



CLINICAL PRACTICE
GUIDELINE
for the Treatment of
PTSD



AMERICAN PSYCHOLOGICAL ASSOCIATION

Guideline Development Panel for the Treatment of Posttraumatic Stress Disorder in Adults
Adopted as APA Policy February 24, 2017

**Clinical Practice Guideline for the Treatment of Posttraumatic Stress Disorder
(PTSD) in Adults**

American Psychological Association

Guideline Development Panel for the Treatment of PTSD in Adults

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Abstract

Description: The American Psychological Association (APA) developed this guideline to provide recommendations on psychological and pharmacological treatments for posttraumatic stress disorder (PTSD) in adults.

Methods: This guideline used methods recommended by the Institute of Medicine report, *Clinical Practice Guidelines We Can Trust* (IOM, 2011). Those methods are designed to produce guidelines that are based on evidence and patient preferences and are transparent, free of conflict of interest, and worthy of public trust. The guideline used a comprehensive systematic review (*Psychological and Pharmacological Treatments for Adults With Posttraumatic Stress Disorder (PTSD)*) conducted by the Research Triangle Institute-University of North Carolina Evidence-based Practice Center as its primary evidence base (Jonas, Cusack, Forneris, Wilkins, Sonis, Middleton, et al., 2013). The systematic review was based on English-language studies published between 1980 and 2012; complementary and alternative treatments were not included in the systematic review. An updated search was conducted by APA to identify studies published between 2012 and June 1, 2016, to determine if the recommendations made by the panel based on the systematic review were likely to hold up based on more recent evidence; risk of bias assessment, strength of evidence rating and meta-analyses were not conducted on the studies identified through the updated search.

The guideline development panel (GDP) consisted of health professionals from the disciplines of psychology, psychiatry, social work, and family medicine as well as community members, who self-identified as having had PTSD. The GDP made recommendations based on 1) strength of evidence; 2) treatment outcomes and the balance of benefits vs. harms and burdens of interventions; 3) patient values and preferences; and 4) applicability of the evidence to various treatment populations. PTSD symptom reduction and serious harms were selected by the GDP as critical outcomes for making recommendations. Various other outcomes were

selected as important, including those related to remission, quality of life, disability, comorbid conditions and adverse events.

The target audience for this guideline includes all clinicians as well as researchers, patients and policy makers.

Recommendations: The panel strongly recommends the use of the following psychotherapies/interventions (all interventions that follow listed in alphabetical order) for adult patients with PTSD: cognitive behavioral therapy (CBT), cognitive processing therapy (CPT), cognitive therapy (CT), and prolonged exposure therapy (PE). The panel suggests the use of brief eclectic psychotherapy (BEP), eye movement desensitization and reprocessing (EMDR), and narrative exposure therapy (NET). There is insufficient evidence to recommend for or against offering Seeking Safety (SS) or relaxation (RLX). For medications, the panel suggests offering the following (in alphabetical order): fluoxetine, paroxetine, sertraline, and venlafaxine. There is insufficient evidence to recommend for or against offering risperidone and topiramate. Based on the updated search, the panel concluded that all of its treatment recommendations, except those for EMDR and NET, were unlikely to change. The panel also concluded that, based on studies published between 2012 and June 2016, the recommendations for EMDR and NET may change from conditional (“the panel suggests”) to strong (“the panel recommends”).

(Note: This abstract was prepared following approval of the guideline document as APA policy by the APA Council of Representatives at its February 2017 meeting.)

Table of Contents

Abstract.....	i
Table of Contents	iii
Disclaimer	vii
Executive Summary	ES-1
Scope of the Document	
What the Guideline Addresses and What it Does Not	1
Table 1. Summary of Recommendations	4
Introduction to the Topic	6
Background and Justification: The Scope of the Problem	6
Defining Trauma	6
Posttraumatic Reactions and Diagnoses.....	7
Available PTSD Treatment Guidelines.....	10
The APA Clinical Practice Guideline for the Treatment of PTSD.....	11
Institute of Medicine Standards as the Basis for this CPG	11
Treatment Outcomes Considered in the Guideline	15
The RTI-UNC Systematic Key Questions and Analytic Framework.....	17
Process and Methods of the CPG	17
Undertaking the Systematic Review	17
Scoping.....	17
Vetting and Appointment of Members to the PTSD Treatment GDP	18
Conflicts of Interest.....	18
Comprehensive Search of the Professional Literature	20
Decisions Regarding Assessment and Inclusion/Exclusion of Studies	21

Table of Contents

Assessing Strength of Evidence.....	21
Types of Comparison (control) Groups Used by Studies Included in the RTI-UNC Systematic Review	23
The Development and Use of Evidence Profiles	24
The Development and Use of Decision Tables.....	25
Completion of Decision Tables	28
Rating of Aggregate/Global SOE	28
Assessing Magnitude of Benefits	29
Assessing Magnitude of Harm/Burdens	31
Assessing Patient Values and Preferences.....	34
Applicability of Evidence	35
Decision-Making Regarding Treatment Recommendations	37
External Review Process	38
Detailed Recommendations.....	39
Impact of New Trials on Recommendations	50
Considerations for Treatment Implementation	61
Informed Consent	62
Role of Patient and Therapist Factors in Treatments for PTSD	62
Professional Competence	64
Monitoring Treatment Response	65
Culture and Diversity Competence	66
Discussion	67
How the APA PTSD Guideline Recommendations Are Similar To or Different From Other PTSD	
Guidelines	67
Strengths and Weaknesses of the RTI-UNC Systematic Review	72

Table of Contents

Treatment Effect Heterogeneity: Subgroup Effects	75
Generalizability (Applicability)	76
Community Member Input	80
Clinician Input Regarding Psychotherapy.....	82
Limitations of Existing Treatment Research Literature: Future Research Needs	83
Gaps in the Literature	83
Methodological Improvements	86
Guideline Summary and Future Directions.....	90
Conflicts of Interest	93
Author Disclosure	95
Developer.....	99
Funding Source/Sponsor.....	100
Acknowledgments	101
References	102

Appendices (New Document)

- A. Descriptions of Treatments and Strength of Recommendations
- B. Treatment Dose, Timing, and Duration as Described in Reviewed Studies
- C. Evidence Profiles Prepared for APA by RTI-UNC Scientists
- D. Decision Tables
- E. Definition of Key Terms
- F. Additional Tables and Figure for Updated Evidence (2012-2016)
- G. Trials Identified Through Search Update (published 2012-2016) Matching One or More Recommendations
- H. Trials Identified Through Search Update (published 2012-2016) Matching One or More Evidence Profiles but Not Matching Any Recommendations
- I. Trials Identified Through Search Update (published 2012-2016) That Would Not Have Met Criteria for Inclusion in Systematic Review
- J. APA Declarations/COI Form
- K. Voting Procedures Established by Advisory Steering Committee (ASC)
- L. Strength of Evidence Ratings for Psychotherapies and Medications

Disclaimer

This guideline is intended to be aspirational and is not intended to create a requirement for practice. It is not intended to limit scope of practice in licensing laws for psychologists or for other independently licensed professionals, nor limit coverage for reimbursement by third party payers.

The term guideline refers to statements that suggest or recommend specific professional behavior, endeavor, or conduct for psychologists or other independently licensed professionals. Guidelines differ from standards in that standards are mandatory and may be accompanied by an enforcement mechanism. In contrast, guidelines are aspirational in intent. They are intended to facilitate the continued systematic development of the profession and to help assure a high level of professional practice by psychologists and other professionals. Guidelines are not intended to be mandatory or exhaustive and may not be applicable to every professional and clinical situation. They are not definitive and they are not intended to take precedence over the judgment of psychologists and other professionals. The different types of guidelines produced by the APA were detailed in an association document published in the American Psychologist in December, 2015 (American Psychological Association, 2015).

The recommendations made by the APA PTSD Guideline Development Panel (GDP) were developed after careful review of the evidence. The GDP endorses the following statement from the British National Institute for Health and Care Excellence (NICE, 2016) *“When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The application of the recommendations in this guideline is not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian,”* (p.18).

Executive Summary

Scope of the Guideline

This guideline is intended to provide treatment recommendations for Posttraumatic Stress Disorder (PTSD) in adults, based on a systematic review of the evidence for treatment *Psychological and Pharmacological Treatments for Adults With Posttraumatic Stress Disorder (PTSD)* conducted by the Research Triangle Institute- University of North Carolina Evidence-Based Practice Center (RTI-UNC EPC) (Jonas, Cusack, Forneris, Wilkins, Sonis, Middleton, et al., 2013). The RTI-UNC Systematic Review addressed the following Key Questions:

1. What is the efficacy of psychological and medication treatments for adults with PTSD, compared to no treatment or to inactive controls?
2. What is their comparative effectiveness (i.e., psychological treatments compared to other psychological treatments, medication treatments compared to other medication treatments, and psychological treatments compared to medication treatments)?
3. Which treatments work best for which patients¹? In other words, do patient characteristics or type of trauma modify treatment effects?
4. Do serious harms of treatments or patient preferences influence treatment recommendations?

Although of considerable importance in the treatment of PTSD, this guideline does not address complementary or alternative treatments, assessment and screening of PTSD, subthreshold PTSD, PTSD prevention, PTSD treatment in children, dose/timing/duration of treatment, or cost. It is the hope of panel members that future iterations of this guideline include these topics as their evidence base develops.

¹ To be consistent with evidence-based clinical practice guidelines in other areas of health care, we use the term *patient* to refer to the person receiving psychological services. However, we recognize that in many situations there are important and valid reasons for using such terms as *client*, *consumer* or *person* in place of *patient* to describe the recipients of services.

Recommendations

Following its detailed review and independent analysis of the findings of the systematic review, the APA Guideline Development Panel (GDP) strongly recommends the use of the following psychotherapies/interventions (all interventions that follow listed in alphabetical order) for adult patients with PTSD: cognitive behavioral therapy (CBT)², cognitive processing therapy (CPT), cognitive therapy (CT), and prolonged exposure therapy (PE). The panel suggests the use of brief eclectic psychotherapy (BEP), eye movement desensitization and reprocessing (EMDR), and narrative exposure therapy (NET). There is insufficient evidence to recommend for or against offering Seeking Safety (SS) or relaxation (RLX). For medications, the panel suggests offering the following (in alphabetical order): fluoxetine, paroxetine, sertraline, and venlafaxine. There is insufficient evidence to recommend for or against offering risperidone and topiramate.

Impact of New Trials on Recommendations

The systematic review that was used as the evidence base for this guideline included trials that had been published prior to May 24, 2012. To determine whether the panel recommendations based on that evidence would hold up in the face of new evidence published since that time, the panel conducted a revised search, to identify trials published between May 25, 2012 and June 1, 2016. The panel concluded that, based on the new trials, its recommendations for all of the interventions except two (EMDR and NET) were unlikely to change; there was insufficient evidence to determine whether the conditional recommendations for EMDR and NET³ would change to strong.

² The systematic review did not evaluate trauma-focused CBT separately from CBT that was not trauma-focused. Accordingly, the panel's recommendations are based on CBT as a category that encompasses all types of CBT and are not limited to trauma-focused CBT.

³ As we discuss later in this report, the panel acknowledges uncertainty in the stability of our conditional recommendations for EMDR and NET on the basis of more recent evidence that could result in an upgraded recommendation pending future meta-analyses.

Introduction

Trauma involves events that pose significant threat (physical, emotional, or psychological) to the safety of the victim or loved ones/friends and are overwhelming and shocking. Many individuals exposed to traumatic events experience a range of posttraumatic psychophysiological reactions though most of these reactions remit spontaneously within approximately the first month of occurrence (Rothbaum, Foa, Riggs, Murdock, & Walsh, 1992; Nugent, Saunders, Williams, Hanson, Smith, & Fitzgerald, 2009; Orcutt, Erickson, & Wolfe, 2004). A number of risk and resilience factors (such as age, severity, duration, and availability of support) may affect whether the reactions remit. If they persist, they might meet criteria for one or more posttraumatic diagnoses such as Acute Stress Disorder (ASD) or Posttraumatic Stress Disorder (PTSD). The 5th edition of the *Diagnostic and Statistical Manual of Mental Disorders, DSM-5*, (American Psychiatric Association, 2013), defines PTSD as comprised of four clusters of symptoms including intrusive and recurrent memories of the trauma, avoidance of trauma-related stimuli, numbing and/or negative changes in mood or cognitions pertaining to the trauma, and changes in reactivity and arousal. The *DSM-IV-TR* (American Psychiatric Association, 2000) previously defined PTSD as being comprised of three symptom clusters including avoidance and numbing, re-experiencing, and hyperarousal. Of note, all of the studies included in the RTI-UNC systematic review that served as the evidence base for that report used *DSM-IV-TR* or earlier *DSM* criteria and are those discussed throughout this guideline.

Furthermore, PTSD can range from relatively mild to totally debilitating and has also been found to create vulnerability for revictimization and retraumatization (see Duckworth and Follette, 2012) for a comprehensive overview). Some individuals and populations are especially at risk and co-morbidities such as substance use and abuse, depression, anxiety, dissociation and dissociative disorders, personality disorders, psychosis, cognitive impairment, violence towards self and others, increased risk of non-suicidal self-injury and of suicide, are common to the diagnosis. Psychosocial impacts can include homelessness, poverty, and incarceration. All

of these factors make PTSD a complicated and challenging psychophysiological and psychosocial disorder to treat and suggest the need for further guidance to indicate which treatments are effective and for whom.

Currently, numerous guidelines from various agencies and professional organizations recommend several trauma-focused psychological interventions for treating PTSD and most acknowledge some benefit of several medication treatments as well. The present guideline differs from other guidelines in several ways. It fully follows and builds upon the standards set forth by the Institute of Medicine (IOM) (now the National Academy of Medicine) of the National Academies of Sciences, Engineering, and Medicine standards for developing high-quality, independent, and reliable practice guidelines (IOM, 2011a & 2011b). Its recommendations and suggestions for treatment are based on an analysis of a comprehensive independent systematic review of the literature for treatment of PTSD in adults. Further, panel members who worked on the present guideline document were an interdisciplinary group from professions including psychology, social work, primary care, and psychiatry--and included consumer members as well. Finally, the present guideline includes attention to potential and actual harms and burdens of PTSD treatments and patient preferences as part of the process.

In addition to these strengths, the guideline also has some limitations. Gaps in the current empirical literature regarding treatment comparisons, evaluation of moderators of treatment effects, inclusion of participants with comorbidities, measurement of potential side effects and harms, and assessment of important outcomes and the timing of their assessment all need to be addressed to answer important clinical questions. Additionally, methodological improvements that minimize attrition/dropout, decrease missing data and ensure sufficient power will improve the quality of the findings and hence the possible conclusions that can be drawn. Finally, the panel did not have data on which to make recommendations for some treatments in use because they arise from traditions with non-RCT research practices or the

quality of the research base has not been subjected to the level of critical appraisal of systematic review.

It was the panel's goal in the development of this guideline to render a collective judgment and decision-making process that is transparent so that interested readers might appropriately appreciate the rationale for the recommendations made in response to the evidence in the systematic review. It is also recognized that this guideline may provide a foundation for developing key questions for future systematic reviews leading to updated recommendations regarding effective treatments for PTSD. Finally, it should be reiterated that a clinical practice guideline is based on the best available evidence at the time and should not be construed as a standard of care or prescribing a specific course of treatment.

Process and Method

At the outset, panel members discussed a range of relevant outcomes and determined which were most critical for deciding whether to recommend or not recommend a treatment through a modified Delphi survey. The panel decided that PTSD symptom reduction and serious harms/adverse events were the most critical outcomes and that remission (no longer having symptoms), loss of PTSD diagnosis, quality of life, disability or functional impairment, prevention or reduction of comorbid medical or psychiatric conditions, adverse events leading to withdrawals (treatment discontinuation), and other adverse events, and burdens were important though not critical.

The primary evidence base for the present guideline was the systematic review, *Psychological and Pharmacological Treatments for Adults With Posttraumatic Stress Disorder (PTSD)* (Jonas et al., 2013) produced by the Research Triangle International- University of North Carolina Evidence Based Practice Center (RTI-UNC EPC) which followed the protocol set forth by the Institute of Medicine (2011b) for conducting systematic reviews. The comprehensive and transparent systematic review addressed psychological and pharmacological treatments for

PTSD. The trials included in the systematic review included samples that, as a whole, were broadly diverse in terms of gender, race, ethnicity and type of trauma.

APA's Advisory Steering Committee for Development of Clinical Practice Guidelines (ASC) issued a call for panel member nominations (including self-nominations) for individuals from a variety of backgrounds (consumer, psychology, social work, psychiatry, general medicine) with content and treatment knowledge or methodological expertise. Conflicts of interest (financial and non-financial) were considered and managed both during panel member selection and throughout the guideline development process. Panel members were asked to complete a COI form (see Appendix J) and that was reviewed by APA staff and ASC members before members were appointed to the GDP. Additionally, they were asked to present the details of their forms to other members in the first face to face meeting and to update their COI's yearly or on an as-needed basis and to submit it to staff for review.

The panel considered four factors as it drafted recommendations: 1) overall strength of the evidence; 2) the balance of benefits vs. harms/burdens; 3) patient values and preferences; and 4) applicability. Based on the combination of these factors, the panel made a strong or conditional recommendation for or against each particular treatment or made a statement that there was insufficient evidence to be able to make a recommendation for or against. The panel used a tool called a *decision table* to document its decision-making process for each recommendation. Copies of the decision tables are available in Appendix D.

Discussion

For treating PTSD in adults, the present guideline strongly recommends cognitive behavioral therapy (CBT), cognitive processing therapy (CPT), cognitive therapy (CT), and prolonged exposure therapy (PE) and suggests the use of brief eclectic psychotherapy (BEP), eye movement desensitization and reprocessing (EMDR), and narrative exposure therapy (NET). These recommendations are largely but not entirely consistent with those of various other organizations. The present guideline also suggests the use of fluoxetine, paroxetine,

sertraline, and venlafaxine. These recommendations add to the pharmacotherapy recommendations of other organizations. Although some psychotherapies (CBT, CPT, CT, PE) received strong recommendations but no medications did, the panel does not make recommendations of psychotherapy before or instead of medications or use the term “first-line” treatment because there was insufficient evidence from the systematic review on direct comparisons between psychotherapy and medications for PTSD. The implications of this distinction are that efficacy inferences for psychotherapies and those for pharmacotherapies may not be truly comparable across these classes of treatment owing to the differential stringency of these typical control conditions. The strength of the panel’s recommendations for all interventions depended, to some extent, on the magnitude of the beneficial effect (i.e., the effect size). But the effect size magnitude in a trial can be influenced by the type of the comparator in the trial. Since all of the medication trials used placebo comparators while the psychotherapy did not (and could not ...) and there was insufficient evidence on direct comparison of the two types of treatments, the panel did not make any recommendations about psychotherapy versus medication treatment. Clinical judgment and patient preferences (as well as patient response to psychotherapy or psychopharmacology) are all important factors in deciding the course of treatment for PTSD.

Treatment effect heterogeneity (sub-group effects) was evaluated in the RTI-UNC Systematic Review. Its authors concluded that the research evidence was insufficient to determine treatment effect heterogeneity by many of the subgroups that were examined. Members of the current guideline development panel agreed that the randomized trials included in the review do not sufficiently address the important issue of which treatments are best for which patients and constitutes an important future research need.

Generalizability (applicability) of systematic review findings to an external population means that the magnitude and direction of an intervention effect, based on included trials, is

similar to the magnitude and direction of intervention effect that would be expected in that external population. Absence of generalizability occurs when there is heterogeneity of treatment effects (e.g., by gender, ethnicity, trauma type or other significant factors) *and* when there are differences between the distribution of those characteristics in the samples included in a systematic review and the external population. The authors of the RTI-UNC Systematic Review concluded that there was insufficient evidence “to determine whether the findings are applicable to all those with PTSD or whether they are applicable only to certain groups” and insufficient evidence about whether there were subgroup effects. Based in part on this conclusion, members of the APA panel did not reach consensus about the generalizability of the systematic review’s findings, reflecting differences of opinion found in the literature about conditions required to demonstrate generalizability (Post, de Beer, & Guyatt, 2013; Rothwell, 2005). Some panel members think that lack of generalizability to all subgroups should be assumed in the face of insufficient evidence about generalizability. Others on the panel believe that, in the face of insufficient evidence about generalizability or strong theoretical rationale to suggest treatment effect heterogeneity, generalizability to most subgroups should be assumed. Panel members agree however that examination of treatment effect heterogeneity with diverse samples should be prioritized for future research.

Community members on the GDP shared what they considered to be important patient values and preferences for PTSD treatment. These included such things as having a psychotherapist who is aware of and knowledgeable about trauma, who offers information about treatment, teaches coping skills, works from a personalized approach, and is sensitive to cultural and socio-demographic differences. Likewise, clinicians on the panel shared their views of general patient values and preferences gained from their experience providing treatment. They found variation in patient preferences for trauma-focused therapies, preference for psychotherapy over medication in many cases (though a minority prefers medication) and some who prefer no treatment whatsoever. Many seek short-term treatment and want to experience

significant symptom relief and alleviation of their suffering. Clinicians and community members also reported that patients want information about treatment, value culturally sensitive therapists, and have various preferences regarding intensity and pace of treatment. An open question is whether patient preference for specific treatment varies by treating provider such that patients choose professionals able to provide preferred treatment or identify a treatment as preferred on the basis of what the provider is able to offer.

In order to implement interventions effectively a number of considerations are relevant, including informed consent and the role of patient and relationship factors in treatment. Informed consent includes providing patients with information about potential available treatments before treatment commences and to aid in decision making. Informed consent includes discussion and can include written material about the process and procedures involved, effectiveness and risks-benefits, and associated emotional and practical demands. Second, there is a body of literature that has shown an association between patient and patient-therapist factors (sometimes referred to as “common factors”), relationship factors, and treatment outcomes. These factors include such things as patient coping style, expectation for change, and therapist empathy and collaboration. Clinicians are encouraged to bear these factors in mind when implementing recommended treatments.

Other treatment considerations include the therapist working from a trauma-informed⁴ approach and attending to the role of socio-economic, cultural or other diversity or contextual issues. These may facilitate whether patients find therapist actions and recommendations intelligible, useful, and worthwhile. They may also have a direct impact on the treatment application. Finally, while monitoring PTSD symptoms during treatment can provide insight into progress and treatment targets and guidance when adjusting treatment seems necessary, it is unclear as of yet whether this treatment monitoring improves patient outcomes.

⁴ Treatment approaches that directly focus on the details of trauma event(s)/experience(s) in order to assist the patient to process the cognitions, emotions, somatic reactions, and/or memories associated with the trauma. The theory is that once these are processed sufficiently to arrive at a point of resolution, completion, or a change of perspective, trauma symptoms should decline or remit.

