

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

3 **from the Guideline Development Panel (GDP) for PTSD Treatment of the American**
4 **Psychological Association (APA)**

5 **Draft October 4, 2016**

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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. 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. 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. 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).

Complete formatting and copyediting will be performed following the public comment period.

1

Abstract

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[To be written at time of submitting for publication]

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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 conducted by the Research Triangle Institute- University of North Carolina Evidence-Based Practice Center (RTI-UNC EBPC) (Jonas, Cusack, Forneris, Wilkins, Sonis, Middleton, et al., 2013).The 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 patients? 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?

This guideline addresses the efficacy of psychological and medication treatment, the comparative effectiveness of these treatments, whether the treatments work best for particular patients¹, and includes examination of harms and burdens of treatment and patient values and preferences. 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.

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.

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Recommendations

The panel strongly recommends offering 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 exposure therapy (EXP). The panel suggests offering the following psychotherapies/interventions: 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, topiramate, and venlafaxine. There is insufficient evidence to recommend for or against offering risperidone.

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, the panel conducted a revised search, to identify trials published between May 25, 2012 and June 1, 2016. Based on the new trials, the panel concluded that none of the recommendations were likely to change; there was insufficient evidence to determine whether the recommendations for eye movement desensitization and reprocessing therapy or for narrative exposure therapy would change.

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

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.

1 shocking. Many individuals exposed to traumatic events experience posttraumatic reactions
2 though most of these reactions remit spontaneously within approximately the first month of
3 occurrence (Rothbaum, Foa, Riggs, Murdock, & Walsh, 1992; Nugent, Saunders, Williams,
4 Hanson, Smith, & Fitzgerald, 2009; Orcutt, Erickson, & Wolfe, 2004). However if reactions
5 persist, they might meet criteria for one or more posttraumatic diagnoses such as Acute Stress
6 Disorder (ASD) or Posttraumatic Stress Disorder (PTSD). The 5th edition of the *Diagnostic and*
7 *Statistical Manual of Mental Disorders, DSM-5*, (American Psychiatric Association, 2013),
8 defines PTSD as comprised of four clusters of symptoms including intrusive and recurrent
9 memories of the trauma, avoidance of trauma-related stimuli, numbing and/or negative changes
10 in mood or cognitions pertaining to the trauma, and changes in reactivity and arousal. The *DSM-*
11 *IV-TR* (American Psychiatric Association, 2000) previously defined PTSD as being comprised of
12 three symptom clusters including avoidance and numbing, re-experiencing, and hyperarousal.
13 Of note, all of the studies included in the RTI-UNC systematic review that served as the
14 evidence base for that report used DSM-IV-TR or earlier DSM criteria and are those discussed
15 throughout this guideline.

16 Currently, numerous guidelines from various agencies and professional organizations
17 recommend several trauma-focused psychological interventions for treating PTSD and most
18 acknowledge some benefit of several medication treatments as well. The present guideline
19 differs from other guidelines in several ways. It fully follows and builds upon the standards set
20 forth by the Institute of Medicine (IOM) (now the National Academy of Medicine) of the National
21 Academies of Sciences, Engineering, and Medicine standards for developing high-quality,
22 independent, and reliable practice guidelines (IOM, 2011a & 2011b). It used a comprehensive
23 independent systematic review of the literature for treatment of PTSD in adults. Further, panel
24 members who worked on the present guideline document were an interdisciplinary group from
25 disciplines including psychology, social work, primary care, and psychiatry--and included

1 consumer members as well. Finally the present guideline includes attention to potential and
2 actual harms and burdens of PTSD treatments and patient preferences as part of the process.

3 **Process and Method**

4 In selecting which outcomes were most critical for deciding whether to recommend or
5 not recommend a treatment, panel members decided that PTSD symptom reduction and
6 serious harms/adverse events were the most critical. Members further decided that the following
7 outcomes were important though not critical: Remission (no longer having symptoms), loss of
8 PTSD diagnosis, quality of life, disability or functional impairment, prevention or reduction of
9 comorbid medical or psychiatric conditions, adverse events leading to withdrawals (treatment
10 discontinuation), and other adverse events, and burdens.

11 The primary evidence base for the present guideline was the systematic review,
12 *Psychological and Pharmacological Treatments for Adults With Posttraumatic Stress Disorder*
13 *(PTSD)* (Jonas et al., 2013) produced by the Research Triangle International- University of
14 North Carolina Evidence Based Practice Center (RTI-UNC EBPC). RTI-UNC EBPC followed the
15 protocol set forth by the Institute of Medicine (2011b) for conducting systematic reviews. The
16 comprehensive and transparent systematic review addressed psychological and
17 pharmacological treatments for PTSD. The trials included in the systematic review included
18 samples that, as a whole, were broadly diverse in terms of gender, race, ethnicity and type of
19 trauma.

20 APA's Advisory Steering Committee issued a call for nominations (including self-nominations)
21 for individuals to serve as panel members from a variety of backgrounds (consumer,
22 psychology, social work, psychiatry, general medicine) with content knowledge or
23 methodological expertise. Conflicts of interest (financial and non-financial) were considered and
24 managed both during panel member selection and throughout the guideline development
25 process.

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

8 **Discussion**

9
10 For treating PTSD in adults, the present guideline strongly recommends cognitive
11 behavioral therapy (CBT), cognitive processing therapy (CPT), cognitive therapy (CT), and
12 exposure therapy (EXP) and suggests the use of brief eclectic psychotherapy (BEP), eye
13 movement desensitization and reprocessing (EMDR), and narrative exposure therapy (NET).
14 These recommendations are consistent with those of various other organizations. Moreover, the
15 present guideline suggests the use of fluoxetine, paroxetine, sertraline, topiramate, and
16 venlafaxine. These recommendations add to the pharmacotherapy recommendations of other
17 organizations. Based on the evidence available to date from the systematic review, the panel
18 was not able to recommend one treatment (psychotherapy or pharmacotherapy) versus
19 another.

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

1 Generalizability (applicability) of systematic review findings to an external population
2 means that the magnitude and direction of an intervention effect, based on included trials, is
3 similar to the magnitude and direction of intervention effect that would be expected in that
4 external population. Absence of generalizability occurs when there is heterogeneity of treatment
5 effects (e.g., by gender, ethnicity, trauma type or other factors) *and* when there are differences
6 between the distribution of those characteristics in the samples included in a systematic review
7 and the external population. The systematic review concluded that there was insufficient
8 evidence “to determine whether the findings are applicable to all those with PTSD or whether
9 they are applicable only to certain groups” and insufficient evidence about whether there were
10 subgroup effects. Thus panel members did not reach consensus about the generalizability of
11 the systematic review’s findings, reflecting differences of opinion found in the literature about
12 conditions required to demonstrate generalizability (Post, de Beer, & Guyatt, 2013; Rothwell,
13 2005). Some panel members think that lack of generalizability to all subgroups should be
14 assumed in the face of insufficient evidence about generalizability. Others on the panel believe
15 that, in the face of insufficient evidence about generalizability or strong theoretical rationale to
16 suggest treatment effect heterogeneity, generalizability to most subgroups should be assumed.
17 Panel members agree however that examination of treatment effect heterogeneity with diverse
18 samples should be prioritized for future research.

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

1 whatsoever. Many seek short-term treatment and want to experience significant symptom relief
2 and alleviation of suffering. They also found that patients want information about treatment,
3 value culturally sensitive therapists, and have various preferences regarding intensity and pace
4 of treatment.

5 In order to implement interventions effectively a number of considerations are relevant,
6 two of which are informed consent and the role of patient and relationship factors in treatment.
7 Informed consent includes providing patients with information about potential available
8 treatments including material about the process and procedures involved, effectiveness and
9 risks-benefits, and associated emotional and practical demands. It is suggested to have a
10 general discussion about informed consent at the beginning of treatment, including the provision
11 of any relevant written consent documents for psychotherapy. Second, there is a body of
12 literature that has shown an association between patient and patient-therapist factors
13 (sometimes referred to as “common factors”) and treatment outcomes. These factors include
14 such things as patient coping style, expectation for change, and therapist empathy. Clinicians
15 are encouraged to bear these factors in mind when implementing recommended treatments.

16 Other treatment considerations include the therapist working from a trauma-informed
17 approach and giving attention to the role of cultural differences as this may facilitate whether
18 clients find therapist actions and recommendations intelligible, useful, and worthwhile. Finally,
19 while monitoring PTSD symptoms during treatment can provide insight into progress and
20 treatment targets, it is unclear as of yet whether this treatment monitoring improves client
21 outcomes.

22 Although the research evidence is strong for the efficacy of particular psychotherapy and
23 pharmacological treatments for adults with PTSD, there are still gaps in the literature. These
24 gaps include the comparative effectiveness of psychological and pharmacological treatments
25 and combinations of treatments, subgroup effects, applicability of findings to patients with
26 comorbidities common among people with PTSD, impact of treatments on important patient-

1 oriented outcomes such as quality of life, long-term treatment effects, adverse effects and
2 harms, and patient preferences. In addition to the research gaps noted, there are also
3 methodological concerns with many of the current PTSD treatment trials that should be
4 addressed in future trials. Specifically, the panel recommends that investigators design trials to
5 minimize attrition, identify reasons for attrition, decrease missing data, and incorporate rigorous
6 methods of handling missing data such as multiple imputation or maximum likelihood. Future
7 trials should report the recency of trauma, address the potential for researcher allegiance
8 effects, provide long term evaluation of outcomes, and include samples large enough to
9 minimize the potential for covariate imbalance. Future trials should also retain rigorous
10 methodologic features that have been commonly used in previous research, such as
11 assessment of treatment fidelity.

12 The panel members applaud the efforts of many professional organizations to design
13 and implement PTSD treatment research studies both nationally and internationally. The panel
14 also supports the continuing efforts to research trauma process and outcome both generally and
15 more specifically to individuals who have experienced trauma. It is also the panel members'
16 hope that noted methodological improvements will serve to enhance future iterations of the
17 present guideline and further alleviate suffering of individuals with PTSD.

18

1 **Clinical Practice Guideline for the Treatment of Posttraumatic Stress Disorder**
2 **(PTSD) in Adults**
3 **from the Guideline Development Panel (GDP) for PTSD Treatment of the American**
4 **Psychological Association (APA)**

5
6 **Guideline Scope: What the Guideline Addresses and What It Does Not**

7 The purpose of this guideline is to provide recommendations on the treatment of
8 posttraumatic stress disorder (PTSD) in adults. This guideline is based on a systematic review
9 of the evidence on treatment of PTSD, sponsored by the Agency for Health Care Research and
10 Quality (AHRQ)³ and conducted by the Research Triangle Institute-University of North Carolina
11 Evidence-Based Practice Center (RTI-UNC EBPC) (Jonas, Cusack, Forneris, Wilkins, Sonis,
12 Middleton, et al., 2013). The intended users include psychologists, other health and mental
13 health professionals, consumers, families of consumers, students/training programs, policy
14 makers, and the public.

15 The guideline addresses the following questions:

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

³ The AHRQ (an agency that works within the U.S. Department of Health and Human Services) strives to improve health care by enhancing access to the relevant evidence bases in collaboration with partners.

1 The guideline does not address any of the following:

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

25

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

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

14 7. Costs of treatments. Treatment costs were not considered in the formulation of the
15 panel’s recommendations.

16
17 Below in Table 1 is a summary of recommendations. More detailed recommendations are
18 provided in Table 5.

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

Psychotherapy	Strength of Recommendation
For adult patients with PTSD, the panel strongly recommends that clinicians offer one of the following psychotherapies/interventions (listed alphabetically): <ul style="list-style-type: none"> • cognitive behavioral therapy- (CBT)⁴ • cognitive processing therapy • cognitive therapy • exposure therapy 	Strong For
For adult patients with PTSD, the panel suggests that clinicians offer one of the following psychotherapies/interventions (listed alphabetically): <ul style="list-style-type: none"> • brief eclectic psychotherapy • eye movement desensitization and reprocessing (EMDR) • narrative exposure therapy 	Weak For
For adult patients with PTSD, there is insufficient evidence to recommend for or against clinicians offering the following psychotherapies/interventions (listed alphabetically): <ul style="list-style-type: none"> • relaxation • seeking safety 	Insufficient
Pharmacotherapy	
For adult patients with PTSD, the panel suggests that clinicians offer one of the following (listed alphabetically): <ul style="list-style-type: none"> • fluoxetine • paroxetine • sertraline • topiramate • venlafaxine 	Weak For
There is insufficient evidence to recommend for or against clinicians offering risperidone for treatment of adults with PTSD.	Insufficient
Comparative Effectiveness	
For adult patients with PTSD, the panel recommends clinicians offer either exposure or exposure plus cognitive restructuring when both are being considered.	Strong For

⁴ 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.

