-34.36 to -21.34)      |
| <b>Usual Care</b> |                  |                         |
| NA                | NA               | NA                      |

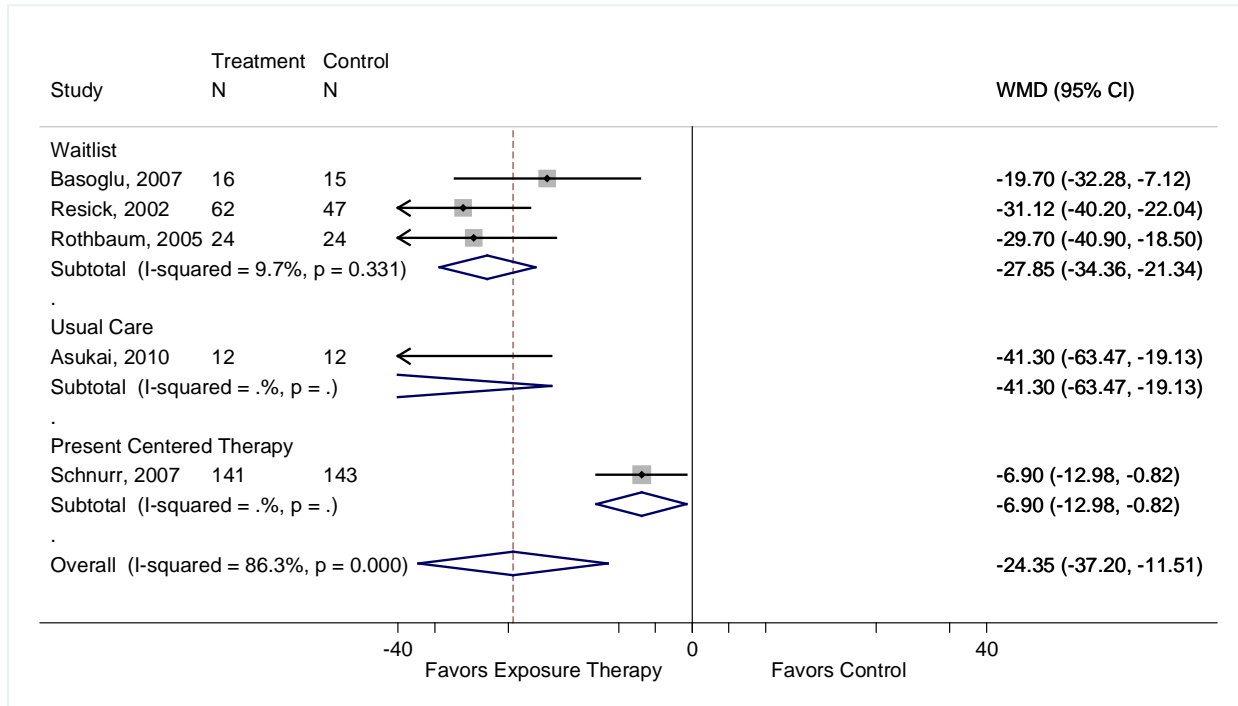
**Figure F-18. Change in CAPS for exposure therapy compared with control, by type of comparator: Sensitivity analysis including high risk of bias studies**



Note: Difede et al., 2007, and Johnson et al., 2006 were rated as having a high risk of bias.

Timing of outcome assessment: 8 weeks (Basoglu, 2007), 24 weeks (Difede, 2007), 6-9 sessions (Johnson, 2006), 6 weeks (Resick, 2002), 4.5 weeks (Rothbaum, 2005), “post-treatment” or 8 to 15 weeks (Asukai, 2010).

**Figure F-19. Change in CAPS for exposure therapy compared with control, by type of comparator: Sensitivity analysis including present centered therapy**



Timing of outcome assessment: 8 weeks (Basoglu, 2007), 6 weeks (Resick, 2002), 4.5 weeks (Rothbaum, 2005), “post-treatment” or 8 to 15 weeks (Asukai, 2010), 10 weeks (Schnurr, 2007).

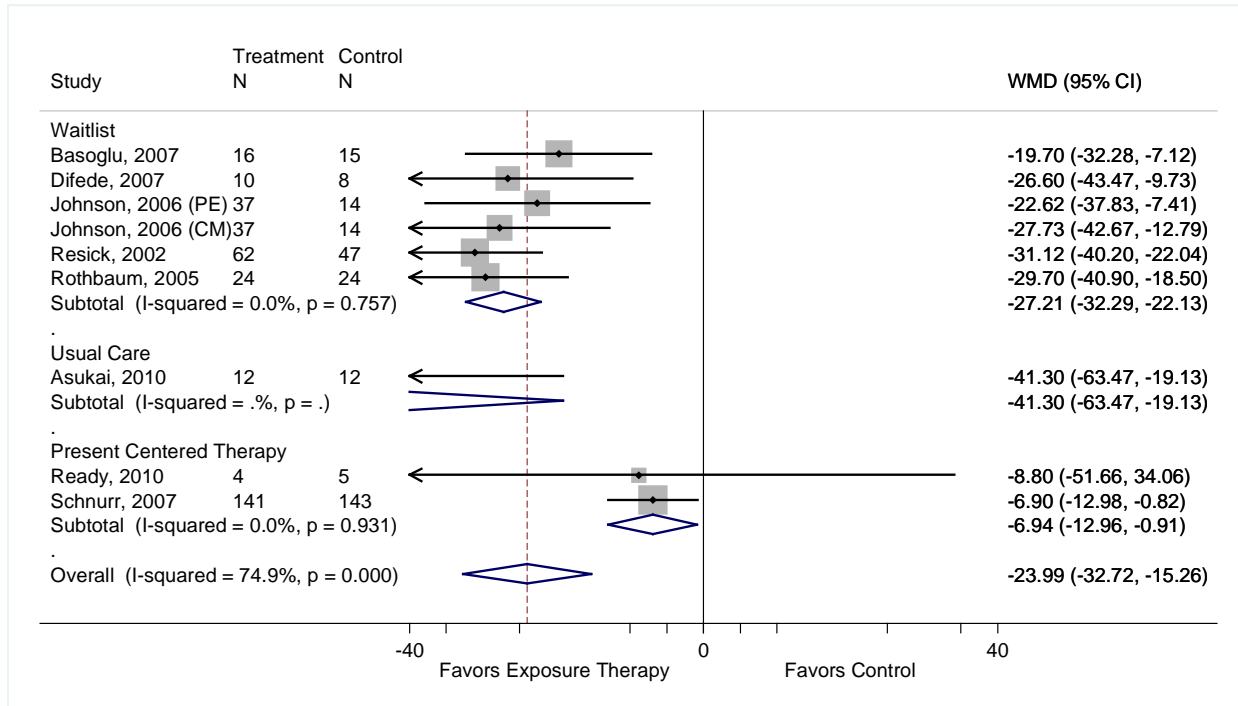
**Table F-12. Change in CAPS for exposure therapy compared with control, by type of comparator: Statistics with one study removed**

| Study Omitted  | Overall Estimate | 95% Confidence Interval |
|----------------|------------------|-------------------------|
| Basoglu, 2007  | -25.82           | (-41.91 to -9.74)       |
| Resick, 2002   | -22.48           | (-37.09 to -7.86)       |
| Rothbaum, 2005 | -23.12           | (-38.38 to -7.86)       |
| Asukai, 2010   | -21.53           | (-34.99 to -8.08)       |
| Schnurr, 2007  | -28.89           | (-35.46 to -22.32)      |
| Combined       | -24.35           | (-37.20 to -11.51)      |

**Table F-13. Change in CAPS for exposure therapy compared with control, by type of comparator: Statistics with one study removed, by type of comparator**

| Study Omitted                   | Overall Estimate | 95% Confidence Interval |
|---------------------------------|------------------|-------------------------|
| <b>Waitlist</b>                 |                  |                         |
| Basoglu, 2007                   | -30.56           | (-37.62 to -23.50)      |
| Resick, 2002                    | -25.13           | (-34.89 to -15.36)      |
| Rothbaum, 2005                  | -26.27           | (-37.34 to -15.21)      |
| Combined                        | -27.85           | (-34.36 to -21.34)      |
| <b>Usual Care</b>               |                  |                         |
| NA                              | NA               | NA                      |
| <b>Present Centered Therapy</b> |                  |                         |
| NA                              | NA               | NA                      |

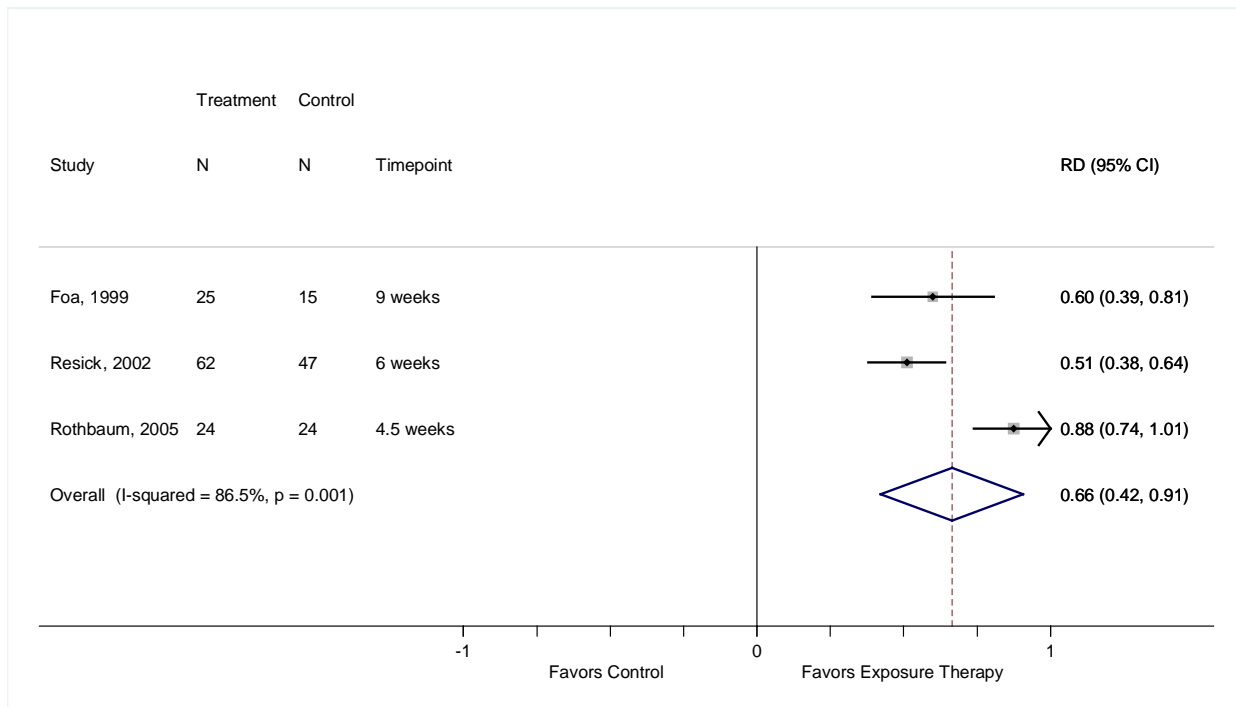
**Figure F-20. Change in CAPS for exposure therapy compared with control, by type of comparator: Sensitivity analysis including present centered therapy and high risk of bias studies**



Note: Difede et al., 2007, Ready et al., 2010, and Johnson et al., 2006 were rated as having a high risk of bias.

Timing of outcome assessment: 8 weeks (Basoglu, 2007), 24 weeks (Difede, 2007), 6 to 9 sessions (Johnson, 2006), 6 weeks (Resick, 2002), 4.5 weeks (Rothbaum, 2005), “post-treatment” or 8 to 15 weeks (Asukai, 2010), 10 sessions (Ready, 2010), 10 weeks (Schnurr, 2007).

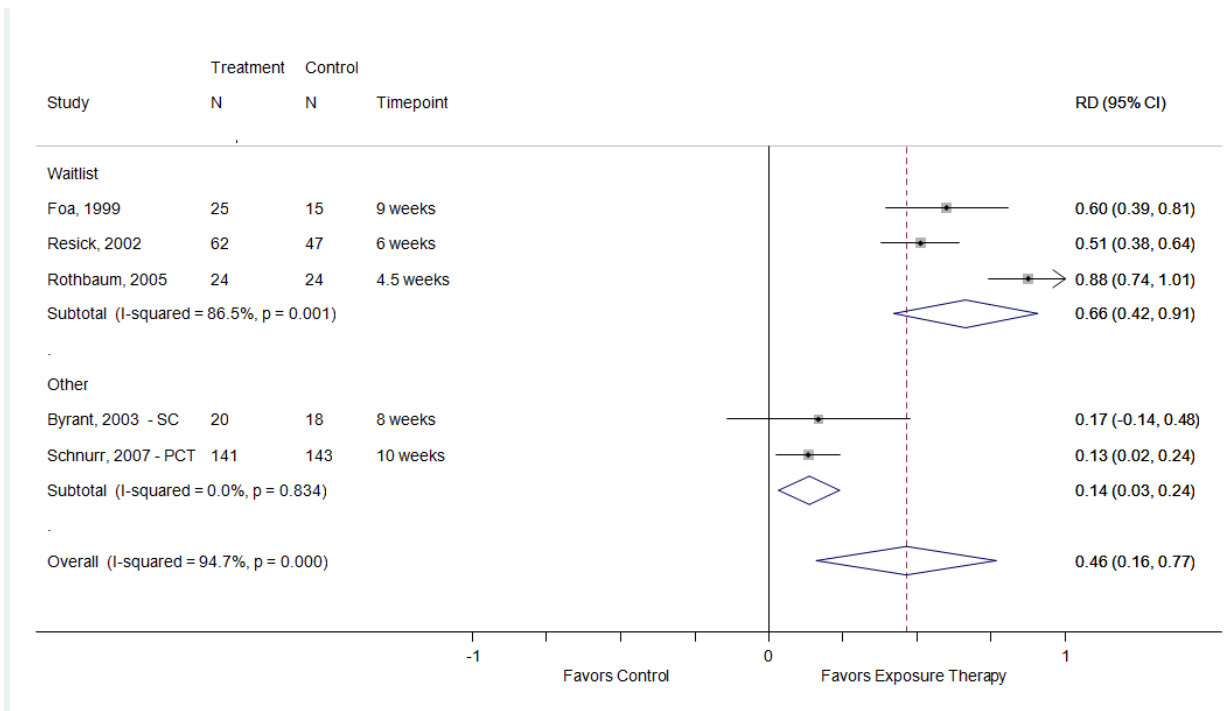
**Figure F-21. Loss of PTSD diagnosis for exposure therapy compared with waitlist**



**Table F-14. Loss of PTSD diagnosis for exposure therapy compared with waitlist: Statistics with one study removed**

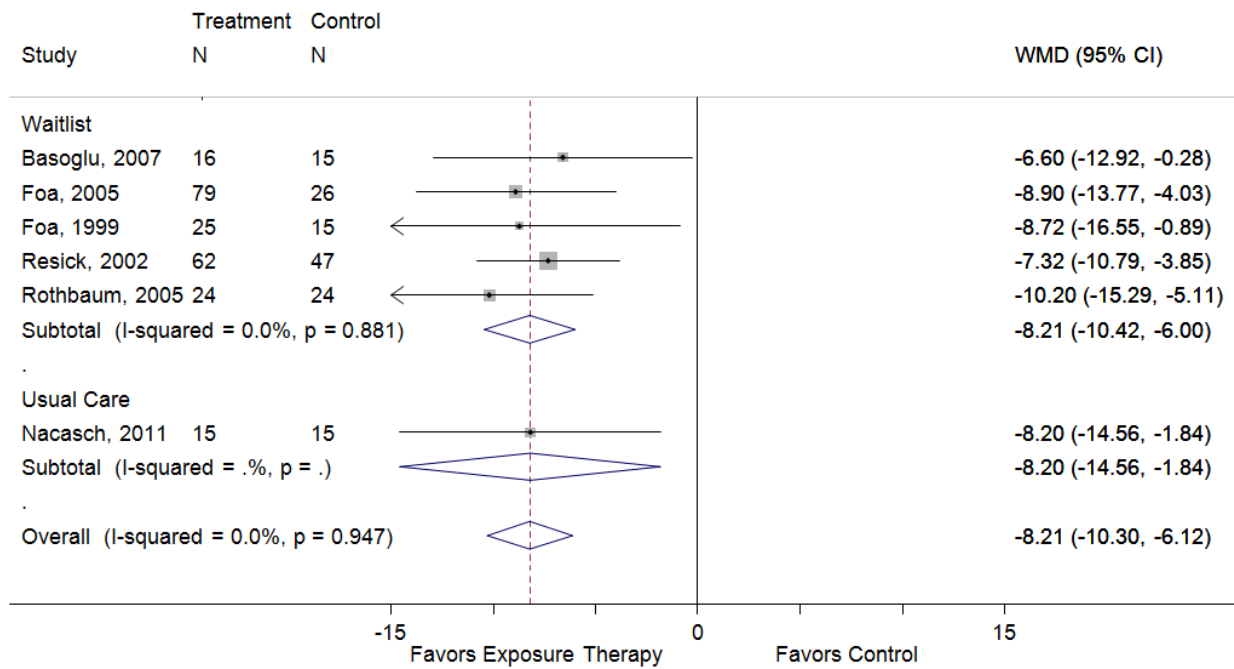
| Study Omitted   | Overall Estimate | 95% Confidence Interval |
|-----------------|------------------|-------------------------|
| <b>Waitlist</b> |                  |                         |
| Foa, 1999       | 0.69             | (0.34 to 1.05)          |
| Resick, 2002    | 0.75             | (0.48 to 1.02)          |
| Rothbaum, 2005  | 0.54             | (0.43 to -0.65)         |
| Combined        | 0.66             | (0.42 to 0.91)          |

**Figure F-22. Loss of PTSD diagnosis for exposure therapy compared with control, by type of comparator: Sensitivity analysis including other comparators**





**Figure F-23. Change in BDI for exposure therapy compared with control, by type of comparator**



Timing of outcome assessment: 8 weeks (Basoglu, 2007), 12 weeks (Foa, 2005), 9 weeks (Foa, 1999), 6 weeks (Resick, 2002), 4.5 weeks (Rothbaum, 2005), 9 to 15 weeks (Nacasch, 2011).

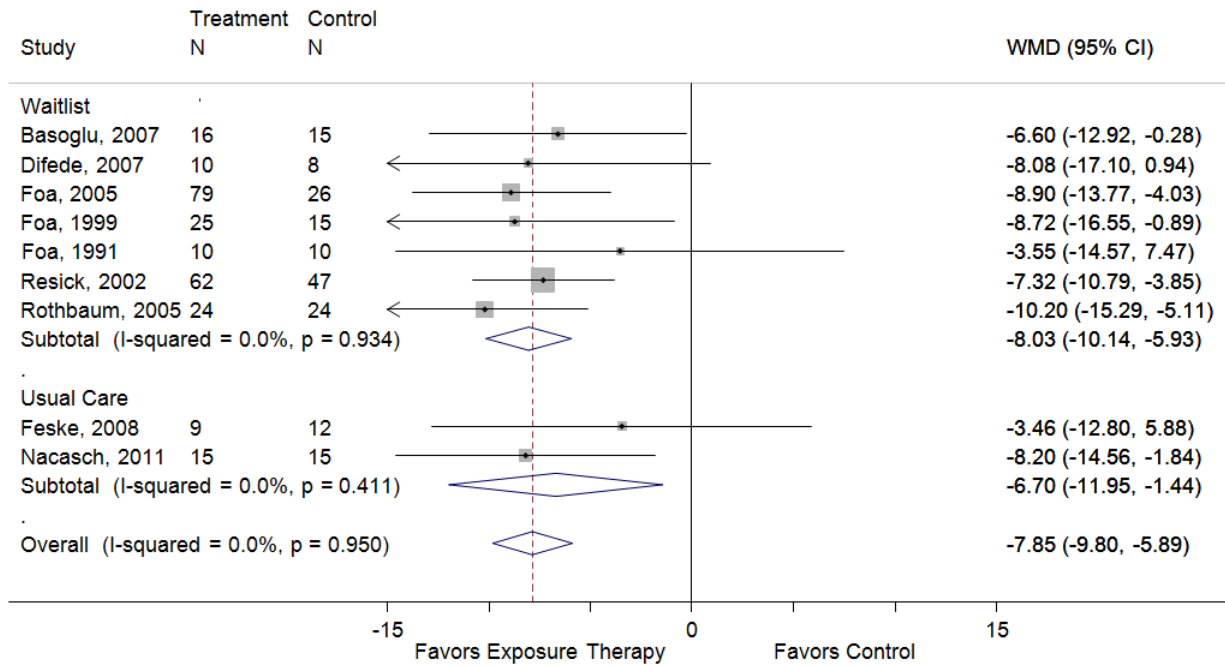
**Table F-15. Change in BDI for exposure therapy compared with control: Statistics with one study removed**

| Study Omitted  | Overall Estimate | 95% Confidence Interval |
|----------------|------------------|-------------------------|
| Basoglu, 2007  | -8.41            | (-10.62 to -6.20)       |
| Foa, 2005      | -8.05            | (-10.36 to -5.75)       |
| Foa, 1999      | -8.17            | (-10.34 to -6.01)       |
| Resick, 2002   | -8.71            | (-11.32 to -6.10)       |
| Rothbaum, 2005 | -7.81            | (-10.09 to -5.52)       |
| Nacasch, 2011  | -8.21            | (-10.42 to -6.00)       |
| Combined       | -8.21            | (-10.30 to -6.12)       |

**Table F-16. Change in BDI for exposure therapy compared with control: Statistics with one study removed, by type of comparator**

| Study Omitted     | Overall Estimate | 95% Confidence Interval |
|-------------------|------------------|-------------------------|
| <b>Waitlist</b>   |                  |                         |
| Basoglu, 2007     | -8.44            | (-10.79 to -6.08)       |
| Foa, 2005         | -8.03            | (-10.51 to -5.55)       |
| Foa, 1999         | -8.17            | (-10.47 to -5.87)       |
| Resick, 2002      | -8.81            | (-11.68 to -5.95)       |
| Rothbaum, 2005    | -7.75            | (-10.20 to -5.30)       |
| Combined          | -8.21            | (-10.42 to -6.00)       |
| <b>Usual Care</b> |                  |                         |
| NA                | NA               | NA                      |

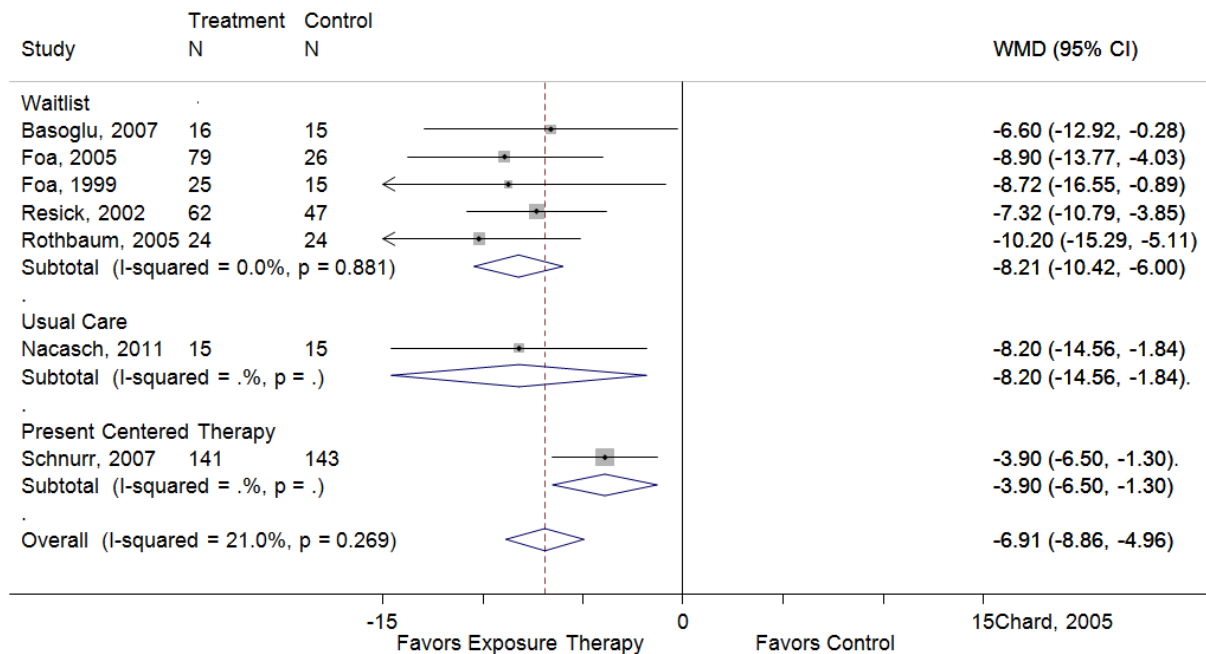
**Figure F-24. Change in BDI for exposure therapy compared with control, by type of comparator: Sensitivity analysis including high risk of bias studies**



Note: Difede et al., 2007, Foa et al., 1991, and Feske et al., 2008 were rated as having a high risk of bias.

Timing of outcome assessment: 8 weeks (Basoglu, 2007), 24 weeks (Difede, 2007), 12 weeks (Foa, 2005), 9 weeks (Foa, 1999 and Foa 1991), 6 weeks (Resick, 2002), 4.5 weeks (Rothbaum, 2005), 6 months (Feske, 2008), 9 to 15 weeks (Nacasch, 2011).

**Figure F-25. Change in BDI for exposure therapy compared with control, by type of comparator: Sensitivity analysis including present centered therapy**



Timing of outcome assessment: 8 weeks (Basoglu, 2007), 12 weeks (Foa, 2005), 9 weeks (Foa, 1999), 6 weeks (Resick, 2002), 4.5 weeks (Rothbaum, 2005), 9 to 15 weeks (Nacasch, 2011), 10 weeks (Schnurr 2007).

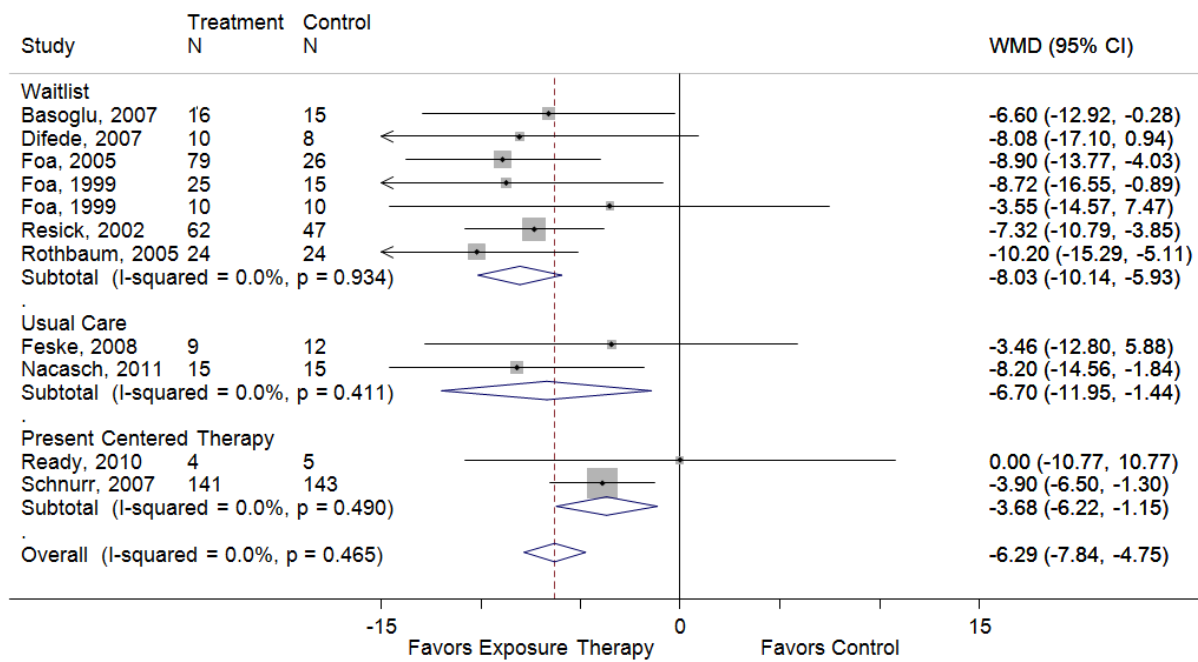
**Table F-17. Change in BDI for exposure therapy compared with control, by type of comparator: Sensitivity analysis including present centered therapy: statistics with one study removed**

| Study Omitted  | Overall Estimate | 95% Confidence Interval |
|----------------|------------------|-------------------------|
| Basoglu, 2007  | -7.12            | (-9.38 to -4.86)        |
| Foa, 2005      | -6.65            | (-8.80 to -4.51)        |
| Foa, 1999      | -6.91            | (-9.06 to -4.76)        |
| Resick, 2002   | -7.05            | (-9.53 to -4.57)        |
| Rothbaum, 2005 | -6.23            | (-8.06 to -4.40)        |
| Nacasch, 2011  | -6.92            | (-9.13 to -4.72)        |
| Schnurr, 2007  | -8.21            | (-10.30 to -6.12)       |
| Combined       | -6.91            | (-8.86 to -4.96)        |

**Table F-18. Change in BDI for exposure therapy compared with control, by type of comparator: Sensitivity analysis including present centered therapy: statistics with one study removed, by type of comparator**

| Study Omitted                   | Overall Estimate | 95% Confidence Interval |
|---------------------------------|------------------|-------------------------|
| <b>Waitlist</b>                 |                  |                         |
| Basoglu, 2007                   | -8.44            | (-10.79 to -6.08)       |
| Foa, 2005                       | -8.03            | (-10.51 to -5.55)       |
| Foa, 1999                       | -8.17            | (-10.47 to -5.87)       |
| Resick, 2002                    | -8.82            | (-11.68 to -5.95)       |
| Rothbaum, 2005                  | -7.75            | (-10.20 to -5.30)       |
| Combined                        | -8.21            | (-10.42 to -6.00)       |
| <b>Usual Care</b>               |                  |                         |
| NA                              | NA               | NA                      |
| <b>Present Centered Therapy</b> |                  |                         |
| NA                              | NA               | NA                      |

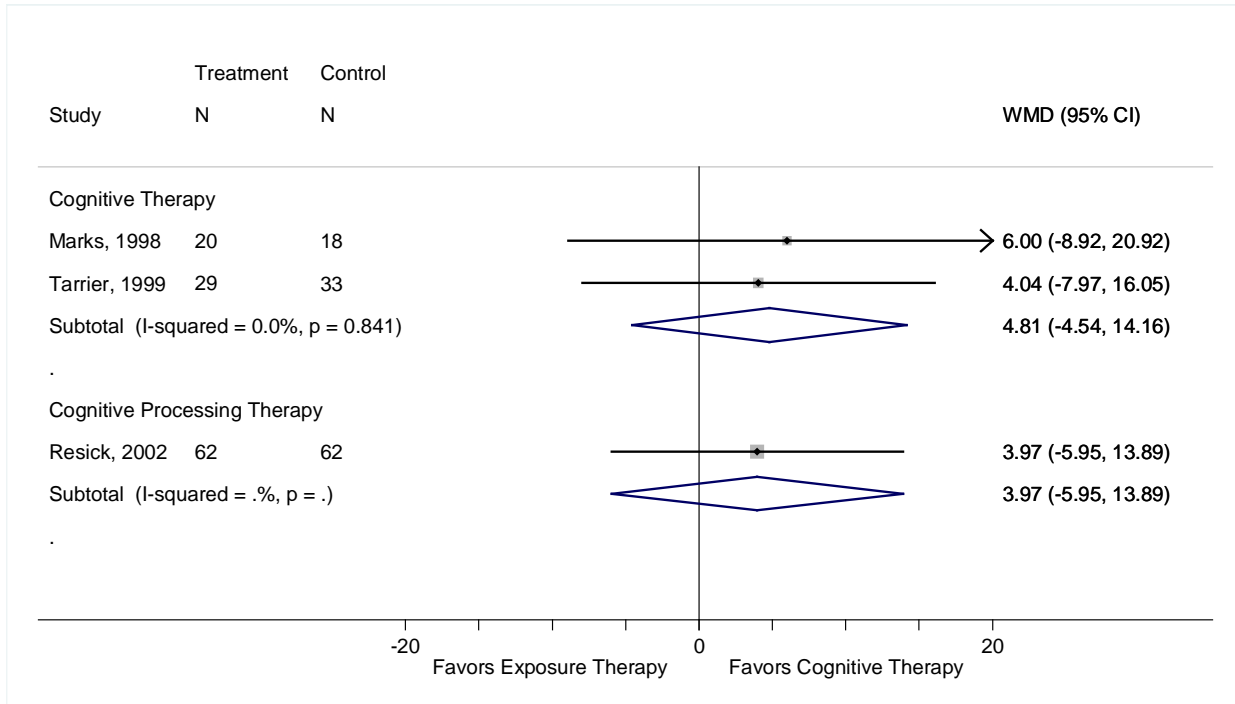
**Figure F-26. Change in BDI for exposure therapy compared with control, by type of comparator: Sensitivity analysis including present centered therapy and high risk of bias studies**



Note: Difede et al., 2007, Foa et al., 1991, Ready et al., 2010, and Feske et al., 2008 were rated as having a high risk of bias.

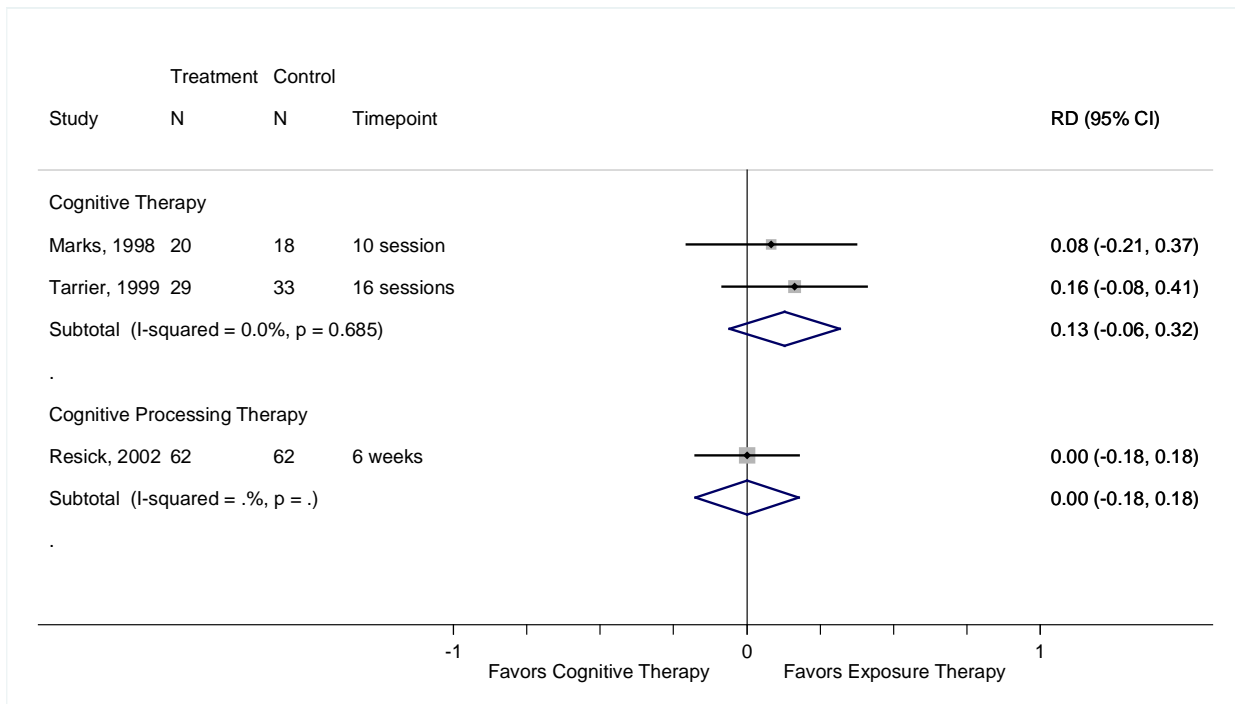
Timing of outcome assessment: 8 weeks (Basoglu, 2007), 24 weeks (Difede, 2007), 12 weeks (Foa, 2005), 9 weeks (Foa, 1991 and Foa 1999), 6 weeks (Resick, 2002), 4.5 weeks (Rothbaum, 2005), 6 months (Feske, 2008), 9 to 15 weeks (Nacasch, 2011), 10 sessions (Ready, 2010), 10 weeks (Schnurr 2007).

**Figure F-27. Change in CAPS for exposure therapy compared with cognitive therapy, by type of cognitive therapy**



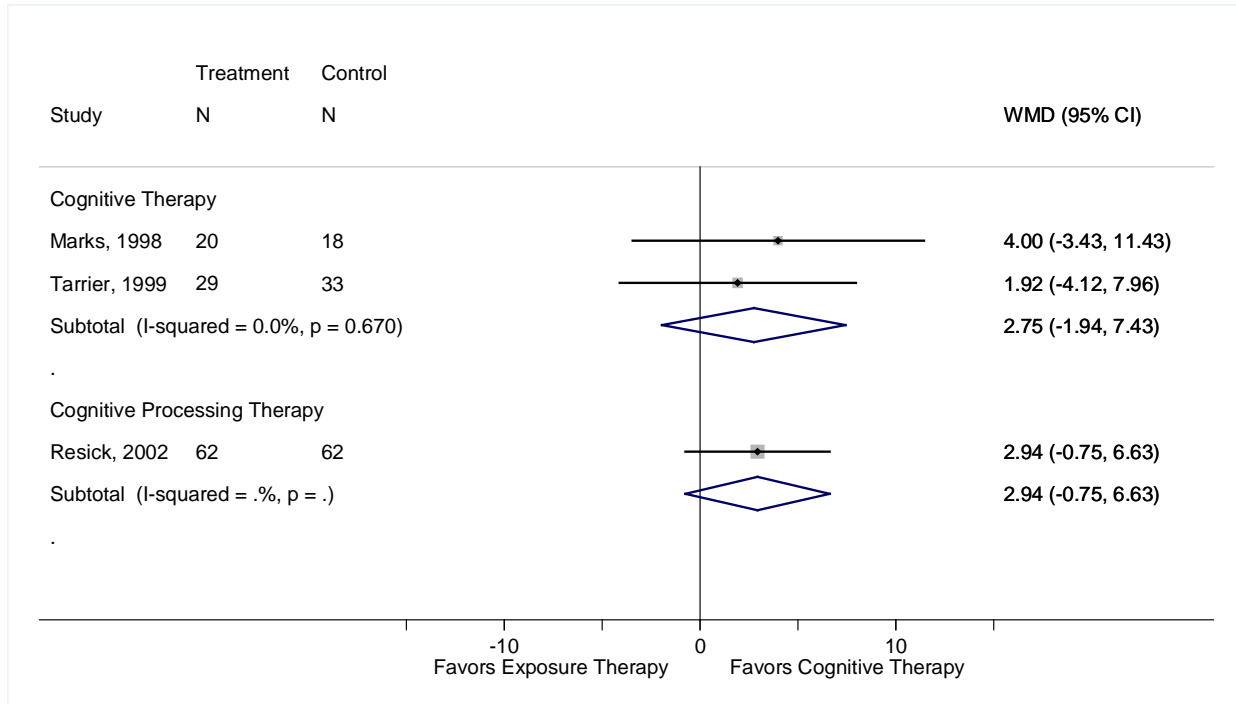
Timing of outcome assessment: mean 16 weeks (Marks, 1998), following 16 sessions (Tarrier, 1999), 6 weeks (Resick, 2002).

**Figure F-28. Loss of PTSD diagnosis for exposure therapy compared with cognitive therapy, by type of cognitive therapy**



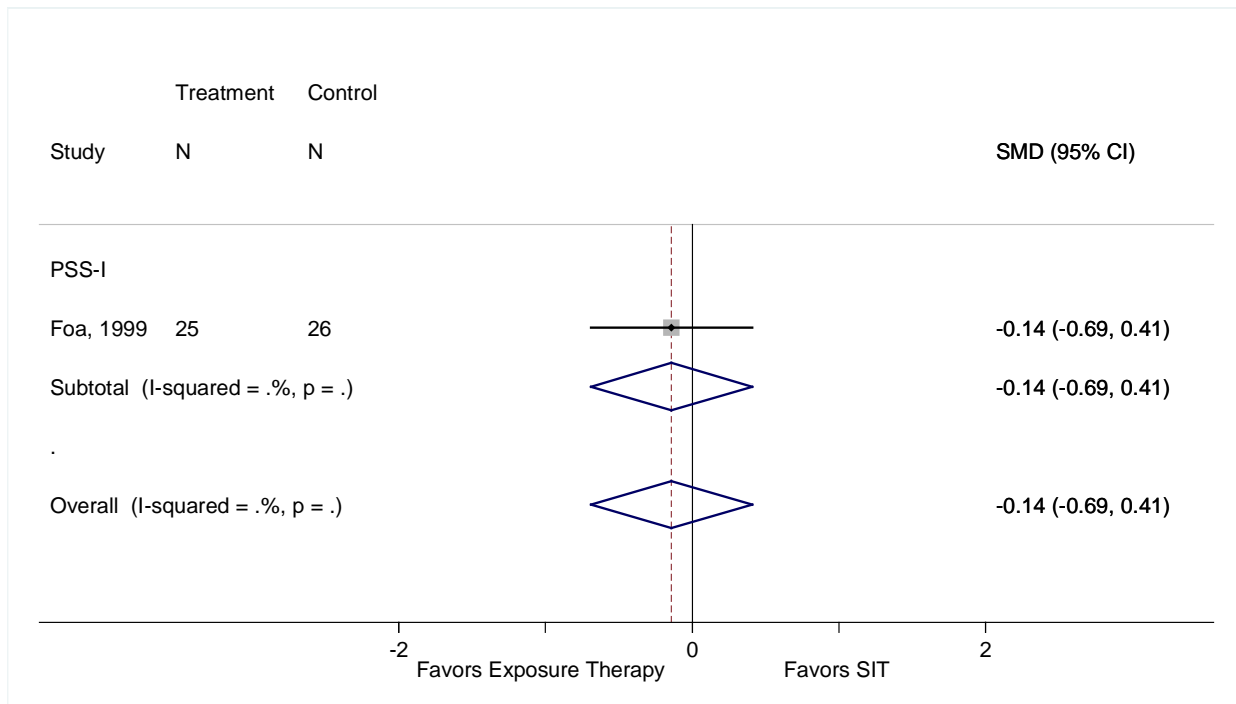
Timing of outcome assessment: mean 16 weeks (Marks, 1998), following 16 sessions (Tarrier, 1999), 6 weeks (Resick, 2002).

**Figure F-29. Change in BDI for exposure therapy compared with cognitive therapy, by type of cognitive therapy**



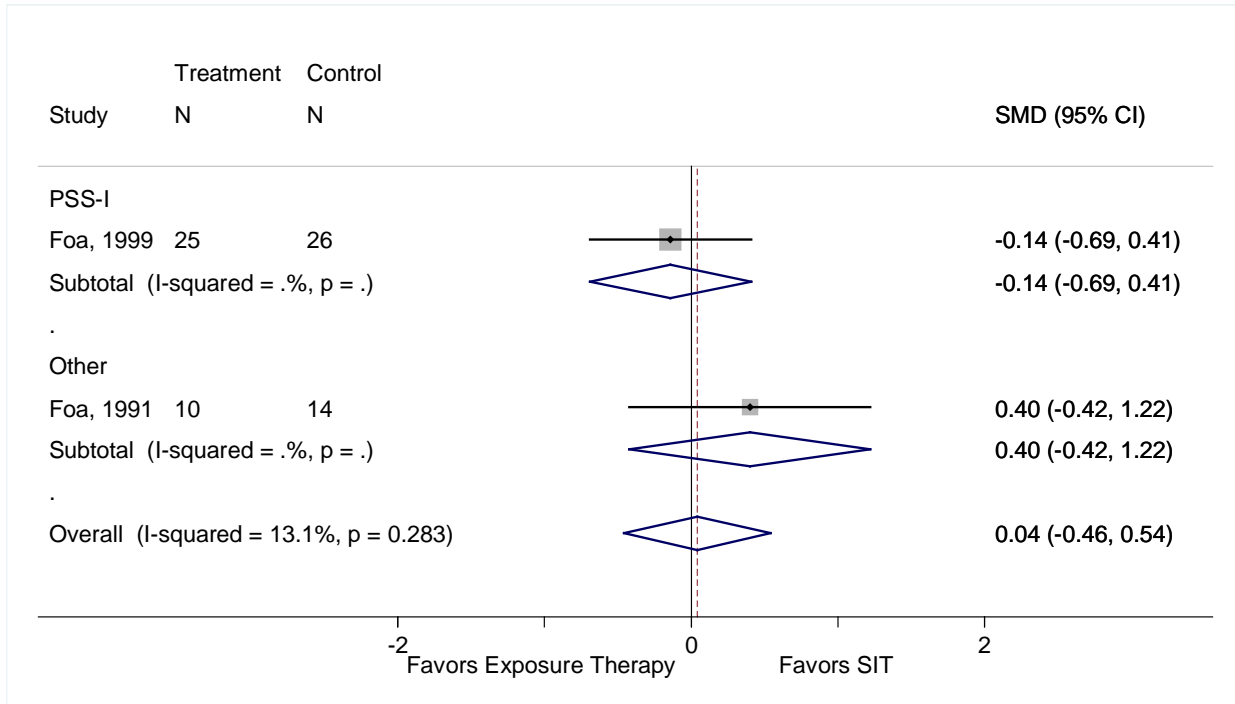
Timing of outcome assessment: mean 16 weeks (Marks, 1998), following 16 sessions (Tarrier, 1999), 6 weeks (Resick, 2002).

**Figure F-30. PTSD symptom reduction for exposure therapy compared with stress inoculation therapy, by instrument**



Timing of outcome assessment: 9 weeks

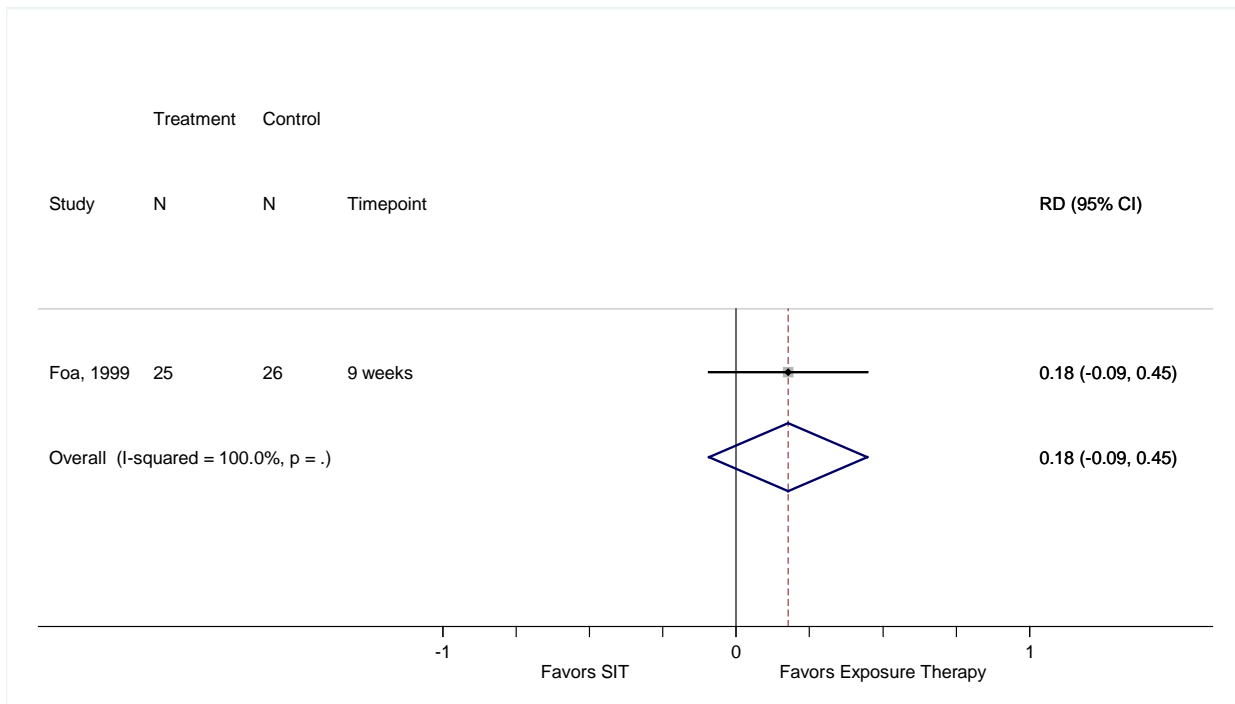
**Figure F-31. PTSD symptom reduction for exposure therapy compared with stress inoculation therapy, by instrument: sensitivity analysis including studies with high risk of bias**



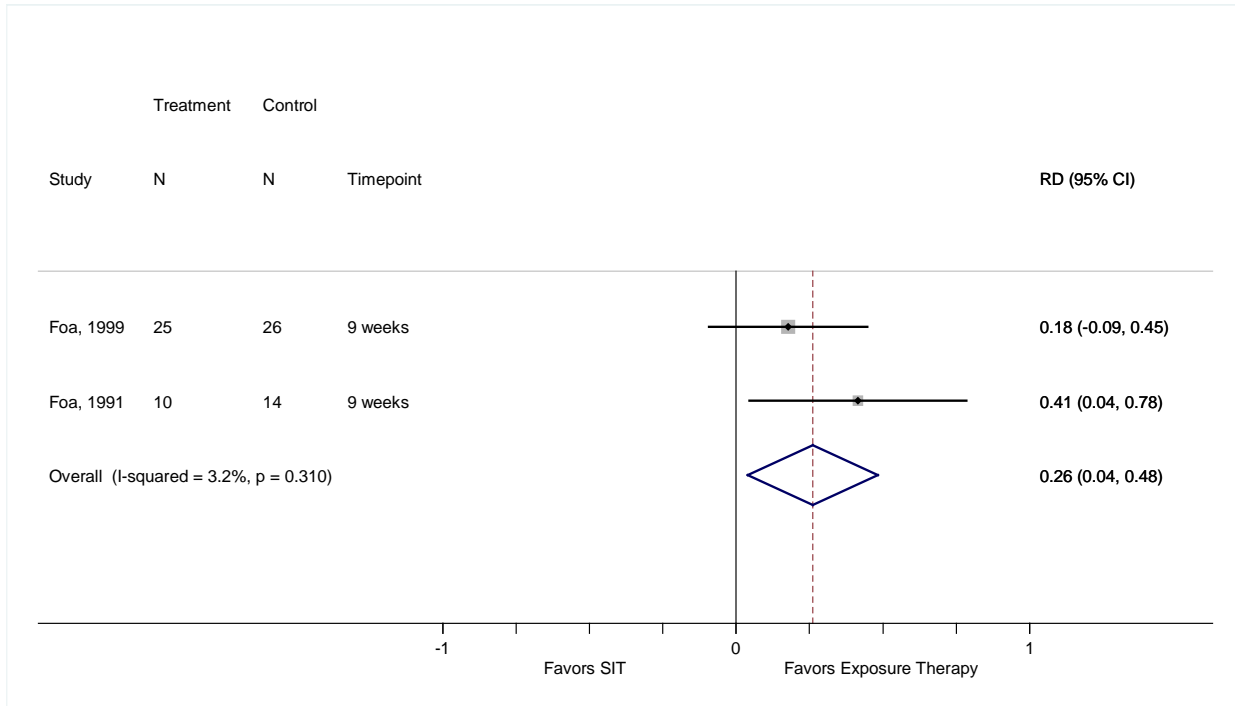
Note: Foa et al., 1991 was rated as having a high risk of bias.

Timing of outcome assessment: 9 weeks for both studies

**Figure F-32. Loss of PTSD diagnosis for exposure therapy compared with stress inoculation therapy**



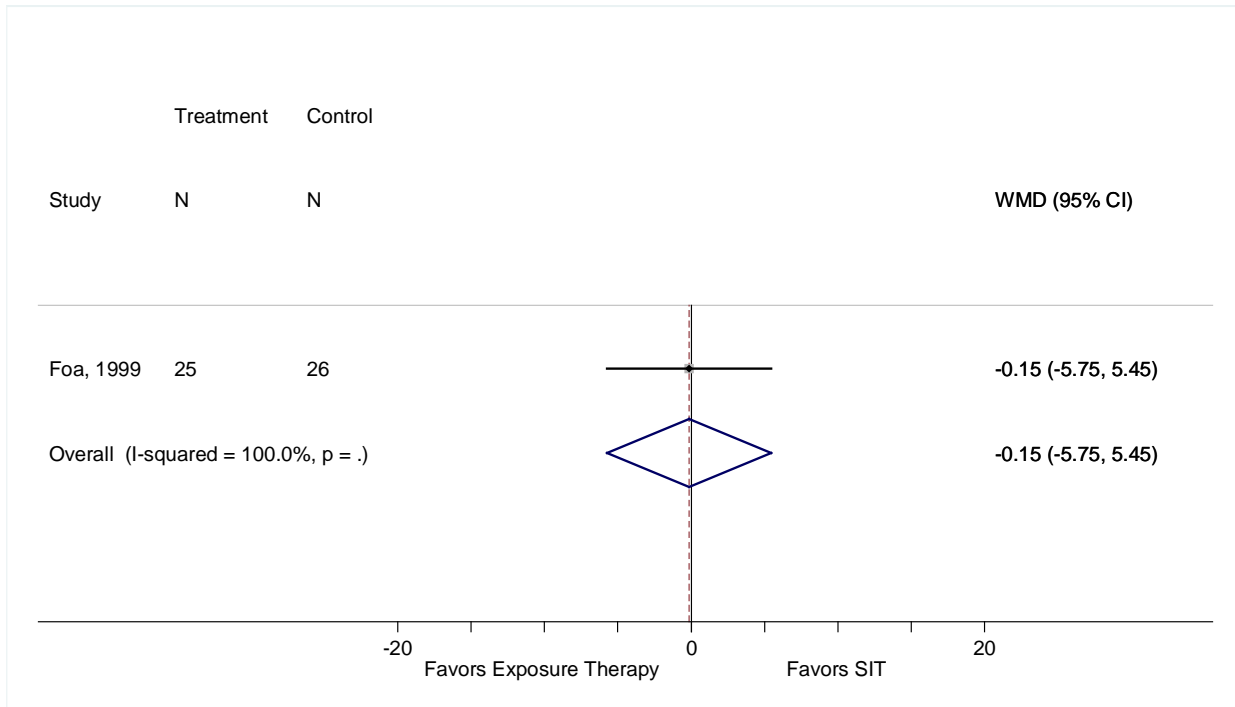
**Figure F-33. Loss of PTSD diagnosis for exposure therapy compared with stress inoculation therapy: sensitivity analysis including studies with high risk of bias**



Note: Foa et al., 1991 was rated as having a high risk of bias.

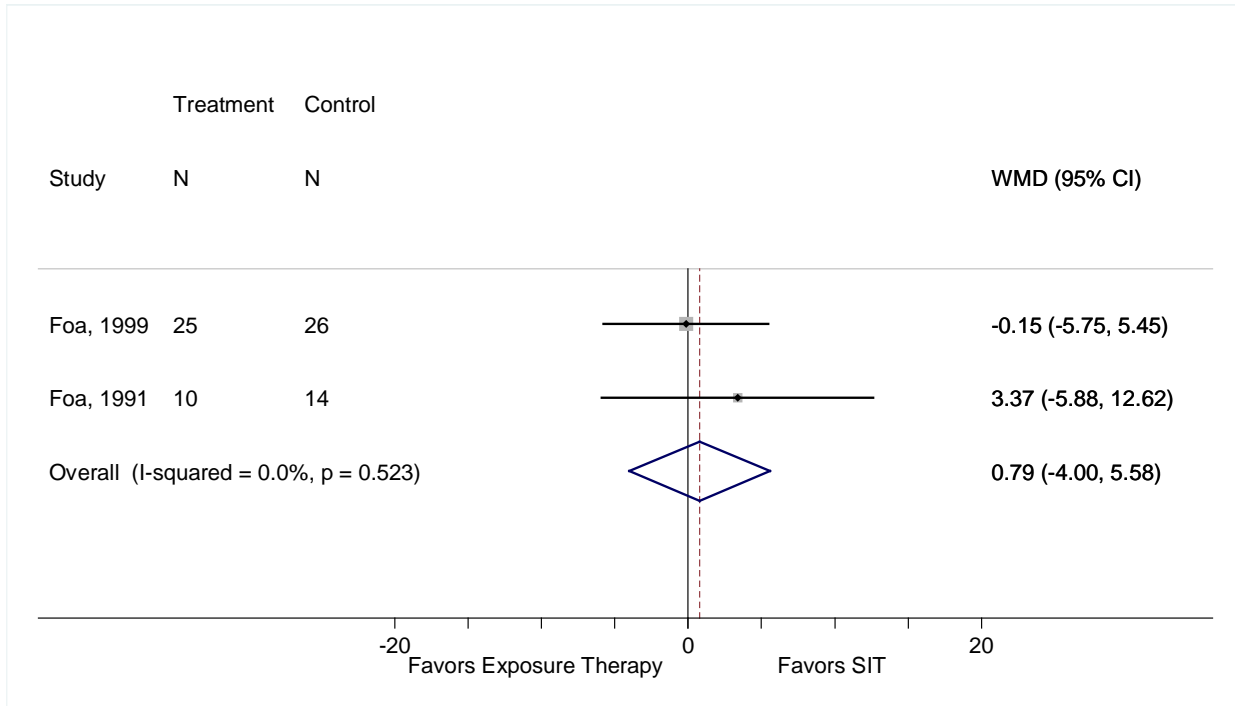


**Figure F-34. Change in BDI for exposure therapy compared with stress inoculation therapy**



Timing of outcome assessment: 9 weeks

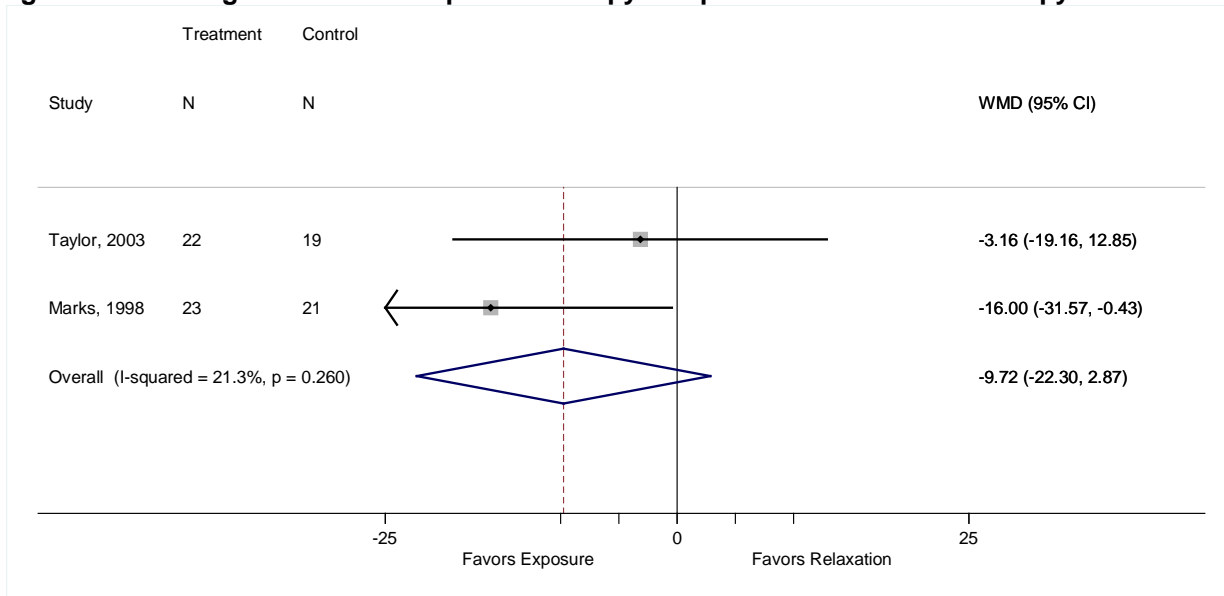
**Figure F-35. Change in BDI for exposure therapy compared with stress inoculation therapy: Sensitivity analysis including studies with high risk of bias**



Note: Foa et al., 1991 was rated as having a high risk of bias.

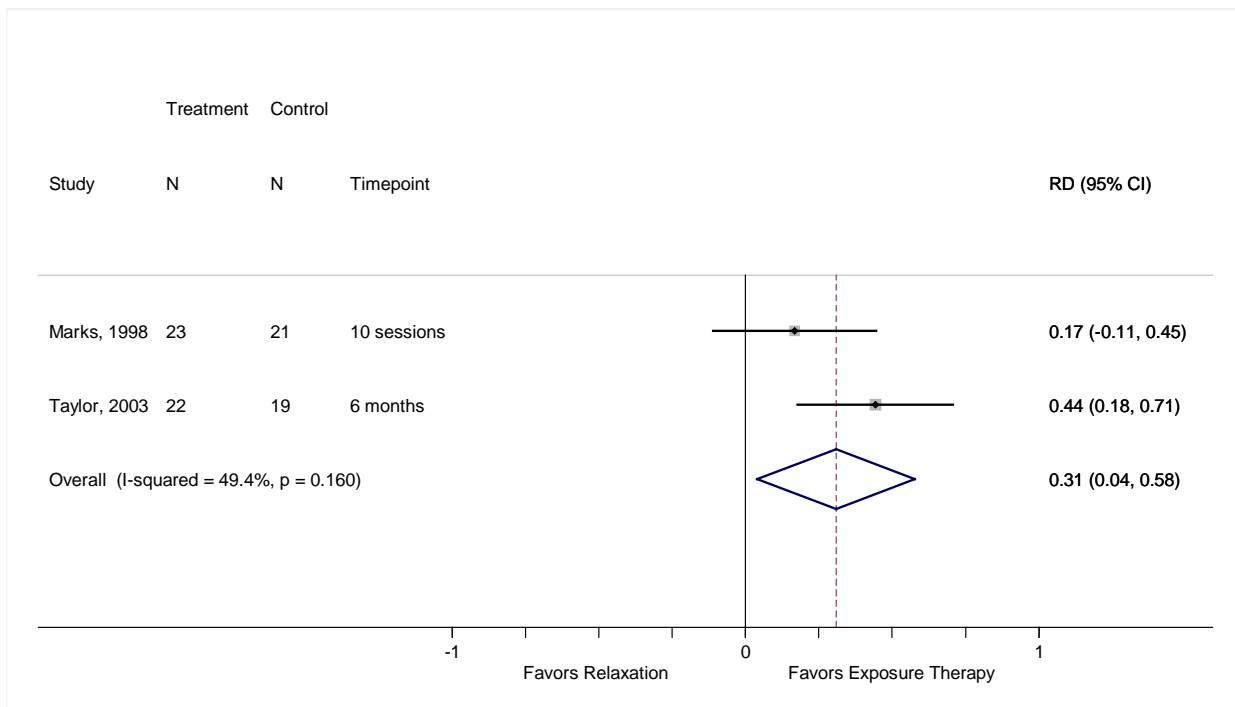
Timing of outcome assessment: 9 weeks for both studies.

**Figure F-36. Change in CAPS for exposure therapy compared with relaxation therapy**

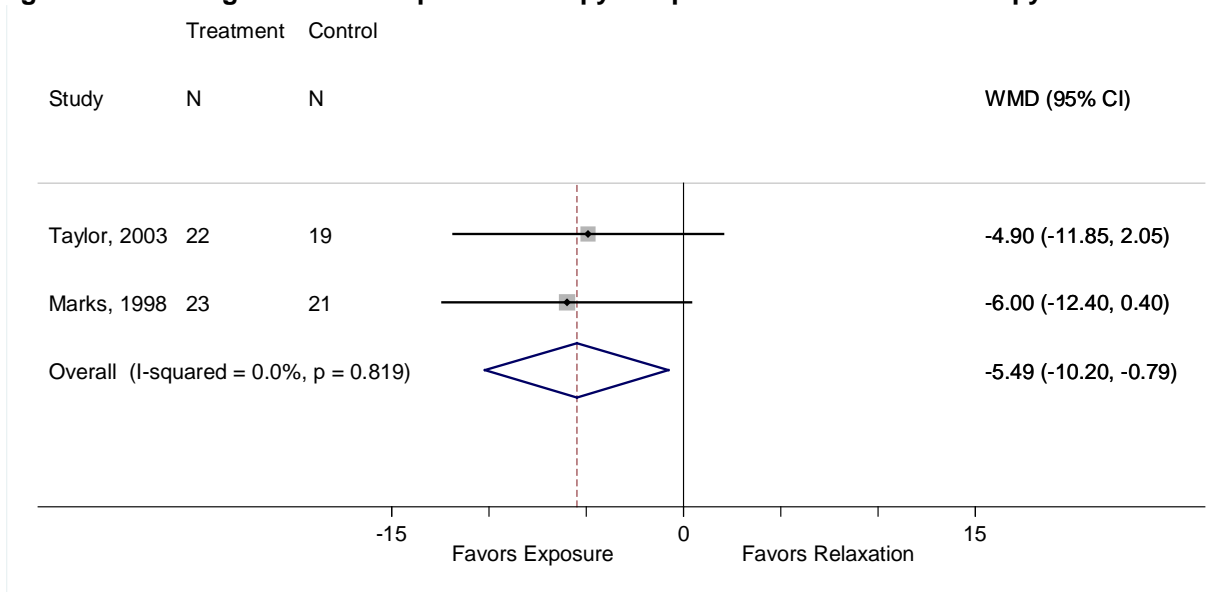


Timing of outcome assessment: 8 weeks (Taylor, 2003), mean 16 weeks (Marks, 1998).

**Figure F-37. Loss of PTSD diagnosis for exposure therapy compared with relaxation therapy**

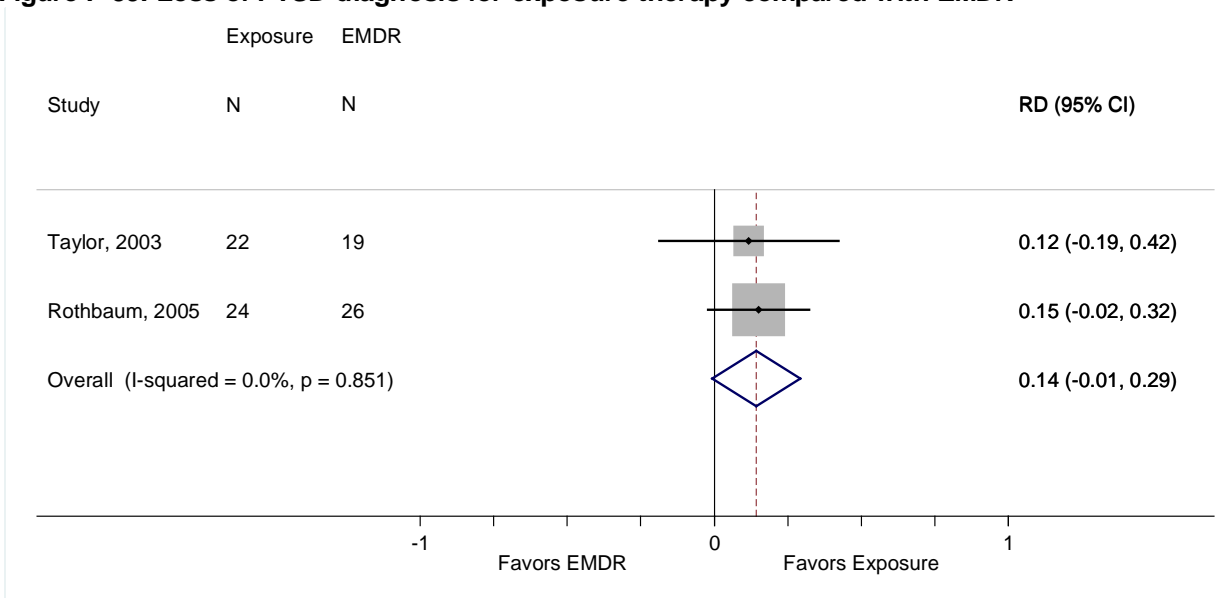


**Figure F-38. Change in BDI for exposure therapy compared with relaxation therapy**



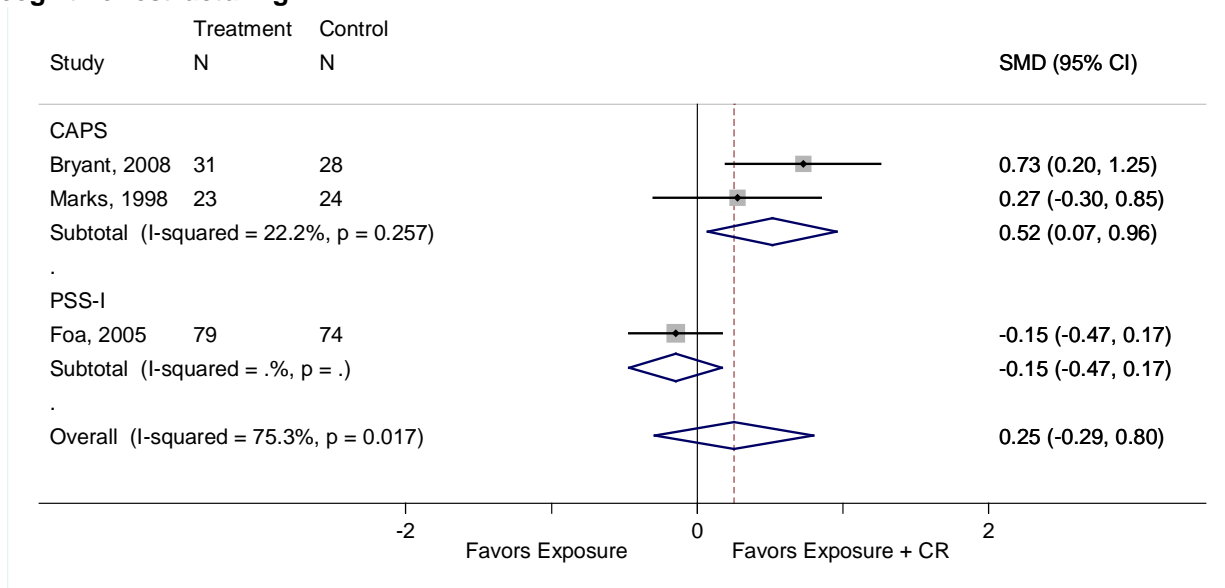
Timing of outcome assessment: 8 weeks (Taylor, 2003), mean 16 weeks (Marks, 1998).

**Figure F-39. Loss of PTSD diagnosis for exposure therapy compared with EMDR**



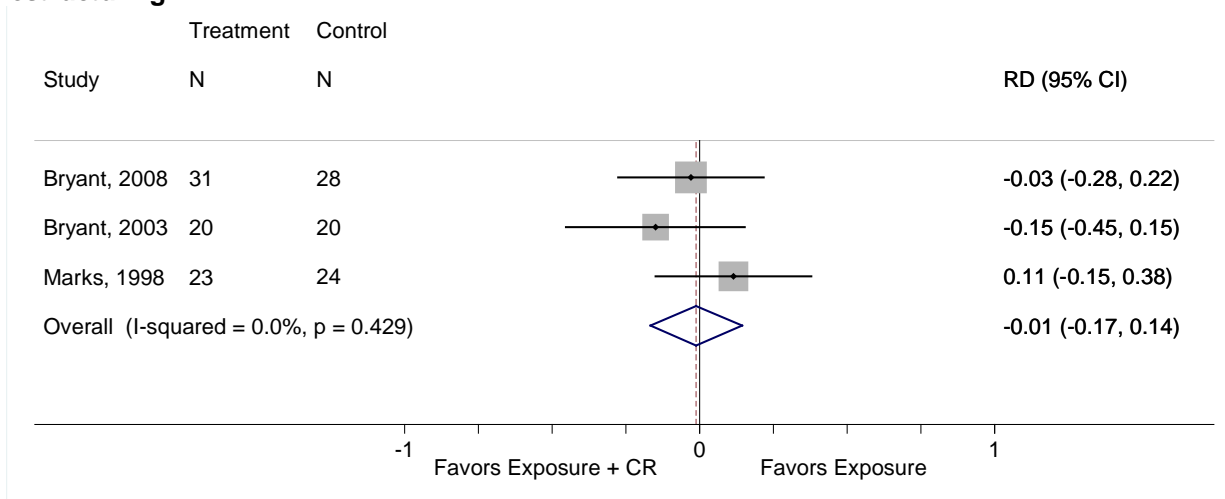
Timing of outcome assessment: 6 months (Taylor, 2003), 4.5 weeks (Rothbaum, 2005).

**Figure F-40. PTSD symptom reduction for exposure therapy compared with exposure plus cognitive restructuring**



Timing of outcome assessment: 8 weeks (Bryant, 2008), mean 16 weeks (Marks, 1998), 12 weeks (Foa, 2005).

**Figure F-41. Loss of PTSD diagnosis for exposure therapy compared with exposure plus cognitive restructuring**

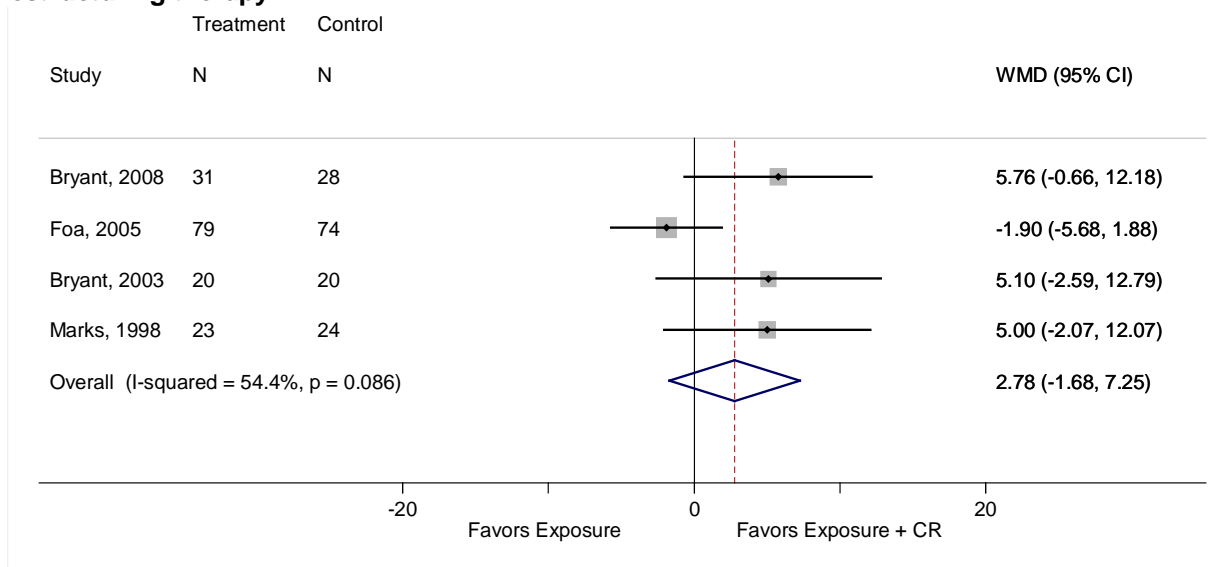


Timing of outcome assessment: 8 weeks (Bryant, 2008 and Bryant, 2003), mean 16 weeks (Marks, 1998).

**Table F-19. Loss of PTSD diagnosis for exposure therapy compared with exposure plus cognitive restructuring: Statistics with one study removed**

| Study Omitted | Overall Estimate | 95% Confidence Interval |
|---------------|------------------|-------------------------|
| Bryant, 2008  | -0.01            | (-0.27 to 0.25)         |
| Bryant, 2003  | 0.04             | (-0.14 to 0.22)         |
| Marks, 1998   | -0.08            | (-0.27 to 0.11)         |
| Combined      | -0.01            | (-0.17 to 0.14)         |

**Figure F-42. Change in BDI for exposure therapy compared with exposure plus cognitive restructuring therapy**



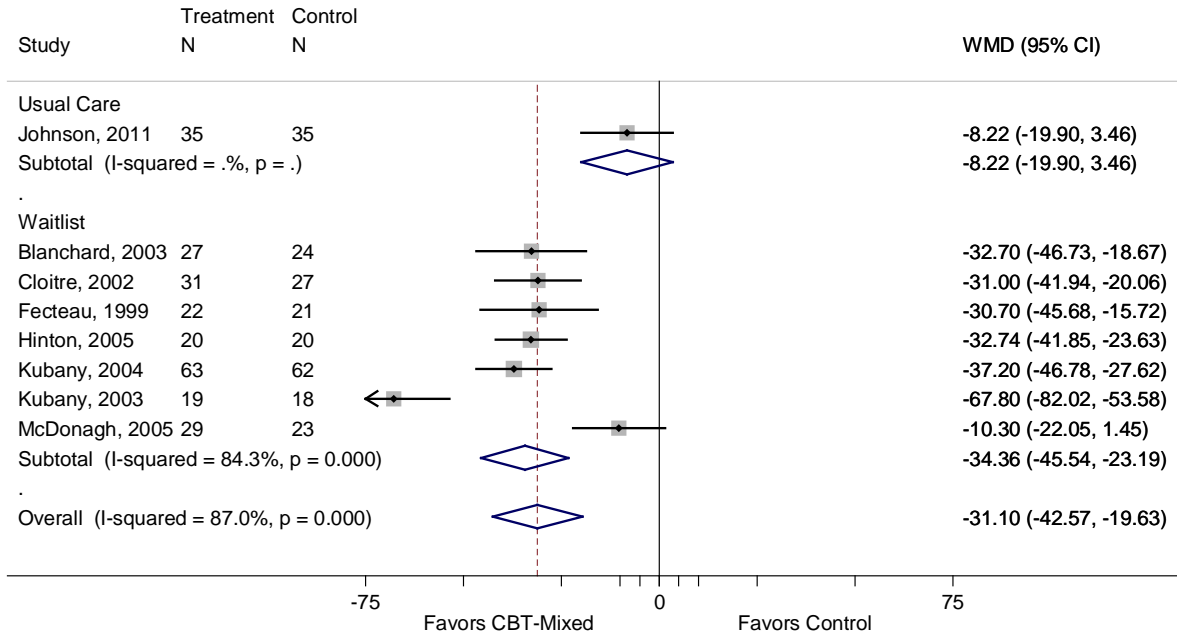
Timing of outcome assessment: 8 weeks (Bryant, 2008 and Bryant, 2003), 12 weeks (Foa, 2005), mean 16 weeks (Marks, 1998),

**Table F-20. Change in BDI for exposure therapy compared with exposure plus cognitive restructuring: Statistics with one study removed**

| Study Omitted | Overall Estimate | 95% Confidence Interval |
|---------------|------------------|-------------------------|
| Bryant, 2008  | 1.88             | (-3.33 to 7.10)         |
| Foa, 2005     | 5.33             | (1.29 to 9.37)          |
| Bryant, 2003  | 2.35             | (-3.12 to 7.82)         |
| Marks, 1998   | 2.32             | (-3.24 to 7.88)         |
| Combined      | 2.78             | (-1.68 to 7.25)         |

# CBT-Mixed: Meta-Analysis Results

Figure F-43. Change in CAPS for CBT-mixed compared with control, by comparator



Timing of outcome assessment: 7 weeks (Johnson, 2011), 8 to 12 weeks (Blanchard, 2003), 12 weeks (Cloitre, 2002), 4 weeks (Fecteau, 1999), 12 weeks (Hinton, 2005), 4 to 5.5weeks (Kubany, 2004), 4.5 months (Kubany, 2003), 14 weeks (McDonagh, 2005).