Although the research evidence is strong for the efficacy of particular psychotherapy and pharmacological treatments for adults with PTSD, many other treatments are being used or are under development and there are still significant gaps in the literature. These include the lack of RCTs for newer treatments, the comparative effectiveness of psychological and pharmacological treatments and combinations of treatments, subgroup effects, applicability of findings to patients with comorbidities and PTSD, patient preferences for care, and impact of treatments on important patient-oriented outcomes such as quality of life, long-term treatment effects, adverse effects and harms, along with other outcomes that are not so easily quantifiable such as moral injury, emotional regulation, identity and sense of self, and ability to form intimate relationships.

In addition to the research gaps noted, there are other methodological concerns with many of the current PTSD treatment trials that should be addressed in future trials. Specifically, the panel recommends that investigators design trials to minimize attrition, identify reasons for attrition/dropout, decrease missing data, and incorporate rigorous methods of handling missing data such as multiple imputation or maximum likelihood. Future trials should report the recency of trauma, address the potential for researcher allegiance effects, provide long term evaluation of outcomes (PTSD symptoms and other outcomes), and include samples large enough to minimize the potential for covariate imbalance. Future trials should also retain rigorous methodologic features that have been commonly used in previous research, such as assessment of treatment fidelity.

The panel members applaud treatment developers and national and international professional organizations for their efforts in designing and implementing PTSD treatment research studies. The panel also supports the continuing efforts to research trauma process and outcome both generally and more specifically to individuals who have experienced trauma. It is also the hope of members of this panel that suggested methodological improvements will serve

to enhance future iterations of the present guideline and continue to alleviate the suffering of individuals with PTSD.

This document will be reviewed within five years following adoption as policy. A decision to sunset, update or revise the document will be made at that time.

See in Appendix E for definitions of terms used in this guideline.

Clinical Practice Guideline for the Treatment of Posttraumatic Stress Disorder (PTSD) in Adults

American Psychological Association

Guideline Development Panel for the Treatment of PTSD in Adults

Scope of the Document: What the Guideline Addresses and What It Does Not

The purpose of this guideline is to provide recommendations on the treatment of posttraumatic stress disorder (PTSD) in adults. This guideline is based on a systematic review of the evidence on treatment of PTSD *Psychological and Pharmacological Treatments for Adults With Posttraumatic Stress Disorder (PTSD)*, sponsored by the Agency for Health Care Research and Quality (AHRQ)⁵ and conducted by the Research Triangle Institute-University of North Carolina Evidence-Based Practice Center (RTI-UNC EPC) (Jonas, Cusack, Forneris, Wilkins, Sonis, Middleton, et al., 2013). The intended users include psychologists, other health and mental health professionals, consumers, families of consumers, students/training programs, policy makers, and the public.

The guideline addresses the following Key Questions:

1. What is the efficacy of psychological and medication treatments for adults with PTSD, compared to no treatment or to inactive treatments?
2. What is their comparative effectiveness (i.e., psychological treatments compared to other psychological treatments, medication treatments compared other medication treatments, and psychological treatments compared to medication treatments)?
3. Which treatments work best for which patients? In other words, do patient characteristics or type of trauma modify treatment effects?

⁵ The Agency for Healthcare Research and Quality's (AHRQ) mission is to produce evidence to make health care safer, higher quality, more accessible, equitable, and affordable, and to work within the U.S. Department of Health and Human Services and with other partners to make sure that the evidence is understood and used.

4. Do serious harms of treatments or patient preferences influence treatment recommendations?

The guideline does not address any of the following:

1. Complementary or alternative treatments, such as yoga or acupuncture. Because the systematic review that served as the evidence base for the guideline excluded studies that focused exclusively on complementary and alternative approaches, treatment of PTSD with those types of interventions is beyond the scope of this guideline.
2. Screening for exposure to psychological trauma, screening for and assessment of PTSD, assessment of associated conditions (e.g., suicidal ideation, intent, or actions, monitoring response to treatment, follow-up after treatment, or locus of care. These are all key elements in the care of patients exposed to trauma or diagnosed with PTSD, but they are beyond the scope of this guideline.
3. Subthreshold PTSD. Studies that did not require a formal diagnosis of PTSD for participant inclusion were not included in the RTI-UNC Systematic Review.
4. Prevention of PTSD. Effectiveness of interventions, such as debriefing, that are designed to reduce the risk of development of PTSD, among persons exposed to trauma but who have not been diagnosed with PTSD have not been evaluated. The RTI-UNC EPC did perform a separate systematic review on prevention of PTSD among persons exposed to trauma but the current guideline, devoted to treatment but not prevention, was not based on findings from that systematic review.
5. Treatment of PTSD in children. The panel considered creating a separate guideline for treatment of PTSD among children. The RTI-UNC EPC performed two systematic reviews on treatment of conditions related to trauma in children (birth to 14 years of age). One review focused on interventions for treatment of conditions related to maltreatment and family violence (including child abuse) and the other review focused on interventions for treatment of conditions related to trauma other than maltreatment and family violence.

The panel decided not to include treatment of PTSD among children in the current report or to issue a separate guideline for treatment of PTSD among children because the vast majority of intervention trials were rated low or insufficient/very low strength of evidence. As noted in one of the reviews, “Our main finding was that the literature in this field is strikingly limited due to numerous substantive and methodological gaps.” Panel members decided it would be unwise to develop a guideline that would not involve substantive recommendations for most of the interventions due to insufficient evidence.

6. Dose, timing or duration of treatments for adults with PTSD. All of those elements can be related to outcome of treatment but the systematic review that constituted the evidence base for this guideline did not provide sufficient information to make evidence-based recommendations on those factors. Included in this document however, is a table (Appendix B) that shows the range of the dose and the timing and duration of the treatments used in the randomized trials that were included in the systematic review for which the panel makes recommendations.
7. Costs of treatments. Treatment costs were not considered in the formulation of the panel’s recommendations.

Below in Table 1 is a summary of recommendations. More detailed recommendations are provided in Table 5.

Table 1. Summary of Recommendations of the APA Guideline Development Panel for the Treatment of PTSD

Psychotherapy	Strength of Recommendation
<p>For adult patients with PTSD, the panel strongly recommends that clinicians offer one of the following psychotherapies/interventions (listed alphabetically):</p> <ul style="list-style-type: none"> • cognitive behavioral therapy- (CBT)⁶ • cognitive processing therapy (CPT) • cognitive therapy (CT) • prolonged exposure therapy (PE) 	Strong For
<p>For adult patients with PTSD, the panel suggests that clinicians offer one of the following psychotherapies/interventions (listed alphabetically):</p> <ul style="list-style-type: none"> • brief eclectic psychotherapy (BEP) • eye movement desensitization and reprocessing therapy (EMDR) • narrative exposure therapy (NET) 	Conditional
<p>For adult patients with PTSD, there is insufficient evidence to recommend for or against clinicians offering the following psychotherapies/interventions (listed alphabetically):</p> <ul style="list-style-type: none"> • relaxation (RX) • Seeking Safety (SS) 	Insufficient
Pharmacotherapy	
<p>For adult patients with PTSD, the panel suggests that clinicians offer one of the following (listed alphabetically):</p> <ul style="list-style-type: none"> • fluoxetine • paroxetine • sertraline • venlafaxine 	Conditional
<p>There is insufficient evidence to recommend for or against clinicians offering the following medications (listed alphabetically) for treatment of adults with PTSD.</p> <ul style="list-style-type: none"> • risperidone • topiramate 	Insufficient
Comparative Effectiveness	
<p>For adult patients with PTSD, the panel recommends clinicians offer either prolonged exposure or prolonged exposure plus cognitive restructuring when both are being considered.</p>	Strong For
<p>For adult patients with PTSD, the panel recommends clinicians offering either venlafaxine ER or sertraline when both are being considered.⁷</p>	Strong For

⁶ The RTI UNC review refers to this as CBT-mixed therapy. CBT-Mixed is a category that includes interventions using aspects of CBT that do not fit neatly into the other CBT categories. It will be referred to in the present document as CBT.

For adult patients with PTSD, the panel suggests clinicians offer CBT rather than relaxation when both CBT and relaxation are being considered.	Conditional For
For adult patients with PTSD, the panel suggests clinicians offer prolonged exposure therapy rather than relaxation when both prolonged exposure therapy and relaxation are being considered.	Conditional For
For adult patients with PTSD, the panel concludes that the evidence is insufficient to recommend for or against clinicians offering Seeking Safety versus active controls.	Insufficient

These recommendations and this clinical practice guideline is not intended to set a standard of care but rather to be a general guide to best practices. A clinical practice guideline can facilitate decision making for both provider and patient.

⁷ The recommendation for the comparison between venlafaxine ER vs sertraline is different than the recommendation for Seeking Safety vs active controls, even though there is moderate evidence of no difference between the two treatments being compared for both comparisons (i.e., venlafaxine ER vs sertraline and Seeking Safety vs active controls). The reason the recommendations are different for venlafaxine ER vs sertraline than for Seeking Safety vs active controls is that the panel made a conditional recommendation for venlafaxine compared to no intervention and a conditional recommendation for sertraline compared to no intervention but did not make any recommendations for Seeking Safety compared to no intervention or active controls compared to no intervention because there was insufficient/very low evidence. In other words, the panel believed that because there was evidence that both venlafaxine and sertraline had demonstrated efficacy compared to inactive intervention, it was reasonable to recommend either treatment when both are being considered. However, because neither Seeking Safety nor active controls had demonstrated efficacy compared to no intervention, the panel concluded that evidence was insufficient to recommend for or against either treatment.

Introduction to the Topic

Background and Justification: The Scope of the Problem

Defining Trauma. According to the 5th edition of the *Diagnostic and Statistical Manual of Mental Disorders, DSM-5*, (American Psychiatric Association, 2013), exposure to traumatic events can occur in one (or more) ways: 1) direct experiencing; 2) witnessing, in person; 3) learning that the traumatic event(s) occurred to a family member, or someone else in close relationship; 4) experiencing repeated or extreme exposure to aversive details of the traumatic event(s) (common in first responders and emergency personnel). *Trauma* refers to events or experiences that are shocking and overwhelming, typically involving major threat to the physical, emotional, or psychological safety and well-being of the individual victim(s) and loved ones and friends (as well as to others). Its original occurrence is usually sudden and unexpected and it may be a one-time event. In some cases, after the first incident, it may recur on either a short-term or intermittent basis or it may occur on a regular or prolonged basis to the point of becoming continuous and chronic. Examples of traumatic events include: military combat, acts of terror; motor vehicle and other accidents; natural or human-caused disasters and accidents, sudden or violent death of loved ones; interpersonal violence, such as mass shootings, assaults, and physical, sexual, and emotional abuse; traumatic separations and other significant losses (including neglect and abandonment); hostage-taking; torture; slavery; and certain types of disability, illness, and medical treatment, especially for life-threatening conditions. The definition of psychological trauma has been widely debated and the delineation of a traumatic event in *DSM* (known as Criterion A) has gone through numerous revisions (Weathers & Keane, 2007). Due to the varying magnitude, complexity, intensity, frequency and duration of potential stressors, mental health experts have grappled to create an all-encompassing definition of trauma.

Epidemiological research has demonstrated that traumatic events are common and thus most humans will experience a potentially traumatic event at some point in their lifetime (Breslau & Kessler, 2001; Copeland, Keeler, Angold, & Costello, 2007; Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995; McLaughlin, Koenen, Hill, Petukhova, Sampson, Zaslavsky & Kessler, 2013). At the time of occurrence or shortly thereafter, trauma generally causes physiological and psychological stress responses that are overwhelming and exceed or greatly challenge the affected individual's capacity to cope. Individuals' post-trauma reactions show great variability, ranging from those that are highly resilient--with little or no emotional distress--to those that are relatively mild and short-term, to those that are major, chronic, and highly debilitating. Disorders of medical or mental health may or may not follow (Bonanno, 2004). Trauma can also impact others besides the primary victim(s), for example, relatives/loved ones, first responders, therapists and other helpers, and others who can be affected vicariously (Badger, Royse, & Craig, 2008; Hojat, 2007; Hojat, Gonnella, Nasca, Mangione, Vergare, & Magee, 2002; Huddleston, Paton, & Stephens, 2006; McLean, Wade, & Encel, 2003; Pearlman & Saakvitne, 1995; Schauben & Frazier, 1995). Thus, the toll of trauma can be wide ranging and quite uneven.

Posttraumatic Reactions and Diagnoses. The vast majority of individuals exposed to potentially traumatic events experience posttraumatic *reactions*, such as intrusive memories of the event or autonomic arousal (e.g., difficulty concentrating, hyper-alertness, increased physiological activation and reactivity) within hours or days of the traumatic event. Most reactions remit spontaneously within the first month or so, as the individual processes them and comes to term with what happened (Rothbaum, Foa, Riggs, Murdock, & Walsh, 1992; Nugent, Saunders, Williams, Hanson, Smith, & Fitzgerald, 2009; Orcutt, Erickson, & Wolfe, 2004). However, in some cases, the reactions persist and some become clinical *symptoms* that meet criteria for one or more posttraumatic diagnoses, per the *DSM-5* (Marshall, Olfson, Hellman, Blanco, Guardino, & Struening, 2001). In the early aftermath (ranging from two days to a month)

post-trauma, these symptoms may meet criteria for Acute Stress Disorder (ASD). If they last more than a month, they may then meet criteria for PTSD. According to the *DSM-5*, “The essential feature of PTSD is the development of characteristic symptoms following exposure to one or more traumatic events,” (American Psychiatric Association, 2013; p. 274). Additionally, “The symptoms of PTSD and the relative predominance of different symptoms may vary over time....Symptom recurrence and intensification may occur in response to reminders of the original trauma, ongoing life stressors, or newly experienced traumatic events” (American Psychiatric Association, 2013; p. 277). A delay of months or even years may occur before the full criteria for the diagnosis are met (“delayed expression” PTSD).

In *DSM-5*, PTSD was moved from a fear-based anxiety disorder to a new category entitled, “Trauma- and Stressor-Related Disorders.” PTSD as now defined in the *DSM-5*, is characterized by four core symptom clusters: (1) recurrent, involuntary, and intrusive recollections of the event, (2) avoidance of stimuli associated with the trauma, (3) negative alterations in cognitions or moods associated with the event, or numbing (or both), and (4) alterations in arousal and reactivity, including a heightened sensitivity to potential threat, as opposed to three symptom clusters (1) re-experiencing, (2) avoidance and numbing, and (3) hyperarousal contained in the previous version, *DSM-IV-TR* (American Psychiatric Association, 2000). In addition there is now a dissociative subtype (Friedman, Resick, Bryant, & Brewin, 2011), which seems to be found in 12-30% of individuals meeting criteria for PTSD and may be marked by a unique pattern of brain activation in response to trauma cues (hypo-aroused/emotionally over-modulated (dissociative) and hyper-aroused/emotional under-modulated PTSD (Miller, Wolf & Keane, 2014). Of significance, all of the studies included in the RTI-UNC Systematic Review that served as the evidence base for this report used *DSM-IV-TR* or earlier *DSM* criteria and are those discussed throughout this guideline.

PTSD is associated with emotional dysregulation ranging from heightened reactivity (intrusive memories, flashbacks, startle responses, hypervigilance, and feeling as though the

trauma is recurring) to emotional withdrawal and shutdown (i.e., numbing, alexithymia, and dissociation), as well as oscillation between the two (American Psychiatric Association, 2013; Dalgliesh & Power, 2004; Herman, 1992; Rasmussen & Shalev, 2014). It further involves physiological activation/hyperarousal and hypervigilance, changes in cognitions and beliefs about self and others--including alienation and mistrust, spiritual and moral questioning and difficulty with meaning-making. Research is increasingly documenting that, when trauma occurs and recurs during the course of childhood, it can create attachment and developmental disruption in a range of major life domains that are in addition to the classic symptoms of PTSD (referred to as Complex PTSD [Herman, 1992] or Developmental Trauma Disorder [van der Kolk, 2005]).⁸

PTSD often results in secondary (mal) adaptations to the traumatization and/or as a means of coping with and blunting physical and emotional/existential pain. These can include increased risks to safety and well-being of self and others (i.e., risk of suicide and self-injury, exposure to physical danger, violence and abuse to and from others, and sexual risk-taking); a range of substance and behavioral addictions; physical injury, medical conditions and illnesses (and their associated treatment burdens and medical costs); relational distress and discord (such as difficulty developing and maintaining intimate and trusting relationships and problems with parenting) as well as social disruption (American Psychiatric Association, 2013; Dalgliesh & Power, 2004; Herman, 1992a; Rasmussen & Shalev, 2014). Many individuals with PTSD have decreased ability to function at work or school (although some are exemplary, with work serving as a means of keeping the trauma at bay or coping with their ongoing or intermittent trauma symptoms). As a result, they may have reduced educational and economic attainment due to underemployment, job loss, anger, difficulty with authority figures and criminal justice

⁸ Complex PTSD has been the subject of ongoing professional debate since its introduction by Herman (1992). It was included as an associated feature of PTSD in the *DSM-IV* and again in the *DSM-5* and the revised diagnosis of PTSD in the *DSM-5* encompasses more of the criteria that had been associated with Complex PTSD. Complex PTSD will likely be included in the next edition of the *International Classification of Diseases* (ICD-11) by the World Health Organization as a freestanding diagnosis so is included in this document.

involvement. Epidemiologic studies also have found that a high percentage of individuals with PTSD suffer from co-occurring mental disorders, most notably substance abuse, anxiety, or major depressive disorders and a heightened risk for a variety of other mental health and health/medical problems, social problems, and early death (Felitti & Anda, 2010). All of these various symptoms of PTSD and their variable manifestations make it a challenging and often excruciating disorder to experience. It is also a challenging diagnosis to treat. In recent decades, numerous psychosocial and pharmacological treatment approaches and modalities have been developed all aimed at its amelioration; consequently, there is an urgent need for mental health professionals and the public to discern what is and is not known about these treatments and what is effective and for whom.

Available PTSD Treatment Guidelines. To date, numerous professional organizations and agencies have reviewed the available trials for a variety of treatment approaches for PTSD in order to develop guidelines, including the American Psychiatric Association, the Australian Centre for Posttraumatic Mental Health (part of the National Health and Medical Research Council), the International Society for Traumatic Stress Studies (ISTSS), the Institute of Medicine (IOM) of the National Academies of Sciences, Engineering, and Medicine, the United Kingdom's National Institute for Health and Care Excellence (NICE), the US Department of Veterans Affairs and Department of Defense (VA, DoD) and the World Health Organization (WHO). All of these guidelines have found evidence in support of several trauma-focused psychological interventions (i.e., those that treat the symptoms of PTSD usually by directly addressing thoughts, feelings, and/or memories of the traumatic event) as first-line⁹ treatments for adults with PTSD, and all, with the exception of the IOM report, recognize at least some benefit of pharmacologic treatments for PTSD (Jonas et al., 2013, ES, p.2).

As noted by Jonas et al., (2013) "... most guidelines identify trauma-focused psychological treatments over psychopharmacological treatments as the preferred first step and

⁹ Note that the APA PTSD GDP is not using the terminology "first line" etc. when recommending treatments.

view medications as an adjunct or a next-line treatment” (ES, p.3). The ISTSS PTSD guideline (2008) acknowledges that practical considerations, such as unavailability of trauma-focused psychological treatment or patient preferences, may guide treatment decisions, including the use of medications. The guidelines developed by the Australian Centre for Posttraumatic Mental Health (Australian Centre for Posttraumatic Mental Health, 2007, 2013) and the International Society for Traumatic Stress Studies guidelines for the treatment of complex trauma (Cloitre, Courtois, Charuvastra, Carapezza, Stolbach, & Green, 2011; Cloitre, Courtois, Ford, Green, Alexander, Briere, et al., 2012) call for a sequencing of treatment, with initial emphasis placed on personal safety, skills for emotional regulation and life stabilization as well as the development of the treatment relationship, before the application of trauma-focused treatment modalities specifically for the symptoms of PTSD.

The APA Clinical Practice Guideline for the Treatment of PTSD in Adults

Institute of Medicine Standards as the Basis for this Clinical Practice Guideline (CPG).

Leadership of the American Psychological Association determined that developing evidence based clinical practice guidelines would be in keeping with the mission of the organization and a valuable initiative for advancing APA’s goals of expanding psychology’s role in advancing health and increasing the recognition of psychology as a science. As a first step, an Advisory Steering Committee for Clinical Practice Guidelines (ASC) was formed, and in conjunction with APA senior staff from the Practice and Science Directorates, determined APA’s procedures for guideline development. After reviewing emerging best practices in guideline development, the ASC decided that the standards established by the Institute of Medicine (IOM) of the National Academies of Sciences, Engineering, and Medicine for developing independent, reliable, and high quality practice guidelines (IOM, 2011a & 2011b) (listed in Table 2) were best. (Please refer to Hollon et al., (2014) for a detailed discussion of the rationale and multi-year preparatory process undertaken by the ASC for APA’s Clinical Practice Guideline initiative).

The ASC chose the Agency for Healthcare Research and Quality (AHRQ) systematic review process due to its consistency with IOM standards (IOM, 2011 b) and its inclusion of important features not found in reviews produced by other organizations and agencies or in other systematic reviews of PTSD treatments (Adamou, Puchalska, Plummer, & Hale, 2007; Bisson et al., 2007; Bisson, Roberts, Andrew, Cooper, & Lewis, 2013; Goodson et al., 2011; Hetrick, Purcell, Garner, & Parslow, 2010; Stewart & Wrobel, 2009; Watts et al., 2013). This selection resulted in a core methodological strength of the current effort. The chosen review was an independent, comprehensive systematic review of the adult PTSD treatment literature that provided clearly specified inclusion and exclusion criteria, a standard method for grading risk of bias of individual studies and strength of evidence for bodies of evidence, and sensitivity analyses to assess the impact of excluding studies judged to be at high risk of bias (Jonas et al., 2013). “Evidence-based clinical practice guidelines represent a systematic approach to translating the best available research evidence into clear statements regarding treatments for various health conditions” as an aid to the practitioner and the patient (Hollon et al., 2014, p. 214). Moreover, this guideline attends to the three dimensions identified by the American Psychological Association Presidential Task Force on Evidence-Based Practice (2006): (1) grounding in the best available science; (2) practitioner expertise in application decisions; and (3) patient preferences and values, even as it places primary emphasis on the first dimension

This American Psychological Association CPG fully applies and builds upon the standards established by the Institute of Medicine (IOM) of the National Academies of Sciences, Engineering, and Medicine standards for developing independent, reliable, and high-quality practice guidelines (IOM, 2011a & 2011b). As such, the current undertaking adds value beyond previously published PTSD guidelines and literature in several important, distinguishable ways. These include (a) an independent and comprehensive systematic review (SR) of the PTSD treatment literature; (b) a transparent process for involving consumer stakeholders and professionals from multiple disciplines in the PTSD GDP; (c) procedures for identifying and

managing real and potential conflicts of interest throughout the guideline development process; (d) identification of patient values and preferences through review of published research literature and input from consumer and clinician members of the panel; (e) identification of harms and burdens of treatments through review of published research literature and input of consumers and clinician members of the panel; and (f) systematic use of evidence profiles and decision-table templates. These documents were used to guide panel members in the development of recommendations that take into account the strength of the research evidence for benefit and harm, the relative magnitude of treatment benefit and treatment harm, the values and preferences of patients, and the applicability of the evidence to external populations.