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For adult patients with PTSD, the panel recommends clinicians offering either venlafaxine ER or sertraline when both are being considered. ⁵	Strong For
For adult patients with PTSD, the panel suggests clinicians offer CBT rather than relaxation when both CBT and relaxation are being considered.	Weak For
For adult patients with PTSD, the panel suggests clinicians offer exposure therapy rather than relaxation when both exposure therapy and relaxation are being considered.	Weak 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

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⁵ 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 weak recommendation for venlafaxine compared to no intervention and a weak 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

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3 *Background and Justification: The Scope of the Problem*

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

25 Epidemiological research has demonstrated that traumatic events are common and thus
26 most humans will experience a potentially traumatic event at some point in their lifetime

1 (Breslau & Kessler, 2001; Copeland, Keeler, Angold, & Costello, 2007; Kessler, Sonnega,
2 Bromet, Hughes, & Nelson, 1995; McLaughlin, Koenen, Hill, Petukhova, Sampson, Zaslavsky &
3 Kessler, 2013). At the time of occurrence or shortly thereafter, trauma generally causes
4 physiological and psychological stress responses that are overwhelming and that exceed or
5 greatly challenge the affected individual's capacity to cope. Individuals' post-trauma reactions
6 show great variability. Reactions range from those that are highly resilient with little or no
7 emotional distress to those that are relatively mild and short-term, to those that are major,
8 chronic, and highly debilitating. Disorders of medical or mental health may or may not follow
9 (Bonanno, 2004). Trauma can also impact others besides the primary victim(s), for example,
10 relatives/loved ones, first responders, therapists and other helpers, and others who can be
11 affected vicariously (Badger, Royse, & Craig, 2008; Hojat, 2007; Hojat, Gonnella, Nasca,
12 Mangione, Vergare, & Magee, 2002; Huddleston, Paton, & Stephens, 2006; McLean, Wade, &
13 Encel, 2003; Pearlman & Saakvitne, 1995; Schauben & Frazier, 1995). Thus, the toll of trauma
14 can be wide ranging and quite uneven.

15 Posttraumatic Reactions and Diagnoses. The vast majority of individuals exposed to
16 potentially traumatic events experience posttraumatic *reactions*, such as intrusive memories of
17 the event or autonomic arousal (e.g., difficulty concentrating, hyper-alertness, increased
18 physiological activation and reactivity) within hours or days of the traumatic event. Most
19 reactions remit spontaneously within the first month or so, as the individual processes them and
20 comes to term with what happened (Rothbaum, Foa, Riggs, Murdock, & Walsh, 1992; Nugent,
21 Saunders, Williams, Hanson, Smith, & Fitzgerald, 2009; Orcutt, Erickson, & Wolfe, 2004).
22 However, in some cases, the reactions persist and some become clinical *symptoms* that meet
23 criteria for one or more posttraumatic diagnoses, per the *DSM-5* (Marshall, Olfson, Hellman,
24 Blanco, Guardino, & Struening, 2001). In the early aftermath (ranging from two days to a month)
25 post-trauma, these symptoms may meet criteria for Acute Stress Disorder (ASD). If they last
26 more than a month, they may then meet criteria for PTSD. According to the *DSM-5*, "The

1 essential feature of PTSD is the development of characteristic symptoms following exposure to
2 one or more traumatic events,” (American Psychiatric Association, 2013; p. 274). Additionally,
3 “The symptoms of PTSD and the relative predominance of different symptoms may vary over
4 time.... Symptom recurrence and intensification may occur in response to reminders of the
5 original trauma, ongoing life stressors, or newly experienced traumatic events” (American
6 Psychiatric Association, 2013; p. 277). A delay of months or even years may occur before the
7 full criteria for the diagnosis are met (“delayed expression” PTSD).

8 In *DSM-5*, PTSD was moved beyond a fear-based anxiety disorder to a new category
9 entitled, “Trauma- and Stressor-Related Disorders.” PTSD as now defined in the *DSM-5*, is
10 characterized by four core symptom clusters: (1) recurrent, involuntary, and intrusive
11 recollections of the event, (2) avoidance of stimuli associated with the trauma, (3) negative
12 alterations in cognitions or moods associated with the event, or numbing (or both), and (4)
13 alterations in arousal and reactivity, including a heightened sensitivity to potential threat, as
14 opposed to three symptom clusters (1) re-experiencing, (2) avoidance and numbing, and (3)
15 hyperarousal contained in the previous version, *DSM-IV-TR* (American Psychiatric Association,
16 2000). In addition there is now a dissociative subtype (Friedman, Resick, Bryant, & Brewin,
17 2011). Of note, all of the studies included in the RTI-UNC systematic review that served as the
18 evidence base for this report used *DSM-IV-TR* or earlier *DSM* criteria and are those discussed
19 throughout this guideline.

20 PTSD is associated with emotional dysregulation ranging from heightened reactivity
21 (intrusive memories, flashbacks, startle responses, and feeling as though the trauma is
22 occurring again) to emotional withdrawal and shutdown (i.e., numbing, alexithymia, and
23 dissociation), as well as oscillation between the two (American Psychiatric Association, 2013;
24 Dalgliesh & Power, 2004; Herman, 1992; Rasmussen & Shalev, 2014). It further involves
25 physiological activation/hyperarousal and hypervigilance and changes in cognitions and beliefs
26 about self and others including spiritual and moral questioning and meaning making. Moreover,

1 it can involve increased risks to safety and well-being (i.e., risk of suicide and self-injury,
2 exposure to physical danger, and sexual risk-taking); behavioral and substance addictions (i.e.,
3 as means of coping with physical and emotional pain); physical injury, medical conditions and
4 illnesses, and their associated treatment burdens and medical costs; and relational distress and
5 social disruption (American Psychiatric Association, 2013; Dalgliesh & Power, 2004; Herman,
6 1992; Rasmussen & Shalev, 2014). Many individuals with PTSD have decreased ability to
7 function at work or school and experience other life adversities including job loss; difficulty with
8 authority figures; difficulty maintaining intimate relationships and in child rearing; family discord;
9 and reduced educational and economic attainment. Epidemiologic studies also have found that
10 a high percentage of individuals with PTSD suffer from co-occurring mental disorders, most
11 notably substance abuse, anxiety, or major depressive disorder, and a heightened risk for a
12 variety of health problems.

13 Available PTSD Treatment Guidelines. Given that numerous treatment approaches for
14 the amelioration of PTSD symptoms have been developed in recent years, there is an urgent
15 need for mental health professionals and the public to discern what is and is not known and
16 what is effective and for whom. To date, numerous professional organizations and agencies
17 have developed guidelines for the treatment of patients with PTSD, including the American
18 Psychiatric Association, the Australian Centre for Posttraumatic Mental Health (part of the
19 National Health and Medical Research Council), the International Society for Traumatic Stress
20 Studies (ISTSS), the Institute of Medicine (IOM) of the National Academies of Sciences,
21 Engineering, and Medicine, the United Kingdom's National Institute for Health and Care
22 Excellence (NICE), and the US Department of Veterans Affairs and Department of Defense (VA,
23 DoD). All of these guidelines have found evidence in support of several trauma-focused
24 psychological interventions (i.e., those that treat the symptoms of PTSD by directly addressing

1 thoughts, feelings, or memories of the traumatic event) as first-line⁶ treatments for adults with
2 PTSD, and all, with the exception of the IOM report, recognize at least some benefit of
3 pharmacologic treatments for PTSD (Jonas et al., 2013, ES, p.2).

4 As noted by Jonas et al., (2013) "... most guidelines identify trauma-focused
5 psychological treatments over psychopharmacological treatments as the preferred first step and
6 view medications as an adjunct or a next-line treatment" (ES, p.3). The ISTSS PTSD guideline
7 (2008) acknowledges that practical considerations, such as unavailability of trauma-focused
8 psychological treatment or patient preferences, may guide treatment decisions. The guidelines
9 developed by the Australian Centre for Posttraumatic Mental Health (Australian Centre for
10 Posttraumatic Mental Health, 2013) call for a sequencing of treatment, with initial emphasis
11 placed on personal safety, skills for emotional regulation and life stabilization as well as the
12 development of the treatment relationship, before the application of trauma-focused treatment
13 modalities specifically for the symptoms of PTSD.

14 **The APA Clinical Practice Guideline for the Treatment of PTSD**

15

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

17 This American Psychological Association CPG differs in substantive ways from others
18 that are currently available. The current effort is the first to develop a PTSD clinical practice
19 guideline that fully applies and builds upon the standards established by the Institute of
20 Medicine (IOM) of the National Academies of Sciences, Engineering, and Medicine standards
21 for developing independent, reliable, and high-quality practice guidelines (IOM, 2011a & 2011b).
22 As such, the current undertaking adds value beyond previously published PTSD guidelines and
23 literature in several important, distinguishable ways. These include (a) an independent and
24 comprehensive systematic review (SR) of the PTSD treatment literature; (b) a transparent

⁶ Note that the APA PTSD GDP is not using the terminology "first line" etc. when recommending treatments.

1 process for involving consumer stakeholders and professionals from multiple disciplines in the
2 PTSD GDP; (c) procedures for identifying and managing real and potential conflicts of interest
3 throughout the guideline development process; (d) identification of patient values and
4 preferences through review of published research literature and input from consumer and
5 clinician members of the panel; (e) identification of harms and burdens of treatments through
6 review of published research literature and input of consumers and clinician members of the
7 panel; (f) systematic use of decision-table templates to guide panel members in the
8 development of recommendations that take into account the strength of the research evidence
9 for benefit and harm, the relative magnitude of treatment benefit and treatment harm, the values
10 and preferences of patients, and the applicability of the evidence to external populations.

11 A core methodological component of the current effort was the use of an independent,
12 comprehensive systematic review of the adult PTSD treatment literature that provided clearly
13 specified inclusion and exclusion criteria, a standard method for grading risk of bias of individual
14 studies and strength of evidence for bodies of evidence, and sensitivity analyses to assess the
15 impact of excluding studies judged to be at high risk of bias (Jonas et al., 2013). “Evidence-
16 based clinical practice guidelines represent a systematic approach to translating the best
17 available research evidence into clear statements regarding treatments for various health
18 conditions” as an aid to the practitioner and the patient (Hollon et al., 2014, p. 214). Moreover,
19 this guideline includes the three dimensions identified by the American Psychological
20 Association Presidential Task Force on Evidence-Based Practice (2006): (1) grounding in the
21 best available science; (2) practitioner expertise in application decisions; and (3) patient
22 preferences and values.

23 Constituting an interdisciplinary PTSD GDP that included representation from mental
24 health consumer groups and multiple professional disciplines -- psychology, social work,
25 psychiatry, and primary care -- was another cardinal feature of the current effort that was clearly

1 aligned with the IOM standard on GDP composition. A significant limitation of many already
2 published treatment guidelines is a lack of attention to providing information on financial,
3 intellectual, and other potential and real conflicts of interest (COIs) among the members of
4 either the SR and/or the guideline development panel (Lenzer, Hoffman, Furberg, & Ioannidis,
5 2013). In the current effort panel members were required to disclose all COIs, as will be
6 discussed in detail later.

7 This is the first guideline for PTSD treatment that explicitly incorporates actual and
8 potential harms and burdens of treatments into the recommendation process. Because the
9 strength of evidence for harms and burdens for all psychological treatments in this systematic
10 review was insufficient/very low, harms and burdens did not, in practice, have a substantial
11 impact on the recommendations for psychological treatments. However, as more data on harms
12 and burdens for PTSD treatments accrue from additional research studies, recommendations
13 for treatments, based on the process reported here, will more precisely represent a balancing of
14 benefits and harms of treatments. The need for more data on harms/adverse effects of
15 psychological treatments is described at greater length in the section on research gaps.

16 The IOM standards include reliance on independent and systematic reviews (SR) of the
17 literature organized around key questions (KQ). As discussed in more detail below in the
18 Process and Methods Section, the following IOM standards in Table 2 have been closely
19 followed in the development of this clinical practice guideline for PTSD. Please refer to Hollon et
20 al. (2014) for additional details about APA's Clinical Practice Guideline initiative.

21

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1 **Table 2**

2 *IOM Standards for Developing Trustworthy Clinical Practice Guidelines*

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

1 interventions, (d) evidence that current practice is not optimal, (e) value placed on
2 different outcomes, or (f) resources available for health care.

3 _____

4

5 *Treatment Outcomes Considered in the Guideline.*

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

12 From this original list, the members of the APA PTSD GDP (hereafter referred to as the
13 panel) identified and rated treatment outcomes to prioritize them, using the Delphi method
14 following the GRADE consortium system recommendation (Guyatt et al., 2011). In assigning
15 their ratings, panel members were asked to consider the importance of the outcome for
16 decision-making in the treatment of symptoms of PTSD in adults. They considered the
17 importance of an outcome for someone making a decision to use or not to use a particular
18 treatment, taking into consideration the perspectives of both providers and patients. They rated
19 the absolute importance of each outcome on a 9-point scale ranging from 1 (not important) to 9
20 (critical). At the same time, the panel also generated a list of outcomes that would be included in
21 an ideal world, identifying outcomes of importance whether or not they were among the
22 outcomes included in the RTI-UNC Systematic Review. A wide range of outcomes, including
23 maintenance of treatment gains and peer support were considered but were not rated

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

12 Table 3. *Outcomes Considered by the Panel*

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

13
 14 *The RTI-UNC Systematic Key Questions and Analytic Framework*. The RTI-UNC review
 15 examined key questions listed on page seven of the systematic review. In keeping with the
 16 AHRQ system for formulating these questions, the PICOTS framework (which stands for

1 Populations, Interventions, Comparators, Outcomes, Timing, and Settings) (Samson &
2 Schoeller, 2012) was considered. The analytic framework for the RTI-UNC Systematic Review
3 is also on page seven of the report (Jonas et al., 2013). The APA PTSD GDP followed a multi-
4 step process for making clinical recommendations based upon the empirical findings included in
5 the RTI-UNC Systematic Review. The process and methods of the systematic review resulting
6 in these treatment recommendations are described in the section following these
7 recommendations.