**Table F-21. Change in CAPS for CBT-mixed compared with control, by comparator: Statistics with one study removed**

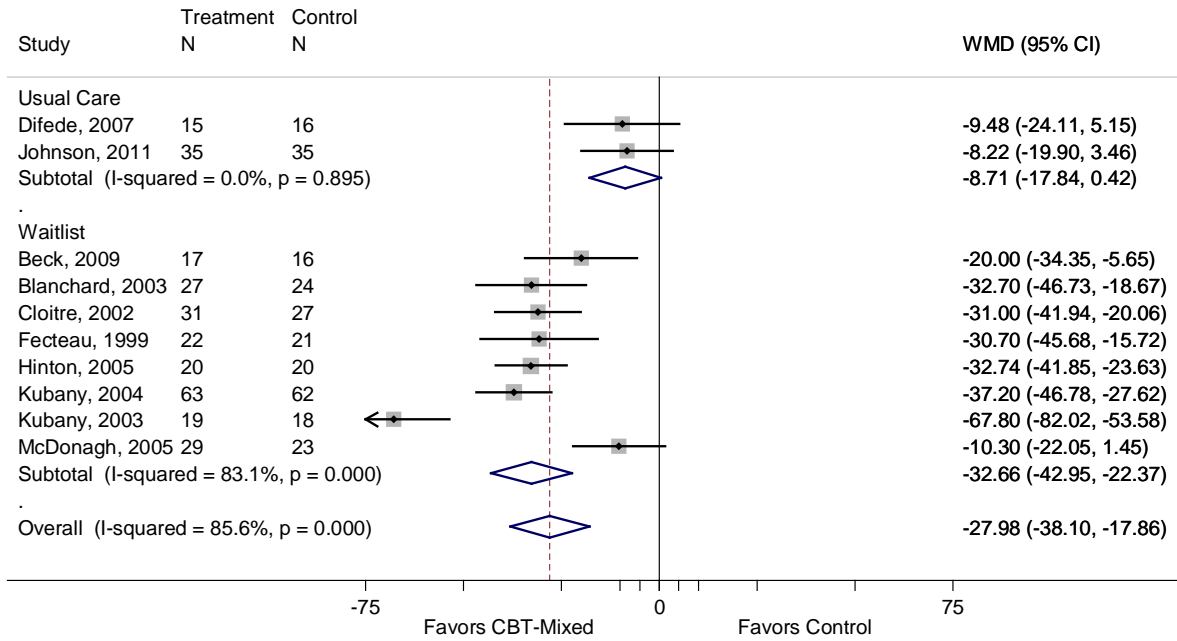
| <b>Study Omitted</b> | <b>Overall Estimate</b> | <b>95% Confidence Interval</b> |
|----------------------|-------------------------|--------------------------------|
| Johnson, 2011        | -34.36                  | (-45.54 to -23.19)             |
| Blanchard, 2003      | -30.91                  | (-43.84 to -17.98)             |
| Cloitre, 2002        | -31.16                  | (-44.54 to -17.78)             |
| Fecteau, 1999        | -31.18                  | (-44.02 to -18.33)             |
| Hinton, 2005         | -30.91                  | (-44.67 to -17.14)             |
| Kubany, 2004         | -30.22                  | (-43.60 to -16.85)             |
| Kubany, 2003         | -26.21                  | (-35.02 to -17.40)             |
| McDonagh, 2005       | -34.08                  | (-45.67 to -22.48)             |
| Combined             | -31.10                  | (-42.57 to -19.63)             |

**Table F-22. Change in CAPS for CBT-mixed compared with control, by comparator: Statistics with one study removed, by type of comparator**

| <b>Study Omitted</b> | <b>Overall Estimate</b> | <b>95% Confidence Interval</b> |
|----------------------|-------------------------|--------------------------------|
| <b>Waitlist</b>      |                         |                                |
| Blanchard, 2003      | -34.66                  | (-47.54 to -21.79)             |
| Cloitre, 2002        | -35.00                  | (-48.36 to -21.64)             |
| Fecteau, 1999        | -34.96                  | (-47.70 to -22.22)             |
| Hinton, 2005         | -34.73                  | (-48.61 to -20.84)             |
| Kubany, 2004         | -33.92                  | (-47.54 to -20.31)             |
| Kubany, 2003         | -29.30                  | (-36.96 to -21.63)             |
| McDonagh, 2005       | -38.29                  | (-48.14 to -28.44)             |
| Combined             | -34.36                  | (-45.54 to -23.19)             |
| <b>Usual Care</b>    |                         |                                |
| NA                   | NA                      | NA                             |



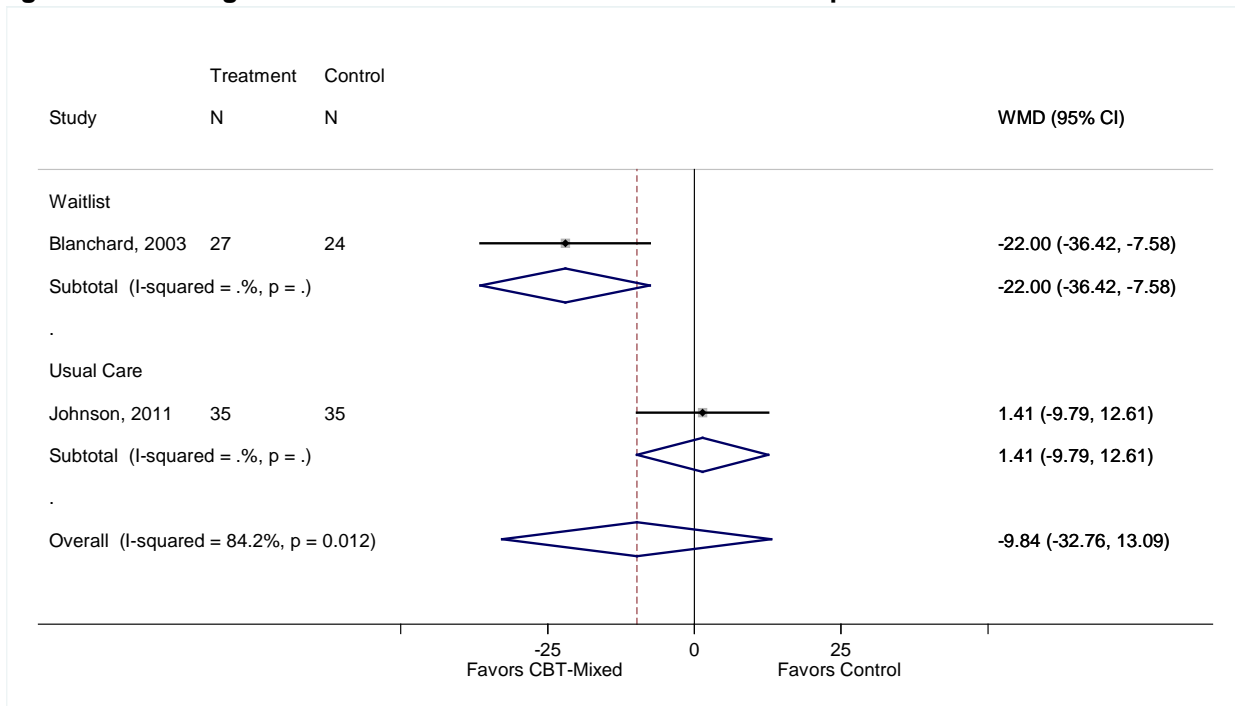
**Figure F-44. Change in CAPS for CBT-mixed compared with control, by comparator: Sensitivity analysis including studies with high risk of bias**



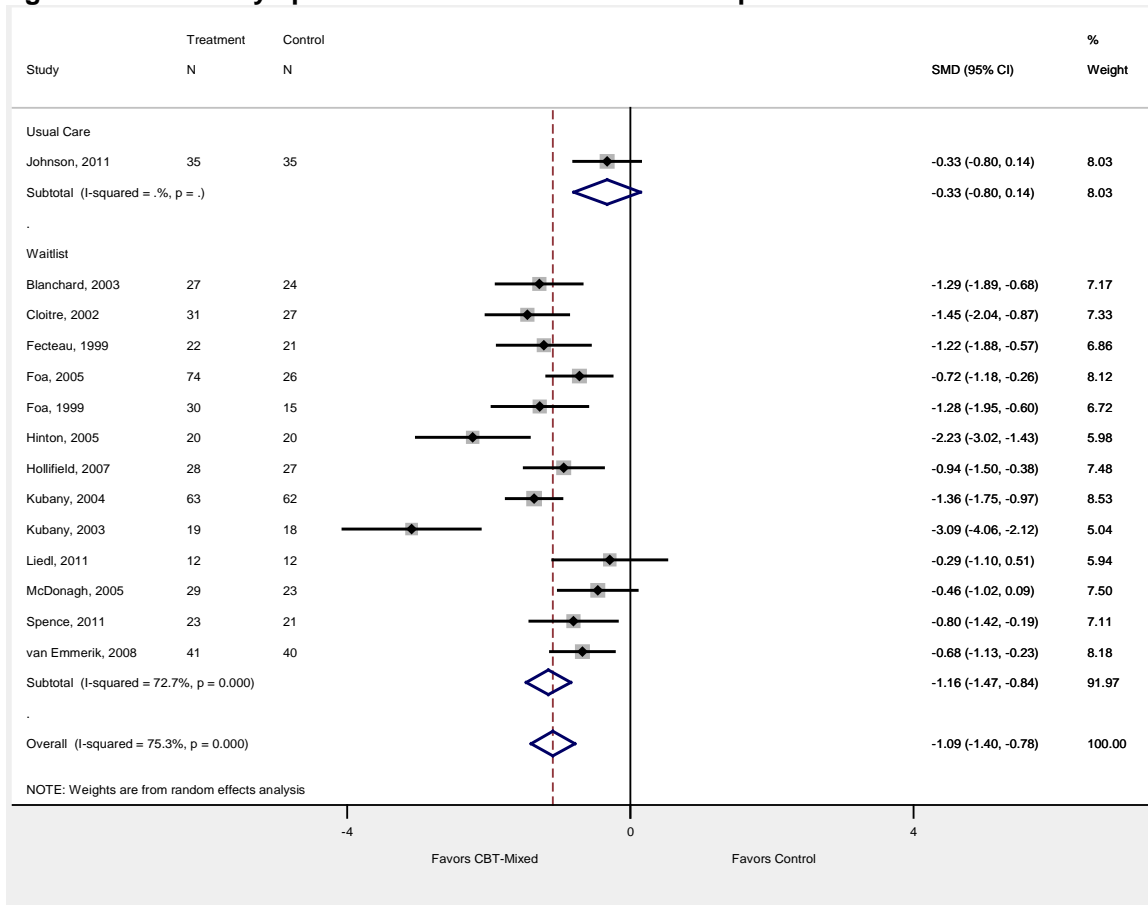
Note: Difede et al., 2007, and Beck et al, 2009 were rated as having a high risk of bias.

Timing of outcome assessment: 12 weeks (Difede, 2007), 7 weeks (Johnson, 2011), 14 weeks (Beck, 2009), 8 to 12 weeks (Blanchard, 2003), 12 weeks (Cloitre, 2002), 4 weeks (Fecteau, 1999), 12 weeks (Hinton, 2005), 4 to 5.5 weeks (Kubany, 2004), 4.5 months (Kubany, 2003), 14 weeks (McDonagh, 2005).

**Figure F-45. Change in CAPS at 3 to 6 months for CBT-mixed compared with control**

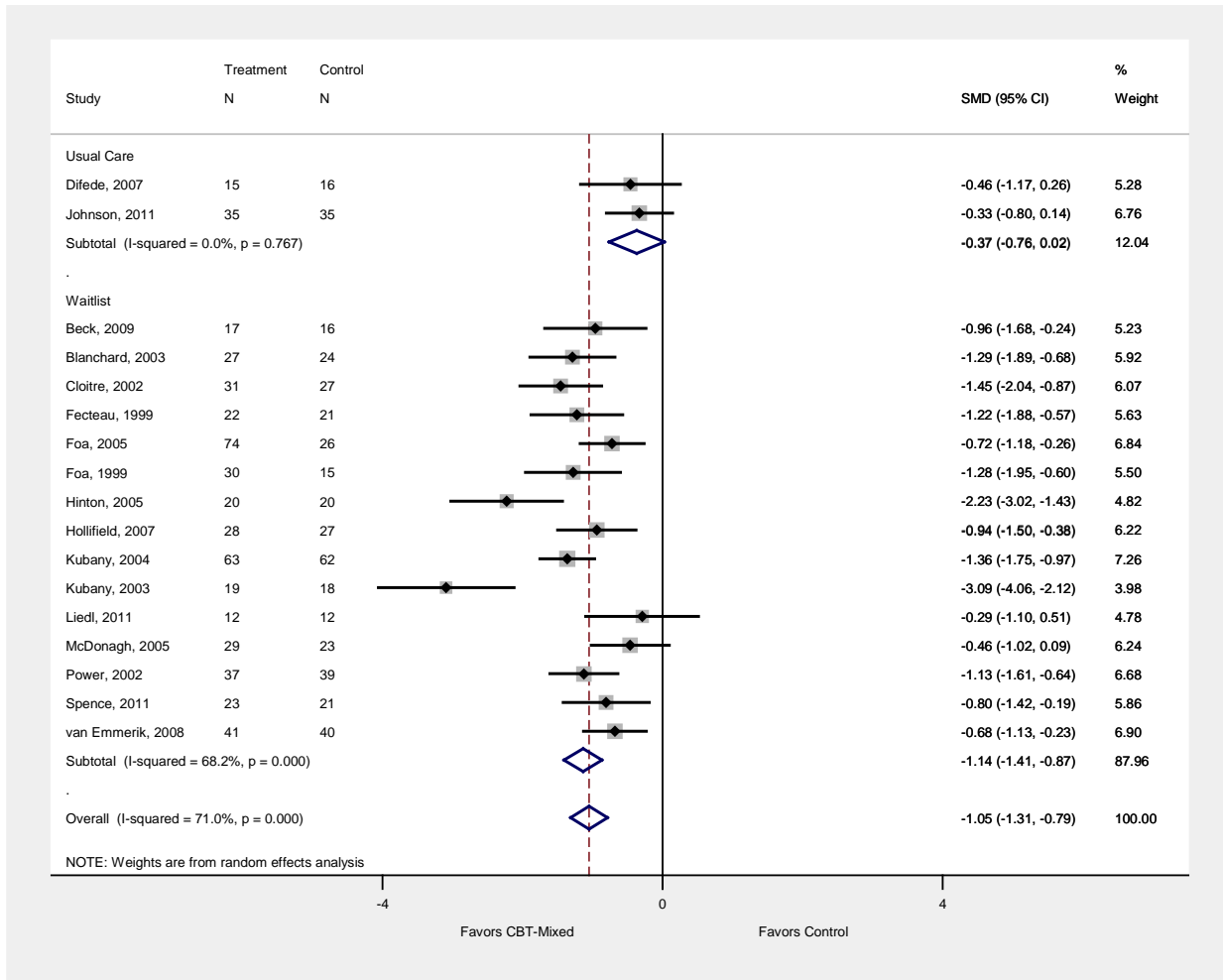


**Figure F-46. PTSD symptom reduction for CBT-mixed compared with control**



Timing of outcome assessment: 7 weeks (Johnson, 2011), 8 to 12 weeks (Blanchard, 2003), 12 weeks (Cloitre, 2002), 4 weeks (Fecteau, 1999), 12 weeks (Foa, 2005), 9 weeks (Foa, 1999), 12 weeks (Hinton, 2005), 12 weeks (Hollifield, 2007) 4 to 5.5 weeks (Kubany, 2004), 4.5 months (Kubany, 2003), 4.8 months (Liedl, 2011), 14 weeks (McDonagh, 2005), 8 weeks (Spence, 2011), 5 sessions (van Emmerik, 2008).

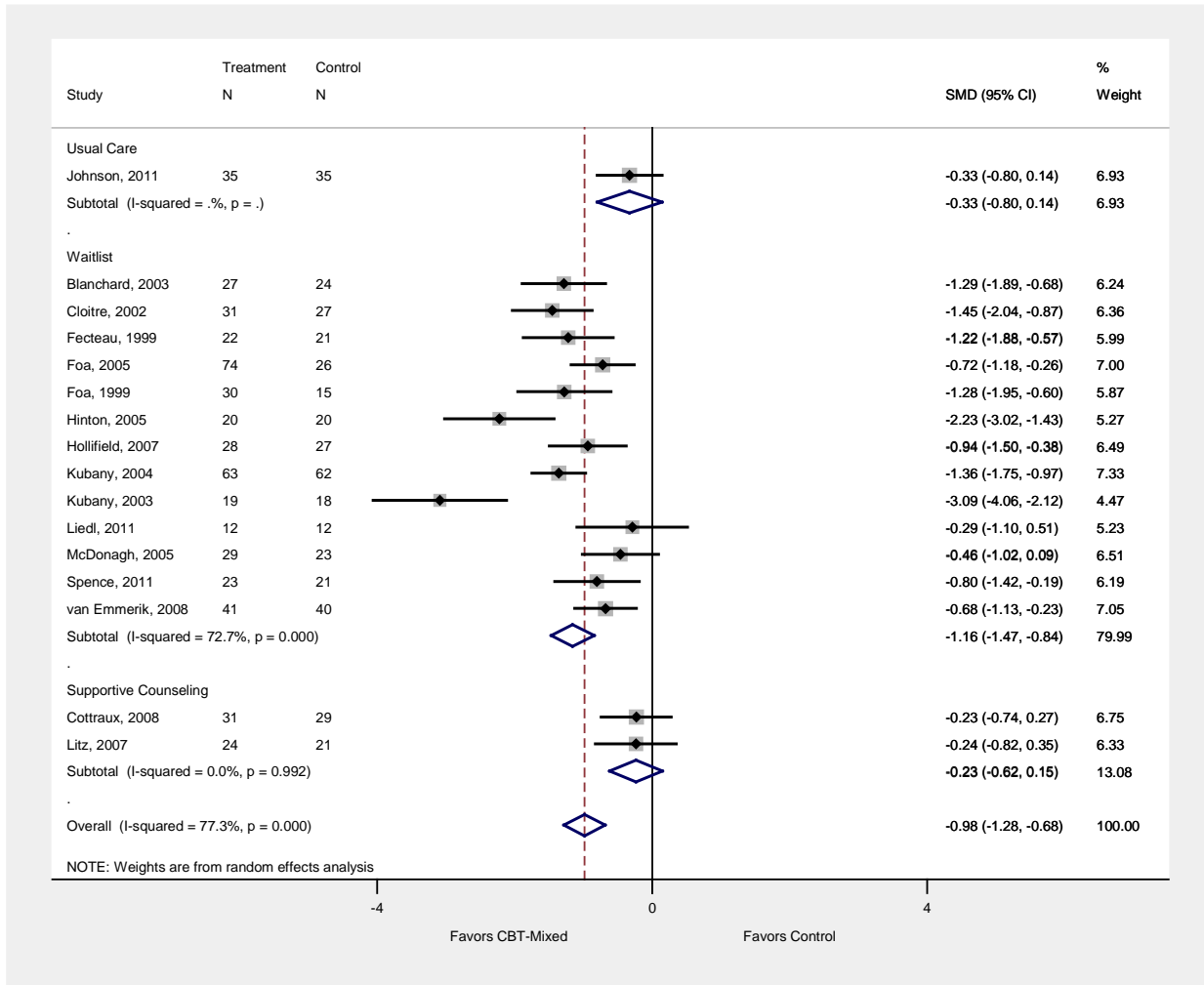
**Figure F-47. PTSD symptom reduction for CBT-mixed compared with control: Sensitivity analysis including studies with high risk of bias**



Note: Difede et al., 2007, Power et al., 2002, and Beck et al, 2009 were rated as having a high risk of bias.

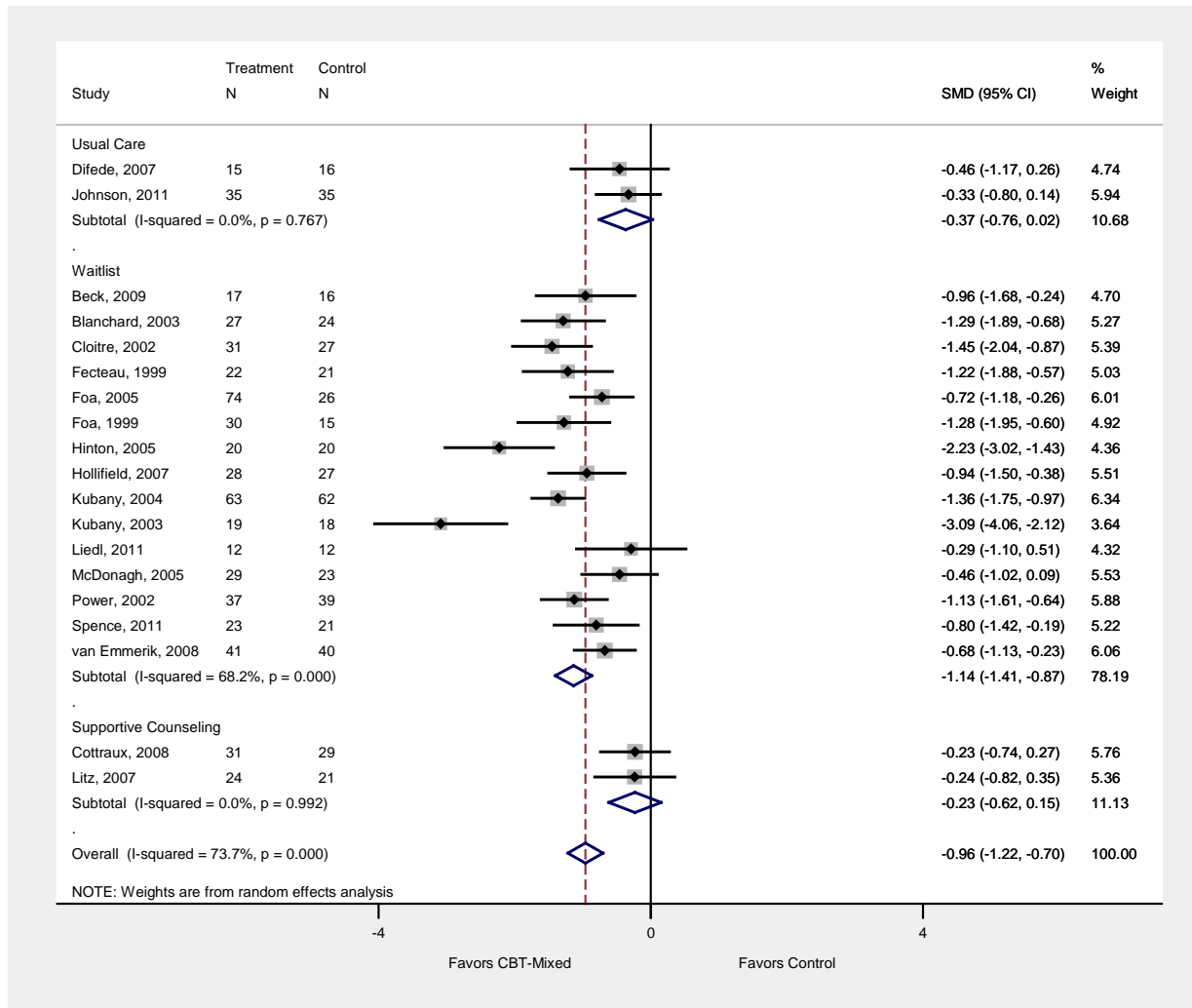
Timing of outcome assessment: 12 weeks (Difede, 2007), 7 weeks (Johnson, 2011), 14 weeks (Beck, 2009), 8 to 12 weeks (Blanchard, 2003), 12 weeks (Cloitre, 2002), 4 weeks (Fecteau, 1999), 12 weeks (Foa, 2005), 9 weeks (Foa, 1999), 12 weeks (Hinton, 2005), 12 weeks (Hollifield, 2007), 4 to 5.5 weeks (Kubany, 2004), 4.5 months (Kubany, 2003), 4.8 months (Liedl, 2011), 14 weeks (McDonagh, 2005), 10 weeks (Power, 2002), 8 weeks (Spence, 2011), 5 sessions (van Emmerik, 2008)

**Figure F-48. PTSD symptom reduction for CBT-mixed compared with control: Sensitivity analysis including other comparators**



Timing of outcome assessment: 7 weeks (Johnson, 2011), 8 to 12 weeks (Blanchard, 2003), 12 weeks (Cloitre, 2002), 4 weeks (Fecteau, 1999), 12 weeks (Foa, 2005), 9 weeks (Foa, 1999), 12 weeks (Hinton, 2005), 12 weeks (Hollifield, 2007), 4 to 5.5 weeks (Kubany, 2004), 4.5 months (Kubany, 2003), 4.8 months (Liedl, 2011), 14 weeks (McDonagh, 2005), 8 weeks (Spence, 2011), 5 sessions (van Emmerik, 2008), 16 weeks (Cottraux, 2008), 8 weeks (Litz, 2007).

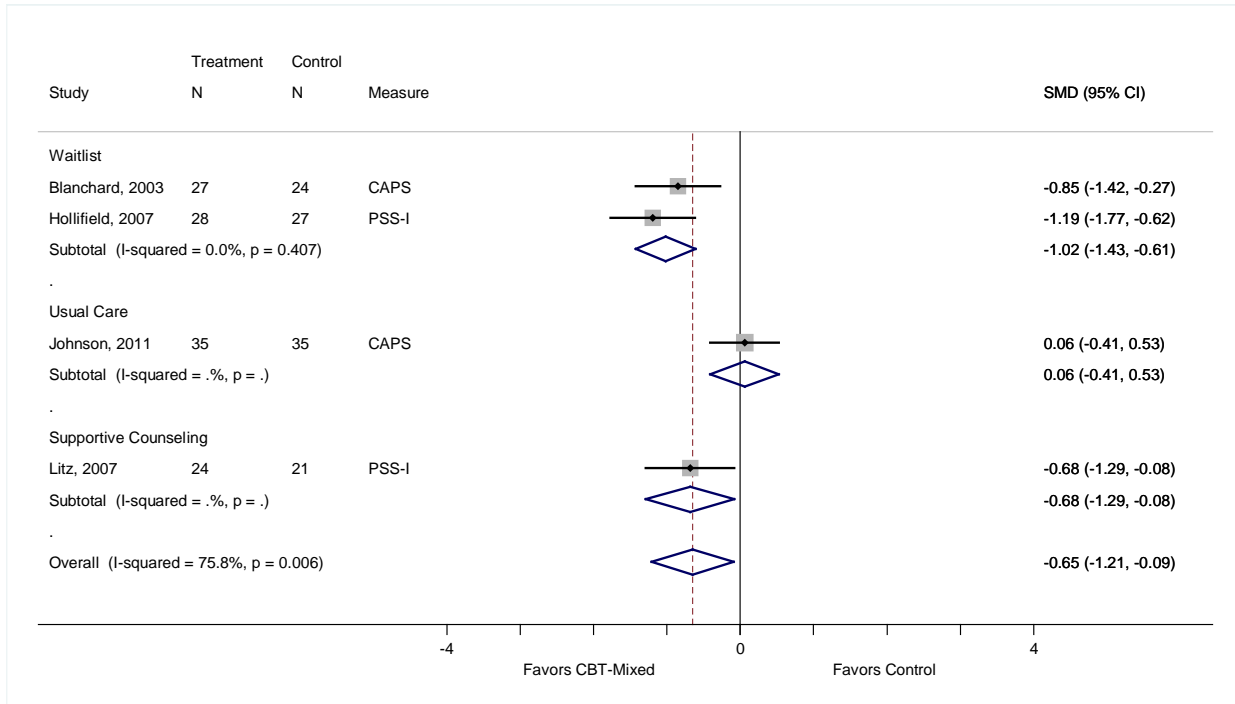
**Figure F-49. PTSD symptom reduction for CBT-mixed compared with control: Sensitivity analysis including other comparators and studies with high risk of bias**



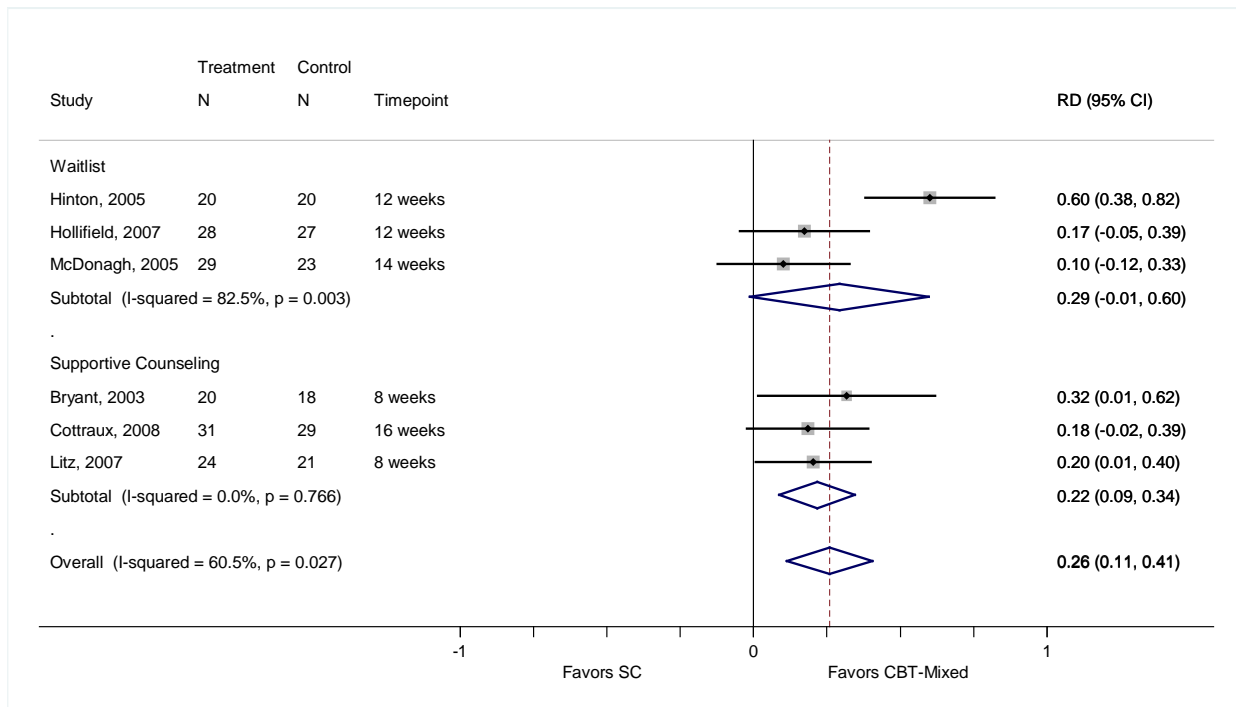
Note: Difede et al., 2007, Power et al., 2002, and Beck et al., 2009 were rated as having a high risk of bias.

Timing of outcome assessment: 12 weeks (Difede, 2007), 7 weeks (Johnson, 2011), 14 weeks (Beck, 2009), 8 to 12 weeks (Blanchard, 2003), 12 weeks (Cloitre, 2002), 4 weeks (Fecteau, 1999), 12 weeks (Foa, 2005), 9 weeks (Foa, 1999), 12 weeks (Hinton, 2005), 12 weeks (Hollifield, 2007), 4 to 5.5 weeks (Kubany, 2004), 4.5 months (Kubany, 2003), 4.8 months (Liedl, 2011), 14 weeks (McDonagh, 2005), 10 weeks (Power, 2002), 8 weeks (Spence, 2011), 5 sessions (van Emmerik, 2008), 16 weeks (Cottraux, 2008), 8 weeks (Litz, 2007).

**Figure F-50. PTSD symptom reduction at 3 to 6 months for CBT-mixed compared with control, by type of comparator**



**Figure F-51. Loss of PTSD diagnosis for CBT-mixed compared with control, by type of comparator**



**Table F-23. Loss of PTSD diagnosis for CBT-mixed compared with control, by type of comparator: Statistics with one study removed**

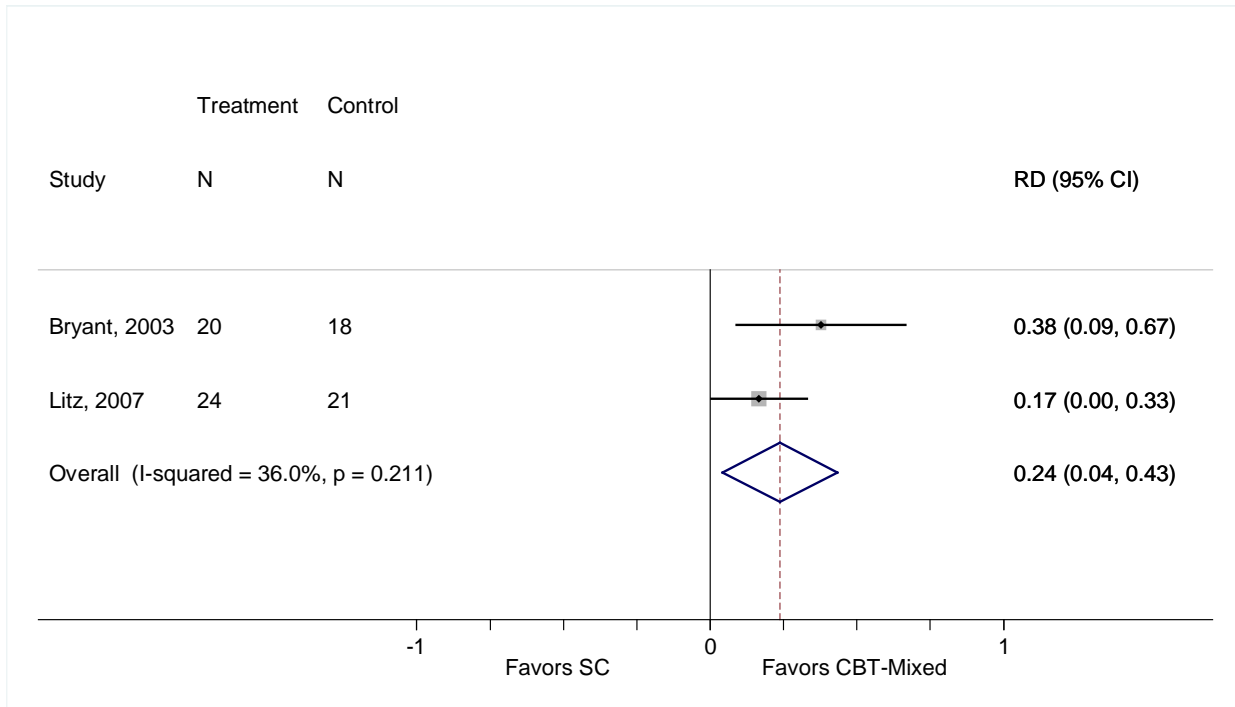
| Study Omitted    | Overall Estimate | 95% Confidence Interval |
|------------------|------------------|-------------------------|
| <b>Waitlist</b>  |                  |                         |
| Hinton, 2005     | 0.18             | (0.09 to 0.28)          |
| Hollifield, 2007 | 0.28             | (0.10 to 0.45)          |
| McDonagh, 2005   | 0.29             | (0.13 to 0.45)          |
| Bryant, 2003     | 0.25             | (0.08 to 0.42)          |
| Cottraux, 2008   | 0.28             | (0.10 to 0.45)          |
| Litz, 2007       | 0.27             | (0.09 to 0.45)          |
| Combined         | -1.23            | (-1.60 to -0.87)        |

**Table F-24. Loss of PTSD diagnosis for CBT-mixed compared with control, by type of comparator: Statistics with one study removed, by type of comparator**

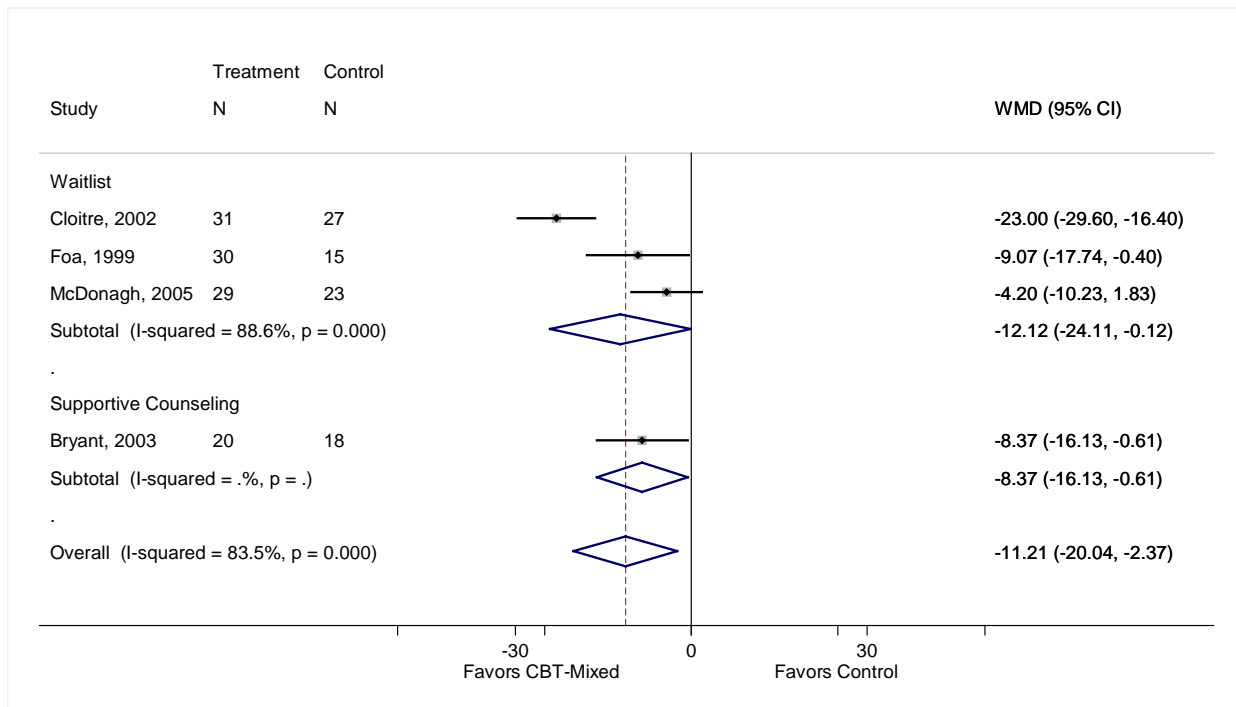
| Study Omitted                | Overall Estimate | 95% Confidence Interval |
|------------------------------|------------------|-------------------------|
| <b>Waitlist</b>              |                  |                         |
| Hinton, 2005                 | 0.14             | (-0.02 to 0.29)         |
| Hollifield, 2007             | 0.35             | (-0.14 to 0.84)         |
| McDonagh, 2005               | 0.39             | (-0.03 to 0.80)         |
| Combined                     | 0.29             | (-0.01 to 0.60)         |
| <b>Supportive Counseling</b> |                  |                         |
| Bryant, 2003                 | 0.19             | (0.05 to 0.34)          |
| Cottraux, 2008               | 0.24             | (0.07 to 0.40)          |
| Litz, 2007                   | 0.23             | (0.06 to 0.40)          |
| Combined                     | 0.22             | (0.09 to 0.34)          |



**Figure F-52. Loss of PTSD diagnosis at 3 to 6 months for CBT-mixed compared with supportive counseling**



**Figure F-53. Change in STAI for CBT-mixed compared with control, by type of comparator**



Timing of outcome assessment: 12 weeks (Cloitre, 2002), 9 weeks (Foa, 1999), 14 weeks (McDonagh, 2005), 8 weeks (Bryant, 2003).

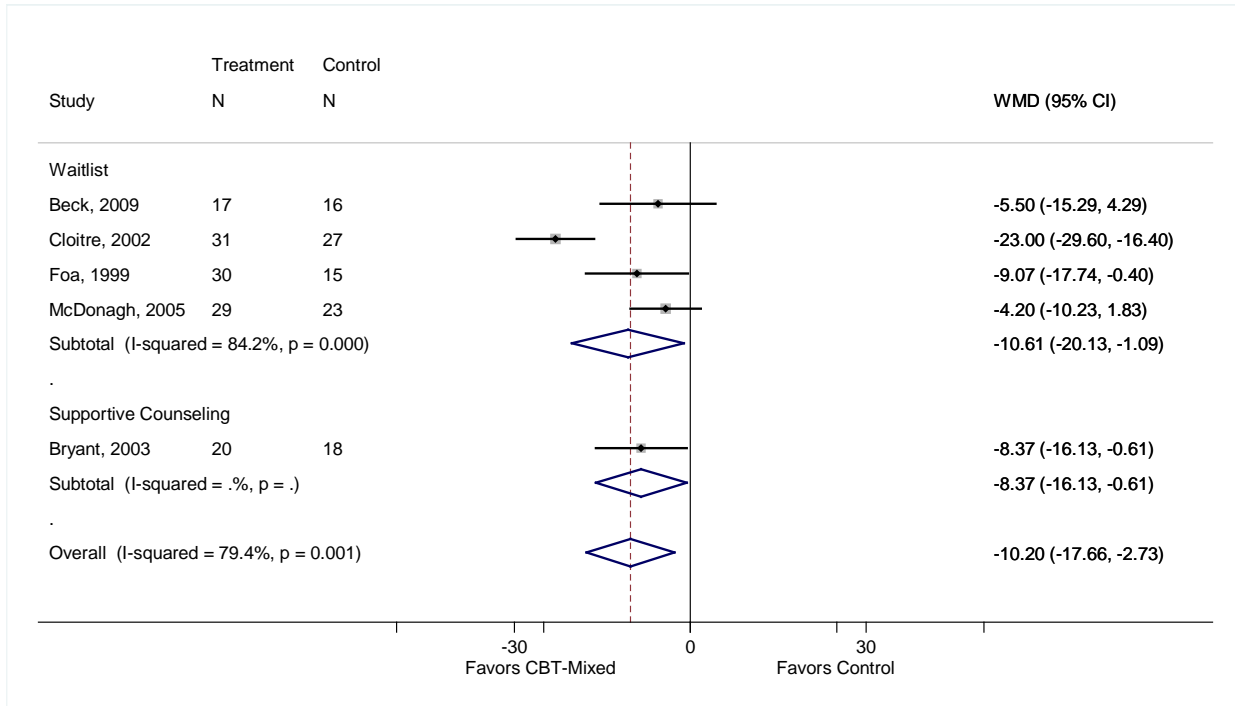
**Table F-25. Change in STAI for CBT-mixed compared with control, by type of comparator: Statistics with one study removed**

| Study Omitted  | Overall Estimate | 95% Confidence Interval |
|----------------|------------------|-------------------------|
| Cloitre, 2002  | -6.53            | (-10.71 to -2.36)       |
| Foa, 1999      | -11.86           | (-23.54 to -0.17)       |
| McDonagh, 2005 | -13.74           | (-23.72 to -3.74)       |
| Bryant, 2003   | -12.11           | (-24.11 to -0.12)       |
| Combined       | -11.20           | (-20.04 to -2.37)       |

**Table F-26. Change in STAI for CBT-mixed compared with control, by type of comparator: Statistics with one study removed, by type of comparator**

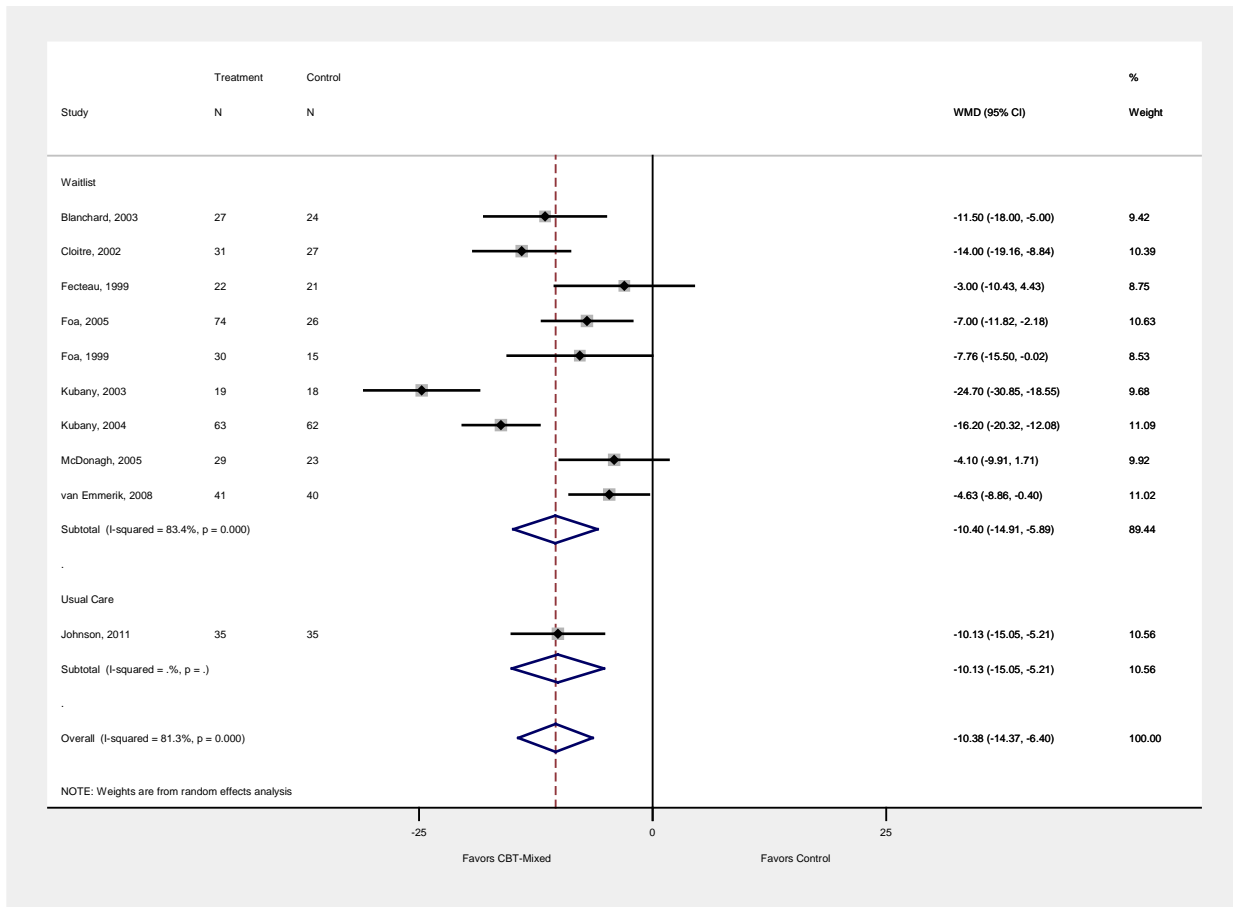
| Study Omitted                | Overall Estimate | 95% Confidence Interval |
|------------------------------|------------------|-------------------------|
| <b>Waitlist</b>              |                  |                         |
| Cloitre, 2002                | -5.79            | (-10.73 to -0.84)       |
| Foa, 1999                    | -13.55           | (-31.97 to 4.87)        |
| McDonagh, 2005               | -16.33           | (-29.97 to -2.69)       |
| Combined                     | -12.11           | (-24.11 to -0.12)       |
| <b>Supportive Counseling</b> |                  |                         |
| NA                           | NA               | NA                      |

**Figure F-54. Change in STAI for CBT-mixed compared with control, by type of comparator: Sensitivity analysis including studies with high risk of bias**



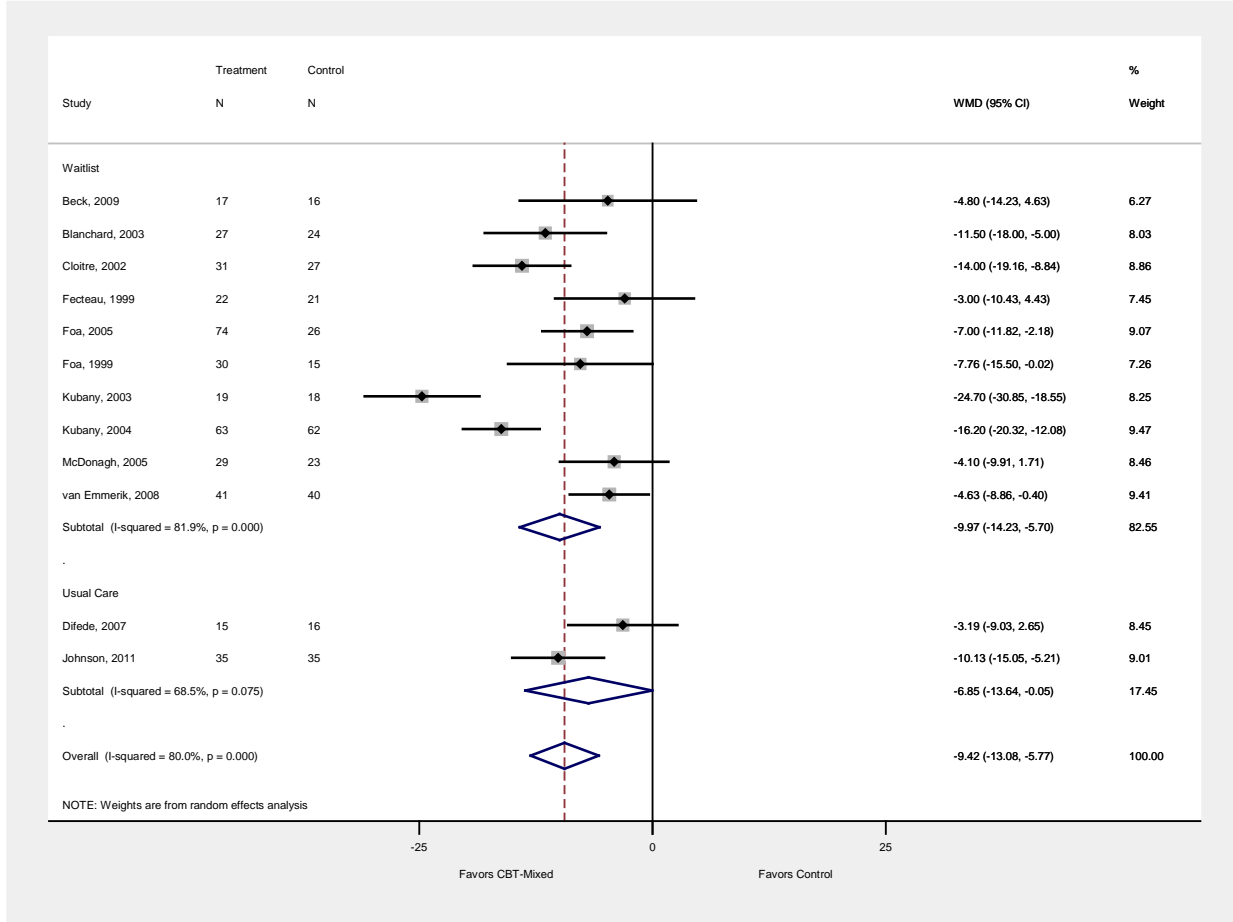
Timing of outcome assessment: 14 weeks (Beck, 2009), 12 weeks (Cloitre, 2002), 9 weeks (Foa, 1999), 14 weeks (McDonagh, 2005), 8 weeks (Bryant, 2003).

**Figure F-55. Change in BDI for CBT-mixed compared with control, by type of comparator**



Timing of outcome assessment: 8 to 12 weeks (Blanchard, 2003), 12 weeks (Cloitre, 2002), 4 weeks (Fecteau, 1999), 12 weeks (Foa, 2005), 9 weeks (Foa, 1999), 4.5 months (Kubany, 2003), 14 weeks (McDonagh, 2005), 5 sessions (van Emmerik, 2008), 4 to 5.5 weeks (Kubany, 2004), 7 weeks (Johnson, 2011).

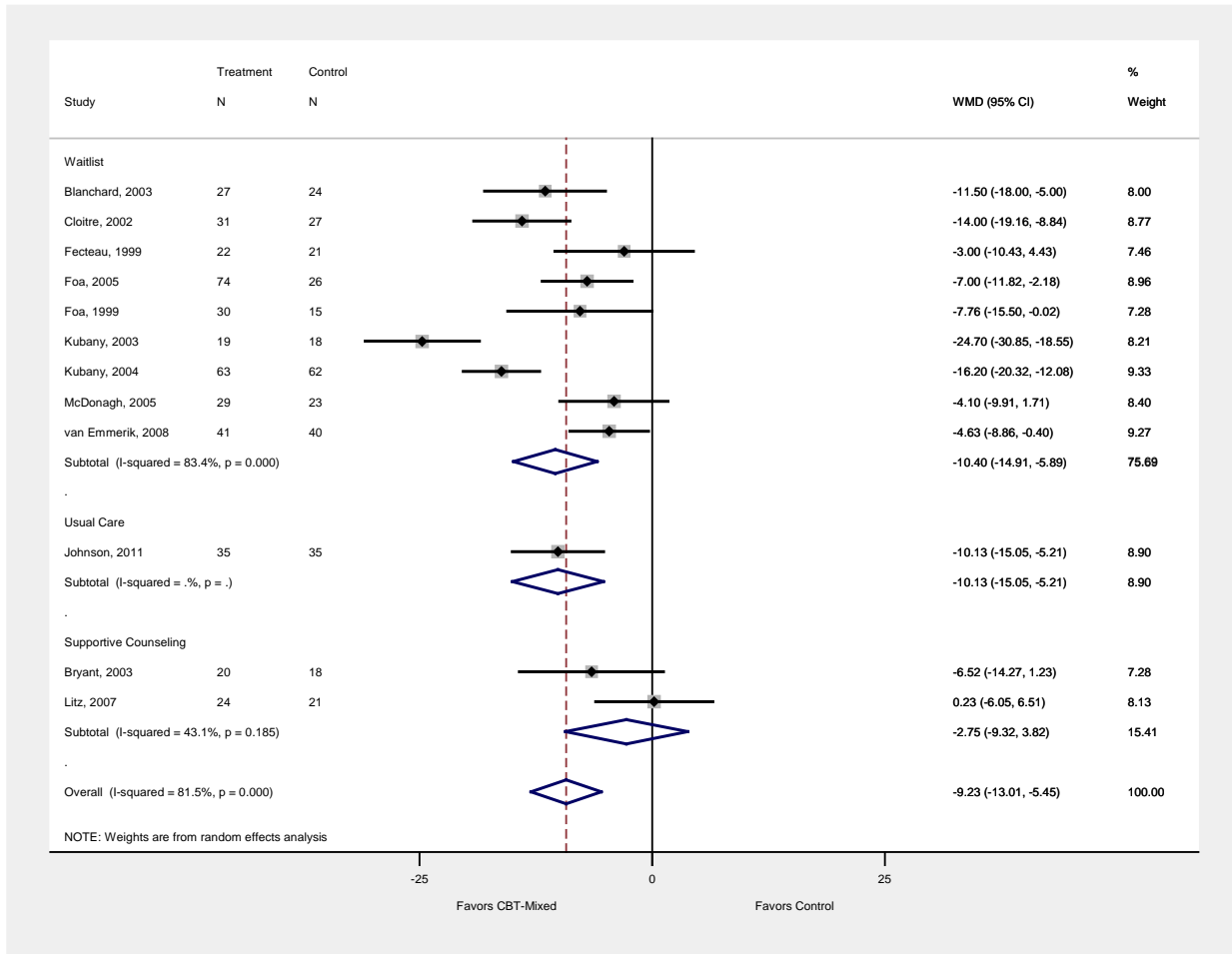
**Figure F-56. Change in BDI for CBT-mixed compared with control, by type of comparator: Sensitivity analysis including studies with high risk of bias**



Note: Difede et al., 2007, and Beck et al., 2009 were rated as having high risk of bias.

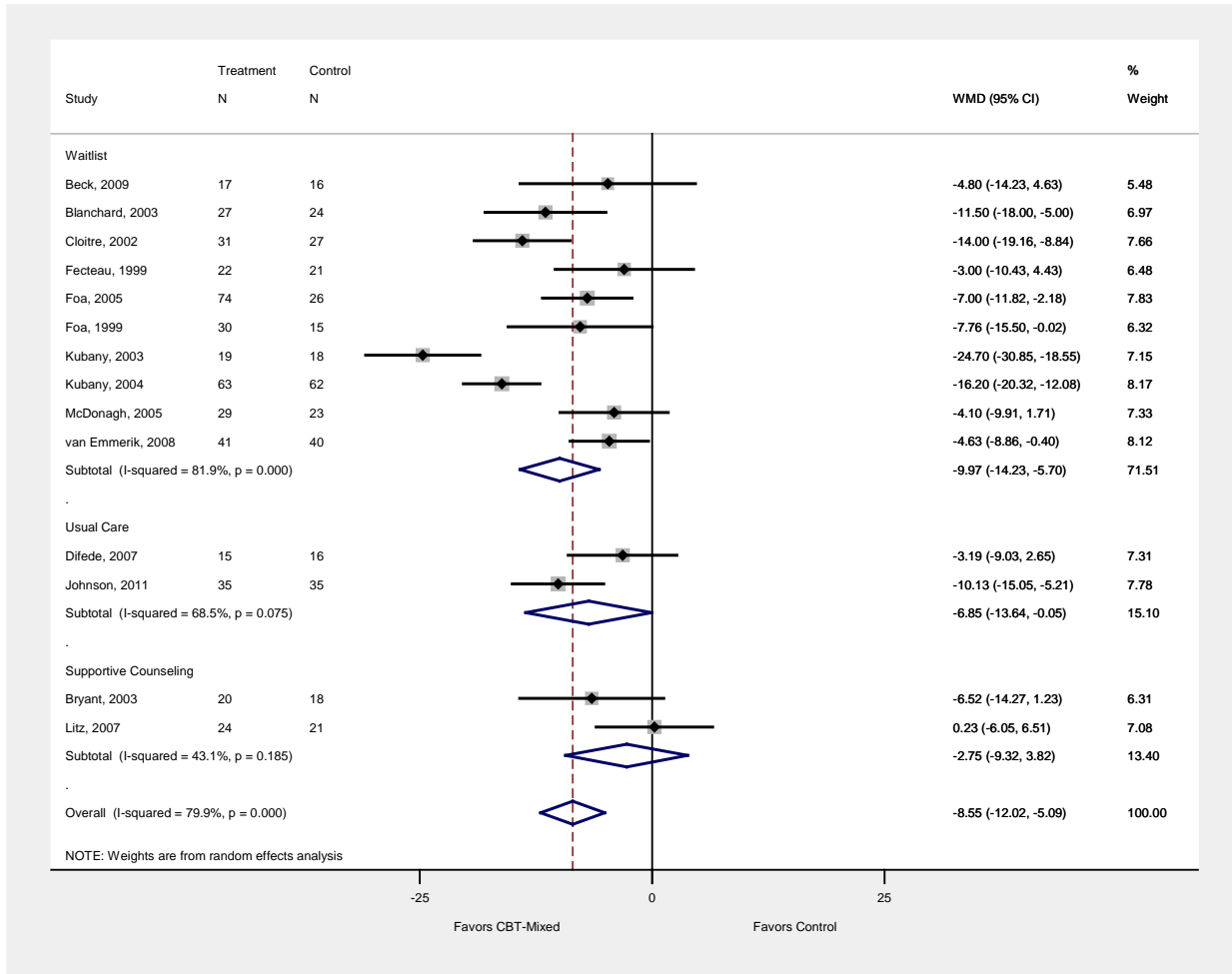
Timing of outcome assessment: 14 weeks (Beck, 2009), 8 to 12 weeks (Blanchard, 2003), 12 weeks (Cloitre, 2002), 4 weeks (Fecteau, 1999), 12 weeks (Foa, 2005), 9 weeks (Foa, 1999), 4.5 months (Kubany, 2003), 14 weeks (McDonagh, 2005), 5 sessions (van Emmerik, 2008), 4 to 5.5 weeks (Kubany, 2004), 12 weeks (Difede, 2007), 7 weeks (Johnson, 2011).

**Figure F-57. Change in BDI for CBT-mixed compared with control, by type of comparator: Sensitivity analysis including other comparators**



Timing of outcome assessment: 8 to 12 weeks (Blanchard, 2003), 12 weeks (Cloitre, 2002), 4 weeks (Fecteau, 1999), 12 weeks (Foa, 2005), 9 weeks (Foa, 1999), 4.5 months (Kubany, 2003), 14 weeks (McDonagh, 2005), 5 sessions (van Emmerik, 2008), 4 to 5.5 weeks (Kubany, 2004), 7 weeks (Johnson, 2011), 8 weeks (Bryant, 2003), 8 weeks (Litz).

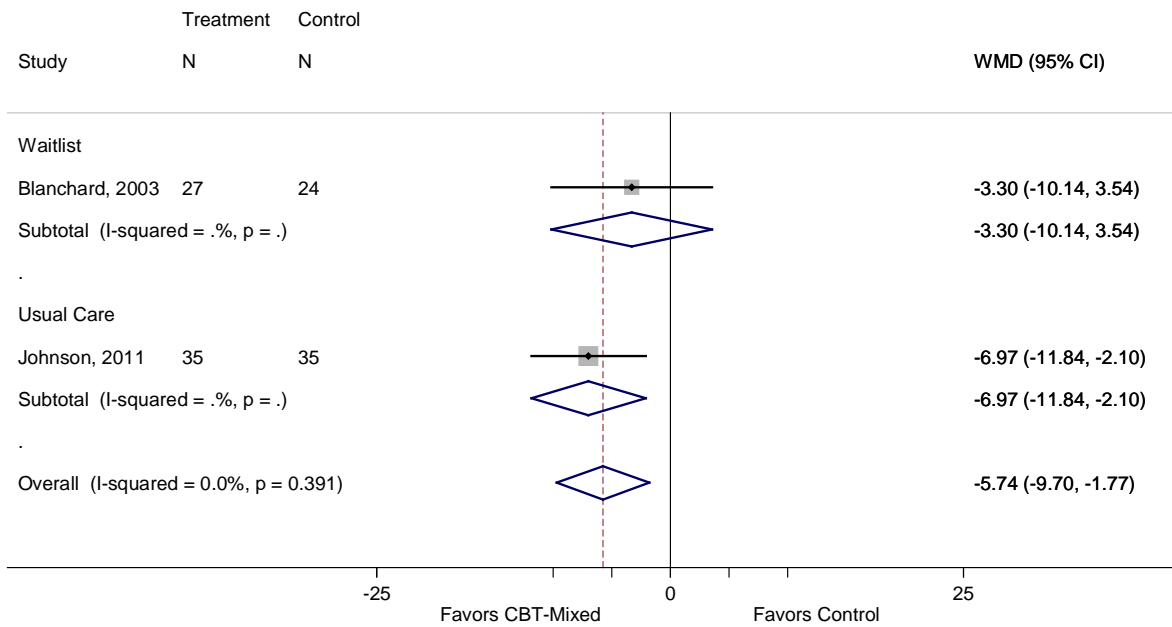
**Figure F-58. Change in BDI for CBT-mixed compared with control, by type of comparator: Sensitivity analysis including other comparators and studies with high risk of bias**



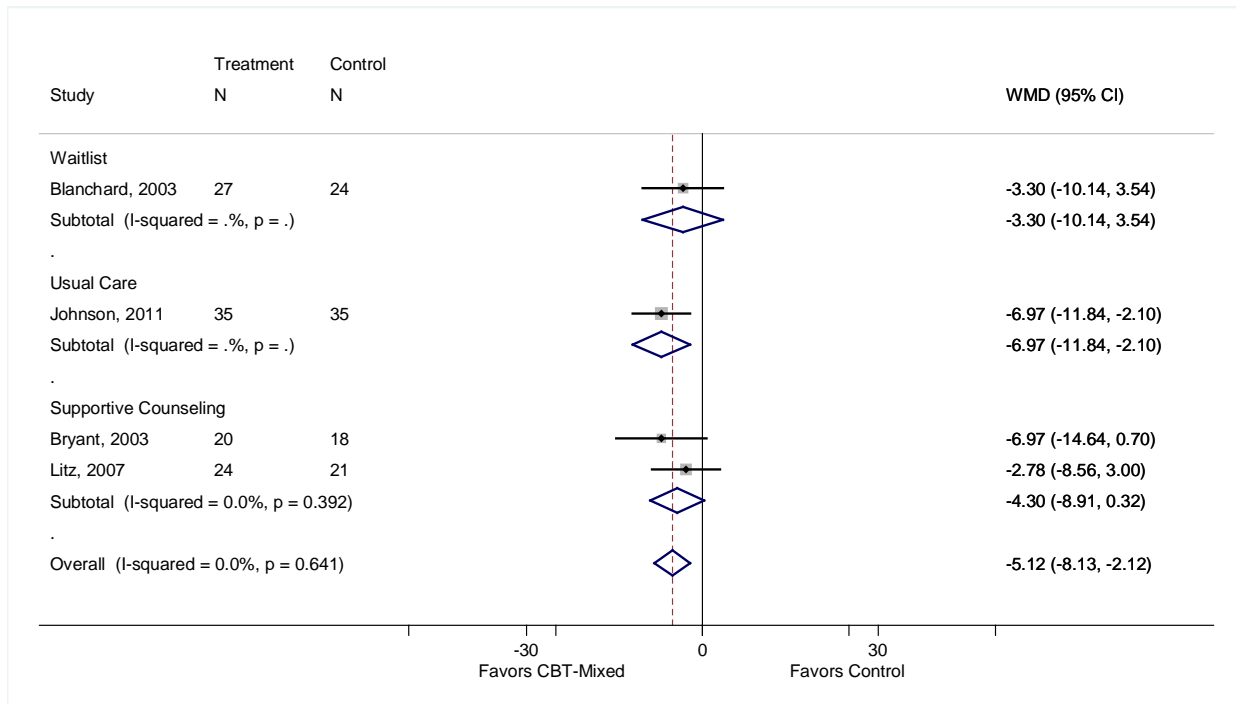
Note: Difede et al., 2007, and Beck et al., 2009 were rated as having high risk of bias.

Timing of outcome assessment: 14 weeks (Beck, 2009), 8 to 12 weeks (Blanchard, 2003), 12 weeks (Cloitre, 2002), 4 weeks (Fecteau, 1999), 12 weeks (Foa, 2005), 9 weeks (Foa, 1999), 4.5 months (Kubany, 2003), 14 weeks (McDonagh, 2005), 5 sessions (van Emmerik, 2008), 4 to 5.5 weeks (Kubany, 2004), 12 weeks (Difede, 2007), 7 weeks (Johnson, 2011), 8 weeks (Bryant, 2003), 8 weeks (Litz).

**Figure F-59. Change in BDI at 3 to 6 months for CBT-mixed compared with control, by type of comparator**

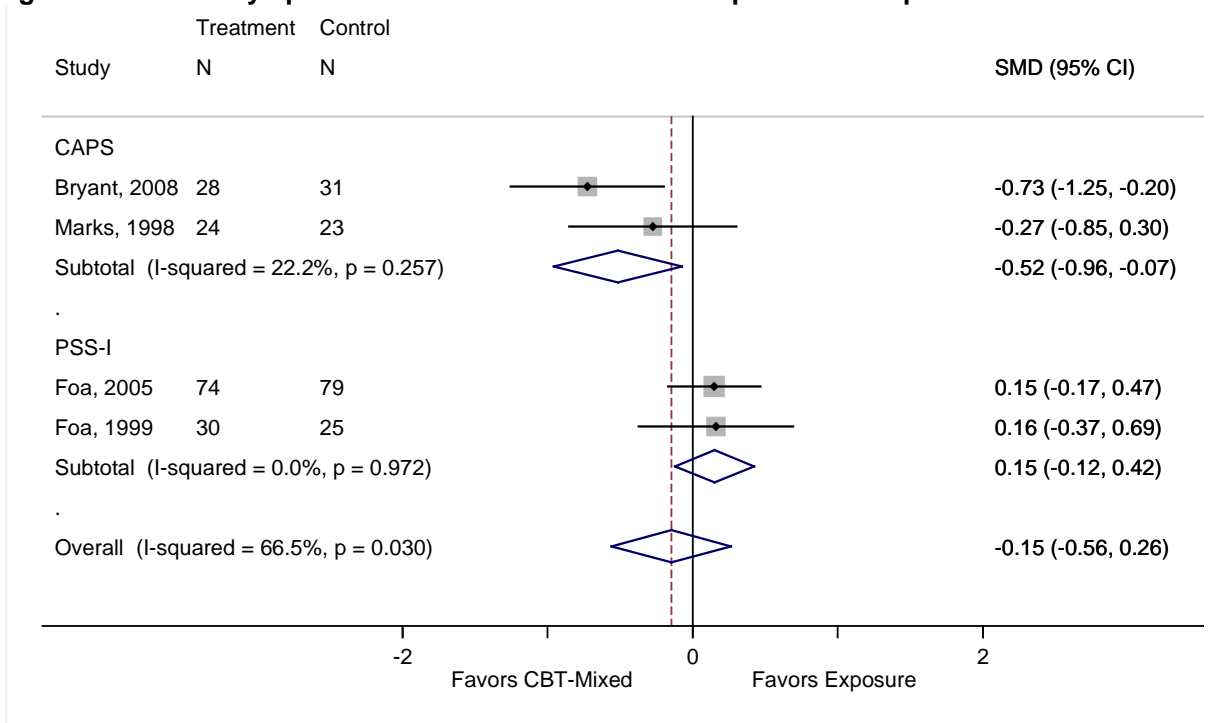


**Figure F-60. Change in BDI at 3 to 6 months for CBT-mixed compared with control, by type of comparator: Sensitivity analysis including other comparators**



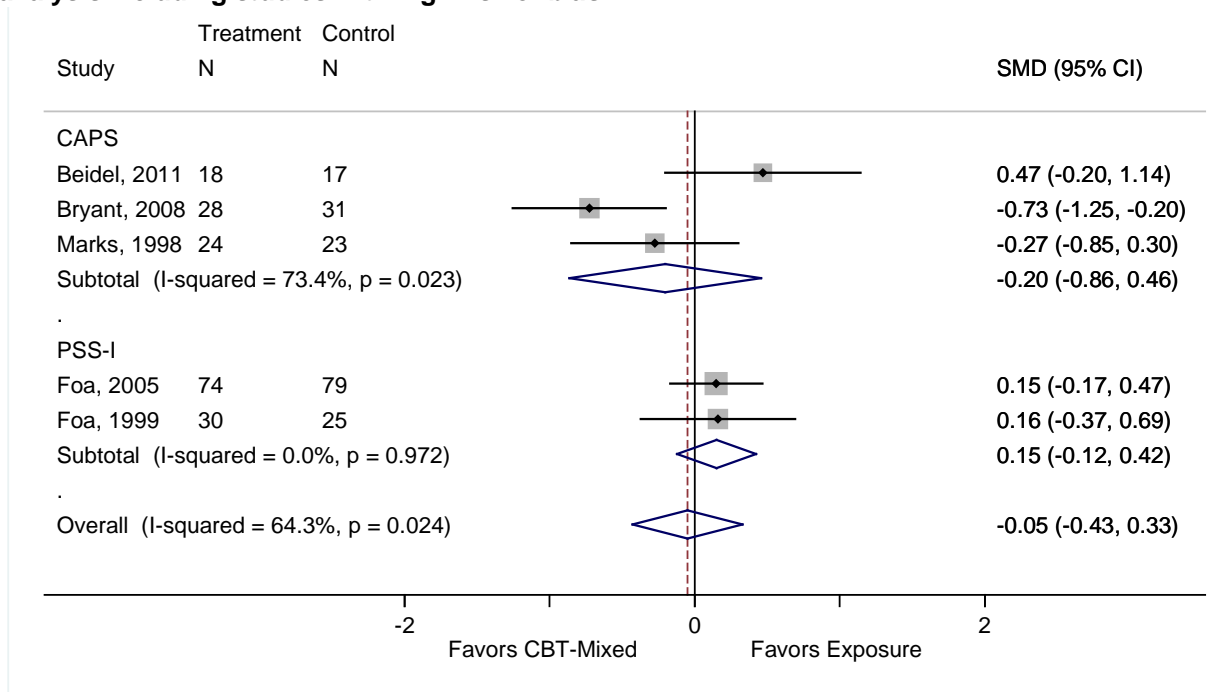


**Figure F-61. PTSD symptom reduction for CBT-mixed compared with exposure**



Timing of outcome assessment: 8 weeks (Bryant, 2008), mean 16 weeks (Marks, 1998), 12 weeks (9 to 12 weekly sessions; Foa, 2005), 9 weeks (Foa, 1999).

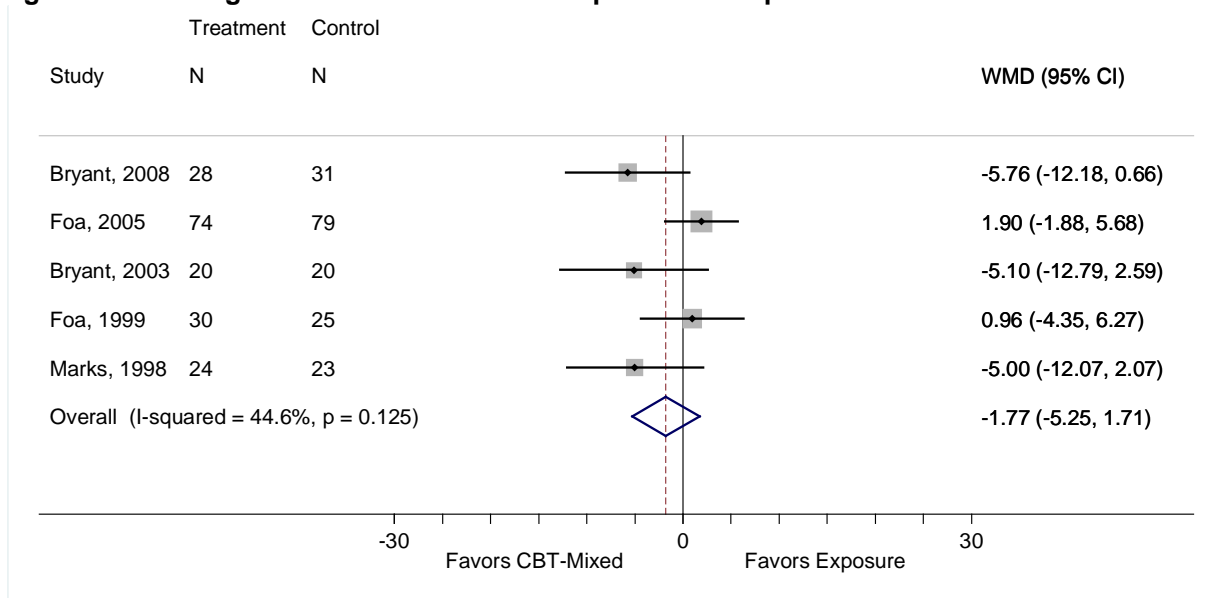
**Figure F-62. PTSD symptom reduction for CBT-mixed compared with exposure: Sensitivity analysis including studies with high risk of bias**



Note: Beidel et al., 2011 was rated as having high risk of bias.

Timing of outcome assessment: 17 weeks (Beidel, 2011), 8 weeks (Bryant, 2008), mean 16 weeks (Marks, 1998), 12 weeks (9 to 12 weekly sessions; Foa, 2005), 9 weeks (Foa, 1999).

**Figure F-63. Change in BDI for CBT-mixed compared with exposure**

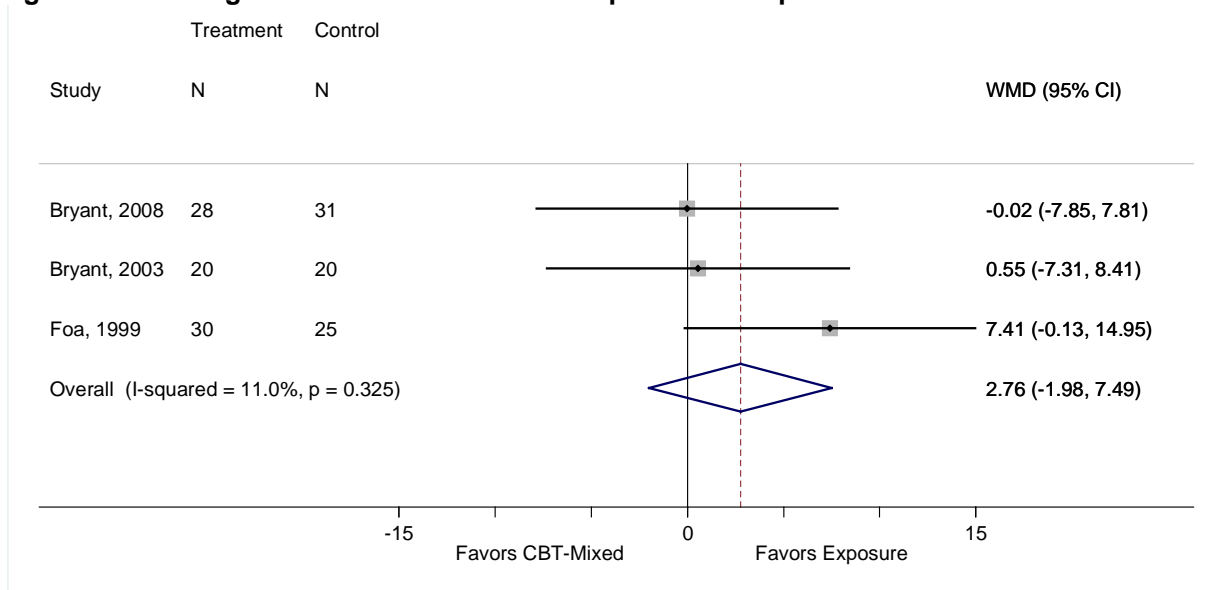


Timing of outcome assessment: 8 weeks (Bryant, 2008), 12 weeks (9 to 12 weekly sessions; Foa, 2005), 8 weeks (Bryant, 2003) 9 weeks (Foa, 1999), mean 16 weeks (Marks, 1998).

**Table F-27. Change in BDI for CBT-mixed compared with exposure: Statistics with one study removed**

| Study Omitted | Overall Estimate | 95% Confidence Interval |
|---------------|------------------|-------------------------|
| Bryant, 2008  | -0.75            | (-4.28 to 2.78)         |
| Foa, 2005     | -3.13            | (-6.60 to 0.34)         |
| Bryant, 2003  | -1.26            | (-5.11 to 2.60)         |
| Foa, 1999     | -2.78            | (-7.25 to 1.68)         |
| Marks, 1998   | -1.19            | (-5.05 to 2.67)         |
| Combined      | -1.77            | (-5.25 to 1.71)         |

**Figure F-64. Change in STAI for CBT-mixed compared with exposure**

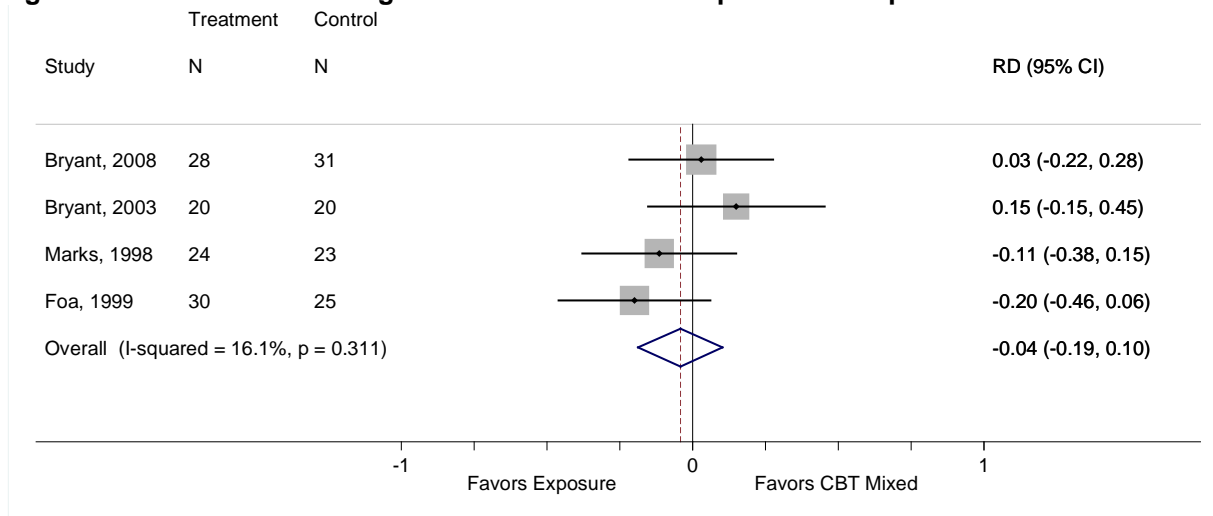


Timing of outcome assessment: 8 weeks (Bryant, 2008 and Bryant 2003), 8 weeks (Bryant, 2003) 9 weeks (Foa, 1999).

**Table F-28. Change in STAI for CBT-mixed compared with exposure: Statistics with one study removed**

| Study Omitted | Overall Estimate | 95% Confidence Interval |
|---------------|------------------|-------------------------|
| Bryant, 2008  | 4.07             | (-2.65 to 10.79)        |
| Bryant, 2003  | 3.77             | (-3.51 to 11.05)        |
| Foa, 1999     | 0.26             | (-5.28 to 5.81)         |
| Combined      | 2.76             | (-1.98 to 7.49)         |

**Figure F-65. Loss of PTSD diagnosis for CBT-mixed compared with exposure**



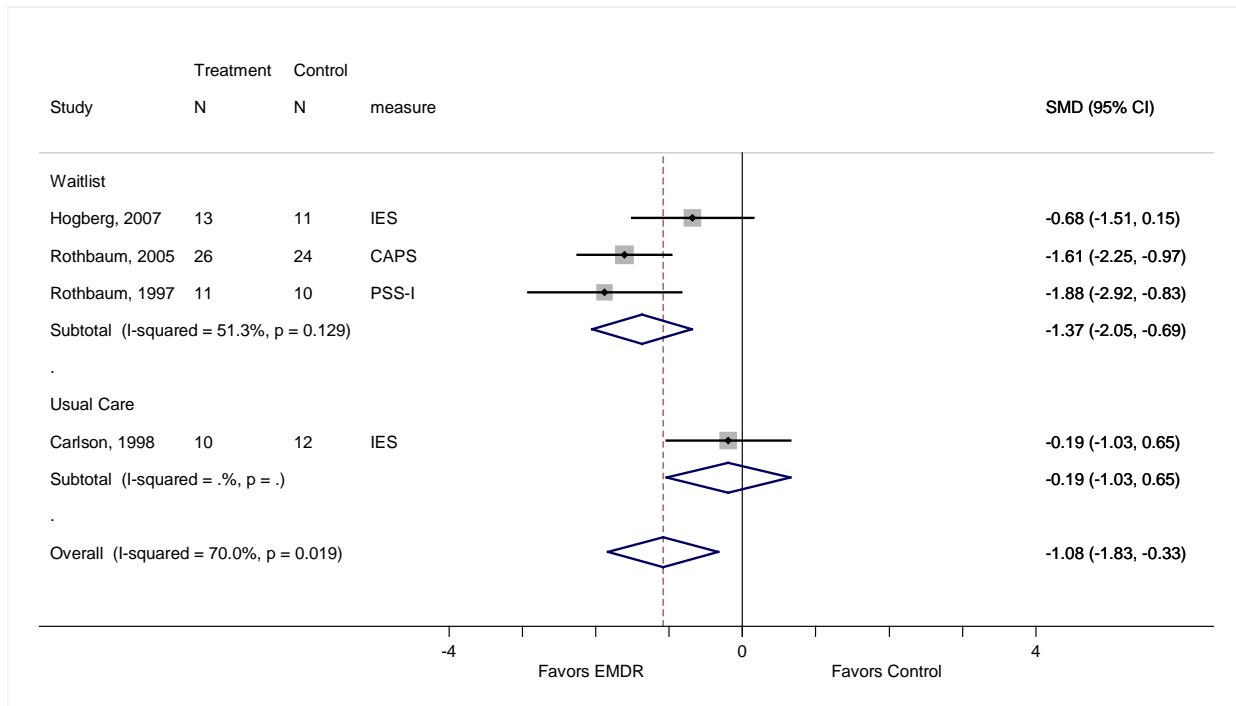
Timing of outcome assessment: 8 weeks (Bryant, 2008), 8 weeks (Bryant, 2003), mean 16 weeks (Marks, 1998), 9 weeks (Foa, 1999).