An interdisciplinary guideline development panel that included representation from mental health consumer groups and multiple professional disciplines-- psychology, social work, psychiatry, and primary care -- was another cardinal feature of the current effort that was clearly aligned with the IOM standard on GDP composition. A significant limitation of many already published treatment guidelines is a lack of attention to providing information on financial, intellectual, and other potential and real conflicts of interest (COIs) among the members of either the SR and/or the guideline development panel (Lenzer, Hoffman, Furberg, & Ioannidis, 2013). In the current effort panel members were required to disclose all COIs, as discussed below.

Additionally, this is the first guideline for PTSD treatment that explicitly incorporates actual and potential harms and burdens of treatments into the recommendation process. Because the strength of evidence for harms and burdens for all psychological treatments in this systematic review was insufficient/very low, harms and burdens did not, in practice, have a substantial impact on the recommendations for psychological treatments. Although the panel attempted to address the issue of harms/burdens, because most studies did not report on that, clear conclusions on this issue cannot be made. However, as more data on harms and burdens for PTSD treatments accrue from additional research studies, recommendations for treatments,

based on the process conducted here, will more precisely represent a balancing of benefits and harms of treatments. The need for more data on harms/adverse effects of psychological treatments is described at greater length in the section on Research Gaps.

Table 2: *Institute of Medicine Standards for Developing Trustworthy Clinical Practice Guidelines*

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- (1) Establishing transparency of the recruitment and selection of Guideline Development Panel (GDP) members.
 - (2) Management of conflict of interest as identified a priori and to be published as part of the guideline.
 - (3) GDP composition that is multidisciplinary, representative of key specialties involved in the treatment of PTSD, and includes consumer members.
 - (4) Interaction between the GDP members and the Systematic Review (SR) team.
 - (5) Rating strength of recommendations, which involves an appraisal of the strength of the relevant evidence, a comparison of benefits and harms of particular clinical interventions, and value judgments regarding the importance of specific benefits and harms based on a modified version of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) consortium system, the most widely used of such systems (Andrews et al., 2013).
 - (6) Articulation of recommendations that are clear and specific about what actions are being recommended.
 - (7) External review from selected external reviewers and the general public prior to publication.

- (8) Updating completed guidelines when significant changes occur in (a) evidence of benefits and harms, (b) outcomes that are considered important, (c) available interventions, (d) evidence that current practice is not optimal, (e) value placed on different outcomes, or (f) resources available for health care.
-

Treatment Outcomes Considered in the Guideline

Treatment outcomes included in the RTI-UNC Systematic Review, *Psychological and Pharmacological Treatments for Adults With Posttraumatic Stress Disorder (PTSD)* (referred to below as the RTI-UNC Systematic Review or Jonas et al., 2013) were: 1) PTSD symptom reduction; 2) Remission (no longer having symptoms); 3) Loss of PTSD diagnosis; 4) Prevention or reduction of comorbid psychiatric or medical conditions; 5) Quality of life; 6) Disability or functional impairment; and, 7) Return to work or return to active duty.

From this original list, the members of the APA PTSD GDP (hereafter referred to as the panel or members of the panel) identified and prioritized treatment outcomes, using the Delphi method following the GRADE Consortium system recommendation (Guyatt et al., 2011). In assigning their ratings, panel members were asked to consider the importance of the outcome for decision-making in the treatment of symptoms of PTSD in adults. They considered the importance of an outcome for someone making a decision to use or not to use a particular treatment, taking into consideration the perspectives of both providers and patients. They rated the absolute importance of each outcome on a 9-point scale ranging from 1 (not important) to 9 (critical). At the same time, the panel also generated a list of outcomes that would be included in an ideal world, identifying outcomes of importance whether or not they were among the

outcomes included in the RTI-UNC Systematic Review. A wide range of outcomes, including maintenance of treatment gains and peer support were considered but were not rated sufficiently important to include in the process of making recommendations about treatments for PTSD.

Members were asked to differentiate between critical and important outcomes. *Critical outcomes* were defined as those that are essential and necessary, to the treatment decision-making process. *Important outcomes* were defined as those that were significant but not critical for making a decision. The strength of evidence and magnitude of effects for both the critical and important outcomes were considered when the panel made decisions about the strength of recommendations. However, critical outcomes were weighted more heavily in those decisions than important outcomes. *PTSD symptom reduction* and *serious harms (adverse events; i.e., hospitalization secondary to suicidal ideation or attempt, violence towards self or others)* were deemed *critical outcomes* by the panel. All others were deemed *important outcomes*. Please refer to Table 3 for the list of outcomes considered by the panel.

Table 3. <i>Outcomes Considered by the Panel</i> Outcome Considered	Decision
PTSD symptom reduction	Critical
Serious harms (adverse events)	Critical
Remission (no longer having symptoms)	Important
Loss of PTSD diagnosis	Important
Quality of life	Important
Disability or functional impairment	Important
Prevention or reduction of comorbid medical or psychiatric conditions	Important
Adverse events leading to withdrawals (treatment discontinuation)	Important
Other adverse events	Important
Burdens	Important
Return to work or return to active duty	Not included
Maintenance of treatment gains	Not included
Aggressive behavior	Not included
Peer support	Not included

The RTI-UNC Systematic Review Key Questions and Analytic Framework. The RTI-UNC review examined a number of Key Questions and used the AHRQ analytic framework for formulating these questions (see listing of key questions and analytic framework on p. 7 of the RTI-UNC Systematic Review; Jonas et al., 2013). In keeping with the AHRQ system for formulating these questions, the PICOTS framework (which stands for Populations, Interventions, Comparators, Outcomes, Timing, and Settings) (Samson & Schoeller, 2012) was used. The panel followed a multi-step process for making clinical recommendations based upon the empirical findings included in the RTI-UNC Systematic Review as described in the following section.

Process and Methods of the Clinical Practice Guideline

Undertaking the Systematic Review

Scoping. Prior to the empanelment of members to the PTSD GDP, members of the APA ASC proposed the topic “PTSD treatment efficacy and effectiveness” to the Agency for Healthcare Research and Quality (AHRQ) due to what it perceived to be an urgent need regarding the treatment of this disorder. The nomination process, called “scoping,” involves providing rationale for the need for a new systematic review on a topic and the proposing of key questions and issues. The AHRQ staff accepted the topic nomination and commissioned the production of the systematic review on the treatment of PTSD in adults to the Research Triangle Institute International-University of North Carolina Evidence-Based Practice Center (RTI-UNC EPC), one of 13 sites funded by AHRQ for the development of systematic reviews on a variety of health topics. The RTI-UNC EPC has specialized in detailed and highly transparent systematic reviews in the area of mental health and substance use disorders and thus could be expected to do the same regarding the systematic review of PTSD treatment for adults. The RTI-UNC EPC conducted the literature review and analysis for the systematic review in 2012

and produced it as the report, *Psychological and Pharmacological Treatments for Adults With Posttraumatic Stress Disorder (PTSD)* a year later (Jonas et al., 2013). It is 760 pages, including raw and synthesized data for all comparisons described in the report and has appendices including the ratings of all of the reviewed articles. The APA GDP used this systematic review as its primary base of evidence. Importantly, as anticipated, it gave the panel the ability to investigate the data and rationale for conclusions included in the report.

Vetting and Appointment of Members to the PTSD GDP. The ASC put out a call for the nomination (including self-nomination) of both researchers and clinicians across various professional disciplines (psychology, social work, psychiatry, general medicine) with content expertise in the topic area of trauma treatment and PTSD as well as in biostatistics or methodology. The ASC sought those with knowledge of PTSD across age groups, gender, populations (veterans, immigrants) and treatment settings and type of trauma (combat, interpersonal violence) in order to seat a diverse panel with a variety of perspectives on PTSD and its treatment that could discuss the research data and its applicability to those seeking treatment. Treatment developers who might have a strong allegiance to their particular method were not selected to serve on the GDP but their participation in the public comment period was encouraged. Additionally, community members, self-identified as having had PTSD (currently or in the past), who were active in the leadership of groups that sought to enhance public awareness and access to services, were sought.

Conflicts of Interest. Before final appointment to the GDP, nominees provided information regarding possible *Conflicts Of Interest (COI)*, a significant issue in the AHRQ and IOM standards. (COI) are defined as, “a divergence between an individual’s private interests and his or her professional obligations such that an independent observer might reasonably question whether the individual’s professional actions or decisions are motivated by personal gain, such as financial, academic advancement, clinical revenue streams, or community

standing” (Institute of Medicine, 2011, p. 78; the definition is drawn from Schünemann et al., 2009, p. 565). The IOM report additionally discusses intellectual COIs relevant to clinical practice guidelines, which are defined as “academic activities that create the potential for an attachment to a specific point of view that could unduly affect an individual’s judgment about a specific recommendation” (Institute of Medicine, 2011, p. 78; the definition is drawn from Guyatt et al., 2010, p. 739).

COI disclosure is routinely undertaken by an EPC before the start of a systematic review. So, even before the APA GDP was formed, the RTI-UNC researchers completed their own COI disclosure procedure, giving their review transparency. Candidates to the GDP followed a similar procedure and each completed an APA COI form. Emphasis was placed on their disclosing all potential conflicts for the APA staff and ASC members to review and decide upon. While intellectual affiliations were expected, no panel members were to be singularly identified with particular interventions nor were they to have significant known financial conflicts that would compromise their ability (or appearance thereof) to weigh evidence fairly. It was understood however that some “adversarial collaboration,” a term coined by Mellers, Hertwig and Kahneman (2001), to indicate different points of view are to be expected and are actually encouraged as part of the process, would occur. Upon successful completion of the reviews, the ASC made final membership recommendations to the APA Board of Directors for confirmation.

Once the panel was formed, all members completed an educational module on COI that underscored the importance of continuous identification and management of current or future conflicts. They were asked to verbalize any actual or potential conflicts to the other members in their first face to face meetings so all members would be familiar with the diversity of perspectives and range of possible influences and biases. COI forms were updated on an annual basis or sooner if the need arose and reviewed by staff, the panel chair and the ASC as needed. While panel members had a range of activities pertinent to their roles on the panel and the treatment of PTSD, no member was deemed to have intellectual or financial conflicts of

interest that would limit participation in decision-making. The APA COI policy and disclosure form can be found in Appendix J along with a summary of panel member disclosures at the end of this document.

Comprehensive Search of the Professional Literature. As the name implies, a *systematic review* involves a methodical and organized search for studies and evidence of efficacy and effectiveness regarding the treatment under consideration (IOM, 2011 b). For the RTI-UNC Systematic Review, a variety of scientific data-bases were searched using selective search terms in order to identify relevant studies. The list of search terms is too extensive to include in this document but can be found on pp. B1 – B 19 of the RTI-UNC Systematic Review. The identified individual studies were then assessed to determine whether they met inclusion criteria (e.g., were adults, not children, included in the study?) and assessed, using pre-defined criteria to assess risk of bias. The criteria for assessment of risk of bias are used by all of the AHRQ EPCs (Viswanathan et al., 2012) and are quite similar to the criteria used to rate risk of bias by the GRADE Consortium (Guyatt et al., 2011) and the Cochrane Collaboration (Higgins, Altman, & Sterne, 2011). A diagram on page ES-8 of Jonas et al., (2013) shows the disposition of articles included and excluded in the systematic review. In brief, after an exhaustive search strategy that had a high sensitivity, screening of 3,048 records, review of the full-text of 527 articles by researchers with expertise in meta-analysis or PTSD or both, there were 147 studies that were eligible for inclusion in the systematic review. Of those, 46 were rated as high risk of bias and included only in sensitivity analyses. Of the 101 studies that were low or medium risk of bias, 77 were included in quantitative meta-analyses. The remaining 24 trials that were low or medium risk of bias were evaluated qualitatively in the systematic review but were not entered into quantitative meta-analyses most commonly because there was only one trial of a particular treatment.

Decisions Regarding Assessment and Inclusion/Exclusion of Studies. Identified studies were then screened and selected for inclusion on the basis of *Risk of Bias* (ROB) ratings

assigned to each. The criteria for assessment of risk of bias are used by all of the AHRQ EPCs (Viswanathan et al., 2012) and are quite similar to the criteria used to rate risk of bias by the GRADE Consortium (Guyatt et al., 2011) and the Cochrane Collaboration (Higgins, Altman, & Sternem 2011). Risk of bias assessment considers the degree to which an individual study is free of systematic error (bias), i.e., the degree to which the study has high internal validity. Risk of bias ratings are key components of any systematic review because they reduce the risk that conclusions are based on studies that are methodologically flawed in some significant way. Twelve items were included in the ROB assessment to evaluate the potential for the following biases: selection bias (adequacy of randomization process and concealment of randomization allocation); confounding (comparability of baseline covariates); performance bias (adequacy of masking of participants and researchers); detection bias (masking of outcome assessment); attrition bias (i.e., attrition rate, differential attrition rate across treatment groups, handling of missing data, use of intention-to-treat analysis); and measurement bias (validity and reliability of outcome measures; treatment fidelity). For the RTI-UNC Systematic Review, the assessment was conducted by two investigators, one of whom was an experienced researcher; differences in ratings were resolved by consensus or by review by another experienced researcher. Studies were rated as low, medium, or high risk of bias, with high risk signifying results of questionable validity, typically due to a fatal flaw, such as very high attrition. Appendix E, pages E1 – E27 of the RTI-UNC document describes the risk of bias criteria, questions used to assess those criteria, and ratings of all individual studies included in the systematic review.

Assessing Strength of Evidence.

Strength of Evidence (SOE) rating of randomized trials by the AHRQ EPCs is the assessment of a body of evidence (i.e., the aggregated data for a particular intervention for a particular outcome from more than one study. For instance, the findings on the effects of cognitive processing therapy on PTSD symptoms reduction, based on the four studies of medium risk of bias or less that were included in the meta-analysis, is a body of evidence) based

on four major criteria, of which *risk of bias* (defined and discussed above) is the first, followed by *consistency*, *directness*, and *precision* (Owens et al., 2010). *Consistency* is the degree to which the direction of effect is the same or different in the studies included in a body of evidence. If several studies find that an intervention leads to a reduction in PTSD symptoms but other studies find that the intervention leads to an increase in PTSD, the body of evidence is rated as inconsistent. *Directness* is the degree to which the evidence linking the effect of an intervention to an outcome is based on: 1) the true health outcome, as opposed to a surrogate marker of that health outcome and 2) head-to-head comparison of individual interventions as opposed to comparison of two separate bodies of evidence. For example, if a body of evidence in which the effect of an intervention on the outcome “loss of PTSD diagnosis” were to include only data on PTSD symptom reduction, it would be rated as indirect. *Precision* of an estimate is based on the width of the confidence interval around the estimated summary effect size in a meta-analysis; the narrower the confidence interval, the greater the precision. A more precise estimate provides stronger evidence that the estimated magnitude of effect for the results of an intervention is the true effect. If two clinically distinct conclusions (e.g., that an intervention is better than inactive control and that an intervention is worse than inactive control) are possible based on a wide confidence interval, the body of evidence is rated as imprecise.

Strength of evidence rating of randomized trials by the AHRQ EPCs also depends on three additional minor domains: *dose-response relationship* (evidence that higher “doses” of an intervention are associated with larger effects represents higher strength evidence), *magnitude of an effect* (large-magnitude effects represent higher strength evidence), and, *publication bias* (evidence that unpublished studies were not included in summary effect estimates lowers the strength of evidence). For the RTI-UNC Systematic Review, two researchers conducted strength of evidence assessments for each body of evidence (which could include one or more studies). Each was rated as high, moderate, low, or insufficient/very low strength.

Disagreements between the two raters were resolved by consensus or by the assessment of another experienced researcher.

The goal of grading the SOE is to determine the confidence that the estimated effect of an intervention is the true effect, something that has broad implications for reliability of the findings and the public's confidence in them. For high strength evidence, "future research is very unlikely to change confidence in the estimate of the effect" per Owens et al., (2010). Appendix G (pp. G1-G54) of the RTI-UNC review describes the strength of evidence criteria and questions (items) used to assess those criteria. Strength of evidence for all bodies of evidence used in the development of the current guideline is shown in the Evidence Profiles, included in Appendix C. A description of Evidence Profiles is found below.

Types of Comparison (Control) Groups Used by Studies Included in the RTI-UNC Systematic Review. Among the randomized trials of psychological interventions for which the panel completed Decision Tables, *inactive control* groups typically consisted of either treatment as usual (TAU) or wait-list (WL) controls. The elements included in treatment as usual depended to some extent on the setting in which the trial was conducted. For wait list control groups, participants were allocated to a waiting list and then given the active treatment after those allocated initially to active treatment; outcomes for those in the wait-list control groups were assessed before they received active treatment. Some of the trials of psychological interventions for which the panel conducted decision tables used *active controls*, such as psychoeducation or substance abuse treatment¹⁰, that had not been specifically developed for treatment of PTSD, but which was thought to have elements that might have a beneficial impact on PTSD symptoms or other critical or important outcomes. Finally, some of the trials of psychological interventions and trials of pharmacological trials used other active treatments for PTSD as comparators.

¹⁰ Substance abuse treatment was used as an active control when a treatment for PTSD was evaluated in individuals with both PTSD and co-morbid substance use problems.

For randomized trials of pharmacotherapy interventions for which the panel conducted decision tables, inactive controls were placebos, designed to be indistinguishable from active medications.

Although wait-list controls, treatment as usual and placebos are all characterized as inactive controls, there is evidence from meta-analyses in a variety of content areas that the effect size for an active treatment compared to an inactive control depends on the type of inactive control (Huhn et. al., 2014; Karlsson & Bergmark, 2014; Sturmey & Hursen, 2012). Accordingly, the panel makes recommendations for psychological interventions compared to inactive controls and for pharmacotherapy compared to inactive controls, but does not draw inferences about the indirect comparison of psychological interventions to pharmacotherapy on the basis of those trials alone.

Some of the trials of psychological interventions for which the panel conducted decision tables used *active controls*, such as psychoeducation or substance abuse treatment i.e., those that had not been specifically developed for treatment of PTSD, but which were thought to have elements that might have a beneficial impact on PTSD symptoms or other critical or important outcomes. Finally, some of the trials of psychological interventions and trials of pharmacological trials used other active treatments for PTSD as comparators.

In this guideline, the term *efficacy* refers to the impact of a treatment compared to an inactive control. The term *comparative effectiveness* of two treatments refers to the impact of two active treatments compared to each other or the impact of a PTSD treatment to an active control.

The Development and Use of Evidence Profiles. *Evidence Profiles* (summaries of data in available studies) were created by the RTI-UNC team from evidence collected for the systematic review regarding the efficacy of psychological or pharmacological treatments or the comparative effectiveness of psychological and pharmacological treatments in head-to-head trials. These profiles contain the foundational evidence on which current recommendations were

made and generated some of the information included on the Decision Tables. The evidence profiles were abstracts of data included in the systematic review and include, for each body of evidence, the number of studies, absolute effect sizes, confidence intervals (when available) and strength of evidence ratings. These measures were reported according to the specific treatment outcomes that had been investigated in those studies, including the measurement instrument and range of scores and any follow-up.

The Development and Use of Decision Tables. *Decision Tables* are documents subsequently developed and then used by panel members to summarize and evaluate the evidence generated in the systematic review (included in the evidence profiles), along with any supplemental information. Panel ratings and judgments were documented on the decision tables to assist in the formulation of recommendations (EBM Guidelines Editorial Team, 2011; Treweek et al., 2013). These tables allow panel members to document decisions, compare consistency across decisions, and provide transparency to reviewers and users of the guideline document. Decisions regarding treatment are documented in four main domains: 1) *strength of evidence*; 2) *treatment outcomes and the balance of benefits vs. harms and burdens of interventions*; 3) *patient values and preferences*; and, 4) *applicability of the evidence to various treatment populations*.

Decision tables were completed only for interventions that had at least low strength of evidence for one of the critical outcomes. Studies that did not address any of the eight important outcomes or those that did but had insufficient/very low SOE (typically due to a combination of risk of bias, inconsistency, indirectness, or imprecision) were excluded from the analysis. Evidence meeting these criteria was generated for the completion of 19 decision tables on which to base the APA PTSD Guideline recommendations.

The panel decided to not supplement the randomized trials included in the SR with observational (i.e., non-randomized and less methodologically rigorous) treatment studies, due to the potential for confounding bias in observational studies (Fewell, Smith, & Sterne, 2007;

Rothman, Greenland, & Lash, 2008). Although some have questioned the applicability of some randomized trials due to potential differences between sample characteristics or treatment settings and the “real world,” this decision is consistent with the position of all major organizations that evaluate research and conduct systematic reviews, including GRADE, Cochrane, NICE, AHRQ Evidence-Based Practice Centers, that randomized trials have lower potential for bias than observational studies (Guyatt et al., 2011; National Institute for Health and Care Excellence, November 2012; Reeves, Deeks, Higgins & Wells on behalf of the Cochrane Non-Randomised Studies Methods Group; Viswanathan et al., 2012).

Panel members made two significant exceptions to this decision when it became clear that data were lacking in randomized trials findings regarding two outcomes, 1) harms and burdens of psychological treatments and 2) patient values and preferences with regard to particular treatments. In response, the panel determined there was a need to gather and review additional information on these topics. Concerning harms, panel members decided to review those observational studies that gave attention to the assessment of harms that were identified in the RTI-UNC Systematic Review. It also authorized APA staff assigned to the GDP to compile information on possible harms and burdens of interventions from an additional review of the literature. Concerning patient values and preferences, the panel decided to use the recently completed systematic review (Simiola, Neilson, Thompson, & Cook, 2015) of this topic. Details of the search process methodology for both of these supplemental sources of information are described below. The findings of these additional reviews along with input from clinicians and consumers on the panel were used to make the treatment recommendations more comprehensive with regard to the risk of harm or adverse events associated with various interventions for PTSD (determined to be a *critical outcome*) and patient values and preferences.

After the guideline process was completed and recommendations drafted, the panel made the important decision to conduct a new and separate search process to identify

randomized trials that would have met criteria for inclusion in the RTI-UNC Systematic Review but were published between May 24, 2012 (the end date for the search conducted for the systematic review) and June 1, 2016. The goal of this update search process was to determine whether randomized trials published after the systematic review was completed might change any of the panel's recommendations. Please see the section Update Search Process following the recommendations below for a description of and conclusions from the updated search process.

Additionally, as the panel reviewed the evidence derived from the systematic review, it established some "rules" to govern its process of making recommendations in an effort to prevent or offset potential bias. These included:

- Do not consider mechanisms of change in formulating guideline recommendations about interventions (i.e., consider only evidence for efficacy/effectiveness)
- In addition to listing the overall strength of evidence ratings (as required by GRADE), separate strength of evidence ratings for benefits and for harms will be listed
- If no data, including anecdotal report, are available related to patient preferences/values, low rating of certainty and unknown rating of variability will be assigned
- Panel members will examine primary studies included in the RTI-UNC Systematic Review (in addition to the decision table) only under agreed upon conditions to avoid introducing bias into the process (i.e., to avoid giving greater attention and examination to one study versus another without a pre-determined rationale). The goal was to use a systematic method for examining primary studies in order to avoid a process in which they were selected based on particular panel member's interest that could bias the process. Possible conditions for examining primary studies included:

- Where there is a large magnitude of effect for a benefit yet low or insufficient/very low strength of evidence
- For evidence on critical outcomes only

Each panel member was given an explicit opportunity to raise any questions or concerns about how each decision table was completed. The panel as a group reviewed each decision table to identify any questions or concerns that audiences of the guideline (including patients, clinicians, and scientists) might raise. After completing all the decision tables, the panel globally reviewed all tables to assess any inconsistency between them in order to assure consistency in decision-making across tables. For purposes of consistency across all current and future guideline development panels, the ASC established voting procedures that can be found in Appendix K.