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Process and Method

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Undertaking the Systematic Review

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Scoping. Prior to the empanelment of members to the PTSD GDP, members of the APA
Advisory Steering Committee (ASC) proposed a 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 proposal of key questions and issues. Although there have been multiple
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) (in
addition to the clinical guidelines produced by organizations and agencies that were discussed
above), the ASC chose to use the AHRQ exclusively because the organization had developed a
systematic review process consistent with IOM standards (IOM, 2011 b) that included important
features not found in reviews produced by other organizations.

26

27

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

1 International-University of North Carolina Evidence-Based Practice Center (RTI-UNC EBPC),
2 one of 13 sites funded by AHRQ for the development of systematic reviews on a variety of
3 health topics. The RTI-UNC EBPC has specialized in detailed and highly transparent systematic
4 reviews in the area of mental health and substance use disorders and thus could be expected to
5 do the same regarding the systematic review of PTSD treatment for adults. The RTI-UNC EBPC
6 conducted the literature review and analysis for the systematic review in 2012 and produced it
7 as the report, *Psychological and Pharmacological Treatments for Adults With Posttraumatic*
8 *Stress Disorder (PTSD)* a year later (Jonas et al., 2013). It is 760 pages, including raw and
9 synthesized data for all comparisons described in the report and has appendices including the
10 ratings of all of the reviewed articles. The APA GPD used this systematic review as its primary
11 base of evidence. Importantly, as anticipated, it gave the panel the ability to investigate the data
12 and rationale for conclusions included in the report.

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

1 Conflicts of interest. As noted above, before final appointment to the GDP, nominees
2 provided information regarding possible conflicts of interest, a significant issue in the AHRQ and
3 IOM standards. *Conflicts of interest* (COI) are defined as, “a divergence between an individual’s
4 private interests and his or her professional obligations such that an independent observer
5 might reasonably question whether the individual’s professional actions or decisions are
6 motivated by personal gain, such as financial, academic advancement, clinical revenue
7 streams, or community standing” (Institute of Medicine, 2011, p. 78; the definition is drawn from
8 Schünemann et al., 2009, p. 565). The IOM report additionally discusses intellectual COIs
9 relevant to clinical practice guidelines, which are defined as “academic activities that create the
10 potential for an attachment to a specific point of view that could unduly affect an individual’s
11 judgment about a specific recommendation” (Institute of Medicine, 2011, p. 78; the definition is
12 drawn from Guyatt et al., 2010, p. 739).

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

25 Once the panel was formed, all members completed an educational module on COI that
26 underscored the importance of identifying and managing any that had either been identified or

1 that might come to light. Members were asked to verbalize any actual or potential conflicts in
2 their face to face meetings so all members of the GDP would be familiar with the diversity of
3 perspectives and range of possible influences and biases. COI forms were updated on an
4 annual basis and panel members and staff were asked to provide more timely updates if there
5 were any changes in their disclosures that could be relevant to the development of an unbiased
6 guideline. The APA COI policy and disclosure form can be found in Appendix F.

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

1 quantitative meta-analyses most commonly because there was only one trial of a particular
2 treatment.

3 Decisions Regarding Assessment and Inclusion/Exclusion of Studies. Identified studies
4 were then screened and selected for inclusion on the basis of risk of bias (ROB) ratings
5 assigned to each. *Risk of bias* assessment considers the degree to which an individual study is
6 free of systematic error (bias), i.e., the degree to which the study has high internal validity. Risk
7 of bias ratings are key components of any systematic review because they reduce the risk that
8 conclusions are based on studies that are methodologically flawed in some significant way.
9 Twelve items were included in the ROB assessment to evaluate the potential for the following
10 biases: selection bias (adequacy of randomization process and concealment of randomization
11 allocation), confounding (comparability of baseline covariates), performance bias (adequacy of
12 masking of participants and researchers), detection bias (masking of outcome assessment),
13 attrition bias (i.e., attrition rate, differential attrition rate across treatment groups, handling of
14 missing data, use of intention-to-treat analysis), and measurement bias (validity and reliability of
15 outcome measures; treatment fidelity). For the RTI-UNC systematic review, the assessment
16 was conducted by two investigators, one an experienced researcher; differences in ratings were
17 resolved by consensus or by review by another experienced researcher. Studies were rated as
18 low, medium, or high risk of bias, with high risk signifying results of questionable validity,
19 typically due to a fatal flaw, such as very high attrition. Appendix E, pages E1 – E27 of the RTI-
20 UNC systematic review describes the risk of bias criteria, questions used to assess those
21 criteria, and ratings of all individual studies included in the systematic review.

22 Assessing Strength of Evidence. The systematic review included assessment of the
23 strength of evidence for all bodies of evidence. A body of evidence is the aggregated data, for a
24 particular intervention for a particular outcome, from more than one study. For instance, the
25 findings on the effects of cognitive processing therapy on PTSD symptom reduction, based on

1 the four studies of medium risk of bias or less that were included in the meta-analysis, is a body
2 of evidence.

3 *Strength of evidence* (SOE) refers to a body of evidence--the results from one or more
4 studies, rather than of a single research study for a specific outcome--that address a specific
5 research question. The goal of grading the SOE is to determine the confidence that the
6 estimated effect of an intervention is the true effect, something that has broad implications for
7 reliability of the findings and the public's confidence in them. For high strength evidence, "future
8 research is very unlikely to change confidence in the estimate of the effect," per Owens et al.,
9 (2010).

10 SOE rating of randomized trials by the AHRQ EBPCs is the assessment of a body of
11 evidence based on four major criteria, of which *risk of bias* (defined and discussed above) is the
12 first, followed by *consistency*, *directness*, and *precision* (Owens et al., 2010). *Consistency* is the
13 degree to which the direction of effect is the same or different in the studies included in a body
14 of evidence. If several studies find that an intervention leads to a reduction in PTSD symptoms
15 but other studies find that the intervention leads to an increase in PTSD, the body of evidence is
16 rated as inconsistent. *Directness* is the degree to which the evidence linking the effect of an
17 intervention to an outcome is based on: 1) the true health outcome, as opposed to a surrogate
18 marker of that health outcome and 2) head-to-head comparison of individual interventions as
19 opposed to comparison of two separate bodies of evidence. For example, if a body of evidence
20 in which the effect of an intervention on the outcome "loss of PTSD diagnosis" were to include
21 only data on PTSD symptom reduction, it would be rated as indirect. *Precision* of an estimate is
22 based on the width of the confidence interval around the estimated summary effect size in a
23 meta-analysis; the narrower the confidence interval, the greater the precision. A more precise
24 estimate provides stronger evidence that the estimated magnitude of effect for the results of an
25 intervention is the true effect. If two clinically distinct conclusions (e.g., that an intervention is

1 better than inactive control and that an intervention is worse than inactive control) are possible
2 based on a wide confidence interval, the body of evidence is rated as imprecise.

3 Strength of evidence rating of randomized trials by AHRQ EBPCs also depends on three
4 additional minor domains: *dose-response relationship* (evidence that higher “doses” of an
5 intervention are associated with larger effects represents higher strength evidence), *magnitude*
6 *of an effect* (large-magnitude effects represent higher strength evidence), and, *publication bias*
7 (evidence that unpublished studies were not included in summary effect estimates lowers the
8 strength of evidence). For the RTI-UNC systematic review, two researchers conducted strength
9 of evidence assessments for each body of evidence (which could include one or more studies).
10 Each was rated as high, moderate, low, or insufficient/very low strength. Disagreements
11 between the two raters were resolved by consensus or by the assessment of another
12 experienced researcher. Appendix G (pp. G1-G54) of the RTI-UNC review describes the
13 strength of evidence criteria and questions (items) used to assess those criteria. Strength of
14 evidence for all bodies of evidence used in the development of the current guideline is shown in
15 the Evidence Profiles, included in Appendix C. Please see the section on Evidence Profiles
16 below for a description of Evidence Profiles.

17 Types of Comparison (Control) Groups Used by Studies Included in the RTI-UNC
18 Systematic Review

19 Among the randomized trials of psychological interventions for which the panel
20 conducted decision tables, *inactive control* groups typically consisted of either treatment as
21 usual (TAU) or wait-list (WL) controls. The elements included in treatment as usual depended
22 to some extent on the setting in which the trial was conducted. For wait list control groups,
23 participants were allocated to a waiting list and then given the active treatment after those
24 allocated initially to active treatment; outcomes for those in the wait-list control groups were
25 assessed before they received active treatment.

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

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

12 Some of the trials of psychological interventions for which the panel conducted decision
13 tables used *active controls*, such as psychoeducation or substance abuse treatment, that had
14 not been specifically developed for treatment of PTSD, but which were thought to have
15 elements that might have a beneficial impact on PTSD symptoms or other critical or important
16 outcomes.

17 Finally, some of the trials of psychological interventions and trials of pharmacological
18 trials used other active treatments for PTSD as comparators.

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

23 The Development of Evidence Profiles. *Evidence profiles* (summaries of data in
24 available studies) were created by the RTI-UNC team from evidence collected for the
25 systematic review regarding the efficacy of psychological or pharmacological treatments or the
26 comparative effectiveness of psychological and pharmacological treatments in head-to-head

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

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

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

24 Although some have questioned the applicability of some randomized trials due to
25 potential differences between sample characteristics or treatment settings and the “real world,”
26 the panel decided to not supplement the randomized trials included in the SR with observational

1 (i.e., non-randomized and less methodologically rigorous) treatment studies, due to the potential
2 for confounding bias in observational studies (Fewell, Smith, & Sterne, 2007; Rothman,
3 Greenland, & Lash, 2008). This decision is consistent with the position of all major organizations
4 that evaluate research and conduct systematic reviews, including GRADE, Cochrane, NICE,
5 AHRQ Evidence-Based Practice Centers, that randomized trials have lower potential for bias
6 than observational studies (Guyatt et al., 2011; National Institute for Health and Care
7 Excellence, November 2012; Reeves, Deeks, Higgins & Wells on behalf of the Cochrane Non-
8 Randomised Studies Methods Group; Viswanathan et al., 2012).

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

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

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- 1 • Do not consider mechanisms of change in formulating guideline recommendations
- 2 about interventions (i.e., consider only evidence for efficacy/effectiveness)
- 3 • In addition to listing the overall strength of evidence ratings (as required by GRADE),
- 4 separate strength of evidence ratings for benefits and for harms will be listed
- 5 • If no data are available related to patient preferences/values, low rating of certainty and
- 6 unknown rating of variability will be assigned
- 7 • Panel members will examine primary studies included in the RTI-UNC systematic
- 8 review (in addition to the decision table) only under agreed upon conditions to avoid
- 9 introducing bias into the process (i.e., to avoid giving greater attention and examination
- 10 to one study versus another without a pre-determined rationale). The goal was to use a
- 11 systematic method for examining primary studies in order to avoid a process in which
- 12 they were selected based on particular panel member's interest that could bias the
- 13 process. Possible conditions for examining primary studies included:
- 14 ○ Where there is a large magnitude of effect for a benefit yet low or
- 15 insufficient/very low strength of evidence
- 16 ○ For evidence on critical outcomes only

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

24

1 *Completion of Decision Tables*

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

6 Rating of aggregate/ global SOE. For each of the 19 Decision Tables, *aggregate/global*
7 *SOE* was based on the SOE from the systematic review for the two critical outcomes, namely,
8 PTSD symptom reduction and serious adverse events. *In accordance with the GRADE*
9 *consortium system, the panel concluded that the aggregate SOE could be no higher than the*
10 *lowest individual SOE for each of the critical outcomes (Guyatt et al 2012).* For example, if one
11 critical outcome had 'high' strength of evidence but the other critical outcome had 'low' strength
12 of evidence, the global quality of evidence for that particular decision table would have to be
13 'low,' since that is the lowest SOE for an individual critical outcome. The strength of evidence for
14 serious harms, one of the panel's critical outcomes, was insufficient/very low, for all
15 interventions for which decision tables were completed. This explains why the global strength of
16 evidence was insufficient/very low for all interventions, despite low, moderate or high strength of
17 evidence for the critical outcome of PTSD symptom reduction.

18 Assessing Magnitude of Benefits. One of the key components of the decision-making
19 process for the GDP was assessment of the balance between benefits and harms. This required
20 that both benefits and harms be quantified. This section describes the methods used to quantify
21 the *magnitude (size) of benefits*. Quantification of benefits was based on data from the
22 quantitative meta-analyses for each of the important and critical outcomes that the panel had
23 selected at the start of the GDP process for those interventions that had at least low quality of
24 evidence for the critical outcome, PTSD symptoms reduction. For each of the outcomes,
25 magnitude of benefits was rated on a five-point scale: 1) large/medium benefit; 2) small benefit;
26 3) no effect; 4) small harm; 5) medium/ large harm. To reduce the potential for end-aversion

1 (i.e., central tendency) bias (Streiner & Norman, 2008), the panel chose to combine medium
2 benefits and large benefits into one category rather than including them as separate categories.
3 The same was done for medium and large harms.