**Table F-29. Loss of PTSD diagnosis for CBT-mixed compared with exposure: Statistics with one study removed**

| Study Omitted | Overall Estimate | 95% Confidence Interval |
|---------------|------------------|-------------------------|
| Bryant, 2008  | -0.68            | (-0.26 to 0.13)         |
| Bryant, 2003  | -0.09            | (-0.24 to 0.06)         |
| Marks, 1998   | -0.02            | (-0.21 to 0.18)         |
| Foa, 1999     | 0.01             | (-0.14 to 0.17)         |
| Combined      | -0.04            | (-0.19 to 0.10)         |

# EMDR: Meta-Analysis Results

Figure F-66. PTSD symptom reduction for EMDR compared with control, by type of comparator



Timing of outcome assessment: 2 months (Hogberg, 2007), 4.5 weeks (Rothbaum, 2005), 4 weeks (Rothbaum, 1997), 6 weeks (Carlson, 1998).

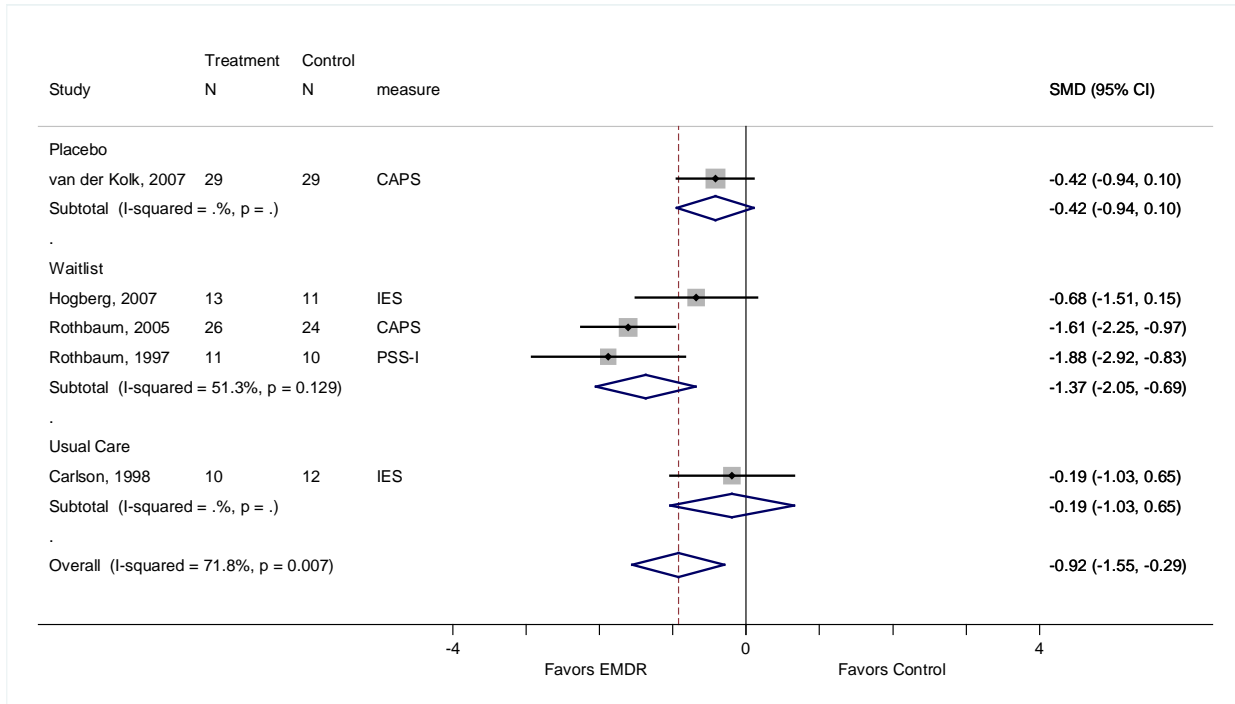
Table F-30. PTSD symptom reduction for EMDR compared with control, by type of comparator: Statistics with one study removed

| Study Omitted  | Overall Estimate | 95% Confidence Interval |
|----------------|------------------|-------------------------|
| Hogberg, 2007  | -1.21            | (-2.21 to -0.22)        |
| Rothbaum, 2005 | -0.87            | (-1.78 to 0.04)         |
| Rothbaum, 1997 | -0.86            | (-1.72 to -0.00)        |
| Carlson, 1998  | -1.37            | (-2.05 to -0.69)        |
| Combined       | -1.08            | (-1.83 to -0.33)        |

Table F-31. PTSD symptom reduction for EMDR compared with control, by type of comparator: Statistics with one study removed, by type of comparator

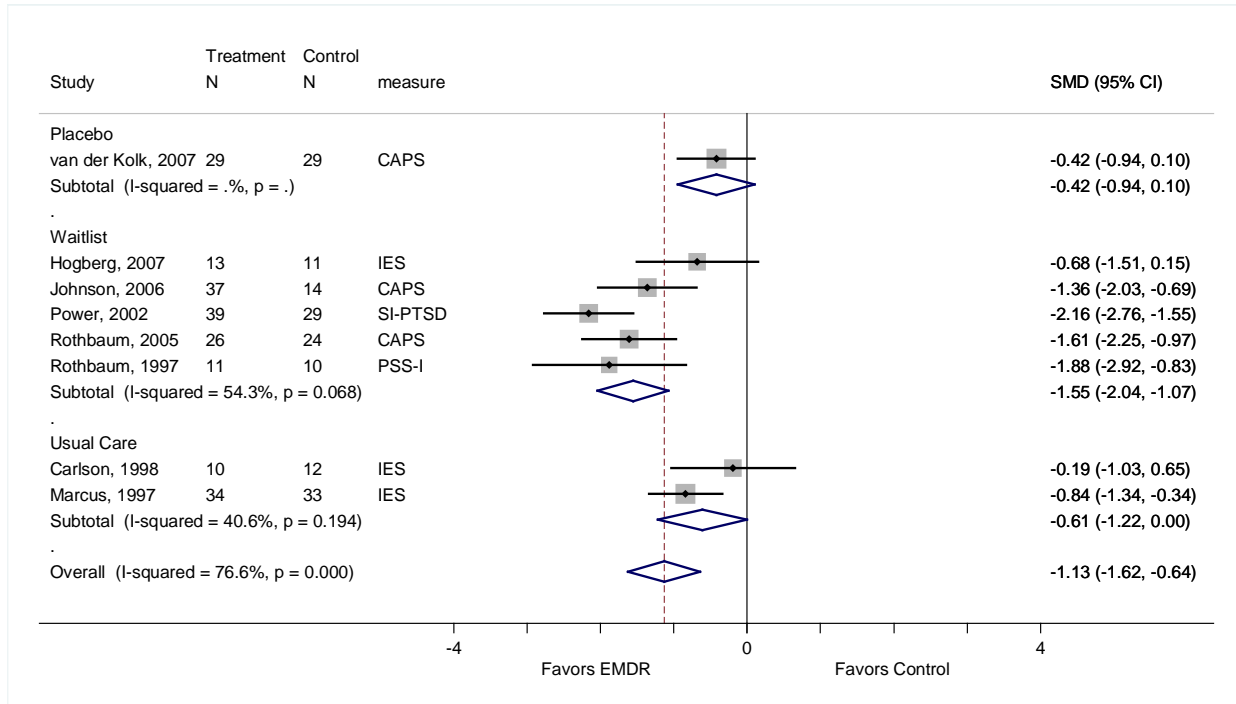
| Study Omitted     | Overall Estimate | 95% Confidence Interval |
|-------------------|------------------|-------------------------|
| <b>Waitlist</b>   |                  |                         |
| Hogberg, 2007     | -1.68            | (-2.23 to -1.13)        |
| Rothbaum, 2005    | -1.23            | (-2.40 to -0.06)        |
| Rothbaum, 1997    | -1.18            | (-2.09 to -0.28)        |
| Combined          | -1.37            | (-2.05 to -0.69)        |
| <b>Usual Care</b> |                  |                         |
| NA                | NA               | NA                      |

**Figure F-67. PTSD symptom reduction for EMDR compared with control, by type of comparator: Sensitivity analysis including placebo**



Timing of outcome assessment: 8 weeks (van der Kolk, 2007), 2 months (Hogberg, 2007), 4.5 weeks (Rothbaum, 2005), 4 weeks (Rothbaum, 1997), 6 weeks (Carlson, 1998).

**Figure F-68. PTSD symptom reduction for EMDR compared with control, by type of comparator: Sensitivity analysis including high risk of bias studies**

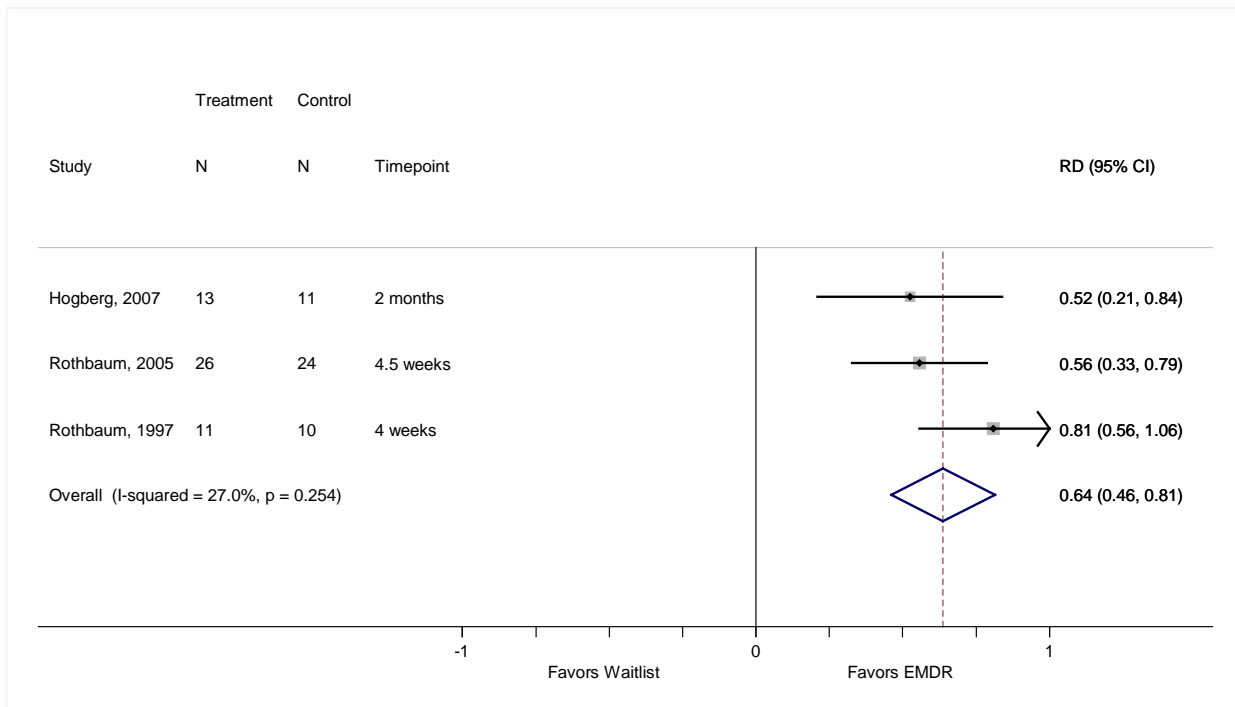


Note: Johnson et al., 2006, Power et al., 2002, and Marcus et al., 1997 were rated as having high risk of bias.

Timing of outcome assessment: 8 weeks (van der Kolk, 2007), 2 months (Hogberg, 2007), mean number of weekly sessions = 6.33 (Johnson, 2006), 10 weeks (Power, 2002), 4.5 weeks (Rothbaum, 2005), 4 weeks (Rothbaum, 1997), 6 weeks (Carlson, 1998), variable number of sessions (Marcus, 1997).



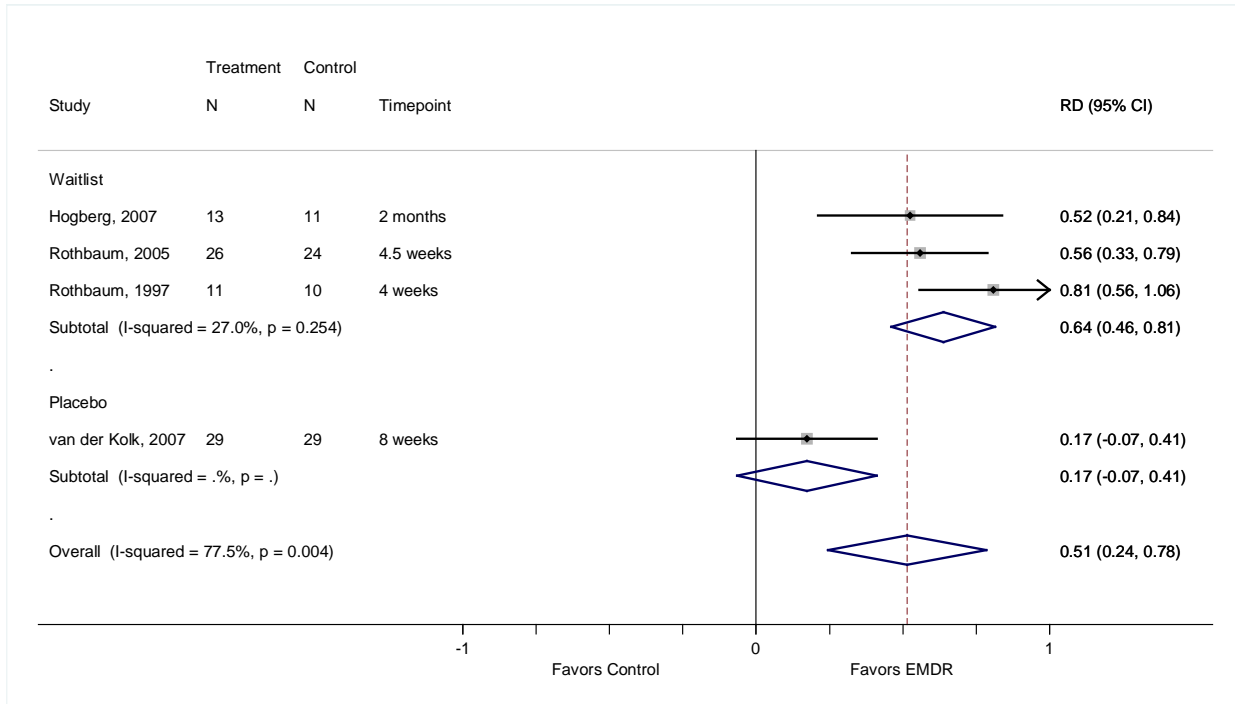
**Figure F-69. Loss of PTSD diagnosis for EMDR compared with waitlist**



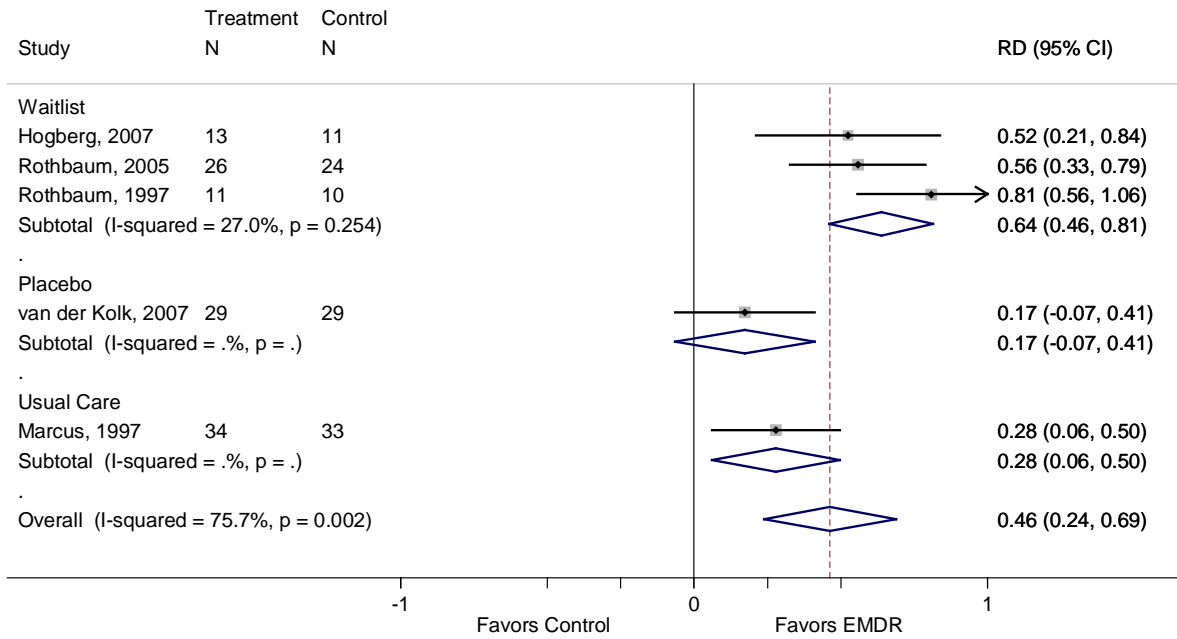
**Table F-32. Loss of PTSD diagnosis for EMDR compared with waitlist: Statistics with one study removed**

| Study Omitted   | Overall Estimate | 95% Confidence Interval |
|-----------------|------------------|-------------------------|
| <b>Waitlist</b> |                  |                         |
| Hogberg, 2007   | 0.68             | (0.43 to 0.92)          |
| Rothbaum, 2005  | 0.68             | (0.41 to 0.96)          |
| Rothbaum, 1997  | 0.55             | (0.36 to 0.73)          |
| Combined        | 0.64             | (0.46 to 0.81)          |

**Figure F-70. Loss of PTSD diagnosis for EMDR compared with control, by type of comparator: Sensitivity analysis including placebo**



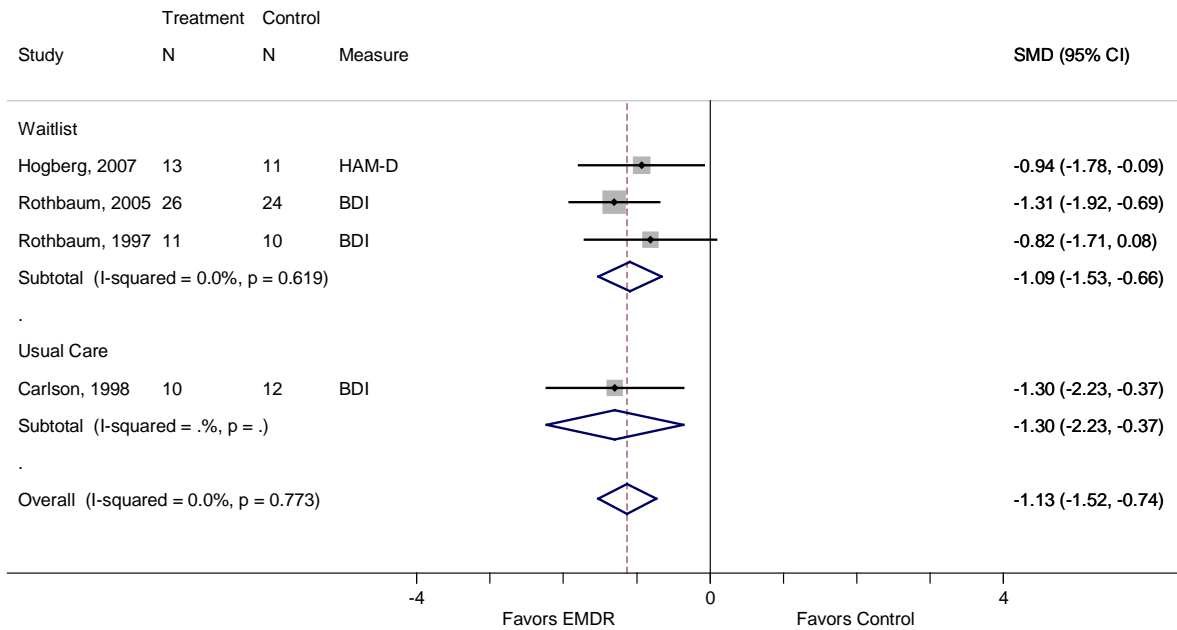
**Figure F-71. Loss of PTSD diagnosis for EMDR compared with control, by type of comparator: Sensitivity analysis including high risk of bias studies**



Note: Marcus et al, 1997 was rated as having high risk of bias.

Timing of outcome assessment: 2 months (Hogberg, 2007), 4.5 weeks (Rothbaum, 2005), 4 weeks (Rothbaum, 1997), 8 weeks (van der Kolk, 2007), variable number of sessions (Marcus, 1997).

**Figure F-72. Depression symptom reduction for EMDR compared with inactive control**



Timing of outcome assessment: 2 months (Hogberg, 2007), 4.5 weeks (Rothbaum, 2005), 4 weeks (Rothbaum, 1997), 6 weeks (Carlson, 1998).

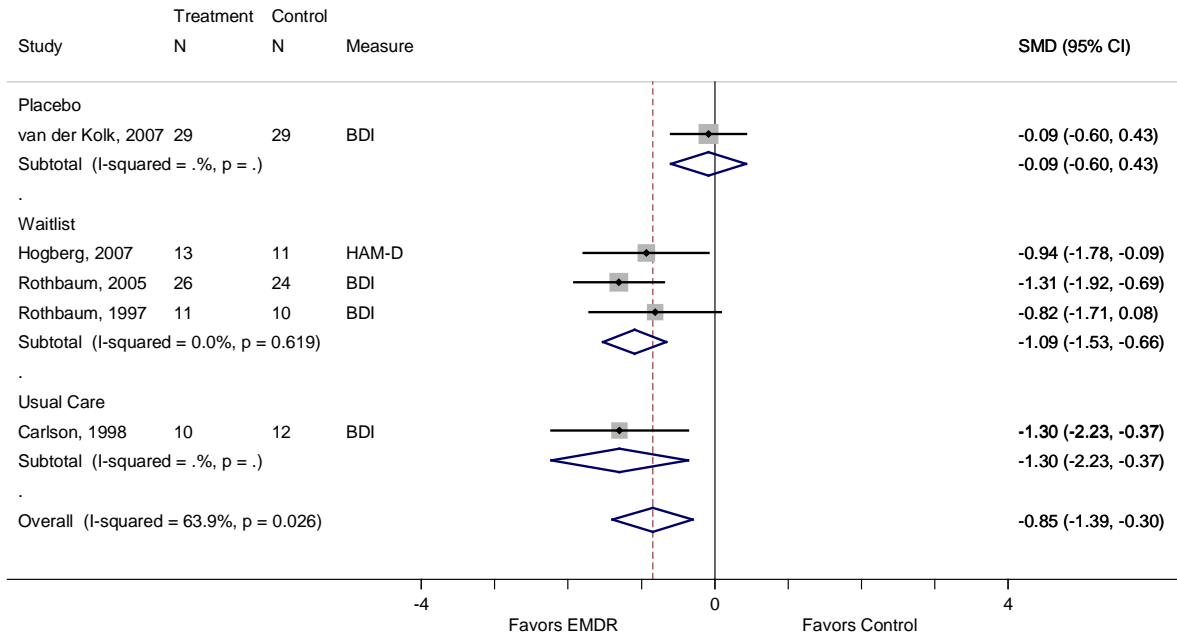
**Table F-33. Depression symptom reduction for EMDR compared with control, by type of comparator: Statistics with one study removed**

| Study Omitted  | Overall Estimate | 95% Confidence Interval |
|----------------|------------------|-------------------------|
| Hogberg, 2007  | -1.18            | (-1.63 to -0.74)        |
| Rothbaum, 2005 | -1.01            | (-1.52 to -0.49)        |
| Rothbaum, 1997 | -1.09            | (-1.53 to -0.66)        |
| Carlson, 1998  | -1.21            | (-1.64 to -0.77)        |
| Combined       | -1.13            | (-1.52 to -0.74)        |

**Table F-34. Depression symptom reduction for EMDR compared with control, by type of comparator: Statistics with one study removed, by type of comparator**

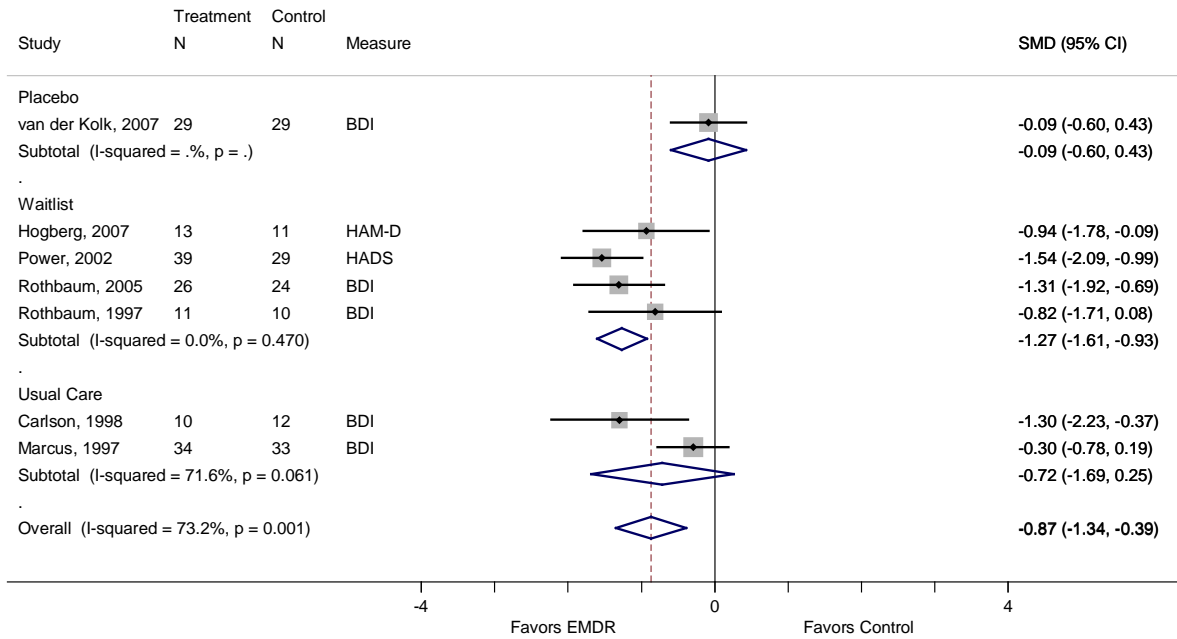
| Study Omitted     | Overall Estimate | 95% Confidence Interval |
|-------------------|------------------|-------------------------|
| <b>Waitlist</b>   |                  |                         |
| Hogberg, 2007     | -1.15            | (-1.66 to -0.64)        |
| Rothbaum, 2005    | -0.88            | (-1.50 to -0.26)        |
| Rothbaum, 1997    | -1.18            | (-1.68 to -0.68)        |
| Combined          | -1.09            | (-1.53 to -0.66)        |
| <b>Usual Care</b> |                  |                         |
| NA                | NA               | NA                      |

**Figure F-73. Depression symptom reduction for EMDR compared with inactive control: Sensitivity analysis including placebo**



Timing of outcome assessment: 8 weeks (van der Kolk, 2007), 2 months (Hogberg, 2007), 4.5 weeks (Rothbaum, 2005), 4 weeks (Rothbaum, 1997), 6 weeks (Carlson, 1998).

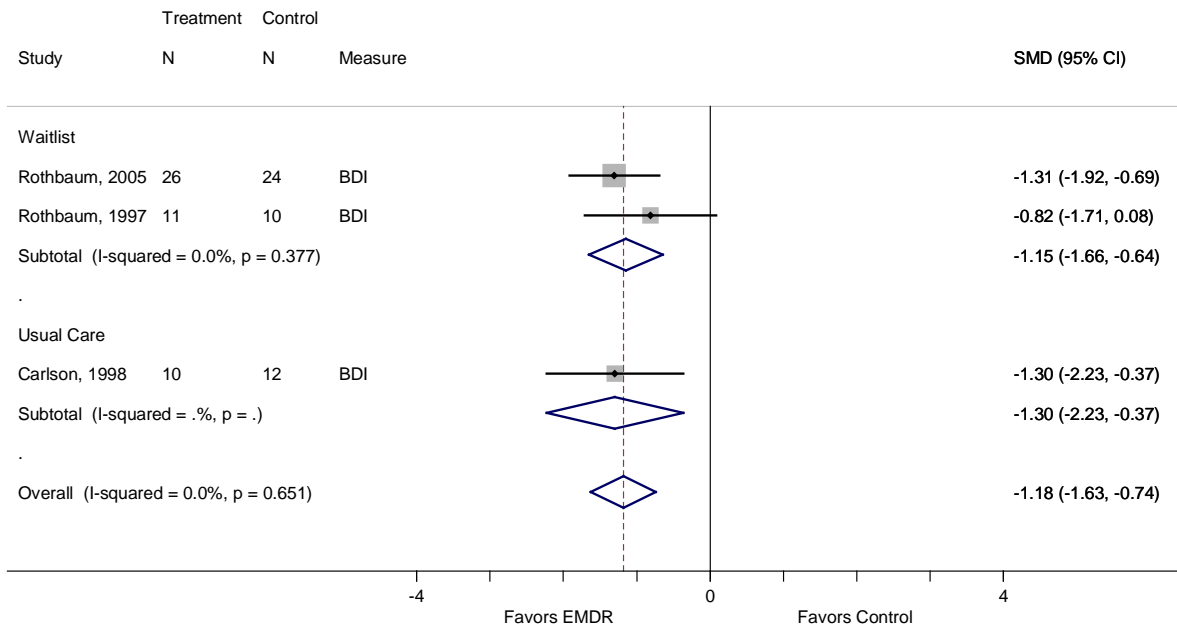
**Figure F-74. Depression symptom reduction for EMDR compared with inactive control: Sensitivity analysis including studies with high risk of bias**



Note: Marcus et al., 1997, and Power et al., 2002 were rated as having high risk of bias.

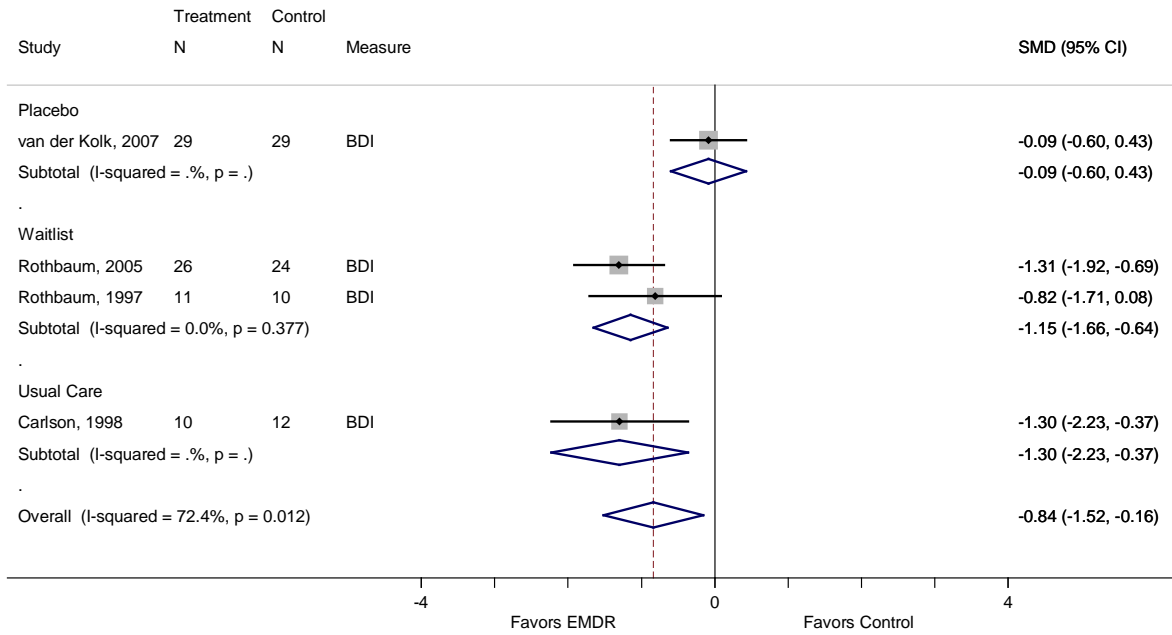
Timing of outcome assessment: 8 weeks (van der Kolk, 2007), 2 months (Hogberg, 2007), 10 weeks (Power, 2002), 4.5 weeks (Rothbaum, 2005), 4 weeks (Rothbaum, 1997), 6 weeks (Carlson, 1998), variable number of sessions (Marcus, 1997).

**Figure F-75. Change in BDI for EMDR compared with an inactive control, by type of comparator**



Timing of outcome assessment: 4.5 weeks (Rothbaum, 2005), 4 weeks (Rothbaum, 1997), 6 weeks (Carlson, 1998).

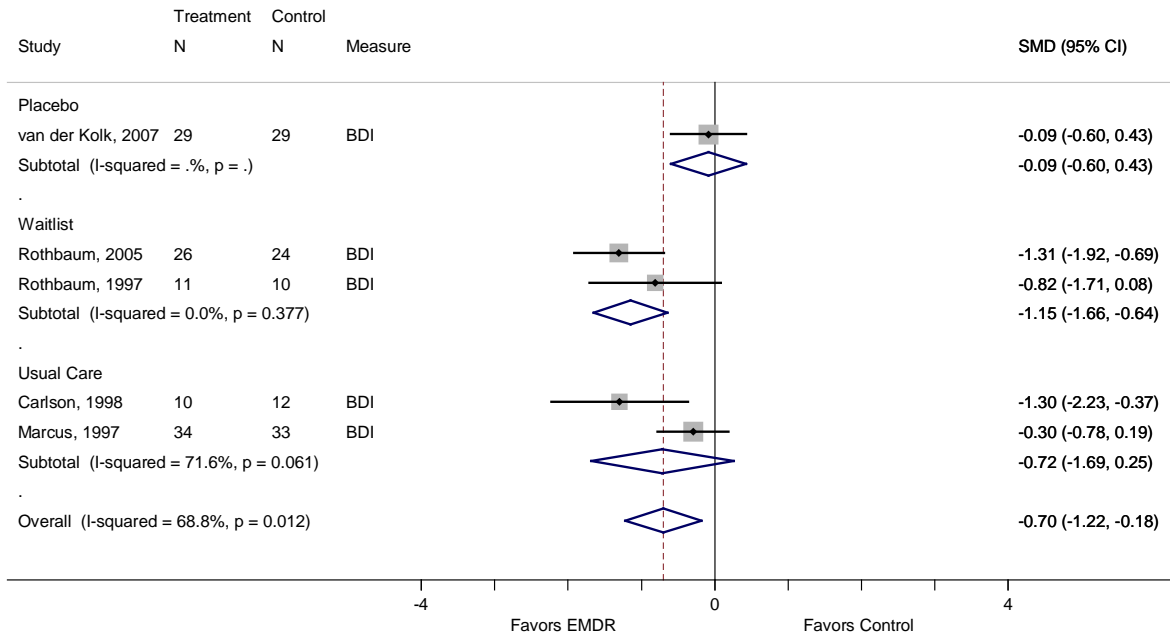
**Figure F-76. Change in BDI for EMDR compared with an inactive control: Sensitivity analysis including placebo**



Timing of outcome assessment: 8 weeks (van der Kolk, 2007), 4.5 weeks (Rothbaum, 2005), 4 weeks (Rothbaum, 1997), 6 weeks (Carlson, 1998).



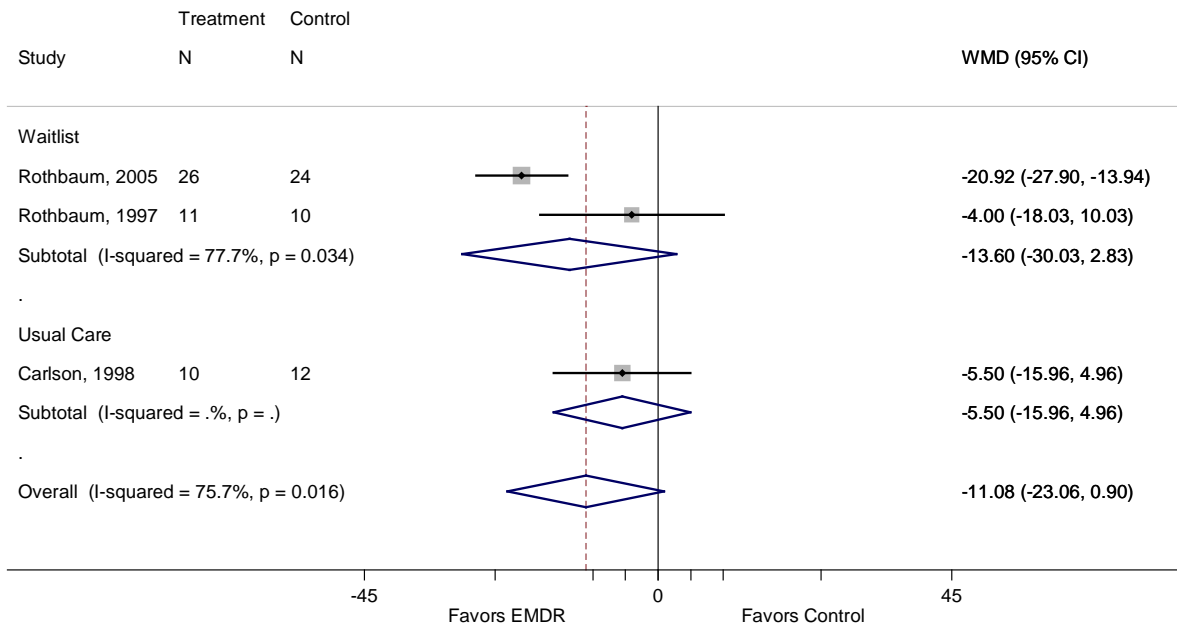
**Figure F-77. Change in BDI for EMDR compared with an inactive control: Sensitivity analysis including studies with high risk of bias**



Note: Marcus et al, 1997 was rated as having high risk of bias.

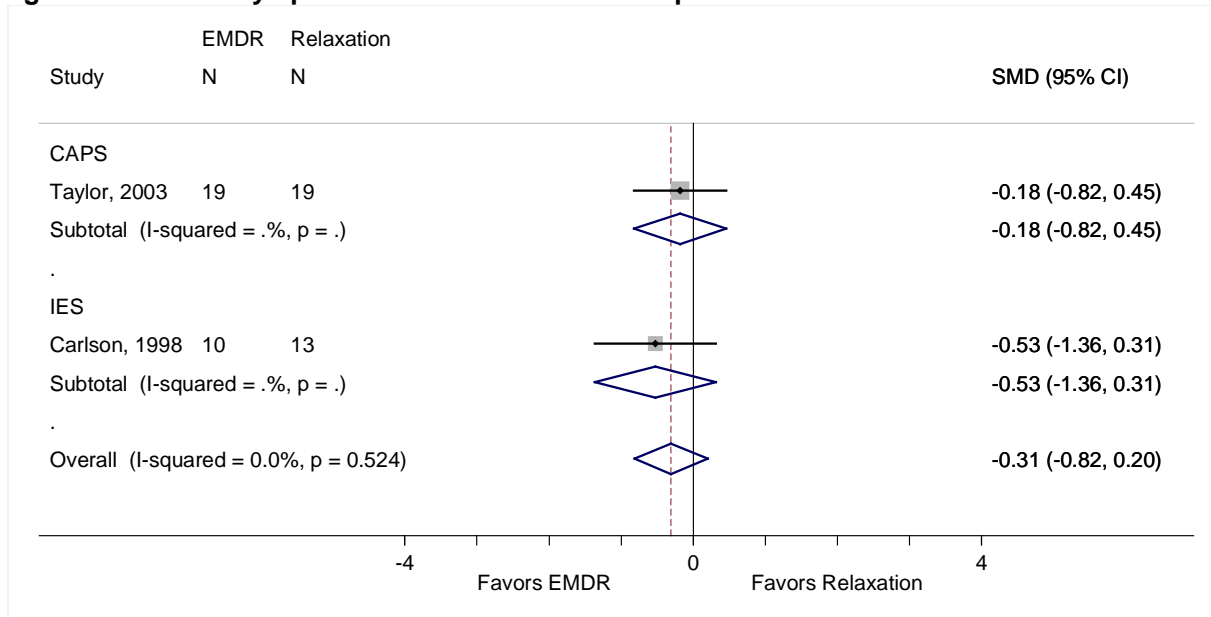
Timing of outcome assessment: 8 weeks (van der Kolk, 2007), 4.5 weeks (Rothbaum, 2005), 4 weeks (Rothbaum, 1997), 6 weeks (Carlson, 1998), variable number of sessions (Marcus, 1997).

**Figure F-78. Change in STAI for EMDR compared with an inactive control, by type of comparator**



Timing of outcome assessment: 4.5 weeks (Rothbaum, 2005), 4 weeks (Rothbaum, 1997), 6 weeks (Carlson, 1998).

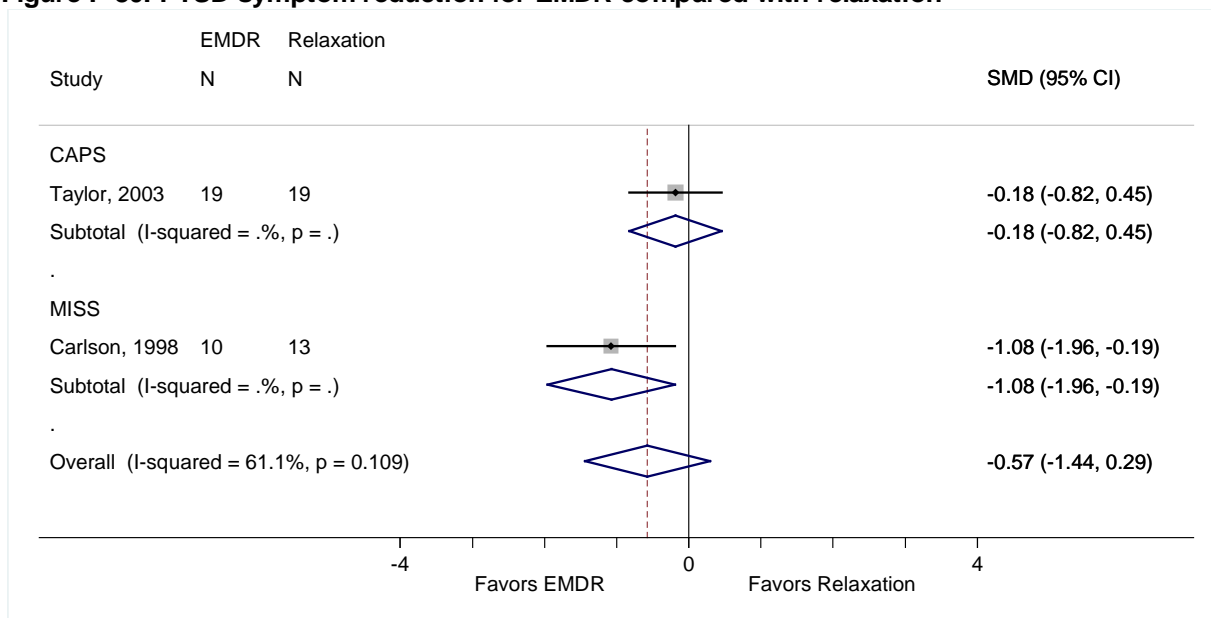
**Figure F-79. PTSD symptom reduction for EMDR compared with relaxation**



Note: This analysis uses the IES instrument data from Carlson et al., 1998.

Timing of outcome assessment: 8 weeks (Taylor, 2003), 6 weeks (Carlson, 1998).

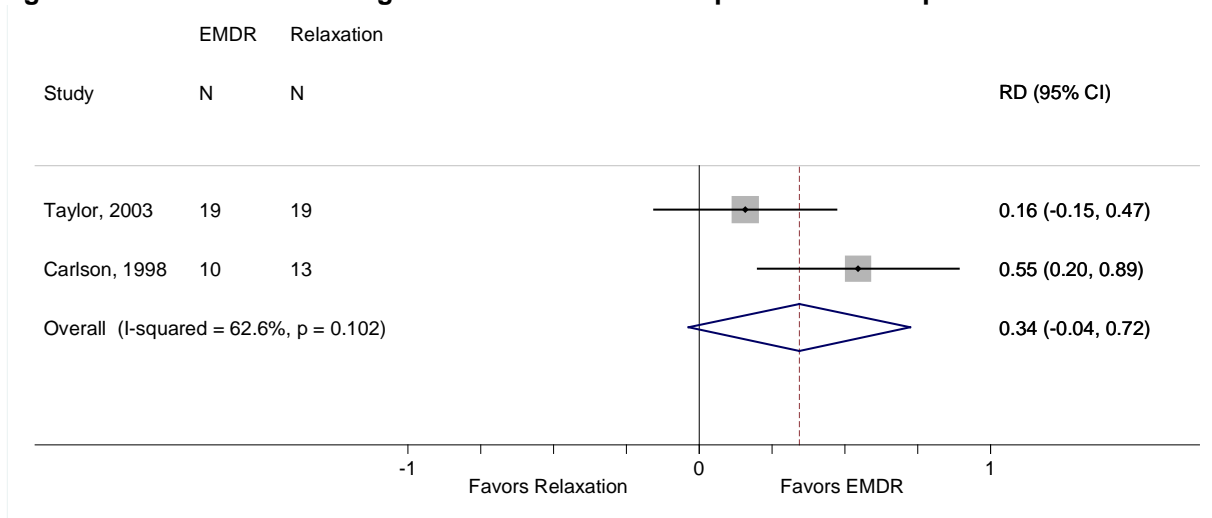
**Figure F-80. PTSD symptom reduction for EMDR compared with relaxation**



Note: This analysis uses the MISS instrument data from Carlson et al., 1998.

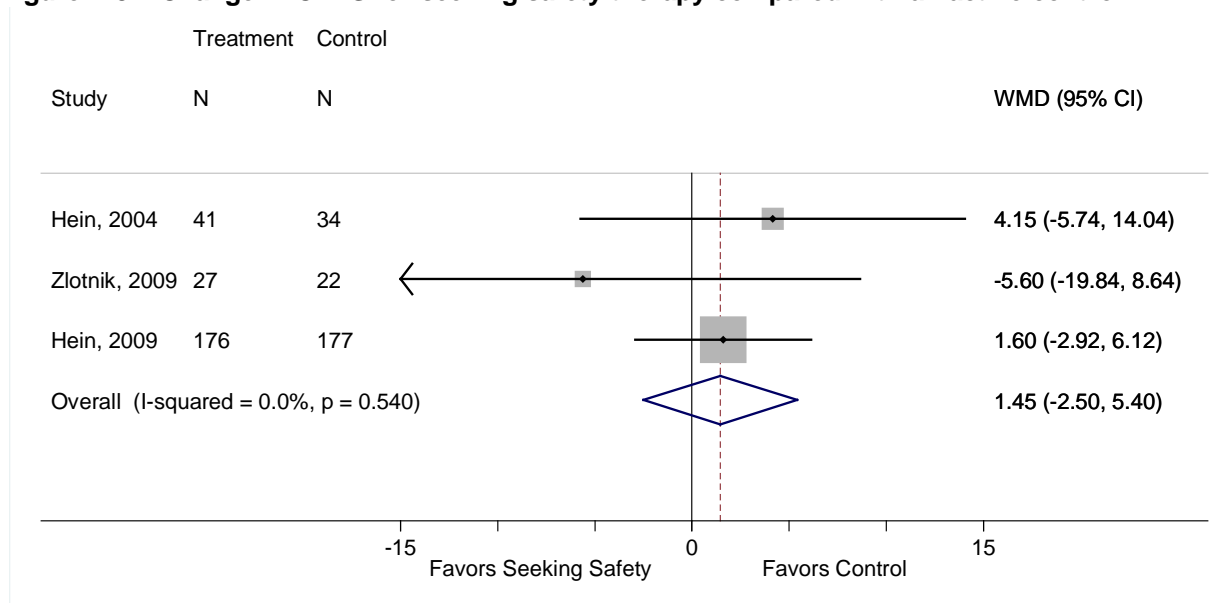
Timing of outcome assessment: 8 weeks (Taylor, 2003), 6 weeks (Carlson, 1998).

**Figure F-81. Loss of PTSD diagnosis at 3 month follow-up for EMDR compared with relaxation**



## Other Psychological Interventions: Meta-Analysis Results

**Figure F-82. Change in CAPS for seeking safety therapy compared with an active control**

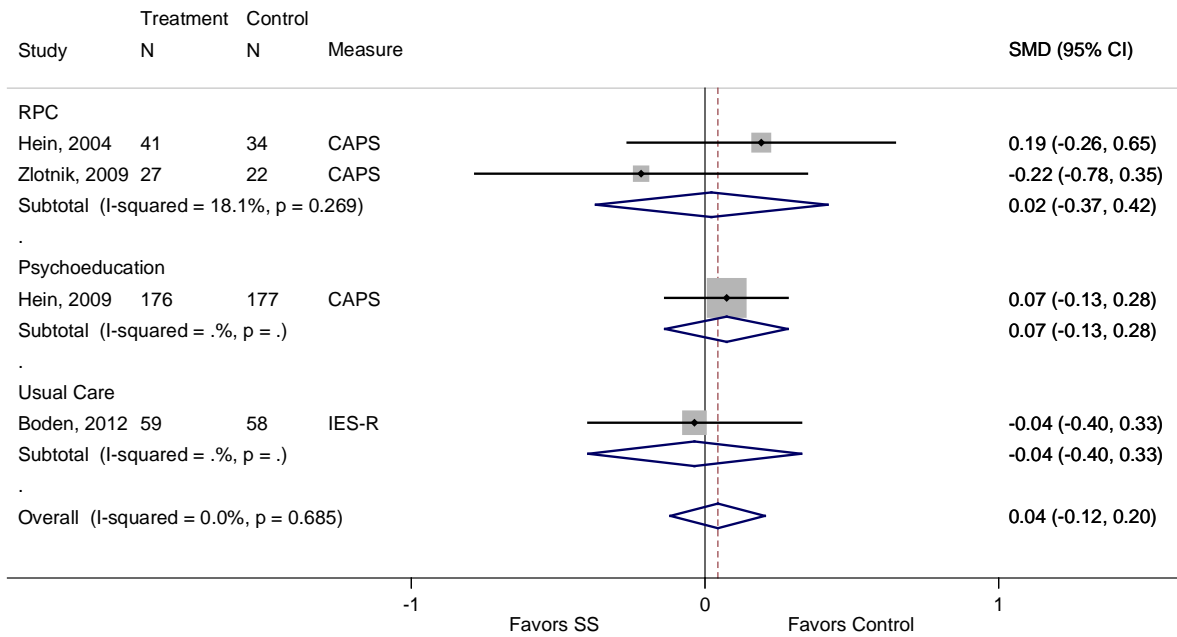


Timing of outcome assessment: 12 weeks (Hien, 2004), 6 to 8 weeks (Zlotnik, 2009), 6 weeks (Hien, 2009).

**Table F-35. Change in CAPS for seeking safety therapy compared with an active control: Statistics with one study removed**

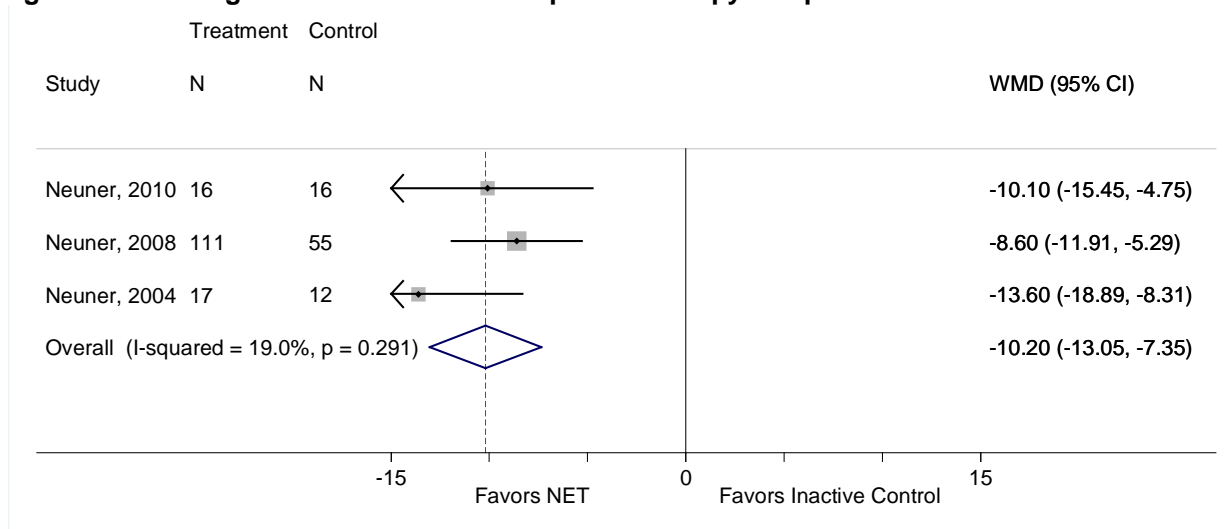
| Study Omitted | Overall Estimate | 95% Confidence Interval |
|---------------|------------------|-------------------------|
| Hein, 2004    | 0.94             | (-3.37 to 5.25)         |
| Zlotnik, 2009 | 2.04             | (-2.07 to 6.15)         |
| Hein, 2009    | 0.68             | (-8.47 to 9.83)         |
| Combined      | 1.45             | (-2.50 to 5.40)         |

**Figure F-83. PTSD symptom reduction for seeking safety therapy compared with control, by type of comparator**



Timing of outcome assessment: 12 weeks (Hien, 2004), 6 to 8 weeks (Zlotnik, 2009), 6 weeks (Hien, 2009), 12 weeks (Boden, 2012).

**Figure F-84. Change in PDS for narrative exposure therapy compared with an inactive control**

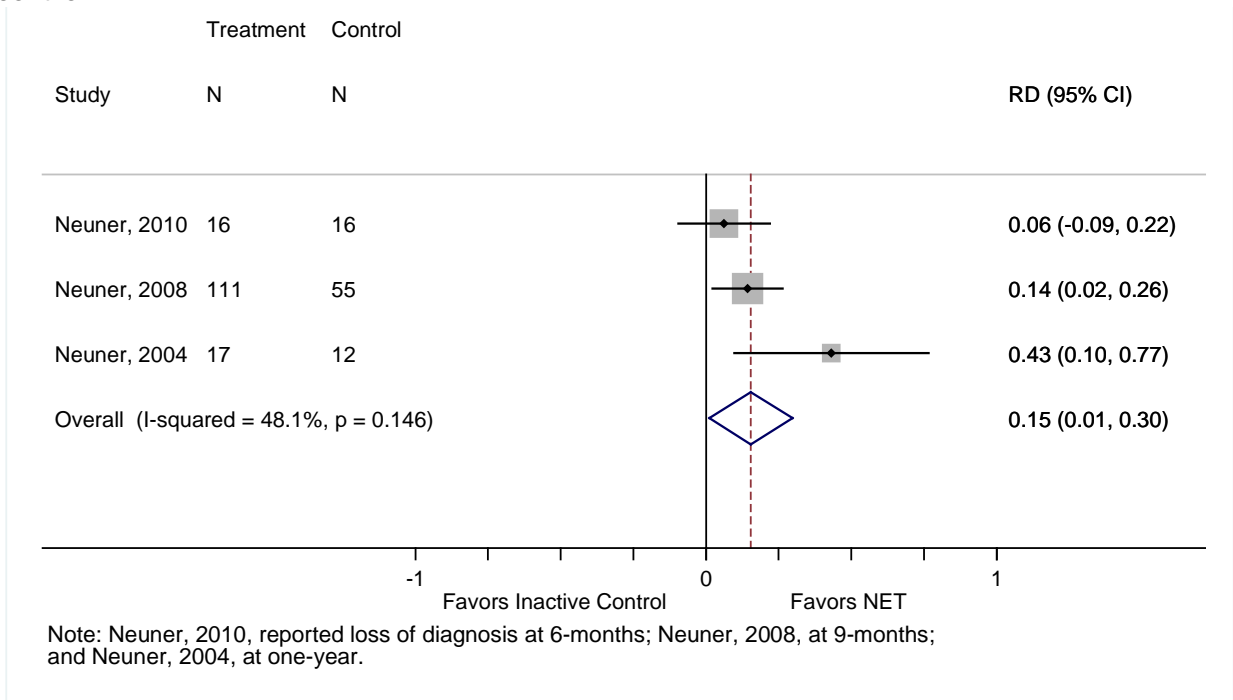


Timing of outcome assessment: 5 to 17 sessions (Neuner, 2010), 3 weeks (Neuner, 2008), 3 to 4 weeks (Neuner, 2004).

**Table F-36. Change in PDS for narrative exposure therapy compared with an inactive control: Statistics with one study removed**

| Study Omitted | Overall Estimate | 95% Confidence Interval |
|---------------|------------------|-------------------------|
| Neuner, 2010  | -10.66           | (-15.48 to -5.83)       |
| Neuner, 2008  | -11.87           | (-15.63 to -8.11)       |
| Neuner, 2004  | -9.02            | (-11.83 to -6.20)       |
| Combined      | -10.20           | (-13.05 to -7.35)       |

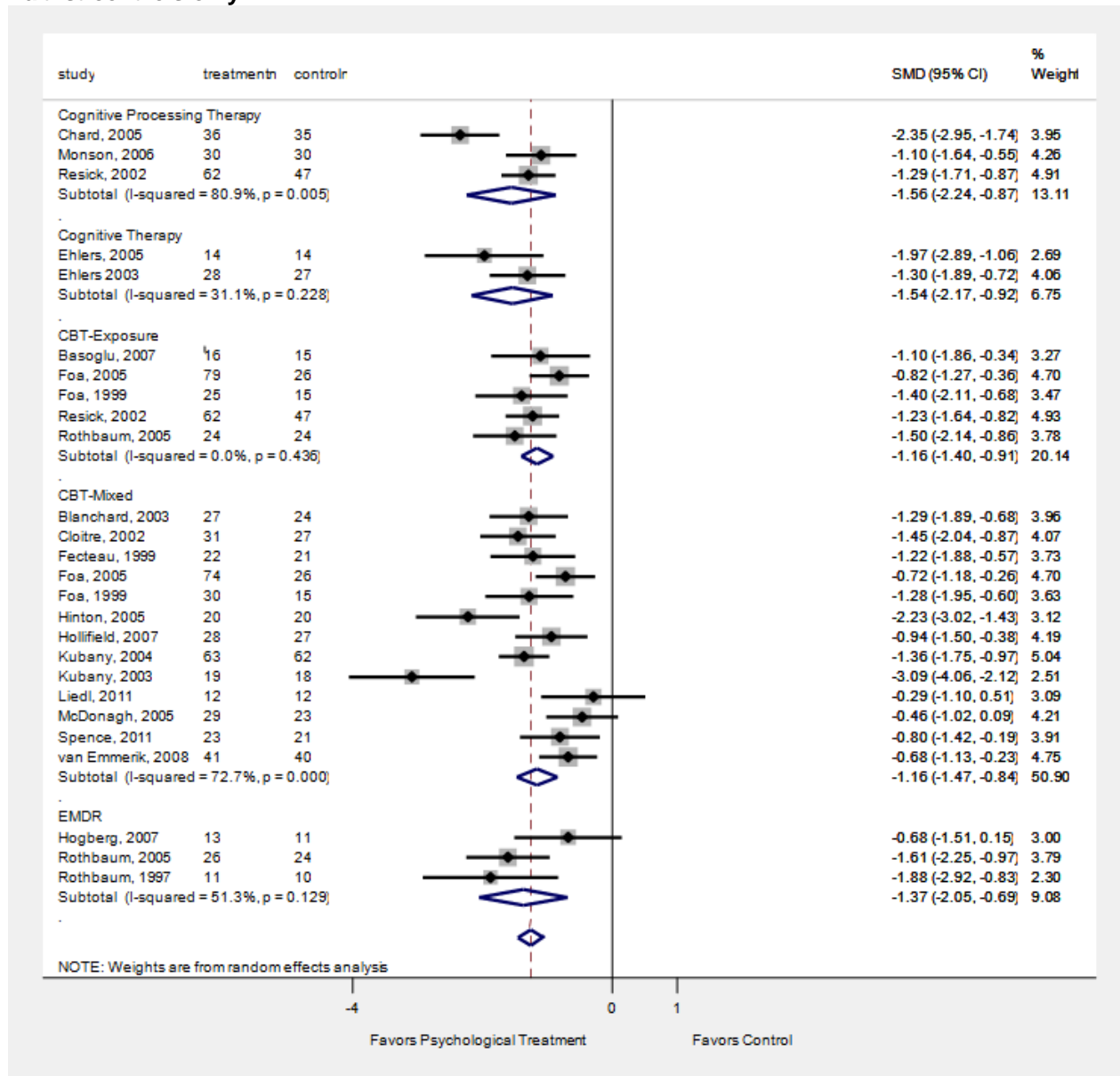
**Figure F-85. Loss of PTSD diagnosis for narrative exposure therapy compared with an inactive control**



**Table F-37. Loss of PTSD diagnosis for narrative exposure therapy compared with an inactive control: Statistics with one study removed**

| Study Omitted | Overall Estimate | 95% Confidence Interval |
|---------------|------------------|-------------------------|
| Neuner, 2010  | 0.24             | (-0.03 to 0.51)         |
| Neuner, 2008  | 0.22             | (-0.14 to 0.57)         |
| Neuner, 2004  | 0.11             | (0.02 to 0.21)          |
| Combined      | 0.15             | (0.01 to 0.30)          |

**Figure F-86. PTSD symptom reduction (any measure) for psychological treatments compared with waitlist controls only**

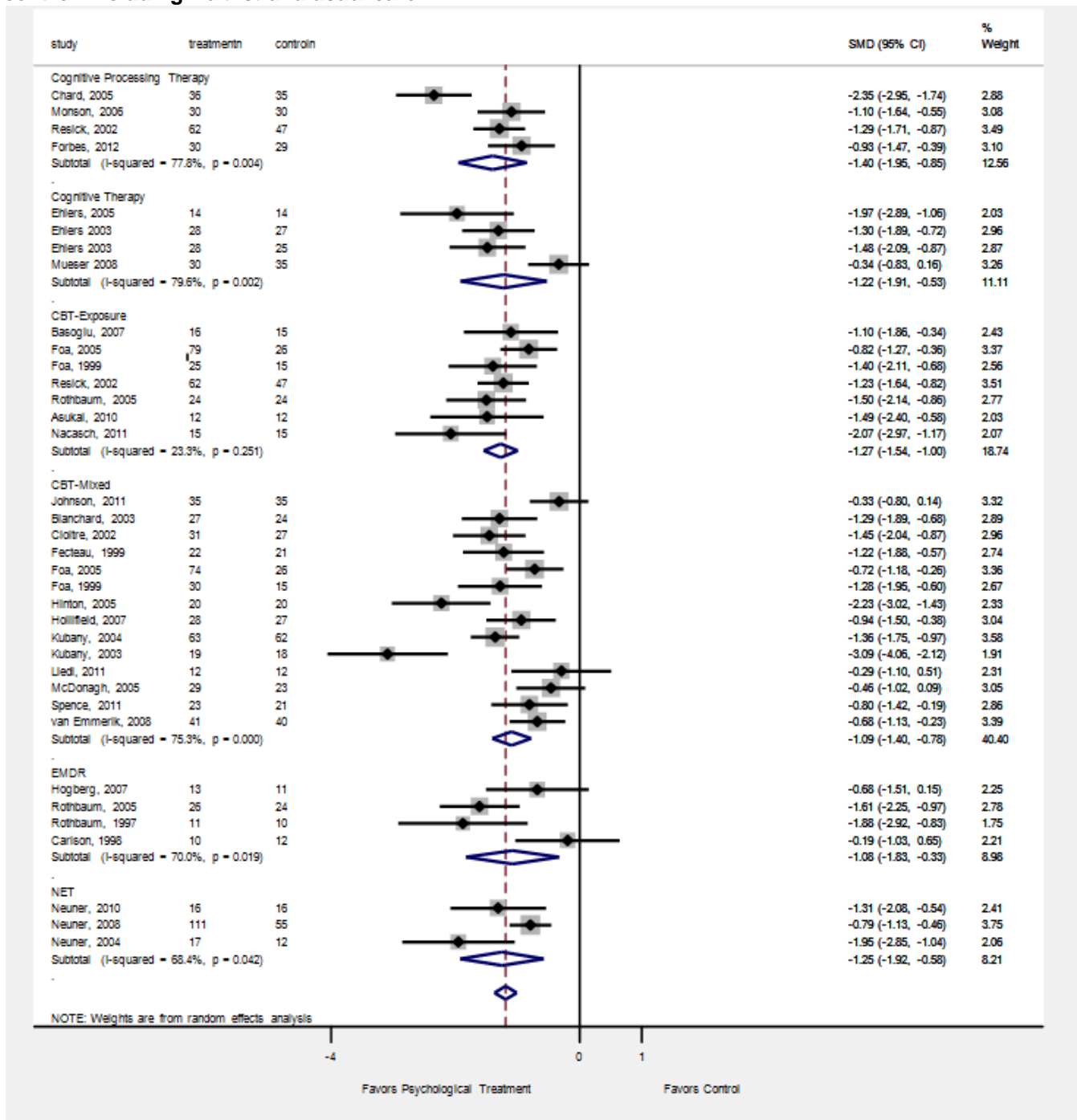


Abbreviations: CBT = cognitive behavioral therapy; CI = confidence interval; EMDR = eye movement desensitization and reprocessing; N = trial arm sample size; SMD = standardized mean difference (Cohen’s d). A small effect size is  $d=0.20$ , medium effect size is  $d=0.50$ , and large effect size is  $d=0.80$ .<sup>25</sup>

Timing of outcome assessment: 17 weeks (Chard, 2005), 10 weeks (Monson, 2006), 6 weeks (Resick, 2002), 3 months (Ehlers 2005 and Ehlers 2003), 8 weeks (Basoglu, 2007), 12 weeks (Foa, 2005), 9 weeks (Foa, 1999), 4.5 weeks (Rothbaum, 2005), 8 to 12 weeks (Blanchard, 2003), 12 weeks (Cloitre, 2002), 4 weeks (Fecteau, 1999), 12 weeks (Hinton, 2005), 12 weeks (Hollifield, 2007) 4 to 5.5 weeks (Kubany, 2004), 4.5 months (Kubany, 2003), 4.8 months (Liedl, 2011), 14 weeks (McDonagh, 2005), 8 weeks (Spence, 2011), 5 sessions (van Emmerik, 2008), 2 months (Hogberg, 2007), 4 weeks (Rothbaum, 1997).



**Figure F-87. PTSD symptom reduction (any measure) for psychological treatments compared with control: including waitlist and usual care**

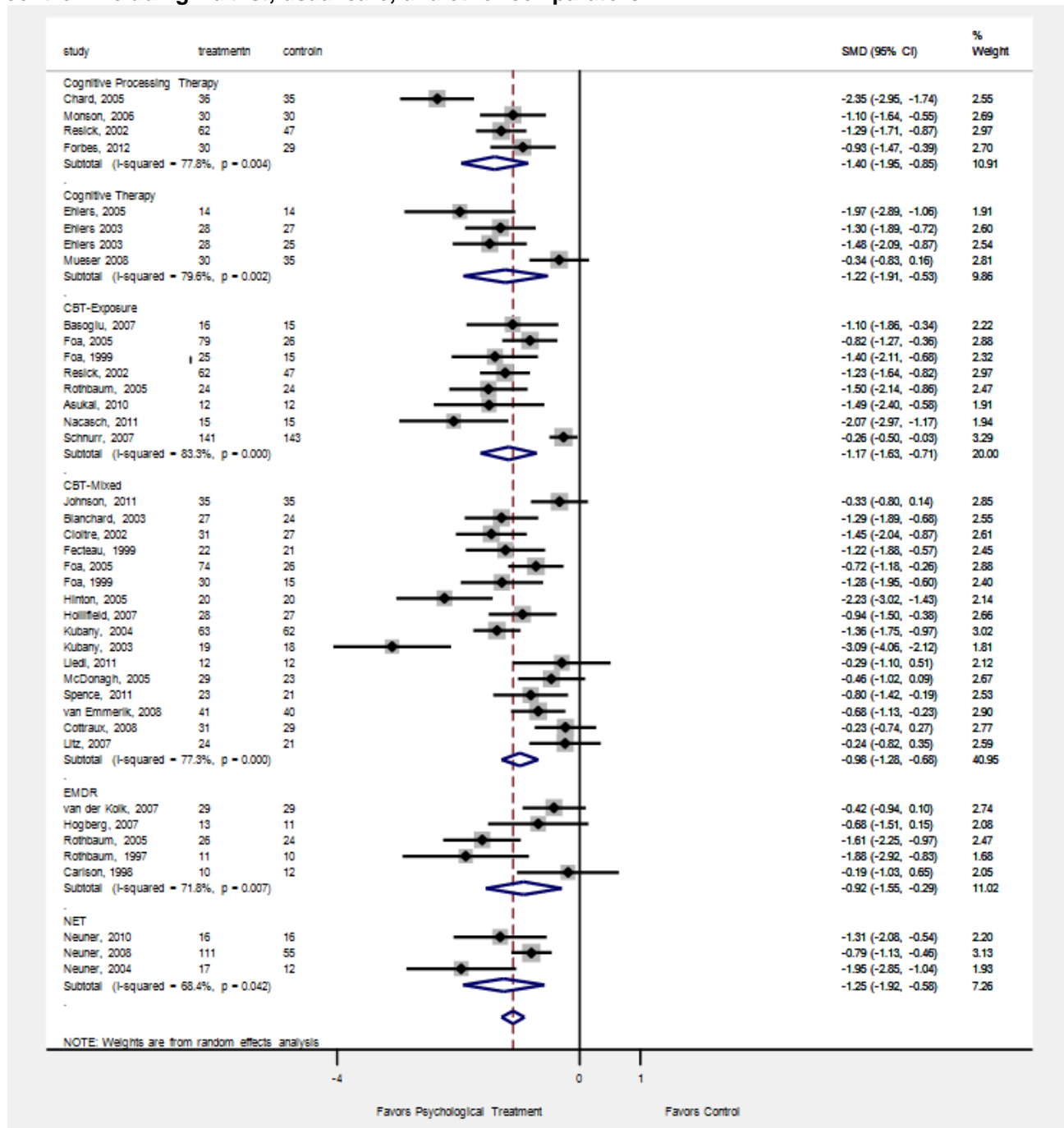


Timing of outcome assessment: 17 weeks (Chard, 2005), 12 weeks (Forbes, 2012), 10 weeks (Monson, 2006), 6 weeks (Resick, 2002), 3 months (Ehlers 2005, Ehlers 2003, and Mueser 2008), 8 weeks (Basoglu, 2007), 12 weeks (Foa, 2005), 9 weeks (Foa, 1999), 4.5 weeks (Rothbaum, 2005), 8 to 15 weekly sessions (Asukai, 2010), 9 to 15 weeks (Nacasch, 2011), 7 weeks (Johnson, 2011), 8 to 12 weeks (Blanchard, 2003), 12 weeks (Cloitre, 2002), 4 weeks (Fecteau, 1999), 12 weeks (Foa, 2005), 9 weeks (Foa, 1999), 12 weeks (Hinton, 2005), 12 weeks (Hollifield, 2007), 4 to 5.5 weeks (Kubany, 2004), 4.5 months (Kubany, 2003), 4.8 months (Liedl, 2011), 14 weeks (McDonagh, 2005), 8 weeks (Spence, 2011), 5 sessions (van Emmerik, 2008), 2 months (Hogberg, 2007), 4 weeks (Rothbaum, 1997), 6 weeks (Carlson, 1998), 5 to 17 sessions (Neuner, 2010), 3 weeks (Neuner, 2008), 3 to 4 weeks (Neuner, 2004).

Note: A couple of the comparison groups were not defined as usual care or treatment as usual by the authors, but we determined that they were minimal interventions and approximated usual care. These included (1) one comparison group for Ehlers 2003 was a self-help booklet, and (2) the included comparison group for Neuner 2004 was a form of psychoeducation.

Abbreviations: CBT = cognitive behavioral therapy; CI = confidence interval; EMDR = eye movement desensitization and reprocessing; N = trial arm sample size; SMD = standardized mean difference (Cohen's d). A small effect size is  $d=0.20$ , medium effect size is  $d=0.50$ , and large effect size is  $d=0.80$ .25

**Figure F-88. PTSD symptom reduction (any measure) for psychological treatments compared with control: including waitlist, usual care, and other comparators**



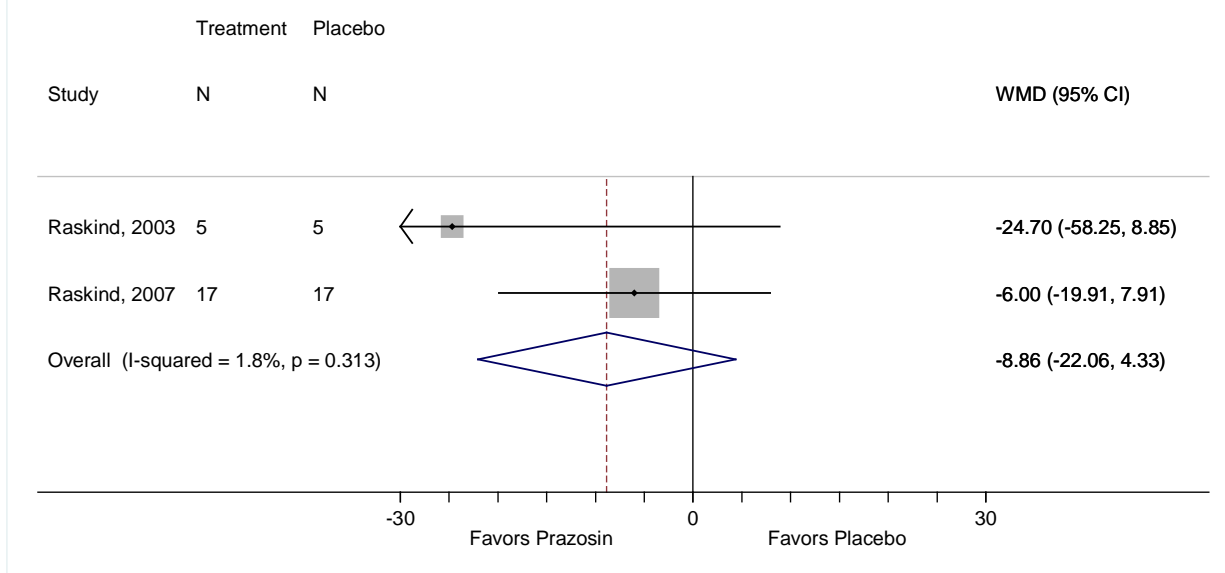
Timing of outcome assessment: 17 weeks (Chard, 2005), 12 weeks (Forbes, 2012), 10 weeks (Monson, 2006), 6 weeks (Resick, 2002), 3 months (Ehlers 2005, Ehlers 2003, and Mueser 2008), 8 weeks (Basoglu, 2007), 12 weeks (Foa, 2005), 9 weeks (Foa, 1999), 4.5 weeks (Rothbaum, 2005), 8 to 15 weekly sessions (Asukai, 2010), 9 to 15 weeks (Nacasch, 2011), 10 weeks (Schnurr, 2007), 7 weeks (Johnson, 2011), 8 to 12 weeks (Blanchard, 2003), 12 weeks (Cloitre, 2002), 4 weeks (Fecteau, 1999), 12 weeks (Foa, 2005), 9 weeks (Foa, 1999), 12 weeks (Hinton, 2005), 12 weeks (Hollifield, 2007), 4 to 5.5 weeks (Kubany, 2004), 4.5 months (Kubany, 2003), 4.8 months (Liedl, 2011), 14 weeks (McDonagh, 2005), 8 weeks (Spence, 2011), 5 sessions (van Emmerik, 2008), 16 weeks (Cottraux, 2008), 8 weeks (Litz, 2007), 8 weeks (van der Kolk, 2007), 2 months (Hogberg, 2007), 4 weeks (Rothbaum, 1997), 6 weeks (Carlson, 1998), 5 to 17 sessions (Neuner, 2010), 3 weeks (Neuner, 2008), 3 to 4 weeks (Neuner, 2004).

Abbreviations: CBT = cognitive behavioral therapy; CI = confidence interval; EMDR = eye movement desensitization and reprocessing; N = trial arm sample size; SMD = standardized mean difference (Cohen's d). A small effect size is  $d=0.20$ , medium effect size is  $d=0.50$ , and large effect size is  $d=0.80$ .<sup>25</sup>

## Key Question 2

### Alpha-Blockers: Meta-Analysis Results

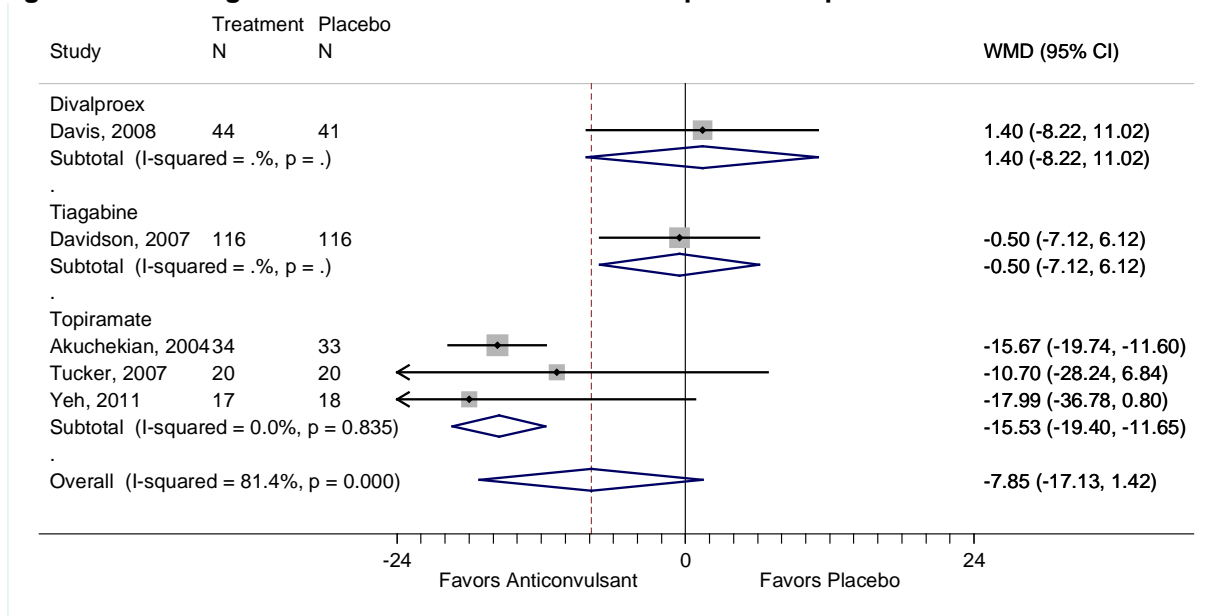
Figure F-89. Change in CAPS for prazosin compared with placebo



Timing of outcome assessment: 20 weeks (Raskind, 2003), 8 weeks (Raskind).

# Anticonvulsants/Mood Stabilizers: Meta-Analysis Results

**Figure F-90. Change in CAPS for anticonvulsants compared with placebo**

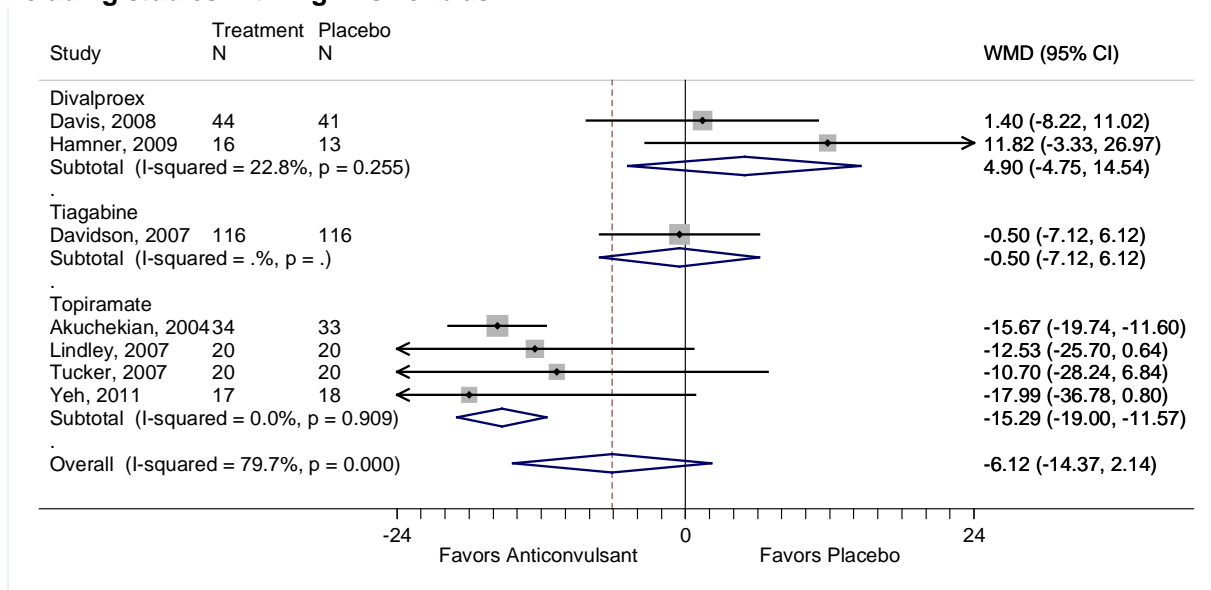


Timing of outcome assessment: 8 weeks (Davis, 2008), 12 weeks (Davidson, 2007; Akuchekian, 2004; Tucker, 2007; Yeh, 2011).