Completion of Decision Tables

The following four domains of information constituted the basis on which each treatment recommendation and its strength were determined. For each recommendation, text description and a justification for the recommendation were included on the Decision Table (See Appendix D).

Rating of Aggregate/Global Strength of Evidence. For each of the 19 Decision Tables, *aggregate/global SOE* was based on the SOE from the systematic review for the two critical outcomes, namely, PTSD symptom reduction and serious harms. *In accordance with the GRADE Consortium system, the panel concluded that the aggregate SOE could be no higher than the lowest individual SOE for each of the critical outcomes (Guyatt et al 2013).* For example, if one critical outcome had high strength of evidence but the other critical outcome had low strength of evidence, the global quality of evidence for that particular decision table would have to be low, since that is the lowest SOE for an individual critical outcome. Thus, the strength of evidence for serious harms, one of the panel's critical outcomes, was insufficient/very low, for all interventions for which decision tables were completed. This explains

why the global strength of evidence was insufficient/very low for all interventions, despite low, moderate or high strength of evidence for the critical outcome of PTSD symptom reduction. This is identified by some researchers as a limitation of the GRADE system.

Assessing Magnitude of Benefits. One of the key components of the decision-making process for the GDP was assessment of the balance between benefits and harms. This required that both benefits and harms be quantified. Quantification of the *magnitude (size) of benefits* was based on data from the quantitative meta-analyses for each of the important and critical outcomes for those interventions that had at least low quality of evidence for the critical outcome, PTSD symptom reduction. For each of the outcomes, magnitude of benefits was rated on a five-point scale: 1) large/medium benefit; 2) small benefit; 3) no effect; 4) small harm; 5) medium/ large harm. To reduce the potential for end-aversion (i.e., central tendency) bias (Streiner & Norman, 2008), the panel chose to combine medium and large benefits into one category rather than including them as separate categories. The same was done for medium and large harms.

For outcomes measured on a continuous scale (e.g., PTSD symptom reduction), *mean differences* (MDs) and *standardized mean differences* (SMDs) were used to quantify the effect. MDs are differences in means for each treatment group, weighted by the inverse of the variance within the study and by the degree of heterogeneity across the included studies (Borenstein, Hedges, Higgins, & Rothstein, 2009). MDs were used when all of the studies for a particular outcome used the same instrument. The *magnitude of effect* (e.g., small benefit vs medium/ large benefit) was based on assessment of clinically meaningful change, on the instrument in question, when available. An unweighted mean difference, also abbreviated MD, was used in circumstances in which only one study was used for a treatment comparison.

SMDs are also reported for continuous outcomes. An SMD is the mean difference divided by the pooled standard deviation of the outcome among participants. It is also known as an “effect size” and is equivalent to Cohen’s *d* (Borenstein et al., 2009). An SMD is expressed in

terms of standard deviation units; an SMD equal to 1 means that there was a 1 standard deviation difference in the outcome measure between interventions being compared. The panel used the same criteria for assessing *magnitude of effect* using SMDs as the systematic review: approximately 0.2 or less was rated as a small effect, 0.5 as a medium effect, and 0.9 or greater as a large effect.

For dichotomous outcomes, such as loss of PTSD diagnosis (yes/no), the magnitude of effect was measured as a *risk difference*, defined as the difference in incidence (risk) of the outcome across treatment groups. The *summary (pooled) risk difference* is based on combining risk differences from multiple studies in a meta-analysis, after weighting the individual study risk differences by the inter-study variance (in a random-effects meta-analysis) (Borenstein et al., 2009).

For deliberations about the role of chance in the estimation of effect magnitude, the APA PTSD GDP developed practices consistent with the recommendations of the APA Task Force on Statistical Inference (Wilkinson and Task Force on Statistical Inference, 1999). Specifically, the panel assessed point estimates of effects and the precision with which they were estimated, based on 95% confidence intervals, rather than relying on p values, because p values conflate magnitude of effect with the precision of the estimates (i.e., a low p value can be due to a large magnitude effect or a large sample size or both; a high p value can be due to a small magnitude effect or a small sample size or both).

The panel used a general rule that the magnitude of benefit would be rated as “no effect” if the point estimate was near the null value of zero and it was estimated precisely (i.e., the confidence interval was narrow). Conversely, a magnitude of benefit was characterized as “unable to rate” if the point estimate was far from the null value of zero and it was estimated imprecisely (i.e., the confidence interval was wide and included values consistent with a large effect in favor of either intervention). An example will illustrate how the panel reached different conclusions for two meta-analyses in which the p value for the summary pooled estimate was

greater than .05 in both. In the meta-analysis for Seeking Safety compared to active controls, the weighted mean difference for PTSD symptom reduction was 1.45, 95% CI, (-2.50 to 5.40). Because the point estimate (1.45) was near the null value of zero, the confidence interval was relatively narrow and contained the null value of zero and the null value was near the middle of the confidence interval, the panel concluded that there was no difference in effect between Seeking Safety and active control treatment. In the meta-analysis for EMDR compared to inactive controls, the weighted mean difference for prevention or reduction of co-morbid anxiety was -11.08; 95% CI (-23.06 to 0.90). Because the point estimate was moderate and far from the null value, but the confidence interval was wide and contained the null value of zero, the panel concluded that it was unable to rate the magnitude of benefit for EMDR compared to inactive controls. Thus, although the p value was greater than .05 in both situations (based on the fact the 95% CI included the null value of zero) and thus “nonsignificant” using the traditional hypothesis-testing framework, the panel came to a different conclusion in these two situations, based on the magnitude of the point estimate, its relation to the null value, the width of the confidence interval and the relation between the null value and confidence interval.

Assessing Magnitude of Harm/burdens. Since harms (otherwise termed serious adverse events) was one of the two critical outcomes of treatment decided upon by the panel, these needed more precise specification and definition. Ultimately, panel members considered events such as the need for hospitalization secondary to risk for suicide or a suicide attempt as a serious adverse event and then identified additional harms such as medication side effects. Harms were differentiated from burdens. Burdens refer to encumbrances associated with treatment (i.e., time spent, homework/need to practice, cost, inconvenience) rather than as damages. As discussed earlier, the systematic review of the treatment literature did not generate sufficient data on harms and burdens of interventions because, unfortunately, this information is not routinely reported in studies of psychosocial or in detail in many studies of psychopharmacological interventions.

In response to this deficit, the panel commissioned APA staff to examine each article in the systematic review and to extract data regarding harms and burdens, such as dropout/attrition, symptom worsening, homework, etc. The same data extraction was also conducted on studies excluded from the systematic review due to high risk of bias or the wrong study design ($n = 33$) since the IOM standards allow more relaxed criteria when examining literature on harms/burdens (IOM, 2011b, p. 8). In addition, a focused literature search of the PsycINFO® database was conducted to identify articles from the years 1980 to June 2014 by combining the search term “PTSD” with each of the following key words: “iatrogenic,” “negative effects,” “side effects,” “feasibility,” “adverse events,” “relapse,” “recurrence,” “exacerbation,” “failure,” “dropout,” “spike,” “residual,” and “worsening.” Then this same series of key words were combined with “trauma treatment” and for each of the treatment domains included in the decision tables (both abbreviation and full name): “EMDR” “Exposure” “CPT” “CT” “CBT,” “NET,” “Seeking Safety,” “brief eclectic therapy,” “relaxation,” “topiramate,” “fluoxetine,” “paroxetine,” “sertraline,” “risperidone,” and “venlafaxine.” Titles and abstracts ($n = 2,448$) were reviewed for papers that focused on PTSD treatment in adult populations. After removing duplicates and non-peer reviewed articles (i.e., dissertations, chapters, reviews), 150 articles were identified through this focused literature search. Of these, 90 were excluded because they utilized a treatment intervention not included in the systematic review (e.g., mirtazapine, escitalopram), combined multiple treatment interventions (e.g., Dialectical Behavior Therapy + prolonged exposure), were only theoretical in nature, or were reviews or meta-analyses. The 60 remaining articles included case study designs, observational studies, archival data extractions, randomized controlled trials (RCTs) completed after the systematic review was conducted (i.e., after May 2012), and secondary analyses of RCTs that were included in the systematic review. It was from these studies that the panel had additional information on possible harms or burdens associated with the interventions under consideration. With the exception of the studies conducted after May 2012 (which were not rated), these studies were rated insufficient/very low

strength of evidence due to inclusion of observational study designs, which have a higher risk of bias than randomized trials. See Table 4 for a listing of harms/burdens articles by intervention.

The issue of attrition/dropout as a possible harm was also addressed in this review. Attrition in a randomized trial can signify different things (i.e., it may be evidence that a treatment is not acceptable or tolerable to patients but it can also signify that a treatment is working and the patient leaves treatment when symptoms are ameliorated and before it is concluded); therefore, the panel did not consider attrition to be a harm unless information on the reasons for its occurrence were specified or unless there were differential attrition rates across treatment groups (Zandberg, Rosenfield, Alpert, et al., 2016). Attrition was considered in the assessment of risk of bias in the RTI-UNC Systematic Review, but that is a separate issue from the one under discussion here.

Finally, in order to supplement the limited information on harms and burdens gleaned from published research, clinicians on the panel reported their experiences in delivering, supervising, or training in particular interventions and the concerns noted by colleagues. Consumer members reported on both their own and peer experiences with various interventions. In general, many of the identified harms and burdens are found in response to many, more general, psychosocial treatments (e.g., the potential for short-term exacerbation of symptoms [harm] or the time necessary for multiple therapy sessions [burden]). The inclusion of information from both peer reviewed articles and anecdotal (i.e., clinician and consumer report) resulted in a rating of insufficient/very low strength of evidence for the data on harms and burdens.

Once possible harms and burdens were identified, panel members then compared these with the benefits of the interventions. On the decision table for each intervention, the panel rated whether the benefits “clearly outweigh” or “slightly outweigh” the harms and burdens or the reverse.

Table 4: *Articles Reviewed for Harms/Burdens*

Treatment	Articles Included in AHRQ	Articles Excluded from AHRQ	Articles Identified in Additional Search
Cognitive Processing Therapy	6	4	7
Cognitive Therapy	4	0	2
Prolonged Exposure	18	6	30
Cognitive Behavioral Therapy-Mixed	25	0	1
Eye Movement Desensitization and Reprocessing Therapy	6	6	4
Narrative Exposure Therapy	3	2	0
Seeking Safety	5	0	2
Topiramate	3	1	2
Fluoxetine	5	1	4
Paroxetine	3	2	1
Sertraline	8	4	1
Venlafaxine	2	1	3
Risperidone	5	2	2
Brief Eclectic Psychotherapy	4	0	0
Relaxation	5	4	0

Assessing Patient Values and Preferences. In addition to assessing the benefits and the harms/burdens, the panel sought to ascertain patient *values and preferences* associated with specific interventions. As described above the panel relied on a recently conducted systematic review (Simiola et al., 2015) of the literature conducted by a member of the GDP and her research team (independent of the RTI-UNC Systematic Review team and its report), supplemented by additional careful searching of the professional literature by APA staff. Studies were identified through comprehensive searches of the *PsycINFO*, *Medline*, *PubMed*, *Published International Literature on Traumatic Stress*, and *Cumulative Index to Nursing and Allied Health Literature* electronic databases for research published between January 1980 and September 2014. Combinations of the following sets of search terms were used in each bibliographic database: 1) preferences, patient preferences, choice behavior, decision making, patient satisfaction and 2) PTSD, trauma, emotional trauma. Quantitative or qualitative research studies that reported on participant preference of treatment for PTSD or a dual diagnosis including

PTSD in either clinical or non-clinical (e.g., analog) samples were reviewed. Data extraction included study population demographics (e.g., age, ethnicity), type of trauma exposure, PTSD and other diagnostic prevalence, research design, treatment options presented, method and procedures to evaluate treatment preferences, and outcomes (Simiola et al., 2015).

Unfortunately, the identified literature generally compared an intervention to no treatment and only rarely addressed the specific comparison of interventions to one another in any given decision table. As a result, the panel had very little direct information about relative preference for the specific treatments for which decision tables were completed.

In addition to the literature review, clinicians and consumers on the panel voiced their perspectives about patient preferences for different interventions, as well as the value that they might subjectively place on different outcomes or harms/burdens associated with particular treatments. Once these issues were discussed, panel members rated how variable they thought patient values and preferences were in relation to the intervention under consideration and how certain they were about their judgment, ultimately combining into an overall judgment of variability and certainty of patient values and preferences. The SOE for all of this information was very low because, like the information on harms/burdens, it included observational studies and “expert” (i.e., panel member) opinion.

Applicability of Evidence. The final determinant that panel members considered, before making recommendations, was the *applicability (generalizability)* of the evidence to various populations and settings. To organize information on applicability, panel members applied the PICOTS framework (referring to Populations, Interventions, Comparators, Outcomes, Time and Settings) (Samson & Schoelles, 2012) - the same framework originally used by RTI-UNC EPC to identify the Key Questions guiding the systematic review. The panel reviewed the studies included in the review to determine if additional information concerning applicability pertaining to population, interventions, comparators, outcomes, timing, or settings needed to be included and noted in each decision table.

One applicability issue had to do with the relatively recent changes in the *DSM* criteria for PTSD. All of the studies in the systematic review are based on the PTSD diagnostic criteria found in the *DSM-IV-TR* or earlier versions of the *DSM*. The new *DSM-5* criteria are different in several important ways (American Psychiatric Association, 2015) making it reasonable to ask whether the results of trials based on inclusion of participants who met criteria for PTSD based on *DSM-IV-TR* or earlier are applicable to patients who are diagnosed with PTSD based on *DSM-5* criteria. The panel identified a research study that examined this very issue. In a large national sample in the United States, Kilpatrick et al. (2013) showed 96.5% concordance between *DSM-IV-TR* and *DSM-5* on diagnosis or absence of diagnosis of PTSD. Based on this study, panel members believe that the findings regarding treatment reported in the RTI-UNC Systematic Review and this guideline are likely to be applicable to patients who are diagnosed with PTSD based on *DSM-5*.

An additional applicability issue is whether the recommendations in this guideline apply to patient populations that differ in other identifiable ways from those included in study samples. Potential domains of difference include many facets of social identity (such as ethnicity, race, gender, gender identity and gender expression, culture, sexual orientation, religious beliefs, disability status, and so on), as well as the cultural and material realities that structure how people interact with each other, engage the world, adapt to new challenges, and find meaning. As noted in the Discussion section of this guideline, the RTI-UNC Systematic Review concluded that the evidence was insufficient to identify treatment effects by any subgroup on the basis of these kinds of indicators. Nevertheless, it is useful to consider that many of the studies in the systematic review on which these guideline recommendations are based included diverse samples in terms of type of trauma and other characteristics. For example, study samples included military veterans, sexual assault survivors, international refugees, and participants from the Americas, Africa, Australia, Europe, and the Middle East. (These details can be explored further in Appendix D, Table D-2 of the RTI-UNC Systematic Review).

Decision-making Regarding Treatment Recommendations. On the basis of the ratings of these four factors (strength of evidence, balance of benefits versus harms/burdens, patient values and preferences, and applicability) the guideline panel then made a decision regarding its recommendation for a particular treatment or comparison of treatments. The scale for recommendations included the following: strong for, conditional for, insufficient evidence, conditional against, strong against. Panel members were able to reach consensus regarding the strength of recommendation given to each treatment in most cases but, for several, a vote was required. When a vote was called, the tally was included on the corresponding decision table found in Appendix D.

External Review Process. This document was submitted for feedback to the APA Advisory Steering Committee (ASC) for Development of Clinical Practice Guidelines. The comprehensive comments of ASC members were given a detailed review and response and the guideline draft was modified based on that feedback. The draft was subsequently posted on the APA web site (October 5- December 4, 2016) and public feedback was solicited for 60 days. More than 890 responses were received. These were catalogued by comment topic and by theme and the main document was revised based on that feedback. In addition to the document text, four specific recommendations were modified following the public comment period. While the Systematic Review reported findings for exposure therapy, commenters noted that the majority of the research reviewed was specific to prolonged exposure. The panel undertook an analysis and determined that it was more appropriate to call the intervention prolonged exposure (PE) specifically. Furthermore, three decision tables were revisited resulting in a change regarding topiramate (now insufficient evidence to make a recommendation) and an acknowledgment of increased uncertainty in the stability of the conditional recommendations for EMDR and NET as future meta-analyses may result in one or both treatments receiving a

strong recommendation. Detailed responses to public comments are available from APA staff (cpg@apa.org).

Detailed Recommendations of the APA GDP for the Treatment of PTSD¹¹

Table 5a. *Efficacy of Psychological Interventions Compared to No Intervention*¹²

Topic ¹³ :	Recommendation:	Summary Rationale Statement ¹⁴ :
#1: Efficacy of Cognitive Behavioral Therapy	Among adult patients with PTSD, the panel strongly recommends that clinicians offer cognitive behavioral therapy compared to no intervention.	<ul style="list-style-type: none"> • There is moderate strength of evidence of a medium to large magnitude benefit for the critical outcome of PTSD symptom reduction.¹⁵ • There is moderate strength of evidence of a medium to large magnitude benefit for three additional important outcomes: remission, loss of PTSD diagnosis, and prevention/reduction of comorbid depression. • There was insufficient/very low strength of evidence for the critical outcome of serious harms. The panel found no other interpretable evidence of serious harms.¹⁶ • Benefits clearly outweigh harms/burdens. • Patient values and preferences were considered but owing to unknown variability did not substantially factor into the recommendation. • There is no evidence that raises concern about applicability.
#2: Efficacy of Cognitive	Among adult patients with PTSD, the panel strongly	<ul style="list-style-type: none"> • There is moderate strength of evidence

¹¹ Please see Table 17 and Table 18 in Appendix L for a comparison of the strength of evidence ratings for critical and important outcomes for the psychological interventions and medications, respectively, for which the panel made substantive recommendations.

¹² These recommendations are framed as psychological intervention compared to no treatment for parsimony but they are based on data from the systematic review of randomized trials comparing psychological interventions to inactive control groups. Inactive control groups received either treatment as usual or wait-list controls (no treatment).

¹³ The panel used a structured process to develop recommendations for each intervention. That process incorporated the following elements: 1) strength of evidence for benefits and harms of the intervention; 2) balance of benefits vs. harms/burdens; 3) patient values and preferences; 4) applicability. The decision-making process was incorporated into a Decision Table for each intervention and those Decision Tables are found in Appendix D.

¹⁴ Magnitude of benefit indicates the size of the effect and is based on standardized mean differences (SMDs) for continuous outcomes, rated using the same criteria as the systematic review: approximately 0.2 or greater was rated as a small effect, 0.5 as a medium effect, and 0.9 or greater as a large effect. For dichotomous outcomes in which odds ratios were the measure of effect, an odds ratio of 1.44 was rated as a small effect, 2.47 a medium effect and 5.10 as a large effect, corresponding to the effect sizes of 0.2, 0.5 and 0.9 for small, medium and large effects for continuous outcomes (Chin, 2000). Strength of evidence (SOE) was rated, similarly to the systematic review, on the following scale: insufficient/very low, low, moderate and high. See the methods section for an explanation of the factors that determined SOE ratings.

¹⁵ The number of articles for each outcome for benefits and for harms/burdens can be found in the decision tables for each intervention, in Appendix D.

¹⁶ Based on additional literature review conducted by APA staff to further review harms. This applies to each time this is stated in this and subsequent tables.

Processing Therapy	recommends that clinicians offer cognitive processing therapy compared to no intervention.	<p>of a medium to large magnitude benefit for the critical outcome of PTSD symptom reduction.</p> <ul style="list-style-type: none"> • There is moderate strength of evidence of a medium to large magnitude benefit for two additional important outcomes: loss of PTSD diagnosis and prevention/reduction of comorbid depression. • There was insufficient/very low strength of evidence for the critical outcome of serious harms. The panel found no other interpretable evidence of serious harms. • Benefits clearly outweigh harms/burdens. • Patient values and preferences were considered but owing to low certainty did not substantially factor into the recommendation. • There is no evidence that raises concern about applicability.
#3: Efficacy of Cognitive Therapy	Among adult patients with PTSD, the panel strongly recommends that clinicians offer cognitive therapy compared to no intervention.	<ul style="list-style-type: none"> • There is moderate strength of evidence of a medium to large magnitude benefit for the critical outcome of PTSD symptom reduction. • There is moderate strength of evidence of a medium to large magnitude benefit for four additional important outcomes: loss of PTSD diagnosis, prevention/reduction of comorbid depression, prevention/reduction of comorbid anxiety, and disability or functional impairment. • There is moderate strength of evidence of a small magnitude benefit for one additional important outcome: the physical component of quality of life. • There was insufficient/very low strength of evidence for the critical outcome of serious harms. The panel found no other interpretable evidence of serious harms. • Benefits clearly outweigh harms/burdens. • Patient values and preferences were considered but owing to low certainty did not substantially factor into the recommendation. • There is no evidence that raises concern

		about applicability.
#4: Efficacy of Prolonged Exposure	Among adult patients with PTSD, the panel strongly recommends that clinicians offer prolonged exposure therapy compared to no intervention.	<ul style="list-style-type: none"> • There is high strength of evidence of a medium to large magnitude benefit for the critical outcome of PTSD symptom reduction. • There is high strength of evidence of a medium to large magnitude benefit for one additional important outcome: prevention/reduction of comorbid depression and moderate strength of evidence of a medium to large magnitude of benefit for one additional important outcome: loss of PTSD diagnosis. • There was insufficient/very low strength of evidence for the critical outcome of serious harms. The panel found no other interpretable evidence of serious harms. There was low strength of evidence that prolonged exposure therapy is associated with increases in PTSD symptoms in some patients. • Benefits clearly outweigh harms/burdens. • Patient values and preferences were considered but owing to low certainty did not substantially factor into the recommendation. • There is no evidence that raises concern about applicability.
#5: Efficacy of Brief Eclectic Psychotherapy	Among adult patients with PTSD, the panel suggests that clinicians offer brief eclectic psychotherapy compared to no intervention.	<ul style="list-style-type: none"> • There is low strength of evidence of a small magnitude benefit for the critical outcome of PTSD symptom reduction. • There is low strength of evidence of a medium to large magnitude benefit for two additional important outcomes: prevention/reduction of comorbid depression and prevention/reduction of comorbid anxiety) and low strength of evidence of a small magnitude benefit for loss of PTSD diagnosis • There was insufficient/very low strength of evidence for the critical outcome of serious harms. The panel found no other interpretable evidence of serious harms. • Benefits slightly outweigh harms/burdens. • Patient values and preferences were considered but owing to low certainty did not substantially factor into the

		<p>recommendation.</p> <ul style="list-style-type: none"> • There is no evidence that raises concern about applicability.
#6: Efficacy of Eye Movement Desensitization and Reprocessing Therapy	Among adult patients with PTSD, the panel suggests that clinicians offer EMDR compared to no intervention. ¹⁷	<ul style="list-style-type: none"> • There is low strength of evidence of a medium to large magnitude benefit for the critical outcome of PTSD symptom reduction. • There is moderate strength of evidence of a medium to large magnitude benefit for two additional important outcomes: loss of PTSD diagnosis and prevention/reduction of comorbid depression. • There was insufficient/very low strength of evidence for the critical outcome of serious harms. The panel found no other interpretable evidence of serious harms. • Benefits clearly outweigh harms/burdens. • Patient values and preferences were considered but owing to low certainty did not substantially factor into the recommendation. • There is no evidence that raises concern about applicability.
#7: Efficacy of Narrative Exposure Therapy	Among adult patients with PTSD, the panel suggests that clinicians offer narrative exposure therapy compared to no intervention. ¹⁸	<ul style="list-style-type: none"> • There is moderate strength of evidence of a medium to large magnitude benefit for the critical outcome of PTSD symptom reduction. • There is low strength of evidence of a small magnitude benefit for one additional important outcome: loss of PTSD diagnosis. • There was insufficient/very low strength of evidence for the critical outcome of serious harms. The panel found no other interpretable evidence of serious harms. • Benefits clearly outweigh harms/burdens. • Patient values and preferences were considered but owing to low certainty did not substantially factor into the

¹⁷ EMDR received a conditional recommendation because of low strength of evidence for the critical outcome of PTSD symptom reduction. All interventions that received a strong recommendation by the panel had at least moderate strength of evidence for PTSD symptom reduction and also at least moderate strength of evidence for other important outcomes, such as remission or loss of PTSD diagnosis.