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

13 SMDs are also reported for continuous outcomes. An SMD is the mean difference
14 divided by the pooled standard deviation of the outcome among participants. It is also known as
15 an “effect size” and is equivalent to Cohen’s *d* (Borenstein et al., 2009). An SMD is expressed in
16 terms of standard deviation units; an SMD equal to 1 means that there was a 1 standard
17 deviation difference in the outcome measure between interventions being compared. The panel
18 used the same criteria for assessing *magnitude of effect* using SMDs as the systematic review:
19 approximately 0.2 or less was rated as a small effect, 0.5 as a medium effect, and 0.9 or greater
20 as a large effect.

21 For dichotomous outcomes, such as loss of PTSD diagnosis (yes/no), the magnitude of
22 effect was measured as a *risk difference*, defined as the difference in incidence (risk) of the
23 outcome across treatment groups. The *summary (pooled) risk difference* is based on combining
24 risk differences from multiple studies in a meta-analysis, after weighting the individual study risk
25 differences by the inter-study variance (in a random-effects meta-analysis) (Borenstein et al.,
26 2009).

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

9 The panel used a general rule that the magnitude of benefit would be rated as “no effect”
10 if the point estimate was near the null value of zero and it was estimated precisely (i.e., the
11 confidence interval was narrow). Conversely, a magnitude of benefit was characterized as
12 “unable to rate” if the point estimate was far from the null value of zero and it was estimated
13 imprecisely (i.e., the confidence interval was wide and included values consistent with a large
14 effect in favor of either intervention.) An example will illustrate how the panel reached different
15 conclusions for two meta-analyses in which the p value for the summary pooled estimate was
16 greater than .05 in both. In the meta-analysis for Seeking Safety compared to active controls,
17 the weighted mean difference for PTSD symptom reduction was 1.45, 95% CI, (-2.50 to 5.40).
18 Because the point estimate (1.45) was near the null value of zero, the confidence interval was
19 relatively narrow and contained the null value of zero and the null value was near the middle of
20 the confidence interval, the panel concluded that there was no difference in effect between
21 Seeking Safety and active control treatment. In the meta-analysis for EMDR compared to
22 inactive controls, the weighted mean difference for prevention or reduction of co-morbid anxiety
23 was -11.08; 95% CI (-23.06 to 0.90). Because the point estimate was moderate and far from the
24 null value, but the confidence interval was wide and contained the null value of zero, the panel
25 concluded that it was unable to rate the magnitude of benefit for EMDR compared to inactive
26 controls. Thus, although the p value was greater than .05 in both situations (based on the fact

1 the 95% CI included the null value of zero) and thus “nonsignificant” using the traditional
2 hypothesis-testing framework, the panel came to a different conclusion in these two situations,
3 based on the magnitude of the point estimate, its relation to the null value, the width of the
4 confidence interval and the relation between the null value and confidence interval.

5 Assessing magnitude of harm/burdens. Since “serious adverse events” was one of the
6 two critical outcomes of treatment decided upon by the panel, these needed more precise
7 specification and definition. Ultimately, panel members considered events such as the need for
8 hospitalization secondary to suicidality as a serious adverse event and then identified additional
9 harms such as medication side effects. Harms were differentiated from burdens that were
10 identified as disruptions associated with treatment (i.e., time spent, homework/need to practice,
11 cost, convenience) rather than as injury. As discussed earlier, the systematic review of the
12 treatment literature did not generate sufficient data on harms and burdens of interventions
13 because, unfortunately, this information is not routinely reported in studies of psychosocial
14 interventions and not reported in detail in many studies of psychopharmacological interventions.

15 In response to this deficit, the panel commissioned APA staff to examine each article in
16 the systematic review in order to extract data regarding harms and burdens, such as
17 dropout/attrition, symptom worsening, homework, etc. The same data extraction was also
18 conducted on studies excluded from the systematic review because of high risk of bias or due to
19 the wrong study design ($n = 33$). Information regarding harms and burdens contained in these
20 excluded studies was examined because doing so is acceptable under the IOM standards,
21 which allow more relaxed criteria when examining literature on harms/burdens (IOM, 2011b, p.
22 8). In addition, a focused literature search of the PsycINFO® database was conducted to
23 identify articles from the years 1980 to June 2014 by combining the search term “PTSD” with
24 each of the following key words: “iatrogenic,” “negative effects,” “side effects,” “feasibility,”
25 “adverse events,” “relapse,” “recurrence,” “exacerbation,” “failure,” “dropout,” “spike,” “residual,”
26 and “worsening.” Then this same series of key words were combined with “trauma treatment”

1 and for each of the treatment domains included in the decision tables (both abbreviation and full
2 name): “EMDR” “Exposure” “CPT” “CT” “CBT,” “NET,” “Seeking Safety,” “brief eclectic therapy,”
3 “relaxation,” “topiramate,” “fluoxetine,” “paroxetine,” “sertraline,” “risperidone,” and “venlafaxine.”
4 Titles and abstracts ($n = 2,448$) were reviewed for papers that focused on PTSD treatment in
5 adult populations. After removing duplicates and non-peer reviewed articles (i.e., dissertations,
6 chapters, reviews), 150 articles were identified through this focused literature search. Of these,
7 90 were excluded because they utilized a treatment intervention not included in the systematic
8 review (e.g., mirtazapine, escitalopram), combined multiple treatment interventions (e.g.,
9 Dialectical Behavior Therapy + exposure), were only theoretical in nature, or were reviews or
10 meta-analyses. The 60 remaining articles included case study designs, observational studies,
11 archival data extractions, randomized controlled trials (RCTs) completed after the systematic
12 review was conducted (i.e., after May 2012), and secondary analyses of RCTs included in the
13 systematic review. It was from these studies that the panel had additional information on
14 possible harms or burdens associated with the interventions under consideration. See Table 4
15 for a listing of harms/burdens articles by intervention. All of this evidence was rated
16 insufficient/very low strength of evidence due to inclusion of observational study designs, which
17 have a higher risk of bias than randomized trials.

18 The issue of attrition as a possible harm was also addressed in this review. Since
19 attrition in a randomized trial can signify different things (i.e., it may be evidence that a treatment
20 is not acceptable or tolerable to patients but it can also be evidence that a treatment is working
21 and the patient leaves treatment when symptoms are ameliorated and before it is concluded)
22 the panel did not consider it to be a harm unless information on the reasons for attrition were
23 specified or unless there were differential attrition rates across treatment groups (Zandberg,
24 Rosenfield, Alpert, et al., 2016). Attrition was considered in the assessment of risk of bias by the
25 systematic review but that is a separate issue.

1 Finally, in order to supplement the limited information on harms and burdens gleaned
 2 from published research, clinicians on the panel reported their experiences in delivering,
 3 supervising or training in particular interventions and the concerns noted by colleagues.
 4 Consumer members reported on both their own and peer experiences with various
 5 interventions. In general, many of the identified harms and burdens were common to many,
 6 more general, psychosocial treatments, for example, the potential for short-term exacerbation of
 7 symptoms (harm) or the time necessary for multiple therapy sessions (burden). Though it was
 8 important to obtain all available sources of information on patient values and preferences, due
 9 to the inclusion of both anecdotal (i.e., clinician and consumer report) and peer reviewed article
 10 information, the Strength of Evidence on these topics was rated as insufficient/very low.

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

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19 **Table 4**

20 **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
Exposure	18	6	30
Cognitive Behavioral Therapy-Mixed	25	0	1
Eye Movement Desensitization and	6	6	4

22

Reprocessing Therapy			
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

1

2 Assessing patient values and preferences. In addition to assessing the benefits and the
3 harms/burdens associated with specific interventions, the panel attempted to ascertain patient
4 *values and preferences*. As described above, in order to ascertain this information, the panel
5 relied on a recently conducted systematic review (Simiola et al., 2015) of the literature by a
6 member of the GPD and her research team, supplemented by additional careful searching of
7 the professional literature by APA staff. Studies were identified through comprehensive
8 searches of the *PsycINFO*, *Medline*, *PubMed*, *Published International Literature on Traumatic*
9 *Stress*, and *Cumulative Index to Nursing and Allied Health Literature* electronic databases for
10 research published between January 1980 and September 2014. Combinations of the following
11 sets of search terms were used in each bibliographic database: (1) preferences, patient
12 preferences, choice behavior, decision making, patient satisfaction and (2) PTSD, trauma,
13 emotional trauma. Quantitative or qualitative research studies that reported on participant
14 preference of treatment for PTSD or a dual diagnosis including PTSD in either clinical or non-
15 clinical (e.g., analog) samples were reviewed. Data extraction included study population
16 demographics (e.g., age, ethnicity), type of trauma exposure, PTSD and other diagnostic
17 prevalence, research design, treatment options presented, method and procedures to evaluate
18 treatment preferences, and outcomes (Simiola et al., 2015). Unfortunately, the identified

1 literature only rarely addressed the specific comparison of interventions considered in any given
2 decision table. As a result, the panel had very little direct information about relative preference
3 for the specific treatments for which decision tables were completed.

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

12 Applicability of evidence. The final determinant that panel members considered, before
13 making recommendations, was the *applicability (generalizability)* of the evidence to various
14 populations and settings. To organize information on applicability, panel members applied the
15 PICOTS framework (referring to Populations, Interventions, Comparators, Outcomes, Time and
16 Settings) (Samson & Schoelles, 2012) because this was the same framework originally used by
17 RTI-UNC EPC to identify the key questions guiding the systematic review. The panel reviewed
18 specific information from the studies to determine if further information concerning applicability
19 pertaining to population, interventions, comparators, outcomes, timing, or settings needed to be
20 included and noted in each decision table.

21 All of the studies included in the systematic review are based on inclusion of participants
22 who met criteria for PTSD diagnosis based on *DSM-IV-TR* or earlier versions of the *DSM*. The
23 new *DSM-5* criteria for diagnosis of PTSD are different in several important ways from the
24 previous *DSM* iterations (American Psychiatric Association, 2015). It is therefore reasonable to
25 ask whether the results of trials based on inclusion of participants who met criteria for PTSD
26 based on *DSM-IV-TR* or earlier are applicable to patients who are diagnosed with PTSD based

1 on *DSM-5* criteria. In a large national sample in the United States, Kilpatrick et al. (2013)
2 showed 96.5% concordance between *DSM-IV-TR* and *DSM-5* on diagnosis or absence of
3 diagnosis of PTSD. We therefore believe that the findings from the systematic review and this
4 guideline, based on that systematic review, are likely to be applicable to patients who are
5 diagnosed with PTSD based on *DSM-5*.

6 An additional consideration is whether the recommendations in this guideline apply to
7 client populations that differ in other identifiable ways from those included in study samples.
8 Potential domains of difference include many facets of social identity (such as ethnicity, race,
9 gender, sexual orientation, disability status, and so on), as well as the cultural and material
10 realities that structure how people interact with each other, engage the world, adapt to new
11 challenges, and find meaning. As the panel observes in the Discussion section, the systematic
12 review concluded that the evidence was insufficient to identify treatment effects by any
13 subgroup on the basis of these kinds of indicators. Nevertheless, it is useful to note that many of
14 the studies from the RTI-UNC systematic review on which these guideline recommendations are
15 based included diverse samples. For example, study samples included military veterans, sexual
16 assault survivors, international refugees, and participants from the Americas, Africa, Australia,
17 Europe, and the Middle East. (These details can be explored further in Appendix D, Table D-2
18 of the RTI UNC systematic review.)

19 Decision-making regarding treatment recommendations. On the basis of the ratings of
20 these four factors (strength of evidence, balance of benefits versus harms/burdens, patient
21 values and preferences, and applicability) the panel then made a decision regarding its
22 recommendation for a particular treatment or comparison of treatments. The scale for
23 recommendations included the following: strong for, weak for, insufficient evidence, weak
24 against, strong against. Panel members were able to reach consensus regarding the strength of
25 recommendation given to each treatment in most cases but, for several, a vote was required.
26 The tally of votes is included on each decision table.

Complete formatting and copyediting will be performed following the public comment period.

1 External review process. This document was submitted to the APA Advisory Steering
2 Committee (ASC) for Development of Clinical Practice Guidelines for feedback. The ASC
3 comments were given a detailed review and response and the document was modified based
4 on that feedback. The document was subsequently posted on the APA web site (October 5-
5 December 4, 2016) and public feedback was solicited for 60 days. The document was revised
6 based on that feedback. Detailed responses to public comments are available on the APA web
7 site <http://apacustomout.apa.org/commentPracGuidelines/comment.aspx> .

8

Detailed Recommendations of the APA GDP for the Treatment of PTSD

Table 5. Efficacy of Psychological Compared to No Intervention⁷

Topic ⁸ :	Recommendation:	Summary Rationale Statement ⁹ :
#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.¹⁰ • 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.¹¹ • 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 Processing Therapy	Among adult patients with PTSD, the panel strongly recommends that clinicians offer cognitive	<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.

⁷ 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).

⁸ 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 XX.

⁹ 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 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 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.

¹⁰ 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.

¹¹ 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.

	<p>processing therapy compared to no intervention.</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.
<p>#3: Efficacy of Cognitive Therapy</p>	<p>Among adult patients with PTSD, the panel strongly recommends that clinicians offer cognitive therapy compared to no intervention.</p>	<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 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.

<p>#4: Efficacy of Exposure</p>	<p>Among adult patients with PTSD, the panel strongly recommends that clinicians offer exposure therapy compared to no intervention.</p>	<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 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.
<p>#5: Efficacy of Brief Eclectic Psychotherapy</p>	<p>Among adult patients with PTSD, the panel suggests that clinicians offer brief eclectic psychotherapy compared to no intervention.</p>	<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.