**Table F-38. Change in CAPS for anticonvulsants compared with placebo: Statistics with one study removed for topiramate**

| Study Omitted    | Overall Estimate | 95% Confidence Interval |
|------------------|------------------|-------------------------|
| Akuchekian, 2004 | -14.09           | (-26.92 to -1.27)       |
| Tucker, 2007     | -15.77           | (-19.75 to -11.80)      |
| Yeh, 2011        | -15.42           | (-19.38 to -11.46)      |
| Combined         | -15.53           | (-19.40 to -11.65)      |

**Figure F-91. Change in CAPS for anticonvulsants compared with placebo: Sensitivity analysis including studies with high risk of bias**

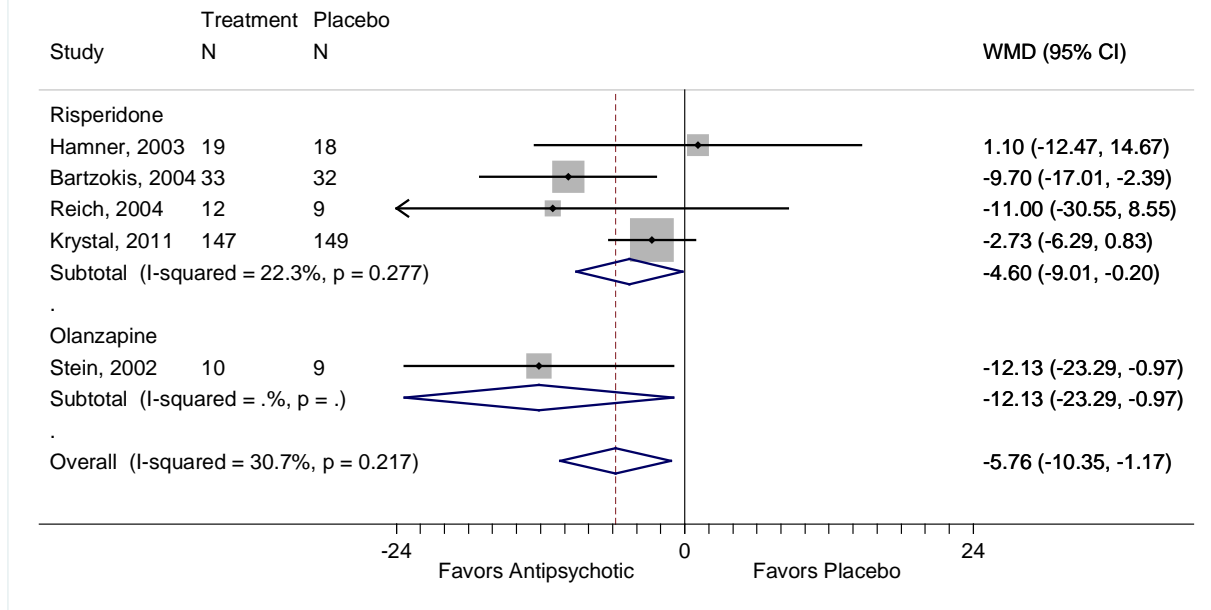


Note: Hamner et al., 2009 and Lindley et al., 2007 were rated as high risk of bias.

Timing of outcome assessment: 8 weeks (Davis, 2008), 10 weeks (Hamner, 2009), 7 weeks (Lindley, 2007); 12 weeks (Davidson, 2007; Akuchekian, 2004; Tucker, 2007; Yeh, 2011).

# Atypical Antipsychotics: Meta-Analysis Results

**Figure F-92. Change in CAPS for atypical antipsychotics compared with placebo**



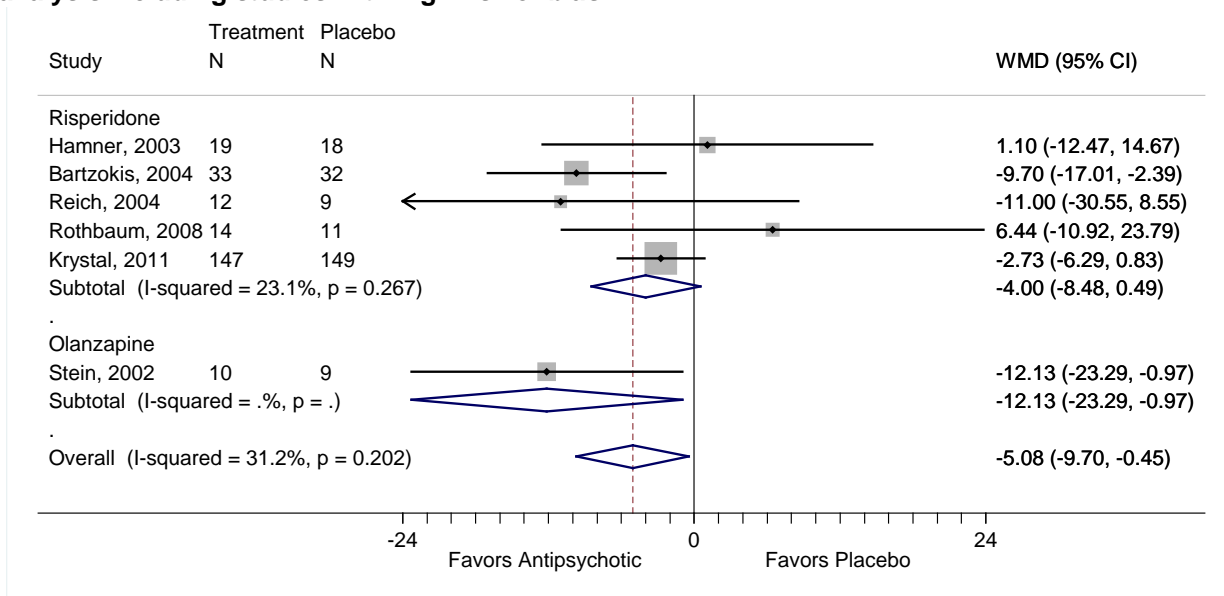
Timing of outcome assessment: 5 weeks (Hamner, 2003), 16 weeks (Bartzokis, 2003), 8 weeks (Reich, 2004), 24 weeks (Krystal, 2011), 8 weeks (Stein, 2002).

**Table F-39. Change in CAPS for atypical antipsychotics compared with placebo: Statistics with one study removed for risperidone**

| Study Omitted   | Overall Estimate | 95% Confidence Interval |
|-----------------|------------------|-------------------------|
| Hamner, 2003    | -5.62            | (-11.10 to -0.15)       |
| Bartzokis, 2004 | -2.74            | (-6.13 to 0.65)         |
| Reich, 2004     | -4.39            | (-9.59 to 0.80)         |
| Krystal, 2011   | -7.62            | (-13.77 to -1.46)       |
| Combined        | -4.60            | (-9.01 to -0.20)        |



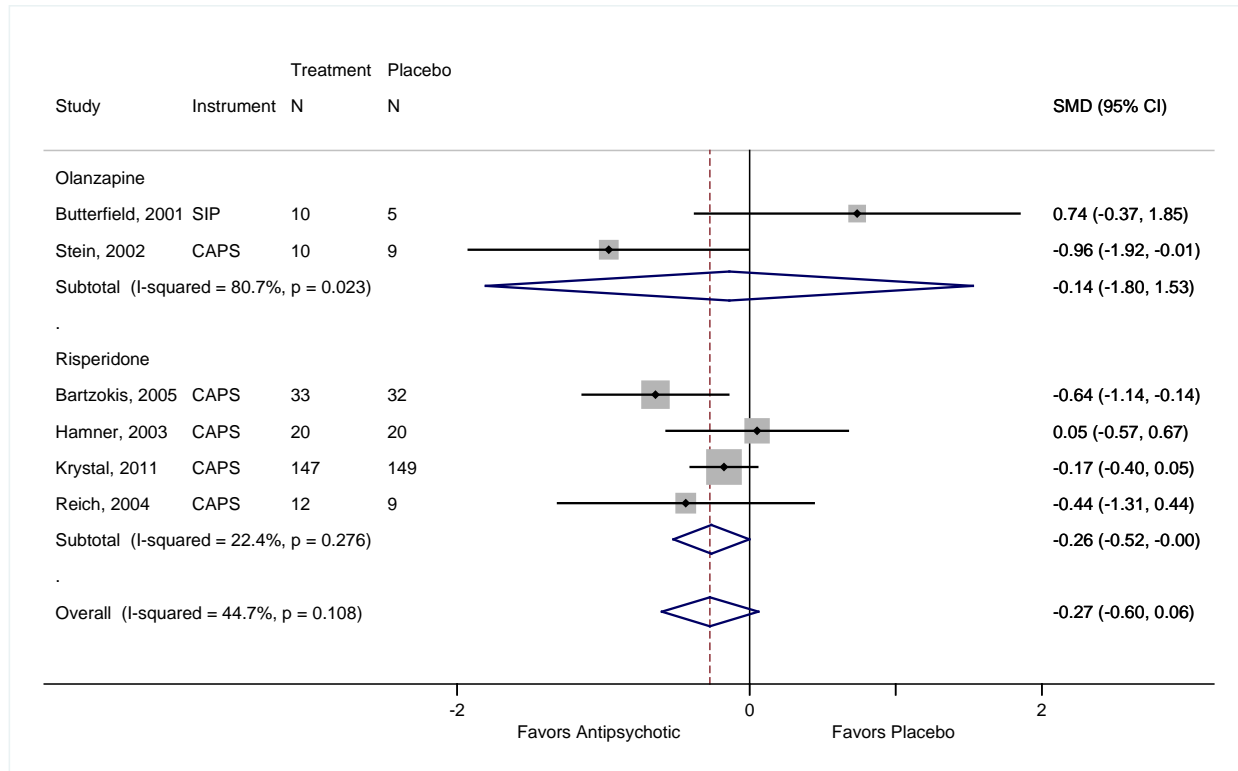
**Figure F-93. Change in CAPS for atypical antipsychotics compared with placebo: Sensitivity analysis including studies with high risk of bias**



Note: Rothbaum et al., 2008 was rated as high risk of bias.

Timing of outcome assessment: 5 weeks (Hamner, 2003), 16 weeks (Bartzokis, 2003), 8 weeks (Reich, 2004), 16 weeks (Rothbaum, 2008), 24 weeks (Krystal, 2011), 8 weeks (Stein, 2002).

**Figure F-94. PTSD symptom reduction (any measure) for atypical antipsychotics compared with placebo**



Timing of outcome assessment: 10 weeks (Butterfield, 2001), 8 weeks (Stein, 2002), 16 weeks (Bartzokis, 2003), 5 weeks (Hamner, 2003), 24 weeks (Krystal, 2011), 8 weeks (Reich, 2004).

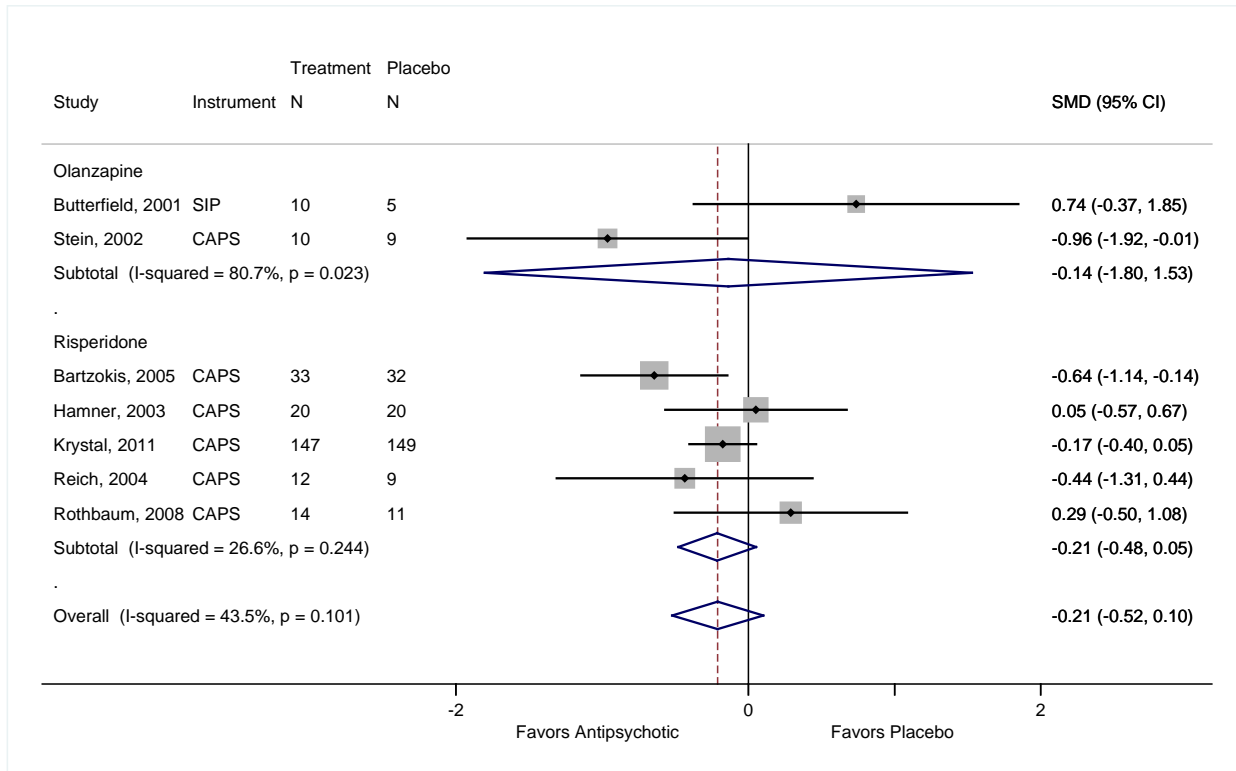
**Table F-40. PTSD symptom reduction (any measure) for atypical antipsychotics compared with placebo: Statistics with one study removed**

| Study Omitted     | Overall Estimate | 95% Confidence Interval |
|-------------------|------------------|-------------------------|
| Butterfield, 2001 | -0.33            | (-0.62 to -0.04)        |
| Stein, 2002       | -0.20            | (-0.53 to 0.12)         |
| Bartzokis, 2005   | -0.17            | (-0.52 to 0.18)         |
| Hamner, 2003      | -0.33            | (-0.73 to 0.05)         |
| Krystal, 2011     | -0.30            | (-0.80 to 0.19)         |
| Reich, 2004       | -0.25            | (-0.63 to 0.13)         |
| Combined          | -0.27            | (-0.60 to 0.06)         |

**Table F-41. PTSD symptom reduction (any measure) for atypical antipsychotics compared with placebo: Statistics with one study removed, by drug**

| Study Omitted      | Overall Estimate | 95% Confidence Interval |
|--------------------|------------------|-------------------------|
| <b>Olanzapine</b>  |                  |                         |
| Butterfield, 2001  | -0.96            | (-1.92 to -0.01)        |
| Stein, 2002        | 0.74             | (-0.37 to 1.85)         |
| Combined           | -0.14            | (-1.80 to 1.53)         |
| <b>Risperidone</b> |                  |                         |
| Bartzokis, 2005    | -0.16            | (-0.37 to 0.04)         |
| Hamner, 2003       | -0.33            | (-0.65 to -0.02)        |
| Krystal, 2011      | -0.36            | (-0.81 to 0.09)         |
| Reich, 2004        | -0.26            | (-0.59 to 0.08)         |
| Combined           | -0.26            | (-0.52 to -0.00)        |

**Figure F-95. PTSD symptom reduction (any measure) for atypical antipsychotics compared with placebo: Sensitivity analysis including studies with high risk of bias**



Note: Rothbaum et al., 2008 was rated as high risk of bias.

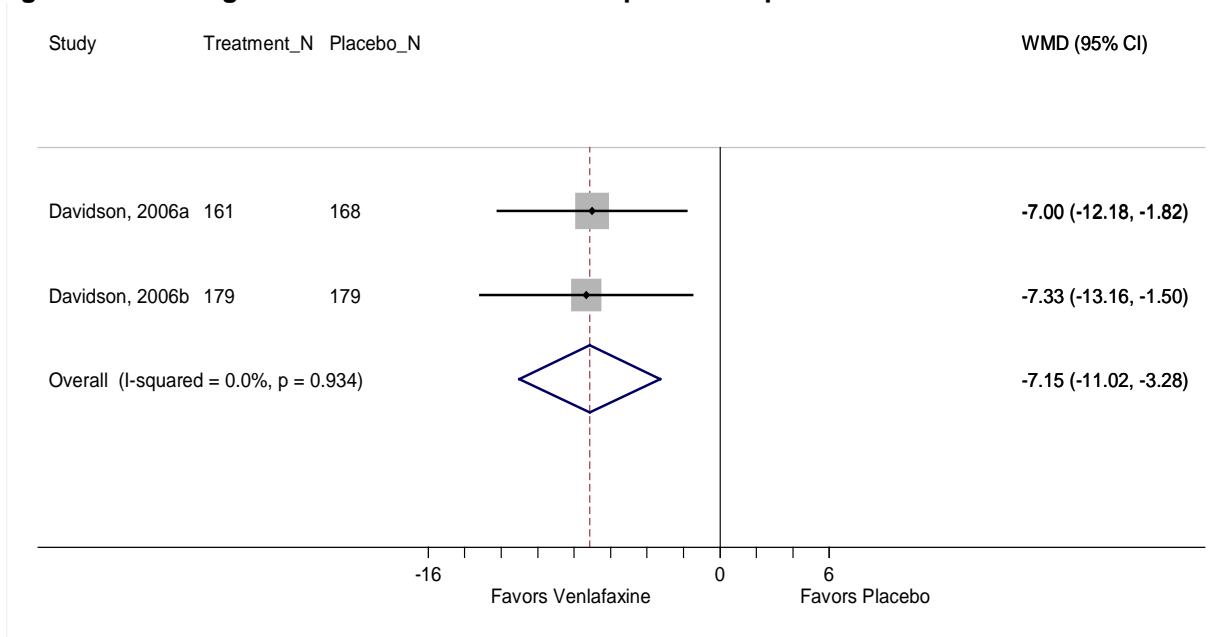
Timing of outcome assessment: 10 weeks (Butterfield, 2001), 8 weeks (Stein, 2002), 16 weeks (Bartzokis, 2003), 5 weeks (Hamner, 2003), 24 weeks (Krystal, 2011), 8 weeks (Reich, 2004), 16 weeks (Rothbaum, 2008).

## **Benzodiazepines: Meta-Analysis Results**

None

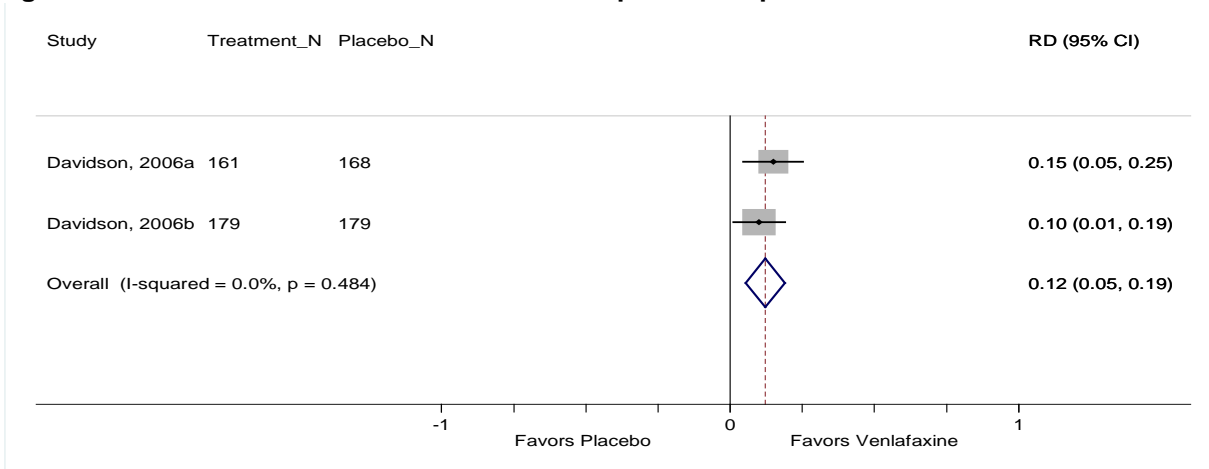
# SNRIs: Meta-Analysis Results

**Figure F-96. Change in CAPS for venlafaxine compared with placebo**



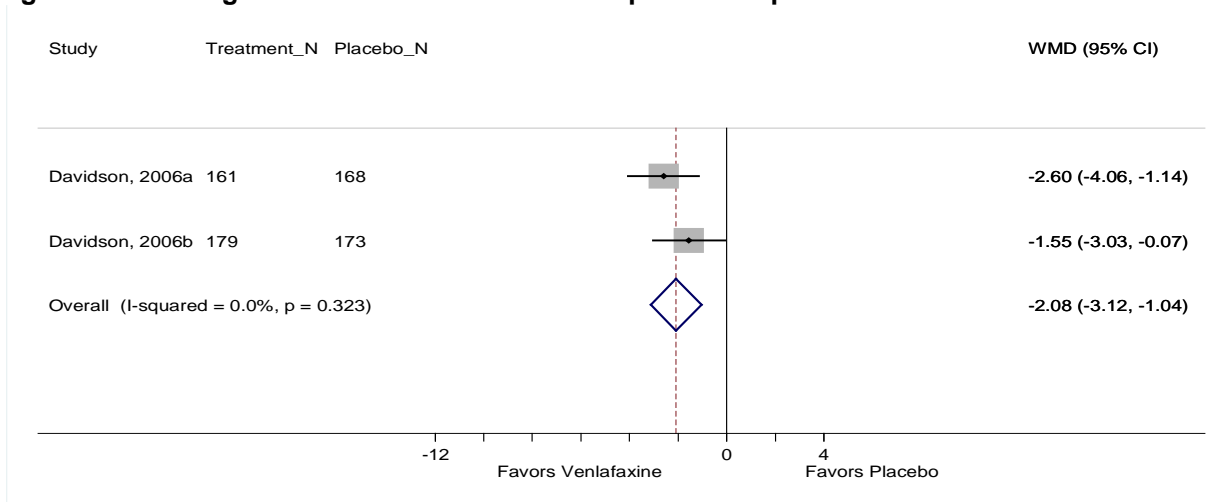
Timing of outcome assessment: 24 weeks (Davidson, 2006a), 12 weeks (Davidson, 2006b).

**Figure F-97. PTSD remission for venlafaxine compared with placebo**

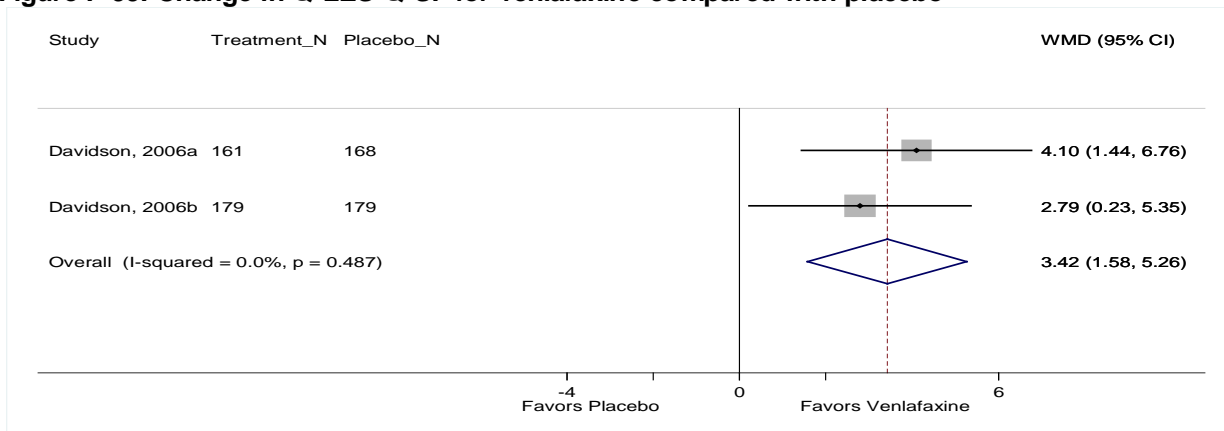


Timing of outcome assessment: 24 weeks (Davidson, 2006a), 12 weeks (Davidson, 2006b).

**Figure F-98. Change in HAMD for venlafaxine compared with placebo**

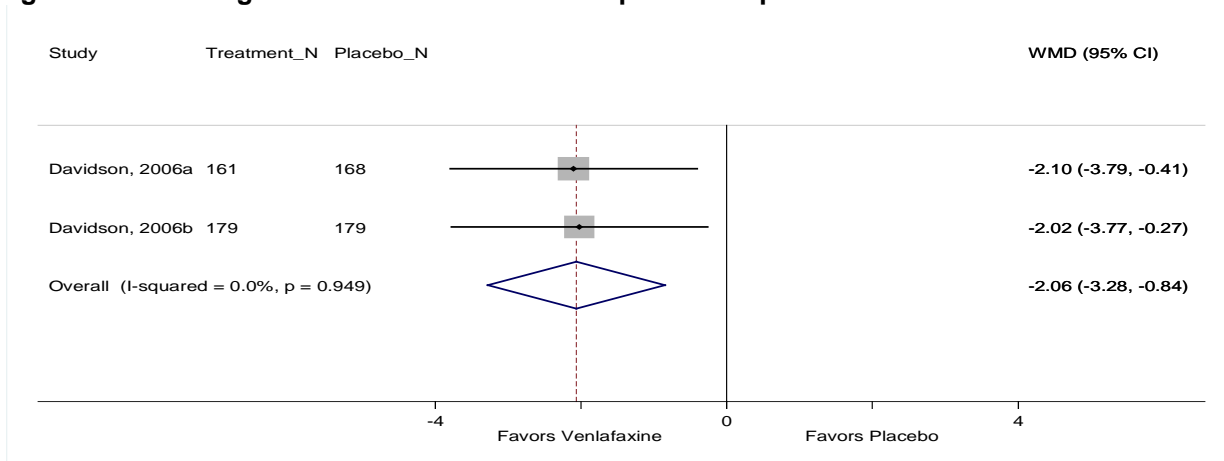


**Figure F-99. Change in Q-LES-Q-SF for venlafaxine compared with placebo**



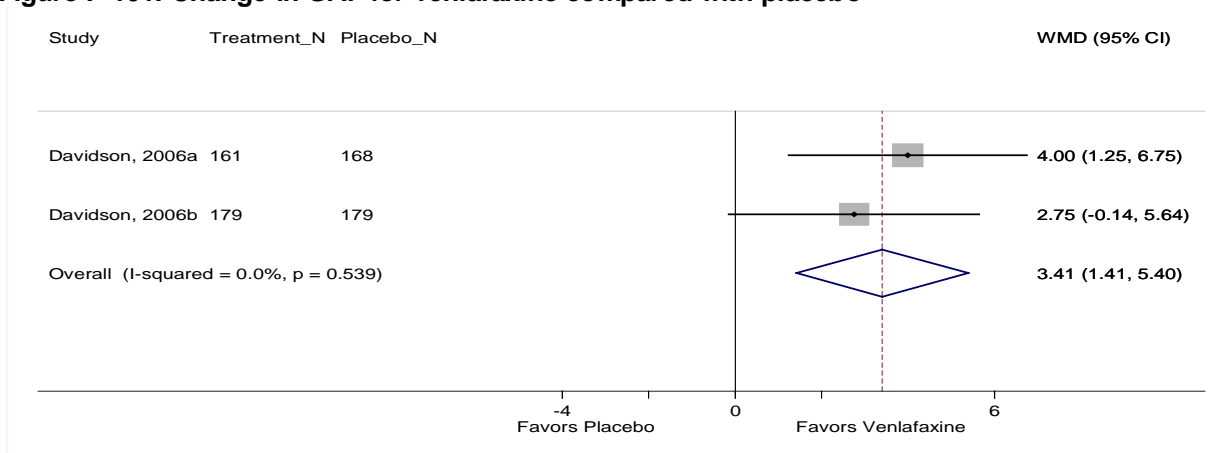
Timing of outcome assessment: 24 weeks (Davidson, 2006a), 12 weeks (Davidson, 2006b).

**Figure F-100. Change in SDS for venlafaxine compared with placebo**



Timing of outcome assessment: 24 weeks (Davidson, 2006a), 12 weeks (Davidson, 2006b).

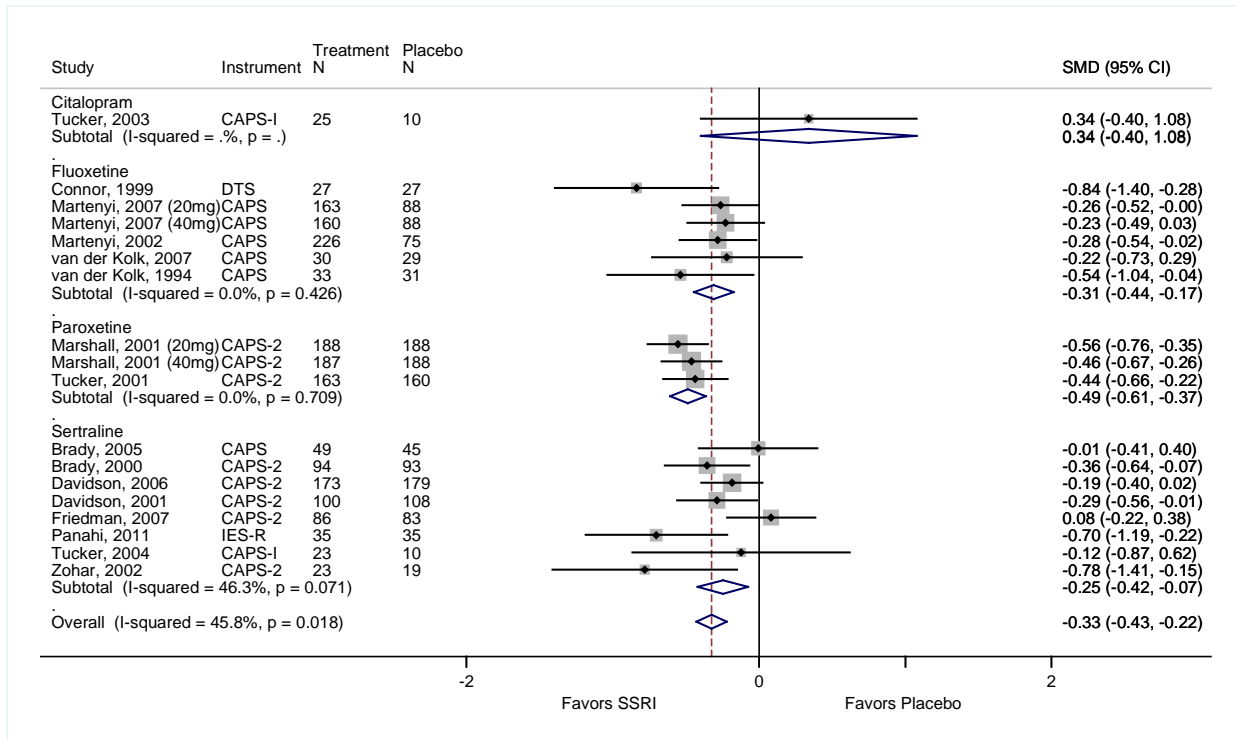
**Figure F-101. Change in GAF for venlafaxine compared with placebo**



Timing of outcome assessment: 24 weeks (Davidson, 2006a), 12 weeks (Davidson, 2006b).

# SSRIs: Meta-Analysis Results

Figure F-102. PTSD symptom reduction (any measure) for SSRIs compared with placebo



Timing of outcome assessment: 10 weeks (Tucker, 2003; Panahi, 2011; Tucker, 2004; Zohar, 2002), 12 weeks (Connor, 1999; Martenyi, 2007; Marshall, 2001; Tucker, 2001; Brady, 2005; Brady, 2000; Davidson, 2001; Friedman, 2007), 8 weeks (van der Kolk, 2007), 5 weeks (van der Kolk, 1994), 24 weeks (Davidson, 2006).

**Table F-42. PTSD symptom reduction (any measure) for SSRIs compared with placebo: Statistics with one study removed**

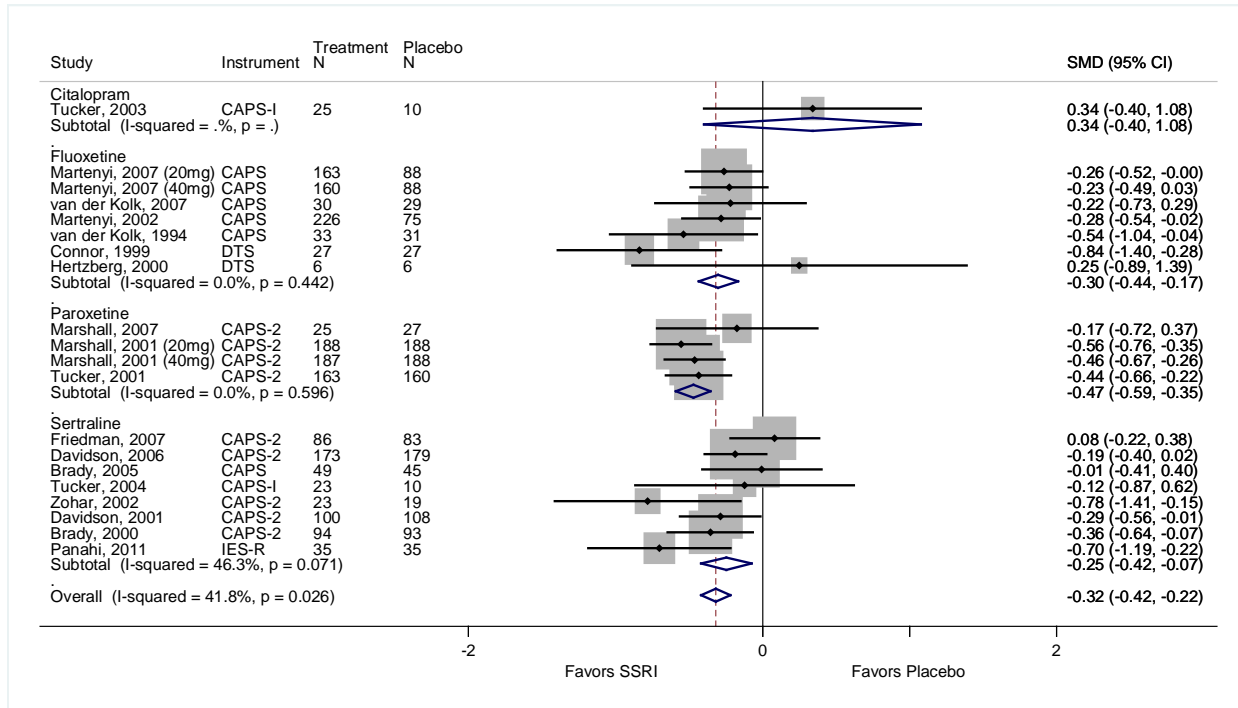
| <b>Study Omitted</b>  | <b>Overall Estimate</b> | <b>95% Confidence Interval</b> |
|-----------------------|-------------------------|--------------------------------|
| Tucker, 2003          | -0.34                   | (-0.44 to -0.24)               |
| Connor, 1999          | -0.31                   | (-0.41 to -0.21)               |
| Martenyi, 2007 (20mg) | -0.33                   | (-0.44 to -0.22)               |
| Martenyi, 2007 (40mg) | -0.33                   | (-0.44 to -0.22)               |
| Martenyi, 2002        | -0.33                   | (-0.44 to -0.22)               |
| van der Kolk, 2007    | -0.33                   | (-0.44 to -0.22)               |
| van der Kolk, 1994    | -0.32                   | (-0.43 to -0.21)               |
| Marshall, 2001 (20mg) | -0.30                   | (-0.41 to -0.20)               |
| Marshall, 2001 (40mg) | -0.31                   | (-0.42 to -0.20)               |
| Tucker, 2001          | -0.32                   | (-0.43 to -0.20)               |
| Brady, 2005           | -0.34                   | (-0.44 to -0.24)               |
| Brady, 2000           | -0.32                   | (-0.43 to -0.21)               |
| Davidson, 2006        | -0.34                   | (-0.45 to -0.23)               |
| Davidson, 2001        | -0.33                   | (-0.44 to -0.22)               |
| Freidman, 2007        | -0.35                   | (-0.45 to -0.26)               |
| Panahi, 2011          | -0.31                   | (-0.42 to -0.21)               |
| Tucker, 2004          | -0.33                   | (-0.44 to -0.22)               |
| Zohar, 2002           | -0.32                   | (-0.42 to -0.21)               |
| Combined              | -0.33                   | (-0.43 to -0.22)               |

**Table F-43. PTSD symptom reduction (any measure) for SSRIs compared with placebo: Statistics with one study removed, by drug**

| <b>Study Omitted</b>  | <b>Overall Estimate</b> | <b>95% Confidence Interval</b> |
|-----------------------|-------------------------|--------------------------------|
| Fluoxetine            |                         |                                |
| Connor, 1999          | -0.28                   | (-0.42 to -0.14)               |
| Martenyi, 2007 (20mg) | -0.34                   | (-0.52 to -0.16)               |
| Martenyi, 2007 (40mg) | -0.35                   | (-0.52 to -0.18)               |
| Martenyi, 2002        | -0.33                   | (-0.52 to -0.15)               |
| van der Kolk, 2007    | -0.33                   | (-0.48 to -0.17)               |
| van der Kolk, 1994    | -0.29                   | (-0.43 to -0.15)               |
| Combined              | -0.31                   | (-0.44 to -0.17)               |
| Paroxetine            |                         |                                |
| Marshall, 2001 (20mg) | -0.45                   | (-0.60 to -0.30)               |
| Marshall, 2001 (40mg) | -0.50                   | (-0.65 to -0.35)               |
| Tucker, 2001          | -0.51                   | (-0.65 to -0.36)               |
| Combined              | -0.49                   | (-0.61 to -0.37)               |
| Sertraline            |                         |                                |
| Brady, 2005           | -0.28                   | (-0.47 to -0.09)               |
| Brady, 2000           | -0.23                   | (-0.43 to -0.03)               |
| Davidson, 2006        | -0.27                   | (-0.49 to -0.05)               |
| Davidson, 2001        | -0.25                   | (-0.46 to -0.04)               |
| Friedman, 2007        | -0.30                   | (-0.46 to -0.14)               |
| Panahi, 2011          | -0.20                   | (-0.36 to -0.04)               |
| Tucker, 2004          | -0.26                   | (-0.44 to -0.07)               |
| Zohar, 2002           | -0.21                   | (-0.37 to -0.05)               |
| Combined              | -0.25                   | (-0.42 to -0.07)               |



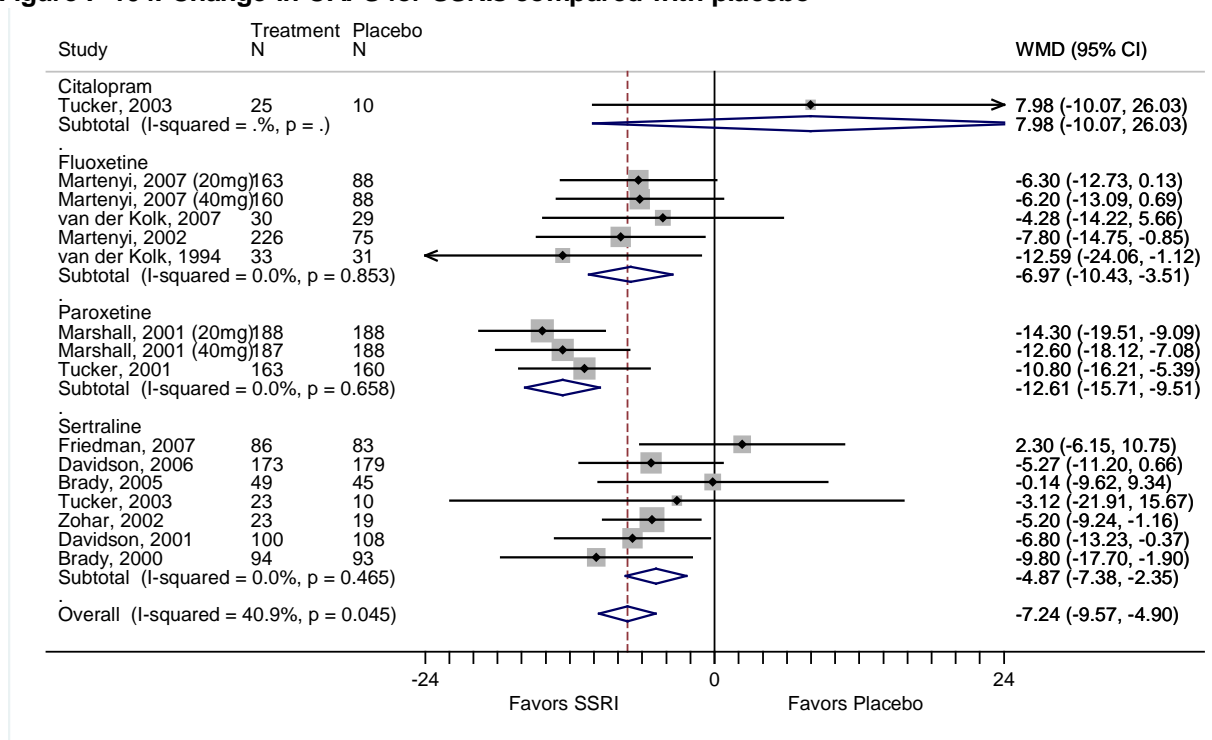
**Figure F-103. PTSD symptom reduction (any measure) for SSRIs compared with placebo: Sensitivity analysis including studies with high risk of bias**



Note: Hertzberg et al., 2000, and Marshall et al., 2007, were rated as having a high risk of bias.

Timing of outcome assessment: 10 weeks (Tucker, 2003; Marshall, 2007; Panahi, 2011; Tucker, 2004; Zohar, 2002), 12 weeks (Connor, 1999; Hertzberg, 2000; Martenyi, 2007; Marshall, 2001; Tucker, 2001; Brady, 2005; Brady, 2000; Davidson, 2001; Friedman, 2007), 8 weeks (van der Kolk, 2007), 5 weeks (van der Kolk, 1994), 24 weeks (Davidson, 2006).

**Figure F-104. Change in CAPS for SSRIs compared with placebo**

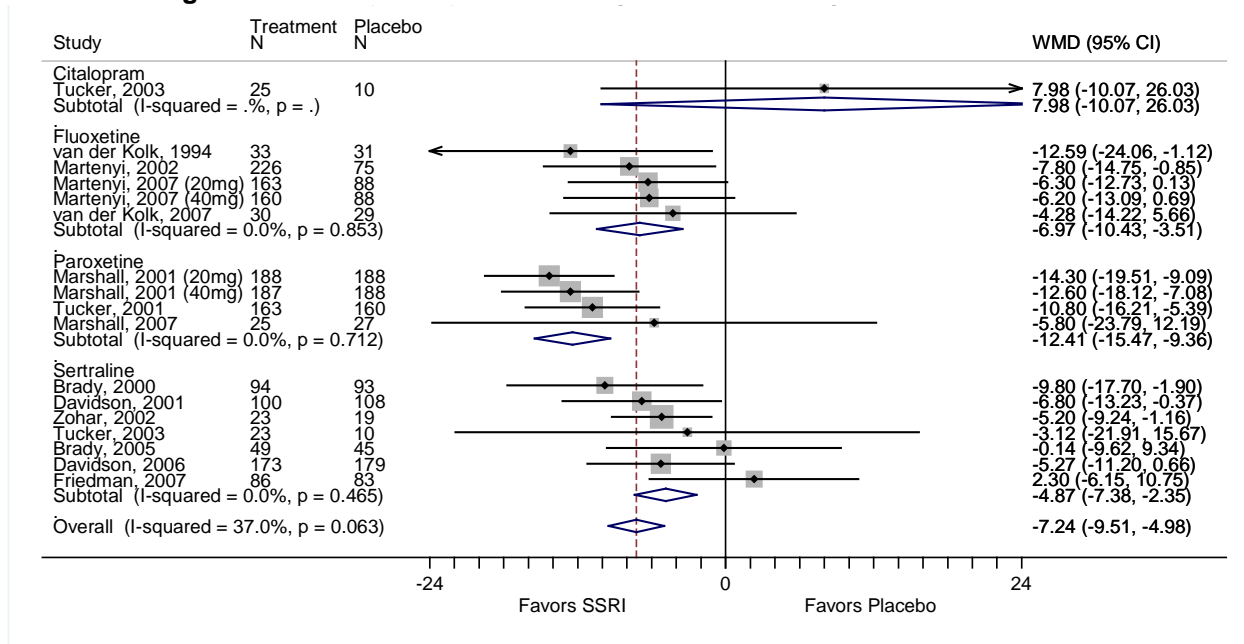


Timing of outcome assessment: 10 weeks (Tucker, 2003; Zohar, 2002), 12 weeks (Martenyi, 2007; Martenyi, 2002; Marshall, 2001; Tucker, 2001; Brady, 2005; Brady, 2000; Davidson, 2001; Friedman, 2007; Davidson, 2006), 8 weeks (van der Kolk, 2007), 5 weeks (van der Kolk, 1994).

**Table F-44. Change in CAPS for SSRIs compared with placebo: Statistics with one study removed, by drug**

| Study Omitted         | Overall Estimate | 95% Confidence Interval |
|-----------------------|------------------|-------------------------|
| <b>Fluoxetine</b>     |                  |                         |
| Martenyi, 2007 (20mg) | -7.25            | (-11.35, -3.15)         |
| Martenyi, 2007 (40mg) | -7.23            | (-11.23, -3.24)         |
| van der Kolk, 2007    | -7.34            | (-11.03, -3.66)         |
| Martenyi, 2002        | -6.70            | (-10.69, -2.71)         |
| van der Kolk, 1994    | -6.41            | (-10.04, -2.78)         |
| Combined              | -6.97            | (-10.43, -2.78)         |
| <b>Paroxetine</b>     |                  |                         |
| Marshall, 2001 (20mg) | -11.68           | (-15.54, -7.82)         |
| Marshall, 2001 (40mg) | -12.62           | (-16.37, -8.87)         |
| Tucker, 2001          | -13.50           | (-17.29, -9.71)         |
| Combined              | -12.61           | (-15.71, -9.51)         |
| <b>Sertraline</b>     |                  |                         |
| Friedman, 2007        | -5.56            | (-8.20, -2.93)          |
| Davidson, 2006        | -4.68            | (-7.77, -1.59)          |
| Brady, 2005           | -5.22            | (-7.83, -2.61)          |
| Tucker, 2003          | -4.84            | (-7.60, -2.08)          |
| Zohar, 2002           | -4.57            | (-8.03, -1.11)          |
| Davidson, 2001        | -4.47            | (-7.33, -1.62)          |
| Brady, 2000           | -4.31            | (-6.96, -1.65)          |
| Combined              | -4.87            | (-7.38, -2.35)          |

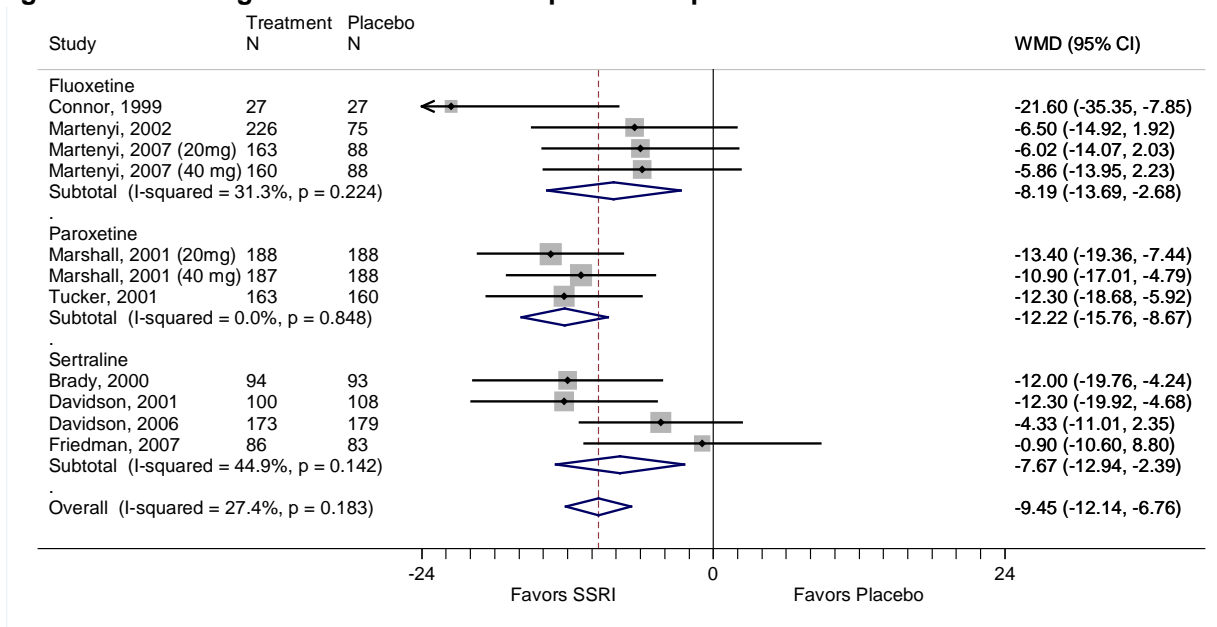
**Figure F-105. Change in CAPS for SSRIs compared with placebo: Sensitivity analysis including studies with high risk of bias**



Note: Marshall et al., 2007 was rated as high risk of bias.

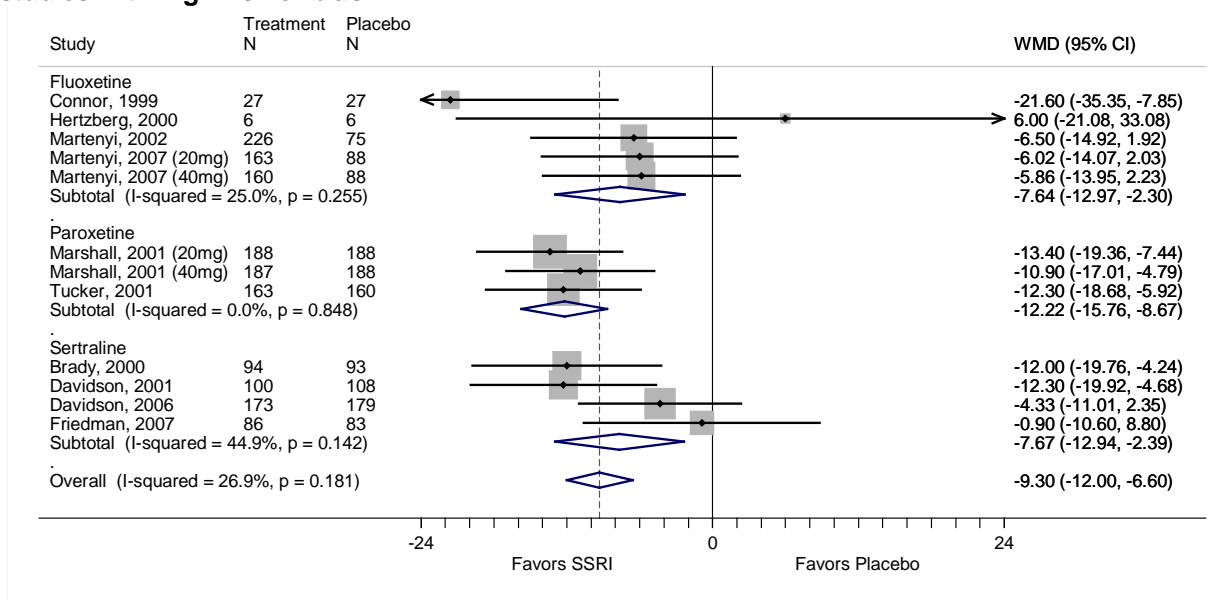
Timing of outcome assessment: 10 weeks (Tucker, 2003; Marshall, 2007; Zohar, 2002), 12 weeks (Martenyi, 2007; Martenyi, 2002; Marshall, 2001; Tucker, 2001; Brady, 2005; Brady, 2000; Davidson, 2001; Friedman, 2007; Davidson, 2006), 8 weeks (van der Kolk, 2007), 5 weeks (van der Kolk, 1994).

**Figure F-106. Change in DTS for SSRIs compared with placebo**



Timing of outcome assessment: 12 weeks for all included studies.

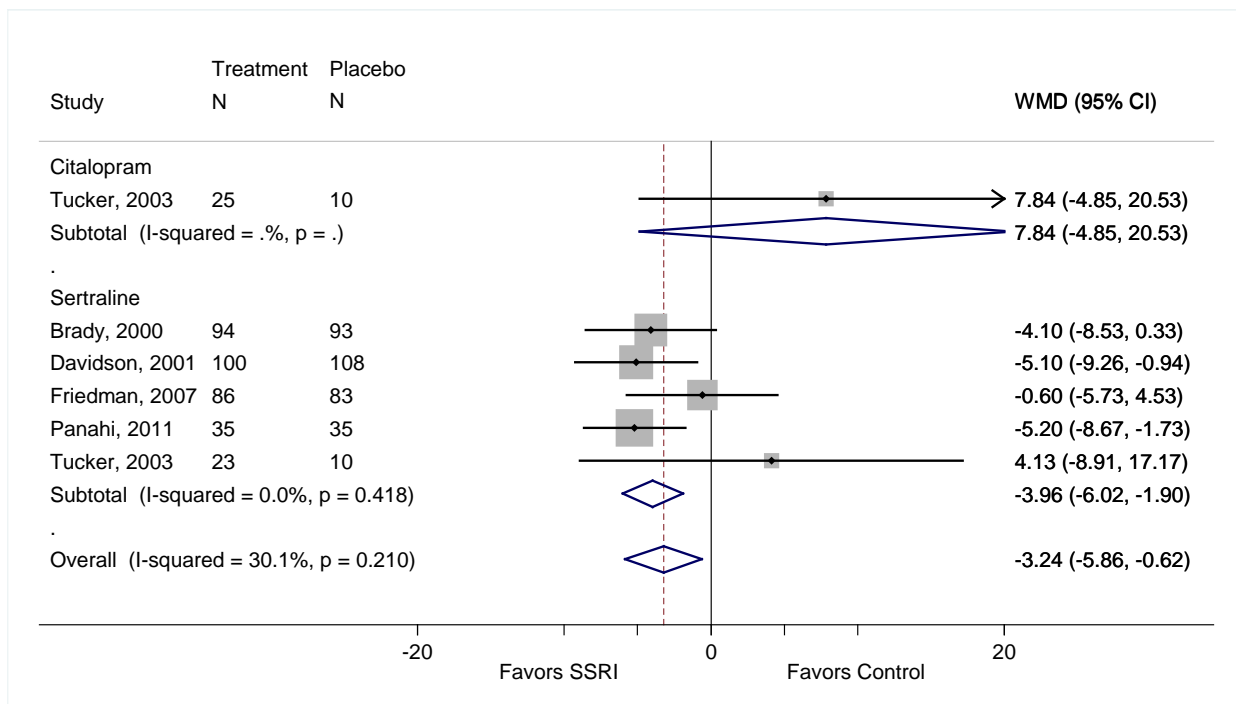
**Figure F-107. Change in DTS for SSRIs compared with placebo: Sensitivity analysis including studies with high risk of bias**



Note: Hertzberg et al., 2000 was rated as high risk of bias.

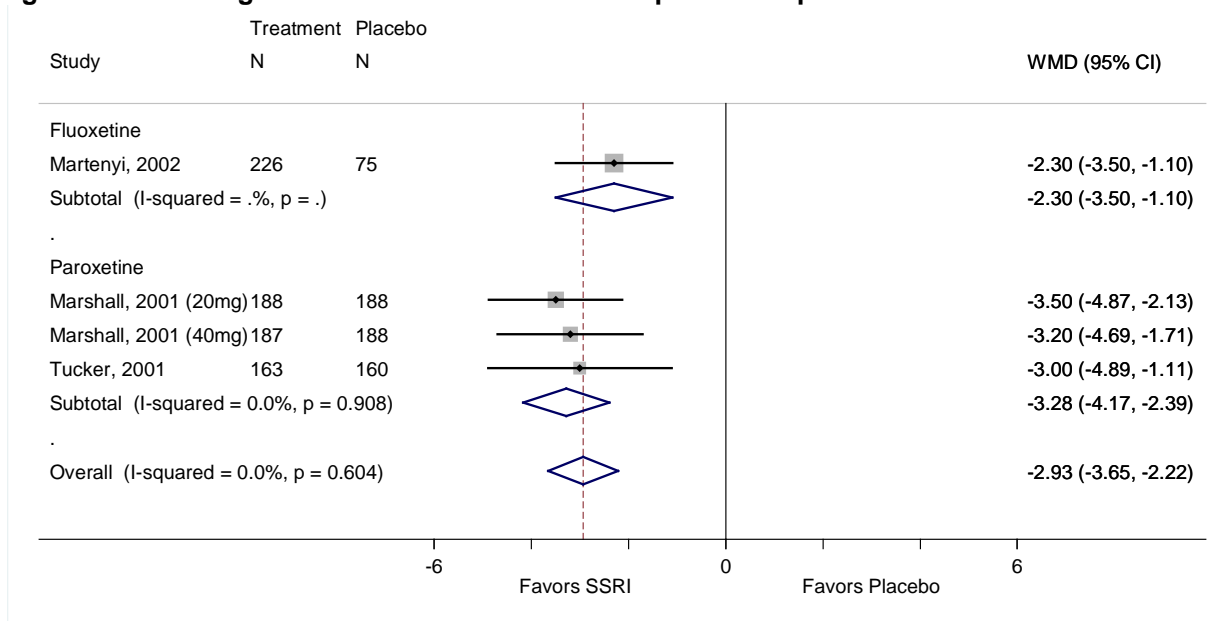
Timing of outcome assessment: 12 weeks for all included studies.

**Figure F-108. Change in IES for SSRIs compared with placebo**



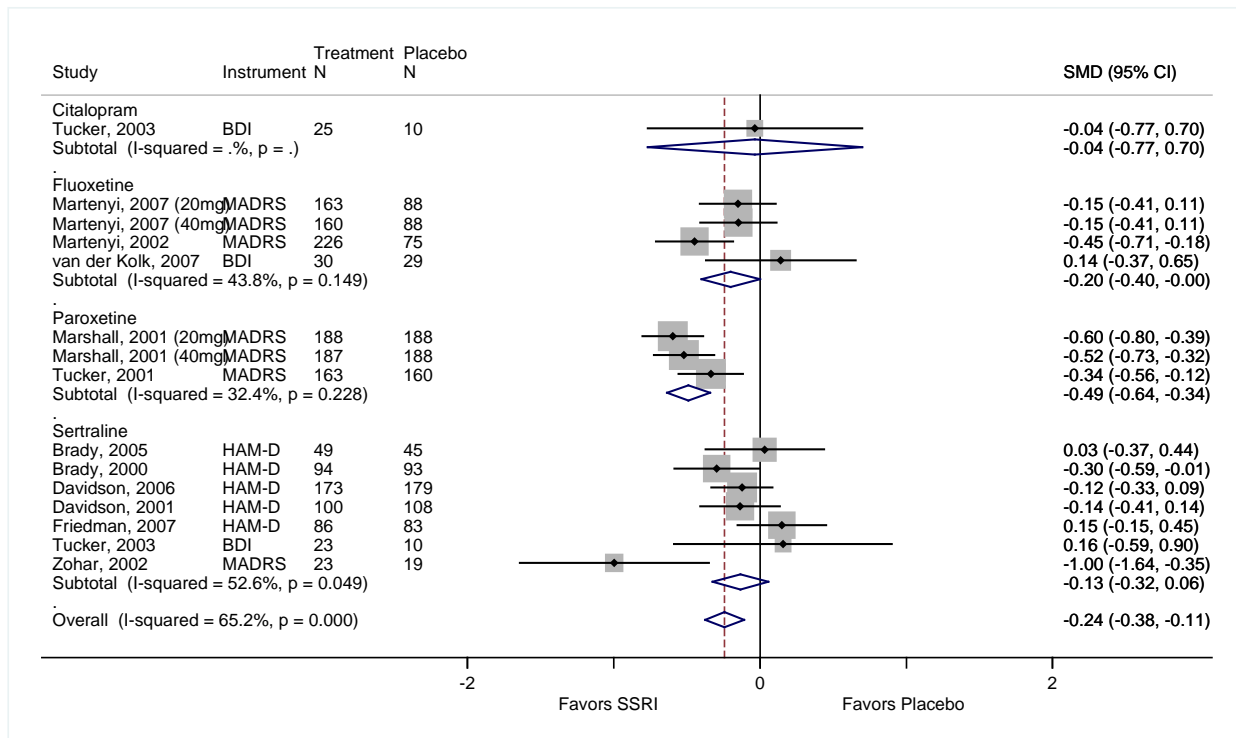
Timing of outcome assessment: 10 weeks (Tucker, 2003; Panahi, 2011), 12 weeks (Brady, 2000; Davidson, 2001; Friedman, 2007).

**Figure F-109. Change in TOPS/TOP-8 for SSRIs compared with placebo**



Timing of outcome assessment: 12 weeks for all included studies.

**Figure F-110. Depression symptom reduction (any measure) for SSRIs compared with placebo**



Timing of outcome assessment: 10 weeks (Tucker, 2003; Zohar, 2002), 12 weeks (Martenyi, 2007; Martenyi, 2002; Marshall, 2001; Tucker, 2001; Brady, 2005; Brady, 2000; Davidson, 2001; Friedman, 2007; Davidson, 2006), 8 weeks (van der Kolk, 2007).

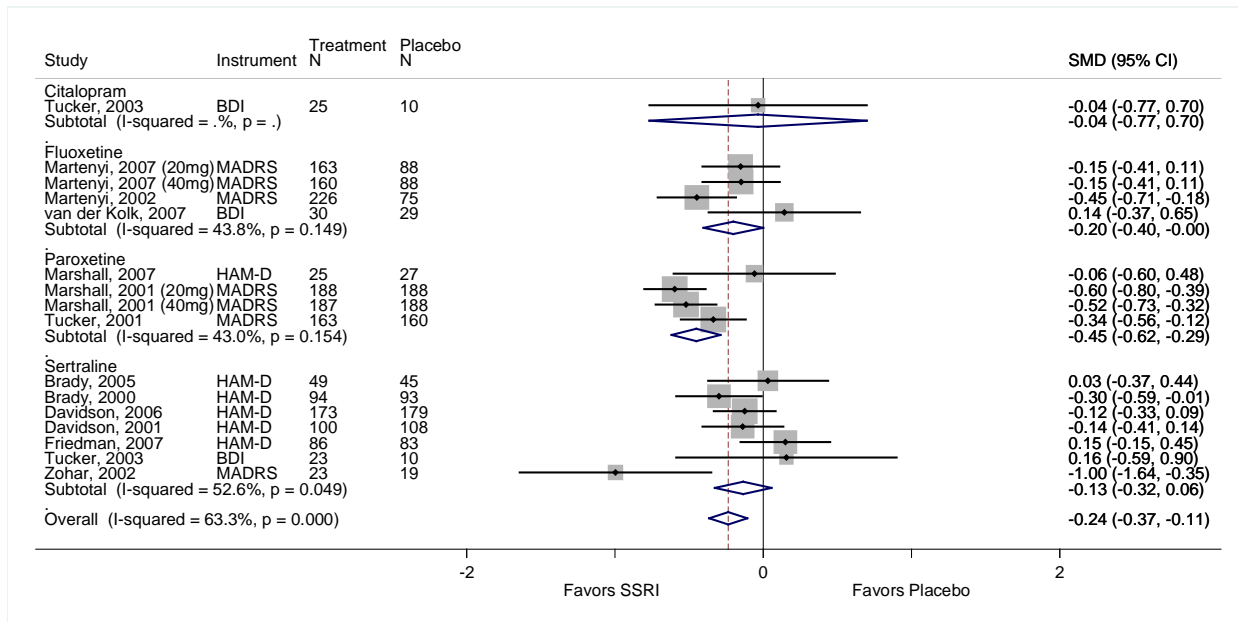
**Table F-45. Depression symptom reduction (any measure) for SSRIs compared with placebo: Statistics with one study removed**

| <b>Study Omitted</b>  | <b>Overall Estimate</b> | <b>95% Confidence Interval</b> |
|-----------------------|-------------------------|--------------------------------|
| Tucker, 2003          | -0.25                   | (-0.38 to -0.11)               |
| Martenyi, 2007 (20mg) | -0.25                   | (-0.39 to -0.11)               |
| Martenyi, 2007 (40mg) | -0.25                   | (-0.39 to -0.11)               |
| Martenyi, 2002        | -0.22                   | (-0.37 to -0.08)               |
| van der Kolk, 2007    | -0.26                   | (-0.39 to -0.13)               |
| Marshall, 2001 (20mg) | -0.21                   | (-0.34 to -0.08)               |
| Marshall, 2001 (40mg) | -0.22                   | (-0.35 to -0.08)               |
| Tucker, 2001          | -0.23                   | (-0.38 to -0.09)               |
| Brady, 2005           | -0.26                   | (-0.40 to -0.12)               |
| Brady, 2000           | -0.24                   | (-0.38 to -0.09)               |
| Davidson, 2006        | -0.25                   | (-0.40 to -0.11)               |
| Davidson, 2001        | -0.25                   | (-0.39 to -0.11)               |
| Friedman, 2007        | -0.28                   | (-0.40 to -0.15)               |
| Tucker, 2004          | -0.25                   | (-0.39 to -0.12)               |
| Zohar, 2002           | -0.22                   | (-0.35 to -0.09)               |
| Combined              | -0.24                   | (-0.38 to -0.11)               |

**Table F-46. Depression symptom reduction (any measure) for SSRIs compared with placebo: Statistics with one study removed, by drug**

| <b>Study Omitted</b>  | <b>Overall Estimate</b> | <b>95% Confidence Interval</b> |
|-----------------------|-------------------------|--------------------------------|
| <b>Fluoxetine</b>     |                         |                                |
| Martenyi, 2007 (20mg) | -0.21                   | (-0.50 to -0.09)               |
| Martenyi, 2007 (40mg) | -0.21                   | (-0.50 to -0.09)               |
| Martenyi, 2002        | -0.12                   | (-0.29 to -0.06)               |
| van der Kolk, 2007    | -0.25                   | (-0.44 to -0.06)               |
| Combined              | -0.20                   | (-0.40 to -0.00)               |
| <b>Paroxetine</b>     |                         |                                |
| Marshall, 2001 (20mg) | -0.43                   | (-0.61 to -0.25)               |
| Marshall, 2001 (40mg) | -0.47                   | (-0.72 to -0.22)               |
| Tucker, 2001          | -0.56                   | (-0.70 to -0.41)               |
| Combined              | -0.49                   | (-0.64 to -0.34)               |
| <b>Sertraline</b>     |                         |                                |
| Brady, 2005           | -0.16                   | (-0.37 to 0.05)                |
| Brady, 2000           | -0.10                   | (-0.32 to 0.12)                |
| Davidson, 2006        | -0.15                   | (-0.40 to 0.11)                |
| Davidson, 2001        | -0.14                   | (-0.38 to 0.10)                |
| Friedman, 2007        | -0.19                   | (-0.38 to 0.00)                |
| Tucker, 2004          | -0.15                   | (-0.35 to 0.05)                |
| Zohar, 2002           | -0.09                   | (-0.22 to 0.04)                |
| Combined              | -0.13                   | (-0.32 to 0.06)                |

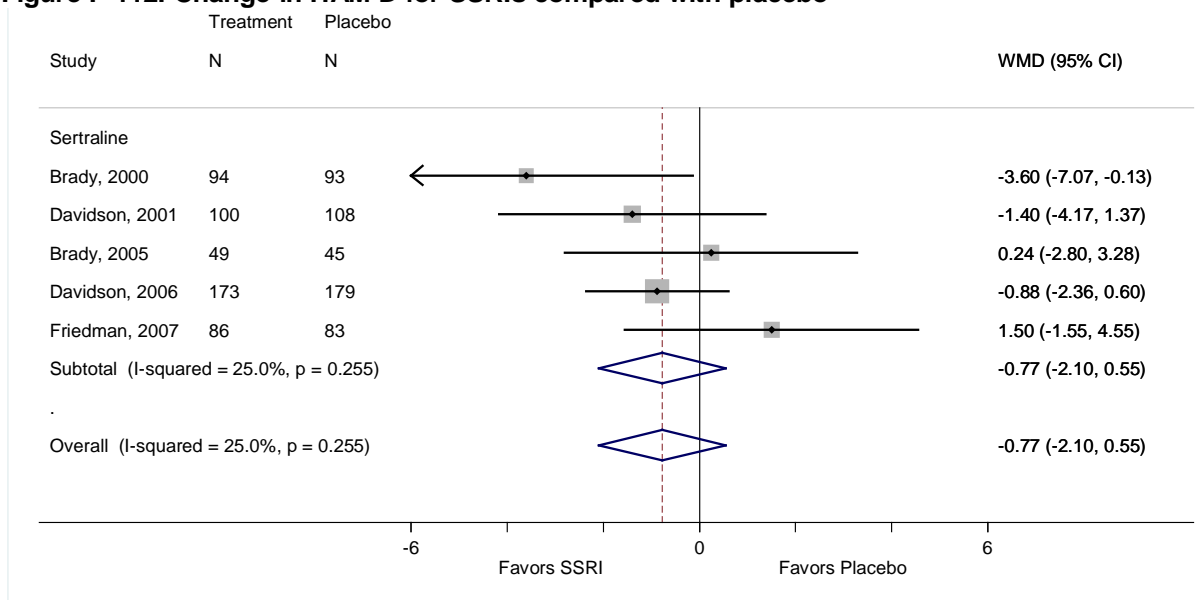
**Figure F-111. Depression symptom reduction (any measure) for SSRIs compared with placebo: Sensitivity analysis including studies with high risk of bias**



Note: Marshall et al., 2007 was rated as high risk of bias.

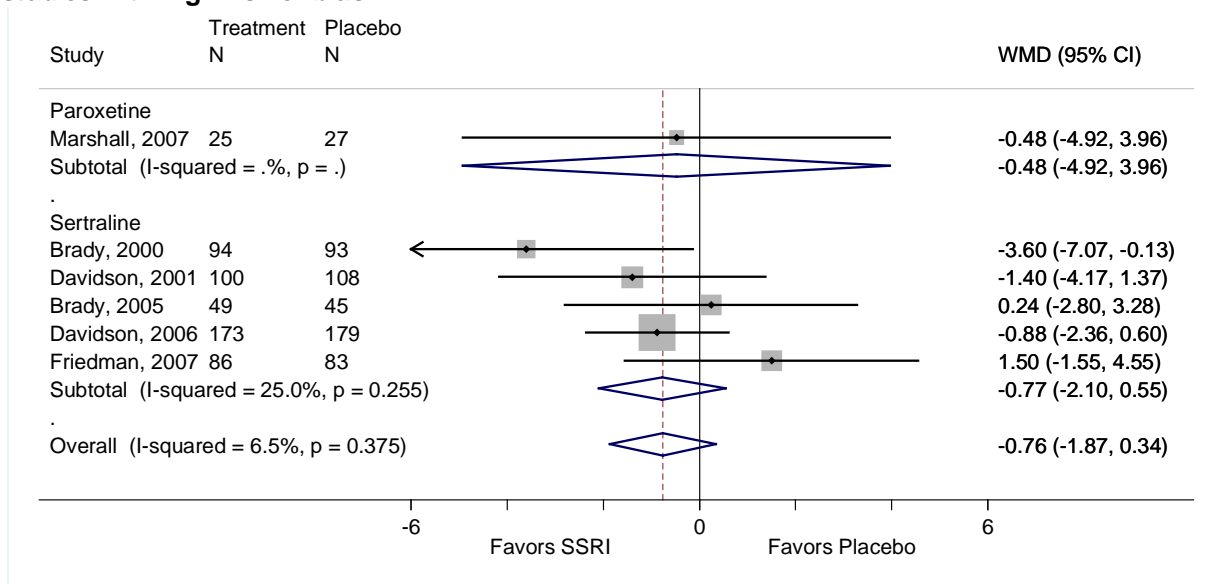
Timing of outcome assessment: 10 weeks (Tucker, 2003; Marshall, 2007; Zohar, 2002), 12 weeks (Martenyi, 2007; Martenyi, 2002; Marshall, 2001; Tucker, 2001; Brady, 2005; Brady, 2000; Davidson, 2001; Friedman, 2007; Davidson, 2006), 8 weeks (van der Kolk, 2007).

**Figure F-112. Change in HAM-D for SSRIs compared with placebo**



Timing of outcome assessment: 12 weeks for all included studies.

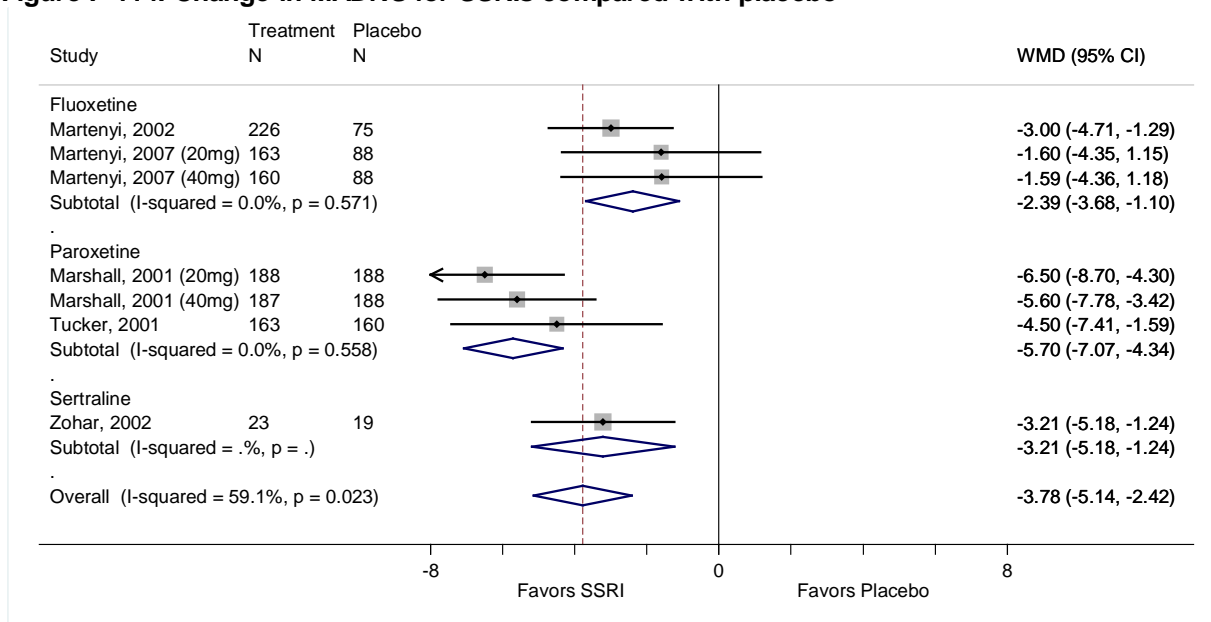
**Figure F-113. Change in HAM-D for SSRIs compared with placebo: Sensitivity analysis including studies with high risk of bias**



Note: Marshall et al., 2007 was rated as high risk of bias.

Timing of outcome assessment: 10 weeks (Marshall, 2007), 12 weeks (Brady, 2005; Brady, 2000; Davidson, 2001; Friedman, 2007; Davidson, 2006).

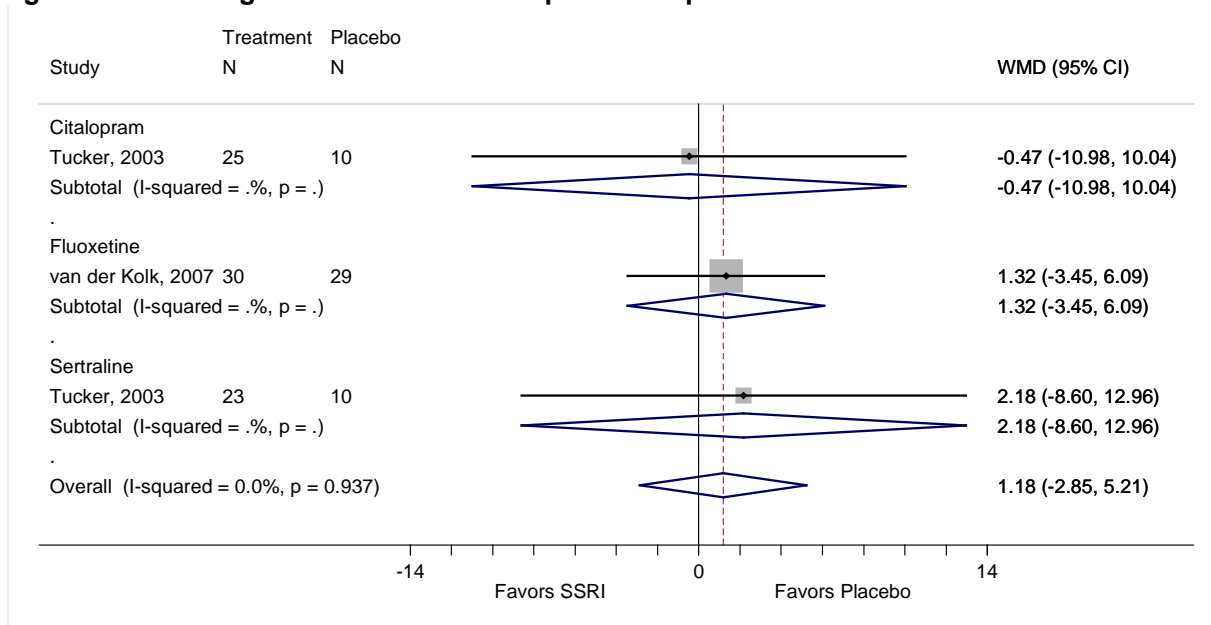
**Figure F-114. Change in MADRS for SSRIs compared with placebo**



Timing of outcome assessment: 10 weeks (Zohar, 2002), 12 weeks (Martenyi, 2007; Martenyi, 2002; Marshall, 2001; Tucker, 2001).

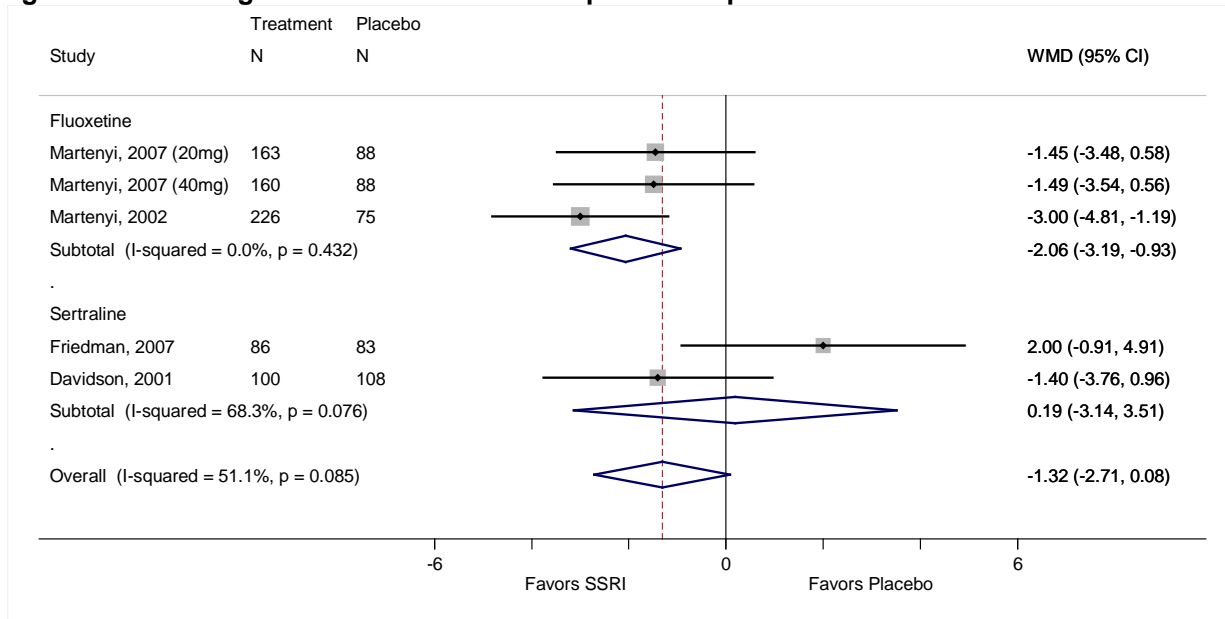


**Figure F-115. Change in BDI for SSRIs compared with placebo**



Timing of outcome assessment: 10 weeks (Tucker, 2003), 12 weeks (van der Kolk, 2007).

**Figure F-116. Change in HAM-A for SSRIs compared with placebo**

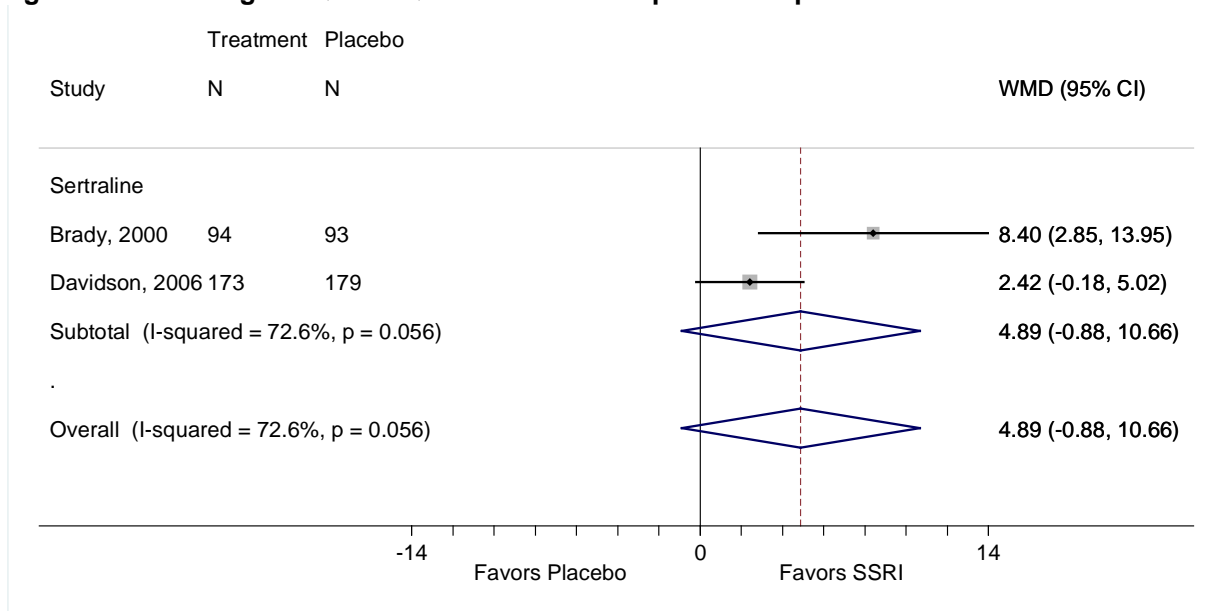


Timing of outcome assessment: 12 weeks for all included studies.