¹⁸ Narrative Exposure Therapy received a conditional recommendation, despite evidence of a large/medium magnitude of benefit for the critical outcome of PTSD symptom reduction, because there was low or insufficient/very low strength of evidence for all other important benefit outcomes. All interventions that received a strong recommendation by the panel had at least moderate strength of evidence for PTSD symptom reduction and also at least moderate strength of evidence for other important outcomes, such as remission or loss of PTSD diagnosis or reduction/prevention of comorbid depression.

		<p>recommendation.</p> <ul style="list-style-type: none"> • There is no evidence that raises concern about applicability.
#8: Efficacy of Relaxation	<p>Among adult patients with PTSD, the panel concludes that the evidence is insufficient to recommend for or against clinicians offering relaxation compared to inactive treatment.</p>	<ul style="list-style-type: none"> • There is insufficient/very low strength evidence of a benefit for the critical outcome of PTSD symptom reduction. • There was insufficient/very low strength of evidence for the critical outcome of serious harms. The panel found no other interpretable evidence of serious harms. • The panel is unable to evaluate benefits vs. harms/burdens. • Patient values and preferences were considered but owing to unknown variability and moderate certainty, did not substantially factor into the recommendation. • There is no evidence that raises concern about applicability.

Table 5b. *Efficacy of Pharmacological Interventions Compared to No Intervention*¹⁹

Topic:	Recommendation:	Summary Rationale Statement ²⁰ :
#9: Efficacy of Fluoxetine	Among adult patients with PTSD, the panel suggests that clinicians offer fluoxetine compared to no intervention.	<ul style="list-style-type: none"> • There is moderate strength of evidence of a small magnitude benefit for the critical outcome of PTSD symptom reduction.²¹ • There is moderate strength of evidence of a small to large magnitude benefit for two additional important outcomes: prevention/reduction of comorbid depression and prevention/reduction of comorbid anxiety. • There was low strength of evidence of a small harm/burden for the critical outcome of serious harms. The panel found no other interpretable evidence of serious harms. • Benefits slightly outweigh harms/burdens. • Patient values and preferences were considered but owing to low certainty did not substantially factor into the recommendation. • There is no evidence that raises concern about applicability.
#10: Efficacy of Paroxetine	Among adult patients with PTSD, the panel suggests that clinicians offer paroxetine compared to no intervention.	<ul style="list-style-type: none"> • There is moderate strength of evidence of a small magnitude benefit for the critical outcome of PTSD symptom reduction. • There is moderate strength of evidence of a medium to large magnitude benefit for one additional important outcome: remission. • There is moderate strength of evidence of a small magnitude benefit for two additional important outcomes: prevention/reduction of comorbid depression and disability/functional impairment. • There was moderate strength of

¹⁹ These recommendations are framed as pharmacological intervention compared to no treatment, because that is a decision that clinicians face, but they are based on the systematic review of randomized trials comparing pharmacological interventions to placebo.

²⁰ Magnitude of benefit indicates the size of the effect and is based on standardized mean differences (SMDs), rated using the same criteria as the systematic review: approximately 0.2 or less was rated as a small effect, 0.5 as a medium effect, and 0.9 or greater as a large effect. Strength of evidence (SOE) was rated, similarly to the systematic review, on the following scale: insufficient/very low, low, moderate and high. See the methods section for an explanation of the factors that determined SOE ratings.

²¹ The number of articles for each outcome for benefits and for harms/burdens can be found in the decision tables for each intervention, in Appendix D.

		<p>evidence for no effect of the critical outcome of serious harms. The panel found no other interpretable evidence of serious harms.</p> <ul style="list-style-type: none"> • Benefits clearly outweigh harms/burdens. • Patient values and preferences were considered but owing to low certainty did not substantially factor into the recommendation. • There is no evidence that raises concern about applicability.
#11: Efficacy of Sertraline	Among adult patients with PTSD, the panel suggests that clinicians offer sertraline compared to no intervention.	<ul style="list-style-type: none"> • There is moderate strength of evidence of a small magnitude benefit for the critical outcome of PTSD symptom reduction. There is low strength of evidence of no effect for one additional important outcome: prevention/reduction of comorbid depression. • There was low strength of evidence of a small magnitude harm/burden for the critical outcome of serious harms. The panel found no other interpretable evidence of serious harms. • Benefits slightly outweigh harms/burdens. • Patient values and preferences were considered but owing to low certainty did not substantially factor into the recommendation. • There is no evidence that raises concern about applicability.
#13: Efficacy of Venlafaxine	Among adult patients with PTSD, the panel suggests that clinicians offer venlafaxine compared to no intervention.	<ul style="list-style-type: none"> • There is moderate strength of evidence of a small magnitude of benefit for the critical outcome of PTSD symptom reduction. There is moderate strength of evidence of a medium to large magnitude benefit for one additional important outcome: remission. • There was low strength of evidence of no effect for the critical outcome of serious harms. The panel found no other interpretable evidence of serious harms. • Benefits slightly outweigh harms/burdens. • Patient values and preferences were considered but owing to low certainty did not substantially factor into the recommendation. • There is no evidence that raises concern

		about applicability.
#14: Efficacy of Risperidone	Among adult patients with PTSD, the panel concludes that the evidence is insufficient to recommend for or against clinicians offering risperidone compared to no intervention.	<ul style="list-style-type: none"> • There is low strength of evidence of a small magnitude benefit for the critical outcome of PTSD symptom reduction. • There was insufficient/very low strength of evidence for the critical outcome of serious harms. The panel found no other interpretable evidence of serious harms. • Benefits and harms/ burdens are balanced. • Patient values and preferences were considered but owing to low certainty did not substantially factor into the recommendation. • There is no evidence that raises concern about applicability.
#12: Efficacy of Topiramate	Among adult patients with PTSD, the panel concludes that the evidence is insufficient to recommend for or against clinicians offering topiramate compared to no intervention. ²²	<ul style="list-style-type: none"> • There is moderate strength of evidence of a medium to large magnitude benefit for the critical outcome of PTSD symptom reduction. • There was insufficient/very low strength of evidence for all other benefit outcomes. • There was insufficient/very low strength of evidence for the critical outcome of serious harms. The panel found no other interpretable evidence of serious harms. • Benefits and harms/ burdens are balanced. • Patient values and preferences were considered but owing to low certainty did not substantially factor into the recommendation. • There is no evidence that raises concern about applicability.

²² Topiramate received an insufficient recommendation, despite the moderate strength of evidence of a medium to large magnitude benefit for the critical outcome of PTSD symptom reduction, primarily because the severity of the adverse effects; this led the panel to conclude that there was a balance of benefits to harms. The strength of evidence for those adverse effects was insufficient / very low, as for adverse effects for other treatments, because some of that evidence was from non-randomized studies and input from clinicians on the panel. However, those adverse effects, primarily CNS effects (e.g., memory difficulties, dizziness, somnolence) were thought to be more serious and more common than adverse effects for other medications that received substantive recommendations from the panel.

Table 5c. *Comparative Effectiveness of Psychological Interventions and of Pharmacological Interventions*

Topic:	Recommendation:	Summary Rationale Statement ²³ :
#15: Prolonged Exposure Therapy vs. Relaxation	Among adult patients with PTSD, the panel suggests clinicians offer prolonged exposure therapy rather than relaxation when both prolonged exposure therapy and relaxation are being considered.	<ul style="list-style-type: none"> • There is insufficient/very low strength of evidence that the critical outcome of PTSD symptom reduction is the same in prolonged exposure based therapy and relaxation therapy²⁴. • There is moderate strength of evidence of a medium to large magnitude benefit of prolonged exposure relative to relaxation for one additional important outcome: loss of PTSD diagnosis. • There is moderate strength of evidence of a small magnitude benefit of prolonged exposure relative to relaxation for one additional important outcome: prevention/reduction of comorbid depression. • There was insufficient/very low strength of evidence for the critical outcome of serious harms. The panel found no other interpretable evidence of serious harms. • Balance of benefits to harms/burdens slightly favors prolonged exposure over relaxation. • Patient values and preferences were considered but owing to low certainty did not substantially factor into the recommendation. • There is no evidence that raises concern about applicability.
#16: Prolonged Exposure vs. Prolonged Exposure Plus Cognitive Restructuring	Among adult patients with PTSD, the panel recommends clinicians offer either prolonged exposure or exposure plus cognitive restructuring when both are being considered.	<ul style="list-style-type: none"> • There is insufficient/very low strength of evidence that the critical outcome of PTSD symptom reduction is the same in prolonged exposure and prolonged exposure plus cognitive restructuring. • There is moderate strength of evidence that loss of PTSD diagnosis is the same in exposure and exposure plus cognitive restructuring. • There was insufficient/very low strength

²³ Magnitude of benefit indicates the size of the effect and is based on standardized mean differences (SMDs), rated using the same criteria as the systematic review: approximately 0.2 or less was rated as a small effect, 0.5 as a medium effect, and 0.9 or greater as a large effect. Strength of evidence (SOE) was rated, similarly to the systematic review, on the following scale: insufficient/very low, low, moderate and high. See the methods section for an explanation of the factors that determined SOE ratings.

²⁴ The number of articles for each outcome for benefits and for harms/burdens can be found in the decision tables for each intervention, in Appendix D.

		<p>of evidence for the critical outcome of serious harms. The panel found no other interpretable evidence of serious harms.</p> <ul style="list-style-type: none"> • Balance of benefits to harms/burdens is the same for prolonged exposure as prolonged exposure plus cognitive restructuring. • Patient values and preferences were considered but owing to low certainty did not substantially factor into the recommendation. • There is no evidence that raises concern about applicability.
#17: Cognitive Behavioral Therapy vs. Relaxation	Among adult patients with PTSD, the panel suggests clinicians offer CBT rather than relaxation when both CBT and relaxation are being considered.	<ul style="list-style-type: none"> • There is low to moderate strength of evidence of a medium to large magnitude benefit for CBT compared to relaxation for the critical outcome of PTSD symptom reduction. • There was insufficient/very low strength of evidence for the critical outcome of serious harms. The panel found no other interpretable evidence of serious harms. • Balance of benefits to harms/burdens clearly favors CBT over relaxation. • Patient values and preferences were considered but owing to low certainty did not substantially factor into the recommendation. • There is no evidence that raises concern about applicability.
#18: Seeking Safety ²⁵ vs. active controls	Among adult patients with PTSD, the panel concludes that the evidence is insufficient to recommend for or against clinicians offering Seeking Safety versus active controls.	<ul style="list-style-type: none"> • There is moderate strength of evidence that the critical outcome of PTSD symptom reduction is the same in Seeking Safety and active controls. • There was insufficient/very low strength of evidence for the critical outcome of serious harms. The panel found no other interpretable evidence of serious harms. • Balance of benefits to harms/burdens is the same for Seeking Safety as active controls. • Patient values and preferences were considered but owing to low certainty did not substantially factor into the

²⁵ Active controls received cognitive therapy that addressed only substance abuse relapse prevention (Hien, Cohen, Miele, Litt and Capstick, 2004) or a manualized women’s health education intervention “without explicit focus or psychoeducation specific to substance abuse or trauma” (Hien et. al., 2009) or substance abuse treatment that was “abstinence-oriented, focused on the 12-step model (Alcohol Anonymous, Cocaine Anonymous, Narcotics Anonymous), and took place in a psychoeducational large-group format, with weekly individual case management and drug counseling” (Zlotnick, Johnson and Najavits, 2009).”

		<p>recommendation.</p> <ul style="list-style-type: none"> • There is no evidence that raises concern about applicability.
#19: Venlafaxine ER vs. Sertraline	<p>Among adult patients with PTSD, the panel recommends clinicians offering either venlafaxine ER or sertraline when both are being considered.²⁶</p>	<ul style="list-style-type: none"> • There is moderate strength of evidence that the critical outcome of PTSD symptom reduction is the same in venlafaxine ER and sertraline. • There is low to moderate strength of evidence that four additional outcomes (remission, prevention/reduction of comorbid depression, quality of life, disability/functional impairment) were the same in venlafaxine ER and sertraline.²⁷ • There was insufficient/very low strength of evidence for the critical outcome of serious harms for both treatments. The panel found no other interpretable evidence of serious harms. • Balance of benefits to harms/burdens is the same for Venlafaxine ER as Sertraline. • Patient values and preferences were considered but owing to low certainty did not substantially factor into the recommendation. • There is no evidence that raises concern about applicability.

How these recommendations compare to recommendations in other PTSD guidelines is addressed in the Discussion section.

Impact of New Trials on Recommendations

²⁶ The recommendation for the comparison between venlafaxine ER vs sertraline is different than the recommendation for Seeking Safety vs active controls, even though there is moderate evidence of no difference between the two treatments being compared for both comparisons (i.e., venlafaxine ER vs sertraline and Seeking Safety vs active controls). The reason the recommendations are different for venlafaxine ER vs sertraline than for Seeking Safety vs active controls is that the panel made a conditional recommendation for venlafaxine compared to no intervention and a conditional recommendation for sertraline compared to no intervention but did not make any recommendations for Seeking Safety compared to no intervention or active controls compared to no intervention because there was insufficient/very low evidence. In other words, the panel believed that because there was evidence that both venlafaxine and sertraline had demonstrated efficacy compared to inactive intervention, it was reasonable to recommend either treatment when both are being considered. However, because neither Seeking Safety nor active controls had demonstrated efficacy compared to no intervention, the panel concluded that evidence was insufficient to recommend for or against either treatment.

²⁷ In the summary rationale statements for treatment recommendations in these tables, the panel used the SOE ratings that had been assigned by the systematic review to describe individual outcomes. When more than one outcome is described in the same sentence in these rationale statements, the panel used a range of strengths of evidence when the strengths for different outcomes were different. For Venlafaxine ER vs sertraline, the SOE for prevention/reduction of comorbid depression was low and SOE for PTSD remission, quality of life and disability/functional impairment was moderate. Accordingly, in the rationale statement, the panel states that for those outcomes, "There is low to moderate evidence."

Introduction

The search process for the RTI-UNC Systematic Review that the panel used as the evidence base for its recommendations ended on May 24, 2012. For multiple reasons, it was not feasible for the panel to conduct an entirely new systematic review on RCTs that were published thereafter and then re-do the decision tables based on the updated evidence. But, because of the time lag and the possibility that new evidence was available that might impact its recommendations, panel members decided it was important to conduct a comprehensive literature review to identify recent RCTs germane to the comparisons evaluated in this report. Following the process described below on the methodology, a subcommittee of the panel consisting of five members²⁸ volunteered and assessed the potential impact of those new RCTs on its recommendations. They then presented their assessment to the entire panel for discussion and decision-making.

Methodology

The overall goal of this search process was to identify RCTs of interventions that would have been included in the systematic review if they had been published during the systematic review time frame (January 1, 1980 to May 24, 2012). The inclusion and exclusion criteria used by the panel for this search process are shown in Table 7 of the Appendices. These criteria differ from the criteria used by the systematic review (Jonas et al., 2013, p 11 – 12) in two ways: 1) the panel did not search for observational studies to assess harms; 2) the panel focused only on PTSD symptom reduction, since that critical outcome was a primary (though not only) determinant of the panel's recommendations.

The research librarian at the APA (D.H.) conducted a comprehensive search of the databases used in the systematic review: Medline, Cochrane, International Pharmaceutical Abstracts (IPA), The Cumulative Index to Nursing and Allied Health Literature (CINAHL), PsychINFO, Web of Science, and Excerpta Medica database (EMBASE). The librarian used the

²⁸ Drs. Cook, Courtois, Fairbank and Sonis, and Ms. Schulz.

same search terms used by systematic review (Jonas et al., 2013, Appendix H) with the following exceptions:

1. Dates: May 25, 2012 to June 1, 2016
2. The search terms for cohort studies, case control studies, and cross sectional studies were excluded because the goal was to search only for RCTs. (The systematic review included study designs other than RCTs only for data on adverse effects).

The librarian also searched the same databases for systematic reviews and meta-analyses of treatment of adult PTSD published between May 25, 2012 and June 1, 2016, using the same search terms as the systematic review. One member of this panel then conducted a manual search of the references lists of those publications to identify randomized trials that might meet inclusion criteria.

The panel did not search for unpublished trials or dissertations. Trials that investigated complementary and alternative medicine interventions and articles published in languages other than English were not eligible for inclusion in the systematic review and therefore were not included in this subsequent review.

The disposition of the database and systematic review / meta-analysis reference list search is shown in Figure 1, in the Appendices. The titles and abstracts of all articles that were identified through the database search (n=947) were reviewed, independently, by two trained research assistants and one of two experienced researchers to determine whether they might meet inclusion criteria. Articles that were identified as possibly meeting inclusion criteria (n = 129) were subjected to full-text search by one of two experienced researchers to determine whether inclusion or exclusion criteria used by the systematic review were met. Disagreements at the full-text review stage were resolved by consensus, or, if necessary, votes from a five-member subcommittee of the panel. All of the trials identified through search of reference lists of meta-analyses and systematic reviews (n = 6) were subjected to full-text review. Common reasons for exclusion at the full-text review stage were:

1. No original data on the effect of a treatment on an outcome (e.g., protocol for a trial)
2. Incompatible study design: case series, open trial without randomization, cohort analysis of a subset of trial participants, such as responders, etc.
3. Incompatible population: PTSD diagnosis not required for inclusion in the trial, subthreshold PTSD (i.e., not meeting full criteria for the diagnosis), persons exposed to trauma but not diagnosed with PTSD, unpublished instrument with unknown psychometric properties used for PTSD diagnosis, participants not required to be greater than 18 years of age and others.
4. Incompatible intervention: Any intervention other than those listed in inclusion criteria.
5. Incompatible outcome: Any outcome other than PTSD symptom reduction.
6. Incompatible duration: Time between study entry and outcome assessment not reported as greater than or equal to 4 weeks.

The full-text review determined whether a trial met inclusion criteria shown in Table 6. The intervention and comparators in each of those included trials was then compared to the intervention and comparators for each of the panel recommendations to determine whether there was a match. For instance, van den Berg et al. (2015) matched to the recommendation on the efficacy of prolonged exposure (compared to controls), based on one treatment arm of prolonged exposure and one treatment arm of wait-list control. On the other hand, Spence et al. (2014) was not considered a match of the panel recommendation for prolonged exposure because one treatment arm consisted of prolonged exposure plus psychoeducation plus stress management plus cognitive restructuring while the other treatment arm consisted of all of those components without prolonged exposure. In one sense, it could be considered a comparison of prolonged exposure to no treatment (since the treatments other than prolonged exposure were the same in both treatment arms) but in a more accurate sense, it is a trial of adding prolonged exposure to those other components, a comparison for which the panel did not make a recommendation. To be consistent with the systematic review, the panel did not consider internet implementation of a treatment (such as the trial that evaluated internet application of

CBT (Ivarsson et al., 2014) or group forms of a treatment (such as Resick's trial of group CPT (Resick et al., 2015) as new treatments but simply variants of the original treatment. Those trials were, therefore, considered as matches for the recommendations for efficacy of CBT and efficacy of CPT, respectively. On the other hand, if a trial specifically compared a new form of implementation modality for a treatment (e.g., CPT via video conferencing compared to CPT in person; Morland et al., 2014), the trial was not considered a match for the recommendation of the treatment, CPT, since that comparison specifically tests mode of implementation (video conferencing vs. in-person) rather than treatment itself.

For each of the original recommendations matched by one or more of the trials identified by the new search, the panel subcommittee assessed whether the recommendation was likely to change on the basis of the new evidence or was unlikely to change. To make this decision, the panel compared the effect sizes (Cohen's *d*) for PTSD symptom reduction in the new trials for that recommendation to the SMD for PTSD symptom reduction from the systematic review, for that same recommendation. Cohen's *d* for the new trials was based on the effect sizes for PTSD symptom reduction reported in the published articles. If Cohen's *d* was not reported in the article, it was calculated, based on standard formulas (Thalheimer & Cook, 2002). Because confidence intervals around the estimated effect sizes were rarely reported, the panel used the sample size in each study as a proxy for the precision (i.e., confidence interval width) of the effect size precision.

As in the deliberations by the full panel for the decision tables, effect sizes were characterized initially as small (0.2), medium (0.5) and large (0.9), but were categorized as small or medium / large (i.e., medium and large effect sizes were considered together as one category) for decision making about the magnitude of benefits. All effect sizes for efficacy comparisons (i.e., active intervention compared to a control comparator) were reported as positive numbers if the result favored the active intervention (i.e., if the group randomized to active intervention had greater PTSD symptom reduction than those randomized to controls).

Negative effect sizes indicate that the control group had greater reductions in PTSD symptoms than those in the active intervention group. For comparative effectiveness comparisons in which two active interventions were compared, effect sizes were reported as positive when the participants allocated to the first listed intervention had greater improvement in PTSD symptom reduction than those who were allocated to the second intervention.