		<ul style="list-style-type: none"> • 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.
#6: Efficacy of EMDR	Among adult patients with PTSD, the panel suggests that clinicians offer EMDR compared to no intervention.	<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. ¹²	<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.

¹² Narrative Exposure Therapy received a weak 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.

		<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.
#8: Efficacy of Relaxation	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.	<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.

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Table 5 (Continued). Efficacy of Pharmacological Compared to No Intervention¹³

Topic:	Recommendation:	Summary Rationale Statement ¹⁴ :
#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 evidence of a small magnitude benefit for the critical outcome of PTSD symptom reduction.¹⁵ • There is moderate 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 evidence of a small magnitude benefit for the critical outcome of PTSD symptom reduction. • There is moderate evidence of a medium to large magnitude benefit for one additional important outcome: remission. • There is moderate 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 evidence for no effect of the critical

¹³ 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.

¹⁴ 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.

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.

		<p>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 evidence of a small magnitude benefit for the critical outcome of PTSD symptom reduction. There is low 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.
#12: Efficacy of Topiramate	Among adult patients with PTSD, the panel suggests that clinicians offer topiramate compared to no intervention. ¹⁶	<ul style="list-style-type: none"> • There is moderate 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 slightly outweigh harms/ burdens.

¹⁶ Topiramate received a weak rather than a strong recommendation, despite moderate strength of evidence of a large/medium magnitude of benefit for the critical outcome of PTSD symptom reduction, because there was very low strength of evidence for all other important benefit outcomes. All interventions that received a strong recommendation by the panel had not only at least moderate strength of evidence for PTSD symptom reduction but 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.

		<ul style="list-style-type: none"> • 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 evidence of a small magnitude of benefit for the critical outcome of PTSD symptom reduction. There is moderate 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.	<ul style="list-style-type: none"> • There is low 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.

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Table 5 (continued) Comparative Effectiveness

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Topic: Recommendation: Summary Rationale Statement¹⁷:

<p>#15: Exposure-based Therapy vs. Relaxation</p>	<p>Among adult patients with PTSD, the panel suggests clinicians offer exposure therapy rather than relaxation when both exposure therapy and relaxation are being considered.</p>	<ul style="list-style-type: none"> • There is insufficient/very low evidence that the critical outcome of PTSD symptom reduction is the same in exposure based therapy and relaxation therapy¹⁸. • There is moderate evidence of a medium to large magnitude benefit of exposure relative to relaxation for one additional important outcome: loss of PTSD diagnosis. • There is moderate evidence of a small magnitude benefit of 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 Exposure Based Therapy 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.
<p>#16: Exposure vs. Exposure Plus Cognitive Restructuring</p>	<p>Among adult patients with PTSD, the panel recommends clinicians offer either exposure or exposure plus cognitive restructuring when both are being considered.</p>	<ul style="list-style-type: none"> • There is insufficient/very low evidence that the critical outcome of PTSD symptom reduction is the same in exposure and exposure plus cognitive restructuring. • There is moderate evidence that loss of PTSD diagnosis is the same in exposure and exposure plus cognitive restructuring. • There was insufficient/very low strength of evidence for the critical outcome of

¹⁷ 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.

¹⁸ 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>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 Exposure as 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 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 ¹⁹ 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 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 recommendation.

¹⁹ 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).”

		<ul style="list-style-type: none"> • There is no evidence that raises concern about applicability.
#19: Venlafaxine ER vs. Sertraline	Among adult patients with PTSD, the panel recommends clinicians offering either venlafaxine ER or sertraline when both are being considered. ²⁰	<ul style="list-style-type: none"> • There is moderate evidence that the critical outcome of PTSD symptom reduction is the same in venlafaxine ER and sertraline. • There is low to moderate 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.²¹ • 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.

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²⁰ 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 weak recommendation for venlafaxine compared to no intervention and a weak 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.

²¹ 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."

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How these recommendations compare to recommendations in other PTSD guideline documents is addressed in the discussion section.

Impact of New Trials on Recommendations

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 a new systematic review on the RCTs that were published thereafter and then re-do the decision tables based on the revised evidence. However, the panel believed it was imperative to evaluate the impact of new evidence on its recommendations. Therefore, the panel did a comprehensive literature review to identify recent RCTs germane to the comparisons evaluated in this report and then assessed the potential impact of those new RCTs on its recommendations.

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. These criteria differ from the criteria used by the systematic review (Jonas, Cusack, Forneris, Wilkins, Sonis, Middleton, 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),

1 PsychINFO, Web of Science, and Excerpta Medica database (EMBASE). The librarian used the
2 same search terms used by systematic review (Jonas et al., 2013, Appendix H) with the
3 following exceptions:

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

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

13 The panel did not search for unpublished trials or dissertations. Trials that investigated
14 complementary and alternative medicine interventions and articles published in languages other
15 than English were not eligible for inclusion in the systematic review and were not subjected to
16 full-text search.

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

1 analyses and systematic reviews (n = 6) were subjected to full-text review. Common reasons for
2 exclusion at the full-text review stage are shown below:

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

14 The full-text review determined whether a trial met inclusion criteria shown in Table 7. The
15 intervention and comparators in each of those included trials was then compared to the
16 intervention and comparators for each of the panel recommendations to determine whether
17 there was a match. For instance, van den Berg et al. (2015) matched to the recommendation
18 on the efficacy of exposure (compared to controls), based on one treatment arm of exposure
19 and one treatment arm of wait-list control. On the other hand, Spence et al. (2014) was not
20 considered a match of the panel recommendation for exposure because one treatment arm
21 consisted of exposure plus psychoeducation plus stress management plus cognitive
22 restructuring while the other treatment arm consisted of all of those components without
23 exposure. In one sense, it could be considered a comparison of exposure to no treatment (since
24 the treatments other than exposure were the same in both treatment arms) but in a more
25 accurate sense, it is a trial of adding exposure to those other components (i.e., a trial of
26 adjunctive exposure), a comparison for which the panel did not make a recommendation. To be

1 consistent with the systematic review, the panel did not consider internet implementation of a
2 treatment (such as the trial that evaluated internet application of CBT (Ivarsson et al., 2014) or
3 group forms of a treatment (such as Resick's trial of group CPT (Resick et al., 2015) as new
4 treatments but simply variants of the original treatment. Those trials were, therefore, considered
5 as matches for the recommendations for efficacy of CBT and efficacy of CPT, respectively. On
6 the other hand, if a trial specifically compared a new form of implementation modality for a
7 treatment (e.g., CPT via video conferencing compared to CPT in person; Morland et al.,
8 2014), the trial was not considered a match for the recommendation of the treatment, CPT,
9 since that comparison specifically tests mode of implementation (video conferencing vs in-
10 person) rather than treatment itself.

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

22 As in the deliberations by the full panel for the decision tables, effect sizes were
23 characterized initially as small (0.2), medium (0.5) and large (0.9), but were categorized as
24 small or medium / large (i.e., medium and large effect sizes were considered together as one
25 category) for decision making about the magnitude of benefits. All effect sizes for efficacy
26 comparisons (i.e., active intervention compared to a control comparator) were reported as

1 positive numbers if the result favored the active intervention (i.e., if the group randomized to
2 active intervention had greater PTSD symptom reduction than those randomized to controls).
3 Negative effect sizes indicate that the control group had greater reductions in PTSD symptoms
4 than those in the active intervention group. For comparative effectiveness comparisons, in
5 which two active interventions were compared, effect sizes are reported as positive if the
6 participants allocated to the first listed intervention had greater improvement in PTSD symptom
7 reduction than those allocated to the second intervention.

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

16 *Results*

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

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

4 Table 6 summarizes the impact of the new trials on the panel's recommendations.
5 Tables 8-16 provide detailed information about the effect sizes for PTSD symptom reduction in
6 the new trials compared to the summary effect size from the systematic review. They also show
7 panel members' reasoning supporting the conclusion about the effect of the new trials on the
8 recommendations.

9 The strong recommendations for the following psychological interventions (i.e.,
10 compared to controls) were unlikely to change, based on the new trials: CBT, CPT, CT, and
11 exposure (Table 6). There is insufficient information to determine whether the weak
12 recommendation for EMDR, compared to inactive controls, would be likely to change based on
13 the new trials (Table 6). There were no new trials available for brief eclectic psychotherapy or
14 relaxation, compared to controls.

15 There is insufficient evidence available to determine whether the weak recommendation
16 for NET would change based on the evidence from new trials (Table 13). The effect size for
17 PTSD symptom reduction was medium / large in the systematic review and in the new trials. In
18 its original deliberations on NET, the panel concluded that unlike other treatments for which
19 strong recommendations were being made, there was only low strength of evidence for other
20 important outcomes for NET; this is why NET received a weak rather than a strong
21 recommendation. Since the effect size for PTSD symptom reduction is unlikely to change from
22 medium / large based on the new trials and the panel did not include information on other
23 important outcomes for NET from the new trials (the data on which a change in the
24 recommendation strength might hinge), the panel concluded that there is insufficient evidence to
25 determine whether the weak recommendation for NET efficacy is likely to change.

1 The weak recommendation for topiramate, compared to placebo, was unlikely to change
2 based on the new trials. There were no new trials that assessed efficacy of fluoxetine,
3 paroxetine, sertraline, or venlafaxine, or risperidone.

4 For comparative effectiveness recommendations, the following recommendations are
5 unlikely to change based on evidence from the new trials: the recommendation of exposure
6 instead of relaxation and the suggestion that clinicians offer either exposure or exposure plus
7 cognitive restructuring. There were no new trials available for comparative effectiveness
8 recommendations for CBT vs. relaxation, seeking safety vs. active controls, and venlafaxine ER
9 vs. sertraline.

10 As shown in the detailed tables for each recommendation, the effect sizes in the new
11 trials for PTSD symptom reduction were generally similar in magnitude and direction to the
12 SMDs for PTSD symptom reduction from the trials included in the systematic review.

13 *Discussion*

14 None of the panel's recommendations, made on the basis of evidence from the
15 systematic review, are likely to change as a result of new evidence from randomized trials
16 published between May 25, 2012 and June 1, 2016, with the possible exception of NET.

17 These conclusions must be tempered by several limitations. First, the panel did not rate
18 trials for risk of bias. It is possible that the findings would be different if risk of bias ratings were
19 conducted on the new trials. However, the panel believes that this is unlikely because most of
20 the effect estimates were grossly similar in magnitude (small vs medium/large) and almost all
21 were in the same direction as the SMDs for PTSD symptom reduction from the systematic
22 review. Further, in the systematic review, when sensitivity analyses were conducted by adding
23 into the meta-analysis those trials that were rated high risk of bias, they "did not produce
24 significantly different results for our pairwise meta-analyses; point estimates and confidence
25 intervals were generally very similar, and the sensitivity analyses did not alter any of our main
26 conclusions." (Jonas et al, 2012; p ES-16).

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

7 Third, it was sometimes difficult for the panel to determine whether an intervention in a
8 new trial should have been considered a minor modification of an intervention for which the
9 panel made a recommendation (and thus included in the new trials to compare to the
10 recommendation) or whether it should have been considered a completely new intervention and
11 thus not included in the trials compared to the recommendation. These ambiguous trials were
12 discussed by the panel subcommittee and disagreement was resolved by consensus. It is
13 possible that other reviewers would have come to different conclusions about those trials. That
14 is unlikely to have had a substantial impact on the overall conclusions since there were
15 relatively few of those trials.

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

1 systematic review, but it is possible that evidence on other important outcomes, could lead the
2 panel to conclude that the recommendation might change.

3 Fifth, the panel did not search for serious harms in the newly identified trials and did not
4 include serious harms in its deliberations about the likelihood that recommendations would
5 change based on evidence from the new trials. Because serious harms were rarely reported in
6 trials of psychological interventions included in the systematic review, the panel made the
7 decision to not search for serious harms in the new trials. If serious harms that had not been
8 reported in the trials included in the systematic review were detected and reported in the new
9 trials, that information could have had an impact on the panel's decisions. The panel believes
10 that this is unlikely.

11 Overall, with the exception of the recommendations for NET and EMDR, the findings
12 from this search update process indicate that the panel's recommendations would be unlikely to
13 change if the meta-analyses reported in the systematic review were updated to include the new
14 trials. The recommendations might change based on future trials, but the panel is confident
15 that, based on the trials published to June 1, 2016, the recommendations proffered by the panel
16 on the specific interventions discussed in this guideline, with the possible exception of NET, are
17 up to date.