**Table F-47. Change in HAM-A for SSRIs compared with placebo: Statistics with one study removed, by drug**

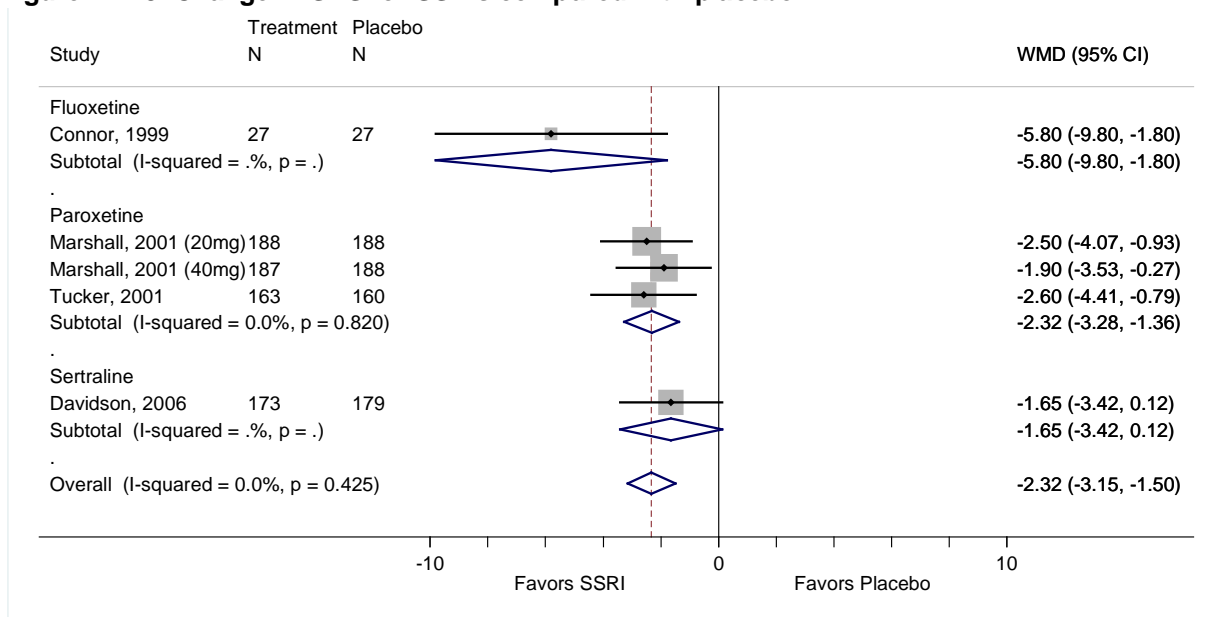
| Study Omitted         | Overall Estimate | 95% Confidence Interval |
|-----------------------|------------------|-------------------------|
| <b>Fluoxetine</b>     |                  |                         |
| Martenyi, 2007 (20mg) | -2.32            | (-3.79 to -0.85)        |
| Martenyi, 2007 (40mg) | -2.30            | (-3.81 to -0.78)        |
| Martenyi, 2002        | -1.47            | (-2.91 to -0.03)        |
| Combined              | -2.06            | (-3.19 to -0.93)        |
| <b>Sertraline</b>     |                  |                         |
| Friedman, 2007        | -1.40            | (-3.76 to 0.96)         |
| Davidson, 2001        | 2.00             | (-0.91 to 4.91)         |
| Combined              | 0.19             | (-3.14 to 3.51)         |

**Figure F-117. Change in Q-LES-Q-SF for SSRIs compared with placebo**



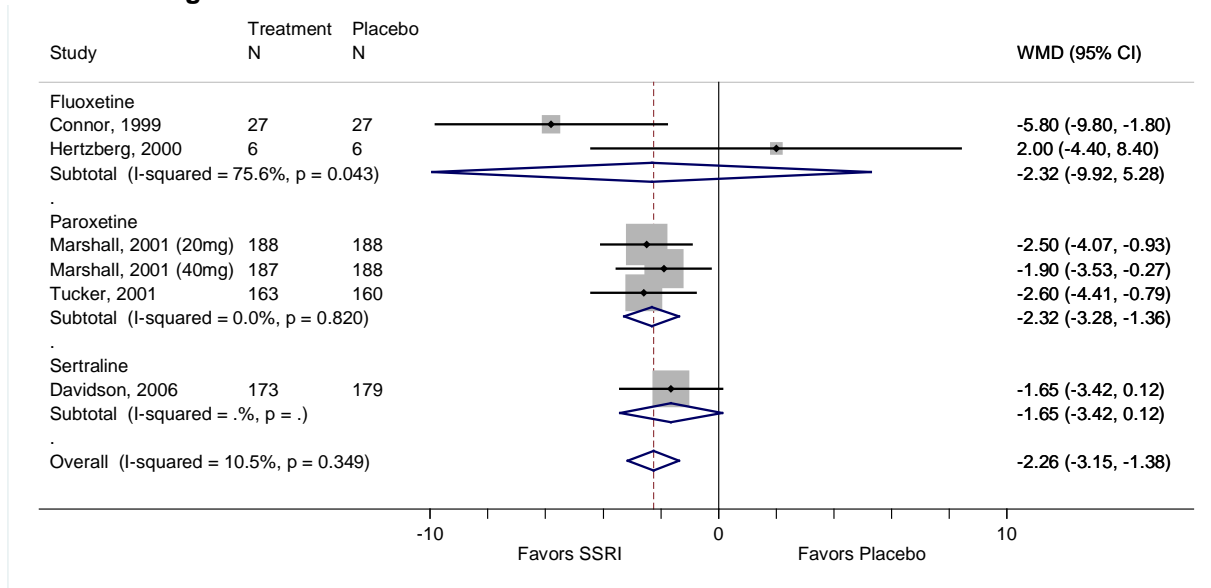
Timing of outcome assessment: 12 weeks for all included studies.

**Figure F-118. Change in SDS for SSRIs compared with placebo**



Timing of outcome assessment: 12 weeks for all included studies.

**Figure F-119. Change in SDS for SSRIs compared with placebo: Sensitivity analysis including studies with high risk of bias**



Note: Hertzberg et al., 2000 was rated as high risk of bias.

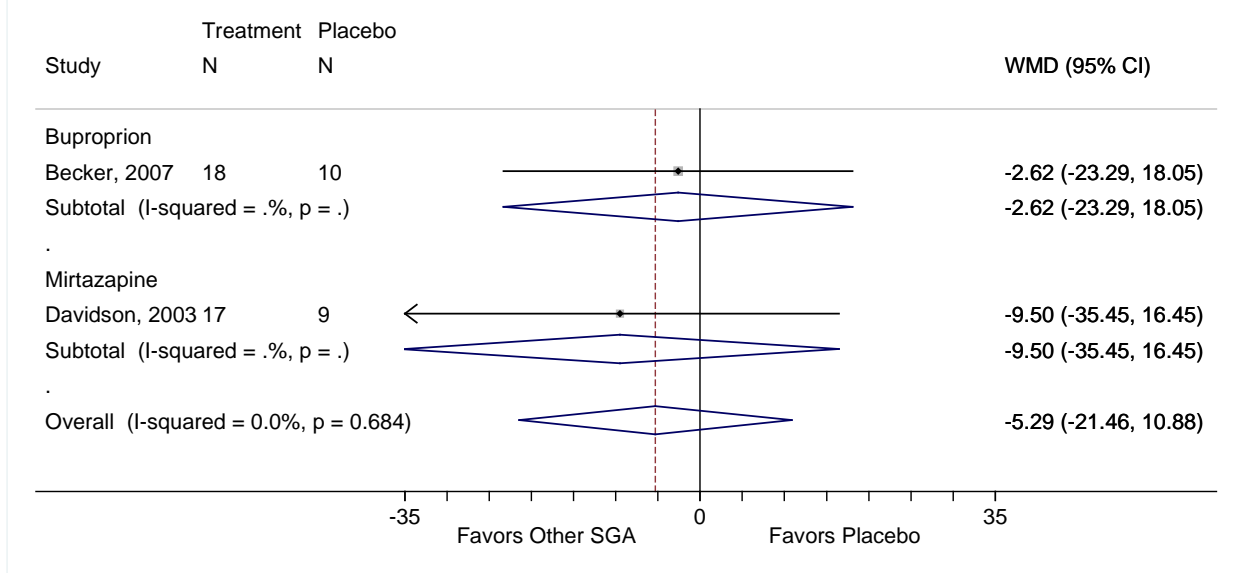
Timing of outcome assessment: 12 weeks for all included studies.

# Tricyclic Antidepressants: Meta-Analysis Results

None

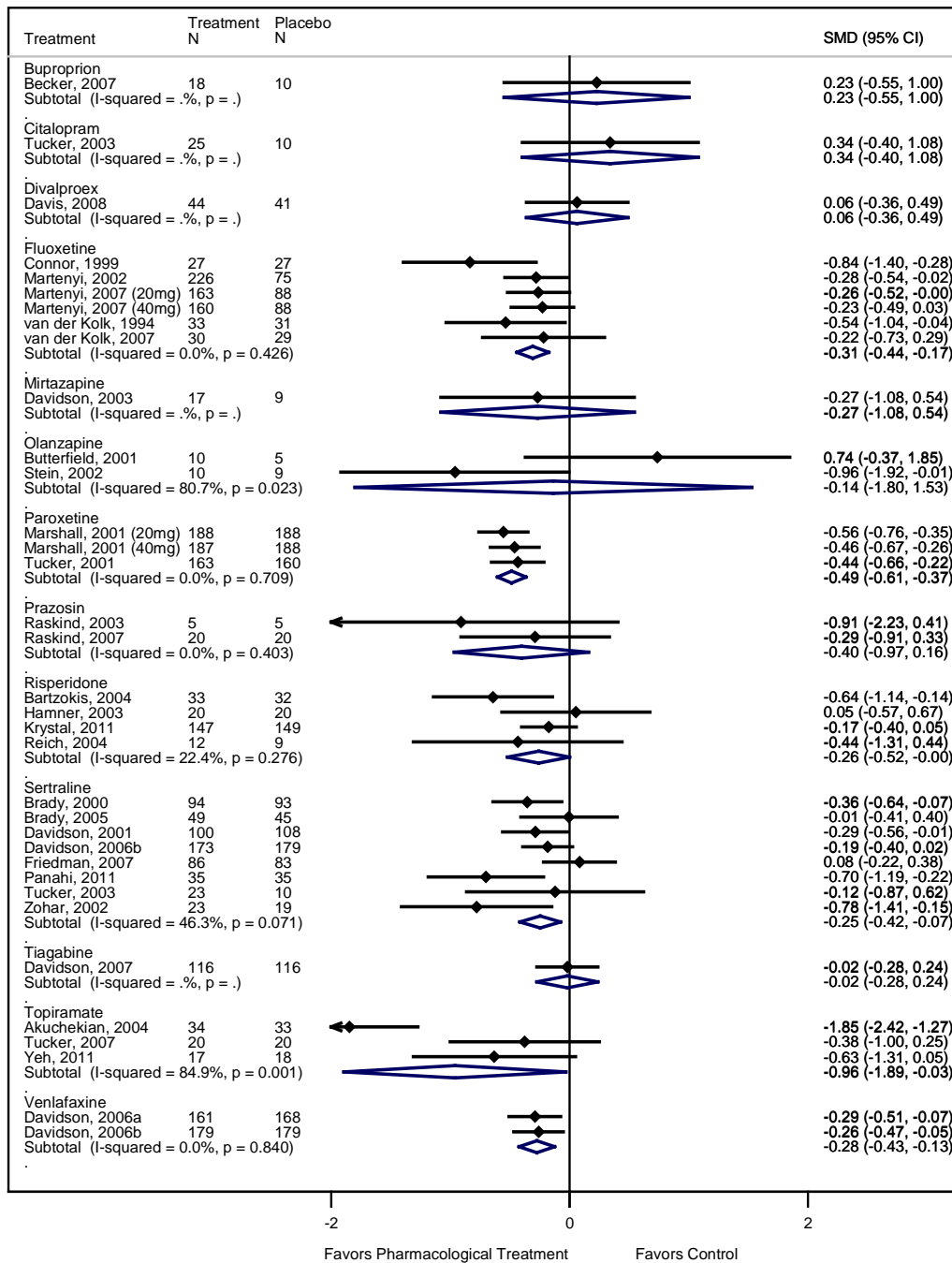
# Other Second-Generation Antidepressants: Meta-Analysis Results

Figure F-120. Change in DTS for other second-generation antidepressants compared with placebo



Timing of outcome assessment: 8 weeks for all included studies.

**Figure F-121. PTSD symptom reduction (any measure) for pharmacological treatments compared with placebo**



Timing of outcome assessment: 8 weeks (Becker, 2007; Davis, 2008; van der Kolk, 2007; Davidson, 2003; Stein, 2002; Raskind, 2007; Reich, 2004), 10 weeks (Tucker, 2003; Butterfield, 2001; Panahi, 2011; Zohar, 2002), 12 weeks (Connor, 1999; Martenyi, 2007; Martenyi, 2002; Marshall, 2001; Tucker, 2001; Brady, 2005; Brady, 2000; Davidson, 2001; Friedman, 2007; Davidson, 2006b; Davidson, 2007; Akuchekian, 2004; Tucker, 2007; Yeh, 2011), 5 weeks (van der Kolk, 1994; Hamner, 2003), 20 weeks (Raskind, 2003), 16 weeks (Bartzokis, 2004); 24 weeks (Davidson, 2006a).

# Network Meta-Analysis of Pharmacotherapy Trials

Figure F-122. Change in CAPS total score

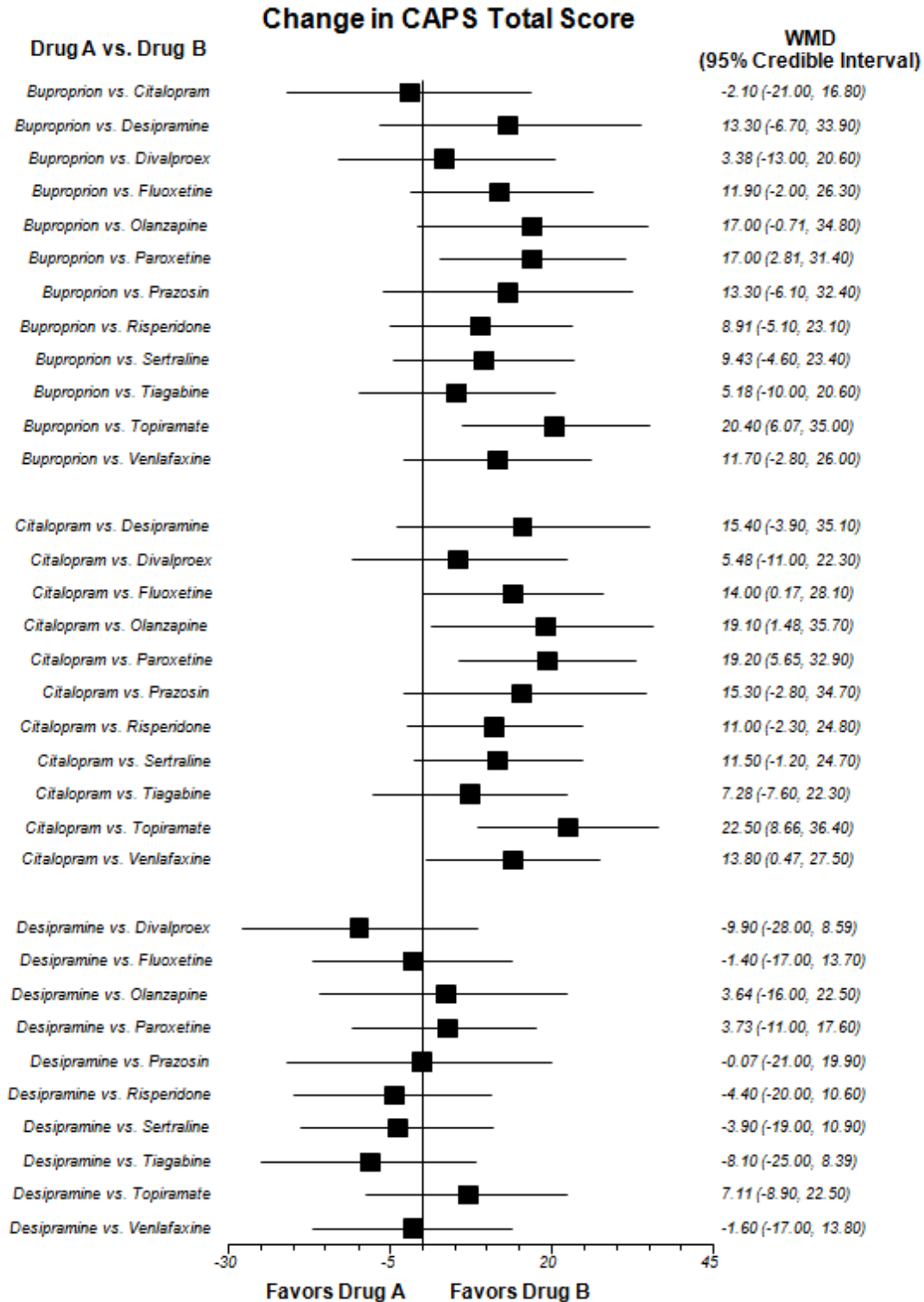


Figure F-122. Change in CAPS total score (continued)

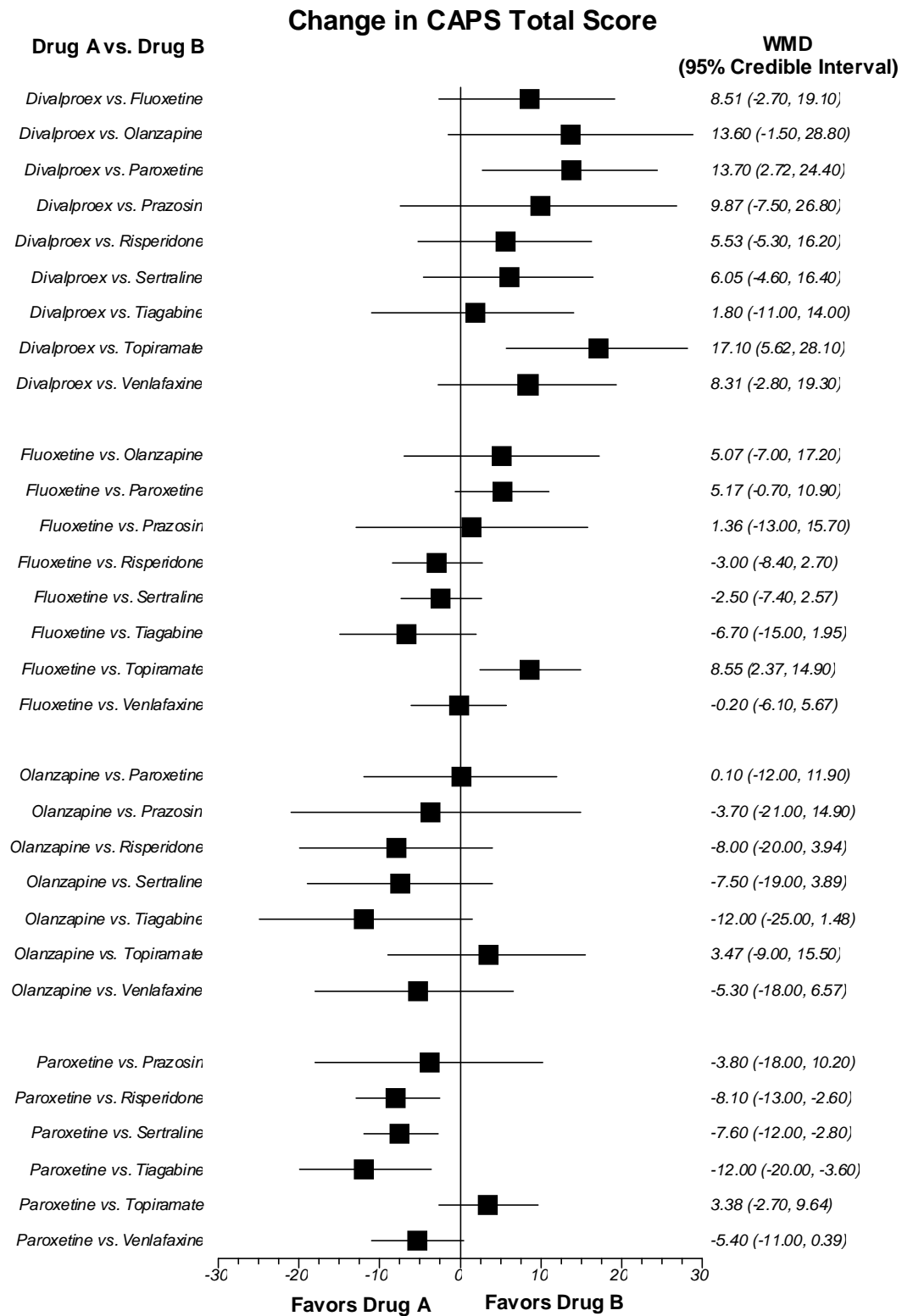
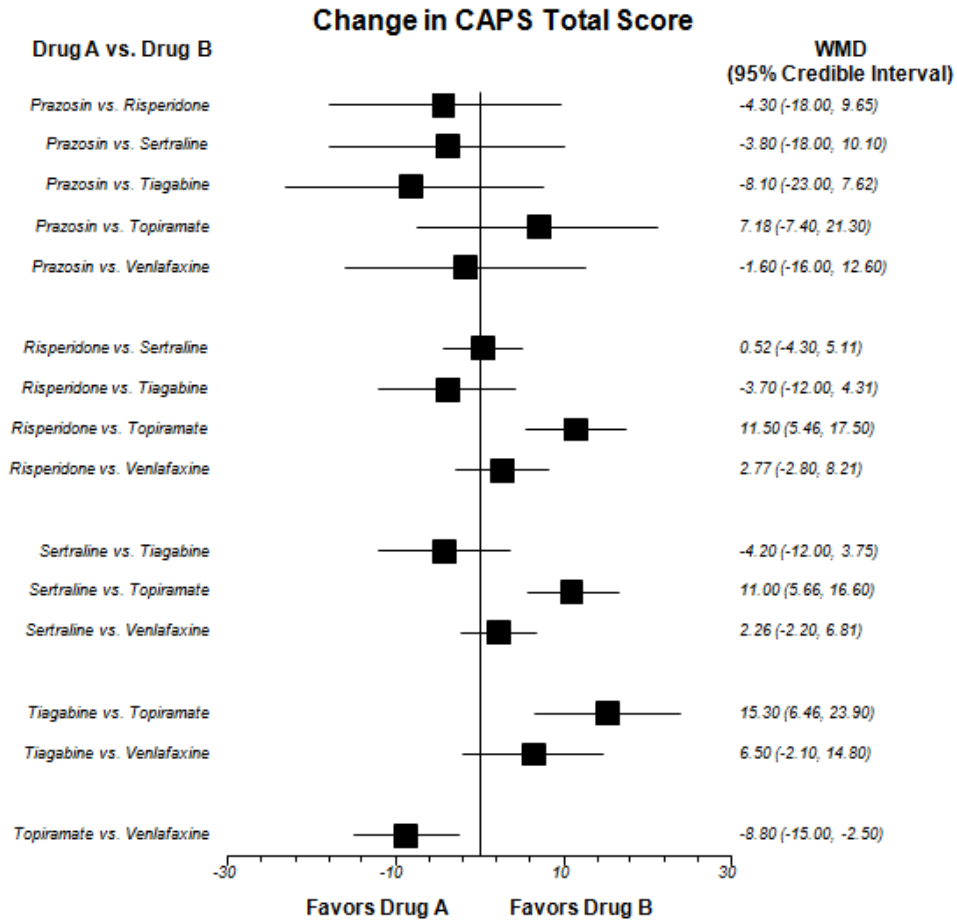
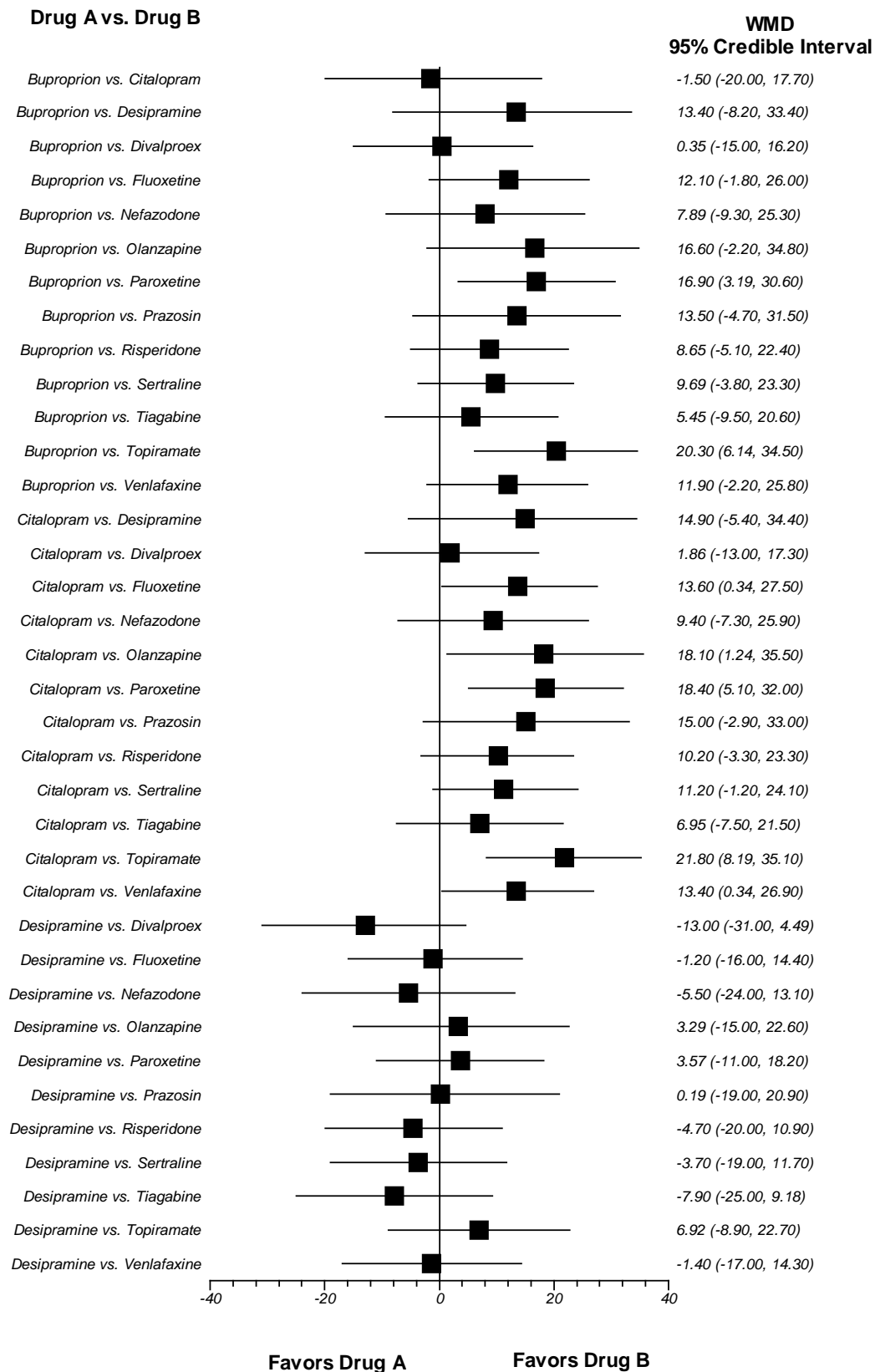




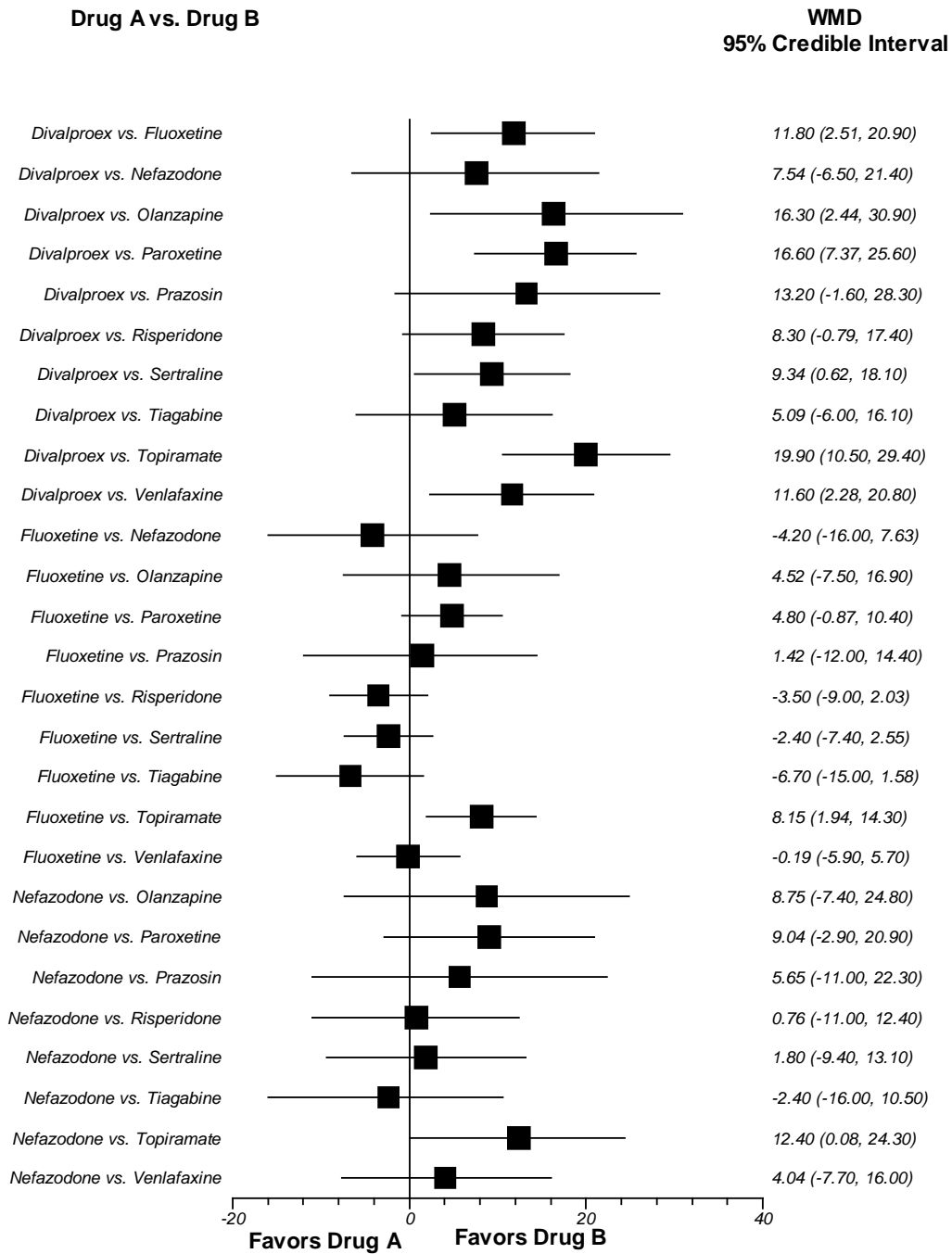
Figure F-122. Change in CAPS total score (continued)



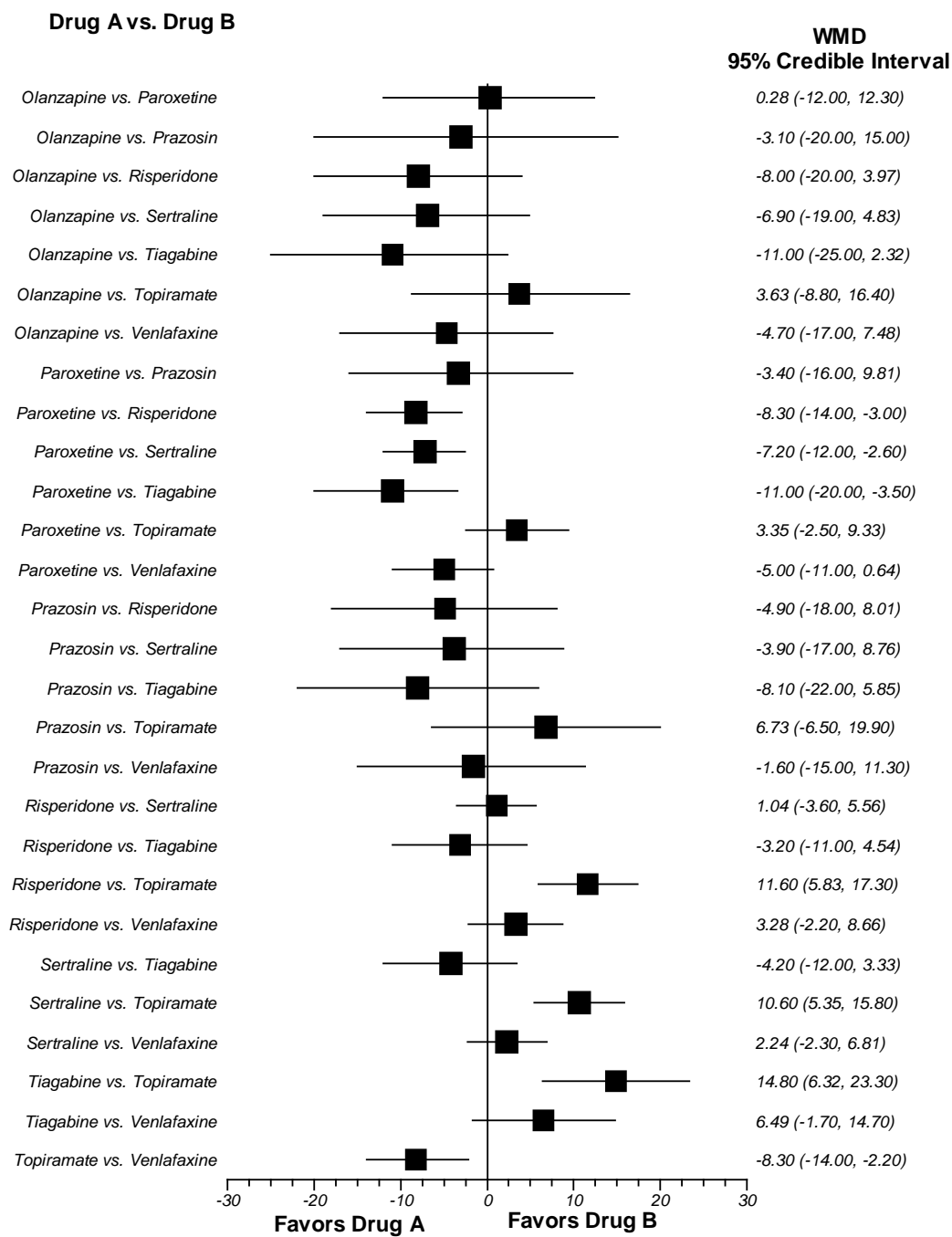
**Figure F-123. Change in CAPS total score: Sensitivity analysis**



**Figure F-123. Change in CAPS total score: Sensitivity analysis (continued)**



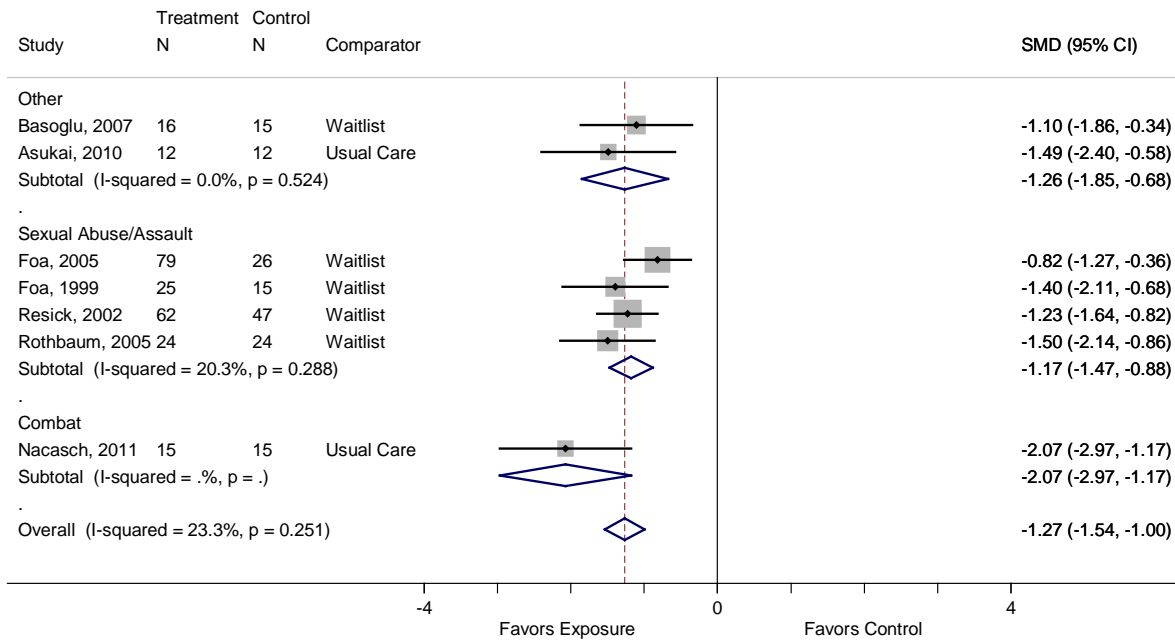
**Figure F-123. Change in CAPS total score: Sensitivity analysis (continued)**



## Key Question 5

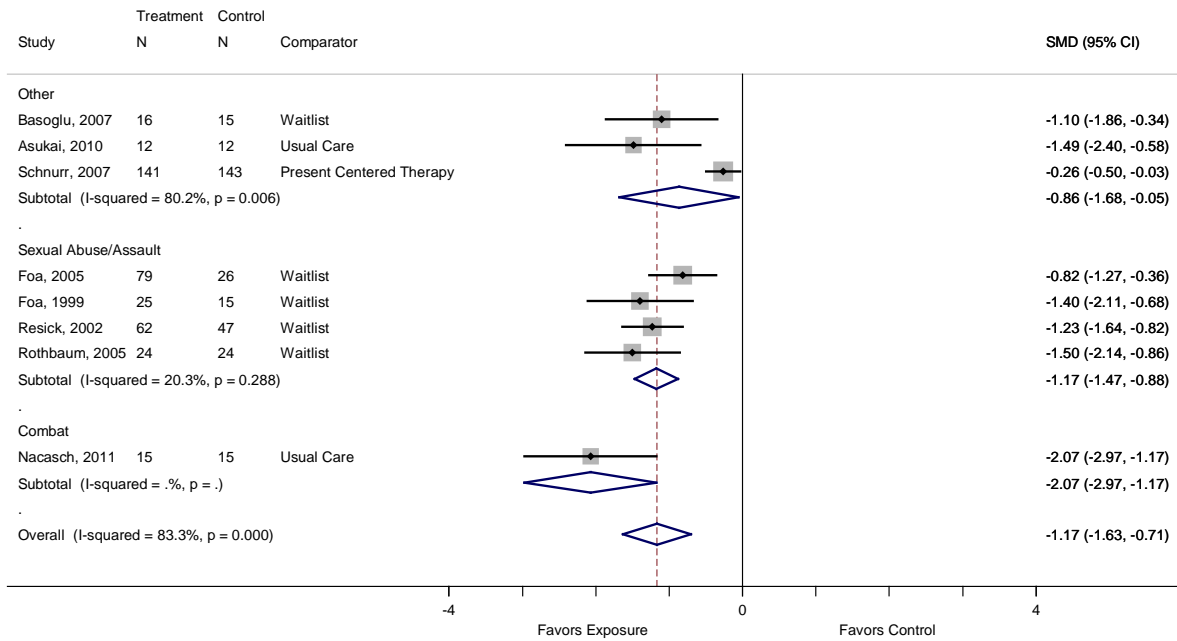
### CBT Exposure-Based Therapy: Meta-Analysis Results

Figure F-124. PTSD symptom reduction for exposure compared with control, by trauma population



Timing of outcome assessment: 1 session (Basoglu, 2007), 8 to 15 sessions (Asukai, 2010), 12 weeks (Foa, 2005), 9 weeks (Foa, 1999), 6 weeks (Resick, 2002), 4.5 weeks (Rothbaum), 9 to 15 weeks (Nacasch, 2011).

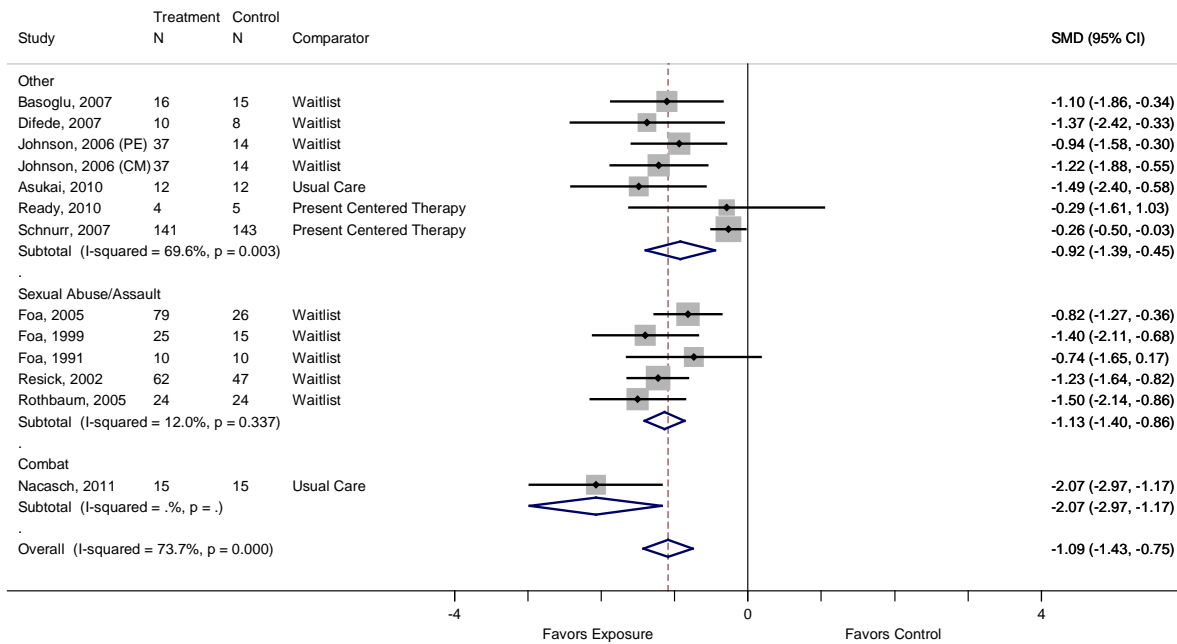
**Figure F-125. PTSD symptom reduction for exposure compared with control, by trauma population: Sensitivity analysis including other comparators**



Note: Schnurr et al, 2007 was rated as high risk of bias.

Timing of outcome assessment: 1 session (Basoglu, 2007), 8 to 15 sessions (Asukai, 2010), 10 weeks (Schnurr, 2007), 12 weeks (Foa, 2005), 9 weeks (Foa, 1999), 6 weeks (Resick, 2002), 4.5 weeks (Rothbaum), 9 to 15 weeks (Nacasch, 2011).

**Figure F-126. PTSD symptom reduction for exposure compared with control, by trauma population: Sensitivity analysis including other comparators and studies with high risk of bias**

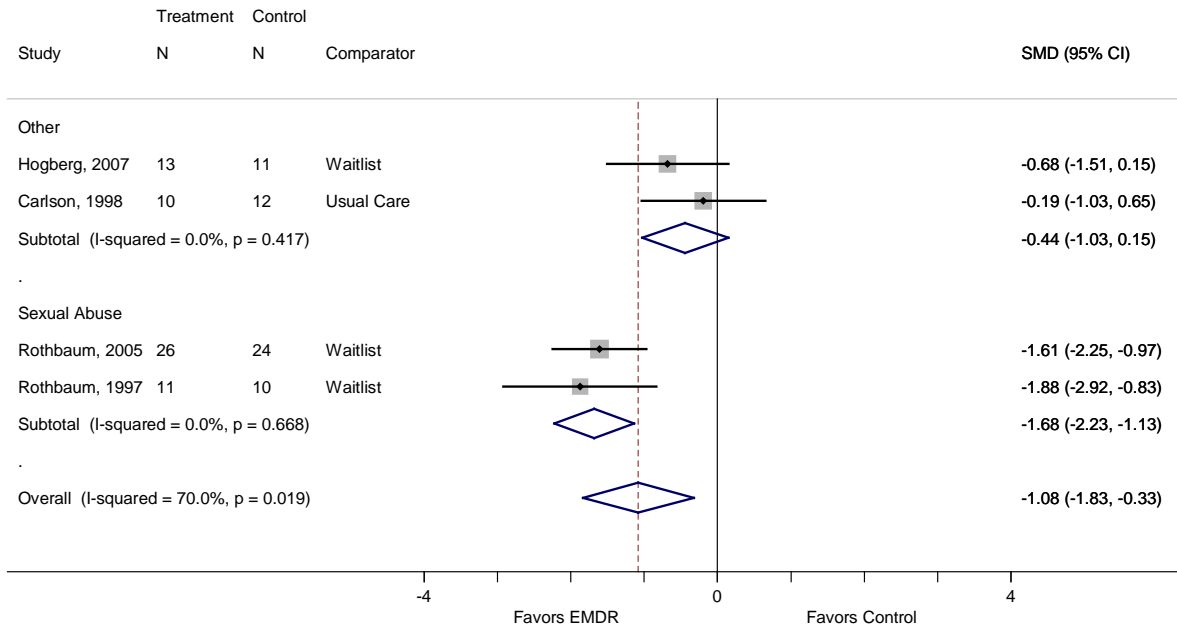


Note: Ready et al., 2010, Difede et al., 2007, Johnson et al., 2006, and Foa et al., 1991 were rated as high risk of bias.

Timing of outcome assessment: 1 session (Basoglu, 2007), 24 weeks (Difede, 2007), mean number of sessions for PE = 9.66 (Johnson, 2006), 8 to 15 sessions (Asukai, 2010), 10 sessions (Ready, 2010), 10 weeks (Schnurr, 2007), 12 weeks (Foa, 2005), 9 weeks (Foa, 1999), 9 weeks (Foa, 1991), 6 weeks (Resick, 2002), 4.5 weeks (Rothbaum), 9 to 15 weeks (Nacasch, 2011).

# EMDR: Meta-Analysis Results

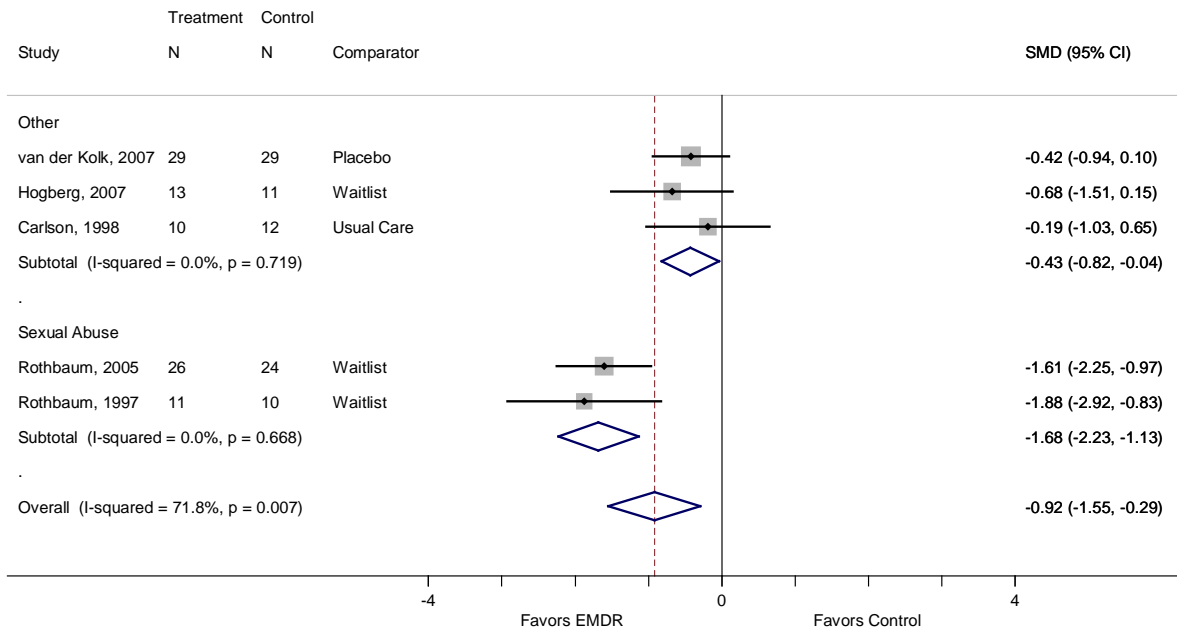
Figure F-127. PTSD symptom reduction for EMDR compared with control, by trauma population



Timing of outcome assessment: 4 months (Hogberg, 2007), 6 weeks (Carlson, 1988), 4.5 weeks (Rothbaum, 2005), 4 weeks (Rothbaum).

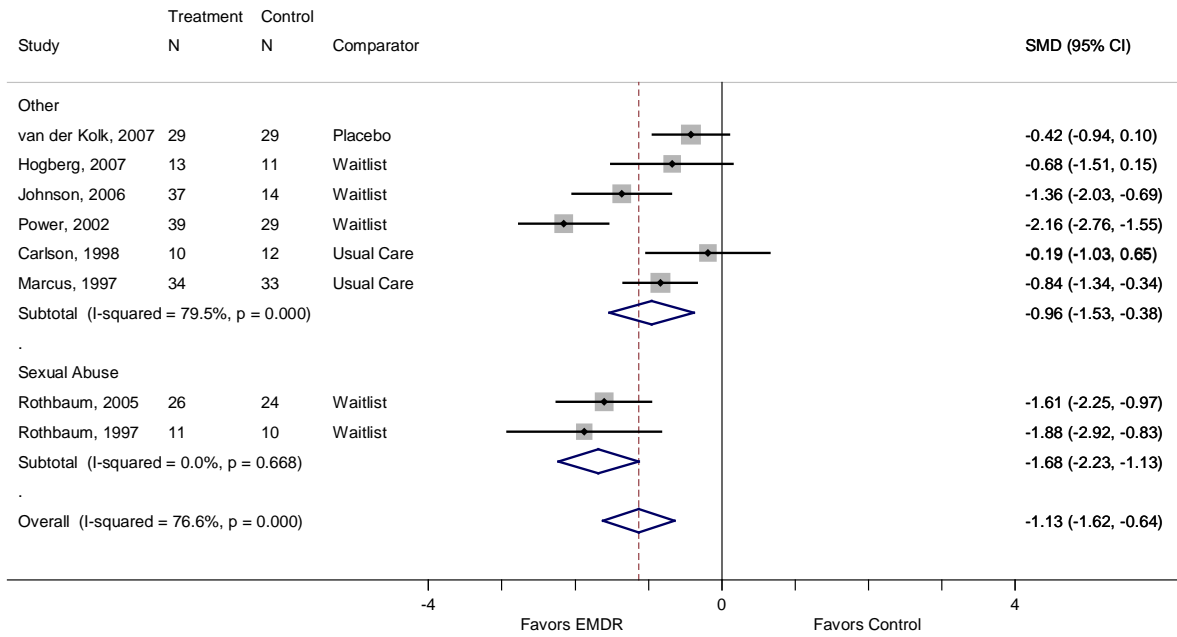


**Figure F-128. PTSD symptom reduction for EMDR compared with control, by trauma population: Sensitivity analysis including other comparators**



Timing of outcome assessment: 8 weeks (van der Kolk, 2007), 4 months (Hogberg, 2007), 6 weeks (Carlson, 1988), 4.5 weeks (Rothbaum, 2005), 4 weeks (Rothbaum).

**Figure F-129. PTSD symptom reduction for EMDR compared with control, by trauma population: Sensitivity analysis including other comparators and studies with high risk of bias**

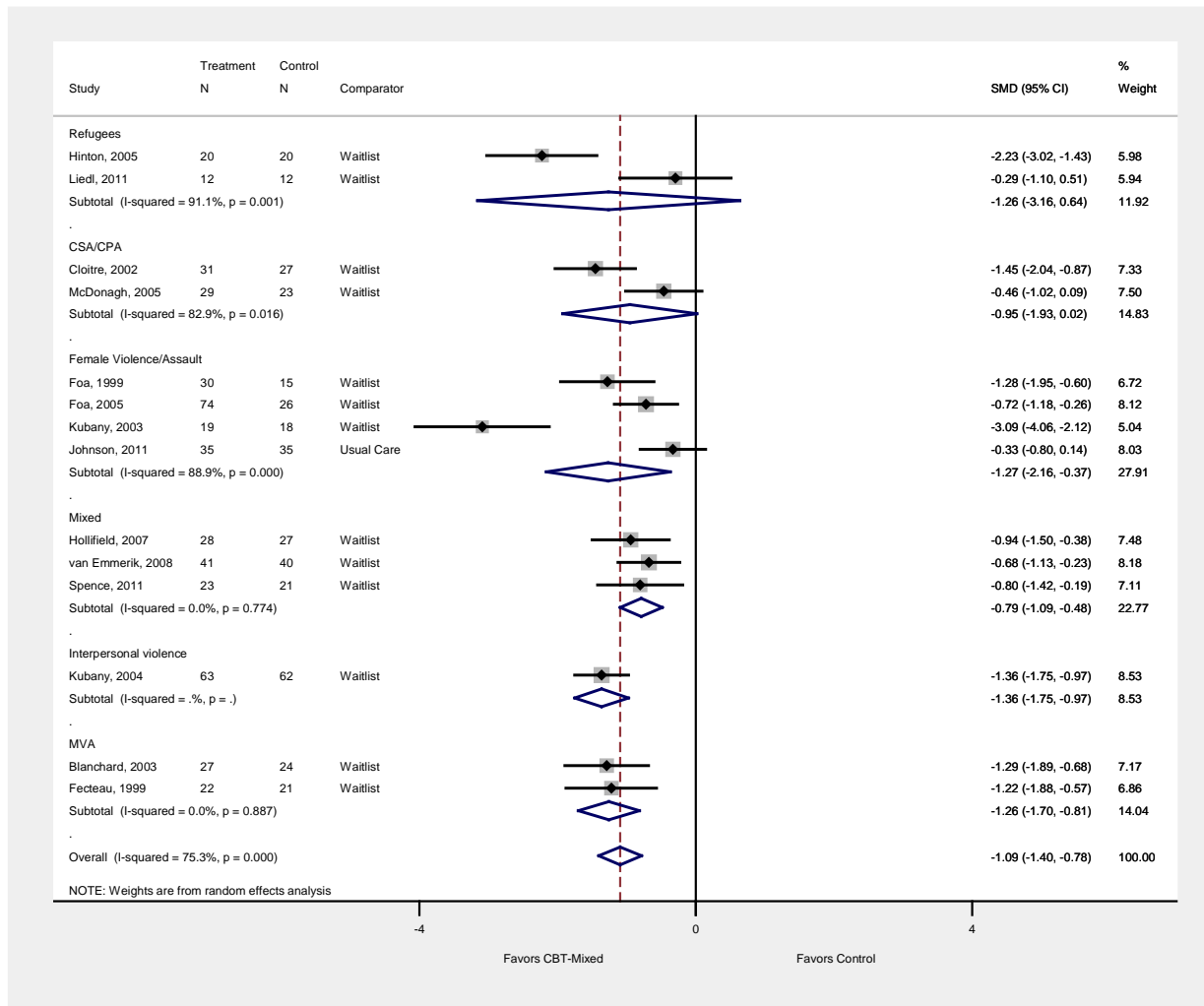


Note: Johnson et al., 2006, Power et al., 2002 and Marcus et al., 1997 were rated as high risk of bias.

Timing of outcome assessment: 8 weeks (van der Kolk, 2007), 4 months (Hogberg, 2007), mean number of sessions = 6.33 (Johnson, 2006), 10 weeks (Power, 2002), 6 weeks (Carlson, 1988), variable number of sessions (Marcus, 1997), 4.5 weeks (Rothbaum, 2005), 4 weeks (Rothbaum).

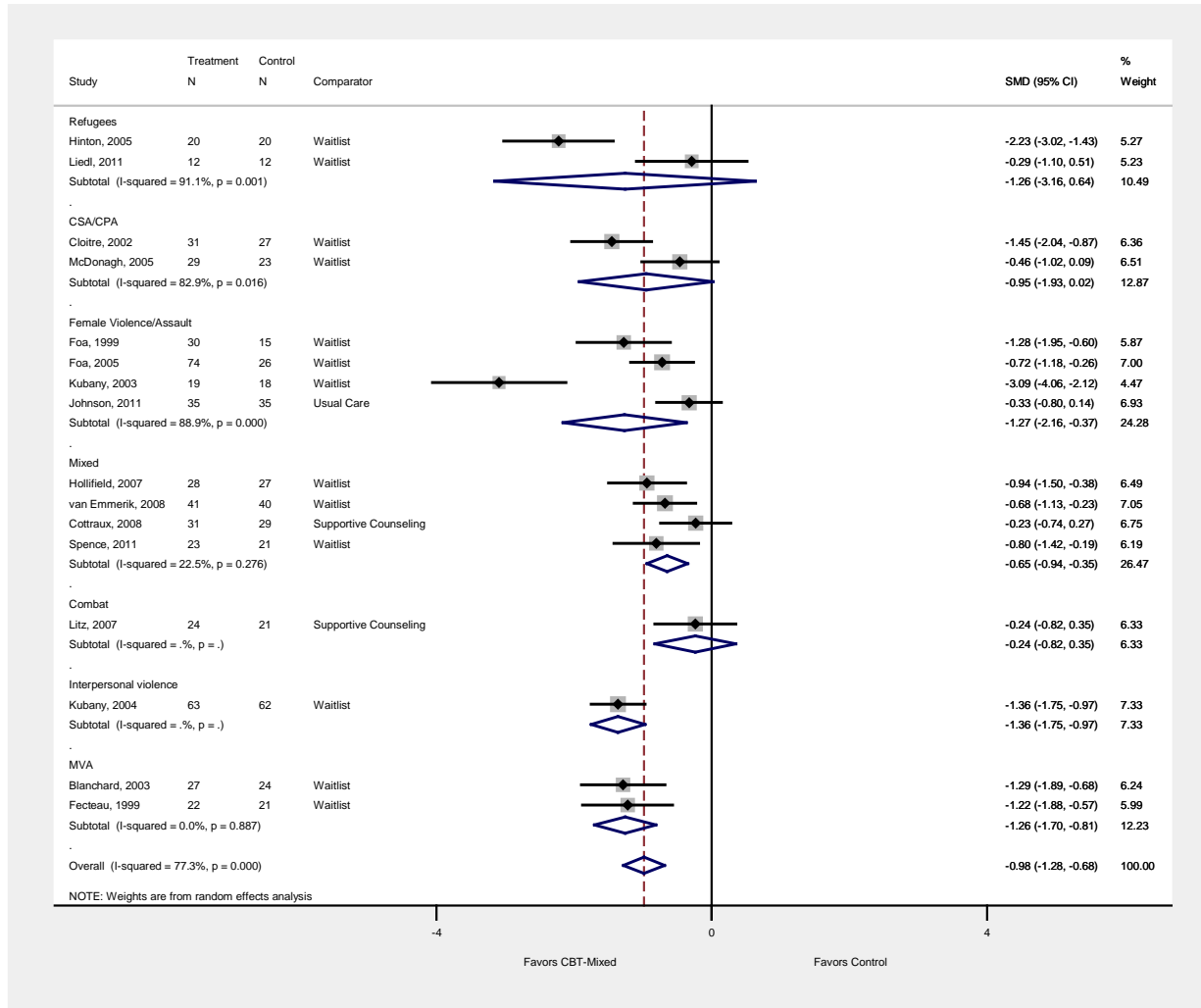
# CBT-Mixed Therapy: Meta-Analysis Results

Figure F-130. PTSD symptom reduction for CBT-mixed compared with an inactive control



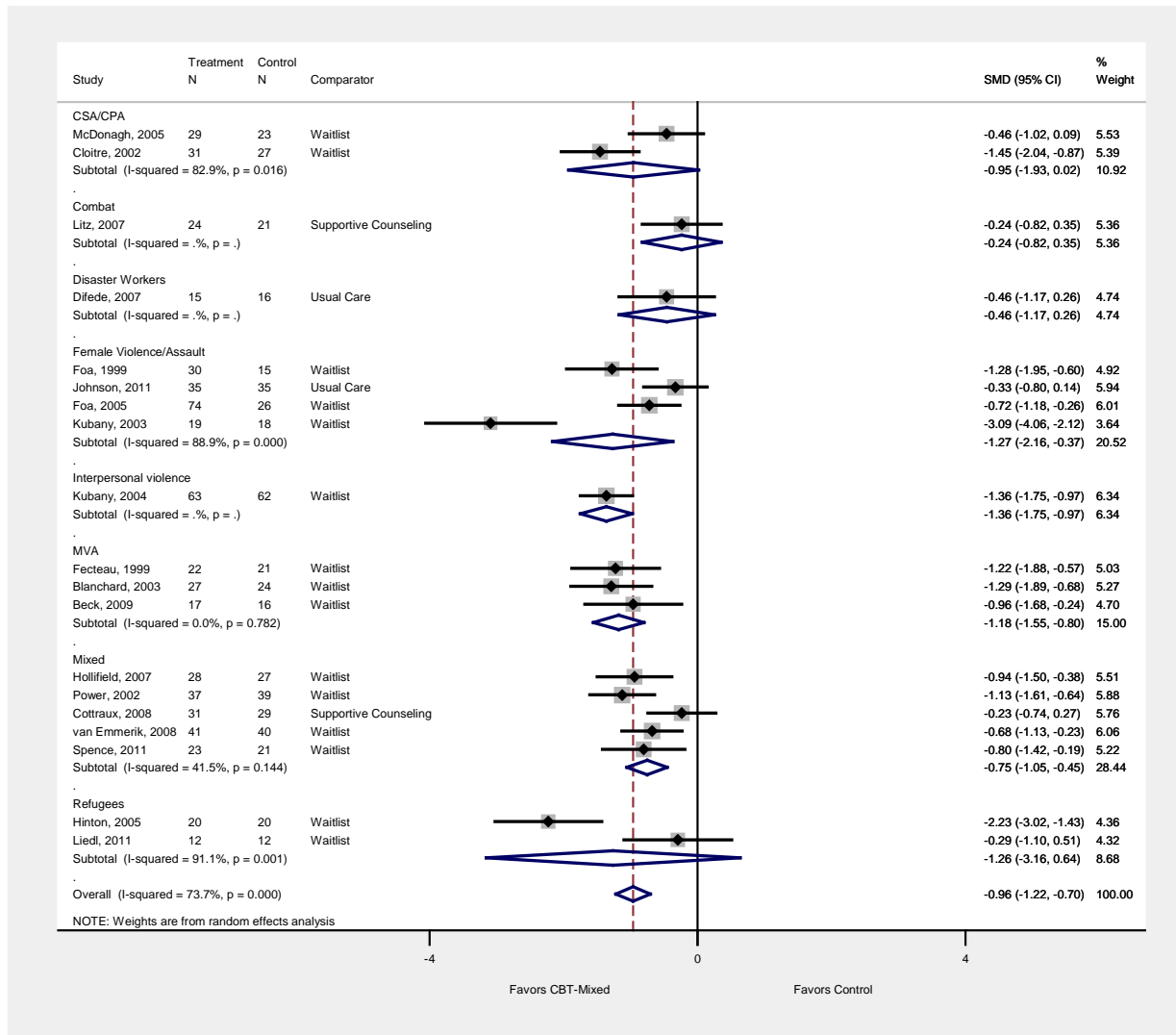
Timing of outcome assessment: 7 weeks (Johnson, 2011), 12 weeks (Foa, 2005), 9 weeks (Foa 1999), 4.5 months (Kubany, 2003), 8 to 12 weeks (Blanchard, 2003), 4 weeks (Fecteau, 1999), 12 weeks (Cloitre, 2002), 14 weeks (McDonagh, 2005), 12 weeks (Hollifield, 2007), 8 weeks (Spence, 2011), 5 sessions (van Emmerik, 2008), 12 weeks (Hinton, 2005), 4.8 months (Liedl, 2011), 4 to 5.5 weeks (Kubany, 2004).

**Figure F-131. PTSD symptom reduction for CBT-mixed compared with an inactive control: Sensitivity analysis including other comparators**



Timing of outcome assessment: 7 weeks (Johnson, 2011), 12 weeks (Foa, 2005), 9 weeks (Foa 1999), 4.5 months (Kubany, 2003), 8 to 12 weeks (Blanchard, 2003), 4 weeks (Fecteau, 1999), 12 weeks (Cloitre, 2002), 14 weeks (McDonagh, 2005), 12 weeks (Hollifield, 2007), 8 weeks (Spence, 2011), 5 sessions (van Emmerik, 2008), 16 weeks (Cottraux, 2008), 12 weeks (Hinton, 2005), 4.8 months (Liedl, 2011), 4 to 5.5 weeks (Kubany, 2004), 8 weeks (Litz, 2007).

**Figure F-132. PTSD symptom reduction for CBT-mixed compared with an inactive control: Sensitivity analysis including other comparators and studies with a high risk of bias**

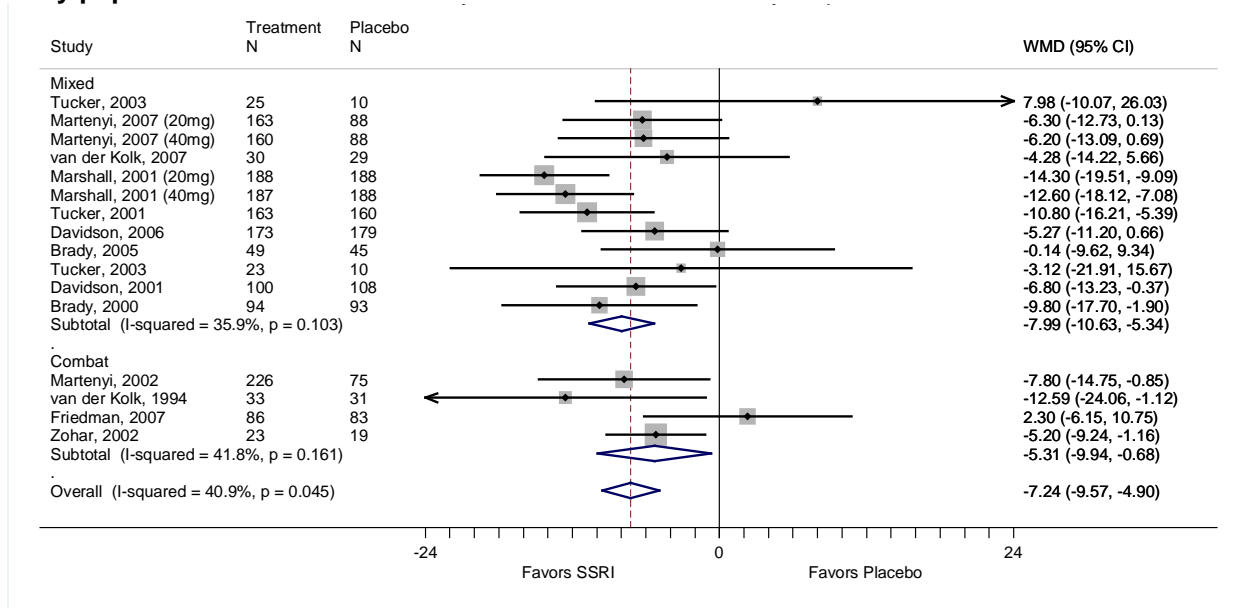


Note: Power et al., 2002, Beck et al., 2009, and Difede et al., 2007 were rated as high risk of bias.

Timing of outcome assessment: 12 weeks (Difede, 2007), 7 weeks (Johnson, 2011), 12 weeks (Foa, 2005), 9 weeks (Foa 1999), 4.5 months (Kubany, 2003), 14 weeks (Beck, 2009), 8 to 12 weeks (Blanchard, 2003), 4 weeks (Fecteau, 1999), 12 weeks (Cloitre, 2002), 14 weeks (McDonagh, 2005), 12 weeks (Hollifield, 2007), 10 weeks (Power, 2002), 8 weeks (Spence, 2011), 5 sessions (van Emmerik, 2008), 16 weeks (Cottraux, 2008), 12 weeks (Hinton, 2005), 4.8 months (Liedl, 2011), 4 to 5.5 weeks (Kubany, 2004), 8 weeks (Litz, 2007).

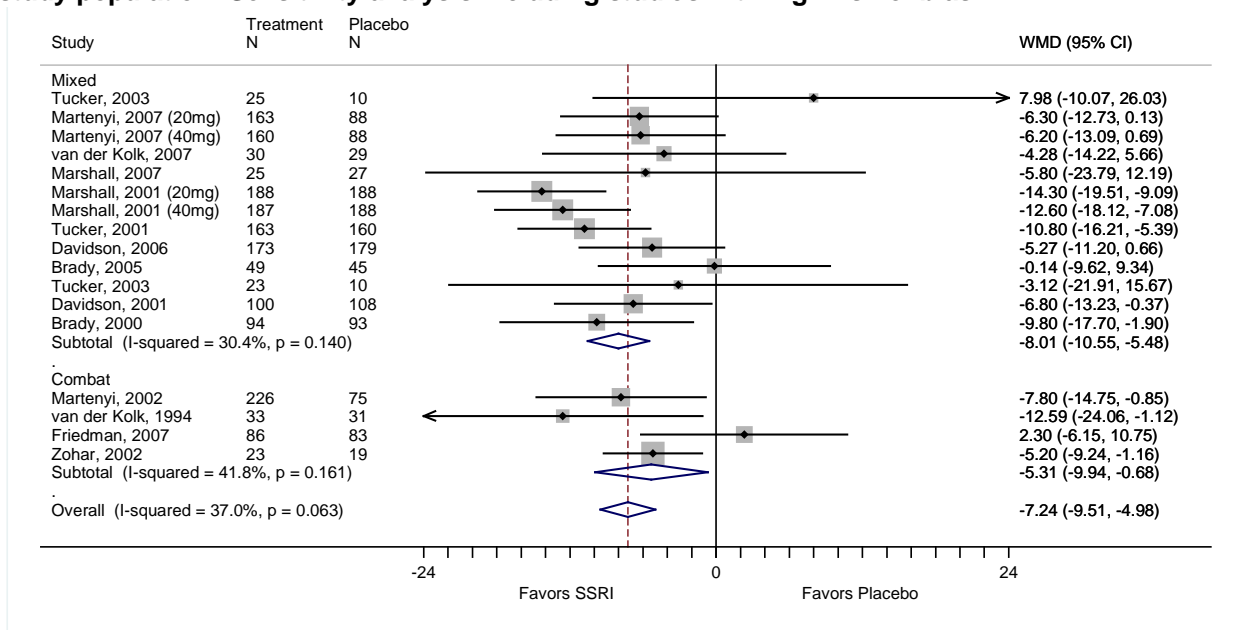
# SSRIs: Meta-Analysis Results

**Figure F-133. Change in CAPS for SSRIs compared with placebo, stratified by mixed and combat study population**



Timing of outcome assessment: 10 weeks (Tucker, 2003; Zohar, 2002), 12 weeks (Martenyi, 2007; Marshall, 2001; Tucker, 2001; Davidson, 2006; Brady, 2005; Davidson, 2001; Brady, 2000; Martenyi 2002; Friedman, 2007); 8 weeks (van der Kolk, 2007), 5 weeks (van der Kolk, 1994).

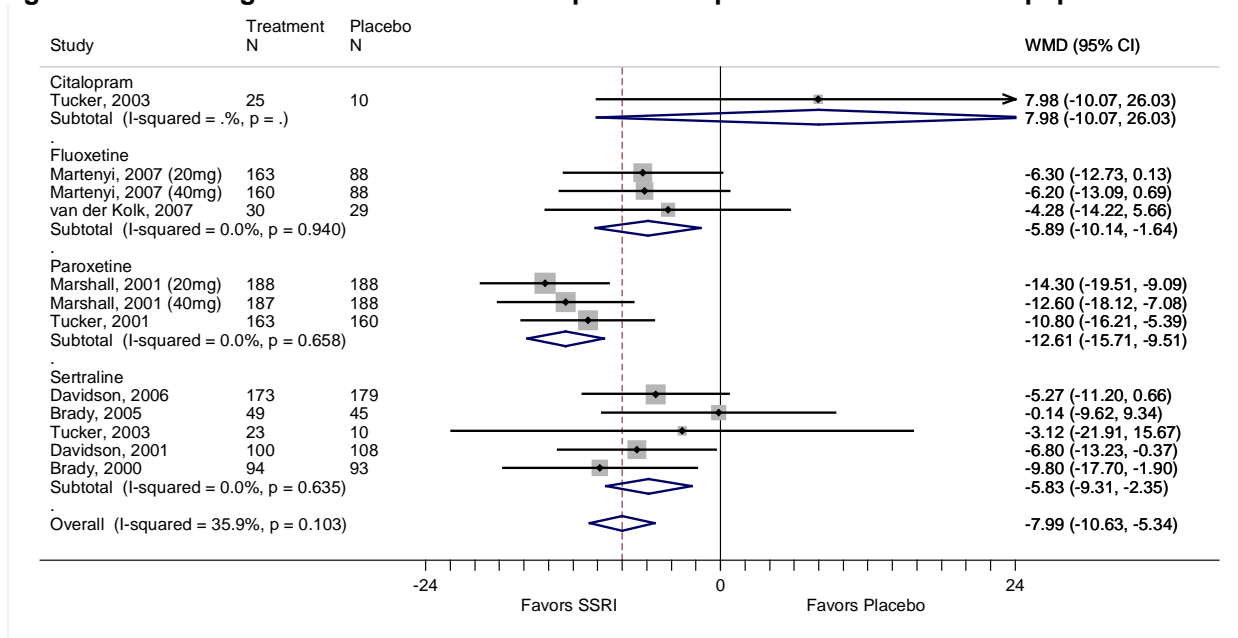
**Figure F-134. Change in CAPS for SSRIs compared with placebo, stratified by mixed and combat study population: Sensitivity analysis including studies with high risk of bias**



Note: Marshall et al., 2007 was rated high risk of bias.

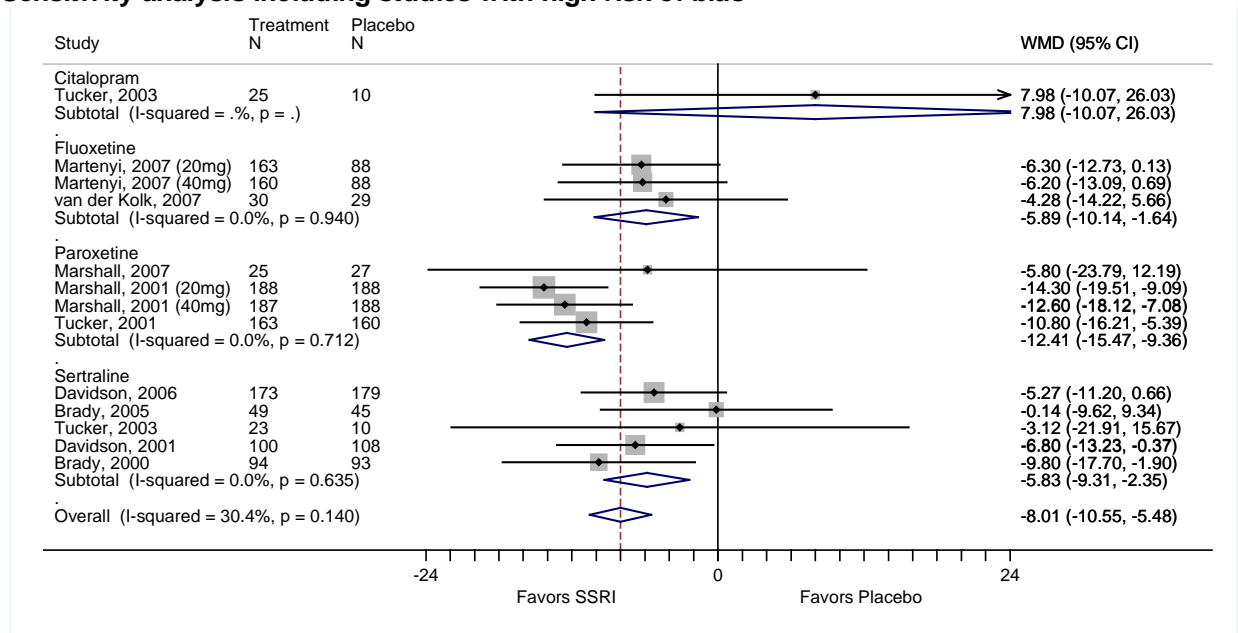
Timing of outcome assessment: 10 weeks (Tucker, 2003; Marshall, 2007; Zohar, 2002), 12 weeks (Martenyi, 2007; Marshall, 2001; Tucker, 2001; Davidson, 2006; Brady, 2005; Davidson, 2001; Brady, 2000; Martenyi 2002; Friedman, 2007); 8 weeks (van der Kolk, 2007), 5 weeks (van der Kolk, 1994).

**Figure F-135. Change in CAPS for SSRIs compared with placebo – mixed trauma population**



Timing of outcome assessment: 10 weeks (Tucker, 2003), 12 weeks (Martenyi, 2007; Marshall, 2001; Tucker, 2001; Davidson, 2006; Brady, 2005; Davidson, 2001; Brady, 2000); 8 weeks (van der Kolk, 2007).

**Figure F-136. Change in CAPS for SSRIs compared with placebo – mixed trauma population: Sensitivity analysis including studies with high risk of bias**

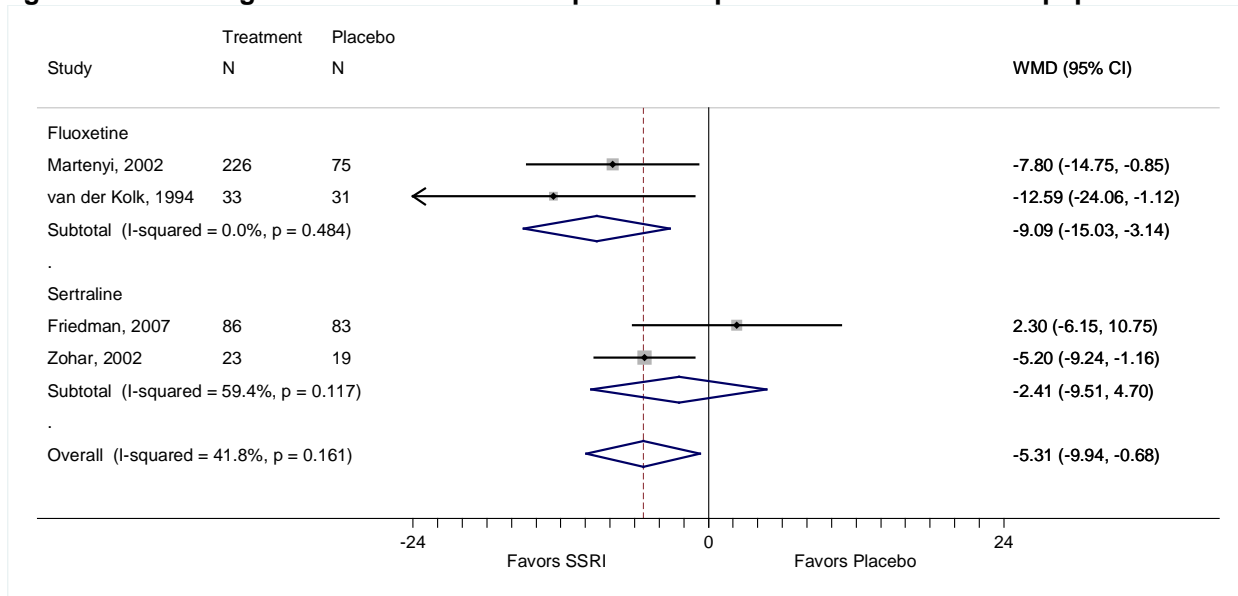


Note: Marshall et al., 2007 was rated high risk of bias.

Timing of outcome assessment: 10 weeks (Tucker, 2003; Marshall, 2007), 12 weeks (Martenyi, 2007; Marshall, 2001; Tucker, 2001; Davidson, 2006; Brady, 2005; Davidson, 2001; Brady, 2000); 8 weeks (van der Kolk, 2007).