The panel did not have the time or resources to assess risk of bias for the newly identified individual trials. The panel members recognized that this lack of risk of bias assessment placed significant bounds on the certainty with which conclusions could be drawn since any one or more of the new trials might be rated high risk of bias and therefore not included in future meta-analyses. However, if all of the effect sizes for a group of trials that matched to a recommendation were on the same side of the null (i.e., favoring one intervention versus a comparator) or if all of the effect sizes were not only on the same side of the null but were of comparable magnitude, then even if one or more of the trials were rated high risk of bias, the conclusions would be unlikely to change.

Results

Of the 129 articles evaluated by full-text review, 26 met inclusion criteria. Nineteen of the twenty six matched one recommendation and one (van den Berg et al., 2015) matched two recommendation statements, one for efficacy of prolonged exposure vs. control and one for efficacy of EMDR vs. control. Appendix G shows articles that met inclusion criteria and matched a recommendation. Six of those that met inclusion criteria matched to an evidence profile but not a recommendation statement and are not discussed further. (As described above in this report, the panel did not complete decision tables or make recommendations for interventions for which the strength of evidence was very low or insufficient). Appendix H shows articles that met inclusion criteria and matched an evidence profile but not a recommendation.

There were 104 articles of the 129 that underwent full-text review, that were excluded, for the reasons shown in Figure 1, in the Appendix. The trials that were excluded are shown in the Appendix J, by reason for exclusion.

Table 6 summarizes the impact of the new trials on the panel's recommendations. Tables 7-16 (Appendix F) provide detailed information about the effect sizes for PTSD symptom reduction in the new trials compared to the summary effect size from the systematic review. They also show panel members' reasoning supporting the conclusion about the effect of the new trials on the recommendations.

The strong recommendations for the following psychological interventions compared to controls were unlikely to change, based on the new trials: CBT, CPT, CT, and PE (Table 6). There is insufficient information to determine whether the conditional recommendation for EMDR, compared to inactive controls, would be likely to change based on the new trials (Table 6). The one new trial identified (van der Berg, 2015) reported a medium effect size for PTSD symptom reduction and included a sample nearly equivalent to the sample size from all of the trials, in toto, from the systematic review. It is possible that the strength of evidence for PTSD symptom reduction could be upgraded from low to moderate, if a meta-analysis incorporating the van der Berg trial were done, due to improved precision. However, because none of the studies identified in the search update process were rated for risk of bias, the panel was reluctant to conclude, with certainty, that strength of evidence for PTSD symptom reduction would be upgraded to moderate. Accordingly, the panel decided to maintain its conditional recommendation for EMDR, with the caveat that there is greater uncertainty about this recommendation than for other recommendations and with future meta-analysis the recommendation could be strong.

There were no new trials available for brief eclectic psychotherapy or relaxation, compared to controls. The panel determined there is insufficient evidence available to determine whether the conditional recommendation for NET would change based on the evidence from

new trials (Table 13). The effect size for PTSD symptom reduction was medium / large in the systematic review and in the new trials. In its original deliberations on NET, the panel concluded that unlike other treatments for which strong recommendations were being made, there was only low strength of evidence for other important outcomes for NET which is why NET received a conditional rather than a strong recommendation. Since the effect size for PTSD symptom reduction is unlikely to change from medium / large based on the new trials and the panel did not have information on other important outcomes for NET from the new trials (the data on which a change in the recommendation strength might hinge), the panel concluded that there is insufficient evidence to determine whether the conditional recommendation for NET efficacy is likely to change to strong. Accordingly, the panel decided to maintain its conditional recommendation for NET, however with the caveat that there is greater uncertainty about this recommendation than for other recommendations.

The recommendation that the evidence was insufficient to determine the efficacy of topiramate, compared to placebo, was unlikely to change based on the new trials. There were no new trials that assessed efficacy of fluoxetine, paroxetine, sertraline, or venlafaxine, or risperidone.

For comparative effectiveness recommendations, the following recommendations are unlikely to change based on evidence from the new trials: the recommendation of prolonged exposure instead of relaxation and the suggestion that clinicians offer prolonged exposure or prolonged exposure plus cognitive restructuring. There were no new trials available for comparative effectiveness recommendations for CBT vs. relaxation, Seeking Safety vs. active controls, and venlafaxine ER vs. sertraline.

Discussion

None of the panel's recommendations originally made on the basis of evidence from the RTI-UNC Systematic Review are likely to change as a result of new evidence from randomized

trials published between May 25, 2012 and June 1, 2016, with the possible exceptions of EMDR and NET. As shown in the detailed tables for each recommendation, the effect sizes in the new trials for PTSD symptom reduction were generally similar in magnitude and direction to the SMDs for PTSD symptom reduction from the trials included in the systematic review.

These conclusions must be tempered by several limitations. First, the panel did not rate trials for risk of bias. It is possible that the findings would be different if risk of bias ratings were conducted on the new trials. However, the panel believes that this is unlikely because most of the effect estimates were grossly similar in magnitude (small vs medium/large) and almost all were in the same direction as the SMDs for PTSD symptom reduction from the systematic review. Further, in the systematic review, when sensitivity analyses were conducted by adding into the meta-analysis those trials that were rated high risk of bias, they “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.” (Jonas et al, 2013; p ES-16).

Second, although the panel conducted a rigorous search of the literature using the same terms and the same databases as the systematic review, it is possible that relevant published trials were missed. Unlike what was done in the systematic review, the panel did not search for unpublished studies or the grey literature. However, inclusion of unpublished studies is not without controversy, since some believe that it can introduce bias into systematic reviews (Egger, Juni, Bartlett, Hoenstein & Sterne, 2003).

Third, it was sometimes difficult for the panel to determine whether an intervention in a new trial should have been considered a minor modification of an intervention for which the panel made a recommendation (and thus included in the new trials to compare to the recommendation) or whether it should have been considered a completely new intervention and thus not included in the trials compared to the recommendation. These ambiguous trials were discussed by the panel subcommittee and disagreement was resolved by consensus. While it is

possible that other reviewers would have come to different conclusions about those trials, it is unlikely to have had a substantial impact on the overall conclusions since there were relatively few of those trials.

Fourth, for this search update process, the panel looked only at the outcome of PTSD symptom reduction because it was the only critical benefit outcome and, as such, was a major determinant of the panel's recommendations. Important but not critical benefit outcomes, including PTSD remission, quality of life, functional impairment, prevention or reduction of comorbid medical conditions and others, were not assessed in this update process. For most recommendations, this absence is unlikely to have had a major impact on the panel's decision about the likelihood that the recommendation would change based on the new trials. However, for NET, the effect size for PTSD symptom reduction in the systematic review was large and it was the absence of at least moderate evidence for other benefit outcomes that led the panel to make a conditional rather than strong recommendation. The effect sizes from the new trials for PTSD symptom reduction for NET are similar to the SMD from the systematic review, but it is possible that evidence on other important outcomes, could lead the panel to conclude that the recommendation might change.

Fifth, because serious harms were rarely reported in trials of psychological interventions included in the systematic review, the panel made the decision to not search for serious harms in the new trials. It therefore could not include them in its deliberations about the likelihood that recommendations would change based on evidence from the new trials. Moreover, the panel believed it unlikely that serious harms not reported in the trials included in the systematic review would be detected and reported in the new trials.

Overall, with the exception of the recommendations for NET and EMDR, the findings from this search update process indicate that the panel's recommendations would be unlikely to change if the meta-analyses reported in the systematic review were updated to include the new trials. The recommendations might change based on future trials, but the panel is confident that,

based on the trials published to June 1, 2016, the recommendations proffered by the panel on the specific interventions discussed in this guideline, with the possible exceptions of NET and EMDR, are up to date.

Table 6. *Effect of New Trials on Recommendations*

Recommendation	Strength and direction of recommendation	Effect of new trials on recommendation
#1: Efficacy of Cognitive Behavior Therapy	Strong for	Recommendation unlikely to change
#2: Efficacy of Cognitive Processing Therapy	Strong for	Recommendation unlikely to change
#3: Efficacy of Cognitive Therapy	Strong for	Recommendation unlikely to change
#4: Efficacy of Prolonged Exposure	Strong for	Recommendation unlikely to change
#5: Efficacy of Brief Eclectic Psychotherapy	Conditional for	No new trials for comparison
#6: Efficacy of Eye Movement Desensitization and Reprocessing Therapy	Conditional for	Insufficient evidence
#7: Efficacy of Narrative Exposure Therapy	Conditional for	Insufficient evidence
#8: Efficacy of Relaxation	Conditional for	No new trials for comparison
#9: Efficacy of Fluoxetine	Conditional for	No new trials for comparison
#10 Efficacy of Paroxetine	Conditional for	No new trials for comparison
#11 Efficacy of Sertraline	Conditional for	No new trials for comparison
Recommendation	Strength and direction of recommendation	Effect of new trials on recommendation
#12 Efficacy of Topiramate	Evidence is insufficient to recommend for or against	Recommendation unlikely to change
#13: Efficacy of Venlafaxine	Conditional for	No new trials for comparison
#14: Efficacy of Risperidone	Evidence is insufficient to recommend for or against	No new trials for comparison
#15: Comparative effectiveness of Prolonged Exposure vs. Relaxation	Panel recommends prolonged exposure vs. relaxation	Recommendation unlikely to change
#16: Comparative effectiveness of	Panel suggests offering either	Recommendation unlikely to change

Prolonged Exposure vs. Prolonged Exposure Plus Cognitive Restructuring	prolonged exposure or prolonged exposure plus cognitive restructuring	
#17: Comparative effectiveness of Cognitive Behavior Therapy vs. Relaxation	Panel suggests offering CBT vs. relaxation	No new trials for comparison
#18: Comparative effectiveness of Seeking Safety vs. active controls	Evidence is insufficient to recommend for or against clinicians offering Seeking Safety versus active controls	No new trials for comparison
#19: Comparative effectiveness of Venlafaxine ER vs. Sertraline	Panel recommends clinicians offering either venlafaxine ER or sertraline	No new trials for comparison

All of these findings and recommendations have implications for treatment, discussed in the next section.

Considerations for Treatment Implementation

As detailed above, these recommendations for PTSD treatments were developed using rigorous processes promulgated by the Institute of Medicine and based on evidence from a strong and transparent systematic review conducted by RTI-UNC Evidence-based Practice Center (Jonas et al, 2013). In keeping with the tripartate evidence based approach that has been the APA standard (consisting of research evidence, clinician input and judgment, and patient preference and values (American Psychological Association, 2006), panel members recognize that psychotherapy is a complex endeavor and that important factors contribute to ethical and effective implementation of all treatments. Several of these, including informed consent, patient characteristics and patient-therapist relationship factors (also known as “common factors”) along with therapist competence and cultural, diversity, and socio-economic and demographic vulnerability issues and applicability are considered below.

Informed Consent

Patients benefit from receiving information about the treatments that are available and under consideration, including their effectiveness, the procedures and process involved, risk-benefits of each, and their practical as well as emotional demands. General informed consent discussion is suggested to occur at the beginning of psychotherapy or pharmacological treatment, as recommended by Bennett et al. (2006), and especially when a specialized technique is under consideration. Since PTSD is believed to result (in at least some instances) from the avoidance of painful trauma-related memories and emotions, it is suggested patients be specifically informed that most (if not all) recommended psychological treatments, especially those with the deepest evidence base for effectiveness, included in this guideline and others, involve some degree of directed exposure to the avoided material. This is with the specific goal of re-processing emotions and cognitions to the point of resolution and symptom reduction and remission. In working to achieve this goal, patients might feel worse for a period of time before beginning to feel better, something they should be informed about as part of the preparation for the treatment. However, they should also be informed that if feeling worse puts them at risk in any way (i.e., increases their rage and impulsivity, violence towards self or others, return to substances), the treatment may be overly stimulating. They should bring this up with their therapist who can then make adjustments in the pace or intensity of the treatment, stopping it altogether, or initiating a different treatment. Optimally, informed consent results in collaboration and shared decision-making between patient and provider over the entire course of the treatment, factors that have been identified as important to the success of treatment.

Role of Patient and Therapist Factors Relationship Factors in Treatments for PTSD

Panel members recognize there is a body of psychotherapy process research distinct from the research findings about efficacy of treatments that were the focus of the RTI-UNC Systematic Review and the basis for the guideline recommendations. This research has shown an association between *patient factors* and *patient-therapist factors* (including the treatment

relationship) and treatment outcome among persons with a variety of mental disorders, independent of the type of psychotherapy utilized. *Patient factors* associated with psychotherapy outcome include reactance level, stages of change, preferences, coping style, culture, personal characteristics, and religion/spirituality. *Relationship variables* associated with treatment outcome include therapeutic alliance, empathy, and the collection and utilization of patient feedback (for reviews, see Norcross, 2011; Norcross & Wampold, 2011). A detailed discussion is beyond the scope of this guideline; however, mention of these factors serves as a reminder that different sources of data are available about other aspects of psychotherapy that contribute to its success.

Patient factors such as hope and expectation for change, are likely components of most, though not all, therapeutic encounters and procedures. Many individuals with PTSD experience a great deal of hopelessness, despair, alienation, and cynicism and these issues influence how they approach treatment and relate to those perceived as authority figures. These issues, along with the patient's motivation, are issues that therapists should expect to encounter and be prepared to discuss and work with. Hope and positive expectancies may compare to the placebo effect that has been identified in pharmacotherapy trials for mental health disorders. A placebo effect occurs when an active medication is compared to an inert pill, and individuals who receive that inert pill experience or express improvement. Psychotherapies, like medications, have both specific effects as well as these non-specific effects on important outcomes.

Above and beyond their general applicability, there is a theoretical rationale for believing that the patient and relationship factors may be especially important in the psychotherapy of PTSD, especially when the trauma was interpersonal and/or occurred in the context of a significant relationship. Those with PTSD commonly have difficulties trusting others, a stance that impedes the development of sustaining relationships both within and outside of psychotherapy (Zubriggen, Gobin, & Kaehler, 2012). In addition, many empirical studies (e.g.,

Cloitre, Chase, Stovall-McClough, Regina, & Chemtob, 2004; Ormhaug, Jensen, Wentzel-Larsen, & Shirk, 2014; Wagner, Brand, Shulz, & Knaevelsrud, 2012) though not all (Forbes et al., 2008; van Minnen, Arntz, & Keijsers, 2002) that examined relationship variables in the treatment of adults with PTSD have shown that therapeutic alliance is associated with positive outcomes in treatment. A recent review of the literature specific to psychological treatment for trauma-related distress found that therapeutic alliance was predictive of or associated with a reduction in symptomology (Ellis, Simiola, Brown, Courtois, & Cook, under review). Accordingly, it is prudent for clinicians to be cognizant of these issues in psychotherapy with persons with PTSD. They may need to give extra attention to the development of the relationship, keeping in mind the mistrust that they may encounter.

Professional Competence

Ever accumulating research evidence documents that a high percentage of medical and mental health patients have had trauma experiences in their backgrounds that directly or indirectly relate to their reasons for seeking treatment (Felitti & Anda, 2010). At minimum, practitioners need to be aware of this possibility and approach patients from a perspective that is *trauma-informed* (for information on the trauma-informed care movement, see Clark, Classen, Fourt, & Shetty, 2015 and Falloot & Harris, 2001). A clinical consensus has emerged that the treatment of traumatized individuals requires specialized knowledge and skills on the part of the therapist or other practitioner regarding trauma and its psychology (see Cook, Newman, & The New Haven Trauma Competency Group, 2014 for a listing of five competency and several cross-cutting categories, each graded for different levels of practitioner expertise, from basic/expected of all staff to advanced/expected in expert trauma treatment practitioners). There is also clinical consensus that, in addition to proficiency in professional and foundational aspects of mental health care (APA, 2006; Barber et al., 2007a; Newman, 2010; Rodolfa et al., 2013), specialized training in specific techniques is needed before their application in clinical practice, whatever the focus of treatment. Research investigating training in particular treatment

modalities and adherence and fidelity to the application of those modalities is presently underway in a number of settings. Although there may be less need for specialized training in psychopharmacology management in general, a number of psychiatrists who specialize in psychopharmacological research and the treatment of the traumatized also find additional preparation and training helpful (due to the complexity of the symptom picture in PTSD and associated comorbid conditions and the variability in presentation and response to medication) (Friedman & Davidson, 2014).

Monitoring Treatment Response through Measurement Based Care

Measurement Based Care (MBC) is the practice of basing clinical care on patient data collected throughout treatment (Scott & Lewis, 2015). Although the use of MBC has received empirical support in the management of chronic medical illnesses (e.g., blood pressure, diabetes), it has not been widely investigated in mental health treatment and is not yet considered standard clinical practice (Harding, Rush, Arbuckle, Trivedi, & Pincus, 2011). Some research on the efficacy of measurement-based care for the treatment of depression exists (e.g., Guo et al., 2015), but there is little information on the use of detailed measurements across time with specified symptom severity scales in order to increase efficacy or quality of care for PTSD (a notable variation is the model developed by Briere and Lanktree that incorporates ongoing assessment and customization of treatment foci and goals as a basic component of their model (Briere & Lanktree, 2012). While the Department of Veterans Affairs (VA) recently developed a guideline and a mandate for measurement based care in mental health, including PTSD (Landes et al., 2015), there are not yet research data supporting this particular practice. Although monitoring PTSD symptoms across the course of treatment likely provides insight into progress and highlights ongoing clinical targets, research is needed to determine whether monitoring of PTSD symptoms improves patient outcomes. For those clinicians not providing a recommended evidence-based treatment, collecting systematic data on patient outcomes becomes imperative to not only demonstrate quality of care for the local

clinician-patient dyad but to contribute to the larger data base of outcome assessment for PTSD treatment.²⁹

Culture and Diversity Competence

Competence regarding culture and diversity involves the recognition that all humans have multiple and intersecting social identities based on variables such as, gender identity and gender expression, race, ethnicity, sexual orientation, socioeconomic class and sociodemographic characteristics, spiritual and religious identification, and linguistic status (among many others; Hays, 2015) that can be similar to or divergent from those of the therapist. Moreover, the variables associated with social, socio-economic, and sexual identities can reflect an accompanying diversity in lived and felt experience that is grounded in shared orientations, understandings, and preferences labeled as culture. In the context of clinical intervention, culturally grounded meanings and practices can afford therapeutic possibility even as they complicate whether and how patients find therapist actions and recommendations intelligible, useful, and worthwhile. Cultural and diversity competence (also called cultural humility—see Hunt, 2001) involves a willingness on the part of the practitioner to not only learn about the patient directly from the patient or from other sources of information but to also engage in ongoing self-reflection regarding the ability to be respectful and appreciative of differences and diversities while treating the patient (Comas-Diaz, 2012).

Many other issues are involved in addressing issues of culture and diversity, in general but especially as pertain to the traumatized. Brown (2008) and others have written extensively on the importance of integrating principles of cultural competence into trauma treatment that in turn apply to the utilization of evidence-based interventions for PTSD. She has particularly noted that barriers to treatment-- especially mistrust, access, socio-demographic characteristics, and culture and linguistics--should be recognized and addressed. These are important components

²⁹ Increasingly payers expect providers to demonstrate the quality of care through measurement of outcomes or participation in clinical data registries. Numerous tools have been developed that are appropriate for this purpose.

of the therapeutic relationship and context that support treatment. Issues of generalizability and applicability were addressed in this guideline but need ongoing attention in future research efforts. For further reading, see Brown (2008), Comas-Diaz (2012) and Hays (2015).

Discussion

How the APA PTSD Guideline Recommendations Are Similar to or Different from Other PTSD Guidelines

This APA PTSD treatment guideline a) strongly recommends the following as evidence-based psychotherapies for PTSD in adults: cognitive behavioral therapy (CBT), cognitive processing therapy (CPT), cognitive therapy (CT), and prolonged exposure therapy (PE) and b) suggests the use of brief eclectic psychotherapy (BEP), eye movement desensitization and reprocessing therapy (EMDR), and narrative exposure therapy (NET). With some exceptions, these conclusions are largely consistent with guideline recommendations previously published (in chronological order) by the Australian National Health and Medical Research Council (NHMRC, 2013, 2007), the World Health Organization (WHO, 2013), the US Department of Veterans Affairs/Department of Defense (VA/DoD, 2010), the International Society for Traumatic Stress Studies (ISTSS, 2009, 2000,), the UK National Institute for Health and Care Excellence (NICE, 2005), and the American Psychiatric Association (American Psychiatric Association, 2004).

Although some other guidelines prioritize treatments into those that are “first-line” or “second-line,” the APA panel chose not to use these terms in its recommendations because sufficient evidence from comparative effectiveness studies was lacking to justify their use. The panel does, however, offer strong recommendations for some PTSD treatments and conditional recommendations for others.

Forbes et al. (2010) described similarities and differences in recommendations for treatments for PTSD across the different guidelines. The 2010 VA/DoD guideline provides a strong recommendation for cognitive therapy, exposure therapy, stress inoculation training and

EMDR therapy, promoting these as first line treatments for PTSD in adults. Similarly, the 2009 ISTSS guideline gives A level ratings to exposure/ prolonged exposure, cognitive processing therapy, cognitive therapy, EMDR, Seeking Safety, and stress inoculation training. The 2007 NHMRC guideline recommends that adults with PTSD be offered trauma-focused CBT, EMDR, or *in vivo* exposure, and the 2005 NICE guideline recommends that 100% of individuals with PTSD be offered trauma-focused CBT or EMDR. The 2004 American Psychiatric Association guideline recommends CBT for treatment of PTSD with substantial clinical confidence (Category I), and recommends EMDR, stress inoculation therapy, imagery rehearsal, and exposure/ prolonged exposure with moderate clinical confidence (Category II). The 2013 WHO guideline does not give the highest recommendation in its grading system (i.e., “strong”) to any evidence-based psychotherapy for PTSD, but gives CBT with a trauma focus, EMDR, and stress management a standard recommendation -- a rubric indicating that there may be circumstances in which these treatments do not apply for persons with PTSD. All in all, the current effort contributes to the compendium of guidelines that recommend, with varying levels of strength and confidence, a core set of evidence-based psychotherapies for adults with PTSD: cognitive behavioral therapy, cognitive processing therapy, cognitive therapy, prolonged exposure therapy, brief eclectic psychotherapy, eye movement desensitization and reprocessing therapy and narrative exposure therapy. Although stress inoculation training was given an A-level rating by the 2008 ISTSS Guideline and Category II rating by the 2004 American Psychiatric Association Guideline, the panel is not including it in this core set of evidence-based psychotherapies because the RTI-UNC Systematic Review assigned a very low strength of evidence to stress inoculation training versus inactive controls. Consistent with its rule to complete decision tables and provide recommendations only on those interventions for which the strength of evidence was at least low, the panel did not complete a decision table or provide recommendations for stress inoculation therapy.

In terms of pharmacotherapy for PTSD in adults, the current APA PTSD guideline suggests the use of three from the class of selective serotonergic reuptake inhibitors (SSRIs), fluoxetine, paroxetine, or sertraline, as well as venlafaxine from the class of serotonin norepinephrine reuptake inhibitors (SNRIs). The conclusions from the current effort add to the pharmacotherapy recommendations from the PTSD guidelines previously published by the WHO, VA/DoD, ISTSS, NHMRC, NICE, and the American Psychiatric Association.