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3 Table 6. Effect of new trials on recommendation

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 Exposure	Strong for	Recommendation unlikely to change
#5: Efficacy of Brief Eclectic Psychotherapy	Weak for	No new trials for comparison
#6: Efficacy of EMDR	Weak for	Insufficient evidence
#7: Efficacy of Narrative Exposure Therapy	Weak for	Insufficient evidence
#8: Efficacy of Relaxation	Weak for	No new trials for comparison
#9: Efficacy of Fluoxetine	Weak for	No new trials for comparison
#10: Efficacy of Paroxetine	Weak for	No new trials for comparison
#11: Efficacy of Sertraline	Weak for	No new trials for comparison
Recommendation	Strength and direction of recommendation	Effect of new trials on recommendation
#12: Efficacy of Topiramate	Weak for	Recommendation unlikely to change
#13: Efficacy of Venlafaxine	Weak for	No new trials for comparison
#14: Efficacy of Risperidone	Weak for	No new trials for comparison
#15: Comparative effectiveness of Exposure vs. Relaxation	Panel recommends exposure vs. relaxation	Recommendation unlikely to change
#16: Comparative effectiveness of Exposure vs. Exposure Plus Cognitive Restructuring	Panel suggests offering either exposure or exposure plus	Recommendation unlikely to change

	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

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3 **Considerations for Treatment Implementation**

4 The panel used rigorous processes promulgated by the Institute of Medicine for
5 developing this guideline and based its recommendations for PTSD treatments on evidence
6 from a strong and transparent systematic review conducted by RTI-UNC Evidence-based
7 Practice Center (Jonas et al, 2013). The panel recognizes, though, that there are important
8 factors that contribute to ethical and effective implementation of those treatments, including
9 informed consent and patient and patient-therapist relationship factors. Several such factors are
10 considered below.

11 *Informed Consent*

12 Patients benefit from receiving information about the treatments that are available and
13 under consideration, including their effectiveness, the procedures and process involved, risk-
14 benefits of each, and their practical as well as emotional demands. General informed consent
15 discussion is suggested to occur at the beginning of psychotherapy or pharmacological
16 treatment, as recommended by Bennett et al. (2006). Since PTSD often results from the

1 avoidance of painful trauma-related memories and emotions, it is suggested patients be
2 specifically informed that most (if not all) recommended psychological treatments involve some
3 degree of directed exposure to the avoided material with the specific goal of re-processing
4 emotions and cognitions to the point of resolution and symptom reduction. It is suggested
5 patients be informed they might feel worse for a period of time before beginning to feel better.
6 Optimally, informed consent results in collaboration and shared decision-making between
7 patient and provider over the entire course of the treatment.

8 *Role of Patient and Relationship Factors in Treatments for PTSD*

9 It is important to recognize that there is a body of literature distinct from this systematic
10 review that has shown an association between patient and patient-therapist factors (sometimes
11 called “common factors” and including relationship factors) and treatment outcome among
12 persons with a variety of mental disorders, independent of the type of psychotherapy utilized.

13 *Patient factors* associated with psychotherapy outcome include reactance level, stages of
14 change, preferences, coping style, culture, and religion/ spirituality. *Relationship variables*
15 associated with treatment outcome include therapeutic alliance, empathy, and the collection and
16 utilization of client feedback (for reviews, see Norcross, 2011; Norcross & Wampold, 2011).

17 There is a theoretical rationale for believing that the patient and relationship factors may
18 be especially important in psychotherapy for PTSD, particularly interpersonal trauma. Persons
19 with PTSD commonly have difficulties with trust and the development and sustaining of intimate
20 relationships both within and outside of psychotherapy (Zubriggen, Gobin, & Kaehler, 2012). In
21 addition, many (e.g., Cloitre, Chase, Stovall-McClough, Regina, & Chemtob, 2004; Ormhaug,
22 Jensen, Wentzel-Larsen, & Shirk, 2014; Wagner, Brand, Shulz, & Knaevelsrud, 2012) though
23 not all (Forbes et al., 2008; van Minnen, Arntz, & Keijsers, 2002) empirical studies that
24 examined relationship variables in the treatment of adults with PTSD have shown that
25 therapeutic alliance is directly associated with positive outcomes in treatment. For example, a
26 recent review of the literature specific to psychological treatment for trauma-related distress

1 found that therapeutic alliance was predictive of or associated with a reduction in symptomology
2 (Ellis, Simiola, Brown, Courtois, & Cook, under review). Accordingly, although it is beyond the
3 scope of this guideline to make recommendations regarding patient and therapist variables in
4 psychotherapy, it is prudent for clinicians to remain alert to these issues in psychotherapy with
5 persons with PTSD.

6 Patient variables, such as hope and expectation for change, are likely present in most
7 therapeutic encounters and procedures, including pharmacotherapy trials for mental health
8 disorders. When an active medication is compared to an inert pill, and individuals who receive
9 that inert pill experience or express improvement, this is called a placebo effect. Medications,
10 like psychotherapies, have both specific effects as well as these non-specific effects on
11 important outcomes.

12 *Professional Competence*

13 Research evidence documents that a large number of medical and mental health
14 patients have had trauma experiences in their backgrounds that directly or indirectly relate to
15 their reasons for seeking treatment (Felitti & Anda, 2010). At minimum, practitioners need to be
16 aware of this possibility and approach patients from a perspective that is trauma-informed (for
17 information on the trauma-informed care movement, see Clark, Classen, Fourn, & Shetty, 2015
18 and Falloot & Harris, 2001). There is clinical consensus that the treatment of traumatized
19 individuals requires specialized knowledge and skills regarding trauma and its psychology (see
20 Cook, Newman, & The New Haven Trauma Competency Group, 2014 for a listing of five
21 competency and several cross-cutting categories, each graded for different levels of practitioner
22 expertise, from basic/expected of all staff to advanced/expected in expert trauma treatment
23 practitioners). There is also clinical consensus that, in addition to proficiency in professional and
24 foundational aspects of mental health care (APA 2006; Barber et al., 2007a; Newman, 2010;
25 Rodolfa et al., 2013), specialized training in specific techniques is needed before their
26 application in clinical practice. At the present time, research investigations of training in

1 particular treatment modalities and adherence and fidelity to the application of the modality are
2 underway.

3 *Monitoring Treatment Response through Measurement Based Care*

4 MBC is the practice of basing clinical care on client data collected throughout treatment
5 (Scott & Lewis, 2015). Although the use of Measurement Based Care (MBC) has received
6 empirical support in the management of chronic medical illnesses (e.g., blood pressure,
7 diabetes), it has not been widely investigated in mental health treatment and is not yet
8 considered standard clinical practice (Harding, Rush, Arbuckle, Trivedi, & Pincus, 2011). Some
9 research on the efficacy of measurement-based care for the treatment of depression exists
10 (e.g., Guo et al., 2015), but there is little information on the use of detailed measurements
11 across time with specified symptom severity scales in order to increase efficacy or quality of
12 care for PTSD. While the Department of Veterans Affairs (VA) recently developed a guideline
13 and a mandate for measurement based care in mental health, including PTSD (Landes et al.,
14 2015), there is not yet research data supporting this particular practice. Although monitoring
15 PTSD symptoms across the course of treatment likely provides insight into progress and
16 highlights ongoing clinical targets, research is needed to determine whether monitoring of PTSD
17 symptoms improves client outcomes.

18 *Culture and Diversity Competence*

19 Competence regarding culture and diversity involves the recognition that all humans
20 have multiple and intersecting social identities based on variables such as sex, gender, race,
21 ethnicity, sexuality, social class, spiritual and religious identification, and linguistic status (among
22 many others, Hays, 2015) that can be similar to or divergent from those of the therapist.
23 Moreover, the variables associated with social identities can reflect an accompanying diversity
24 in lived and felt experience that is grounded in shared orientations, understandings, and
25 preferences labeled as culture. In the context of clinical intervention, culturally grounded
26 meanings and practices can afford therapeutic possibility even as they complicate whether and

1 how clients find therapist actions and recommendations intelligible, useful, and worthwhile.
2 Cultural competence (also called cultural humility—see Hunt, 2001) involves a willingness on
3 the part of the practitioner to not only learn about the patient directly from the patient or from
4 other sources of information but to also engage in ongoing self-reflection regarding the ability to
5 be respectful and appreciative of differences and diversities while treating the patient (Comas-
6 Diaz, 2012).

7 Many other issues are involved in addressing issues of culture and diversity. Brown
8 (2008) and others have written extensively on the importance of integrating principles of cultural
9 competence into trauma treatment that in turn apply to the utilization of evidence-based
10 interventions for PTSD. She has particularly noted that barriers to treatment-- especially
11 mistrust, access, and culture and linguistics--should be recognized and addressed. These are
12 important components of the therapeutic relationship and context that support treatment but are
13 beyond the purview of this document. For further reading, see Brown (2008), Comas-Diaz
14 (2012) and Hays (2015).

15 **Discussion**

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

18 This APA PTSD treatment guideline a) strongly recommends the following evidence
19 based psychotherapies for PTSD in adults: cognitive behavioral therapy (CBT), cognitive
20 processing therapy (CPT), cognitive therapy (CT), and exposure therapy (EXP) and b) suggests
21 the use of brief eclectic psychotherapy (BEP), eye movement desensitization and reprocessing
22 (EMDR), and narrative exposure therapy (NET). Overall, these conclusions are largely
23 consistent with guideline recommendations previously published by the World Health
24 Organization (WHO, 2013), the US Department of Veterans Affairs/Department of Defense
25 (VA/DOD, 2010), the International Society for Traumatic Stress Studies (ISTSS, 2009), the
26 Australian National Health and Medical Research Council (NHMRC, 2007), the UK National

1 Institute for Health and Care Excellence (NICE, 2005), and the American Psychiatric
2 Association (ApA, 2004).

3 Although some other guidelines prioritize treatments into “first-line” or “second-line”
4 treatments, the APA panel chose not to use these terms in its recommendations because
5 sufficient evidence from comparative effectiveness studies was lacking to justify using them.
6 The panel does, however, offer strong recommendations for some PTSD treatments and weak
7 recommendations for others.

8 Forbes et. al (2010) describe similarities and differences in recommendations for
9 treatments for PTSD across different guidelines. The 2010 VA/DoD guideline provides a strong
10 recommendation for CT, exposure therapy, stress inoculation training (SIT) and EMDR,
11 promoting these as first line treatments for PTSD in adults. Similarly, the 2009 ISTSS guideline
12 gives A level ratings to EX, CPT, CT, EMDR and SIT. The 2007 NHMRC guideline recommends
13 that adults with PTSD be offered trauma-focused CBT, EMDR, or *in vivo* exposure, and the
14 2005 NICE guideline recommends that 100% of individuals with PTSD be offered trauma-
15 focused CBT or EMDR. The 2004 American Psychiatric Association guideline recommends
16 CBT for treatment of PTSD with substantial clinical confidence (Category I), and recommends
17 EMDR, SIT, imagery rehearsal, and EX/PE with moderate clinical confidence (Category II). The
18 2013 WHO guideline does not give the highest recommendation in its grading system (i.e.,
19 “strong”) to any evidence-based psychotherapy for PTSD, but gives CBT with a trauma focus,
20 EMDR, and stress management a standard recommendation -- a rubric indicating that there
21 may be circumstances in which these treatments do not apply for persons with PTSD. All in all,
22 the current effort contributes to the compendium of guidelines that recommend, with varying
23 levels of strength and confidence, a core set of evidence-based psychotherapies for adults with
24 PTSD: cognitive behavioral therapy, cognitive processing therapy, cognitive therapy, exposure
25 therapy, brief eclectic psychotherapy, eye movement desensitization and reprocessing and
26 narrative exposure therapy. Although stress inoculation training (SIT) was given an A-level

1 rating by the 2008 ISTSS Guideline and Category II rating by the 2004 American Psychiatric
2 Association Guideline, the panel is not including it in this core set of evidence-based
3 psychotherapies. The RTI-UNC systematic review assigned a very low strength of evidence to
4 SIT versus inactive controls. Consistent with its rule to complete decision tables and provide
5 recommendations only on those interventions for which the strength of evidence was at least
6 low, the panel did not do a decision table or provide recommendations for SIT.

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

14 The 2013 WHO guideline recommends that the SSRIs and tricyclic antidepressants
15 (TCAs) be considered under circumstances in which recommended psychotherapies (stress
16 management, CBT with a trauma focus and EMDR therapy) have failed or are unavailable or
17 when patients present with co-morbid depression of moderate or greater severity. Similarly, both
18 the 2007 NHMRC and 2005 NICE guidelines caution that medications should not be used as a
19 *routine* first-line treatment for adults with PTSD in either general medical or specialty mental
20 health care, in preference to evidence-based trauma-focused psychotherapies. The NHMRC
21 guideline specifies that where medication is considered, SSRI antidepressants should be the
22 first choice and the other new generation antidepressants (notably mirtazapine) and TCAs
23 should be considered as a second line options. The current panel did not complete a decision
24 table or make recommendations for tricyclic antidepressants because the strength of evidence
25 was rated insufficient in the systematic review. Three RCTs were identified that were rated high
26 risk of bias due to completer-only analysis (instead of intention to treat) or high attrition. The

1 2010 VA/DOD guideline gives a strong recommendation to three SSRIs (paroxetine, sertraline,
2 and fluoxetine) and the SNRI, venlafaxine, describing them as first line (Category I) treatments
3 for PTSD in adults. Similarly, the 2004 ApA guideline recommends the SSRIs with substantial
4 clinical confidence (Category I) for adults with PTSD, and the 2009 ISTSS guideline
5 recommends the SSRIs (sertraline, paroxetine, and fluoxetine), venlafaxine, the TCAs,
6 mirtazapine, nefazodone, phenelzine and prazosin as A-level treatments that have accrued the
7 best evidence. Medications rated by the 2010 VA/DOD guideline as having fair evidence and
8 some benefit for treatment of PTSD in adults are mirtazapine, prazosin for sleep/nightmares,
9 nefazodone, phenelzine, and the TCAs. The VA/DoD guideline rates several medications as
10 ineffective or harmful, including topiramate, which in the current guideline is suggested for
11 PTSD in adults on the basis of the strength of new evidence. The panel did not complete
12 decision tables or make recommendations for mirtazapine, nefazodone, phenelzine, or
13 prazosin. The systematic review found insufficient/very low SOE for the critical outcome of
14 PTSD symptom reduction and the important outcome of reduction of comorbid depression or
15 anxiety for mirtazapine. There was one trial of nefazadone evaluated in the systematic review
16 but it was rated high risk of bias. Although some guidelines have recommended prazosin for
17 nightmares, the panel did not make any recommendations for prazosin because the panel did
18 not include nightmares as a critical or important outcome. The SOE was rated insufficient/very
19 low for PTSD symptom reduction, remission or loss of diagnosis for prazosin.