**Figure F-137. Change in CAPS for SSRIs compared with placebo – combat trauma population**

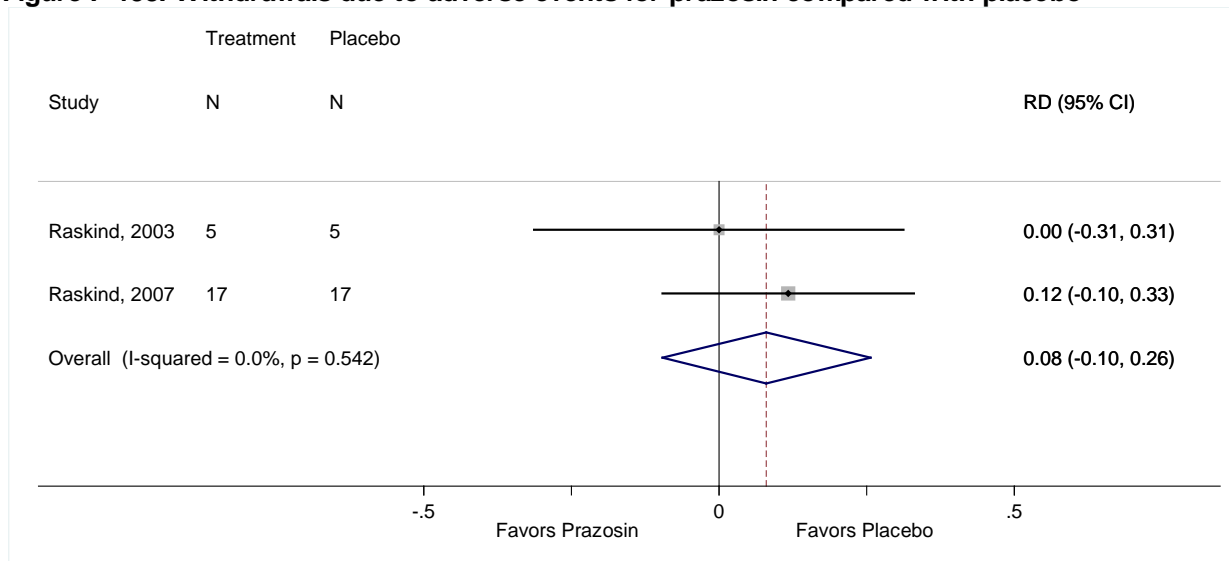


Timing of outcome assessment: 12 weeks (Martenyi, 2002; Friedman, 2007), 5 weeks (van der Kolk, 1994), 10 weeks (Zohar, 2002).

## Key Question 6

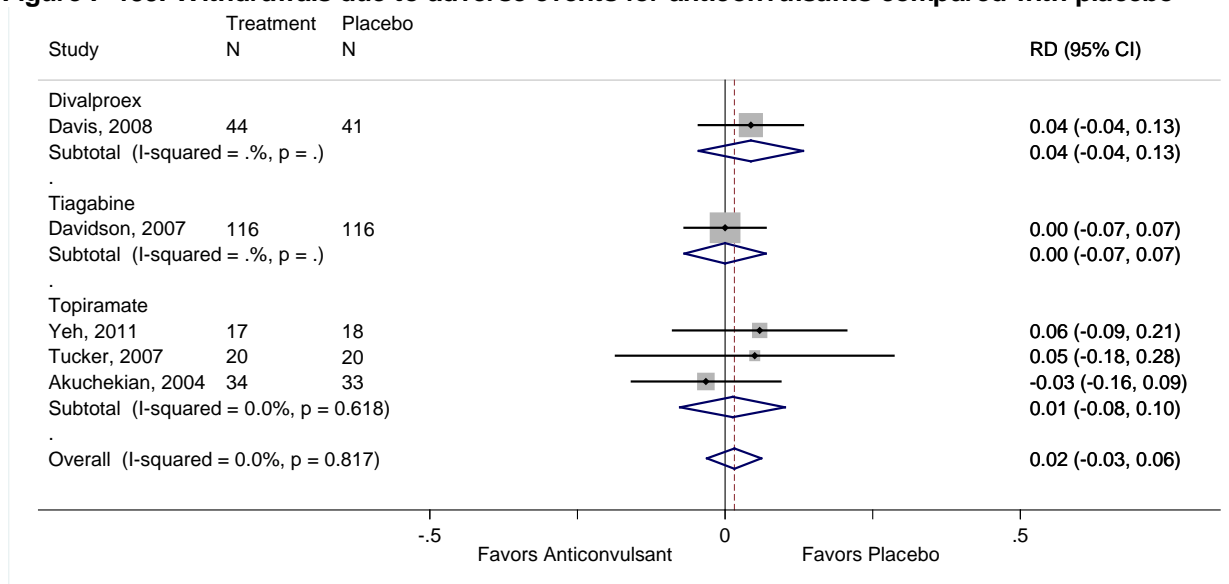
### Withdrawals Due to Adverse Events: Meta-analysis Results

Figure F-138. Withdrawals due to adverse events for prazosin compared with placebo



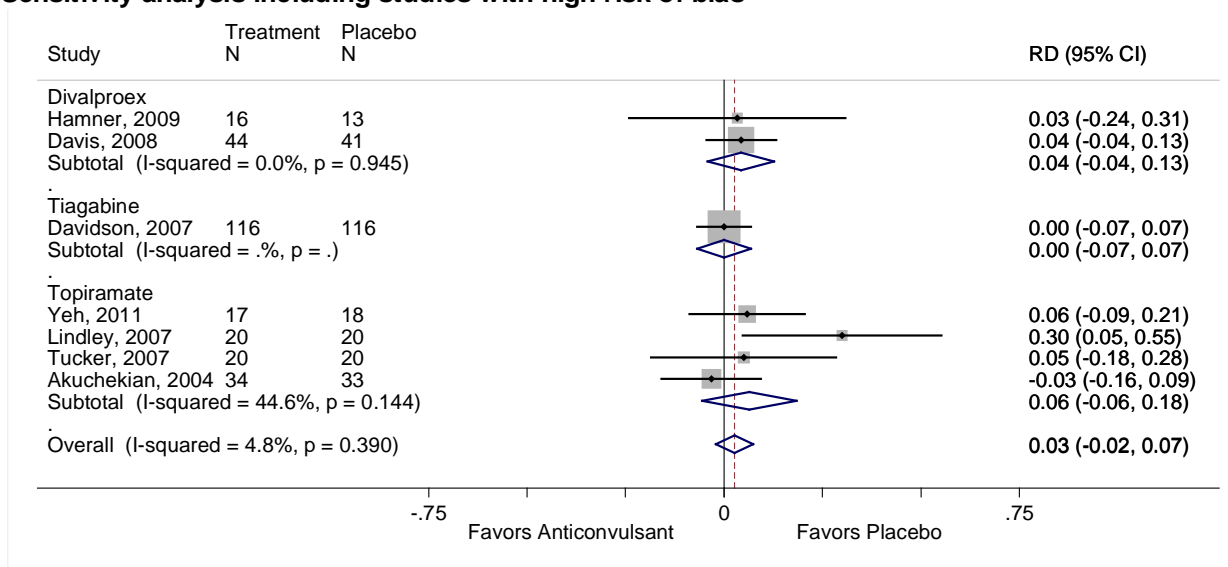
Timing of outcome assessment: 20 weeks (Raskind, 2003), 8 weeks (Raskind, 2007).

Figure F-139. Withdrawals due to adverse events for anticonvulsants compared with placebo



Timing of outcome assessment: 8 weeks (Davis, 2008), 12 weeks (Davidson, 2007; Yeh, 2011; Tucker, 2007; Akuchekian, 2004).

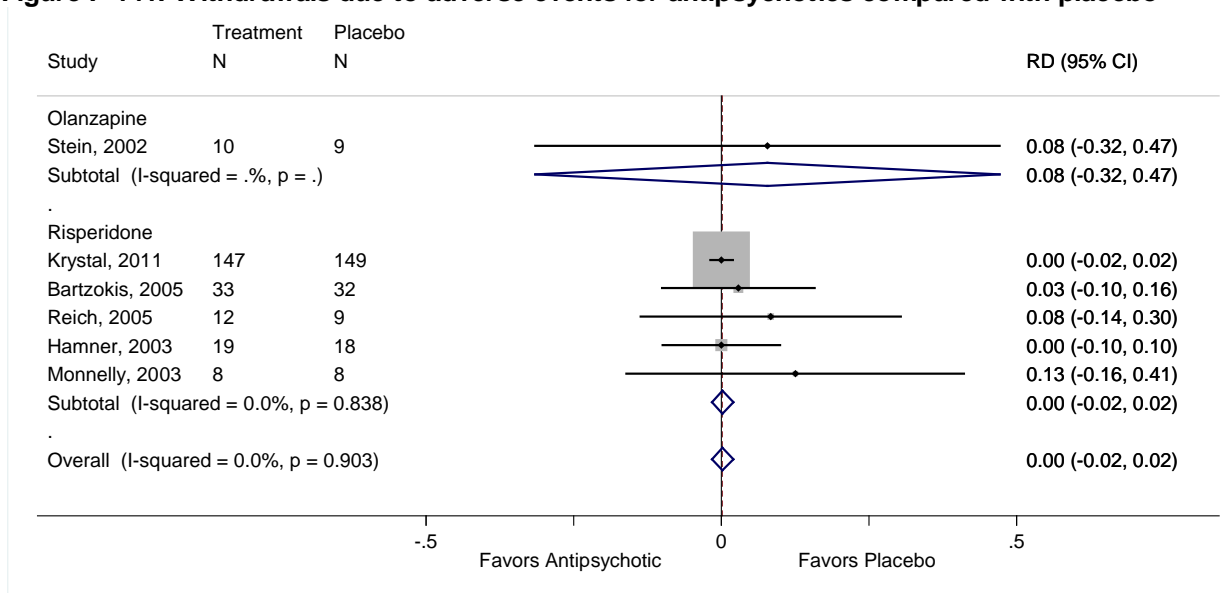
**Figure F-140. Withdrawals due to adverse events for anticonvulsants compared with placebo: Sensitivity analysis including studies with high risk of bias**



Note: Hammer et al., 2009 and Lindley et al., 2007 were rated as high risk of bias.

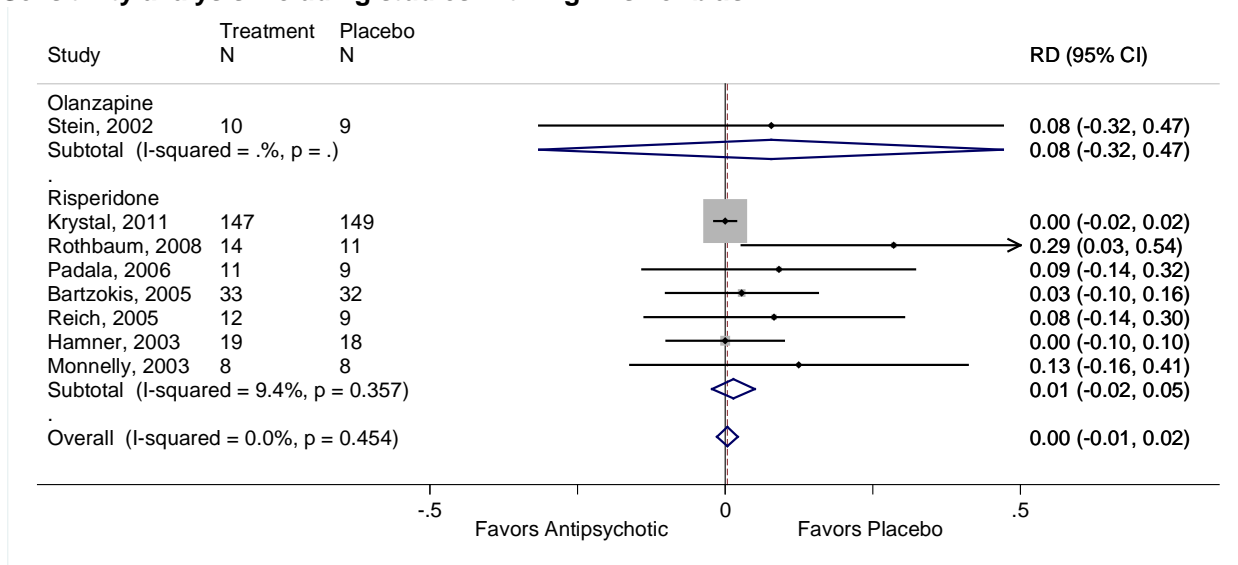
Timing of outcome assessment: 10 weeks (Hamner, 2009), 8 weeks (Davis, 2008), 12 weeks (Davidson, 2007; Yeh, 2011; Tucker, 2007; Akuchekian, 2004, 7 weeks (Lindley, 2007).

**Figure F-141. Withdrawals due to adverse events for antipsychotics compared with placebo**



Timing of outcome assessment: 8 weeks (Stein, 2002; Reich, 2005), 24 weeks (Krystal, 2011), 16 weeks (Bartzokis, 2005), 5 weeks (Hamner, 2003), 6 weeks (Monnelly, 2003).

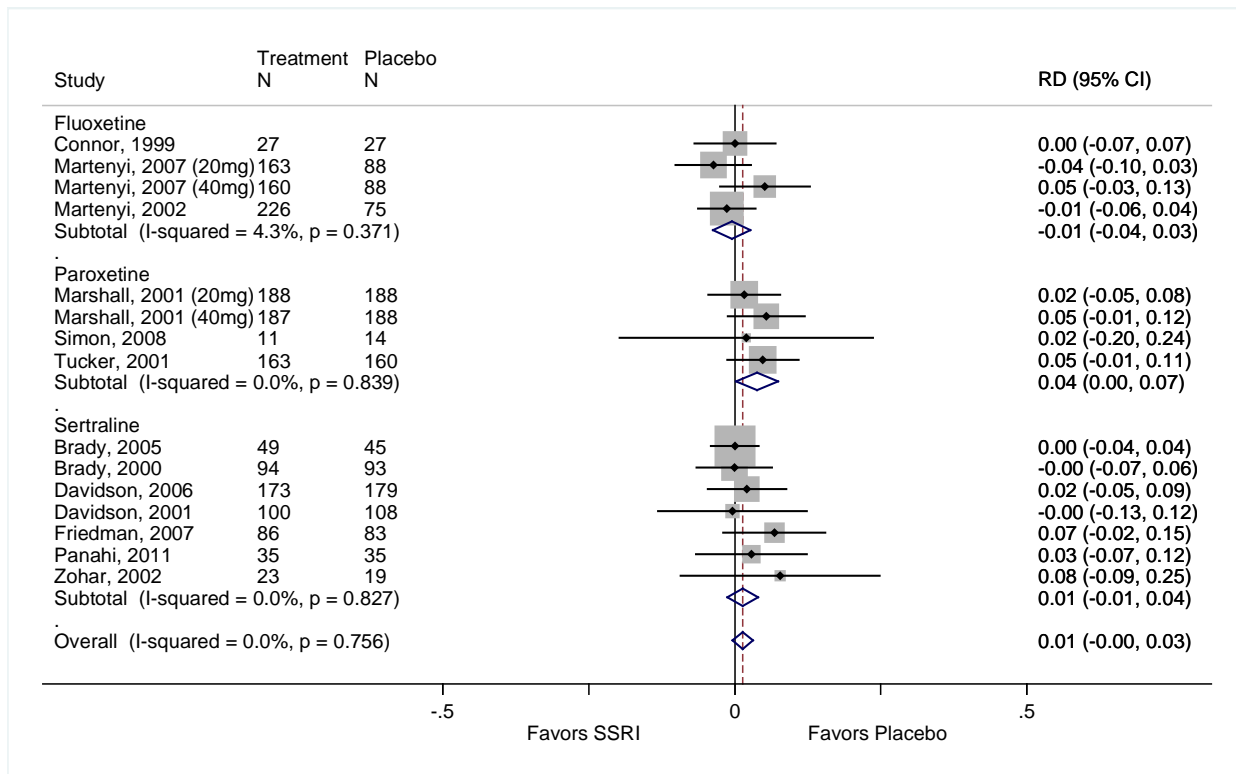
**Figure F-142. Withdrawals due to adverse events for antipsychotics compared with placebo: Sensitivity analysis including studies with high risk of bias**



Note: Rothbaum et al., 2008 and Padala et al., 2006 were rated as high risk of bias.

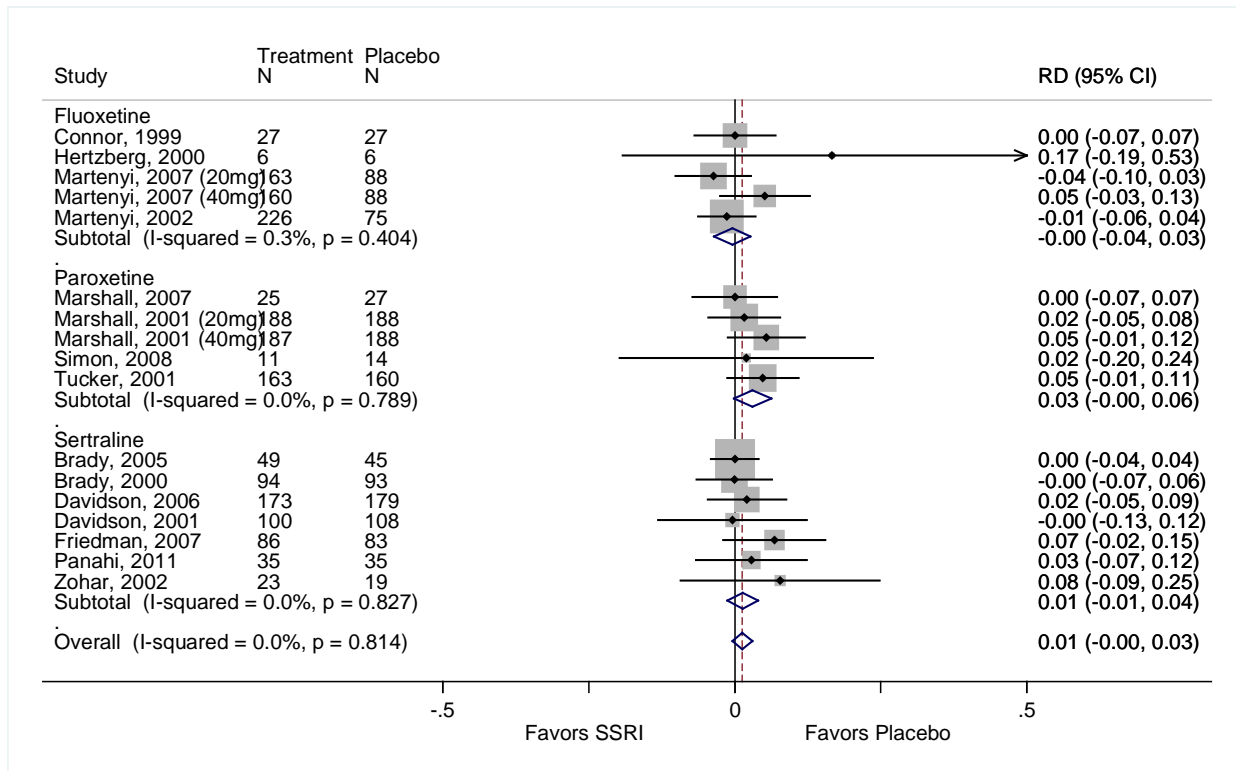
Timing of outcome assessment: 8 weeks (Stein, 2002; Reich, 2005), 24 weeks (Krystal, 2011), 16 weeks (Rothbaum, 2008; Bartzokis, 2005), 5 weeks (Hamner, 2003), 6 weeks (Monnelly, 2003), 12 weeks (Padala, 2006).

**Figure F-143. Withdrawals due to adverse events for SSRIs compared with placebo**



Timing of outcome assessment: 10 weeks (Simon, 2008; Panahi, 2011, Zohar, 2002), 12 weeks (Connor, 1999; Martenyi, 2007; Martenyi 2002; Marshall, 2001; Tucker, 2001; Davidson, 2006; Brady, 2005; Davidson, 2001; Brady, 2000; Friedman, 2007); 8 weeks (van der Kolk, 2007), 5 weeks (van der Kolk, 1994).

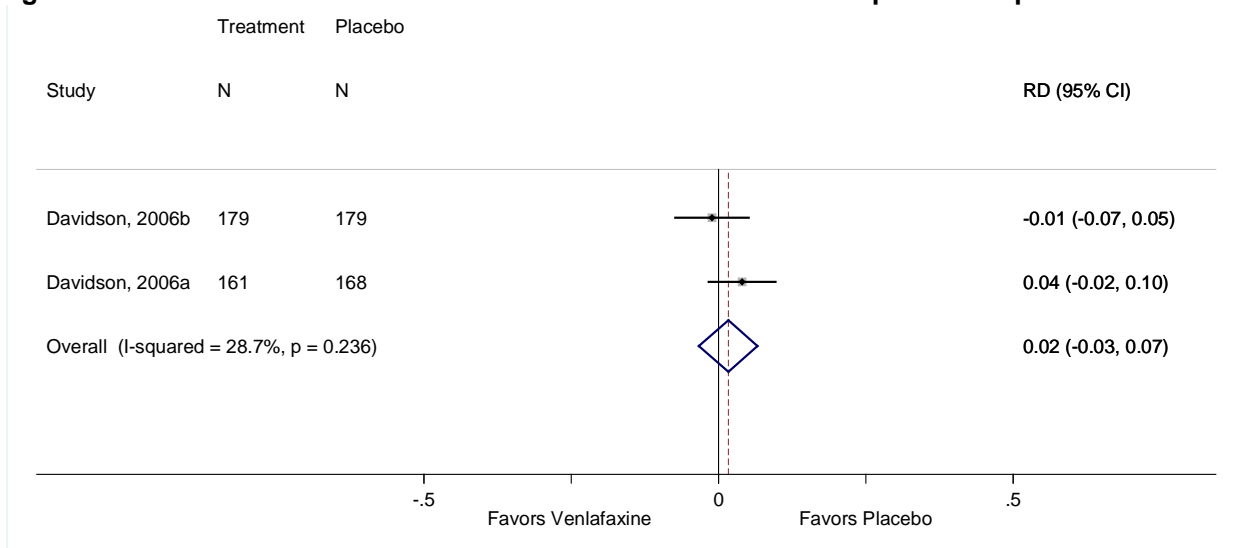
**Figure F-144. Withdrawals due to adverse events for SSRIs compared with placebo: Sensitivity analysis including studies with high risk of bias**



Note: Hertzberg et al., 2007, and Marshall et al., 2007 were rated as high risk of bias.

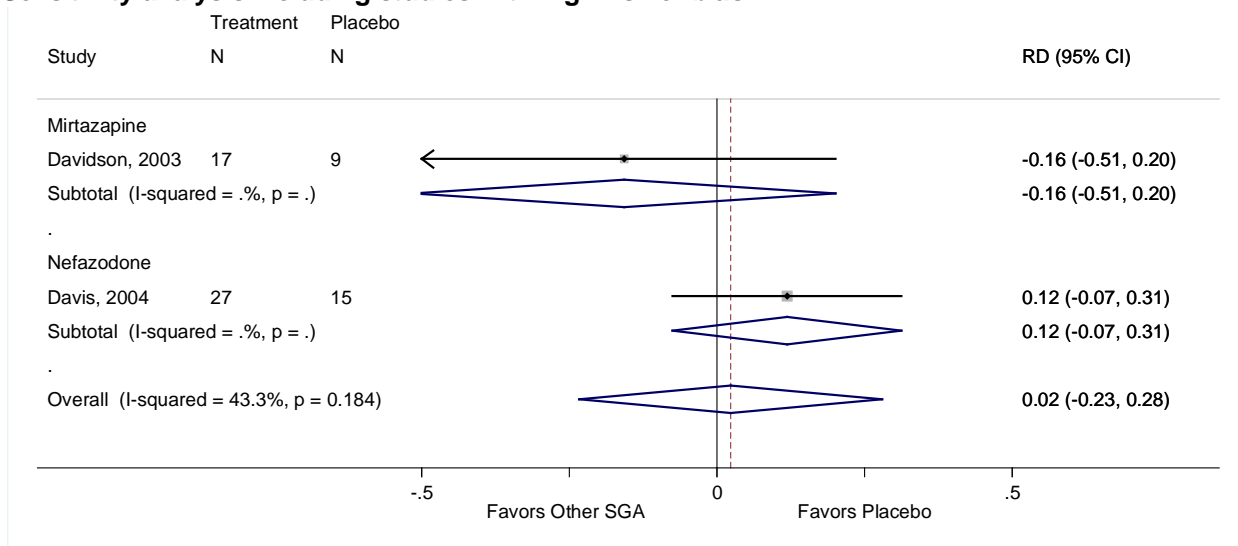
Timing of outcome assessment: 10 weeks (Marshall, 2007; Simon, 2008; Panahi, 2011, Zohar, 2002), 12 weeks (Connor, 1999; Hertzberg, 2000; Martenyi, 2007; Martenyi 2002; Marshall, 2001; Tucker, 2001; Davidson, 2006; Brady, 2005; Davidson, 2001; Brady, 2000; Friedman, 2007); 8 weeks (van der Kolk, 2007), 5 weeks (van der Kolk, 1994).

**Figure F-145. Withdrawals due to adverse events for venlafaxine compared with placebo**



Timing of outcome assessment: 12 weeks (Davidson, 2006b), 24 weeks (Davidson, 2006a).

**Figure F-146. Withdrawals due to adverse events for other SGAs compared with placebo: Sensitivity analysis including studies with high risk of bias**

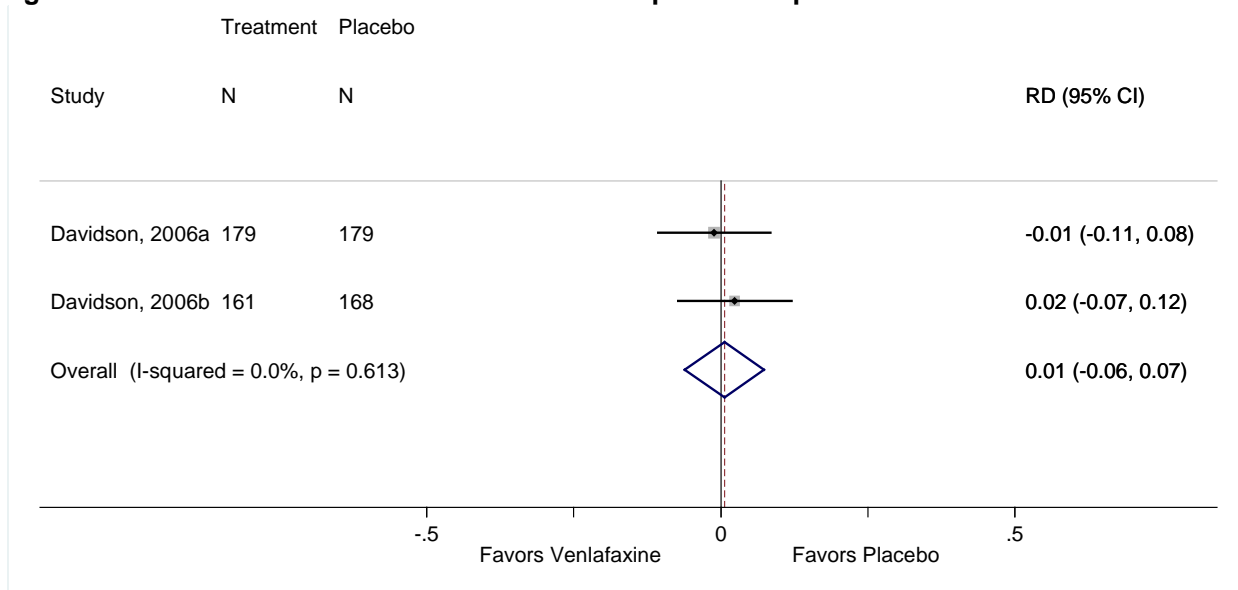


Note: Davis et al, 2004 was rated high risk of bias.

Timing of outcome assessment: 8 weeks (Davidson, 2003), 12 weeks (Davis, 2004).

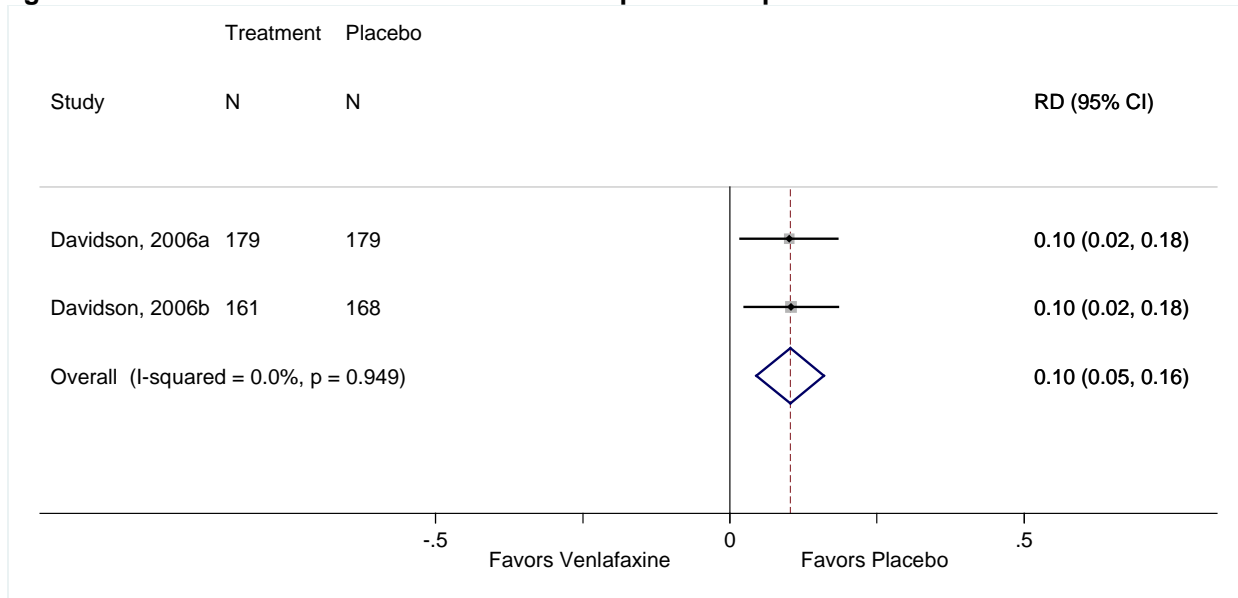
## Adverse Events - Venlafaxine: Meta-analysis Results

**Figure F-147. Rate of headache for venlafaxine compared with placebo**



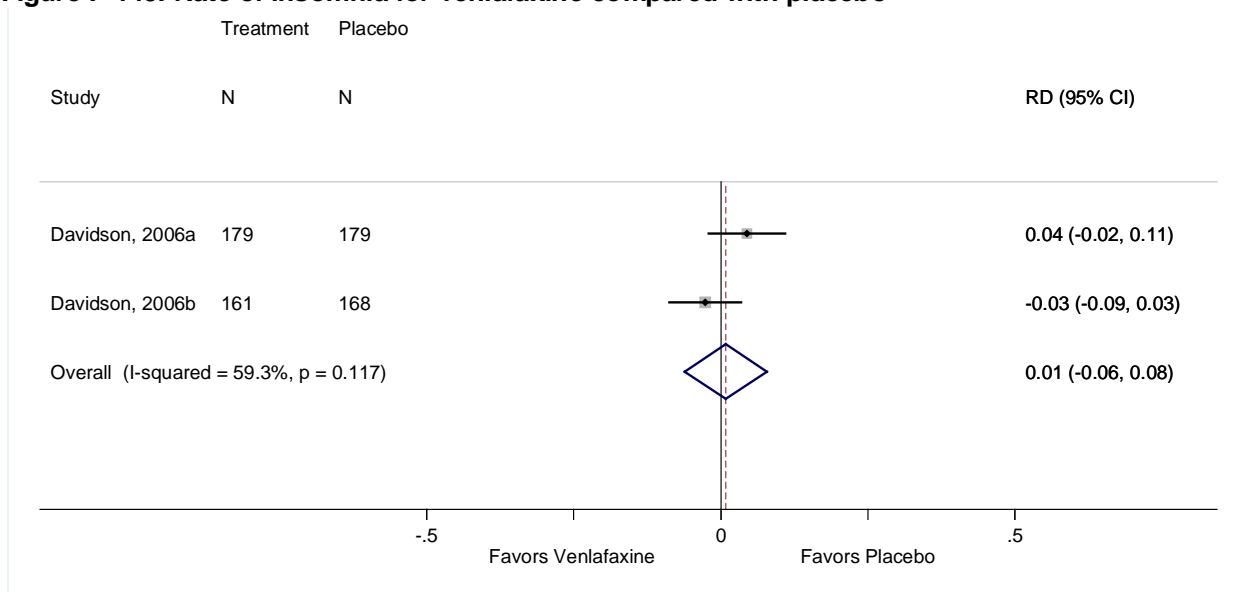
Timing of outcome assessment: 12 weeks (Davidson, 2006a), 24 weeks (Davidson, 2006b).

**Figure F-148. Rate of nausea for venlafaxine compared with placebo**



Timing of outcome assessment: 12 weeks (Davidson, 2006a), 24 weeks (Davidson, 2006b).

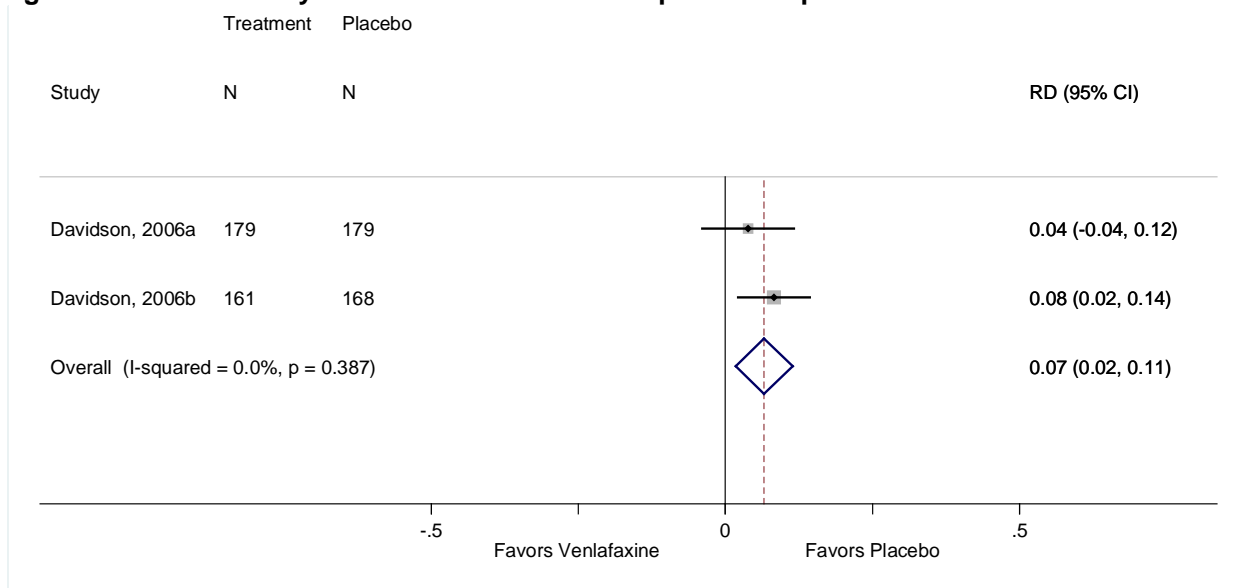
**Figure F-149. Rate of insomnia for venlafaxine compared with placebo**



Timing of outcome assessment: 12 weeks (Davidson, 2006a), 24 weeks (Davidson, 2006b).

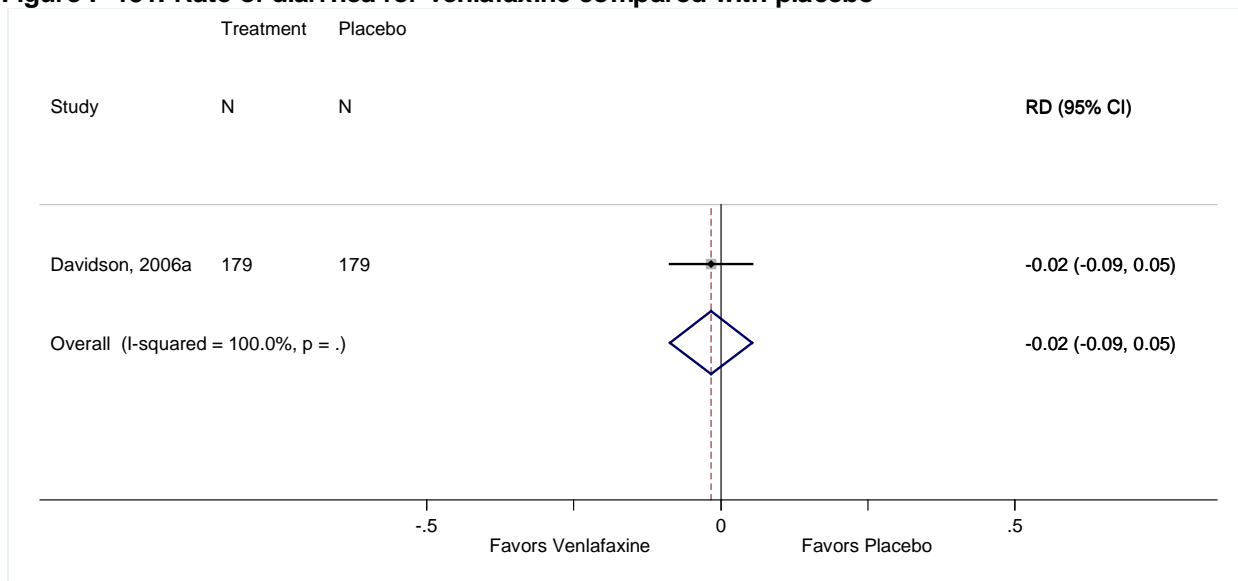


**Figure F-150. Rate of dry mouth for venlafaxine compared with placebo**



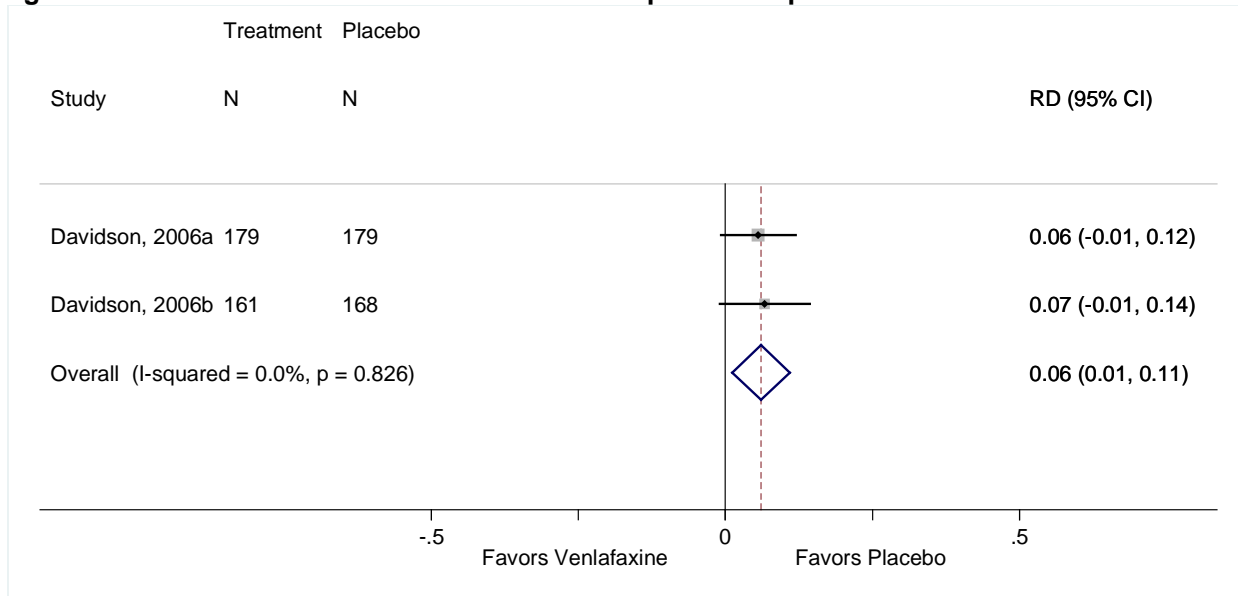
Timing of outcome assessment: 12 weeks (Davidson, 2006a), 24 weeks (Davidson, 2006b).

**Figure F-151. Rate of diarrhea for venlafaxine compared with placebo**



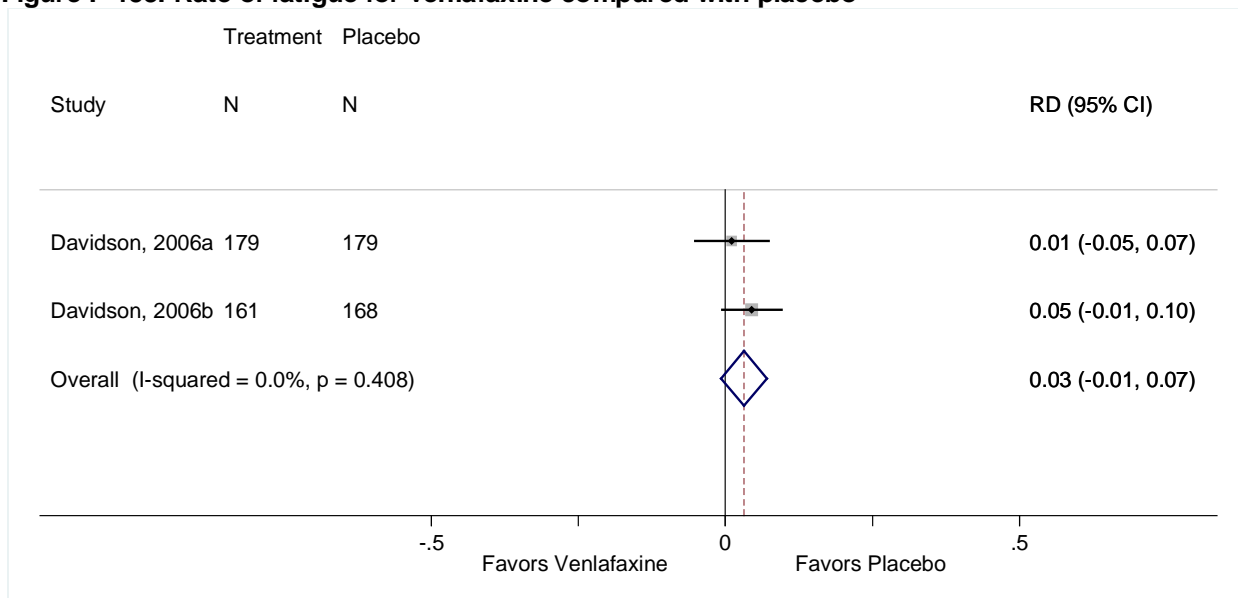
Timing of outcome assessment: 12 weeks.

**Figure F-152. Rate of dizziness for venlafaxine compared with placebo**



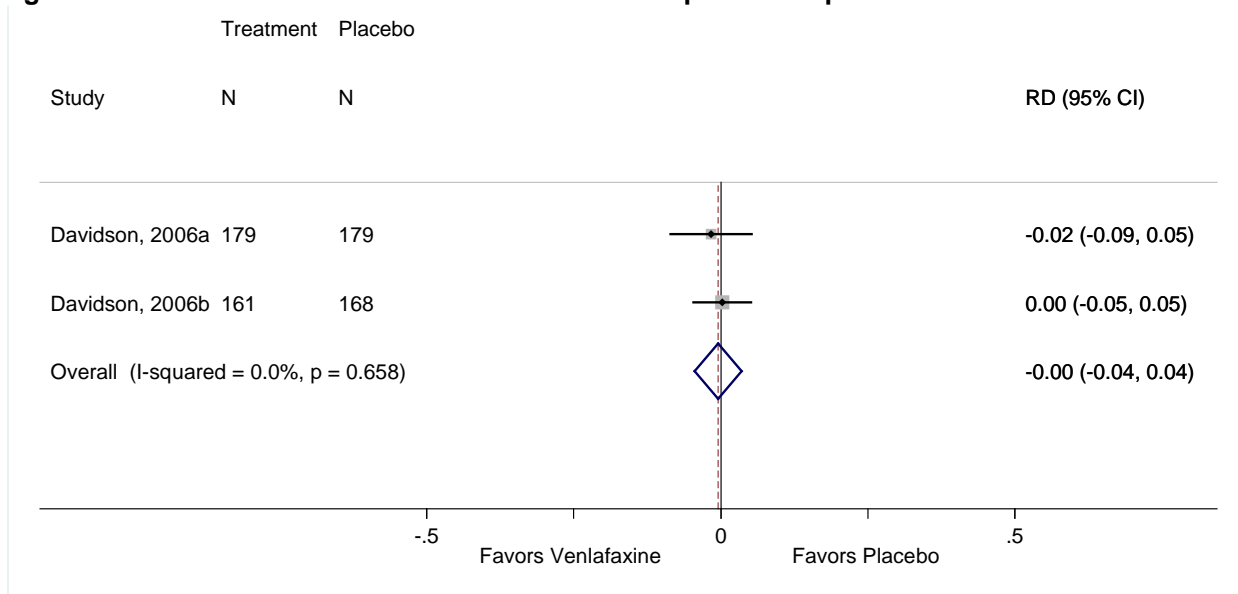
Timing of outcome assessment: 12 weeks (Davidson, 2006a), 24 weeks (Davidson, 2006b).

**Figure F-153. Rate of fatigue for venlafaxine compared with placebo**



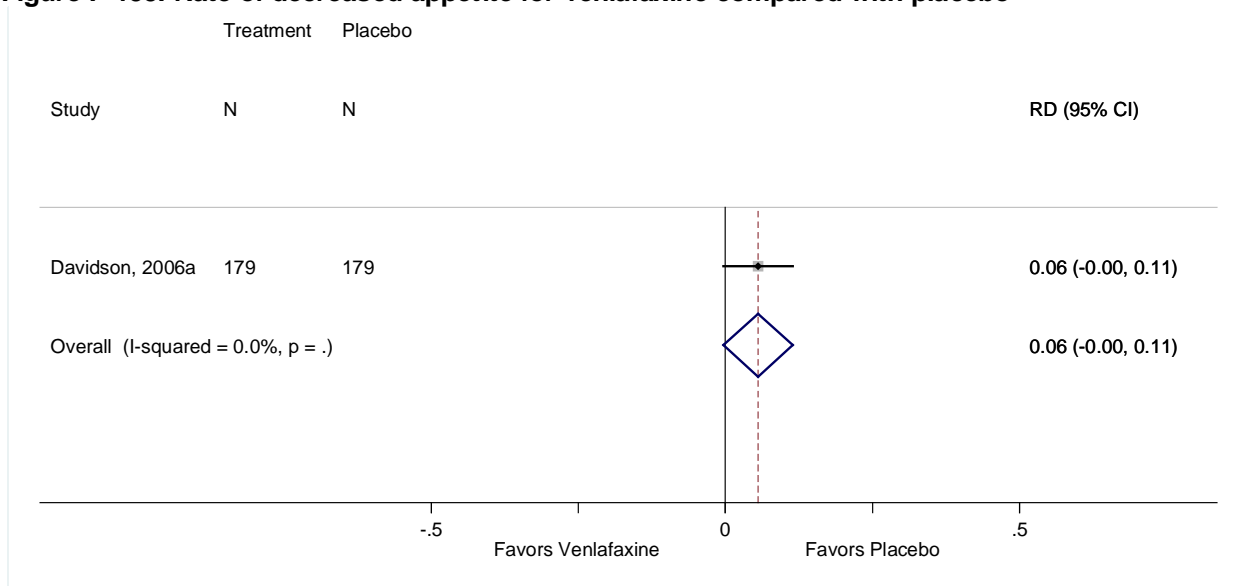
Timing of outcome assessment: 12 weeks (Davidson, 2006a), 24 weeks (Davidson, 2006b).

**Figure F-154. Rate of somnolence for venlafaxine compared with placebo**



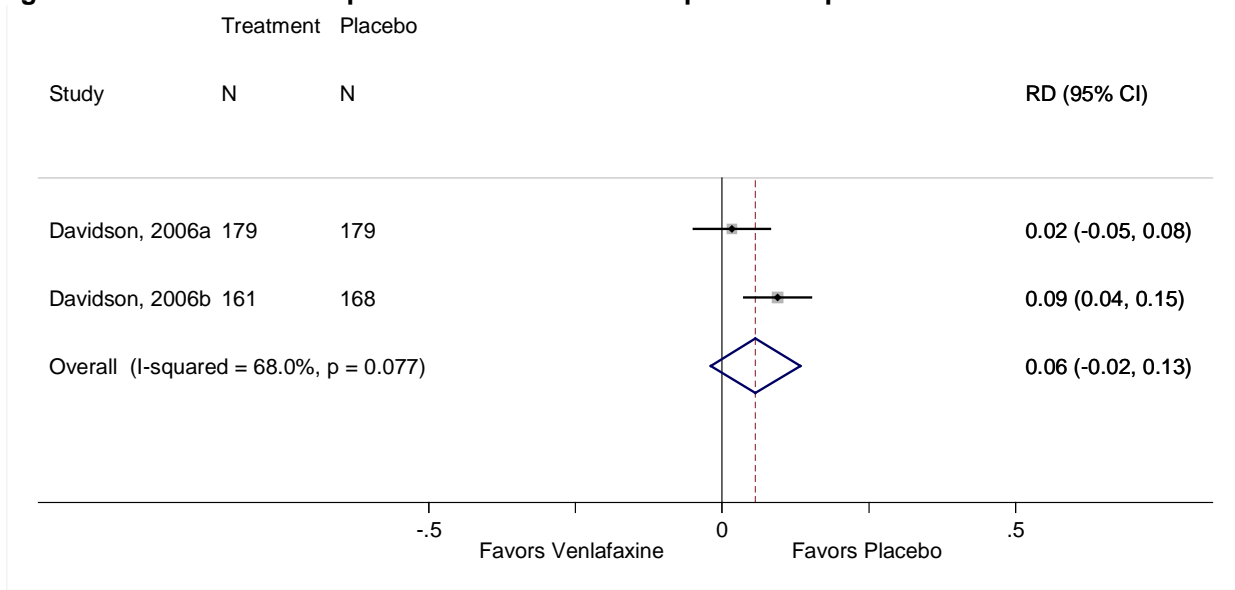
Timing of outcome assessment: 12 weeks (Davidson, 2006a), 24 weeks (Davidson, 2006b).

**Figure F-155. Rate of decreased appetite for venlafaxine compared with placebo**



Timing of outcome assessment: 12 weeks.

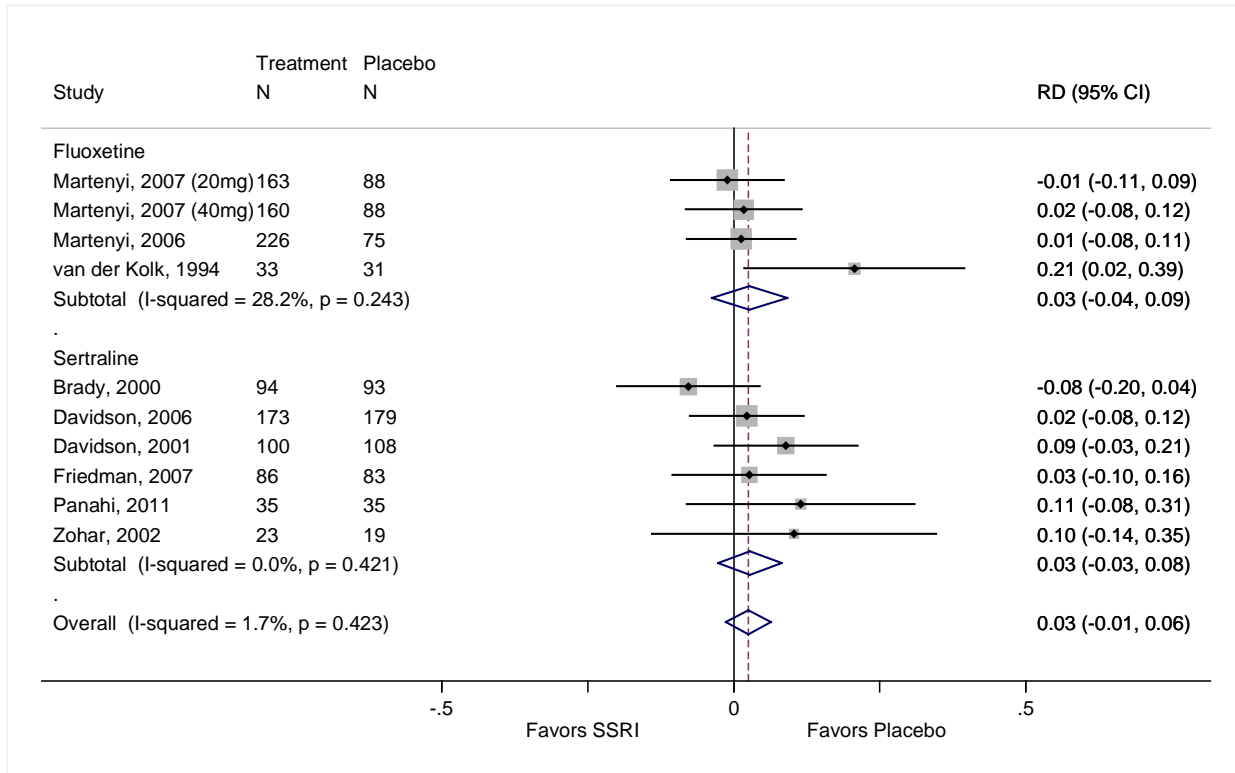
**Figure F-156. Rate of constipation for venlafaxine compared with placebo**



Timing of outcome assessment: 12 weeks (Davidson, 2006a), 24 weeks (Davidson, 2006b).

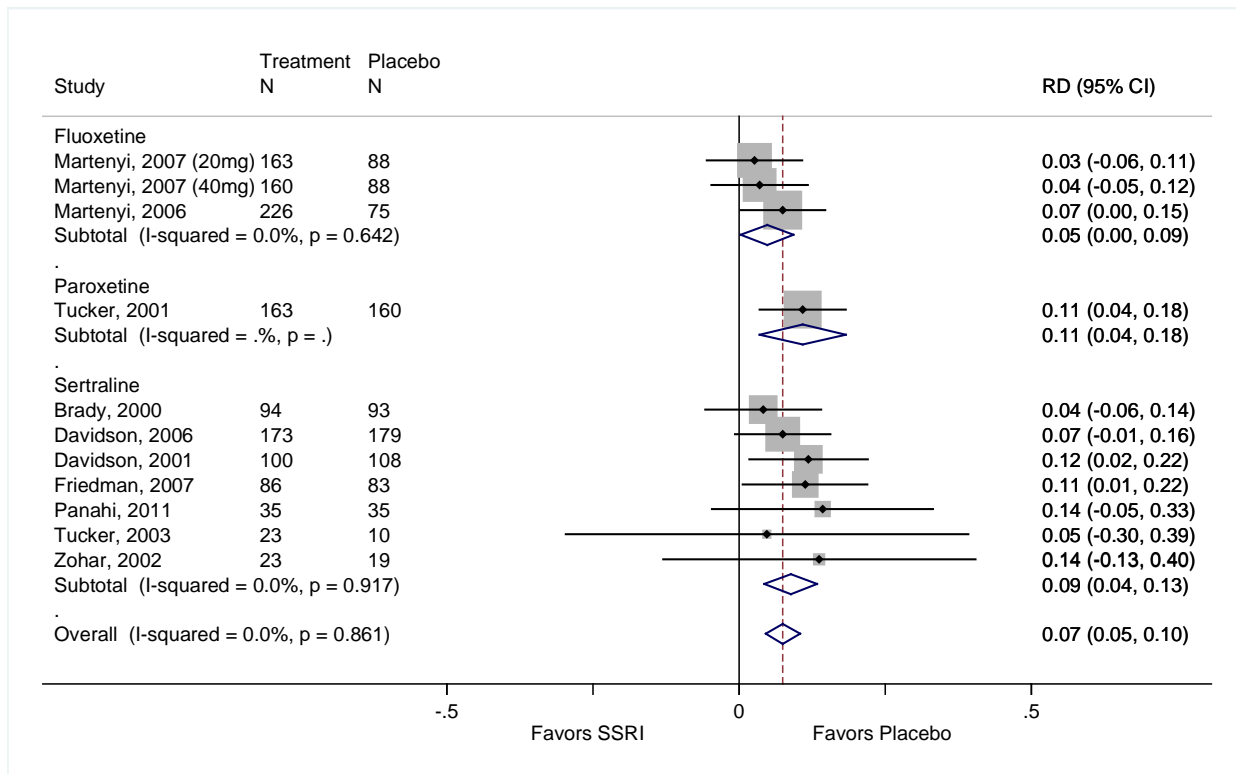
# Adverse Events - SSRIs: Meta-analysis Results

Figure F-157. Rate of headache for SSRIs compared with placebo



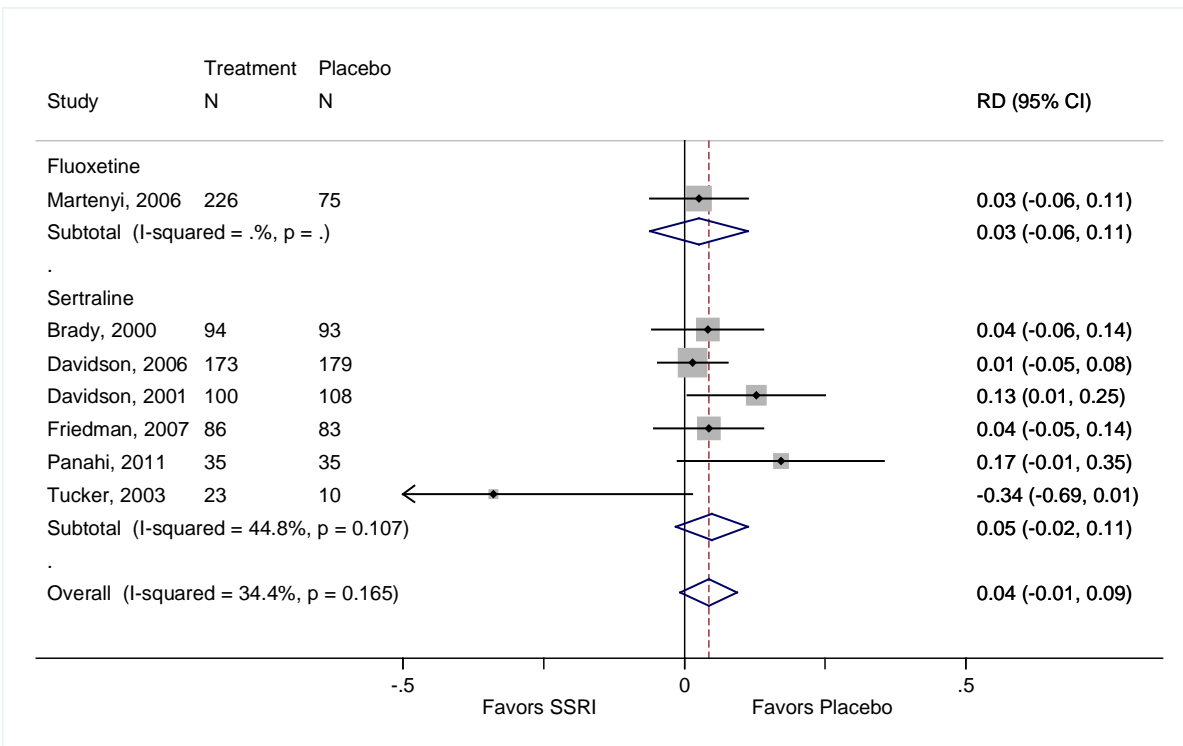
Timing of outcome assessment: 10 weeks (Panahi, 2011, Zohar, 2002), 12 weeks (Martenyi, 2007; Martenyi 2006; Davidson, 2006; Davidson, 2001; Brady, 2000; Friedman, 2007), 5 weeks (van der Kolk, 1994).

**Figure F-158. Rate of nausea for SSRIs compared with placebo**



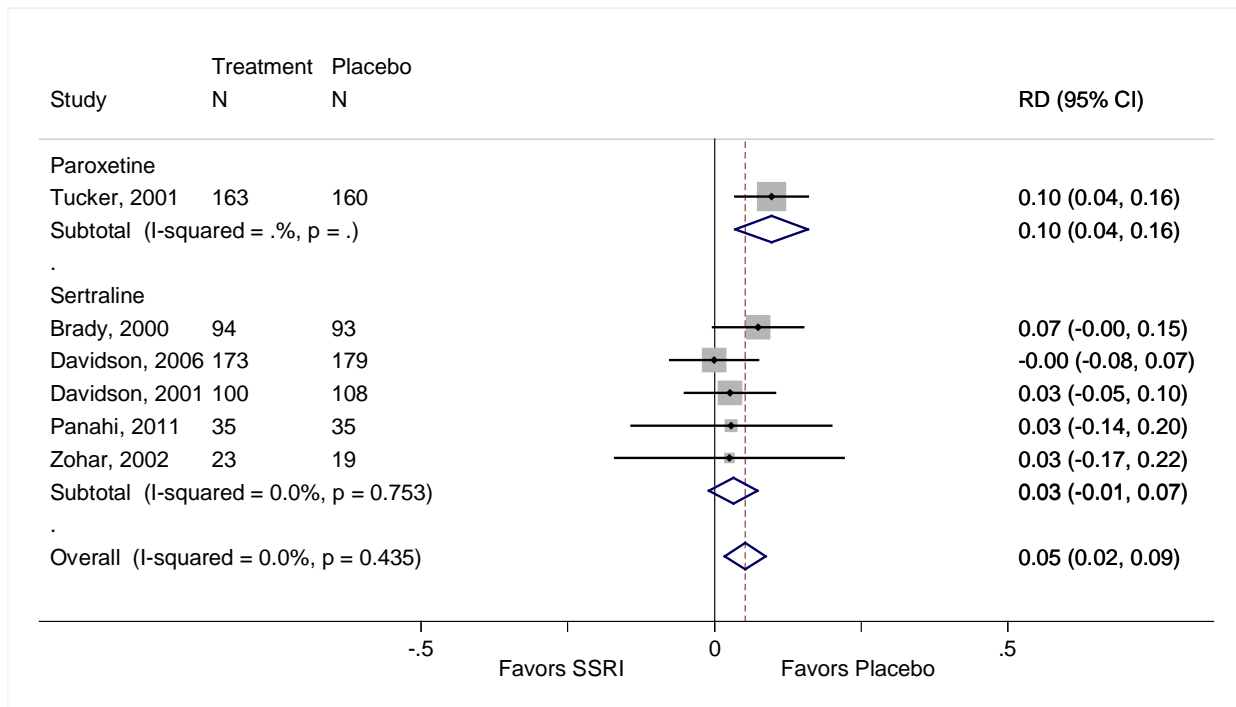
Timing of outcome assessment: 10 weeks (Panahi, 2001; Tucker, 2003; Zohar, 2002), 12 weeks (Martenyi, 2007; Martenyi 2006; Tucker, 2001; Davidson, 2006; Davidson, 2001; Brady, 2000; Friedman, 2007).

**Figure F-159. Rate of insomnia for SSRIs compared with placebo**



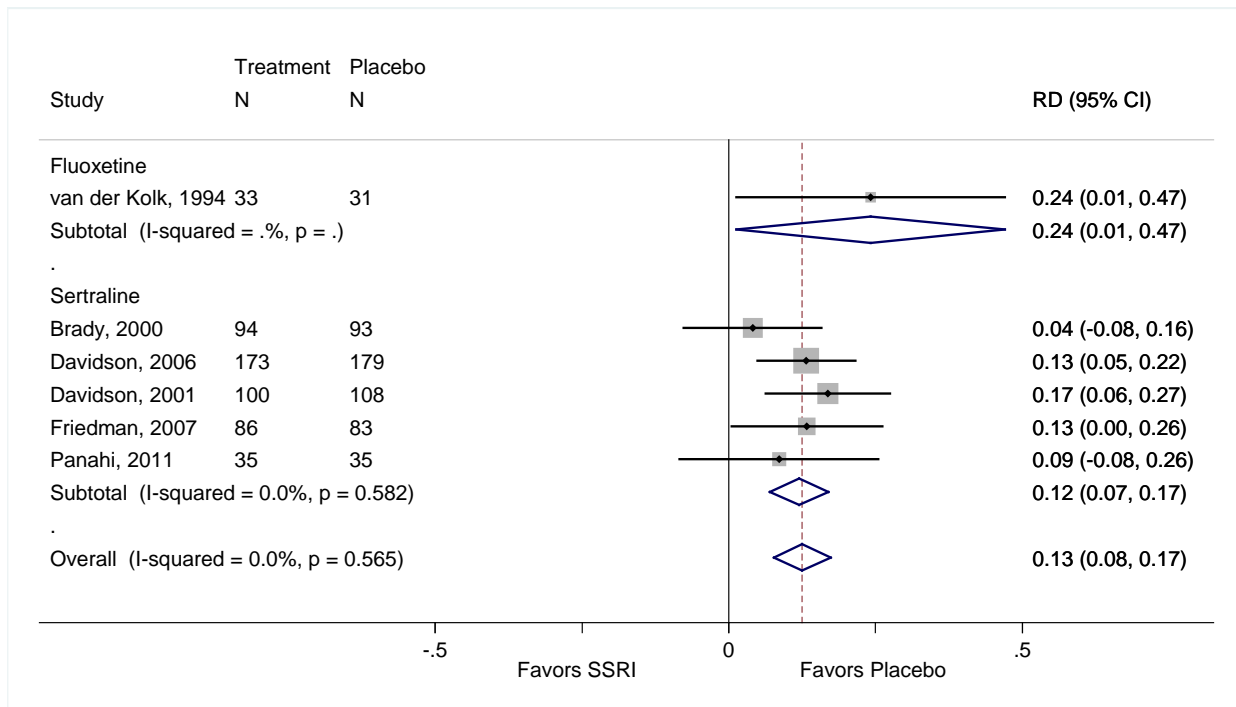
Timing of outcome assessment: 10 weeks (Panahi, 2001; Tucker, 2003), 12 weeks (Martenyi 2006; Davidson, 2006; Davidson, 2001; Brady, 2000; Friedman, 2007).

**Figure F-160. Rate of dry mouth for SSRIs compared with placebo**



Timing of outcome assessment: 10 weeks (Panahi, 2001; Tucker, 2003; Zohar, 2002), 12 weeks (Davidson, 2006; Davidson, 2001; Brady, 2000).

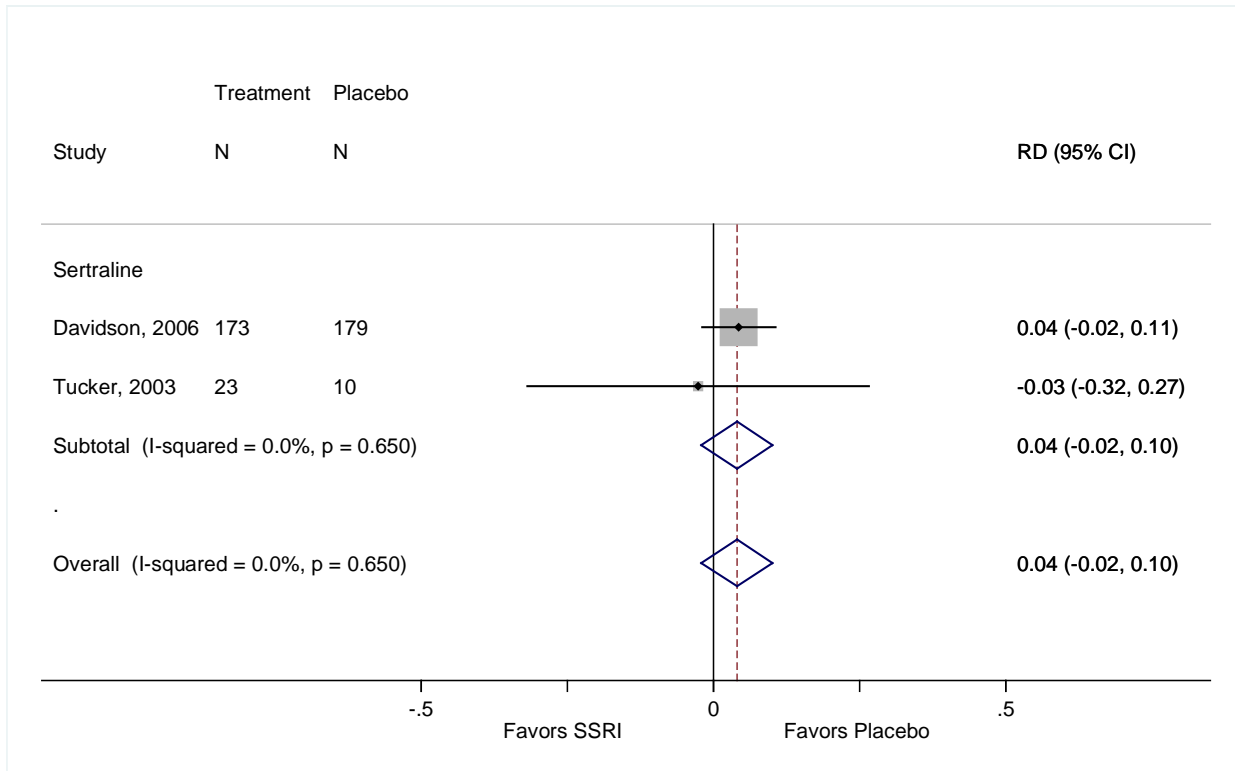
**Figure F-161. Rate of diarrhea for SSRIs compared with placebo**



Timing of outcome assessment: 5 weeks (van der Kolk, 1994); 10 weeks (Panahi, 2001), 12 weeks (Davidson, 2006; Davidson, 2001; Brady, 2000; Friedman, 2007).

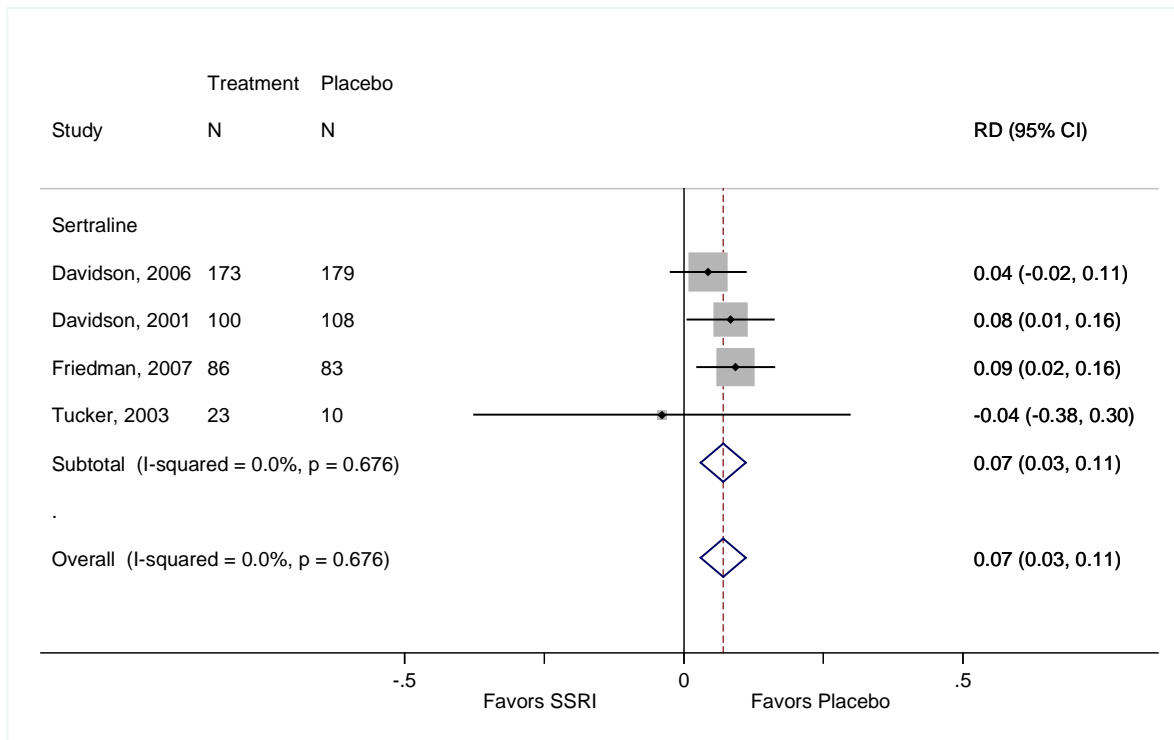


**Figure F-162. Rate of dizziness for SSRIs compared with placebo**



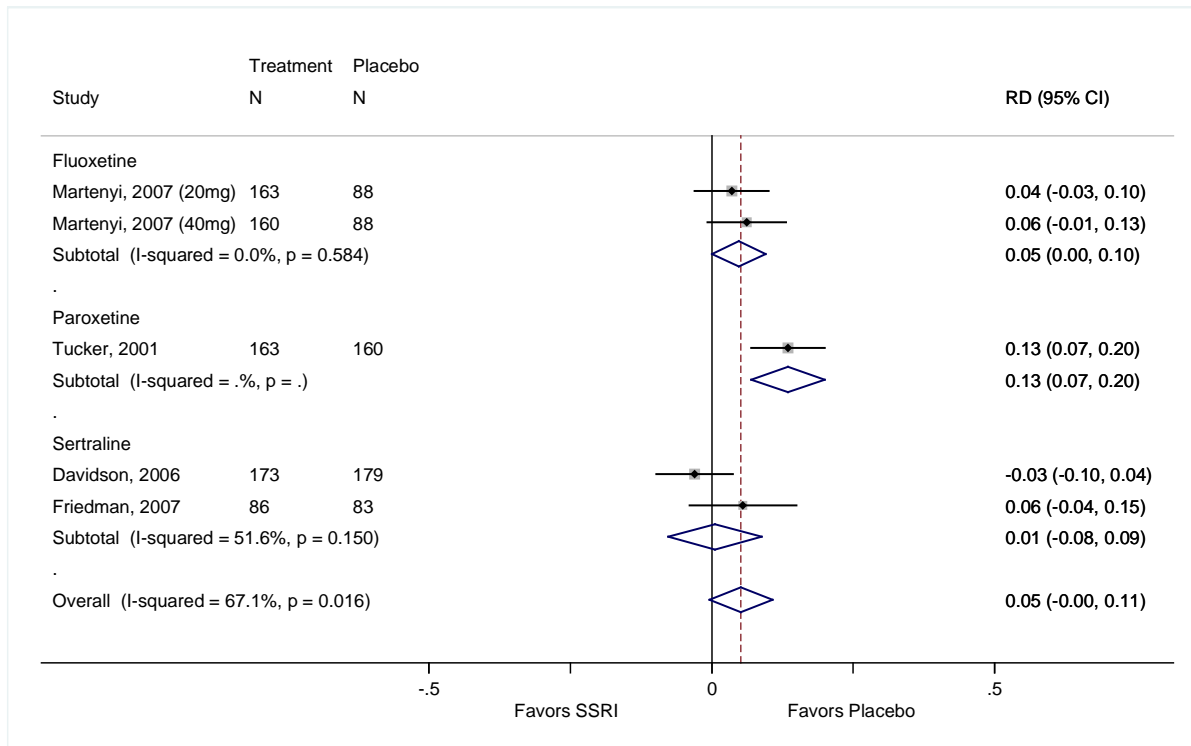
Timing of outcome assessment: 12 weeks (Davidson, 2006), 10 weeks (Tucker, 2003).

**Figure F-163. Rate of fatigue for SSRIs compared with placebo**



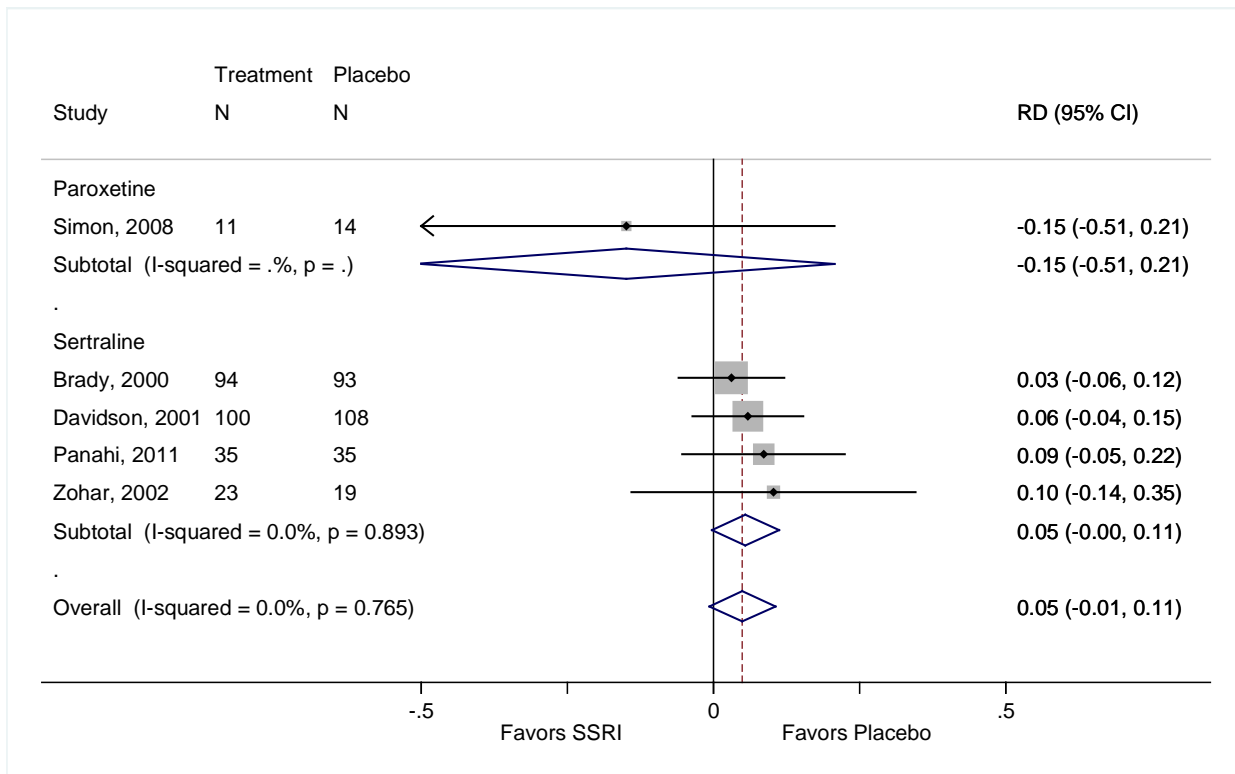
Timing of outcome assessment: 12 weeks (Davidson, 2006; Davidson, 2001; Friedman, 2007), 10 weeks (Tucker, 2003).

**Figure F-164. Rate of somnolence for SSRIs compared with placebo**



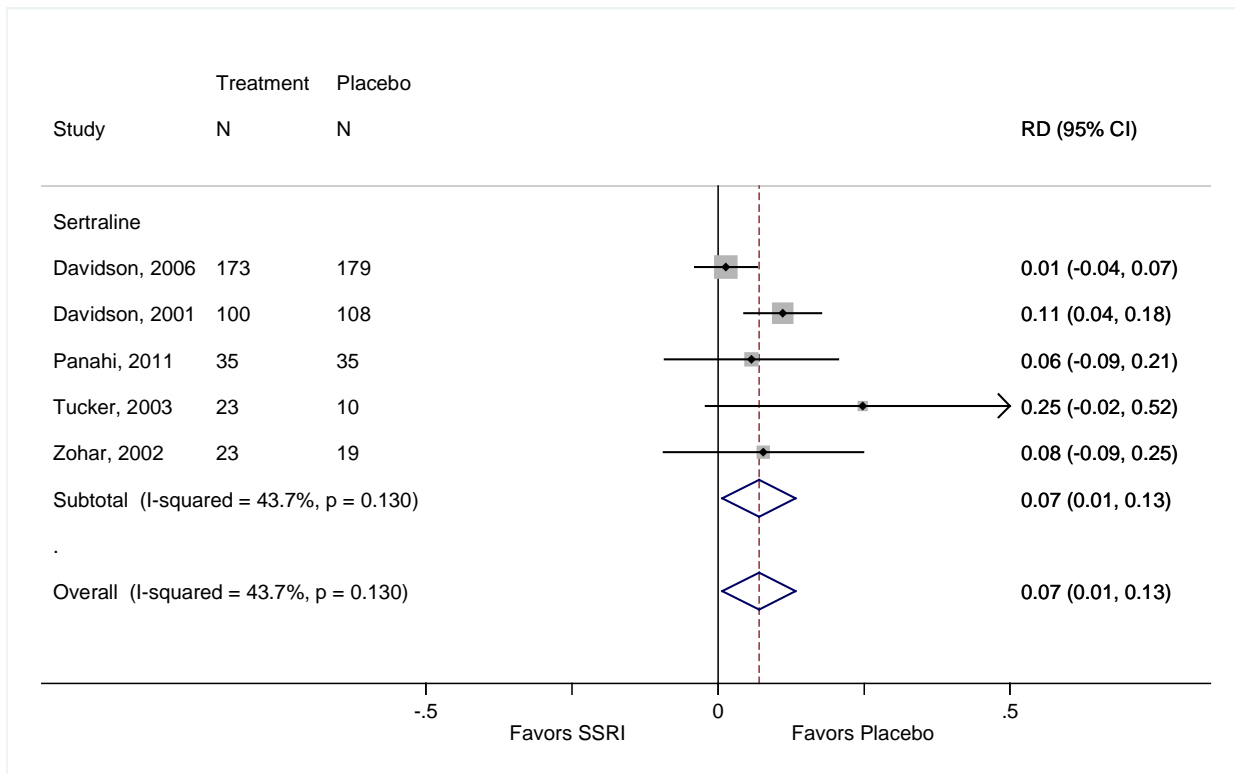
Timing of outcome assessment: 12 weeks for all included studies.