The 2013 WHO guideline offers the recommendation that the SSRIs and tricyclic antidepressants (TCAs) be considered under circumstances in which recommended psychotherapies (stress management, CBT with a trauma focus and EMDR therapy) have failed or are unavailable or when patients present with co-morbid depression of moderate or greater severity. Similarly, both the 2013 NHMRC and 2005 NICE guidelines caution that medications should not be used as a *routine* first-line treatment for adults with PTSD in either general medical or specialty mental health care, in preference to evidence-based trauma-focused psychotherapies. The NHMRC guideline specifies that where medication is considered, SSRI antidepressants should be the first choice and the other new generation antidepressants (notably mirtazapine) and TCAs should be considered as a second line options. The APA panel did not complete a decision table or make recommendations for tricyclic antidepressants because the strength of evidence was rated insufficient in the systematic review. Three RCTs were identified that were rated high risk of bias due to completer-only (instead of intention to treat) analysis or high attrition.

The 2010 VA/DoD guideline gives a strong recommendation to three SSRIs (paroxetine, sertraline, and fluoxetine) and the SNRI, venlafaxine, describing them as first line (Category I) treatments for PTSD in adults. Similarly, the 2004 American Psychiatric Association guideline recommends the SSRIs with substantial clinical confidence (Category I) for adults with PTSD, and the 2009 ISTSS guideline recommends the SSRIs (sertraline, paroxetine, and fluoxetine), venlafaxine, the TCAs, mirtazapine, nefazodone, phenelzine and prazosin as A-level treatments

that have accrued the best evidence. Medications rated by the 2010 VA/DoD guideline as having fair evidence and some benefit for treatment of PTSD in adults are mirtazapine, prazosin for sleep/nightmares, nefazodone, phenelzine, and the TCAs. The VA/DoD guideline rates several medications as ineffective or harmful; topiramate was rated as ineffective which is consistent with the recommendation in the current guideline. The panel did not complete decision tables or make recommendations for mirtazapine, nefazodone, phenelzine, or prazosin. The systematic review found insufficient/very low SOE for the critical outcome of PTSD symptom reduction and the important outcome of reduction of comorbid depression or anxiety for mirtazapine. There was one trial of nefazadone evaluated in the systematic review but it was rated high risk of bias. Although some guidelines have recommended prazosin for nightmares, the panel did not make any recommendations for prazosin because nightmares were not identified as a critical or important outcome (this should not be taken to suggest that they are not a significant hyperarousal symptom, nor that they are not important to address clinically). Additionally, the SOE for prazosin was rated insufficient/very low for PTSD symptom reduction (a critical outcome), or remission or loss of diagnosis (important outcomes).

The current effort expands upon previously published PTSD guidelines by including recommendations on comparative effectiveness of PTSD treatments. For example, among adult patients with PTSD, the current guideline suggests using prolonged exposure rather than relaxation when both prolonged exposure and relaxation are being considered. Similarly, the current guideline suggests using CBT rather than relaxation when both CBT and relaxation are under consideration, and either prolonged exposure or prolonged exposure plus cognitive restructuring when both are being considered. As more data on the comparative effectiveness of PTSD treatments become available, recommendations for treatments, based on the comparison of outcomes for efficacious treatments, will represent a major advancement for future updates of this guideline.

One of the key issues facing clinicians is whether to recommend psychological interventions or medication (or both) at the start of treatment for adults with PTSD. Only one trial (van der Kolk, 2007) comparing a psychological treatment to medication treatment was identified that met inclusion criteria and was medium or low risk of bias. However, because the SOE for PTSD symptom reduction was rated as insufficient/very low in the systematic review due to unknown consistency and lack of precision, its findings were not considered conclusive.

The panel makes strong recommendations for several psychological treatments (cognitive behavioral therapy, cognitive processing therapy, cognitive therapy, prolonged exposure therapy) while it does not make any strong recommendations for medication treatments. These recommendations are based primarily on the larger magnitude of benefits to harms for psychological treatments than for medications that is driven by larger magnitude reduction in PTSD symptoms and fewer known harms for psychological treatments than for medication treatments (although it is assumed that some psychotherapies can cause negative consequences and their use for some individuals can have downsides). Because the systematic review did not report direct comparisons between psychotherapy and pharmacotherapy, the panel did not make recommendations of one treatment before another, despite strong recommendations for some psychotherapies.

It is important to note, however, that the larger magnitude PTSD symptom reduction achieved by psychological treatments *may be* related to the two major methodological differences in the RCTs of psychological and medication treatments: First, all of the participants in medication trials were blinded as to whether they received active medication or placebo, while none of the participants in the psychotherapy efficacy trials were. Three meta-analyses of treatments for mental disorders demonstrated smaller effect sizes for trials with blinding than for trials without it (Huhn, 2014). Second, all of the medication trials used contemporaneous controls while only some of the psychotherapy trials did (some psychotherapy trials used wait-list controls). Eight meta-analyses of psychological and pharmacological treatments for mental

disorders showed substantially smaller effect sizes for trials with contemporaneous controls (Huhn, 2014).

Trials of medications and psychotherapy for depression also raise concern about the potential impact of methodological differences that may apply to PTSD trials. In a systematic overview of meta-analyses of treatments for mental disorders, Huhn et al. (2014) showed that the effect size for psychotherapy, compared to control group, was twice as large as the effect size for medications, compared to placebo. However, in head-to-head trials comparing psychotherapy to medications, there was no difference between those two treatment modalities (Standardized mean difference, -0.05, 95% confidence interval, -0.24 to 0.13). This likely reflects, in part, the fact that efficacy inferences for psychotherapies and those for pharmacotherapies may not be truly comparable across these classes of treatment owing to the differential stringency of these typical control conditions.

The bottom line is that, based on the best available evidence from the systematic review, the panel is able to make strong recommendations for several psychological treatments but only conditional recommendations for some medications, recommendations that may change based on future research. Clearly, head-to-head trials comparing psychological treatments to medications are desperately needed; this issue is discussed in greater detail in the section on Future Research Needs.

Strengths and Weaknesses of the RTI-UNC Systematic Review

The systematic review that served as the evidence base for the panel's recommendations has important strengths. First, it conforms to the Institute of Medicine standards for systematic reviews. Second, the group that performed the systematic review, the RTI-UNC Evidence-Based Practice Center, has conducted more than 50 systematic reviews on a wide range of medical and behavioral topics since 2002. It has developed and refined research methodology for conducting systematic reviews (Berkman et al., 2014; Guise et al.,

2014; Owens et al., 2010; Viswanathan et al., 2014) and has specialized in systematic reviews in the area of mental health and substance abuse.

Third, the systematic review is highly transparent and includes raw data and synthesized data for all comparisons described in the report. It also includes detailed information on risk of bias ratings assigned to each article and strength of evidence for all bodies of evidence that were assessed. This was crucial to the panel's ability to understand not only the findings but how they were obtained.

Fourth, the systematic review met methodological standards that have been developed by independent groups for conduct of a high quality meta-analysis (Murad et al., 2014) as well as standards developed by the PRISMA group for reporting of systematic reviews and meta-analyses (Liberati et. al, 2009).

The systematic review has important limitations as well. First, it was published in 2013 and the articles included in the review were based on a search that ended in 2012. As a result, the guideline is based on literature that is more than four years old. The panel has attempted to mitigate this limitation by conducting a supplementary search for more recent trials of treatments for PTSD and discussing the findings and their potential impact on recommendations based on the RTI-UNC review in a separate section of this report. Of note, none of the meta-analyses reported in the RTI-UNC systematic review were re-done to include findings of the new studies.

Second, for assessment of efficacy and comparative effectiveness of interventions, the systematic review limited its evidence base to randomized trials. This is standard practice for high-quality meta-analyses, including those conducted by the Cochrane Collaboration. It is based on the belief that inclusion of observational studies, such as cohort studies, in systematic reviews of the effect of interventions would increase the risk of confounding bias that threatens the validity of the findings. The downside of this approach, though, is that interventions that have only been investigated in observational studies (i.e., studies that do not randomize individuals to treatments or have highly restrictive inclusion criteria for participation, thus making

the sample characteristics more likely to be similar to those in “real-world” settings), are not included in the review. Moreover, among cohort studies of interventions conducted with a high methodological rigor, the effect estimates that are obtained have been found to be similar to those from randomized trials (Benson & Hartz 2000). This suggests that although confounding is an important theoretical consideration, it can sometimes be overcome and evidence from high-quality cohort studies may be able to contribute to systematic reviews of interventions. Nonetheless, the randomization process, when done well on large samples, prevents confounding by unknown confounders and this can never be done with observational studies.

Third, the systematic review did not include randomized trials of complementary / alternative interventions or trials that included persons with subthreshold PTSD. As a result, the panel did not make any recommendations on those treatments or for that population. This is an important area for future research.

So, while there are strengths and limitations intrinsic to the review process, and while panel members believe that the strategy adopted in the systematic review was methodologically robust, it is important to acknowledge that other strategies adopted at other times might yield somewhat different findings. As a result, it was the panel’s goal in the development of this guideline to render a collective judgment and decision-making process that is transparent so that interested readers might appropriately appreciate the rationale for the choices made in response to the evidence in the systematic review. It is also the hope of panel members that this guideline provide a foundation for developing key questions for additional treatments for future systematic reviews leading to updated recommendations.

Limitation of Guideline Development Process

One limitation of the guideline development process is that the outcomes that drove the recommendations were limited to the outcomes that have been included in most of the randomized trials of PTSD interventions, primarily symptom reduction and loss of diagnosis. Relatively few trials included the important patient-oriented outcome of quality of life and fewer

still included other aspects of life affected by PTSD, including existential/spiritual/meaning-making, identity and self-worth, and relations with other people.

Treatment Effect Heterogeneity: Subgroup Effects

The RTI-UNC systematic review evaluated treatment effect heterogeneity (whether the findings differed by subgroups) by examining analyses conducted in the trials included in the systematic review and also, when there were enough trials for meaningful analysis, through the application of stratified analyses of the meta-analytic data by relevant subgroups. The following factors were considered as possible treatment effect modifiers: sex, ethnic/racial minorities, military veterans, refugees, first responders, disaster victims, coexisting conditions, different PTSD symptoms, complex PTSD, chronic PTSD, childhood developmental trauma, repeat victimization, and level of severity at presentation.

The systematic review rated the evidence as “insufficient” to determine whether there was treatment effect heterogeneity by trauma type or demographic characteristics and the authors concluded that they, “did not find evidence to confirm or refute whether treatments are more or less efficacious for many other subgroups” (e.g., by gender, race, ethnicity, refugee status, repeat victimization, coexisting conditions, symptom severity [Jonas et al., 2013, p. 146]).

Some members of the current panel believe it is important to note that two subgroup effects were reported in the systematic review report: one of the trials reported differential effectiveness for patients with child- versus adult-onset trauma (van der Kolk et al., 2007) and the stratified analysis of four trials conducted as part of the systematic review reported a trend favoring the efficacy of EMDR therapy for female patients with a history of sexual assault (2 trials) versus patients with other types of trauma (Jonas et al., 2013, p. 141).

Other members of the panel believe that there is insufficient evidence to comment on subgroup effects for several reasons. First, most of the subgroup analyses (those conducted by

stratified analysis in the systematic review and those conducted by the trials themselves) showed no treatment effect heterogeneity (Jonas et al, 2013, p. 141). Second, subgroup effects identified through analyses of trials stratified by one characteristic of a trial are frequently confounded by other characteristics of those trials. In the stratified analysis described above, because trauma type (sexual assault) was confounded with gender, the subgroup effect ascribed to trauma type may in fact be due to gender. Third, consideration of the subgroup data, rated as “insufficient” by the systematic review, is inconsistent with the panel approach to other data rated insufficient by the systematic review. Fourth, the subgroup effects described above do not meet widely accepted criteria for evaluating whether subgroup effects reported by trials or meta-analyses are valid or spurious (Sun, Briel, Walter, & Guyatt, 2010; Sun, Ioannidis, Agoritsas, Alba, & Guyatt, 2014; Wang, Lagakos, Ware, Hunter, & Drazen, 2007).

There was consensus among panel members that despite the clinical and policy importance of identifying which treatments work best for which patients, the randomized trials included in the systematic review do not adequately address that issue. Very few trials assessed subgroup effects and the sample sizes of most were not powered to detect subgroup by treatment interactions. This is an important lacuna and it is addressed further in the section on Future Research Needs.

Generalizability (Applicability)

The generalizability of each recommendation to a theoretical population of persons with PTSD was evaluated using the PICOTS framework (Samson & Schoelles, 2012). Those evaluations are noted in the decision tables (Appendix D) for each recommendation. In this section, the overall generalizability of the findings from the RTI-UNC systematic review are discussed.

Generalizability of findings from a systematic review means that the direction and magnitude of effect of an intervention, based on the samples from the trials included in the systematic review, are similar to the direction and magnitude of effect of that intervention in an

external population. Lack of generalizability implies that there is treatment effect heterogeneity (i.e., that the magnitude of the treatment effect varies across specific subgroups) and that there are differences in those subgroup characteristics between the samples in the trials or a systematic review of trials and the external population.

As noted in the section on treatment effect heterogeneity, there is insufficient evidence from the systematic review to know whether any of the psychological or pharmacological treatments have stronger or weaker effects across subgroups based on any of the following: demographic characteristics (e.g., sex, ethnoracial minority status, military veteran, refugee), type of trauma (e.g., sexual assault, community violence, combat, disaster), comorbid diagnoses (e.g., substance use disorder, depression), duration of symptoms, exposure to childhood trauma, repeat victimization, and level of severity at presentation.

In general, the characteristics of persons included in the randomized trials incorporated into the systematic review are, except where noted in the applicability section for specific recommendations, similar to the universe of persons with PTSD, in terms of gender, race, type of index trauma, and exposure to childhood trauma. Other characteristics, such as ethnicity or gender and sexual minority status, were frequently not reported. The trial samples were less likely to include persons with substance use disorders, those who were violent or experiencing psychosis (because these were frequently criteria for exclusion), and more likely to include people with high baseline severity of PTSD.

Based on the rating of insufficient evidence about subgroup effects and sample characteristics of the included trials as noted above, the RTI-UNC EPC authors concluded, “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” (Jonas et al., 2013, p. ES-13). Given this scientific uncertainty, GDP members were unable to reach consensus about generalizability of findings of the systematic review. The divergence of opinion among panel members mirrors different opinions in the literature on the

issue of generalizability of clinical trials (Post, de Beer, & Guyatt, 2013; Rothwell, 2005). Some panel members believe that, in the presence of insufficient evidence on generalizability, clinicians should be cautious about assuming generalizability to all population subgroups. They noted that the systematic review did not show that subgroup effects had been assessed adequately and were found to be absent, but rather that subgroup effects had been assessed infrequently and that study samples were often too small to detect subgroup effects. These members further suggest that psychological treatments, in particular, may have different meanings for people from different backgrounds and may therefore be more likely to have differential effects across those groups (Brown, 2008; Gone & Kirmayer, 2010). Finally, they note that average treatment effects (e.g., the standardized mean differences reported in the systematic review), may be different for individuals who differ from the modal patient on baseline risk, responsiveness to treatment, or vulnerability to adverse effects (Kravitz, Duan, & Braslow, 2004) or that the use of highly trained clinicians with advanced degrees in the research trials do not represent the typical mental health worker in a community treatment setting..

Other members of the panel believe that, in the absence of empirical evidence or strong theoretical rationale to suspect treatment effect heterogeneity (i.e., subgroup effects), one should assume, until demonstrated otherwise, treatment effects from randomized trials to be generalizable across most demographic subgroups. These panel members note that many subgroup effects reported as new findings in randomized trials have been later shown to be spurious (Sun, Ioannidis, Agoritsas, Alba, & Guyatt, 2014; Wang, Lagakos, Ware, Hunter, & Drazen, 2007). They further suggest that it would be inappropriate, for clinical care or policy, to not offer treatment to members of specific demographic subgroups based solely on the possibility, in the absence of demonstrable evidence or strong theoretical rationale, that treatment effects may be shown to vary across those groups in future research.

These panel members do suggest caution in generalizing findings when there is a strong theoretical rationale to expect treatment effect heterogeneity. For example, although baseline

severity was not evaluated as a moderator of treatment effect by the trials included in the systematic review, there is strong evidence that baseline severity moderates the effect of many treatments (Kravitz, et al., 2004), including psychological (Driessen, Cuijpers, Hollon, & Dekker, 2010) and pharmacological (Fournier et al., 2010) treatments for depression. Since the baseline severity of PTSD was high in the trials included in the systematic review, these panel members advise caution in generalizing findings from the systematic review to patients with mild severity PTSD. The expertise of therapists implementing a psychological treatment is another factor that might be expected to create heterogeneity. When a psychotherapy that requires significant training and expertise for implementation has been evaluated only in specialized settings with therapists who have that training, it is reasonable to suspect that the effect magnitude may be lower when therapists in the community who do not have specialized training implement that treatment. Although recent studies of large-scale implementation of prolonged exposure therapy (Eftekhari et. al., 2013) and cognitive processing therapy (Lloyd et. al, 2015) for PTSD reported effect sizes that were similar to randomized trials with highly trained therapists (suggesting that treatment effect heterogeneity by therapist expertise and setting may not be a major issue), those studies were observational studies without control groups and were likely to have obtained larger effect sizes than if large-scale randomized trials, with appropriate control groups, had been conducted.

The panel is in complete agreement that evaluation of treatment effect heterogeneity and inclusion of diverse samples in randomized trials are important priorities for future research. This is discussed in greater detail in the section on Future Research Needs.

Generalizability of findings from the systematic review to persons who have comorbid substance abuse disorders is problematic. A high percentage of persons with PTSD have substance use disorders (Brady, Killeen, Brewerton & Lucerini, 2000), yet most of the trials included in the systematic review excluded those with substance abuse (Jonas et al., 2013.) Of the 92 trials, only 4 included research participants with substance use disorders and 2 included

those with alcohol dependence (though 17 of the 92 trials did not specify substance use in the inclusion or the exclusion criteria, making it unclear if they were included or excluded from those trials). In itself, this does not mean that the findings are not generalizable to persons with comorbid PTSD and substance abuse. Lack of generalizability would also require that the magnitude of treatment effects for PTSD differed among those with and those without substance abuse. Unfortunately, there are no data on PTSD treatment effect heterogeneity by substance abuse status. Further, there are no data from meta-analyses on treatment effect heterogeneity by substance abuse among persons with depression (from which we might be able to reason by analogy). Given these circumstances (i.e., that comorbidity of PTSD and substance abuse is common, but there are few trials that included persons with substance abuse and no data on treatment effect heterogeneity), some panel members believe that the findings from the systematic review should be cautiously applied to persons with PTSD and substance abuse while others do not. All members agree that future treatment trials for PTSD should include persons with substance abuse and assess group (i.e., substance abuse or no substance abuse) by treatment interactions.

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Community Member Input

Community members on the panel expressed a number of general preferences and values about their treatment for PTSD that they determined were important to consumers. These begin with valuing a practitioner who is informed about trauma and its effects, knows how

to approach and work with traumatized individuals (i.e., works from a trauma-informed perspective and has sufficient exposure and desensitization to traumatic material to not be reactive or judgmental to the patient and his or her symptoms or presentation) and has training, experience, and competency in providing the suggested treatment for PTSD. Patients also benefit from receiving information about whether and how a particular treatment works, its typical protocol, and any known complications of the treatment (in this, they may also be influenced by feedback from peers regarding their experience of a particular treatment and whether or not it worked for them) (see Mott, Stanley, Street, Hofstein, & Teng, 2014 for discussion). Community members also suggested that consumers would find strategies for self-soothing and emotional self-regulation helpful and that they would value a personalized approach to treatment. They further pointed out that one particular treatment or medication will not fit the needs of every patient and it may take multiple modalities or combinations of mental health and pharmacological interventions to help a particular individual.

Community members on the panel also indicated that attention to issues of stigma and bias (either provider bias towards or against a particular type of trauma, patient type or presentation style, patient preference, or intervention), and cultural competency, and whether a practitioner is sensitive to different presentations and identities are important considerations. It is also very helpful for the practitioner to become familiar with some of the unique qualities associated with the patient's characteristics, group membership or culture. For example, when working with a military or veteran population, providers may want to familiarize themselves with information about that particular culture. Awareness of military hierarchical functions, organizational structure, terminology, and expectations may help to understand the military patient's service experiences.

In addition, community members noted the importance of the development of a therapeutic relationship. Many trauma survivors enter treatment with great fear and trepidation (tied directly to their trauma and, at times, to negative prior experiences with other health

professionals or organizations), despair and hopelessness about the possibility of being accepted, understood, or helped, and many mistrust therapists as authority figures. As a result, they may be difficult to engage and more prone to talk with their peers (in informal or formal peer support programs) about the trauma rather than with a medical or mental health professional. Members suggest that practitioners present themselves in a very straightforward, respectful, and non-defensive way (professional but not authoritarian) and know they must earn their patients' trust through their empathy, consistency, reliability, and ability to be responsive and calm in their interactions, as well as in their ability to set and maintain reasonable boundaries and to encourage collaboration.

Clinician Input Regarding Psychotherapy

Clinicians on the GDP offered their perspectives on general patient values and preferences gleaned from their treatment experiences. These included that patients vary in their preference regarding trauma-focused therapies (i.e., patient preferences may be related to their tendency to avoid discussion and symptoms on the one hand or their need to discuss their trauma experiences explicitly, graphically, and repeatedly on the other). Other reasons might relate to trauma type, life stage and developmental timing of the emergence or severity of symptoms, the interference of other life issues, psychiatric or medical comorbidities, gender, age, family, culture, treatment setting and more idiosyncratic reasons. Consistent with findings from the systematic review of patient preferences (Simiola et al., 2015), panel clinicians reported that many of their adult patients with PTSD prefer psychotherapy over medication; however, a substantial minority do prefer medication (Feeny et al., 2009b) and some do not want any mental health intervention or treatment at all.

Some clinicians reported that consumers as a group understandably seek treatments that are relatively short-term and will resolve their symptoms and alleviate their suffering. They also appreciate receiving information about the various techniques under consideration including their possible benefits and risks to help them in choosing or refusing the offered

intervention. Information can also allay the anxiety and apprehension many patients have at the start of any kind of treatment. The pace and intensity of treatment can be quite variable and may be determined by the treatment method and the patient's symptomatology and life stability. For example, EX and CPT follow protocols that generally require a shorter but more intensified course of treatment. This works well for some, but not all patients. Some require attention to issues of personal safety and life stabilization and to the development of emotional regulation and life skills before undertaking a trauma-focused treatment and some prefer graduated versus prolonged exposure to the trauma and its effects. Finally, cultural competence (referring to a number of therapist characteristics, including cultural humility, willingness to explore and become aware of non-conscious biases, and attention to issues of power and privilege [Brown, 2008]) is important in the treatment of PTSD.

Limitations of Existing Treatment Research Literature: Future Research Needs

In the sections below, major gaps in the current empirical literature on treatments for PTSD in adults are identified along with methodological issues that limit the current evidence base, with recommendations for future research.