20 The current effort expands upon previously published PTSD guidelines by including
21 recommendations on comparative effectiveness of PTSD treatments. For example, among adult
22 patients with PTSD, the current guideline suggests using exposure therapy rather than
23 relaxation when both exposure therapy and relaxation are being considered. Similarly, the
24 current guideline suggests using CBT rather than relaxation when both CBT and relaxation are
25 under consideration, and either exposure or exposure plus cognitive restructuring when both are
26 being considered. As more data on the comparative effectiveness of PTSD treatments become

1 available, recommendations for treatments, based on the contrast of outcomes for efficacious
2 treatments, will represent a major advancement for future updates of this guideline.

3 One of the key issues facing clinicians is whether to recommend psychological
4 interventions or medication (or both) at the start of treatment for adults with PTSD.
5 Unfortunately, the panel members were not able, based on the evidence available to date from
6 the systematic review, to recommend one treatment (psychotherapy or pharmacotherapy)
7 versus the other. Only one trial (van der Kolk, 2007) comparing a psychological treatment to
8 medication treatment was identified that met inclusion criteria and was medium or lower risk of
9 bias. The SOE for PTSD symptom reduction was rated as insufficient/very low because of
10 unknown consistency and lack of precision.

11 The panel makes strong recommendations for several psychological treatments
12 (cognitive behavioral therapy, cognitive processing therapy, cognitive therapy, exposure
13 therapy) while it does not make any strong recommendations for medication treatments. This is
14 based primarily on the larger magnitude of benefits to harms for psychological treatments than
15 for medications that is driven by larger magnitude reduction in PTSD symptoms and fewer
16 known harms for psychological treatments than for medication treatments.

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

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

3 Trials of medications and psychotherapy for depression also raise concern about the
4 potential impact of methodological differences that may apply to PTSD trials. In a systematic
5 overview of meta-analyses of treatments for mental disorders, Huhn et al. (2014) showed that
6 the effect size for psychotherapy, compared to control group, was twice as large as the effect
7 size for medications, compared to placebo. However, in head-to-head trials comparing
8 psychotherapy to medications, there was no difference between those two treatment modalities
9 (Standardized mean difference, -0.05, 95% confidence interval, -0.24 to 0.13).

10 The bottom line is that, based on the best available evidence from the systematic review,
11 the panel is able to make strong recommendations for several psychological treatments but only
12 weak recommendations for some medications, recommendations that may change based on
13 future research. Clearly, head to head trials comparing psychological treatments to medications
14 are desperately needed; this issue is discussed in greater detail in the section on future
15 research needs.

16 *Strengths and Weaknesses of the RTI-UNC Systematic Review*

17 The systematic review that served as the evidence base for the panel's
18 recommendations has important strengths. First, the group that performed the systematic
19 review, the RTI-UNC Evidence-Based Practice Center, has conducted more than 50 systematic
20 reviews on a wide range of medical and behavioral topics since 2002. It has developed and
21 refined research methodology for conducting systematic reviews (Berkman et al., 2014; Guise
22 et al., 2014; Owens et al., 2010; Viswanathan et al., 2014) and has specialized in systematic
23 reviews in the area of mental health and substance abuse.

24 Second, the systematic review is highly transparent and includes raw data and
25 synthesized data for all comparisons described in the report. It also includes detailed
26 information on risk of bias ratings assigned to each article and strength of evidence for all

1 bodies of evidence that were assessed. This was crucial to the panel’s ability to understand not
2 only the findings but how they were obtained.

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

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

14 Second, for assessment of efficacy and comparative effectiveness of interventions, the
15 systematic review limited its evidence base to randomized trials. This is standard practice for
16 high-quality meta-analyses, including those conducted by the Cochrane Collaboration, based on
17 the belief that inclusion of observational studies, such as cohort studies, in systematic reviews
18 of the effect of interventions would increase the risk of confounding bias that threatens the
19 validity of the findings. The downside of this approach, though, is that interventions that have
20 only been studied in observational studies are not included in the assessment. Moreover, when
21 observational studies do not include highly restrictive inclusion criteria or volunteer samples as
22 in randomized trials, the sample characteristics are more likely to be similar to those in “real-
23 world” settings. Finally, studies have shown that, among cohort studies of interventions
24 conducted with a high methodological rigor, the effect estimates that are obtained are similar to
25 those from randomized trials (Benson & Hartz 2000). This suggests that although confounding
26 is an important theoretical consideration, it can be sometimes be overcome and evidence from

1 high-quality cohort studies may be able to contribute to systematic reviews of interventions.
2 Nonetheless, the randomization process, when done well on large samples, prevents
3 confounding by unknown confounders and this can never be done with observational studies.

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

8 So, while there are strengths and limitations intrinsic to the review process, and while
9 panel members believe that the strategy adopted in the systematic review was a reasonable
10 one, it is important to acknowledge that other strategies adopted at other times might yield
11 somewhat different findings. As a result, it was the panel's goal in the development of this
12 guideline to render a collective judgment and decision-making process that is transparent so
13 that interested readers might appropriately appreciate the rationale for the choices made in
14 response to the evidence in the systematic review.

15 *Treatment Effect Heterogeneity: Subgroup Effects*

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

24 The systematic review rated the evidence as “insufficient” to determine whether there
25 was treatment effect heterogeneity by trauma type or demographic characteristics such as
26 gender or ethnoracial minority status and the authors concluded that they, “did not find evidence

1 to confirm or refute whether treatments are more or less efficacious for many other subgroups”
2 (e.g., by gender, race, ethnicity, refugee status, repeat victimization, coexisting conditions,
3 symptom severity” [Jonas et al., 2013, p. 146]).

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

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

23 There was consensus among panel members that despite the clinical and policy
24 importance of identifying which treatments work best for which patients, the randomized trials
25 included in the systematic review do not adequately address that issue. Very few trials
26 assessed subgroup effects and the sample sizes of most were not powered to detect subgroup

1 by treatment interactions. This is an important lacuna and it is addressed further in the section
2 on future research needs.

3 *Generalizability (Applicability)*

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

9 Generalizability of findings from a systematic review means that the direction and
10 magnitude of effect of an intervention, based on the samples from the trials included in the
11 systematic review, are similar to the direction and magnitude of effect of that intervention in an
12 external population. Lack of generalizability implies that there is treatment effect heterogeneity
13 (i.e., that the magnitude of the treatment effect varies across specific subgroups) *and* that there
14 are differences in those subgroup characteristics between the samples in the trials or a
15 systematic review of trials and the external population.

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

23 In general, the characteristics of persons included in the randomized trials incorporated
24 into the systematic review are, except where noted in the applicability section for specific
25 recommendations, similar to the universe of persons with PTSD, in terms of gender, race, type
26 of index trauma, and exposure to childhood trauma. Other characteristics, such as ethnicity or

1 sexual orientation were frequently not reported. The trial samples were less likely to include
2 persons with substance abuse disorders (because substance abuse was frequently a criterion
3 for exclusion) and more likely to include people with high baseline severity of PTSD.

4 Based on the rating of insufficient evidence about subgroup effects and sample
5 characteristics of the included trials as noted above, the RTI-UNC EBPC authors concluded,
6 “We recognize the hypothesis that treatments proven to be effective for adults with PTSD
7 should be applicable to all adults with PTSD, but we did not find evidence to confirm or refute
8 this hypothesis” (Jonas et al., 2013, p. ES-13). Given this scientific uncertainty, GDP members
9 were unable to reach consensus about generalizability of findings of the systematic review. The
10 divergence of opinion among panel members mirrors different opinions in the literature on the
11 issue of generalizability of clinical trials (Post, de Beer, & Guyatt, 2013; Rothwell, 2005). Some
12 panel members believe that, in the presence of insufficient evidence on generalizability,
13 clinicians should be cautious about assuming generalizability to all population subgroups. They
14 noted that the systematic review did not show that subgroup effects had been assessed
15 adequately and were found to be absent, but rather that subgroup effects had been assessed
16 infrequently and that study samples were often too small to detect subgroup effects. These
17 members further suggest that psychological treatments, in particular, may have different
18 meanings for people from different backgrounds and may therefore be more likely to have
19 differential effects across those groups (Brown, 2008). Finally, they note that average treatment
20 effects (e.g., the standardized mean differences reported in the systematic review), may be
21 different for individuals who differ from the modal patient on baseline risk, responsiveness to
22 treatment or vulnerability to adverse effects (Kravitz, Duan, & Braslow, 2004).

23 Other members of the panel believe that, in the absence of empirical evidence or strong
24 theoretical rationale to suspect treatment effect heterogeneity (i.e., subgroup effects), one
25 should assume, until demonstrated otherwise, treatment effects from randomized trials to be
26 generalizable across most demographic subgroups. These panel members note that many

1 subgroup effects reported as new findings in randomized trials have been later shown to be
2 spurious (Sun, Ioannidis, Agoritsas, Alba, & Guyatt, 2014; Wang, Lagakos, Ware, Hunter, &
3 Drazen, 2007). They further suggest that it would be inappropriate, for clinical care or policy, to
4 not offer treatment to members of specific demographic subgroups based solely on the
5 possibility, in the absence of demonstrable evidence or strong theoretical rationale, that
6 treatment effects may be shown to vary across those groups in future research.

7 These panel members do suggest caution in generalizing findings when there is a strong
8 theoretical rationale to expect treatment effect heterogeneity. For example, although baseline
9 severity was not evaluated as a moderator of treatment effect by the trials included in the
10 systematic review, there is strong evidence that baseline severity moderates the effect of many
11 treatments (Kravitz, et al., 2004), including psychological (Driessen, Cuijpers, Hollon, & Dekker,
12 2010) and pharmacological (Fournier et al., 2010) treatments for depression. Since the baseline
13 severity of PTSD was high in the trials included in the systematic review, these panel members
14 advise caution in generalizing findings from the systematic review to patients with mild severity
15 PTSD. The expertise of therapists implementing a psychological treatment is another factor that
16 might be expected to create heterogeneity. When a psychotherapy that requires significant
17 training and expertise for implementation has been evaluated only in specialized settings with
18 therapists who have that training, it is reasonable to suspect that the effect magnitude may be
19 lower when therapists in the community who do not have specialized training implement that
20 treatment. Although recent studies of large-scale implementation of Exposure Therapy
21 (Eftekhari et. al., 2013) and Cognitive Processing Therapy (Lloyd et. al, 2015) for PTSD
22 reported effect sizes that were similar to randomized trials with highly trained therapists
23 (suggesting that treatment effect heterogeneity by therapist expertise and setting may not be a
24 major issue), those studies were observational studies without control groups and were likely to
25 have obtained larger effect sizes than if large-scale randomized trials, with appropriate control
26 groups, had been conducted.

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

4 Generalizability of findings from the systematic review to persons who have comorbid
5 substance abuse disorders is problematic. A high percentage of persons with PTSD have
6 substance use disorders (Brady, Killeen, Brewerton & Lucerini, 2000), yet most of the trials
7 included in the systematic review excluded those with substance abuse (Jonas et al., 2013.) Of
8 the 92 trials, only 4 included research participants with substance use disorders and 2 included
9 those with alcohol dependence (though 17 of the 92 trials did not specify substance use in the
10 inclusion or the exclusion criteria, making it unclear if they were included or excluded from those
11 trials). In itself, this does not mean that the findings are not generalizable to persons with
12 comorbid PTSD and substance abuse. Lack of generalizability would also require that the
13 magnitude of treatment effects for PTSD differed among those with and those without
14 substance abuse. Unfortunately, there are no data on PTSD treatment effect heterogeneity by
15 substance abuse status. Further, there are no data from meta-analyses on treatment effect
16 heterogeneity by substance abuse among persons with depression (from which we might be
17 able to reason by analogy). Given these circumstances (i.e., that comorbidity of PTSD and
18 substance abuse is common, but there are few trials that included persons with substance
19 abuse and no data on treatment effect heterogeneity), some panel members believe that the
20 findings from the systematic review should be cautiously applied to persons with PTSD and
21 substance abuse while others do not. All members agree that future treatment trials for PTSD
22 should include persons with substance abuse and assess group (i.e., substance abuse or no
23 substance abuse) by treatment interactions.

24 *Community Member Input*

25 Community members on the panel expressed a number of general preferences and
26 values about their treatment for PTSD that they determined were important to consumers.