**Figure F-165. Rate of drowsiness for SSRIs compared with placebo**



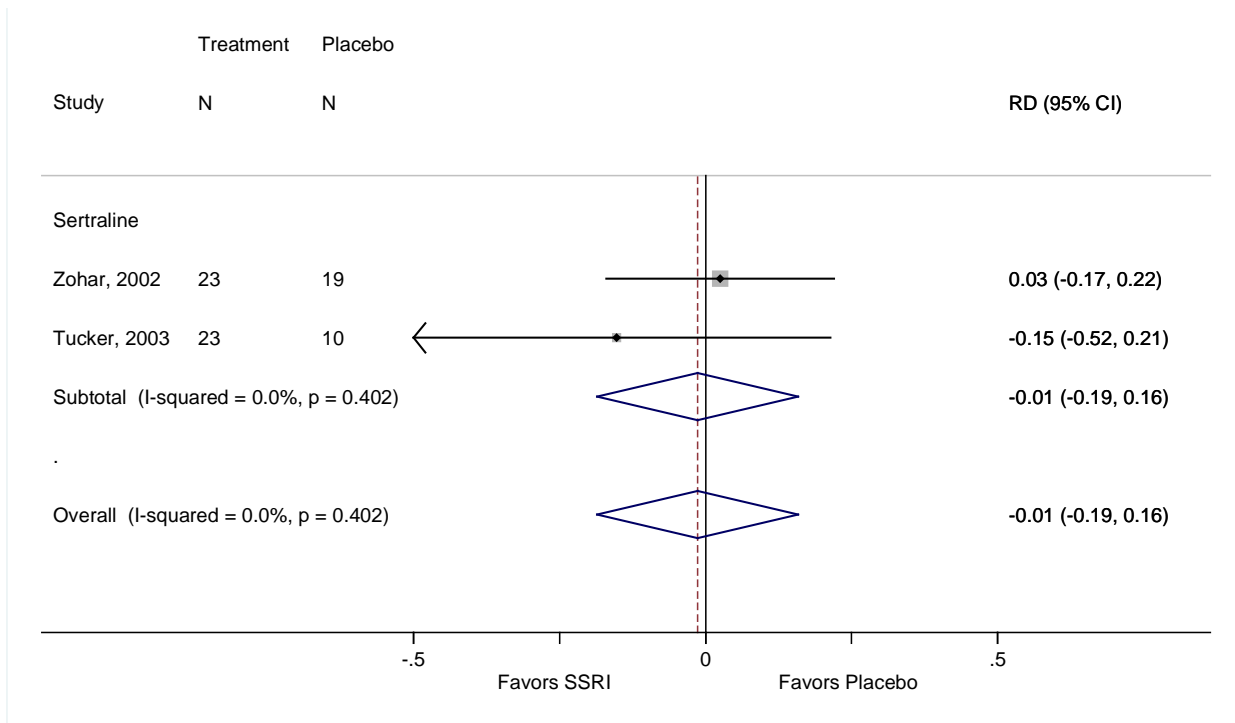
Timing of outcome assessment: 10 weeks (Simon, 2008; Panahi, 2011; Zohar, 2002), 12 weeks (Brady, 2000; Davidson, 2001).

**Figure F-166. Rate of decreased appetite for SSRIs compared with placebo**



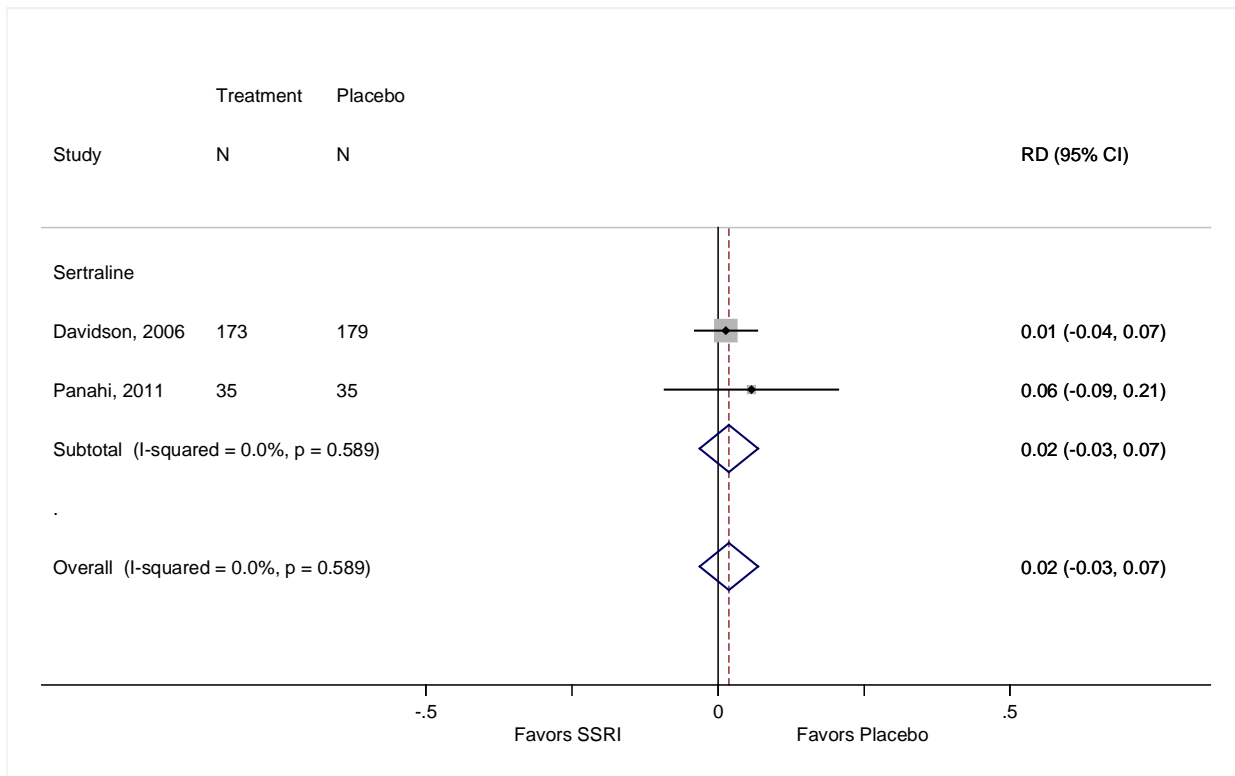
Timing of outcome assessment: 10 weeks (Panahi, 2011; Tucker, 2003; Zohar, 2002), 12 weeks (Davidson, 2006; Davidson, 2001).

**Figure F-167. Rate of increased appetite for SSRIs compared with placebo**



Timing of outcome assessment: 10 weeks for all included studies.

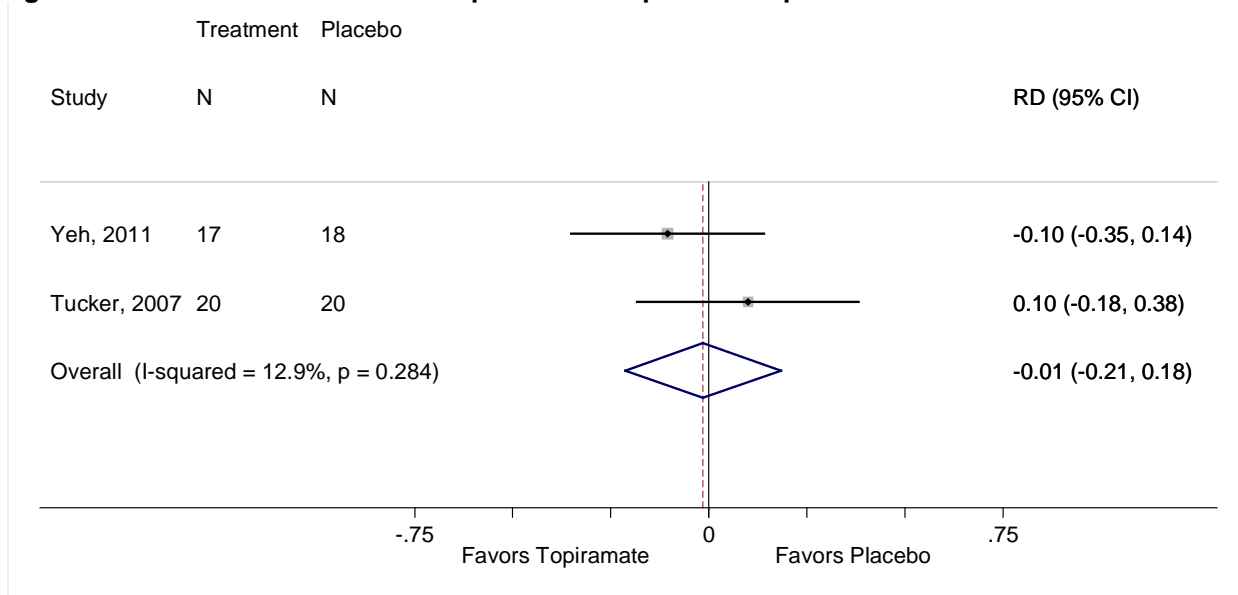
**Figure F-168. Rate of constipation for SSRIs compared with placebo**



Timing of outcome assessment: 12 weeks (Davidson, 2006), 10 weeks (Panahi, 2011).

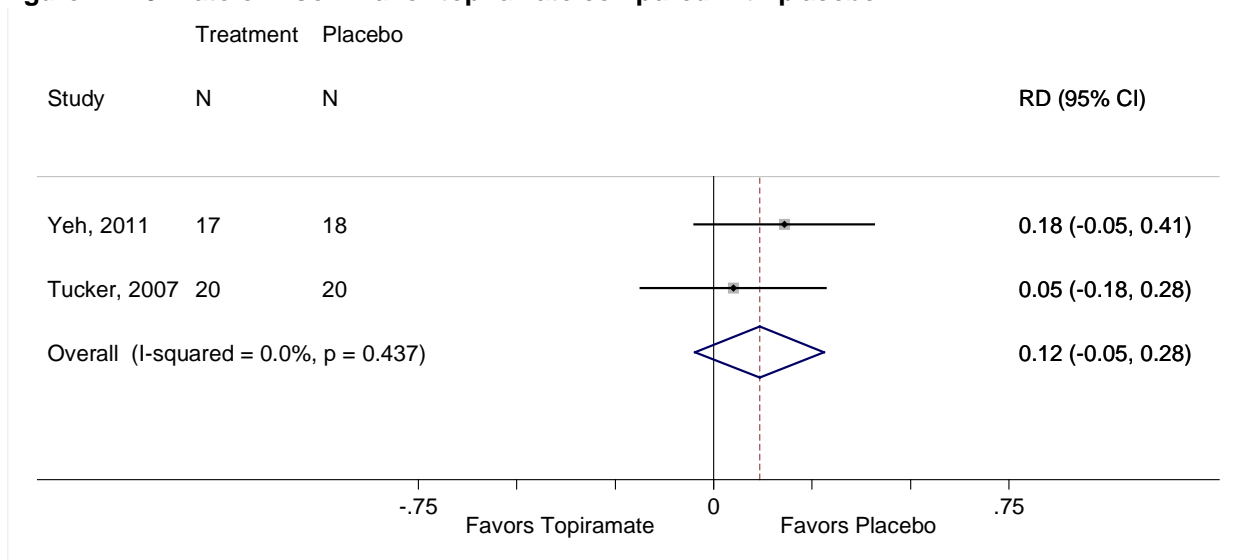
# Adverse Events - Topiramate: Meta-analysis Results

**Figure F-169. Rate of headache for topiramate compared with placebo**



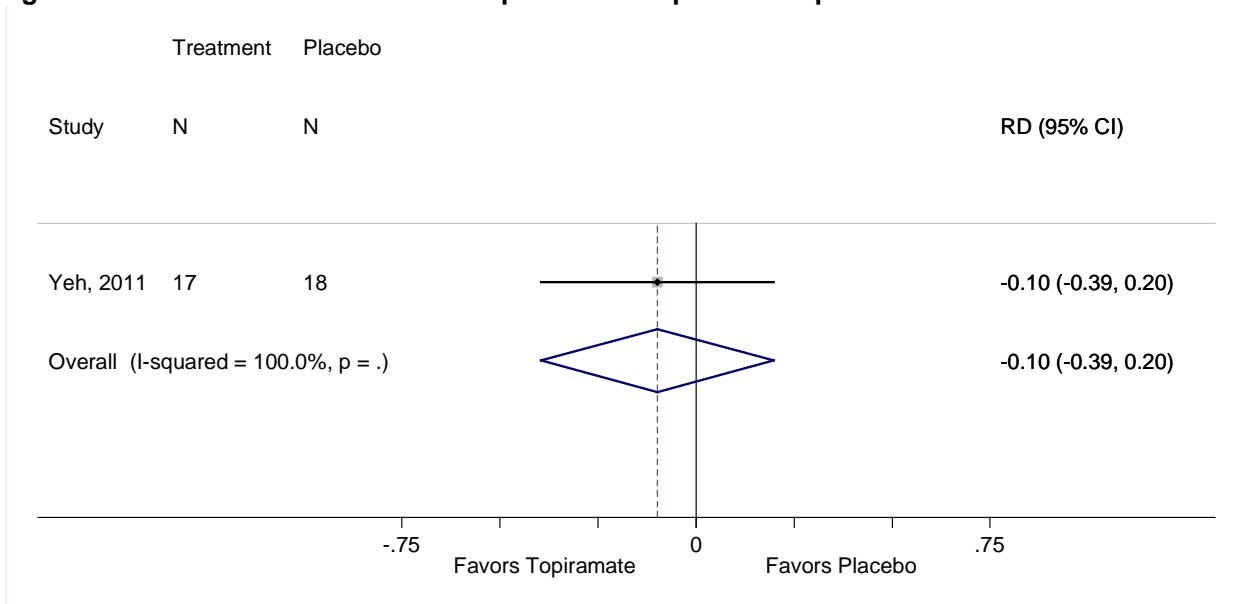
Timing of outcome assessment: 12 weeks for all included studies.

**Figure F-170. Rate of insomnia for topiramate compared with placebo**



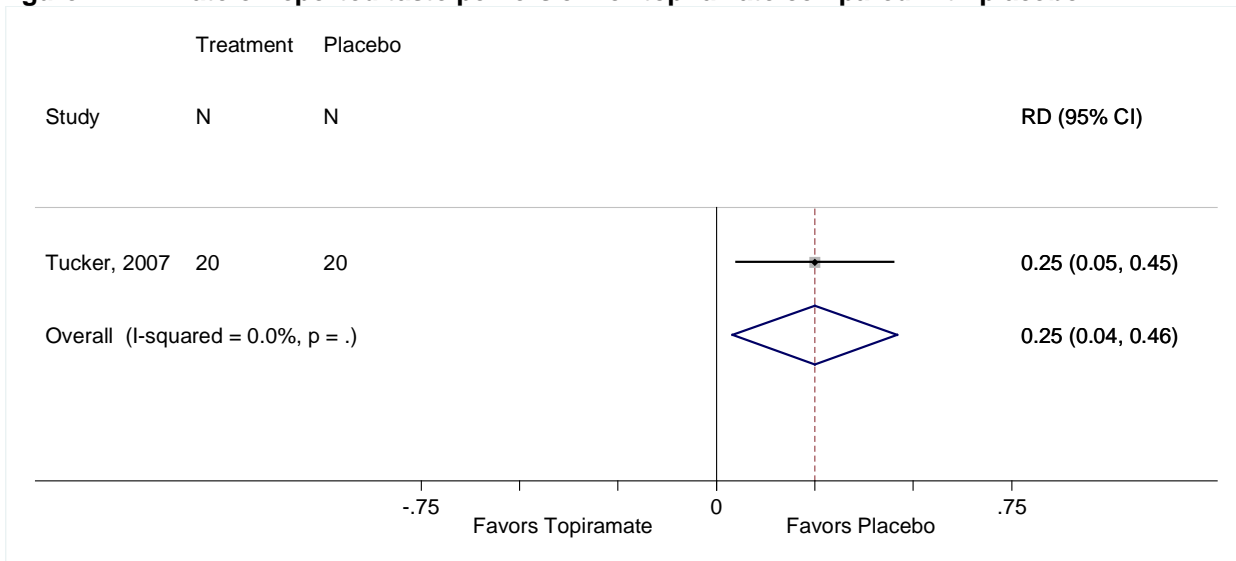
Timing of outcome assessment: 12 weeks for all included studies.

**Figure F-171. Rate of somnolence for topiramate compared with placebo**



Timing of outcome assessment: 12 weeks.

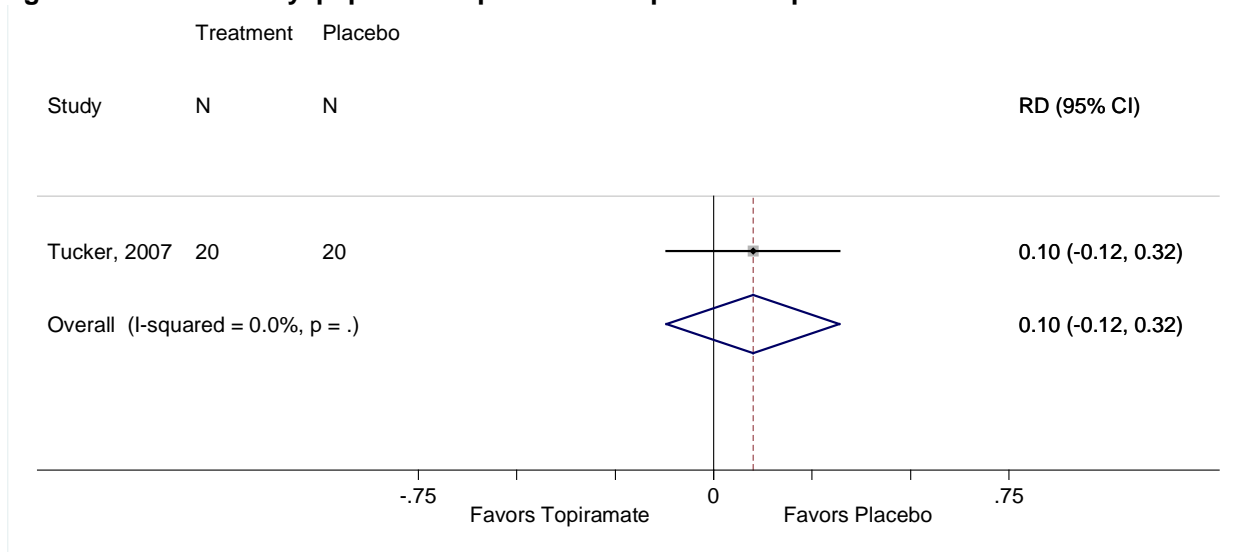
**Figure F-172. Rate of reported taste perversion for topiramate compared with placebo**



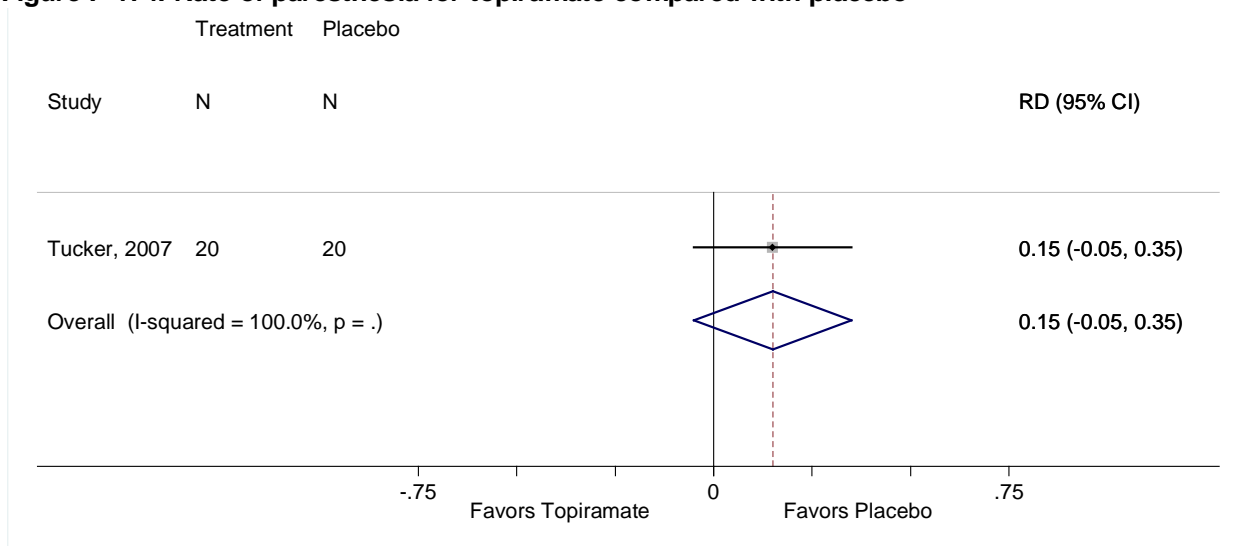
Timing of outcome assessment: 12 weeks.



**Figure F-173. Rate of dyspepsia for topiramate compared with placebo**

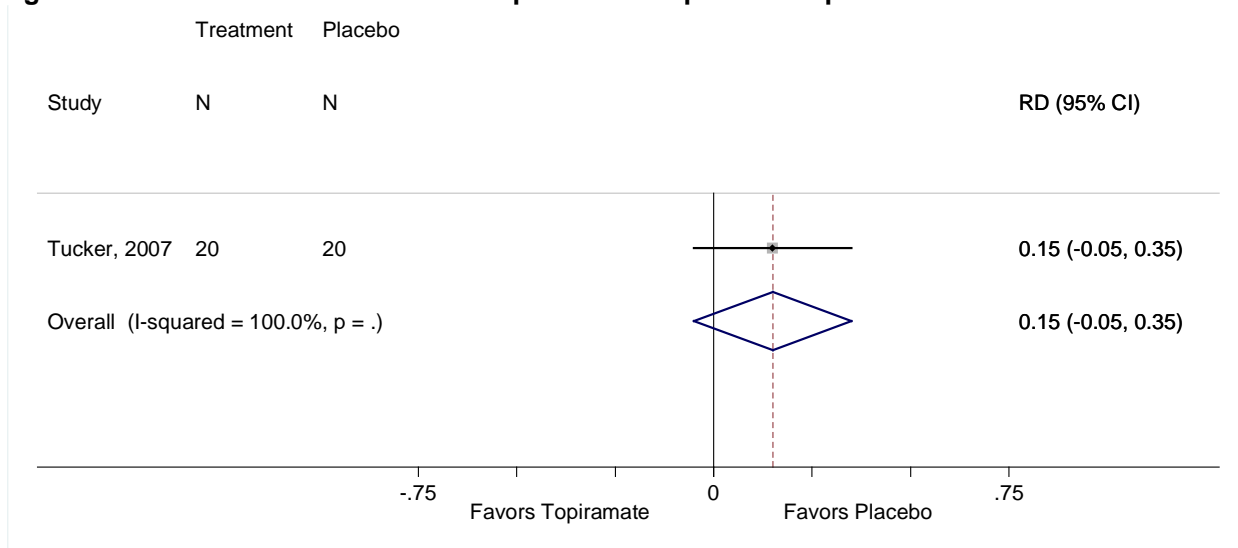


**Figure F-174. Rate of paresthesia for topiramate compared with placebo**



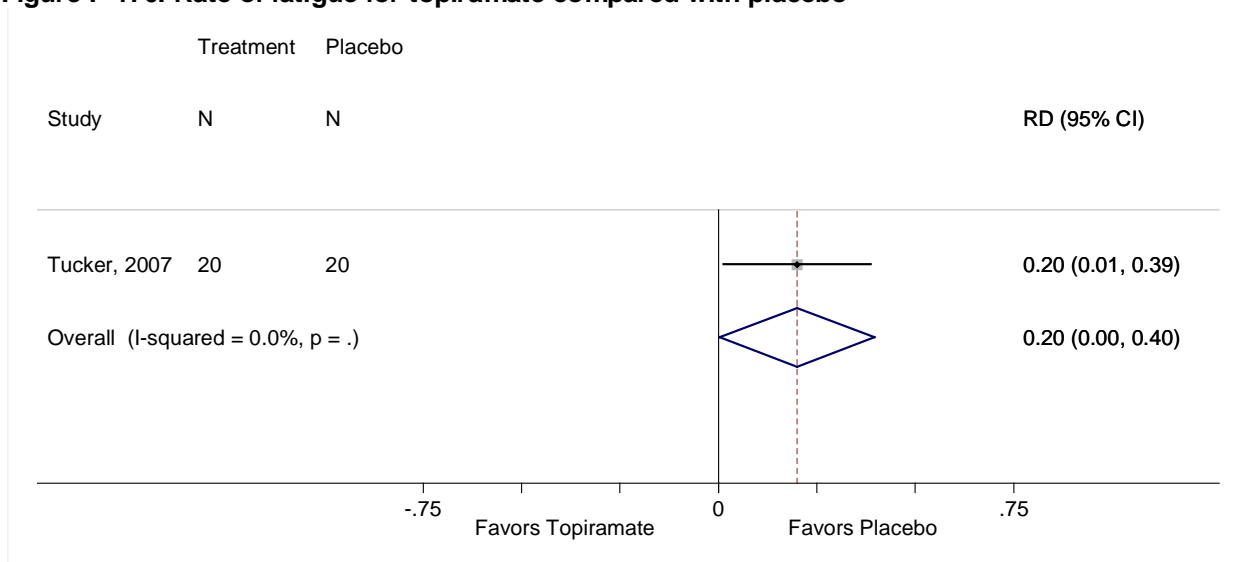
Timing of outcome assessment: 12 weeks.

**Figure F-175. Rate of nervousness for topiramate compared with placebo**



Timing of outcome assessment: 12 weeks.

**Figure F-176. Rate of fatigue for topiramate compared with placebo**



Timing of outcome assessment: 12 weeks.

## Appendix G. Strength of Evidence

### Key Question 1

**Table G-1. Cognitive processing therapy compared with inactive controls (waitlist or usual care)**

| Number of Studies;<br>Number of Subjects  | Domains Pertaining to Strength of Evidence |                         |            |                        | Magnitude of Effect   | Strength of Evidence              |
|---|--|-------------------------|------------|------------------------|---|-----------------------------------|
|   | Risk of Bias;<br>Design                    | Consistency             | Directness | Precision              | Summary Effect Size (95% CI)  | High, Moderate, Low, Insufficient |
| <b><i>PTSD Symptom Reduction: mean change from baseline to end of treatment in CAPS</i></b>                     |  |                         |            |                        |   |                                   |
| 4; 299  | Medium;<br>RCTs                            | Consistent <sup>a</sup> | Direct     | Imprecise <sup>a</sup> | -35.9 (-52.8 to -18.97) vs. WL (3 studies, N=240); -32.2 (-46.3 to -18.05) when also including the study comparing with UC    | Moderate                          |
| <b><i>Remission (no longer having symptoms)</i></b>   |  |                         |            |                        |   |                                   |
| 0; 0  | NA   | NA                      | NA         | NA                     | NA  | Insufficient                      |
| <b><i>Loss of Diagnosis</i></b>   |  |                         |            |                        |   |                                   |
| 4; 299  | Medium;<br>RCTs                            | Consistent <sup>b</sup> | Direct     | Precise                | RD 0.52 (0.37 to 0.67) vs. WL; NNT 1.9; RD 0.44 (0.26 to 0.62) when also including the study comparing with UC                | Moderate                          |
| <b><i>Prevention/reduction of comorbid depression: mean change from baseline to end of treatment in BDI</i></b> |  |                         |            |                        |   |                                   |
| 4; 299  | Medium;<br>RCTs                            | Consistent <sup>b</sup> | Direct     | Precise                | -11.9 (-18.9 to -4.9) vs. WL; -10.7 (-16.5 to -4.9) when also including the study comparing with UC                           | Moderate                          |
| <b><i>Prevention/reduction of comorbid anxiety</i></b>  |  |                         |            |                        |   |                                   |
| 2; 119  | Medium;<br>RCTs                            | Inconsistent            | Direct     | Imprecise              | Conflicting results from the two trials   | Insufficient                      |
| <b><i>Quality of Life</i></b>   |  |                         |            |                        |   |                                   |
| 1; 59   | Medium;<br>RCT                             | NA, single study        | Direct     | Imprecise              | Significant time by condition interactions for social quality of life measures, but not for physical quality of life measures | Insufficient                      |

**Table G-1. Cognitive processing therapy compared with inactive controls (waitlist or usual care) (continued)**

|   | Domains Pertaining to Strength of Evidence |    |    |    | Magnitude of Effect | Strength of Evidence |
|---|--|----|----|----|---------------------|----------------------|
| <b><i>Disability/functional impairment: change in SDS from baseline</i></b> |  |    |    |    |                     |                      |
| 0; 0  | NA   | NA | NA | NA | NA                  | Insufficient         |
| <b><i>Return to work or return to active duty</i></b>                       |  |    |    |    |                     |                      |
| 0; 0  | NA   | NA | NA | NA | NA                  | Insufficient         |

<sup>a</sup> Although the meta-analysis had considerable statistical heterogeneity ( $I^2=86.5%$ ), the direction of effects were consistent, the differences were only in the magnitude of benefit; all trials found moderate or large magnitudes of benefit. The lack of precision involves whether the magnitude of benefit is moderate or large. Therefore, we graded the SOE as moderate rather than low despite the lack of precision.

<sup>b</sup> Like the meta-analysis for PTSD symptoms, the meta-analyses for loss of diagnosis and for BDI had considerable statistical heterogeneity, but the direction of effects were consistent, the differences were only in the magnitude of benefit; all trials found moderate or large magnitudes of benefit.

Abbreviations: CI = confidence interval; CPT = cognitive processing therapy; CR = cognitive restructuring; NA = not applicable; NNT = number needed to treat; RA = repeated assessments (a type of waitlist control group); RCT = randomized controlled trial; RD = risk difference; UC = usual care; WL = waitlist

**Table G-2. Cognitive therapy (not including cognitive processing therapy) compared with inactive controls (waitlist, self-help booklet, usual care)**

| Number of Studies;<br>Number of<br>Subjects   | Domains Pertaining to Strength of<br>Evidence |   |            |           | Magnitude of<br>Effect  | Strength of<br>Evidence                    |
|---|---|---|------------|-----------|---|--|
|   | Risk of<br>Bias;<br>Design                    | Consistency   | Directness | Precision | Summary Effect<br>Size (95% CI)   | High,<br>Moderate,<br>Low,<br>Insufficient |
| <b><i>PTSD Symptom Reduction: mean change from baseline to end of treatment<sup>p</sup></i></b>                 |   |   |            |           |   |  |
| 3 <sup>a</sup> ; 221  | Medium;<br>RCTs                               | Some<br>inconsistency <sup>c</sup><br>(I <sup>2</sup> =79.6%) | Direct     | Imprecise | SMD: -1.22<br>(-1.91, -0.53)<br><br>SMD: -1.54<br>(-2.17, -0.92)<br>when only<br>compared with<br>WL (2 trials)                                   | Moderate                                   |
| <b><i>Remission (no longer having symptoms)</i></b>   |   |   |            |           |   |  |
| 0; 0  | NA  | NA  | NA         | NA        | NA  | Insufficient                               |
| <b><i>Loss of Diagnosis</i></b>   |   |   |            |           |   |  |
| 3 <sup>a</sup> ; 221  | Medium;<br>RCTs                               | Some<br>inconsistency <sup>c</sup><br>(I <sup>2</sup> =84.7%) | Direct     | Imprecise | RD: 0.51 (0.24,<br>0.78); NNT 2<br><br>RD: 0.66 (0.50,<br>0.82) when only<br>compared with<br>WL (2 trials)                                       | Moderate                                   |
| <b><i>Prevention/reduction of comorbid depression: mean change from baseline to end of treatment in BDI</i></b> |   |   |            |           |   |  |
| 3 <sup>a</sup> ; 221  | Medium;<br>RCTs                               | Consistent  | Direct     | Imprecise | SMD: -0.91<br>(-1.20, -0.62);<br>WMD: -8.34 (-<br>10.8, -5.85)<br><br>SMD: -1.06<br>(-1.52, -0.60)<br>when only<br>compared with<br>WL (2 trials) | Moderate                                   |
| <b><i>Prevention/reduction of comorbid anxiety: mean change from baseline to end of treatment in BAI</i></b>    |   |   |            |           |   |  |
| 3 <sup>a</sup> ; 221  | Medium;<br>RCTs                               | Consistent  | Direct     | Imprecise | SMD: -0.93<br>(-1.36, -0.50);<br>WMD: -9.22 (-<br>11.9, -6.5)<br><br>SMD: -1.20<br>(-1.67, -0.73)<br>when only<br>compared with<br>WL (2 trials)  | Moderate                                   |

**Table G-2. Cognitive therapy (not including cognitive processing therapy) compared with inactive controls (waitlist, self-help booklet, usual care) (continued)**

| Number of Studies;<br>Number of Subjects                             | Domains Pertaining to Strength of Evidence |                          |            |           | Magnitude of Effect   | Strength of Evidence              |
|--|--|--------------------------|------------|-----------|---|-----------------------------------|
|  | Risk of Bias;<br>Design                    | Consistency              | Directness | Precision | Summary Effect Size (95% CI)  | High, Moderate, Low, Insufficient |
| <b>Quality of Life: SF-12</b>  |  |                          |            |           |   |                                   |
| 1; 108   | Medium;<br>RCT                             | Unknown,<br>single study | Direct     | Imprecise | Better quality-of-life outcomes for CT group than usual care group for the Physical Component (p=0.002), but not for the Mental Component (p=0.13). | Insufficient                      |
| <b>Disability/functional impairment: change in SDS from baseline</b> |  |                          |            |           |   |                                   |
| 2; 113   | Medium;<br>RCTs                            | Consistent               | Direct     | Imprecise | SMD: -1.13 (-1.76, -0.51);<br>WMD -2.66 (-4.0, -1.33)<br><br>SMD: -1.41 (-2.41, -0.41) when only compared with WL (2 trials)                        | Moderate                          |
| <b>Return to work or return to active duty</b>                       |  |                          |            |           |   |                                   |
| 0; 0   | NA   | NA                       | NA         | NA        | NA  | Insufficient                      |

<sup>a</sup>Included trials compared CT with waitlist (Ehlers 2003 and Ehlers 2005), a self-help booklet (Ehlers 2003), and usual care (Muesser 2008).

<sup>b</sup>Data were based on meta-analysis of CAPS total for Muesser 2008 and CAPS-intensity for the Ehlers 2003 and 2005 studies.

<sup>c</sup>Direction of effects were consistent; magnitude of effects ranged from very large to small

Abbreviations: CI = confidence interval; NA = not applicable; NNT = number needed to treat; RCT = randomized controlled trial; RD = risk difference; WL = waitlist

**Table G-3. Stress inoculation training compared with waitlist**

| Number of Studies;<br>Number of Subjects                       | Domains Pertaining to Strength of Evidence |                  |            |           | Magnitude of Effect   | Strength of Evidence              |
|--|--|------------------|------------|-----------|---|-----------------------------------|
|  | Risk of Bias;<br>Design                    | Consistency      | Directness | Precision | Summary Effect Size (95% CI)  | High, Moderate, Low, Insufficient |
| <b><i>PTSD Symptom Reduction: PSS-I</i></b>                    |  |                  |            |           |   |                                   |
| 1; 41  | Medium;<br>RCT                             | NA, single study | Direct     | Imprecise | Baseline PSS-I: 29.4 vs. 32.9 for WL; Endpoint: 12.9 vs. 26.9; p<0.05 | Insufficient                      |
| <b><i>Remission (no longer having symptoms)</i></b>            |  |                  |            |           |   |                                   |
| 0; 0   | NA   | NA               | NA         | NA        | NA  | Insufficient                      |
| <b><i>Loss of Diagnosis</i></b>                                |  |                  |            |           |   |                                   |
| 1; 41  | Medium;<br>RCT                             | NA, single study | Direct     | Imprecise | 42% vs. 0%, p<0.001   | Insufficient                      |
| <b><i>Prevention/reduction of comorbid depression: BDI</i></b> |  |                  |            |           |   |                                   |
| 1; 41  | Medium;<br>RCT                             | NA, single study | Direct     | Imprecise | Baseline: SIT 21.7 vs. WL 25.2; Endpoint: 10.1 vs. 22.1; p<0.05       | Insufficient                      |
| <b><i>Prevention/reduction of comorbid anxiety: STAI</i></b>   |  |                  |            |           |   |                                   |
| 1; 41  | Medium;<br>RCT                             | NA, single study | Direct     | Imprecise | Baseline: SIT 51.5 vs. WL 51.4; Endpoint: 39.1 vs. 50.4; p=0.14       | Insufficient                      |
| <b><i>Quality of Life</i></b>                                  |  |                  |            |           |   |                                   |
| 0; 0   | NA   | NA               | NA         | NA        | NA  | Insufficient                      |
| <b><i>Disability/functional impairment</i></b>                 |  |                  |            |           |   |                                   |
| 0; 0   | NA   | NA               | NA         | NA        | NA  | Insufficient                      |
| <b><i>Return to work or return to active duty</i></b>          |  |                  |            |           |   |                                   |
| 0; 0   | NA   | NA               | NA         | NA        | NA  | Insufficient                      |

Abbreviations: CI = confidence interval; NA = not applicable; PSS-I = Posttraumatic Stress Disorder Symptom Scale-Interview; RCT = randomized controlled trial

**Table G-4. Relaxation compared with treatment as usual**

| Number of Studies;<br>Number of Subjects                       | Domains Pertaining to Strength of Evidence |                  |            |           | Magnitude of Effect   | Strength of Evidence              |
|--|--|------------------|------------|-----------|---|-----------------------------------|
|  | Risk of Bias;<br>Design                    | Consistency      | Directness | Precision | Summary Effect Size (95% CI)                                | High, Moderate, Low, Insufficient |
| <b><i>PTSD Symptom Reduction</i></b>                           |  |                  |            |           |   |                                   |
| 1; 25  | Medium;<br>RCT                             | NA, single study | Direct     | Imprecise | No benefit found for 3 different measures                   | Insufficient                      |
| <b><i>Remission (no longer having symptoms)</i></b>            |  |                  |            |           |   |                                   |
| 0; 0   | NA   | NA               | NA         | NA        | NA  | Insufficient                      |
| <b><i>Loss of Diagnosis</i></b>                                |  |                  |            |           |   |                                   |
| 1; 25  | Medium;<br>RCT                             | NA, single study | Direct     | Imprecise | Trial did not report data for the inactive comparator group | Insufficient                      |
| <b><i>Prevention/reduction of comorbid depression: BDI</i></b> |  |                  |            |           |   |                                   |
| 1; 25  | Medium;<br>RCT                             | NA, single study | Direct     | Imprecise | Results trend in favor of relaxation                        | Insufficient                      |
| <b><i>Prevention/reduction of comorbid anxiety: STAI</i></b>   |  |                  |            |           |   |                                   |
| 1; 25  | Medium;<br>RCT                             | NA, single study | Direct     | Imprecise | Results trend in favor of relaxation                        | Insufficient                      |
| <b><i>Quality of Life</i></b>                                  |  |                  |            |           |   |                                   |
| 0; 0   | NA   | NA               | NA         | NA        | NA  | Insufficient                      |
| <b><i>Disability/functional impairment</i></b>                 |  |                  |            |           |   |                                   |
| 0; 0   | NA   | NA               | NA         | NA        | NA  | Insufficient                      |
| <b><i>Return to work or return to active duty</i></b>          |  |                  |            |           |   |                                   |
| 0; 0   | NA   | NA               | NA         | NA        | NA  | Insufficient                      |

Abbreviations: CI = confidence interval; NA = not applicable; RCT = randomized controlled trial



**Table G-5. Relaxation compared with cognitive restructuring**

| Number of Studies; Number of Subjects   | Domains Pertaining to Strength of Evidence |                  |            |           | Magnitude of Effect           | Strength of Evidence              |
|---|--|------------------|------------|-----------|-------------------------------|-----------------------------------|
|   | Risk of Bias; Design                       | Consistency      | Directness | Precision | Summary Effect Size (95% CI)  | High, Moderate, Low, Insufficient |
| <b>PTSD Symptom Reduction: percentage of patients improved (IES)</b>                          |  |                  |            |           |                               |                                   |
| 1; 34 <sup>a</sup>  | Medium; RCT                                | NA, single study | Direct     | Imprecise | 20% vs. 50%, p=0.04           | Insufficient                      |
| <b>Remission (no longer having symptoms)</b>  |  |                  |            |           |                               |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA                            | Insufficient                      |
| <b>Loss of Diagnosis</b>  |  |                  |            |           |                               |                                   |
| 1; 34 <sup>a</sup>  | Medium; RCT                                | NA, single study | Direct     | Imprecise | 55% vs. 65%, p=NS             | Insufficient                      |
| <b>Prevention/reduction of comorbid depression: BDI, mean change scores (improvement)</b>     |  |                  |            |           |                               |                                   |
| 1; 34 <sup>a</sup>  | Medium; RCT                                | NA, single study | Direct     | Imprecise | 7 (3 to 11) vs. 17 (11 to 22) | Insufficient                      |
| <b>Prevention/reduction of comorbid anxiety</b>   |  |                  |            |           |                               |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA                            | Insufficient                      |
| <b>Quality of Life</b>  |  |                  |            |           |                               |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA                            | Insufficient                      |
| <b>Disability/functional impairment: End-state functioning (percent of subjects improved)</b> |  |                  |            |           |                               |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA                            | Insufficient                      |
| <b>Return to work or return to active duty</b>  |  |                  |            |           |                               |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA                            | Insufficient                      |

<sup>a</sup>Total trial N was 81. Subjects were randomized to PE (23), CR (13), CBT- Mb (CR+PE) (24), or relaxation (21).<sup>3</sup>

Abbreviations: CI = confidence interval; NA = not applicable; RCT = randomized controlled trial

**Table G-6. Exposure-based therapies compared with inactive controls (waitlist or usual care)**

| Number of Studies;<br>Number of Subjects                | Domains Pertaining to Strength of Evidence |                                      |            |           | Magnitude of Effect  | Strength of Evidence              |
|---|--|--------------------------------------|------------|-----------|--|-----------------------------------|
|   | Risk of Bias;<br>Design                    | Consistency                          | Directness | Precision | Summary Effect Size (95% CI)   | High, Moderate, Low, Insufficient |
| <b>PTSD Symptom Reduction: CAPS</b>                     |  |                                      |            |           |  |                                   |
| 7; 387  | Medium;<br>RCTs                            | Consistent                           | Direct     | Precise   | SMD -1.27 (-1.54 to -1.00)   | High                              |
| <b>Remission (no longer having symptoms)</b>            |  |                                      |            |           |  |                                   |
| 1; 284  | Medium;<br>RCT                             | NA, single study                     | Direct     | Imprecise | OR 2.43 (1.10 to 5.37)   | Insufficient                      |
| <b>Loss of Diagnosis</b>                                |  |                                      |            |           |  |                                   |
| 3; 197  | Medium;<br>RCTs                            | Inconsistent (I <sup>2</sup> =86.5%) | Direct     | Imprecise | RD 0.66 (0.42 to 0.91); NNT of 1.5   | Moderate <sup>a</sup>             |
| <b>Prevention/reduction of comorbid depression: BDI</b> |  |                                      |            |           |  |                                   |
| 6; 363  | Medium;<br>RCTs                            | Consistent (I <sup>2</sup> =0%)      | Direct     | Precise   | WMD -8.2 (-10.3 to -6.1)   | High                              |
| <b>Prevention/reduction of comorbid anxiety</b>         |  |                                      |            |           |  |                                   |
| 0; 0  | N/A  | N/A                                  | N/A        | N/A       | N/A  | Insufficient                      |
| <b>Quality of Life</b>                                  |  |                                      |            |           |  |                                   |
| 0; 0  | N/A  | N/A                                  | N/A        | N/A       | N/A  | Insufficient <sup>b</sup>         |
| <b>Disability/functional impairment</b>                 |  |                                      |            |           |  |                                   |
| 2; 221  | Medium;<br>RCTs                            | Inconsistent                         | Direct     | Imprecise | Cohen's d 0.8 at 4 wks, 0.6 at 8 wks from one trial (N=31); numerically greater improvements on the Social Adjustment Scale for another trial (N=190) exposure and exposure plus CR than for waitlist, but the differences were not statistically significant. | Insufficient                      |
| <b>Return to work or return to active duty</b>          |  |                                      |            |           |  |                                   |
| 0; 0  | N/A  | N/A                                  | N/A        | N/A       | N/A  | N/A                               |

<sup>a</sup> With the very large effect sizes, we graded the SOE as moderate despite the inconsistency; the direction of effects was the same and the inconsistency was only in magnitude of benefit (which was large or very large in the three trials).

<sup>b</sup> One study comparing prolonged exposure with present centered therapy reported a quality of life outcome, finding that groups did not differ across time (Cohen's d 0.09, NS). No studies with a waitlist or usual care comparator reported quality of life outcomes.

Abbreviations: CI = confidence interval; NA = not applicable; RCT = randomized controlled trial

**Table G-7. Exposure-based therapy compared with cognitive restructuring**

| Number of Studies;<br>Number of Subjects  | Domains Pertaining to Strength of Evidence |                                    |            |           | Magnitude of Effect          | Strength of Evidence              |
|---|--|------------------------------------|------------|-----------|------------------------------|-----------------------------------|
|   | Risk of Bias;<br>Design                    | Consistency                        | Directness | Precision | Summary Effect Size (95% CI) | High, Moderate, Low, Insufficient |
| <b>PTSD Symptom Reduction: CAPS</b>   |  |                                    |            |           |                              |                                   |
| 2; 100  | Medium;<br>RCTs                            | Consistent<br>(I <sup>2</sup> =0%) | Direct     | Imprecise | WMD 4.8 (-4.5 to 14.2)       | Insufficient                      |
| <b>Remission (no longer having symptoms)</b>  |  |                                    |            |           |                              |                                   |
| 0; 0  | NA   | NA                                 | NA         | NA        | NA                           | Insufficient                      |
| <b>Loss of Diagnosis</b>  |  |                                    |            |           |                              |                                   |
| 2; 100  | Medium;<br>RCTs                            | Consistent<br>(I <sup>2</sup> =0%) | Direct     | Imprecise | RD 0.13 (-0.06 to 0.32)      | Insufficient                      |
| <b>Prevention/reduction of comorbid depression: BDI</b>   |  |                                    |            |           |                              |                                   |
| 2; 100  | Medium;<br>RCTs                            | Consistent<br>(I <sup>2</sup> =0%) | Direct     | Imprecise | WMD 2.75 (-1.94 to 7.43)     | Insufficient                      |
| <b>Prevention/reduction of comorbid anxiety</b>   |  |                                    |            |           |                              |                                   |
| 1; 72   | Medium;<br>RCT                             | NA, single study                   | Direct     | Imprecise | No significant difference    | Insufficient                      |
| <b>Quality of Life</b>  |  |                                    |            |           |                              |                                   |
| 0; 0  | NA   | NA                                 | NA         | NA        | NA                           | Insufficient                      |
| <b>Disability/functional impairment</b>   |  |                                    |            |           |                              |                                   |
| 0; 0  | NA   | NA                                 | NA         | NA        | NA                           | Insufficient                      |
| <b>Return to work or return to active duty: % of subjects actively working at 6 month follow up</b> |  |                                    |            |           |                              |                                   |
| 1; 72   | Medium;<br>RCT                             | NA, single study                   | Direct     | Imprecise | 44% vs. 37%                  | Insufficient                      |

Abbreviations: CI = confidence interval; NA = not applicable; RCT = randomized controlled trial

**Table G-8. Exposure-based therapy compared with cognitive processing therapy**

| Number of Studies;<br>Number of Subjects   | Domains Pertaining to Strength of Evidence |                  |            |           | Magnitude of Effect          | Strength of Evidence              |
|--|--|------------------|------------|-----------|------------------------------|-----------------------------------|
|  | Risk of Bias;<br>Design                    | Consistency      | Directness | Precision | Summary Effect Size (95% CI) | High, Moderate, Low, Insufficient |
| <b><i>PTSD Symptom Reduction: CAPS</i></b>   |  |                  |            |           |                              |                                   |
| 1; 124   | Medium;<br>RCT                             | NA, single study | Direct     | Imprecise | WMD 3.97 (-5.95 to 13.9)     | Insufficient                      |
| <b><i>Remission (no longer having symptoms)</i></b>  |  |                  |            |           |                              |                                   |
| 0; 0   | NA   | NA               | NA         | NA        | NA                           | Insufficient                      |
| <b><i>Loss of Diagnosis</i></b>  |  |                  |            |           |                              |                                   |
| 1; 124   | Medium;<br>RCT                             | NA, single study | Direct     | Imprecise | RD 0.00 (-0.18 to 0.18)      | Insufficient                      |
| <b><i>Prevention/reduction of comorbid depression: BDI</i></b>   |  |                  |            |           |                              |                                   |
| 1; 124   | Medium;<br>RCT                             | NA, single study | Direct     | Imprecise | WMD 2.94 (-0.75 to 6.63)     | Insufficient                      |
| <b><i>Prevention/reduction of comorbid anxiety</i></b>   |  |                  |            |           |                              |                                   |
| 0; 0   | NA   | NA               | NA         | NA        | NA                           | Insufficient                      |
| <b><i>Quality of Life</i></b>  |  |                  |            |           |                              |                                   |
| 0; 0   | NA   | NA               | NA         | NA        | NA                           | Insufficient                      |
| <b><i>Disability/functional impairment</i></b>   |  |                  |            |           |                              |                                   |
| 0; 0   | NA   | NA               | NA         | NA        | NA                           | Insufficient                      |
| <b><i>Return to work or return to active duty: % of subjects actively working at 6 month follow up</i></b> |  |                  |            |           |                              |                                   |
| 0; 0   | NA   | NA               | NA         | NA        | NA                           | Insufficient                      |

Abbreviations: CI = confidence interval; NA = not applicable; RCT = randomized controlled trial

**Table G-9. Exposure-based therapy compared with stress inoculation training**

| Number of Studies;<br>Number of Subjects                       | Domains Pertaining to Strength of Evidence |                  |            |           | Magnitude of Effect          | Strength of Evidence              |
|--|--|------------------|------------|-----------|------------------------------|-----------------------------------|
|  | Risk of Bias;<br>Design                    | Consistency      | Directness | Precision | Summary Effect Size (95% CI) | High, Moderate, Low, Insufficient |
| <b><i>PTSD Symptom Reduction: CAPS</i></b>                     |  |                  |            |           |                              |                                   |
| 1; 51  | Medium;<br>RCT                             | NA, single study | Direct     | Imprecise | SMD -0.14 (-0.69 to 0.41)    | Insufficient                      |
| <b><i>Remission (no longer having symptoms)</i></b>            |  |                  |            |           |                              |                                   |
| 0; 0   | NA   | NA               | NA         | NA        | NA                           | Insufficient                      |
| <b><i>Loss of Diagnosis</i></b>                                |  |                  |            |           |                              |                                   |
| 1; 51  | Medium;<br>RCT                             | NA, single study | Direct     | Imprecise | RD 0.18 (-0.09 to 0.45)      | Insufficient                      |
| <b><i>Prevention/reduction of comorbid depression: BDI</i></b> |  |                  |            |           |                              |                                   |
| 1; 51  | Medium;<br>RCT                             | NA, single study | Direct     | Imprecise | WMD -0.15 (-5.8 to 5.5)      | Insufficient                      |
| <b><i>Prevention/reduction of comorbid anxiety: STAI</i></b>   |  |                  |            |           |                              |                                   |
| 0; 0   | NA   | NA               | NA         | NA        | NA                           | Insufficient                      |
| <b><i>Quality of Life</i></b>                                  |  |                  |            |           |                              |                                   |
| 0; 0   | NA   | NA               | NA         | NA        | NA                           | Insufficient                      |
| <b><i>Disability/functional impairment</i></b>                 |  |                  |            |           |                              |                                   |
| 0; 0   | NA   | NA               | NA         | NA        | NA                           | Insufficient                      |
| <b><i>Return to work or return to active duty</i></b>          |  |                  |            |           |                              |                                   |
| 0; 0   | NA   | NA               | NA         | NA        | NA                           | Insufficient                      |

Abbreviations: NA = not applicable

**Table G-10. Exposure-based therapy compared with relaxation**

| Number of Studies; Number of Subjects                          | Domains Pertaining to Strength of Evidence |             |            |           | Magnitude of Effect          | Strength of Evidence              |
|--|--|-------------|------------|-----------|------------------------------|-----------------------------------|
|  | Risk of Bias; Design                       | Consistency | Directness | Precision | Summary Effect Size (95% CI) | High, Moderate, Low, Insufficient |
| <b><i>PTSD Symptom Reduction: CAPS</i></b>                     |  |             |            |           |                              |                                   |
| 2; 85  | Medium; RCTs                               | Consistent  | Direct     | Imprecise | WMD -9.7 (-22.3 to 2.9)      | Insufficient                      |
| <b><i>Remission (no longer having symptoms)</i></b>            |  |             |            |           |                              |                                   |
| 0; 0   | NA   | NA          | NA         | NA        | NA                           | Insufficient                      |
| <b><i>Loss of Diagnosis</i></b>                                |  |             |            |           |                              |                                   |
| 2; 85  | Medium; RCTs                               | Consistent  | Direct     | Precise   | RD 0.31 (0.04 to 0.58)       | Moderate                          |
| <b><i>Prevention/reduction of comorbid depression: BDI</i></b> |  |             |            |           |                              |                                   |
| 2; 85  | Medium; RCTs                               | Consistent  | Direct     | Precise   | WMD -5.5 (-10.2 to -0.79)    | Moderate                          |
| <b><i>Prevention/reduction of comorbid anxiety: STAI</i></b>   |  |             |            |           |                              |                                   |
| 0; 0   | NA   | NA          | NA         | NA        | NA                           | Insufficient                      |
| <b><i>Quality of Life</i></b>                                  |  |             |            |           |                              |                                   |
| 0; 0   | NA   | NA          | NA         | NA        | NA                           | Insufficient                      |
| <b><i>Disability/functional impairment</i></b>                 |  |             |            |           |                              |                                   |
| 0; 0   | NA   | NA          | NA         | NA        | NA                           | Insufficient                      |
| <b><i>Return to work or return to active duty</i></b>          |  |             |            |           |                              |                                   |
| 0; 0   | NA   | NA          | NA         | NA        | NA                           | Insufficient                      |

Abbreviations: NA = not applicable

**Table G-11. Exposure-based therapy compared with EMDR**

| Number of Studies; Number of Subjects                          | Domains Pertaining to Strength of Evidence |                  |            |           | Magnitude of Effect                        | Strength of Evidence              |
|--|--|------------------|------------|-----------|--|-----------------------------------|
|  | Risk of Bias; Design                       | Consistency      | Directness | Precision | Summary Effect Size (95% CI)               | High, Moderate, Low, Insufficient |
| <b><i>PTSD Symptom Reduction: CAPS</i></b>                     |  |                  |            |           |  |                                   |
| 2; 91  | Medium; RCTs                               | Consistent       | Direct     | Imprecise | No difference EMDR and PE                  | Insufficient                      |
| <b><i>Remission (no longer having symptoms)</i></b>            |  |                  |            |           |  |                                   |
| 0; 0   | NA   | NA               | NA         | NA        | NA   | Insufficient                      |
| <b><i>Loss of Diagnosis</i></b>                                |  |                  |            |           |  |                                   |
| 2; 91  | Medium; RCTs                               | Inconsistent     | Direct     | Imprecise | RD 0.14 (-0.01 to 0.29)                    | Insufficient                      |
| <b><i>Prevention/reduction of comorbid depression: BDI</i></b> |  |                  |            |           |  |                                   |
| 2; 91  | Medium; RCTs                               | Consistent       | Direct     | Imprecise | No difference EMDR and PE                  | Insufficient                      |
| <b><i>Prevention/reduction of comorbid anxiety: STAI</i></b>   |  |                  |            |           |  |                                   |
| 1; 50  | Medium; RCT                                | NA, single study | Direct     | Imprecise | No difference EMDR and PE on state anxiety | Insufficient                      |
| <b><i>Quality of Life</i></b>                                  |  |                  |            |           |  |                                   |
| 0; 0   | NA   | NA               | NA         | NA        | NA   | Insufficient                      |
| <b><i>Disability/functional impairment</i></b>                 |  |                  |            |           |  |                                   |
| 0; 0   | NA   | NA               | NA         | NA        | NA   | Insufficient                      |
| <b><i>Return to work or return to active duty</i></b>          |  |                  |            |           |  |                                   |
| 0; 0   | NA   | NA               | NA         | NA        | NA   | Insufficient                      |

Abbreviations: CI = confidence interval; NA = not applicable; PE = prolonged exposure; RCT = randomized controlled trial

**Table G-12. Exposure-based therapy compared with exposure therapy + cognitive restructuring**

| Number of Studies; Number of Subjects                   | Domains Pertaining to Strength of Evidence |                               |            |           | Magnitude of Effect          | Strength of Evidence              |
|---|--|-------------------------------|------------|-----------|------------------------------|-----------------------------------|
|   | Risk of Bias; Design                       | Consistency                   | Directness | Precision | Summary Effect Size (95% CI) | High, Moderate, Low, Insufficient |
| <b>PTSD Symptom Reduction: CAPS</b>                     |  |                               |            |           |                              |                                   |
| 3; 259  | Medium; RCTs                               | Inconsistent                  | Direct     | Imprecise | SMD 0.25 (-0.29 to 0.80)     | Insufficient                      |
| <b>Remission (no longer having symptoms)</b>            |  |                               |            |           |                              |                                   |
| 0; 0  | NA   | NA                            | NA         | NA        | NA                           | Insufficient                      |
| <b>Loss of Diagnosis</b>                                |  |                               |            |           |                              |                                   |
| 3; 146  | Medium; RCTs                               | Consistent ( $I^2=0\%$ )      | Direct     | Precise   | RD -0.01 (-0.17 to 0.14)     | Moderate                          |
| <b>Prevention/reduction of comorbid depression: BDI</b> |  |                               |            |           |                              |                                   |
| 4; 299  | Medium; RCTs                               | Inconsistent ( $I^2=54.4\%$ ) | Direct     | Imprecise | WMD 2.78 (-1.68 to 7.25)     | Insufficient                      |
| <b>Prevention/reduction of comorbid anxiety: STAI</b>   |  |                               |            |           |                              |                                   |
| 2; 99   | Medium; RCTs                               | Consistent                    | Direct     | Imprecise | No difference between groups | Insufficient                      |
| <b>Quality of Life</b>                                  |  |                               |            |           |                              |                                   |
| 0; 0  | NA   | NA                            | NA         | NA        | NA                           | Insufficient                      |
| <b>Disability/functional impairment</b>                 |  |                               |            |           |                              |                                   |
| 0; 0  | NA   | NA                            | NA         | NA        | NA                           | Insufficient                      |
| <b>Return to work or return to active duty</b>          |  |                               |            |           |                              |                                   |
| 0; 0  | NA   | NA                            | NA         | NA        | NA                           | Insufficient                      |

Abbreviations: CI = confidence interval; NA = not applicable; RCT = randomized controlled trial



**Table G-13. CBT-mixed interventions compared with inactive controls (waitlist, usual care)**

| Number of Studies; Number of Subjects   | Domains Pertaining to Strength of Evidence |                                     |            | Magnitude of Effect | Strength of Evidence   |                                   |
|---|--|-------------------------------------|------------|---------------------|--|-----------------------------------|
|   | Risk of Bias; Design                       | Consistency <sup>a</sup>            | Directness | Precision           | Summary Effect Size (95% CI)   | High, Moderate, Low, Insufficient |
| <b>PTSD Symptom Reduction: mean change from baseline to end of treatment for CAPS</b>   |  |                                     |            |                     |  |                                   |
| 8; 476  | Medium; RCTs                               | Some inconsistency ( $I^2=87\%$ )   | Direct     | Precise             | WMD -31.1 (-42.6 to -19.6); WMD -34.4 (-45.5, -23.2) when compared with WL (7 of the 8 trials)             | Moderate                          |
| <b>PTSD Symptom Reduction: mean change from baseline to end of treatment for various measures (combined to calculate effect size)</b> |  |                                     |            |                     |  |                                   |
| 14; 825   | Medium; RCTs                               | Some inconsistency ( $I^2=75.3\%$ ) | Direct     | Precise             | SMD -1.09 (-1.4 to -0.78); SMD -1.16 (-1.47, -0.84) when only compared with WL (13 trials)                 | Moderate                          |
| <b>Remission (no longer having symptoms)</b>  |  |                                     |            |                     |  |                                   |
| 2; 114  | Medium; RCTs                               | Consistent                          | Direct     | Precise             | Data not pooled <sup>b</sup>   | Moderate                          |
| <b>Loss of Diagnosis</b>  |  |                                     |            |                     |  |                                   |
| 6; 290  | Medium; RCTs                               | Some inconsistency ( $I^2=60.5\%$ ) | Direct     | Precise             | RD 0.26 (0.11 to 0.41); NNT 3.8; RD 0.29 (-0.01 to 0.60) and NNT 3.4 when only compared with WL (3 trials) | Moderate                          |
| <b>Prevention/reduction of comorbid depression: mean change from baseline in BDI</b>  |  |                                     |            |                     |  |                                   |
| 10; 662   | Medium; RCTs                               | Some inconsistency ( $I^2=81.3\%$ ) | Direct     | Precise             | WMD -10.4 (-14.4 to -6.4); WMD -10.4 when only compared with WL (9 trials)                                 | Moderate                          |
| <b>Prevention/reduction of comorbid anxiety: mean change from baseline in STAI</b>  |  |                                     |            |                     |  |                                   |
| 4; 172  | Medium; RCTs                               | Some inconsistency ( $I^2=83.5\%$ ) | Direct     | Imprecise           | WMD -11.2 (-20 to -2.4); WMD -12.1 when only compared with WL (3 trials)                                   | Low                               |
| <b>Quality of Life</b>  |  |                                     |            |                     |  |                                   |
| 3; 182  | Medium; RCTs                               | Inconsistent                        | Direct     | Imprecise           | Mixed results  | Insufficient                      |

**Table G-13. CBT-mixed interventions compared with inactive controls (waitlist, usual care)  
(continued)**

|   | Domains Pertaining to Strength of Evidence |                         |        |           | Magnitude of Effect                                  | Strength of Evidence |
|---|--|-------------------------|--------|-----------|--|----------------------|
| <b><i>Disability/functional impairment</i></b>        |  |                         |        |           |  |                      |
| 5; 268  | Medium;<br>RCTs                            | Consistent <sup>c</sup> | Direct | Imprecise | Not calculated,<br>heterogeneous<br>outcome measures | Low                  |
| <b><i>Return to work or return to active duty</i></b> |  |                         |        |           |  |                      |
| 0; 0  | NA   | NA                      | NA     | NA        | NA   | Insufficient         |

<sup>a</sup> Although meta-analyses often had considerable statistical heterogeneity for the trials comparing CBT mixed interventions with inactive controls, the direction of effects was generally the same across trials—differences were in the magnitude of effects.

<sup>b</sup> Two trials used different measures for remission found a greater percentages of subjects achieving remission: 61% vs. 21% , p=NR using the PCL;<sup>7</sup> 82.4% vs. 0%,  $P < 0.001$  using the HTQ.<sup>8</sup>

<sup>c</sup> Four of the five trials compared CBT-mixed interventions with WL controls and found similar benefits for CBT-mixed interventions compared with WL; one trial compared with standard care and found similar outcomes for subjects treated with CBT-mixed and those who received standard care.<sup>9</sup>

Abbreviations: CI = confidence interval; NA = not applicable; RCT = randomized controlled trial

**Table G-14. CBT-mixed interventions compared with relaxation: Head-to-head trials**

| Number of Studies;<br>Number of Subjects                  | Domains Pertaining to Strength of Evidence |                  |            |           | Magnitude of Effect   | Strength of Evidence              |
|---|--|------------------|------------|-----------|---|-----------------------------------|
|   | Risk of Bias;<br>Design                    | Consistency      | Directness | Precision | Summary Effect Size (95% CI)  | High, Moderate, Low, Insufficient |
| <b><i>PTSD Symptom Reduction</i></b>                      |  |                  |            |           |   |                                   |
| 2; 85   | Medium;<br>RCTs                            | Consistent       | Direct     | Imprecise | Mean CAPS improvement: 38 (26 to 50) vs. 14 (4 to 25) in one trial. <sup>3</sup><br>Between group effect size: d = 1.6 in another <sup>10</sup> | Moderate                          |
| <b><i>Remission (no longer having symptoms)</i></b>       |  |                  |            |           |   |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA  | Insufficient                      |
| <b><i>Loss of Diagnosis</i></b>                           |  |                  |            |           |   |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA  | Insufficient                      |
| <b><i>Prevention/reduction of comorbid depression</i></b> |  |                  |            |           |   |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA  | Insufficient                      |
| <b><i>Prevention/reduction of comorbid anxiety</i></b>    |  |                  |            |           |   |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA  | Insufficient                      |
| <b><i>Quality of Life</i></b>                             |  |                  |            |           |   |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA  | Insufficient                      |
| <b><i>Disability/functional impairment</i></b>            |  |                  |            |           |   |                                   |
| 1; 45   | Medium;<br>RCT                             | NA, single study | Direct     | Imprecise | GHQ Global Improvement measure: percentage of subjects improved functioning: 70-80% vs. 50-55% p=NS   | Insufficient                      |
| <b><i>Return to work or return to active duty</i></b>     |  |                  |            |           |   |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA  | Insufficient                      |

Abbreviations: CI = confidence interval; NA = not applicable; RCT = randomized controlled trial

**Table G-15. EMDR compared with inactive controls (waitlist, usual care)**

|  | Domains Pertaining to Strength of Evidence |                             |            |           | Magnitude of Effect  | Strength of Evidence              |
|--|--|-----------------------------|------------|-----------|--|-----------------------------------|
| Number of Studies; Number of Subjects  | Risk of Bias; Design                       | Consistency                 | Directness | Precision | Summary Effect Size (95% CI)   | High, Moderate, Low, Insufficient |
| <b>PTSD Symptom Reduction</b>  |  |                             |            |           |  |                                   |
| 4; 117   | Medium; RCTs                               | Inconsistent ( $I^2=70\%$ ) | Direct     | Imprecise | SMD -1.08 (-1.83 to -0.33); SMD -1.37 (-2.05, -0.69) when only compared with WL (3 trials, N=95) | Low                               |
| <b>Remission (no longer having symptoms)</b>                                       |  |                             |            |           |  |                                   |
| 0; 0   | NA   | NA                          | NA         | NA        | NA   | Insufficient                      |
| <b>Loss of Diagnosis</b>   |  |                             |            |           |  |                                   |
| 3; 95  | Medium; RCTs                               | Consistent ( $I^2=27\%$ )   | Direct     | Precise   | RD 0.64 (0.46 to 0.81); NNT 1.56   | Moderate                          |
| <b>Prevention/reduction of comorbid depression</b>                                 |  |                             |            |           |  |                                   |
| 4; 117   | Medium; RCTs                               | Consistent ( $I^2=0\%$ )    | Direct     | Precise   | SMD -1.13 (-1.52 to -0.74)   | Moderate                          |
| <b>Prevention/reduction of comorbid anxiety: mean change from baseline in STAI</b> |  |                             |            |           |  |                                   |
| 3; 93  | Medium; RCTs                               | Inconsistent                | Direct     | Imprecise | No statistically significant difference: WMD -11.08 (-23.06 to 0.90)                             | Insufficient                      |
| <b>Quality of Life</b>   |  |                             |            |           |  |                                   |
| 0; 0   | NA   | NA                          | NA         | NA        | NA   | Insufficient                      |
| <b>Disability/functional impairment</b>  |  |                             |            |           |  |                                   |
| 0; 0   | NA   | NA                          | NA         | NA        | NA   | Insufficient                      |
| <b>Return to work or return to active duty</b>                                     |  |                             |            |           |  |                                   |
| 0; 0   | NA   | NA                          | NA         | NA        | NA   | Insufficient                      |

Abbreviations: CI = confidence interval; EMDR = eye movement desensitization and reprocessing; NA = not applicable; PTSD = post-traumatic stress disorder; RCT = randomized controlled trial; RD = risk difference; SMD = Standardized mean difference; STAI = State Trait Anxiety Inventory; WMD = weighted mean difference

**Table G-16. EMDR compared with relaxation**

| Number of Studies;<br>Number of Subjects                     | Domains Pertaining to Strength of Evidence |                  |            |           | Magnitude of Effect  | Strength of Evidence              |
|--|--|------------------|------------|-----------|--|-----------------------------------|
|  | Risk of Bias;<br>Design                    | Consistency      | Directness | Precision | Summary Effect Size (95% CI)                                     | High, Moderate, Low, Insufficient |
| <b>PTSD Symptom Reduction</b>                                |  |                  |            |           |  |                                   |
| 2; 64  | Medium;<br>RCTs                            | Inconsistent     | Direct     | Imprecise | SMD -0.57 (-1.4 to 0.29)<br>SMD -0.3 (-0.8 to 0.2) <sup>a</sup>  | Insufficient                      |
| <b>Remission (no longer having symptoms)</b>                 |  |                  |            |           |  |                                   |
| 0; 0   | NA   | NA               | NA         | NA        | NA   | Insufficient                      |
| <b>Loss of Diagnosis at 3 month post-treatment follow up</b> |  |                  |            |           |  |                                   |
| 2; 64  | Medium;<br>RCTs                            | Inconsistent     | Direct     | Imprecise | RD 0.34 (-0.04 to 0.72), trend toward greater reduction for EMDR | Insufficient                      |
| <b>Prevention/reduction of comorbid depression: BDI</b>      |  |                  |            |           |  |                                   |
| 2; 64  | Medium;<br>RCTs                            | Inconsistent     | Direct     | Imprecise | Mixed findings   | Insufficient                      |
| <b>Prevention/reduction of comorbid anxiety: STAI</b>        |  |                  |            |           |  |                                   |
| 1; 23  | Medium;<br>RCT                             | NA, single study | Direct     | Imprecise | Cohen's d=1.15 (favoring EMDR), p<0.01                           | Insufficient                      |
| <b>Quality of Life</b>                                       |  |                  |            |           |  |                                   |
| 0; 0   | NA   | NA               | NA         | NA        | NA   | Insufficient                      |
| <b>Disability/functional impairment</b>                      |  |                  |            |           |  |                                   |
| 0; 0   | NA   | NA               | NA         | NA        | NA   | Insufficient                      |
| <b>Return to work or return to active duty</b>               |  |                  |            |           |  |                                   |
| 0; 0   | NA   | NA               | NA         | NA        | NA   | Insufficient                      |

<sup>a</sup>Two SMDs reported here because two meta-analyses were run because one of the two trials reported two measures of PTSD symptoms.<sup>11</sup> The first SMD is from our meta-analysis using the Mississippi Scale for Combat Related PTSD from the study reporting two measures; the second is using the IES from that trial. The other trial reported the CAPS.<sup>12</sup>

Abbreviations: BDI = Beck Depression Inventory; CAPS = Clinician-Administered Post Traumatic Stress Disorder Scale; CI = confidence interval; EMDR = eye movement desensitization and reprocessing; NA = not applicable; PTSD = post-traumatic stress disorder; RCT = randomized controlled trial

**Table G-17. Seeking safety compared with standard community treatment (1 trial<sup>13</sup>)**

| Number of Studies; Number of Subjects   | Domains Pertaining to Strength of Evidence |                  |            |           | Magnitude of Effect  | Strength of Evidence              |
|---|--|------------------|------------|-----------|--|-----------------------------------|
|   | Risk of Bias; Design                       | Consistency      | Directness | Precision | Summary Effect Size (95% CI)                                   | High, Moderate, Low, Insufficient |
| <b><i>PTSD Symptom Reduction: CAPS frequency and intensity, reduction from baseline to post-treatment</i></b> |  |                  |            |           |  |                                   |
| 1; 107  | Medium; RCT                                | NA, single study | Direct     | Imprecise | -15.02 vs. -5.88, p<0.01                                       | Insufficient                      |
| <b><i>Remission (no longer having symptoms)</i></b>   |  |                  |            |           |  |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA   | Insufficient                      |
| <b><i>Loss of Diagnosis</i></b>   |  |                  |            |           |  |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA   | Insufficient                      |
| <b><i>Prevention/reduction of comorbid substance use</i></b>  |  |                  |            |           |  |                                   |
| 1; 107  | Medium; RCT                                | NA, single study | Direct     | Imprecise | greater reduction in substance use/abuse for SS group, p<0.001 | Insufficient                      |
| <b><i>Quality of Life</i></b>   |  |                  |            |           |  |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA   | Insufficient                      |
| <b><i>Disability/functional impairment</i></b>  |  |                  |            |           |  |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA   | Insufficient                      |
| <b><i>Return to work or return to active duty</i></b>   |  |                  |            |           |  |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA   | Insufficient                      |

Abbreviations: CAPS = Clinician-Administered Post Traumatic Stress Disorder Scale; BDI = Beck Depression Inventory; CI = confidence interval; IES = Impact of Events Scale; NA = not applicable; PTSD = post-traumatic stress disorder; RCT = randomized controlled trial

**Table G-18. Seeking safety compared with active controls (relapse prevention, psychoeducation, treatment as usual in a VA substance use disorders clinic)**

| Number of Studies;<br>Number of Subjects                    | Domains Pertaining to Strength of Evidence |                  |            |           | Magnitude of Effect  | Strength of Evidence              |
|---|--|------------------|------------|-----------|--|-----------------------------------|
|   | Risk of Bias;<br>Design                    | Consistency      | Directness | Precision | Summary Effect Size (95% CI)   | High, Moderate, Low, Insufficient |
| <b>PTSD Symptom Reduction: CAPS</b>                         |  |                  |            |           |  |                                   |
| 3; 477  | Medium;<br>RCTs                            | Consistent       | Direct     | Precise   | 1.45 (-2.5 to 5.4)   | Moderate                          |
| <b>PTSD Symptom Reduction: any measure</b>                  |  |                  |            |           |  |                                   |
| 4; 594  | Medium;<br>RCTs                            | Consistent       | Direct     | Precise   | SMD 0.04 (-0.12 to 0.20)   | Moderate                          |
| <b>Remission (no longer having symptoms)</b>                |  |                  |            |           |  |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA   | Insufficient                      |
| <b>Loss of Diagnosis</b>                                    |  |                  |            |           |  |                                   |
| 1; 49   | Medium;<br>RCT                             | NA, single study | Direct     | Imprecise | OR for SS vs. RPC=1.22 (0.48 to 3.13)  | Insufficient                      |
| <b>Prevention/reduction of comorbid substance use/abuse</b> |  |                  |            |           |  |                                   |
| 4; 594  | Medium;<br>RCTs                            | Inconsistent     | Direct     | Imprecise | No statistically significant difference in 3 trials (N=477); better substance use outcomes for 1 trial (N=117) | Insufficient                      |
| <b>Quality of Life</b>                                      |  |                  |            |           |  |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA   | Insufficient                      |
| <b>Disability/functional impairment</b>                     |  |                  |            |           |  |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA   | Insufficient                      |
| <b>Return to work or return to active duty</b>              |  |                  |            |           |  |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA   | Insufficient                      |

Abbreviations: CAPS = Clinician-Administered Post Traumatic Stress Disorder Scale; CI = confidence interval; NA = not applicable; OR = odds ratio; PTSD = post-traumatic stress disorder; RCT = randomized controlled trial; RPC, relapse prevention; SS, seeking safety

**Table G-19. Imagery rehearsal therapy (IRT) compared with waitlist (1 trial<sup>14</sup>)**

| Number of Studies; Number of Subjects                         | Domains Pertaining to Strength of Evidence |                  |            |           | Magnitude of Effect                             | Strength of Evidence              |
|---|--|------------------|------------|-----------|---|-----------------------------------|
|   | Risk of Bias; Design                       | Consistency      | Directness | Precision | Summary Effect Size (95% CI)                    | High, Moderate, Low, Insufficient |
| <b>PTSD Symptom Reduction: CAPS mean change from baseline</b> |  |                  |            |           |   |                                   |
| 1; 168  | Medium; RCT                                | NA, Single study | Direct     | Unknown   | -32.3 vs. -11.3, p=0.001                        | Insufficient                      |
| <b>Remission (no longer having symptoms)</b>                  |  |                  |            |           |   |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA  | Insufficient                      |
| <b>Loss of Diagnosis</b>                                      |  |                  |            |           |   |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA  | Insufficient                      |
| <b>Prevention/reduction of comorbid depression: HAMD</b>      |  |                  |            |           |   |                                   |
| 1; 168  | Medium; RCT                                | NA, Single study | Direct     | Imprecise | Cohen d: 0.57 vs. 0.33, p=NS                    | Insufficient                      |
| <b>Prevention/reduction of comorbid anxiety: HAMA</b>         |  |                  |            |           |   |                                   |
| 1; 168  | Medium; RCT                                | NA, Single study | Direct     | Imprecise | Cohen d: 0.39 vs. -0.16, p=0.04                 | Insufficient                      |
| <b>Quality of Life: SF-36</b>                                 |  |                  |            |           |   |                                   |
| 1; 168  | Medium; RCT                                | NA, Single study | Direct     | Imprecise | No difference between groups; data not reported | Insufficient                      |
| <b>Disability/functional impairment</b>                       |  |                  |            |           |   |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA  | Insufficient                      |
| <b>Return to work or return to active duty</b>                |  |                  |            |           |   |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA  | Insufficient                      |

Abbreviations: CAPS = Clinician-Administered Post Traumatic Stress Disorder Scale; CI = confidence interval; HAM-D = Hamilton Depression Scale; HAM-A = Hamilton Anxiety Scale; IRT = imagery rehearsal therapy; NA = not applicable; NR = Not Reported; PTSD = post-traumatic stress disorder; RCT = randomized controlled trial; SF-36 = 36-Item Short-Form Health Survey; WL = waitlist



**Table G-20. Narrative exposure therapy (NET) compared with an inactive control (waitlist or minimal attention)**

| Number of Studies;<br>Number of Subjects  | Domains Pertaining to Strength of evidence |                  |            |           | Magnitude of Effect  | Strength of Evidence              |
|---|--|------------------|------------|-----------|--|-----------------------------------|
|   | Risk of Bias;<br>Design                    | Consistency      | Directness | Precision | Summary Effect Size (95% CI)   | High, Moderate, Low, Insufficient |
| <b>PTSD Symptom Reduction: mean change from baseline to post-treatment in PDS</b> |  |                  |            |           |  |                                   |
| 3; 227  | Medium;<br>RCTs                            | Consistent       | Direct     | Precise   | -10.2 (-13.1 to -7.4)  | Moderate                          |
| <b>Remission (no longer having symptoms)</b>                                      |  |                  |            |           |  |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA   | Insufficient                      |
| <b>Loss of Diagnosis</b>  |  |                  |            |           |  |                                   |
| 3; 227  | Medium;<br>RCTs                            | Consistent       | Direct     | Imprecise | RD 0.15 (0.01 to 0.30)   | Low                               |
| <b>Prevention/reduction of comorbid depression</b>                                |  |                  |            |           |  |                                   |
| 2; 75   | Medium;<br>RCTs                            | Inconsistent     | Direct     | Imprecise | Mixed evidence; one trial reported efficacy (HSCL-25 Depression scale: cohen's d 0.54); one reported no difference from comparators (SRQ-20: data NR)              | Insufficient                      |
| <b>Prevention/reduction of comorbid pain</b>                                      |  |                  |            |           |  |                                   |
| 1; 32   | Medium;<br>RCT                             | NA, single study | Direct     | Imprecise | d=0.65 for CIDI-C pain score, a significant time by treatment interaction was found, p=0.034, but no significant main effect of time, p=0.46, or treatment, p=0.35 | Insufficient                      |
| <b>Quality of Life</b>  |  |                  |            |           |  |                                   |
| 1; 43   | Medium;<br>RCT                             | NA, single study | Direct     | Imprecise | NET was not significantly different from psychoeducation for improving QOL, p=0.54   | Insufficient                      |
| <b>Disability/functional impairment</b>   |  |                  |            |           |  |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA   | Insufficient                      |
| <b>Return to work or return to active duty</b>                                    |  |                  |            |           |  |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA   | Insufficient                      |

Abbreviations: CI = confidence interval; HSCL-25 = Hopkins Symptom Check List-25; NA = not applicable; NR = not reported; PDS = Posttraumatic Stress Diagnostic Scale; PTSD = post-traumatic stress disorder; RCT = randomized controlled trial; SRQ-20 = Self-Reporting Questionnaire

**Table G-21. Brief eclectic psychotherapy (BEP) compared with waitlist**

|   | Domains Pertaining to Strength of Evidence |                           |            |           | Magnitude of Effect   | Strength of Evidence              |
|---|--|---------------------------|------------|-----------|---|-----------------------------------|
| Number of Studies; Number of Subjects                   | Risk of Bias; Design                       | Consistency               | Directness | Precision | Summary Effect Size (95% CI)  | High, Moderate, Low, Insufficient |
| <b>PTSD Symptom Reduction: various outcome measures</b> |  |                           |            |           |   |                                   |
| 3; 96   | Medium; RCTs                               | Consistent                | Direct     | Imprecise | Not calculated, likely small to medium effect size <sup>a</sup>   | Low                               |
| <b>Remission (no longer having symptoms)</b>            |  |                           |            |           |   |                                   |
| 1; 30 <sup>15</sup>                                     | Medium; RCT                                | NA, single study          | Direct     | Imprecise | 12.5% vs. 0% posttreatment; 18.8% vs. 0% at 6 months  | Insufficient                      |
| <b>Loss of Diagnosis</b>                                |  |                           |            |           |   |                                   |
| 3; 96   | Medium; RCTs                               | Inconsistent <sup>b</sup> | Direct     | Imprecise | Range from 12.5% vs. 0% to 83.3 vs. 25% to 91% vs. 50%  | Low                               |
| <b>Prevention/reduction of comorbid depression</b>      |  |                           |            |           |   |                                   |
| 3; 96   | Medium; RCTs                               | Inconsistent              | Direct     | Imprecise | All 3 found benefits, wide range of effect sizes in the 2 trials reporting sufficient data to determine, from medium to very large                      | Low                               |
| <b>Prevention/reduction of comorbid anxiety</b>         |  |                           |            |           |   |                                   |
| 3; 96   | Medium; RCTs                               | Inconsistent              | Direct     | Imprecise | All 3 found benefits, wide range of effect sizes in the 2 trials reporting sufficient data to determine, from medium to very large                      | Low                               |
| <b>Quality of Life</b>                                  |  |                           |            |           |   |                                   |
| 0; 0  | NA   | NA                        | NA         | NA        | NA  | Insufficient                      |
| <b>Disability/functional impairment</b>                 |  |                           |            |           |   |                                   |
| 0; 0  | NA   | NA                        | NA         | NA        | NA  | Insufficient                      |
| <b>Return to work</b>                                   |  |                           |            |           |   |                                   |
| 2; 66   | Medium; RCTs                               | Inconsistent              | Direct     | Imprecise | One trial found $d=0.33$ $p=0.06$ for percentage of subjects on sick leave; the other found more subjects had returned to work (86% vs. 60%, $p<0.05$ ) | Low                               |

<sup>a</sup> The three trials used different outcome measures—two found small or medium effect sizes using the CAPS<sup>15</sup> and SI-PTSD,<sup>16</sup> respectively. The other did not report enough data to determine effect sizes.<sup>17</sup>