Gaps in the Literature

In general, the research evidence for the efficacy of certain trauma-focused psychotherapies and pharmacologic treatments for adults with PTSD is strong. There exist a number of significant caveats and limitations in the current empirical literature that make it difficult to answer many important clinical questions. There are gaps in treatment comparisons, evaluation of moderators of treatment effects, inclusion of participants with comorbid disorders and coexisting conditions, documentation of patient characteristics to enable subgroup analyses of a wide range of sociodemographic factors, assessment of important outcomes and the timing

of their assessment, measurement of potential side effects and harms, assessment of patient preferences, and follow up on reasons why participants leave a study.

First, the paucity of relevant treatment comparisons (i.e., comparative effectiveness trials) limits the ability of clinicians to make evidence-based recommendations for selecting one treatment versus another or one medication versus another. In addition, there are few comparative effectiveness trials of efficacious psychotherapies compared to efficacious medications. Similarly it is not yet known if treatment combinations, particularly psychotherapy with pharmacotherapy, are more effective than their use alone. Consistent with other PTSD guidelines (Foa, Keane, Friedman & Cohen, 2009) and guideline reviews (Forbes et al., 2010), and in consequence to the findings of this guideline, the panel concludes that more research is needed regarding different mental health treatment methods, combinations, sequences, and integration. Specifically, panel members recommend trials comparing efficacious psychotherapies to each other, efficacious medications to each other, and efficacious psychotherapies to efficacious medications. In addition, trials are needed to determine whether combined treatments enhance the effect of psychotherapies and medications that are effective alone.

Second, a limited number of studies have investigated moderators of treatment effects (or “subgroup analyses”) that evaluate whether treatments are more or less effective for certain groups, such as men or women, specific ethnic, racial or cultural groups, gender differences, persons with acute or chronic/complex PTSD, persons with mild or severe PTSD, or persons exposed to a particular type of trauma (e.g., combat trauma, sexual assault, community violence). At this time, there is little research to indicate which efficacious treatments are most effective for which patients under which conditions. The panel recommends that trials be planned *a priori* to evaluate important potential moderators of treatment effects and include adequate sample sizes and appropriate statistical techniques to evaluate group by treatment interaction effects.

Third, although the RCTs in the RTI-UNC systematic review included heterogeneous groups of participants with a variety of index trauma types, and included participants with comorbid depression, participants with other important comorbid conditions were frequently excluded. Specifically, a majority of the RCTs excluded patients with substance dependence or suicidality, an important limitation given that PTSD, substance dependence and self-harm are so often co-morbid. In addition, in the RCTs reviewed, it was unclear or inconsistently reported whether individuals also had comorbid problems such as dissociation. The *DSM-5* revision of the PTSD criteria now includes a dissociative subtype (Friedman, 2013; Friedman, Resick, Bryant, & Brewin, 2011). Thus, individuals with these and other identified comorbidities or complexities should be included in future clinical trials.

Fourth, although virtually every trial measured PTSD symptom reduction and many measured anxiety reduction, other important outcomes, such as PTSD remission (absence of symptoms) and loss of PTSD diagnosis, were not always measured or reported. Important “patient-centered” outcomes, such as quality of life and functional impairment were also infrequently studied or reported. Future investigations might include PTSD remission or loss of diagnosis as a critical outcome and also systematically evaluate patient-centered outcomes such as functionality and life quality.

Fifth, although the pharmacotherapy trials typically reported information on side effects and serious harms, the psychological intervention studies usually did not. This limitation is not specific to psychotherapy for PTSD per se, given that the field of psychology generally lacks consensus on how to detect harm associated with psychotherapy as discussed by Dimidjian and Hollon (2010). Consistent with IOM recommendations for clinical guidelines and unlike previous guideline panels on PTSD treatment, this GDP based its recommendations on the balance of benefits and harms for all interventions; however, as noted, the strength of evidence on harms of psychotherapy was very low because data have not yet been rigorously collected and comprehensively reported. For the benefit/harm calculus to be based on strong evidence,

solid data on harms must be collected in future trials. Thus, the panel advises that psychometrically sound measures of adverse effects should be included and reported in future RCTs. Such measures should include assessments of suicidal ideation and actions, self-injurious behaviors, risk-taking, hospitalizations, and other important adverse outcomes. Of particular importance, the panel strongly recommends that researchers seek to identify the reasons for participant dropout. If the reasons for attrition are not specified, it is impossible to know whether attrition represents improvement, a response to an adverse effect, patient disaffection with the treatment or the setting, or something else.

Sixth, there is relatively little evidence on patient preferences for different psychotherapies or different medications or the impact of those preferences on treatment engagement, retention, and outcome. A recent meta-analysis examining the impact of patient treatment preference on outcomes for a wide range of disorders and problems (e.g., depression, anxiety, substance use disorders, severe mental illness, chronic pain) indicated that those who received their preferred treatment were 50% less likely to drop out of treatment and had an almost 60% greater chance of demonstrating improvement than those who did not receive their preferred treatment (Swift & Callahan, 2009). Thus, it behooves investigators to include attention to patient preferences for different treatments.

Methodological Improvements

In addition to the research gaps described above, there were significant methodological issues with a substantial proportion of the PTSD treatment trials. Of the 138 randomized trials found to be eligible for inclusion in the RTI-UNC systematic review, 46 (33%) were rated high risk of bias and not included, except for sensitivity analyses³⁰. The most frequent methodological problems among the trials with high risk of bias were elevated rates of attrition/

³⁰ Sensitivity analyses conducted by the RTI-UNC systematic review confirmed that, for all of the interventions for which the panel makes recommendations, the substantive conclusions that were based on the trials at low or medium risk of bias were not altered by inclusion of trials that were judged to be at high risk of bias.

drop-out or differential attrition (i.e., markedly different attrition rates in treatment comparison groups) and inappropriate methods for handling missing data.

Future trials should plan and implement methods designed to minimize the methodological challenges identified in the systematic review. Specifically, the panel recommends that investigators design trials to minimize attrition, decrease missing data, incorporate methods for handling missing data that are less likely to be biased (such as multiple imputation or maximum likelihood). The panel encourages researchers to try to identify the reasons for attrition in their studies and to include this information in their published reports. If resources do not permit the researchers to identify the reasons for attrition in all participants, identifying them in a random sample (e.g., 20%) of those lost to follow-up can provide useful information for future studies. Other important characteristics of rigorous research such as assessing fidelity of the treatment under investigation should always be included.

The methodological rigor and transparency of RCTs on the treatments of adults with PTSD can be increased in a number of ways. First, in the studies included in the systematic review, the time between incident trauma and study entry was often wide and inconsistently reported across studies. If recency of trauma (including whether the person is still in traumatizing circumstances) is related to treatment effect, it can only be identified if it is measured and reported in research reports.

Second, the potential effects of researcher allegiance should be addressed. Many psychotherapy trials for PTSD were conducted by the individuals and investigative teams that developed or modified those techniques. A substantial body of research, including studies of PTSD trials, has shown researcher allegiance effects (i.e., larger treatment effects when the investigators have an allegiance to one or more of the treatments being compared) (see Munder, Brutsch, Leonhart, Gerger, & Barth, 2013; Munder, Gerger, Trelle, & Barth, 2011). For the comparative effectiveness trials that the panel recommends, it would be ideal if study teams

either did not include investigators who developed or substantively modified the constituent interventions or at least included investigators who developed each of those interventions (i.e., balanced allegiance). Another suggestion regarding allegiance effects is having members of the research team who are allegiant to and competent in each of the respective interventions (along with someone competent in the treatment to oversee each intervention) as a way to ensure fair and balanced comparisons. Mellers, Hertwig and Kahneman (2001) coined the term “adversarial collaboration” to describe a strategy for dealing with bias while retaining the expertise to implement.

Third, it is also important that future trials of PTSD treatment evaluate outcomes over longer and defined time periods. In order to pool results across trials that measured outcomes at different times, the UNC-RTI EPC selected the only common metric available: the outcome value at the end of treatment. However, this metric may not be the most clinically relevant time point for outcome assessment. For both psychotherapy and pharmacotherapy, it is important to measure the outcome after the end of treatment. An effort to define ideal (yet feasible) time points to assess treatment outcome would provide useful guidance for future treatment research.

Fourth, trials should include sample sizes large enough to minimize covariate imbalances that are associated with outcomes that occur by chance, not just sample sizes large enough to detect clinically meaningful effects. Many of the trials included in the systematic review had relatively small sample sizes. Even when a trial has sufficient power to detect a clinically meaningful difference between interventions, smaller trials are more likely to have covariate imbalances that may affect the outcome by chance alone. The primary value of a randomized trial is the balance of known and unknown covariates across treatments, which is undone when a trial is small. Studies of published research have shown that findings from smaller studies are less likely to be replicated than those from larger studies. In a study of 49 highly cited original studies, Ioannidis (2005) found that studies that were subsequently

contradicted had much smaller sample sizes (median = 624) than those that were subsequently replicated (median = 2165). Of particular interest here is the fact that these numbers exceed the *combined samples* in the distinct classes of interventions included in the systematic review, the largest of which included a total of 1,301 participants for CBT.

Accordingly, the panel recommends that investigators increase sample sizes, and pool efforts, when necessary and possible, to increase recruitment of participants. When a trial is small, investigators may consider controlling for the potential impact of covariate imbalances through multivariable modeling or propensity score techniques, as is typically done in non-randomized studies of treatment effectiveness. The practice of performing statistical tests of the comparability of baseline demographic covariates is inappropriate and should not be done. By definition, when participants are randomly assigned to treatments, differences in covariates across treatments are the result of “chance”. When a study is small, statistical tests have low power to detect even large covariate imbalances. Since confounding is a bias related only to the magnitude, not the precision, of differences in covariates across treatment groups, the key issue is not whether baseline differences are statistically significant but whether those differences have an impact on the estimated association between treatment and the outcomes of interest (Lavori, Louis, Bailar III, and Polansky, 1983). Accordingly, consistent with the recommendations of CONSORT (Moher et al., 2010), the panel recommends that investigators discontinue the practice of reporting statistical tests of baseline covariate differences across treatment groups.

Guideline Summary and Future Directions

Trauma is now recognized as extremely common in human experience. After traumatic exposure, the most favorable outcome occurs when posttraumatic reactions are naturalistically processed to a degree of resolution and do not subsequently develop into onerous or ongoing symptoms. When trauma is not spontaneously processed in this way (as occurs more frequently in adults with traumatic exposure, but is less likely in children) it can result in serious mental health consequences and symptoms, especially Posttraumatic Stress Disorder, a condition usually accompanied by other mental health comorbidities and a range of medical conditions. Symptoms that are initially acute and that are not resolved can become chronic or can emerge in delayed form across the entire lifespan, causing anguish and suffering of the primary victim and loved ones. Due to the relatively high prevalence rate of PTSD in the general population, there is an urgent need for treatments that effectively ameliorate its symptoms.

In many ways, the available PTSD treatment research is substantial but now requires increased sophistication in design and methodology. Members of this guideline panel applaud treatment developers who have supported ongoing investigations of their particular method and the number of national and international professional organizations for leading the way in the design and implementation of research studies on PTSD treatment and for. In particular, organizations include the International Society for Traumatic Stress Studies, the NIH-funded Conference on Innovations in Trauma Research Methods (CITRM; held annually between 2004 and 2008) (Keane, 2009), the research efforts of the National Center for PTSD of the Veteran's Administration/DOD (including the postdoctoral program at the Boston VA that provides advanced training and mentorship in research design and methods [Sloan, Wisco, Vogt & Keane, 2015]) and the related efforts of the Australian Centre for Posttraumatic Mental Health.

The research context influences the type and quality of available studies in a number of ways. Because funding for research can become circular and create systemic bias, as interventions with the most empirical support receive additional funding, novel or other

treatments may not be adequately researched. Panel members recommend attention to this issue among funders. Other treatments may be more difficult to investigate in randomized controlled trials and thus are deemed to have a high risk of bias and are not included in systematic reviews. Panel members also support the ongoing research pertaining to trauma process and outcome, in general and as it applies more specifically to work with traumatized individuals. It is hoped that future updates of this guideline will benefit from these methodological advances and attention to additional treatments, all in the interest of relieving the suffering associated with PTSD.

Summary

This guideline is the first for the treatment of PTSD that incorporates standards for “clinical practice guidelines we can trust” promulgated by the Institute of Medicine of the National Academy of Sciences (IOM, 2011b), resulting in a guideline that can be considered for inclusion in the National Guideline Clearinghouse. See Table 2 for all the standards but these included an emphasis on transparency, multidisciplinary panels, identification and management of all conflicts of interest and use of a high quality systematic review. This guideline is based on a systematic review that used rigorous standards and transparent processes for identification and evaluation of published research. A unique feature of this guideline was the inclusion of available research findings on reported harms and adverse events of treatment and patient preferences and values in their choice of treatment, the result of additional reviews of the data on the treatment of PTSD. The findings of this guideline are largely in accord with those of other published PTSD treatment guidelines and strongly recommend the use of such trauma-focused psychological interventions as cognitive behavioral therapy, cognitive processing therapy, cognitive therapy and prolonged exposure therapy. It further suggests or conditionally recommends the use of brief eclectic psychotherapy, eye movement desensitization and reprocessing therapy, and narrative exposure therapy. In terms of medication interventions, it supports the use of fluoxetine, paroxetine, sertraline, and venlafaxine.

Panel members recognize that, despite the fact that these recommendations were made on the basis of the most scientifically rigorous methods in determining treatment outcome, many questions remain and much remains to be researched going forward. The PTSD literature is relatively recent and continues to need much greater “real world” application of findings. Furthermore, while research findings establish the foundation for the evidence-base, its application requires clinical judgment, knowledge of treatment methods and their relative effectiveness, and competence to offer the treatment on the part of the clinician. It also requires collaborative decision making that takes into consideration the unique needs and preferences of the patient including his or her contextual and cultural dimensions and the severity and comorbidity of the PTSD. A clinical practice guideline is a general guide to best practices and serves as an aid in decision making but does not define a standard of care nor supplant clinician judgment. Research that investigates all three arms of the evidence-based approach will build upon and broaden effective treatment of individuals suffering PTSD in the aftermath of their traumatic experiences.

Conflicts of Interest

Prior to final appointment to the panel, candidates completed a conflict of interest (COI) form that was then reviewed by members of the Advisory Steering Committee or APA staff to ensure there were no identified conflicts that would prohibit participation, with the understanding that some “adversarial conflict” representing different points of views was to be expected and encouraged in this process. While intellectual affiliations were expected, no panel members had been singularly identified with particular approaches to intervention nor had significant known financial conflicts. Once the panel was formed, all panel members completed an educational module on COI that underscored the importance of identifying and managing any potential conflicts, both financial and intellectual. The APA COI policy and disclosure form are included in the appendix.

All panel members and staff affiliated with development of the PTSD CPG updated their COI form on an annual basis and were asked to provide more timely updates if changes in their disclosures were perceived to be relevant to the development of the guideline. All were asked to disclose all potential COI with the understanding that these would be reviewed and evaluated and a decision would be made regarding how to manage identified conflicts. Conflicts of interest included not only possibilities for financial or professional gain but also strong intellectual viewpoints that might then limit someone from objectively reviewing the evidence. Emphasis was placed on disclosing all potential conflicts and allowing the staff and chair (or other appropriate entity in the case of the chair) to review the disclosures and determine whether or not such information could reasonably be construed as to be a source of possible influence on the guideline development process. Furthermore, upon first joining the initiative and at the initial face to face meeting, panel members were asked to verbalize their conflicts so all present would be familiar with the diversity of perspectives and range of possible influences. This practice continued at subsequent face-to-face meetings.

Lastly, the developers of the SR also had their own COI policy and disclosure. While the SR was completed before the panel was formed, the Panel appreciated that the SR team also had a process to disclose and manage potential COI.

All authors were required to disclose their intellectual interests, financial and professional interests, interests related to APA, and other relevant interests. They were also required to disclose interests of family members, defined as “a spouse, domestic partner, parent, child, or other relative with whom [they] have a comparably close tie.” Authors disclosed the following potential COI: scientific/educational/professional communications, communications to a general audience, roles at APA or other organizations, relevant honoraria, endorsements, research funding or royalties, payment for services or training, and serving as expert witnesses. None of the reported potential conflicts of interest precluded a nominated candidate from serving on the GDP. Excluding all GDP candidates with any potential or identified COIs runs the risks of excluding the level and type of expertise needed.

There is growing recognition that financial relations to the pharmaceutical industry threaten the integrity of research and of CPGs. However, the issue is still contentious, and exclusion of all potential GDP members with such conflicts may itself be seen as biased against pharmacological treatments or particular medical specialties. Similarly, experts with respect to psychotherapy tend to have intellectual passions for specific types of psychosocial interventions that also constitute potential conflicts. Yet, such individuals may be difficult to replace because of their unique insights, as well as their status in the eyes of key stakeholders (IOM, 2011b). Hence, rather than exclude topic experts and risk minimizing expertise, APA follows the principle of adversarial collaboration in which competing interests are balanced on panels and committees, rather than avoided. This approach is also used by other leading developer of CPGs, such as the ACCF/AHA task force (ACCF and AHA, 2008; IOM, 2011b).

Author Disclosures

The Clinical Practice Guideline Panel reported the following disclosures during the development and approval of this guideline:

Christine A. Courtois, PhD (**Chair**), is a board-certified counseling psychologist recently retired from independent practice in Washington, D.C. She regularly leads professional workshops, publishes, and occasionally serves as an expert witness, all on topics related to trauma exposure and PTSD treatment, although not focused exclusively on specific interventions. She receives payment for directly providing or training other individuals to provide health services related to trauma, as well as honoraria for presentations or discussions, royalties, and endorsements. She reports no conflicts of interest with her work on these guidelines.

Jeffrey Sonis, MD, MPH (**Vice Chair**), is associate professor of social medicine and associate professor of family medicine at the University of North Carolina at Chapel Hill. He publishes and conducts research on scientific and/or clinical and/or public policy related to psychological trauma and PTSD with funding from organizations not associated with the APA. He reports no conflicts of interest with his work on these guidelines.

Laura Brown, PhD, is currently a full-time practitioner of psychotherapy, consultation and forensic psychology in Seattle, Washington. She is trained at Level 2 in EMDR and has published on its integration into feminist trauma practice, which she uses regularly in her work. She regularly leads professional workshops, publishes, and serves as an expert witness on topics related to trauma exposure and PTSD treatment, although not focused exclusively on specific interventions. She receives payment for directly providing or training other individuals to provide health services related to trauma, as well as honoraria for presentations or discussions, and royalties. She reports no conflicts of interest with her work on these guidelines.

Joan M. Cook, PhD, is an associate professor at Yale School of Medicine and a researcher at the U.S. Department of Veterans Affairs (VA) National Center for PTSD. She conducts research on scientific and/or clinical issues related to trauma with funding from organizations not associated with the APA. She currently serves on the Board of Directors for the International Society of Traumatic Stress Studies (ISTSS), however, she was not a direct contributor to the organization's guidelines for PTSD. She served as President of APA's Division 56 (Trauma Psychology) in 2016 for a 1-year term, as well as a co-editor of APA's two volume Handbook of Trauma Psychology. She reports no conflicts of interest with her work on these guidelines.

John A. Fairbank, PhD, is a professor in the department of psychiatry and behavioral sciences, Duke University Medical Center, and director of the VA Mid-Atlantic (VISN 6) Mental Illness Research, Education and Clinical Center headquartered at the Durham VA Medical Center. Fairbank serves as co-director of the Substance Abuse and Mental Health Services Administration's National Center for Child Traumatic Stress, co-located at Duke University and UCLA. He regularly leads professional workshops, publishes, and conducts research on scientific and/or clinical issues related to trauma with funding from organizations not associated with the APA. He serves as the Chair of the Scientific Advisory Board (SAB) for the National Center for PTSD. He reports no conflicts of interest with his work on these guidelines.

Matthew Friedman, MD, PhD, was executive director of the U.S. Department of Veterans Affairs (VA) National Center for PTSD between 1989 and 2014 and now serves as senior advisor and professor of psychiatry, and of pharmacology and toxicology, at the Geisel School of Medicine at Dartmouth. He regularly publishes and serves as an expert witness on topics related to trauma exposure and PTSD treatment, although not focused exclusively on specific interventions. He receives payment for directly providing or training other individuals to provide health services related to trauma, as well as honoraria for presentations or discussions, and

royalties. He chaired the American Psychiatric Association's work group that developed DSM-5 criteria for PTSD and other trauma and stress-related disorders. He reports no conflicts of interest with his work on these guidelines.

Joseph P. Gone, PhD, is a professor in the clinical psychology program in the department of psychology at the University of Michigan. He researches historical trauma among American Indians and other Indigenous populations. He previously served on the Executive Committee of APA's Division 45 (Society for the Psychological Study of Culture, Ethnicity, and Race), and is the Treasurer of APA's Division 5, Section 3 (Quantitative and Qualitative Methods). He reports no conflicts of interest with his work on these guidelines.

Russell Jones, PhD, is a professor of psychology at Virginia Polytechnic Institute and State University (Virginia Tech) and a clinical psychologist who specializes in trauma psychology in the areas of natural and technological disasters, as well as interpersonal violence. He regularly presents on issues related to trauma and serves as an expert witness on topics related to trauma exposure and PTSD treatment. He receives payment for directly providing or training other individuals to provide health services related to trauma. He reports no conflicts of interest with his work on these guidelines.

Annette La Greca, PhD, is a distinguished professor of psychology and pediatrics at the University of Miami. She regularly presents scientific research at conferences and publishes on topics related to trauma exposure and PTSD treatment in children, although not focused on specific interventions. She receives honoraria for presentations or discussion of scientific or clinical issues related to trauma in children. As of July 2014, she is a member of the APA Publication and Communications Board. She reports no conflicts of interest with her work on these guidelines.

Thomas A. Mellman, MD, is on the faculty of Howard University where he trains psychiatry residents, provides clinical care and conducts research in the area of PTSD, sleep and mechanisms linking PTSD and sleep disturbance to health risk and health disparities. He reports no conflicts of interest with his work on these guidelines.

John Roberts is a veteran of the U.S. Marine Corps, serving from 1982-96. He has worked in a variety of capacities with veteran organizations and since 2007 has been with the Wounded Warrior Project, Houston, TX. He is currently warrior relations executive vice president. He reports no conflicts of interest with his work on these guidelines.

Priscilla Schulz, LCSW-C, is a clinical social worker with the Peace Corps in Washington, D.C. She contributes to writing and revising the US Peace Corps' policies and procedures related to addressing psychological needs of staff and volunteers suffering with posttraumatic stress symptoms. She reports no conflicts of interest with her work on these guidelines.

Conflict of interest forms for all authors are available by request for public review.

Developer

American Psychological Association (APA) Posttraumatic Stress Disorder (PTSD) Guideline Development Panel (GDP). The PTSD GDP is a multidisciplinary panel of experts.

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This guideline was developed with financial support from the American Psychological Association. The PTSD GDP functioned as an independent Panel of the association. Final recommendations will be reviewed by the APA Council of Representatives for approval (yes or no) as APA policy. However, the Council had no influence on the content of the recommendations.

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