1 These begin with valuing a practitioner who is informed about trauma and its effects, knows how
2 to approach and work with traumatized individuals (i.e., works from a trauma-informed
3 perspective and has sufficient exposure and desensitization to traumatic material to not be
4 reactive or judgmental to the patient and his or her symptoms or presentation) and has training,
5 experience, and competency in providing the suggested treatment for PTSD. Patients also
6 benefit from receiving information about whether and how a particular treatment works, its
7 typical protocol, and any known complications of the treatment (in this, they may also be
8 influenced by feedback from peers regarding their experience of a particular treatment and
9 whether or not it worked for them--see Mott, Stanley, Street, Hofstein, & Teng, 2014).
10 Community members also suggested that consumers would find strategies for self-soothing and
11 self-regulation helpful and that they would value a personalized approach to treatment. They
12 further pointed out that one particular treatment or medication may not fit the needs of every
13 patient since what might be helpful to one might not be to another and it may take multiple
14 modalities or combinations of mental health and pharmacological interventions to help a
15 particular individual.

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

1 In addition, community members noted the importance of the development of a
2 therapeutic relationship. Many survivors enter treatment with great fear and trepidation (tied
3 directly to their trauma and, at times, to negative prior experiences with other health
4 professionals or organizations) and may mistrust therapists as authority figures. As a result,
5 they may be difficult to engage and more prone to talk with their peers (in informal or formal
6 peer support programs) about the trauma rather than with a medical or mental health
7 professional. Members suggest that practitioners present themselves in a very straightforward,
8 respectful, and non-defensive way (professional but not authoritarian) and know they must earn
9 their patients' trust through their empathy, consistency, reliability, and ability to be responsive
10 and calm in their interactions, as well as in their ability to set and maintain reasonable
11 boundaries and to function collaboratively.

12 *Clinician Input*

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

25 According to the clinicians, consumers as a group understandably seek treatments that
26 are relatively short-term and will resolve their symptoms and alleviate their suffering. They also

1 appreciate receiving information about the various techniques under consideration including
2 their possible benefits and risks to help them in choosing or refusing the offered intervention.
3 Information can also allay the anxiety and apprehension many patients have at the start of any
4 kind of treatment. The pace and intensity of treatment can be quite variable and may be
5 determined by the treatment method and the patient's symptomatology and life stability. For
6 example, EX and CPT follow protocols that generally require a shorter but more intensified
7 course of treatment. This works well for some, but not all patients. Some require attention to
8 issues of personal safety and life stabilization and to the development of emotional regulation
9 and life skills before undertaking a trauma- focused treatment and some prefer graduated
10 versus prolonged exposure to the trauma and its effects. Finally, cultural competence (referring
11 to a number of therapist characteristics, including cultural humility, willingness to explore and
12 become aware of non-conscious biases, and attention to issues of power and privilege [Brown,
13 2008]) is important in the treatment of PTSD.

14 **Limitations of Existing Treatment Research Literature: Future Research Needs**

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

18 *Gaps in the Literature*

19 In general, the research evidence for the efficacy of certain psychotherapies and
20 pharmacologic treatments for adults with PTSD is strong. Despite this, there are a number of
21 significant limitations in the current empirical literature that make it difficult to answer many
22 important clinical questions. There are gaps in treatment comparisons, evaluation of moderators
23 of treatment effects, inclusion of participants with comorbidities, assessment of important
24 outcomes and the timing of their assessment, measurement of potential side effects and harms,
25 assessment of patient preferences, and follow up on reasons why participants leave a study.

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

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

23 Third, although the RCTs in the RTI-UNC systematic review included heterogeneous
24 groups of participants with a variety of index trauma types, and included participants with co-
25 morbid depression, participants with other important comorbid conditions were frequently
26 excluded. Specifically, a majority of the RCTs excluded patients with substance dependence or

1 suicidality, an important limitation given that PTSD, substance dependence and self-harm are
2 so often co-morbid. In addition, in the RCTs reviewed, it was unclear or inconsistently reported
3 whether individuals also had comorbid problems such as dissociation. The *DSM-5* revision of
4 the PTSD criteria now includes a dissociative subtype (Friedman, 2013; Friedman, Resick,
5 Bryant, & Brewin, 2011). Thus, individuals with these and other identified comorbidities or
6 complexities should be included in future clinical trials.

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

13 Fifth, although the pharmacotherapy trials typically reported information on side effects
14 and serious harms, the psychological intervention studies usually did not. This limitation is not
15 specific to psychotherapy for PTSD per se, given that the field of psychology generally lacks
16 consensus on how to detect harm associated with psychotherapy as discussed by Dimidjian
17 and Hollon (2010). Consistent with IOM recommendations for clinical guidelines and unlike
18 previous guideline panels on PTSD treatment, our panel based our recommendations on the
19 balance of benefits and harms for all interventions; however, as noted, the strength of evidence
20 on harms of psychotherapy was very low because data have not yet been rigorously collected
21 and comprehensively reported. For the benefit/harm calculus to be based on strong evidence,
22 solid data on harms must be collected in future trials. Thus, the panel advises that
23 psychometrically sound measures of adverse effects should be included in future RCTs and
24 reported in subsequent reports. Such measures should include assessments of suicidal
25 ideation, self-injurious behaviors, hospitalizations, and other important adverse outcomes. Of
26 particular importance, the panel strongly recommends that trialists seek to identify the reasons

1 for participant dropout. If the reasons for attrition are not specified, it is impossible to know
2 whether attrition represents improvement or a response to an adverse effect.

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

12 *Methodological Improvements*

13 In addition to the research gaps described above, there were significant methodological
14 issues with a substantial proportion of the PTSD treatment trials. Of the 138 randomized trials
15 found to be eligible for inclusion in the RTI-UNC systematic review, 46 (33%) were rated high
16 risk of bias and not included, except for sensitivity analyses²². The most frequent
17 methodological problems among the trials judged to be at high risk of bias were high rates of
18 attrition or differential attrition (i.e., markedly different attrition rates in treatment comparison
19 groups) and inappropriate methods for handling missing data.

20 Future trials should plan and implement methods designed to minimize the
21 methodological challenges identified in the systematic review. Specifically, the panel
22 recommends that investigators design trials to minimize attrition, decrease missing data,
23 incorporate methods of handling missing data, such as multiple imputation or maximum

²² 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.

1 likelihood, that are less likely to be biased. The panel encourages researchers to try to identify
2 and include in the published reports the reasons for attrition. If resources do not permit the
3 researchers to identify the reasons for attrition in all participants, identifying causes of attrition in
4 a random sample (e.g., 20%) of those lost to follow-up can provide useful information for future
5 studies. Other important characteristics of rigorous research that have been commonly used in
6 past research, such as assessment of treatment fidelity, should also be maintained.

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

12 Second, the potential effects of researcher allegiance should be addressed. Many
13 psychotherapy trials for PTSD were conducted by the individuals and investigative teams that
14 developed or modified those techniques. A substantial body of research, including studies of
15 PTSD trials, has shown researcher allegiance effects (i.e., larger treatment effects when the
16 investigators have an allegiance to one or more of the treatments being compared) (see
17 Munder, Brusch, Leonhart, Gerger, & Barth, 2013; Munder, Gerger, Trelle, & Barth, 2011). For
18 the comparative effectiveness trials that panel members recommend, it would be ideal if study
19 teams either did not include investigators who developed or substantively modified the
20 constituent interventions or at least included investigators who developed each of those
21 interventions (i.e., balanced allegiance).

22 Third, it is also important that future trials of PTSD treatment evaluate outcomes over
23 longer and defined time periods. In order to pool results across trials that measured outcomes at
24 different times, the UNC-RTI EBPC selected the only common metric available: the outcome
25 value at the end of treatment. However, this metric may not be the most clinically relevant time
26 point for outcome assessment. Particularly for psychotherapy, it is important to measure the

1 outcome after cessation of treatment. An effort to define ideal (yet feasible) time points to
2 assess treatment outcome, that includes both researchers and clinicians who care for persons
3 with PTSD, would provide useful guidance for future treatment research.

4 Fourth, trials should include sample sizes large enough to minimize covariate
5 imbalances that are associated with outcomes that occur by chance, not just sample sizes large
6 enough to detect clinically meaningful effects. Many of the trials included in the systematic
7 review included relatively small sample sizes. Even when a trial has sufficient power to detect a
8 clinically meaningful difference between interventions, smaller trials are more likely to have
9 covariate imbalances that may affect the outcome by chance alone. The primary value of a
10 randomized trial is the balance of known and unknown covariates across treatments, which is
11 undone when a trial is small. Studies of published research have shown that findings from
12 smaller studies are less likely to be replicated than those from larger studies. In a study of 49
13 highly cited original studies, Ioannidis (2005) found that studies that were subsequently
14 contradicted had much smaller sample sizes (median = 624) than those that were subsequently
15 replicated (median = 2165). Of note here is the fact that these numbers exceed the *combined*
16 *samples* in the distinct classes of interventions included in the systematic review, the largest of
17 which included a total of 1,301 participants for CBT.

18 Accordingly, the panel recommends that investigators increase sample sizes, and pool
19 efforts, when necessary, to increase recruitment of participants. When a trial is small,
20 investigators may consider controlling for the potential impact of covariate imbalances through
21 multivariable modeling or propensity score techniques, as is typically done in non-randomized
22 studies of treatment effectiveness. The practice of performing statistical tests of the
23 comparability of baseline demographic covariates is inappropriate and should not be done. By
24 definition, when participants are randomly assigned to treatments, differences in covariates
25 across treatments are the result of “chance”. When a study is small, statistical tests have low
26 power to detect even large covariate imbalances. Since confounding is a bias related only to the

1 magnitude, not the precision, of differences in covariates across treatment groups, the key issue
2 isn't whether baseline differences are statistically significant but whether those differences have
3 an impact on the estimated association between treatment and the outcomes of interest (Lavori,
4 Louis, Bailar III, and Polansky, 1983). Accordingly, consistent with the recommendations of
5 CONSORT (Moher et al., 2010), the panel recommends that investigators discontinue the
6 practice of reporting statistical tests of baseline covariate differences across treatment groups.

7 **Guideline Summary and Future Directions**

8 Trauma is now recognized as extremely common in human experience. In the most
9 favorable outcome, it results in posttraumatic reactions that are naturalistically processed to a
10 degree of resolution that do not result in onerous or ongoing symptoms. When it is not
11 processed in this way, it can result in serious mental health consequences and symptoms,
12 especially Posttraumatic Stress Disorder, a condition usually accompanied by other mental
13 health comorbidities and a range of medical conditions. Due to the relatively high prevalence
14 rate of PTSD in the general population, there is an urgent need for treatments that effectively
15 ameliorate its symptoms.

16 In many ways, the available PTSD treatment research is substantial but now requires
17 increased sophistication in design and methodology. Members of this guideline panel applaud
18 the efforts of a number of national and international professional organizations for leading the
19 way in the design and implementation of research studies on PTSD treatment. In particular,
20 these organizations include the International Society for Traumatic Stress Studies, the NIH-
21 funded Conference on Innovations in Trauma Research Methods (CITRM; held annually
22 between 2004 and 2008) (Keane, 2009), the research efforts of the National Center for PTSD of
23 the Veteran's Administration/DOD (including the postdoctoral program at the Boston VA that
24 provides advanced training and mentorship in research design and methods [Sloan, Wisco,
25 Vogt & Keane, 2015]) and the related efforts of the Australian Centre for Mental Health. Panel
26 members also support the ongoing research pertaining to trauma process and outcome, in

1 general, and as it applies more specifically to work with traumatized individuals. It is the hope of
2 members of this panel that the next iteration of this guideline will benefit from these
3 methodological advances, all in the interest of relieving the suffering associated with PTSD.

4 This guideline is the first for the treatment of PTSD that incorporates standards for
5 “clinical practice guidelines we can trust” promulgated by the Institute of Medicine of the
6 National Academy of Sciences (IOM, 2011b). It is based on a systematic review that used
7 rigorous standards and transparent processes for identification and evaluation of published
8 research. A unique feature of this guideline was the inclusion of available research findings on
9 reported harms and adverse events of treatment and patient preferences and values in their
10 choice of treatment, the result of additional reviews of the data on the treatment of PTSD. The
11 findings of this guideline are largely in accord with those of other published PTSD treatment
12 guidelines and strongly recommend the use of such trauma-focused psychological interventions
13 as cognitive behavioral therapy, cognitive processing therapy, cognitive therapy and exposure
14 therapy. It further suggests the use of brief eclectic psychotherapy, eye movement
15 desensitization and reprocessing therapy, and narrative exposure therapy. In terms of
16 medication interventions, it supports the use of fluoxetine, paroxetine, sertraline, topiramate,
17 and venlafaxine.

18 Panel members recognize that, despite the fact that these recommendations were made
19 on the basis of the most scientifically rigorous methods in determining treatment outcome, many
20 questions remain and much remains to be researched going forward. While research findings
21 establish the foundation for the evidence-base, its application requires clinical judgment,
22 knowledge of treatment methods and their relative effectiveness, and competence to offer the
23 treatment on the part of the clinician. It also requires collaborative decision making that takes
24 into consideration the unique needs and preferences of the patient. Research that investigates
25 all three arms of the evidence-based approach will build upon and broaden effective treatment
26 of individuals suffering PTSD in the aftermath of their traumatic experiences.

Conflicts of Interest

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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.

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

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

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

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

26

Complete formatting and copyediting will be performed following the public comment period.

1

Developer

2 American Psychological Association (APA)- Posttraumatic Stress Disorder (PTSD) Guideline

3 Development Panel (GDP). The PTSD GDP is a multidisciplinary Panel of experts.

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6

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