<sup>b</sup> The three trials were consistent in the sense that they all found more subjects in the BEP group with loss of PTSD diagnosis compared with the WL group. However, the differences between groups were inconsistent, ranging from a small difference (12.5%)<sup>15</sup> to a large difference (58.3%) between groups.<sup>16</sup>

Abbreviations: CI = confidence interval; mths, months; NA = not applicable; PTSD = post-traumatic stress disorder; RCT = randomized controlled trial

**Table G-22. Brief eclectic psychotherapy (BEP) compared with EMDR**

|  | Domains Pertaining to Strength of Evidence |                  |            |           | Magnitude of Effect   | Strength of Evidence              |
|--|--|------------------|------------|-----------|---|-----------------------------------|
| Number of Studies; Number of Subjects                                      | Risk of Bias; Design                       | Consistency      | Directness | Precision | Summary Effect Size (95% CI)  | High, Moderate, Low, Insufficient |
| <b><i>PTSD Symptom Reduction: IES-R and SI-PTSD</i></b>                    |  |                  |            |           |   |                                   |
| 1; 140   | Medium; RCT                                | NA, single study | Direct     | Imprecise | Greater improvement from baseline to the first assessment for those treated with EMDR (SI-PTSD, mean difference 10.80; 95% CI, 6.37 to 15.23); difference was no longer significant at the second assessment, after both groups had completed treatment | Insufficient                      |
| <b><i>Remission (no longer having symptoms)</i></b>                        |  |                  |            |           |   |                                   |
| 0; 0   | NA   | NA               | NA         | NA        | NA  | Insufficient                      |
| <b><i>Loss of Diagnosis</i></b>  |  |                  |            |           |   |                                   |
| 1; 140   | Medium; RCT                                | NA, single study | Direct     | Imprecise | Among completers, EMDR vs. BET: 92.2% vs. 52.3%, p<0.001 at the first assessment; No significant difference at the second assessment: 93.7% vs. 85.7%, p=0.30   | Insufficient                      |
| <b><i>Prevention/reduction of comorbid depression: HADS depression</i></b> |  |                  |            |           |   |                                   |
| 1; 140   | Medium; RCT                                | NA, single study | Direct     | Imprecise | Greater improvement from baseline to the first assessment for those treated with EMDR, but no significant difference between groups at the second assessment  | Insufficient                      |
| <b><i>Prevention/reduction of comorbid anxiety: HADS anxiety</i></b>       |  |                  |            |           |   |                                   |
| 1; 140   | Medium; RCT                                | NA, single study | Direct     | Imprecise | Greater improvement from baseline to the first assessment for those treated with EMDR, but no significant difference between groups at the second assessment  | Insufficient                      |

**Table G-22. Brief eclectic psychotherapy (BEP) compared with EMDR (continued)**

|  | Domains Pertaining to Strength of Evidence |             |            |           | Magnitude of Effect             | Strength of Evidence                       |
|--|--|-------------|------------|-----------|---------------------------------|--|
| Number of Studies;<br>Number of Subjects | Risk of Bias;<br>Design                    | Consistency | Directness | Precision | Summary Effect Size<br>(95% CI) | High,<br>Moderate,<br>Low,<br>Insufficient |
| <b>Quality of Life</b>                   |  |             |            |           |                                 |  |
| 0; 0                                     | NA   | NA          | NA         | NA        | NA                              | Insufficient                               |
| <b>Disability/functional impairment</b>  |  |             |            |           |                                 |  |
| 0; 0                                     | NA   | NA          | NA         | NA        | NA                              | Insufficient                               |
| <b>Return to work</b>                    |  |             |            |           |                                 |  |
| 0; 0                                     | NA   | NA          | NA         | NA        | NA                              | Insufficient                               |

Abbreviations: CI = confidence interval; mths, months; NA = not applicable; PTSD = post-traumatic stress disorder; RCT = randomized controlled trial

**Table G-23. Trauma affect regulation compared with waitlist**

|   | Domains Pertaining to Strength of Evidence |                  |            |           | Magnitude of Effect          | Strength of Evidence              |
|---|--|------------------|------------|-----------|------------------------------|-----------------------------------|
| Number of Studies; Number of Subjects                   | Risk of Bias; Design                       | Consistency      | Directness | Precision | Summary Effect Size (95% CI) | High, Moderate, Low, Insufficient |
| <b>PTSD Symptom Reduction: CAPS</b>                     |  |                  |            |           |                              |                                   |
| 1; 93   | Medium; RCT                                | NA, single study | Direct     | Imprecise | -23.6 vs. -6.2, p<0.001      | Insufficient                      |
| <b>Remission (no longer having symptoms)</b>            |  |                  |            |           |                              |                                   |
| 1; 93   | Medium; RCT                                | NA, single study | Direct     | Imprecise | 21% vs. 0%, p<0.001          | Insufficient                      |
| <b>Loss of Diagnosis</b>                                |  |                  |            |           |                              |                                   |
| 1; 93   | Medium; RCT                                | NA, single study | Direct     | Imprecise | 35% vs. 11%                  | Insufficient                      |
| <b>Prevention/reduction of comorbid depression: BDI</b> |  |                  |            |           |                              |                                   |
| 1; 93   | Medium; RCT                                | NA, single study | Direct     | Imprecise | -4.4 vs. -0.3, p<0.01        | Insufficient                      |
| <b>Prevention/reduction of comorbid anxiety</b>         |  |                  |            |           |                              |                                   |
| 1; 93   | Medium; RCT                                | NA, single study | Direct     | Imprecise | -6.7 vs. -0.4, p=0.19        | Insufficient                      |
| <b>Quality of Life</b>                                  |  |                  |            |           |                              |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA                           | Insufficient                      |
| <b>Disability/functional impairment</b>                 |  |                  |            |           |                              |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA                           | Insufficient                      |
| <b>Return to work</b>                                   |  |                  |            |           |                              |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA                           | Insufficient                      |

Abbreviations: CI = confidence interval; mths, months; NA = not applicable; PTSD = post-traumatic stress disorder; RCT = randomized controlled trial

## Key Question 2

Table G-24. Placebo-controlled trials of alpha-blockers

| Number of Studies;<br>Number of Subjects           | Domains Pertaining to Strength of Evidence |                          |            |           | Magnitude of Effect          | Strength of Evidence              |
|--|--|--------------------------|------------|-----------|------------------------------|-----------------------------------|
|  | Risk of Bias;<br>Design/<br>Quality        | Consistency              | Directness | Precision | Summary Effect Size (95% CI) | High, Moderate, Low, Insufficient |
| <b>PTSD Symptom Reduction: CAPS</b>                |  |                          |            |           |                              |                                   |
| 2; 50  | Medium;<br>RCTs                            | Consistent ( $I^2$ 1.8%) | Direct     | Imprecise | WMD -8.86 (-22.06 to 4.33)   | Insufficient                      |
| <b>Remission (no longer having symptoms)</b>       |  |                          |            |           |                              |                                   |
| 0; 0   | NA   | NA                       | NA         | NA        | NA                           | Insufficient                      |
| <b>Loss of Diagnosis</b>                           |  |                          |            |           |                              |                                   |
| 0; 0   | NA   | NA                       | NA         | NA        | NA                           | Insufficient                      |
| <b>Prevention/reduction of comorbid depression</b> |  |                          |            |           |                              |                                   |
| 1; 40  | Medium;<br>RCT                             | NA, single study         | Direct     | Imprecise | -5.6 vs. -0.6, $p=0.08$      | Insufficient                      |
| <b>Prevention/reduction of comorbid anxiety</b>    |  |                          |            |           |                              |                                   |
| 0; 0   | NA   | NA                       | NA         | NA        | NA                           | Insufficient                      |
| <b>Quality of Life</b>                             |  |                          |            |           |                              |                                   |
| 0; 0   | NA   | NA                       | NA         | NA        | NA                           | Insufficient                      |
| <b>Disability/functional impairment</b>            |  |                          |            |           |                              |                                   |
| 0; 0   | NA   | NA                       | NA         | NA        | NA                           | Insufficient                      |
| <b>Return to work or return to active duty</b>     |  |                          |            |           |                              |                                   |
| 0; 0   | NA   | NA                       | NA         | NA        | NA                           | Insufficient                      |

Abbreviations: CI = confidence interval; NA = not applicable; RCT = randomized controlled trial

**Table G-25. Strength of evidence for divalproex compared with placebo**

| Number of Studies;<br>Number of Subjects                         | Domains Pertaining to Strength of Evidence |             |            |           | Magnitude of Effect          | Strength of Evidence              |
|--|--|-------------|------------|-----------|------------------------------|-----------------------------------|
|  | Risk of Bias;<br>Design                    | Consistency | Directness | Precision | Summary Effect Size (95% CI) | High, Moderate, Low, Insufficient |
| <b><i>PTSD Symptom Reduction: CAPS</i></b>                       |  |             |            |           |                              |                                   |
| 1; 85  | Low; RCT                                   | NA          | Direct     | Imprecise | WMD 1.40 (-8.22 to 11.02)    | Insufficient                      |
| <b><i>PTSD Symptom Reduction: TOP-8</i></b>                      |  |             |            |           |                              |                                   |
| 1; 85  | Low; RCT                                   | NA          | Direct     | Imprecise | -4.0 vs. -3.9, NS            | Insufficient                      |
| <b><i>Remission (no longer having symptoms)</i></b>              |  |             |            |           |                              |                                   |
| 0; 0   | NA   | NA          | NA         | NA        | NA                           | Insufficient                      |
| <b><i>Loss of Diagnosis</i></b>                                  |  |             |            |           |                              |                                   |
| 0; 0   | NA   | NA          | NA         | NA        | NA                           | Insufficient                      |
| <b><i>Prevention/reduction of comorbid depression: MADRS</i></b> |  |             |            |           |                              |                                   |
| 1; 85  | Low; RCT                                   | NA          | Direct     | Imprecise | -5.1 vs. -4.5, NS            | Insufficient                      |
| <b><i>Prevention/reduction of comorbid anxiety: HAM-A</i></b>    |  |             |            |           |                              |                                   |
| 1; 85  | Low; RCT                                   | NA          | Direct     | Imprecise | -15.1 vs. -16.5, NS          | Insufficient                      |
| <b><i>Quality of Life</i></b>                                    |  |             |            |           |                              |                                   |
| 0; 0   | NA   | NA          | NA         | NA        | NA                           | Insufficient                      |
| <b><i>Disability/functional impairment</i></b>                   |  |             |            |           |                              |                                   |
| 0; 0   | NA   | NA          | NA         | NA        | NA                           | Insufficient                      |
| <b><i>Return to work or return to active duty</i></b>            |  |             |            |           |                              |                                   |
| 0; 0   | NA   | NA          | NA         | NA        | NA                           | Insufficient                      |

**Table G-26. Strength of evidence for lamotrigine compared with placebo**

| Number of Studies;<br>Number of Subjects                  | Domains Pertaining to Strength of Evidence |             |            |           | Magnitude of Effect          | Strength of Evidence              |
|---|--|-------------|------------|-----------|------------------------------|-----------------------------------|
|   | Risk of Bias;<br>Design                    | Consistency | Directness | Precision | Summary Effect Size (95% CI) | High, Moderate, Low, Insufficient |
| <b><i>PTSD Symptom Reduction:</i></b>                     |  |             |            |           |                              |                                   |
| 0; 0  | NA   | NA          | NA         | NA        | NA                           | Insufficient                      |
| <b><i>Remission (no longer having symptoms)</i></b>       |  |             |            |           |                              |                                   |
| 0; 0  | NA   | NA          | NA         | NA        | NA                           | Insufficient                      |
| <b><i>Loss of Diagnosis</i></b>                           |  |             |            |           |                              |                                   |
| 0; 0  | NA   | NA          | NA         | NA        | NA                           | Insufficient                      |
| <b><i>Prevention/reduction of comorbid depression</i></b> |  |             |            |           |                              |                                   |
| 0; 0  | NA   | NA          | NA         | NA        | NA                           | Insufficient                      |
| <b><i>Prevention/reduction of comorbid anxiety</i></b>    |  |             |            |           |                              |                                   |
| 0; 0  | NA   | NA          | NA         | NA        | NA                           | Insufficient                      |
| <b><i>Quality of Life</i></b>                             |  |             |            |           |                              |                                   |
| 0; 0  | NA   | NA          | NA         | NA        | NA                           | Insufficient                      |
| <b><i>Disability/functional impairment</i></b>            |  |             |            |           |                              |                                   |
| 0; 0  | NA   | NA          | NA         | NA        | NA                           | Insufficient                      |
| <b><i>Return to work or return to active duty</i></b>     |  |             |            |           |                              |                                   |
| 0; 0  | NA   | NA          | NA         | NA        | NA                           | Insufficient                      |



**Table G-27. Strength of evidence for tiagabine compared with placebo**

| Number of Studies;<br>Number of Subjects                                 | Domains Pertaining to Strength of Evidence |             |            |           | Magnitude of Effect          | Strength of Evidence              |
|--|--|-------------|------------|-----------|------------------------------|-----------------------------------|
|  | Risk of Bias;<br>Design                    | Consistency | Directness | Precision | Summary Effect Size (95% CI) | High, Moderate, Low, Insufficient |
| <b><i>PTSD Symptom Reduction: CAPS</i></b>                               |  |             |            |           |                              |                                   |
| 1; 232   | Medium; RCT                                | NA          | Direct     | Imprecise | WMD -0.50 (-7.12 to 6.12)    | Insufficient                      |
| <b><i>PTSD Symptom Reduction: TOP-8</i></b>                              |  |             |            |           |                              |                                   |
| 1; 232   | Medium; RCT                                | NA          | Direct     | Imprecise | “not significant”            | Insufficient                      |
| <b><i>Remission (CAPS less than 20)</i></b>                              |  |             |            |           |                              |                                   |
| 1; 232   | Medium; RCT                                | NA          | Direct     | Imprecise | 16% vs. 14%, p=0.88          | Insufficient                      |
| <b><i>Loss of Diagnosis</i></b>  |  |             |            |           |                              |                                   |
| 0; 0   | NA   | NA          | NA         | NA        | NA                           | Insufficient                      |
| <b><i>Prevention/reduction of comorbid depression</i></b>                |  |             |            |           |                              |                                   |
| 0; 0   | NA   | NA          | NA         | NA        | NA                           | Insufficient                      |
| <b><i>Prevention/reduction of comorbid anxiety</i></b>                   |  |             |            |           |                              |                                   |
| 0; 0   | NA   | NA          | NA         | NA        | NA                           | Insufficient                      |
| <b><i>Quality of Life</i></b>  |  |             |            |           |                              |                                   |
| 0; 0   | NA   | NA          | NA         | NA        | NA                           | Insufficient                      |
| <b><i>Disability/functional impairment: Sheehan Disability Scale</i></b> |  |             |            |           |                              |                                   |
| 1; 232   | Medium; RCT                                | NA          | Direct     | Imprecise | -5.5 vs. -5.9, p=0.74        | Insufficient                      |
| <b><i>Return to work or return to active duty</i></b>                    |  |             |            |           |                              |                                   |
| 0; 0   | NA   | NA          | NA         | NA        | NA                           | Insufficient                      |

**Table G-28. Strength of evidence for topiramate compared with placebo**

| Number of Studies;<br>Number of Subjects                                 | Domains Pertaining to Strength of Evidence |             |            |           | Magnitude of Effect           | Strength of Evidence              |
|--|--|-------------|------------|-----------|-------------------------------|-----------------------------------|
|  | Risk of Bias;<br>Design                    | Consistency | Directness | Precision | Summary Effect Size (95% CI)  | High, Moderate, Low, Insufficient |
| <b><i>PTSD Symptom Reduction: CAPS</i></b>                               |  |             |            |           |                               |                                   |
| 3; 142   | Medium; RCT                                | Consistent  | Direct     | Precise   | WMD -15.53 (-19.40 to -11.65) | Moderate                          |
| <b><i>PTSD Symptom Reduction: TOP-8</i></b>                              |  |             |            |           |                               |                                   |
| 1; 40  | Medium; RCT                                | NA          | Direct     | Imprecise | -67.9 % vs. -41.6 %, p=0.023  | Insufficient                      |
| <b><i>Remission (no longer having symptoms)</i></b>                      |  |             |            |           |                               |                                   |
| 1; 40  | Medium; RCT                                | NA          | Direct     | Imprecise | 42% vs. 21%, p=0.295          | Insufficient                      |
| <b><i>Loss of Diagnosis</i></b>  |  |             |            |           |                               |                                   |
| 0; 0   | NA   | NA          | NA         | NA        | NA                            | Insufficient                      |
| <b><i>Prevention/reduction of comorbid depression: BDI</i></b>           |  |             |            |           |                               |                                   |
| 1; 35  | Medium; RCT                                | NA          | Direct     | Imprecise | -8.5 vs. -3.9, p=0.72         | Insufficient                      |
| <b><i>Prevention/reduction of comorbid depression: HAM-D</i></b>         |  |             |            |           |                               |                                   |
| 1; 40  | Medium; RCT                                | NA          | Direct     | Imprecise | -50.7% vs. -33.3, p=0.253     | Insufficient                      |
| <b><i>Prevention/reduction of comorbid anxiety: HAM-A</i></b>            |  |             |            |           |                               |                                   |
| 1; 40  | Medium; RCT                                | NA          | Direct     | Imprecise | -53.9% and -40.0%, p=0.331    | Insufficient                      |
| <b><i>Quality of Life</i></b>  |  |             |            |           |                               |                                   |
| 0; 0   | NA   | NA          | NA         | NA        | NA                            | Insufficient                      |
| <b><i>Disability/functional impairment: Sheehan Disability Scale</i></b> |  |             |            |           |                               |                                   |
| 1; 40  | Medium; RCT                                | NA          | Direct     | Imprecise | -30.6% and -35.4% p=0.804     | Insufficient                      |
| <b><i>Return to work or return to active duty</i></b>                    |  |             |            |           |                               |                                   |
| 0; 0   | NA   | NA          | NA         | NA        | NA                            | Insufficient                      |

**Table G-29. Olanzapine compared with placebo**

| Number of Studies;<br>Number of Subjects                  | Domains Pertaining to Strength of Evidence |                  |            |           | Magnitude of Effect          | Strength of Evidence              |
|---|--|------------------|------------|-----------|------------------------------|-----------------------------------|
|   | Risk of Bias;<br>Design/<br>Quality        | Consistency      | Directness | Precision | Summary Effect Size (95% CI) | High, Moderate, Low, Insufficient |
| <b>PTSD Symptom Reduction: CAPS</b>                       |  |                  |            |           |                              |                                   |
| 1; 19   | Medium;<br>RCT                             | NA, single study | Direct     | Imprecise | -12.13 (-23.29 to -0.97)     | Insufficient                      |
| <b>PTSD Symptom Reduction: TOP-8</b>                      |  |                  |            |           |                              |                                   |
| 1; 15   | Medium;<br>RCT                             | NA, single study | Direct     | Imprecise | -6.7 vs. -11.3, (p=NR)       | Insufficient                      |
| <b>PTSD Symptom Reduction: DTS</b>                        |  |                  |            |           |                              |                                   |
| 1; 15   | Medium;<br>RCT                             | NA, single study | Direct     | Imprecise | -34.2 vs. -39.8, p=NR        | Insufficient                      |
| <b>PTSD Symptom Reduction: SPRINT</b>                     |  |                  |            |           |                              |                                   |
| 1; 15   | Medium,<br>RCT                             | NA, single study | Direct     | Imprecise | -13.6 vs. -14.3, p=NR        | Insufficient                      |
| <b>Remission (no longer having symptoms)</b>              |  |                  |            |           |                              |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA                           | Insufficient                      |
| <b>Loss of Diagnosis</b>                                  |  |                  |            |           |                              |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA                           | Insufficient                      |
| <b>Prevention/reduction of comorbid depression: CES-D</b> |  |                  |            |           |                              |                                   |
| 1; 19   | Medium                                     | NA, single study | Direct     | Imprecise | -5.25 vs. -4.88, p<0.03      | Insufficient                      |
| <b>Prevention/reduction of comorbid depression</b>        |  |                  |            |           |                              |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA                           | Insufficient                      |
| <b>Quality of Life</b>                                    |  |                  |            |           |                              |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA                           | Insufficient                      |
| <b>Disability/functional impairment: Sheehan</b>          |  |                  |            |           |                              |                                   |
| 1; 15   | Medium                                     | NA               | Direct     | Imprecise | -7.7 vs. -8.0, (p<0.001)     | Insufficient                      |
| <b>Return to work or return to active duty</b>            |  |                  |            |           |                              |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA                           | Insufficient                      |

Abbreviations: CI = confidence interval; NA = not applicable; RCT = randomized controlled trial

**Table G-30. Risperidone compared with placebo**

| Number of Studies;<br>Number of Subjects                  | Domains Pertaining to Strength of Evidence |                           |            |           | Magnitude of Effect          | Strength of Evidence              |
|---|--|---------------------------|------------|-----------|------------------------------|-----------------------------------|
|   | Risk of Bias;<br>Design/<br>Quality        | Consistency               | Directness | Precision | Summary Effect Size (95% CI) | High, Moderate, Low, Insufficient |
| <b>PTSD Symptom Reduction: CAPS</b>                       |  |                           |            |           |                              |                                   |
| 4; 419  | Medium;<br>RCTs                            | Consistent ( $I^2$ 22.3%) | Direct     | Imprecise | WMD -4.60 (-9.01 to -0.20)   | Low                               |
| <b>PTSD Symptom Reduction: Change in PCL-M</b>            |  |                           |            |           |                              |                                   |
| 1; 16   | Medium;<br>RCT                             | NA, single study          | Direct     | Imprecise | -10.0 vs. -0.50, $p=0.02$    | Insufficient                      |
| <b>Remission (no longer having symptoms)</b>              |  |                           |            |           |                              |                                   |
| 0; 0  | NA   | NA                        | NA         | NA        | NA                           | Insufficient                      |
| <b>Loss of Diagnosis</b>                                  |  |                           |            |           |                              |                                   |
| 0; 0  | NA   | NA                        | NA         | NA        | NA                           | Insufficient                      |
| <b>Prevention/reduction of comorbid depression: Ham-D</b> |  |                           |            |           |                              |                                   |
| 1; 65   | Medium;<br>RCT                             | NA, single study          | Direct     | Imprecise | -3.7 vs. -1.4, $p>0.05$      | Insufficient                      |
| <b>Prevention/reduction of comorbid anxiety: HAM-A</b>    |  |                           |            |           |                              |                                   |
| 1; 65   | Medium;<br>RCT                             | NA, single study          | Direct     | Imprecise | -7.4 vs. -2.0, $p<0.001$     | Insufficient                      |
| <b>Prevention/reduction of comorbid psychosis: PANSS</b>  |  |                           |            |           |                              |                                   |
| 1; 40   | Medium;<br>RCT                             | NA, single study          | Direct     | Imprecise | -10.0 vs. -2.3, $p\leq 0.05$ | Insufficient                      |
| <b>Quality of Life</b>                                    |  |                           |            |           |                              |                                   |
| 0; 0  | NA   | NA                        | NA         | NA        | NA                           | Insufficient                      |
| <b>Disability/functional impairment: Sheehan</b>          |  |                           |            |           |                              |                                   |
| 0; 0  | NA   | NA                        | NA         | NA        | NA                           | Insufficient                      |
| <b>Return to work or return to active duty</b>            |  |                           |            |           |                              |                                   |
| 0; 0  | NA   | NA                        | NA         | NA        | NA                           | Insufficient                      |

Abbreviations: CI = confidence interval; NA = not applicable; RCT = randomized controlled trial

**Table G-31. Benzodiazepines compared with placebo<sup>a</sup>**

|   | Domains Pertaining to Strength of Evidence |             |            |           | Magnitude of Effect          | Strength of Evidence              |
|---|--|-------------|------------|-----------|------------------------------|-----------------------------------|
| Number of Studies; Number of Subjects                     | Risk of Bias; Design/Quality               | Consistency | Directness | Precision | Summary Effect Size (95% CI) | High, Moderate, Low, Insufficient |
| <b><i>PTSD Symptom Reduction: PTSD Scale and IES</i></b>  |  |             |            |           |                              | <b><i>Low</i></b>                 |
| 0; 0  | NA   | NA          | NA         | NA        | NA                           | Insufficient                      |
| <b><i>Remission (no longer having symptoms)</i></b>       |  |             |            |           |                              |                                   |
| 0; 0  | NA   | NA          | NA         | NA        | NA                           | Insufficient                      |
| <b><i>Loss of Diagnosis</i></b>                           |  |             |            |           |                              |                                   |
| 0; 0  | NA   | NA          | NA         | NA        | NA                           | Insufficient                      |
| <b><i>Prevention/reduction of comorbid depression</i></b> |  |             |            |           |                              |                                   |
| 0; 0  | NA   | NA          | NA         | NA        | NA                           | Insufficient                      |
| <b><i>Prevention/reduction of comorbid anxiety</i></b>    |  |             |            |           |                              |                                   |
| 0; 0  | NA   | NA          | NA         | NA        | NA                           | Insufficient                      |
| <b><i>Quality of Life</i></b>                             |  |             |            |           |                              |                                   |
| 0; 0  | NA   | NA          | NA         | NA        | NA                           | Insufficient                      |
| <b><i>Disability/functional impairment</i></b>            |  |             |            |           |                              |                                   |
| 0; 0  | NA   | NA          | NA         | NA        | NA                           | Insufficient                      |
| <b><i>Return to work or return to active duty</i></b>     |  |             |            |           |                              |                                   |
| 0; 0  | NA   | NA          | NA         | NA        | NA                           | Insufficient                      |

<sup>a</sup>We did not identify any studies of low or medium risk of bias meeting our inclusion criteria. We did find 1 study otherwise meeting criteria that we excluded for high risk of bias. The trial (N=16) reported no statistically significant difference between subjects treated with alprazolam and those treated with placebo for reduction of PTSD symptoms (PTSD Scale: -4.3 vs. -1.2, p=NS; IES: -3.3 vs. -0.3, p=NS) or reduction of comorbid depression (HAM-D: -1.1 vs. -0.8, p=NS). It reported greater reduction in anxiety for subjects treated with alprazolam (HAM-A: -7.7 vs. 0.2, p=0.02).

Abbreviations: NA = not applicable; RCT = randomized controlled trial

**Table G-32. Citalopram compared with placebo**

| Number of Studies; Number of Subjects  | Domains Pertaining to Strength of Evidence |                  |            |           | Magnitude of Effect                       | Strength of Evidence              |
|--|--|------------------|------------|-----------|---|-----------------------------------|
|  | Risk of Bias; Design                       | Consistency      | Directness | Precision | Summary Effect Size (95% CI) <sup>a</sup> | High, Moderate, Low, Insufficient |
| <b>PTSD Symptom Reduction: mean change from baseline in CAPS</b>                   |  |                  |            |           |   |                                   |
| 1; 35  | Medium; RCT                                | NA, single study | Direct     | Imprecise | WMD +7.98 (-10.1 to 26.0)                 | Insufficient                      |
| <b>PTSD Symptom Reduction: mean change from baseline in IES</b>                    |  |                  |            |           |   |                                   |
| 1; 35  | Medium; RCT                                | NA, single study | Direct     | Imprecise | WMD 7.8 (-4.8 to 20.5)                    | Insufficient                      |
| <b>Remission (no longer having symptoms)</b>                                       |  |                  |            |           |   |                                   |
| 0; 0   | NA   | NA               | NA         | NA        | NA  | Insufficient                      |
| <b>Loss of Diagnosis</b>   |  |                  |            |           |   |                                   |
| 0; 0   | NA   | NA               | NA         | NA        | NA  | Insufficient                      |
| <b>Prevention/reduction of comorbid depression: BDI, mean change from baseline</b> |  |                  |            |           |   |                                   |
| 1; 35  | Medium; RCT                                | NA, single study | Direct     | Imprecise | WMD -0.47 (-10.9 to 10.0)                 | Insufficient                      |
| <b>Prevention/reduction of comorbid anxiety</b>                                    |  |                  |            |           |   |                                   |
| 0; 0   | NA   | NA               | NA         | NA        | NA  | Insufficient                      |
| <b>Quality of Life</b>   |  |                  |            |           |   |                                   |
| 0; 0   | NA   | NA               | NA         | NA        | NA  | Insufficient                      |
| <b>Disability/functional impairment</b>  |  |                  |            |           |   |                                   |
| 0; 0   | NA   | NA               | NA         | NA        | NA  | Insufficient                      |
| <b>Return to work or return to active duty</b>                                     |  |                  |            |           |   |                                   |
| 0; 0   | NA   | NA               | NA         | NA        | NA  | Insufficient                      |

<sup>a</sup>Data are from a single trial comparing citalopram, sertraline, and placebo.<sup>18</sup>

Abbreviations: CI = confidence interval; NA = not applicable; RCT = randomized controlled trial

**Table G-33. Fluoxetine compared with placebo**

| Number of Studies; Number of Subjects   | Domains Pertaining to Strength of Evidence |                                    |            |           | Magnitude of Effect  | Strength of Evidence              |
|---|--|------------------------------------|------------|-----------|--|-----------------------------------|
|   | Risk of Bias; Design                       | Consistency                        | Directness | Precision | Summary Effect Size (95% CI)   | High, Moderate, Low, Insufficient |
| <b>PTSD Symptom Reduction: mean change from baseline in CAPS</b>                            |  |                                    |            |           |  |                                   |
| 4; 923  | Medium; RCTs                               | Consistent (I <sup>2</sup> =0%)    | Direct     | Precise   | WMD -6.97 (-10.4 to -3.5)  | Moderate                          |
| <b>PTSD Symptom Reduction: mean change from baseline in DTS</b>                             |  |                                    |            |           |  |                                   |
| 3; 766  | Medium; RCTs                               | Consistent (I <sup>2</sup> =31.3%) | Direct     | Precise   | WMD -8.19 (-13.7 to -2.7)  | Moderate                          |
| <b>Remission (no longer having symptoms): Percent of subjects with CAPS less than 20</b>    |  |                                    |            |           |  |                                   |
| 1; 52   | Medium; RCT                                | NA, single study                   | Direct     | Imprecise | 13% vs. 10%, p=0.72  | Insufficient                      |
| <b>Loss of Diagnosis: percent of subjects no longer meeting criteria for PTSD diagnosis</b> |  |                                    |            |           |  |                                   |
| 1; 59   | Medium; RCT                                | NA, single study                   | Direct     | Imprecise | 73% vs. 59%, p=0.23  | Insufficient                      |
| <b>Prevention/reduction of comorbid depression: mean change from baseline in MADRS</b>      |  |                                    |            |           |  |                                   |
| 2; 712  | Medium; RCTs                               | Consistent (I <sup>2</sup> =0%)    | Direct     | Precise   | WMD -2.4 (-3.7 to -1.1)  | Moderate                          |
| <b>Prevention/reduction of comorbid anxiety: mean change from baseline in HAMA</b>          |  |                                    |            |           |  |                                   |
| 2; 712  | Medium; RCTs                               | Consistent (I <sup>2</sup> =0%)    | Direct     | Precise   | WMD -2.1 (-3.2 to -0.9)  | Moderate                          |
| <b>Quality of Life: change in SF-36 mental and physical sub-scores</b>                      |  |                                    |            |           |  |                                   |
| 1; 144  | Medium; RCT                                | NA, single study                   | Direct     |           | Mental health sub-score: 15.5 vs. 0.33, p<0.001<br>Physical functioning sub-score: 8.62 vs. 8.07, p=0.891 <sup>a</sup> | Insufficient                      |
| <b>Disability/functional impairment: mean change from baseline in SDS</b>                   |  |                                    |            |           |  |                                   |
| 1; 54   | Medium; RCT                                | NA, single study                   | Direct     | Imprecise | -5.8 (-9.8 to -1.8)  | Insufficient                      |
| <b>Return to work or return to active duty</b>  |  |                                    |            |           |  |                                   |
| 0; 0  | NA   | NA                                 | NA         | NA        | NA   | Insufficient                      |

<sup>a</sup>Data from subgroup analysis of subjects with combat-related PTSD in one trial (N=144 of the 301 from the main trial).<sup>19</sup>

Abbreviations: CI = confidence interval; NA = not applicable; RCT = randomized controlled trial

**Table G-34. Paroxetine compared with placebo**

| Number of Studies; Number of Subjects  | Domains Pertaining to Strength of Evidence |                                 |            |           | Magnitude of Effect   | Strength of Evidence              |
|--|--|---------------------------------|------------|-----------|---|-----------------------------------|
|  | Risk of Bias; Design                       | Consistency                     | Directness | Precision | Summary Effect Size (95% CI)  | High, Moderate, Low, Insufficient |
| <b>PTSD Symptom Reduction: mean change from baseline in CAPS</b>                       |  |                                 |            |           |   |                                   |
| 2; 1074  | Medium; RCTs                               | Consistent (I <sup>2</sup> =0%) | Direct     | Precise   | WMD -12.6 (-15.7 to -9.5)   | Moderate                          |
| <b>PTSD Symptom Reduction: mean change from baseline in DTS</b>                        |  |                                 |            |           |   |                                   |
| 2; 1074  | Medium; RCTs                               | Consistent (I <sup>2</sup> =0%) | Direct     | Precise   | WMD -12.2 (-15.8 to -8.7)   | Moderate                          |
| <b>Remission (no longer having symptoms)</b>   |  |                                 |            |           |   |                                   |
| 2; 346   | Medium; RCTs                               | Consistent                      | Direct     | Precise   | 12.9% more subjects in paroxetine group achieved remission (p=0.008) <sup>a</sup> | Moderate                          |
| <b>Loss of Diagnosis</b>   |  |                                 |            |           |   |                                   |
| 0; 0   | NA   | NA                              | NA         | NA        | NA  | Insufficient                      |
| <b>Prevention/reduction of comorbid depression: mean change from baseline in MADRS</b> |  |                                 |            |           |   |                                   |
| 2; 886   | Medium; RCTs                               | Consistent (I <sup>2</sup> =0%) | Direct     | Precise   | WMD -5.7 (-7.1 to -4.3)   | Moderate                          |
| <b>Prevention/reduction of comorbid anxiety</b>  |  |                                 |            |           |   |                                   |
| 0; 0   | NA   | NA                              | NA         | NA        | NA  | Insufficient                      |
| <b>Quality of Life</b>   |  |                                 |            |           |   |                                   |
| 0; 0   | NA   | NA                              | NA         | NA        | NA  | Insufficient                      |
| <b>Disability/functional impairment: mean change from baseline in SDS</b>              |  |                                 |            |           |   |                                   |
| 2; 886   | Medium; RCTs                               | Consistent (I <sup>2</sup> =0%) | Direct     | Precise   | WMD -2.3 (-3.3 to -1.4)   | Moderate                          |
| <b>Return to work or return to active duty</b>   |  |                                 |            |           |   |                                   |
| 0; 0   | NA   | NA                              | NA         | NA        | NA  | Insufficient                      |

<sup>a</sup> Data is the best available evidence from a trial of paroxetine (N=323) that defined remission as a CAPS-2 total score less than 20 and found a significantly greater proportion of paroxetine-treated subjects achieved remission compared with placebo at week 12 (29.4% vs. 16.5%, p=0.008). The difference (12.9% difference between paroxetine and placebo) would translate to a number needed to treat of 7.8 to achieve one remission.<sup>20</sup> The other trial contributing data for this outcome found similar percentages of subjects achieving remission (33% vs. 14%), but it was underpowered to detect anything but a very large difference for this outcome.<sup>21</sup>

Abbreviations: CI = confidence interval; NA = not applicable; RCT = randomized controlled trial



**Table G-35. Sertraline compared with placebo**

| Number of Studies; Number of Subjects   | Domains Pertaining to Strength of Evidence |  |            |           | Magnitude of Effect          | Strength of Evidence              |
|---|--|--|------------|-----------|------------------------------|-----------------------------------|
|   | Risk of Bias; Design                       | Consistency  | Directness | Precision | Summary Effect Size (95% CI) | High, Moderate, Low, Insufficient |
| <b>PTSD Symptom Reduction: mean change from baseline in CAPS</b>  |  |  |            |           |                              |                                   |
| 7; 1,085  | Medium; RCTs                               | Consistent (I <sup>2</sup> =0%)  | Direct     | Precise   | WMD -4.87 (-7.4 to -2.4)     | Moderate                          |
| <b>PTSD Symptom Reduction: mean change from baseline in DTS</b>   |  |  |            |           |                              |                                   |
| 4; 916  | Medium; RCTs                               | Consistent (I <sup>2</sup> =0%)  | Direct     | Precise   | WMD -7.7 (-12.9 to -2.4)     | Moderate                          |
| <b>Remission (no longer having symptoms): Percent of subjects achieving CAPS-SX<sub>17</sub> score less than 20</b> |  |  |            |           |                              |                                   |
| 1; 352  | Medium; RCT                                | NA, single study   | Direct     | Unknown   | 24.3% vs. 19.6%, p=NS (NR)   | Insufficient                      |
| <b>Loss of Diagnosis</b>  |  |  |            |           |                              |                                   |
| 0; 0  | NA   | NA   | NA         | NA        | NA                           | Insufficient                      |
| <b>Prevention/reduction of comorbid depression: mean change from baseline in HAMD</b>                               |  |  |            |           |                              |                                   |
| 5; 1,010  | Medium; RCTs                               | Inconsistent: I <sup>2</sup> =25% but 3 trials trended in favor of sertraline; 2 in favor of placebo | Direct     | Imprecise | WMD -0.77 (-2.1 to 0.55)     | Low                               |
| <b>Prevention/reduction of comorbid anxiety: mean change from baseline in HAMA</b>                                  |  |  |            |           |                              |                                   |
| 2; 377  | Medium; RCTs                               | Inconsistent (I <sup>2</sup> =68.3%)   | Direct     | Imprecise | WMD 0.19 (-3.14 to 3.51)     | Insufficient                      |
| <b>Quality of Life: mean change in Q-LES-Q</b>  |  |  |            |           |                              |                                   |
| 2; 539  | Medium; RCTs                               | Inconsistent (I <sup>2</sup> =72.6%)   | Direct     | Imprecise | WMD 4.9 (-0.88 to 10.7)      | Insufficient                      |
| <b>Disability/functional impairment: mean change from baseline in SDS</b>   |  |  |            |           |                              |                                   |
| 1; 352  | Medium; RCT                                | NA, single study   | Direct     | Imprecise | -1.65 (-3.4 to 0.12)         | Insufficient                      |
| <b>Return to work or return to active duty</b>  |  |  |            |           |                              |                                   |
| 0; 0  | NA   | NA   | NA         | NA        | NA                           | Insufficient                      |

Abbreviations: CI = confidence interval; NA = not applicable; RCT = randomized controlled trial

**Table G-36. Venlafaxine compared with placebo**

|  | Domains Pertaining to Strength of Evidence |                        |            |           | Magnitude of Effect   | Strength of Evidence              |
|--|--|------------------------|------------|-----------|---|-----------------------------------|
| Number of Studies; Number of Subjects  | Risk of Bias; Design/Quality               | Consistency            | Directness | Precision | Summary Effect Size (95% CI)  | High, Moderate, Low, Insufficient |
| <b>PTSD Symptom Reduction: Change in CAPS</b>  |  |                        |            |           |   |                                   |
| 2; 687   | Medium/RCT                                 | Consistent ( $I^2$ 0%) | Direct     | Precise   | WMD -7.15 (-11.02 to -3.28)   | Moderate                          |
| <b>Remission (no longer having symptoms): defined by CAPS-Sx total score of 20 or less</b> |  |                        |            |           |   |                                   |
| 2; 687   | Medium/RCT                                 | Consistent ( $I^2$ 0%) | Direct     | Precise   | RD 0.12 (0.05 to 0.19)  | Moderate                          |
| <b>Loss of Diagnosis</b>   |  |                        |            |           |   |                                   |
| 0; 0   | NA   | NA                     | NA         | NA        | NA  | Insufficient                      |
| <b>Prevention/reduction of comorbid depression: change in HAM-D</b>                        |  |                        |            |           |   |                                   |
| 2; 687   | Medium/RCT                                 | Consistent ( $I^2$ 0%) | Direct     | Precise   | WMD -2.08 (-3.12 to -1.04)  | Moderate                          |
| <b>Prevention/reduction of comorbid anxiety</b>  |  |                        |            |           |   |                                   |
| 0; 0   | NA   | NA                     | NA         | NA        | NA  | Insufficient                      |
| <b>Quality of Life (change in Q-LES-Q-SF)</b>  |  |                        |            |           |   |                                   |
| 2; 687   | Medium/RCT                                 | Consistent ( $I^2$ 0%) | Direct     | Precise   | WMD 3.42 (1.58 to 5.26)   | Moderate                          |
| <b>Disability/functional impairment (change in SDS, and change in GAF)</b>                 |  |                        |            |           |   |                                   |
| 2; 687   | Medium/RCT                                 | Consistent ( $I^2$ 0%) | Direct     | Precise   | WMD -2.06 (-3.28 to -0.84) for SDS<br>WMD 3.41 (1.41 to 5.40) for GAF | Moderate                          |
| <b>Return to work or return to active duty</b>   |  |                        |            |           |   |                                   |
| 0; 0   | NA   | NA                     | NA         | NA        | NA  | Insufficient                      |

Abbreviations: CI = confidence interval; NA = not applicable; RCT = randomized controlled trial

**Table G-37. Strength of evidence for tricyclic antidepressants compared to placebo**

| Number of Studies;<br>Number of Subjects                  | Domains Pertaining to Strength of Evidence |             |            |           | Magnitude of Effect          | Strength of Evidence              |
|---|--|-------------|------------|-----------|------------------------------|-----------------------------------|
|   | Risk of Bias;<br>Design/<br>Quality        | Consistency | Directness | Precision | Summary Effect Size (95% CI) | High, Moderate, Low, Insufficient |
| <b><i>PTSD Symptom Reduction</i></b>                      |  |             |            |           |                              |                                   |
| 0; 0  | NA   | NA          | NA         | NA        | NA                           | Insufficient                      |
| <b><i>Remission (no longer having symptoms)</i></b>       |  |             |            |           |                              |                                   |
| 0; 0  | NA   | NA          | NA         | NA        | NA                           | Insufficient                      |
| <b><i>Loss of Diagnosis</i></b>                           |  |             |            |           |                              |                                   |
| 0; 0  | NA   | NA          | NA         | NA        | NA                           | Insufficient                      |
| <b><i>Prevention/reduction of comorbid depression</i></b> |  |             |            |           |                              |                                   |
| 0; 0  | NA   | NA          | NA         | NA        | NA                           | Insufficient                      |
| <b><i>Prevention/reduction of comorbid anxiety</i></b>    |  |             |            |           |                              |                                   |
| 0; 0  | NA   | NA          | NA         | NA        | NA                           | Insufficient                      |
| <b><i>Quality of Life</i></b>                             |  |             |            |           |                              |                                   |
| 0; 0  | NA   | NA          | NA         | NA        | NA                           | Insufficient                      |
| <b><i>Disability/functional impairment</i></b>            |  |             |            |           |                              |                                   |
| 0; 0  | NA   | NA          | NA         | NA        | NA                           | Insufficient                      |
| <b><i>Return to work or return to active duty</i></b>     |  |             |            |           |                              |                                   |
| 0; 0  | NA   | NA          | NA         | NA        | NA                           | Insufficient                      |

**Table G-38. Placebo-controlled trials of bupropion**

|   | Domains Pertaining to Strength of Evidence |                  |            |           | Magnitude of Effect          | Strength of Evidence              |
|---|--|------------------|------------|-----------|------------------------------|-----------------------------------|
| Number of Studies; Number of Subjects                   | Risk of Bias; Design/Quality               | Consistency      | Directness | Precision | Summary Effect Size (95% CI) | High, Moderate, Low, Insufficient |
| <b>PTSD Symptom Reduction: CAPS</b>                     |  |                  |            |           |                              |                                   |
| 1; 30   | Medium; RCT                                | NA, Single Study | Direct     | Imprecise | -12.33 vs. -16.99, NS        | Insufficient                      |
| <b>PTSD Symptom Reduction: DTS</b>                      |  |                  |            |           |                              |                                   |
| 1; 30   | Medium; RCT                                | NA, Single Study | Direct     | Imprecise | -13.22 vs. -10.6, NS         | Insufficient                      |
| <b>Remission (no longer having symptoms)</b>            |  |                  |            |           |                              |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA                           | Insufficient                      |
| <b>Loss of Diagnosis</b>                                |  |                  |            |           |                              |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA                           | Insufficient                      |
| <b>Prevention/reduction of comorbid depression: BDI</b> |  |                  |            |           |                              |                                   |
| 1; 30   | Medium; RCT                                | NA, single study | Direct     | Imprecise | -3.22 vs. -3.61, NS          | Insufficient                      |
| <b>Prevention/reduction of comorbid anxiety</b>         |  |                  |            |           |                              |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA                           | Insufficient                      |
| <b>Quality of Life</b>                                  |  |                  |            |           |                              |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA                           | Insufficient                      |
| <b>Disability/functional impairment</b>                 |  |                  |            |           |                              |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA                           | Insufficient                      |
| <b>Return to work or return to active duty</b>          |  |                  |            |           |                              |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA                           | Insufficient                      |

Abbreviations: CI = confidence interval; NA = not applicable; RCT = randomized controlled trial

**Table G-39. Placebo-controlled trials of mirtazapine**

| Number of Studies;<br>Number of Subjects                          | Domains Pertaining to Strength of Evidence |                  |            |           | Magnitude of Effect          | Strength of Evidence              |
|---|--|------------------|------------|-----------|------------------------------|-----------------------------------|
|   | Risk of Bias; Design/Quality               | Consistency      | Directness | Precision | Summary Effect Size (95% CI) | High, Moderate, Low, Insufficient |
| <b><i>PTSD Symptom Reduction: DTS</i></b>                         |  |                  |            |           |                              |                                   |
| 1; 29   | Medium; RCT                                | NA, single study | Direct     | Imprecise | -20.7 vs. -11.2, NS          | Insufficient                      |
| <b><i>PTSD Symptom Reduction: SPRINT</i></b>                      |  |                  |            |           |                              |                                   |
| 1; 29   | Medium; RCT                                | NA, single study | Direct     | Imprecise | -9.3 vs. -5.6, p=0.20        | Insufficient                      |
| <b><i>PTSD Symptom Reduction: SIPS</i></b>                        |  |                  |            |           |                              |                                   |
| 1; 29   | Medium; RCT                                | NA, single study | Direct     | Imprecise | -17.3 vs. -6.5, p=0.04       | Insufficient                      |
| <b><i>Remission (no longer having symptoms)</i></b>               |  |                  |            |           |                              |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA                           | Insufficient                      |
| <b><i>Loss of Diagnosis</i></b>                                   |  |                  |            |           |                              |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA                           | Insufficient                      |
| <b><i>Prevention/reduction of comorbid depression: HADS-D</i></b> |  |                  |            |           |                              |                                   |
| 1; 29   | Medium; RCT                                | NA, single study | Direct     | Imprecise | -2.2 vs. -0.5, NS            | Insufficient                      |
| <b><i>Prevention/reduction of comorbid anxiety: HADS-A</i></b>    |  |                  |            |           |                              |                                   |
| 1; 29   | Medium; RCT                                | NA, single study | Direct     | Imprecise | -2.8 vs. -1.2, p<0.05        | Insufficient                      |
| <b><i>Quality of Life</i></b>                                     |  |                  |            |           |                              |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA                           | Insufficient                      |
| <b><i>Disability/functional impairment</i></b>                    |  |                  |            |           |                              |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA                           | Insufficient                      |
| <b><i>Return to work or return to active duty</i></b>             |  |                  |            |           |                              |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA                           | Insufficient                      |

**Table G-40. Paroxetine compared with desipramine: Head-to-head trials<sup>a</sup>**

|   | Domains Pertaining to Strength of Evidence |                  |            |           | Magnitude of Effect                                    | Strength of Evidence              |
|---|--|------------------|------------|-----------|--|-----------------------------------|
| Number of Studies; Number of Subjects   | Risk of Bias; Design                       | Consistency      | Directness | Precision | Summary Effect Size (95% CI)                           | High, Moderate, Low, Insufficient |
| <b>PTSD Symptom Reduction: CAPS, mean change from baseline</b>  |  |                  |            |           |  |                                   |
| 1; 88   | Medium; RCT                                | NA, single study | Direct     | Imprecise | -33.5 vs. -33.2 vs. -35.7 vs. -36.4, p=NS <sup>a</sup> | Low                               |
| <b>Remission (no longer having symptoms)</b>  |  |                  |            |           |  |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA   | Insufficient                      |
| <b>Loss of Diagnosis</b>  |  |                  |            |           |  |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA   | Insufficient                      |
| <b>Prevention/reduction of comorbid depression: HAMD, mean change from baseline</b>                         |  |                  |            |           |  |                                   |
| 1; 88   | Medium; RCT                                | NA, single study | Direct     | Imprecise | -3.9 vs. -2.7 vs. -2.6 vs. -4.2, p=NS <sup>a</sup>     | Low                               |
| <b>Prevention/reduction of comorbid alcohol dependence: heavy drinking days and drinks per drinking day</b> |  |                  |            |           |  |                                   |
| 1; 88   | Medium; RCT                                | NA, single study | Direct     | Imprecise | Greater reduction with desipramine <sup>b</sup>        | Low                               |
| <b>Quality of Life</b>  |  |                  |            |           |  |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA   | Insufficient                      |
| <b>Disability/functional impairment</b>   |  |                  |            |           |  |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA   | Insufficient                      |
| <b>Return to work or return to active duty</b>  |  |                  |            |           |  |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA   | Insufficient                      |

<sup>a</sup> Data are from 1 trial of veterans with PTSD and comorbid alcohol dependence that compared Paroxetine + Naltrexone, Paroxetine + Placebo, Desipramine + Naltrexone, and Desipramine + Placebo.

<sup>b</sup> Data NR for drinking outcomes; p=0.009 for percentage of heavy drinking days and p=0.027 for drinks per drinking day; shown in Figure only; magnitude of difference NR and difficult to read clearly from the Figure, all groups ended up less than 20 standard drinks per week (from baselines above 70 drinks per week), but it appears that the Desipramine groups ended up in the 0 to 10 drinks per week range and the paroxetine groups ended up in the 10-20 range at the 12 week endpoint.

Abbreviations: CI = confidence interval; NA = not applicable; NR = not reported; RCT = randomized controlled trial

**Table G-41. Venlafaxine ER compared with sertraline: Head-to-head trials**

|   | Domains Pertaining to Strength of Evidence |                               |            |           | Magnitude of Effect   | Strength of Evidence              |
|---|--|-------------------------------|------------|-----------|---|-----------------------------------|
| Number of Studies; Number of Subjects   | Risk of Bias; Design                       | Consistency                   | Directness | Precision | Summary Effect Size (95% CI) <sup>a</sup>   | High, Moderate, Low, Insufficient |
| <b>PTSD Symptom Reduction: CAPS-SX<sub>17</sub>, mean change from baseline</b>      |  |                               |            |           |   |                                   |
| 1; 538  | Medium; RCT                                | NA, single study <sup>b</sup> | Direct     | Precise   | -41.5 vs. -39.4<br>p=0.49   | Moderate                          |
| <b>PTSD Symptom Reduction: DTS, mean change from baseline</b>                       |  |                               |            |           |   |                                   |
| 1; 538  | Medium; RCT                                | NA, single study <sup>b</sup> | Direct     | Precise   | -42.9 vs. -38.9,<br>p=0.25  | Moderate                          |
| <b>Remission (no longer having symptoms): SX17 score of ≤20 at week 12</b>          |  |                               |            |           |   |                                   |
| 1; 538  | Medium; RCT                                | NA, single study <sup>b</sup> | Direct     | Precise   | V vs. S vs. P<br>~30% vs. ~25% vs.<br>~20%<br>p<0.05 for V vs. P<br>p=NS S vs. P and for<br>V vs. S | Moderate                          |
| <b>Loss of Diagnosis</b>  |  |                               |            |           |   |                                   |
| 0; 0  | NA   | NA                            | NA         | NA        | NA  | Insufficient                      |
| <b>Prevention/reduction of comorbid depression: HAMD, mean change from baseline</b> |  |                               |            |           |   |                                   |
| 1; 538  | Medium; RCT                                | NA, single study <sup>b</sup> | Direct     | Precise   | -7.09 vs. -6.42 vs. -5.54<br>P values:<br>0.38 for V vs. S<br>0.04 for V vs. P<br>0.24 for S vs. P  | Low                               |
| <b>Prevention/reduction of comorbid anxiety</b>                                     |  |                               |            |           |   |                                   |
| 0; 0  | NA   | NA                            | NA         | NA        | NA  | Insufficient                      |
| <b>Quality of Life: Q-LES-Q, mean change</b>  |  |                               |            |           |   |                                   |
| 1; 538  | Medium; RCT                                | NA, single study <sup>b</sup> | Direct     | Precise   | 11.5 vs. 11.2 vs. 8.8<br>P values:<br>V vs. P 0.033;<br>S vs. P 0.068;<br>V vs. S 0.782             | Moderate                          |
| <b>Disability/functional impairment: SDS</b>  |  |                               |            |           |   |                                   |
| 1; 538  | Medium; RCT                                | NA, single study <sup>b</sup> | Direct     | Precise   | -8.5 vs. -8.2 vs. -6.5<br>P values:<br>V vs. P 0.025;<br>S vs. P 0.068;<br>V vs. S 0.683            | Moderate                          |
| <b>Return to work or return to active duty</b>                                      |  |                               |            |           |   |                                   |
| 0; 0  | NA   | NA                            | NA         | NA        | NA  | Insufficient                      |

<sup>a</sup> Data are from 1 multicenter trial comparing venlafaxine ER, sertraline, and placebo.<sup>22</sup>

<sup>b</sup> Although this is a single trial, it was a multicenter trial including 59 outpatient centers in the US. We considered this in our SOE grade.

Abbreviations: CI = confidence interval; NA = not applicable; NR = not reported; p=placebo; RCT = randomized controlled trial; S = sertraline; V = venlafaxine ER

**Table G-42. Sertraline compared with citalopram: Head-to-head trials**

|   | Domains Pertaining to Strength of Evidence |                  |            |           | Magnitude of Effect                            | Strength of Evidence              |
|---|--|------------------|------------|-----------|--|-----------------------------------|
| Number of Studies; Number of Subjects                                 | Risk of Bias; Design                       | Consistency      | Directness | Precision | Summary Effect Size (95% CI) <sup>a</sup>      | High, Moderate, Low, Insufficient |
| <b><i>PTSD Symptom Reduction: CAPS, mean change from baseline</i></b> |  |                  |            |           |  |                                   |
| 1; 58   | Medium; RCT                                | NA, single study | Direct     | Imprecise | S vs. C vs. P: -41.8 vs. -30.7 vs. -38.7, p=NS | Insufficient                      |
| <b><i>PTSD Symptom Reduction: IES, mean change from baseline</i></b>  |  |                  |            |           |  |                                   |
| 1; 58   | Medium; RCT                                | NA, single study | Direct     | Imprecise | -29.1 vs. -19.3 vs. -33.2, p=NS                | Insufficient                      |
| <b><i>Remission (no longer having symptoms)</i></b>                   |  |                  |            |           |  |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA   | Insufficient                      |
| <b><i>Loss of Diagnosis</i></b>                                       |  |                  |            |           |  |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA   | Insufficient                      |
| <b><i>Prevention/reduction of comorbid depression: BDI</i></b>        |  |                  |            |           |  |                                   |
| 1; 58   | Medium; RCT                                | NA, single study | Direct     | Imprecise | -13.4 vs. -16.1 vs. -15.6, p=NR                | Insufficient                      |
| <b><i>Prevention/reduction of comorbid anxiety</i></b>                |  |                  |            |           |  |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA   | Insufficient                      |
| <b><i>Quality of Life: Q-LES-Q, mean change</i></b>                   |  |                  |            |           |  |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA   | Insufficient                      |
| <b><i>Disability/functional impairment: SDS</i></b>                   |  |                  |            |           |  |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA   | Insufficient                      |
| <b><i>Return to work or return to active duty</i></b>                 |  |                  |            |           |  |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA   | Insufficient                      |

<sup>a</sup> Data are from 1 RCT comparing sertraline, citalopram, and placebo.<sup>18</sup>

Abbreviations: C = citalopram; CI = confidence interval; NA = not applicable; NR = not reported; p=placebo; RCT = randomized controlled trial; S = sertraline



## Key Question 3

**Table G-43. Head-to-head trials of psychological and pharmacological treatments: Fluoxetine compared with EMDR**

|   | Domains Pertaining to Strength of Evidence |                           |            |           | Magnitude of Effect   | Strength of Evidence              |
|---|--|---------------------------|------------|-----------|---|-----------------------------------|
| Number of Studies;<br>Number of Subjects            | Risk of Bias;<br>Design                    | Consistency               | Directness | Precision | Mean, %, or Effect Size (ES)  | High, Moderate, Low, Insufficient |
| <b>PTSD Symptom Reduction: CAPS and PSS</b>         |  |                           |            |           |   | <b>Insufficient</b>               |
| Fluoxetine vs. EMDR<br>1; 59 (post)<br>1; 50 (f/up) | Medium;<br>RCT                             | Unknown<br>(single study) | Direct     | Imprecise | CAPS (1 wk): -31.03 vs. -36.85, NS (post);<br>CAPS (1 month): -33.78 vs. -45.91, p<0.005 (f/up) | Insufficient                      |
| <b>Remission (no longer having symptoms):</b>       |  |                           |            |           |   |                                   |
| Fluoxetine vs. EMDR<br>1; 59 (post)<br>1; 50 (f/up) | Medium;<br>RCT                             | Unknown<br>(single study) | Direct     | Imprecise | 13% vs. 28%, NS (post)<br>0% vs. 58%, p<0.001 (f/up)  | Insufficient                      |
| <b>Loss of Diagnosis</b>                            |  |                           |            |           |   |                                   |
| Fluoxetine vs. EMDR<br>1; 59 (post)<br>1; 50 (f/up) | Medium;<br>RCT                             | Unknown<br>(single study) | Direct     | Imprecise | 73% vs. 76%, NS (post)<br>73% vs. 88%, NS (f/up)  | Insufficient                      |
| <b>Prevention/reduction of comorbid depression</b>  |  |                           |            |           |   |                                   |
| Fluoxetine vs. EMDR<br>1; 59 (post)<br>1; 50 (f/up) | Medium;<br>RCT                             | Unknown<br>(single study) | Direct     | Imprecise | BDI: -5.78 vs. -6.99, NS (post);<br>-4.2 vs. -10.95, p<0.001 (f/up)                             | Insufficient                      |
| <b>Prevention/reduction of comorbid anxiety</b>     |  |                           |            |           |   |                                   |
| 0; 0  | NA   | NA                        | NA         | NA        | NA  | Insufficient                      |
| <b>Quality of Life</b>                              |  |                           |            |           |   |                                   |
| 0; 0  | NA   | NA                        | NA         | NA        | NA  | Insufficient                      |
| <b>Disability/functional impairment</b>             |  |                           |            |           |   |                                   |
| 0; 0  | NA   | NA                        | NA         | NA        | NA  | Insufficient                      |
| <b>Return to work or return to active duty</b>      |  |                           |            |           |   |                                   |
| 0; 0  | NA   | NA                        | NA         | NA        | NA  | Insufficient                      |

Abbreviations: BDI = Beck Depression Inventory; CAPS = Clinician Administered PTSD Scale – total; f/up, 6 month follow-up; NR = not reported; NS = non-significant; post = post-treatment; wk = week.

## Key Question 4

**Table G-44. Prolonged exposure plus paroxetine compared with prolonged exposure plus placebo**

| Number of Studies;<br>Number of Subjects  | Domains Pertaining to Strength of Evidence |                  |            |           | Magnitude of Effect  | Strength of Evidence              |
|---|--|------------------|------------|-----------|--|-----------------------------------|
|   | Risk of Bias;<br>Design                    | Consistency      | Directness | Precision | Summary Effect Size (95% CI)   | High, Moderate, Low, Insufficient |
| <b>PTSD Symptom Reduction: CAPS, mean change from baseline to week 10</b>                                   |  |                  |            |           |  |                                   |
| 1; 37   | Medium;<br>RCT                             | NA, single study | Direct     | Imprecise | -51.1 vs. -29.8, p=0.01  | Insufficient                      |
| <b>Remission (no longer having symptoms): CAPS score less than 20 and a CGI-C of 1 (very much improved)</b> |  |                  |            |           |  |                                   |
| 1; 37   | Medium;<br>RCT                             | NA, single study | Direct     | Imprecise | ITT sample: 42.1% vs. 16.7%; Modeled data: OR, 12.6; 95% CI, 1.23 to 129 | Insufficient                      |
| <b>Loss of Diagnosis</b>  |  |                  |            |           |  |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA   | Insufficient                      |
| <b>Prevention/reduction of comorbid depression: HAMD</b>  |  |                  |            |           |  |                                   |
| 1; 37   | Medium;<br>RCT                             | NA, single study | Direct     | Imprecise | HAMD: -9.2 vs. -5.2, p=0.14  | Insufficient                      |
| <b>Prevention/reduction of comorbid anxiety</b>   |  |                  |            |           |  |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA   | Insufficient                      |
| <b>Quality of Life: Q-LES-Q</b>   |  |                  |            |           |  |                                   |
| 1; 37   | High; RCT                                  | NA, single study | Direct     | Imprecise | Increase in Q-LES-Q: 20.8 vs. 9.4, p=0.02                                | Insufficient                      |
| <b>Disability/functional impairment</b>   |  |                  |            |           |  |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA   | Insufficient                      |
| <b>Return to work or return to active duty</b>  |  |                  |            |           |  |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA   | Insufficient                      |

Abbreviations: CI = confidence interval; NA = not applicable; RCT = randomized controlled trial

**Table G-45. Sertraline plus prolonged exposure compared with sertraline**

| Number of Studies; Number of Subjects   | Domains Pertaining to Strength of Evidence |                  |            |           | Magnitude of Effect                 | Strength of Evidence              |
|---|--|------------------|------------|-----------|-------------------------------------|-----------------------------------|
|   | Risk of Bias; Design                       | Consistency      | Directness | Precision | Summary Effect Size (95% CI)        | High, Moderate, Low, Insufficient |
| <b><i>PTSD Symptom Reduction: mean reduction from baseline in SIP</i></b>                 |  |                  |            |           |                                     |                                   |
| 1; 65   | Medium; RCT                                | NA, single study | Direct     | Imprecise | 5.9 with p<0.001 vs. -0.3 with p NS | Insufficient                      |
| <b><i>Remission (no longer having symptoms)</i></b>                                       |  |                  |            |           |                                     |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA                                  | Insufficient                      |
| <b><i>Loss of Diagnosis</i></b>   |  |                  |            |           |                                     |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA                                  | Insufficient                      |
| <b><i>Prevention/reduction of comorbid depression: mean BDI, change from baseline</i></b> |  |                  |            |           |                                     |                                   |
| 1; 65   | Medium; RCT                                | NA, single study | Direct     | Imprecise | -3.2 vs. +0.3, p=NS                 | Insufficient                      |
| <b><i>Prevention/reduction of comorbid anxiety: mean STAI-S, change from baseline</i></b> |  |                  |            |           |                                     |                                   |
| 1; 65   | Medium; RCT                                | NA, single study | Direct     | Imprecise | -3.9 vs. 0, p=NS                    | Insufficient                      |
| <b><i>Quality of Life</i></b>   |  |                  |            |           |                                     |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA                                  | Insufficient                      |
| <b><i>Disability/functional impairment</i></b>  |  |                  |            |           |                                     |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA                                  | Insufficient                      |
| <b><i>Return to work or return to active duty</i></b>                                     |  |                  |            |           |                                     |                                   |
| 0; 0  | NA   | NA               | NA         | NA        | NA                                  | Insufficient                      |

Abbreviations: CI = confidence interval; NA = not applicable; RCT = randomized controlled trial

## Key Question 6

Table G-46. Strength of evidence for adverse events for topiramate compared with placebo

| Number of Studies;<br>Number of Subjects | Domains Pertaining to Strength of Evidence |  |            |           | Magnitude of Effect          | Strength of Evidence              |
|--|--|--|------------|-----------|------------------------------|-----------------------------------|
|  | Risk of Bias;<br>Design                    | Consistency  | Directness | Precision | Summary Effect Size (95% CI) | High, Moderate, Low, Insufficient |
| <b>Withdrawals due to Adverse Events</b> |  |  |            |           |                              |                                   |
| 3; 142                                   | Medium;<br>RCTs                            | Inconsistent<br>(2 trials trend in favor of placebo; 1 does not) | Direct     | Imprecise | RD 0.01 (-0.08 to 0.10)      | Insufficient                      |
| <b>Headaches</b>                         |  |  |            |           |                              |                                   |
| 2; 75                                    | Medium;<br>RCTs                            | Inconsistent   | Direct     | Imprecise | RD -0.01 (-0.21 to 0.18)     | Insufficient                      |
| <b>Insomnia</b>                          |  |  |            |           |                              |                                   |
| 2; 75                                    | Medium;<br>RCTs                            | Inconsistent   | Direct     | Imprecise | RD 0.12 (-0.05 to 0.28)      | Insufficient                      |
| <b>Somnolence</b>                        |  |  |            |           |                              |                                   |
| 1; 35                                    | Medium;<br>RCT                             | NA, single study   | Direct     | Imprecise | RD -0.10 (-0.39 to 0.20)     | Insufficient                      |
| <b>Taste perversion</b>                  |  |  |            |           |                              |                                   |
| 1; 40                                    | Medium;<br>RCT                             | NA, single study   | Direct     | Imprecise | RD 0.25 (0.04 to 0.46)       | Insufficient                      |
| <b>Dyspepsia</b>                         |  |  |            |           |                              |                                   |
| 1; 40                                    | Medium;<br>RCT                             | NA, single study   | Direct     | Imprecise | RD 0.10 (-0.12 to 0.32)      | Insufficient                      |
| <b>Paresthesia</b>                       |  |  |            |           |                              |                                   |
| 1; 40                                    | Medium;<br>RCT                             | NA, single study   | Direct     | Imprecise | RD 0.15 (-0.05 to 0.35)      | Insufficient                      |
| <b>Nervousness</b>                       |  |  |            |           |                              |                                   |
| 1; 40                                    | Medium;<br>RCT                             | NA, single study   | Direct     | Imprecise | RD 0.15 (-0.05 to 0.35)      | Insufficient                      |
| <b>Fatigue</b>                           |  |  |            |           |                              |                                   |
| 1; 40                                    | Medium;<br>RCT                             | NA, single study   | Direct     | Imprecise | RD 0.20 (0.00 to 0.40)       | Insufficient                      |

Abbreviations: CI = confidence interval; NA = not applicable; RCT = randomized controlled trial

**Table G-47. Strength of evidence for adverse events for fluoxetine compared with placebo**

| Number of Studies;<br>Number of Subjects        | Domains Pertaining to Strength of Evidence |                                       |            |           | Magnitude of Effect          | Strength of Evidence              |
|---|--|---------------------------------------|------------|-----------|------------------------------|-----------------------------------|
|   | Risk of Bias;<br>Design                    | Consistency                           | Directness | Precision | Summary Effect Size (95% CI) | High, Moderate, Low, Insufficient |
| <b><i>Withdrawals due to Adverse Events</i></b> |  |                                       |            |           |                              |                                   |
| 3; 766  | Medium;<br>RCTs                            | Consistent<br>(I <sup>2</sup> =4.3%)  | Direct     | Imprecise | RD -0.01 (-0.04 to 0.03)     | Low                               |
| <b><i>Headaches</i></b>                         |  |                                       |            |           |                              |                                   |
| 3; 776  | Medium;<br>RCTs                            | Consistent<br>(I <sup>2</sup> =28.2%) | Direct     | Imprecise | RD 0.03 (-0.04 to 0.09)      | Insufficient                      |
| <b><i>Nausea</i></b>                            |  |                                       |            |           |                              |                                   |
| 2; 712  | Medium;<br>RCTs                            | Consistent<br>(I <sup>2</sup> =0%)    | Direct     | Imprecise | RD 0.05 (0.00 to 0.09)       | Low                               |
| <b><i>Insomnia</i></b>                          |  |                                       |            |           |                              |                                   |
| 1; 301  | Medium;<br>RCT                             | NA, single study                      | Direct     | Imprecise | RD 0.03 (-0.06 to 0.11)      | Insufficient                      |
| <b><i>Dry mouth</i></b>                         |  |                                       |            |           |                              |                                   |
| 0; 0  | NA   | NA                                    | NA         | NA        | NA                           | Insufficient                      |
| <b><i>Diarrhea</i></b>                          |  |                                       |            |           |                              |                                   |
| 1; 64   | Medium;<br>RCT                             | NA, single study                      | Direct     | Imprecise | RD 0.24 (0.01 to 0.47)       | Insufficient                      |
| <b><i>Dizziness</i></b>                         |  |                                       |            |           |                              |                                   |
| 0; 0  | NA   | NA                                    | NA         | NA        | NA                           | Insufficient                      |
| <b><i>Fatigue</i></b>                           |  |                                       |            |           |                              |                                   |
| 0; 0  | NA   | NA                                    | NA         | NA        | NA                           | Insufficient                      |
| <b><i>Somnolence</i></b>                        |  |                                       |            |           |                              |                                   |
| 1; 411  | Medium;<br>RCT                             | NA, single study                      | Direct     | Imprecise | RD 0.05 (0.00 to 0.10)       | Insufficient                      |
| <b><i>Drowsiness</i></b>                        |  |                                       |            |           |                              |                                   |
| 0; 0  | NA   | NA                                    | NA         | NA        | NA                           | Insufficient                      |
| <b><i>Decreased appetite</i></b>                |  |                                       |            |           |                              |                                   |
| 0; 0  | NA   | NA                                    | NA         | NA        | NA                           | Insufficient                      |
| <b><i>Increased appetite</i></b>                |  |                                       |            |           |                              |                                   |
| 0; 0  | NA   | NA                                    | NA         | NA        | NA                           | Insufficient                      |
| <b><i>Constipation</i></b>                      |  |                                       |            |           |                              |                                   |
| 0; 0  | NA   | NA                                    | NA         | NA        | NA                           | Insufficient                      |

Abbreviations: CI = confidence interval; NA = not applicable; RCT = randomized controlled trial

**Table G-48. Strength of evidence for adverse events for paroxetine compared with placebo**

| Number of Studies; Number of Subjects    | Domains Pertaining to Strength of evidence |                          |            |           | Magnitude of Effect   | Strength of Evidence              |
|--|--|--------------------------|------------|-----------|---|-----------------------------------|
|  | Risk of Bias; Design                       | Consistency              | Directness | Precision | Summary Effect Size (95% CI)                                      | High, Moderate, Low, Insufficient |
| <b>Withdrawals due to Adverse Events</b> |  |                          |            |           |   |                                   |
| 3; 911                                   | Medium; RCTs                               | Consistent ( $I^2=0\%$ ) | Direct     | Precise   | RD 0.04 (0.00 to 0.07)  | Moderate                          |
| <b>Headaches</b>                         |  |                          |            |           |   |                                   |
| 0; 0                                     | NA   | NA                       | NA         | NA        | NA  | Insufficient                      |
| <b>Nausea</b>                            |  |                          |            |           |   |                                   |
| 2; 886                                   | Medium; RCTs                               | Consistent               | Direct     | Imprecise | RD 0.11 (0.04 to 0.18) <sup>a</sup>                               | Low                               |
| <b>Insomnia</b>                          |  |                          |            |           |   |                                   |
| 0; 0                                     | NA   | NA                       | NA         | NA        | NA  | Insufficient                      |
| <b>Dry mouth</b>                         |  |                          |            |           |   |                                   |
| 1; 323                                   | Medium; RCT                                | NA, single study         | Direct     | Precise   | RD 0.10 (0.04 to 0.16)  | Low                               |
| <b>Diarrhea</b>                          |  |                          |            |           |   |                                   |
| 1; 563                                   | Medium; RCT                                | NA, single study         | Direct     | Imprecise | Incidence of at least 10% and twice that of placebo <sup>23</sup> | Insufficient                      |
| <b>Dizziness</b>                         |  |                          |            |           |   |                                   |
| 0; 0                                     | NA   | NA                       | NA         | NA        | NA  | Insufficient                      |
| <b>Fatigue</b>                           |  |                          |            |           |   |                                   |
| 0; 0                                     | NA   | NA                       | NA         | NA        | NA  | Insufficient                      |
| <b>Somnolence</b>                        |  |                          |            |           |   |                                   |
| 2; 886                                   | Medium; RCTs                               | Consistent               | Direct     | Imprecise | RD 0.13 (0.07 to 0.20) <sup>a</sup>                               | Low                               |
| <b>Drowsiness</b>                        |  |                          |            |           |   |                                   |
| 1; 25                                    | Medium; RCT                                | NA, single study         | Direct     | Imprecise | RD -0.15 (-0.51 to 0.21)  | Insufficient                      |
| <b>Decreased appetite</b>                |  |                          |            |           |   |                                   |
| 0; 0                                     | NA   | NA                       | NA         | NA        | NA  | Insufficient                      |
| <b>Increased appetite</b>                |  |                          |            |           |   |                                   |
| 0; 0                                     | NA   | NA                       | NA         | NA        | NA  | Insufficient                      |
| <b>Constipation</b>                      |  |                          |            |           |   |                                   |
| 0; 0                                     | NA   | NA                       | NA         | NA        | NA  | Insufficient                      |
| <b>Sexual adverse effects</b>            |  |                          |            |           |   |                                   |
| 1; 563                                   | Medium; RCT                                | NA, single study         | Direct     | Imprecise | Incidence of at least 10% and twice that of placebo <sup>23</sup> | Insufficient                      |

<sup>a</sup>Data are based on the only trial (N=323) reporting sufficient data to determine the risk difference.<sup>20</sup> One additional trial (N=563) that provided narrative description reported that the most commonly reported adverse events associated with paroxetine use (with an incidence of at least 10% and twice that of placebo) were asthenia, diarrhea, abnormal ejaculation, impotence, nausea, and somnolence.<sup>23</sup>

Abbreviations: CI = confidence interval; NA = not applicable; RCT = randomized controlled trial

**Table G-49. Strength of evidence for adverse events for sertraline compared with placebo**

| Number of Studies;<br>Number of Subjects | Domains Pertaining to Strength of Evidence |   |            |           | Magnitude of Effect          | Strength of evidence              |
|--|--|---|------------|-----------|------------------------------|-----------------------------------|
|  | Risk of Bias;<br>Design                    | Consistency                                 | Directness | Precision | Summary Effect Size (95% CI) | High, Moderate, Low, Insufficient |
| <b>Withdrawals due to Adverse Events</b> |  |   |            |           |                              |                                   |
| 7; 1122                                  | Medium;<br>RCTs                            | Consistent<br>( $I^2=0\%$ )                 | Direct     | Imprecise | RD 0.01 (-0.01 to 0.04)      | Low                               |
| <b>Headaches</b>                         |  |   |            |           |                              |                                   |
| 6; 1028                                  | Medium;<br>RCTs                            | Consistent<br>( $I^2=0.0\%$ )               | Direct     | Imprecise | RD 0.03 (-0.03 to 0.08)      | Insufficient                      |
| <b>Nausea</b>                            |  |   |            |           |                              |                                   |
| 7; 1061                                  | Medium;<br>RCTs                            | Consistent<br>( $I^2=0\%$ )                 | Direct     | Precise   | RD 0.09 (0.04 to 0.13)       | Moderate                          |
| <b>Insomnia</b>                          |  |   |            |           |                              |                                   |
| 6; 1019                                  | Medium;<br>RCTs                            | Inconsistent<br>( $I^2=44.8\%$ )            | Direct     | Imprecise | RD 0.05 (-0.02 to 0.11)      | Insufficient                      |
| <b>Dry mouth</b>                         |  |   |            |           |                              |                                   |
| 5; 859                                   | Medium;<br>RCTs                            | Consistent<br>( $I^2=0\%$ )                 | Direct     | Imprecise | RD 0.03 (-0.01 to 0.07)      | Insufficient                      |
| <b>Diarrhea</b>                          |  |   |            |           |                              |                                   |
| 5; 986                                   | Medium;<br>RCTs                            | Consistent<br>( $I^2=0\%$ )                 | Direct     | Precise   | RD 0.12 (0.07 to 0.17)       | Moderate                          |
| <b>Dizziness</b>                         |  |   |            |           |                              |                                   |
| 2; 385                                   | Medium;<br>RCTs                            | Consistent<br>( $I^2=0\%$ )                 | Direct     | Imprecise | RD 0.04 (-0.02 to 0.10)      | Insufficient                      |
| <b>Fatigue</b>                           |  |   |            |           |                              |                                   |
| 4; 762                                   | Medium;<br>RCTs                            | Consistent<br>( $I^2=0\%$ )                 | Direct     | Precise   | RD 0.07 (0.03 to 0.11)       | Moderate                          |
| <b>Somnolence</b>                        |  |   |            |           |                              |                                   |
| 2; 521                                   | Medium;<br>RCTs                            | Inconsistent<br>( $I^2=51.6\%$ )            | Direct     | Imprecise | RD 0.01 (-0.08 to 0.09)      | Insufficient                      |
| <b>Drowsiness</b>                        |  |   |            |           |                              |                                   |
| 4; 507                                   | Medium;<br>RCTs                            | Consistent<br>( $I^2=0\%$ )                 | Direct     | Imprecise | RD 0.05 (-0.00 to 0.11)      | Insufficient                      |
| <b>Decreased appetite</b>                |  |   |            |           |                              |                                   |
| 5; 705                                   | Medium;<br>RCTs                            | Consistent <sup>a</sup><br>( $I^2=43.7\%$ ) | Direct     | Precise   | RD 0.07 (0.01 to 0.13)       | Moderate                          |
| <b>Increased appetite</b>                |  |   |            |           |                              |                                   |
| 2; 75                                    | Medium;<br>RCTs                            | Consistent<br>( $I^2=0\%$ )                 | Direct     | Imprecise | -0.01 (-0.19 to 0.16)        | Insufficient                      |
| <b>Constipation</b>                      |  |   |            |           |                              |                                   |
| 2; 422                                   | Medium;<br>RCT                             | Consistent<br>( $I^2=0\%$ )                 | Direct     | Imprecise | 0.02 (-0.03 to 0.07)         | Insufficient                      |

<sup>a</sup> Although there was some variation in magnitude of effect, the direction of effect favored placebo in all five studies

Abbreviations: CI = confidence interval; NA = not applicable; RCT = randomized controlled trial

**Table G-50. Strength of evidence for adverse events for venlafaxine compared with placebo**

| Number of Studies; Number of Subjects    | Domains Pertaining to Strength of Evidence |                                      |            |           | Magnitude of Effect          | Strength of Evidence              |
|--|--|--------------------------------------|------------|-----------|------------------------------|-----------------------------------|
|  | Risk of Bias; Design                       | Consistency                          | Directness | Precision | Summary Effect Size (95% CI) | High, Moderate, Low, Insufficient |
| <b>Withdrawals due to Adverse Events</b> |  |                                      |            |           |                              |                                   |
| 2; 687                                   | Medium; RCTs                               | Consistent (I <sup>2</sup> =28.7%)   | Direct     | Imprecise | RD 0.02 (-0.03 to 0.07)      | Low                               |
| <b>Headaches</b>                         |  |                                      |            |           |                              |                                   |
| 2; 687                                   | Medium; RCTs                               | Consistent (I <sup>2</sup> =0%)      | Direct     | Imprecise | RD 0.01 (-0.06 to 0.07)      | Low                               |
| <b>Nausea</b>                            |  |                                      |            |           |                              |                                   |
| 2; 687                                   | Medium; RCTs                               | Consistent (I <sup>2</sup> =0%)      | Direct     | Precise   | RD 0.10 (0.05 to 0.16)       | Moderate                          |
| <b>Insomnia</b>                          |  |                                      |            |           |                              |                                   |
| 2; 687                                   | Medium; RCTs                               | Inconsistent (I <sup>2</sup> =59.3%) | Direct     | Imprecise | RD 0.01 (-0.06 to 0.08)      | Insufficient                      |
| <b>Dry mouth</b>                         |  |                                      |            |           |                              |                                   |
| 2; 687                                   | Medium; RCTs                               | Consistent (I <sup>2</sup> =0%)      | Direct     | Precise   | RD 0.07 (0.02 to 0.11)       | Moderate                          |
| <b>Diarrhea</b>                          |  |                                      |            |           |                              |                                   |
| 1; 358                                   | Medium; RCTs                               | NA, single study                     | Direct     | Imprecise | RD -0.02 (-0.09 to 0.05)     | Insufficient                      |
| <b>Dizziness</b>                         |  |                                      |            |           |                              |                                   |
| 2; 687                                   | Medium; RCTs                               | Consistent (I <sup>2</sup> =0%)      | Direct     | Precise   | RD 0.06 (0.01 to 0.11)       | Moderate                          |
| <b>Fatigue</b>                           |  |                                      |            |           |                              |                                   |
| 2; 687                                   | Medium; RCTs                               | Consistent (I <sup>2</sup> =0%)      | Direct     | Imprecise | RD 0.03 (-0.01 to 0.07)      | Insufficient                      |
| <b>Somnolence</b>                        |  |                                      |            |           |                              |                                   |
| 2; 687                                   | Medium; RCTs                               | Consistent (I <sup>2</sup> =0%)      | Direct     | Imprecise | RD -0.00 (-0.04 to 0.04)     | Low                               |
| <b>Decreased appetite</b>                |  |                                      |            |           |                              |                                   |
| 1; 358                                   | Medium; RCTs                               | NA, single study                     | Direct     | Imprecise | RD 0.06 (-0.00 to 0.11)      | Insufficient                      |
| <b>Constipation</b>                      |  |                                      |            |           |                              |                                   |
| 2; 687                                   | Medium; RCTs                               | Inconsistent (I <sup>2</sup> =68%)   | Direct     | Imprecise | RD 0.06 (-0.02 to 0.13)      | Insufficient                      |

Abbreviations: CI = confidence interval; NA = not applicable; RCT = randomized controlled trial