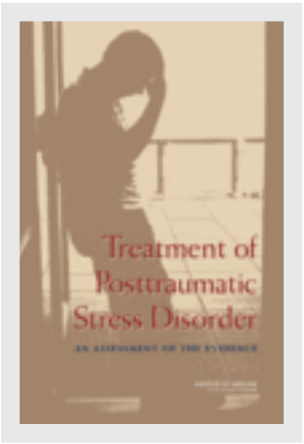

Treatment of Posttraumatic Stress Disorder: An Assessment of the Evidence

DETAILS

224 pages | 6 x 9 | PAPERBACK
ISBN 978-0-309-10926-0 | DOI 10.17226/11955

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Treatment of Posttraumatic Stress Disorder

AN ASSESSMENT OF THE EVIDENCE

Committee on Treatment of Posttraumatic Stress Disorder
Board on Population Health and Public Health Practice

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

THE NATIONAL ACADEMIES PRESS
Washington, D.C.
www.nap.edu

THE NATIONAL ACADEMIES PRESS 500 Fifth Street, N.W. Washington, DC 20001

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This study was supported by Contract No. V101(93)P-2136, Task Order No. 9, between the National Academy of Sciences and the Department of Veterans Affairs. Any opinions, findings, conclusions, or recommendations expressed in this publication are those of the author(s) and do not necessarily reflect the view of the organizations or agencies that provided support for this project.

International Standard Book Number-13: 978-0-309-10926-0
International Standard Book Number-10: 0-309-10926-4

Additional copies of this report are available from the National Academies Press, 500 Fifth Street, N.W., Lockbox 285, Washington, DC 20055; (800) 624-6242 or (202) 334-3313 (in the Washington metropolitan area); Internet, http://www.nap.edu.

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Suggested citation: Institute of Medicine (IOM). 2008. *Treatment of posttraumatic stress disorder: An assessment of the evidence*. Washington, DC: The National Academies Press.

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Willing is not enough; we must do."
—Goethe

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Reviewers

This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the NRC's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

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Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations nor did they see the final draft of the report before its release. The review of this report was overseen by **Elaine L. Larson,** School of Nursing, Columbia University. Appointed by the National Research Council she was responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

Preface

This report was commissioned by the Department of Veterans Affairs (VA) to assess the scientific evidence on treatment modalities for Posttraumatic Stress Disorder (PTSD). Reviewing the PTSD treatment literature dating back to 1980, the year the disorder was first defined by the Diagnostic and Statistical Manual of the American Psychiatric Association, proved to be a challenging task. Assessing the outcomes of treatment depends entirely upon the self-report of those affected, without "objective" measures such as laboratory tests or imaging. Treatment modalities and research methods used in their evaluation have been in continuous development. The last 30 years have also seen dramatic changes in the way scientific evidence has been assessed in general with emerging international standards for conducting systematic qualitative and quantitative reviews that are quite different from the methods used in the 1980s when research on the treatment of PTSD began.

In applying a rigorous approach to the assessment of evidence that meets today's standards, the committee identified significant gaps in the evidence that made it impossible to reach conclusions[1] establishing the efficacy of most treatment modalities. This result was unexpected and may surprise VA and others interested in the disorder. Important treatment decisions for most modalities will need to be made without a strong body

[1]One committee member does not concur with the committee's specific conclusions concerning (a) selective serotonin reuptake inhibitors (SSRIs) and (b) novel antipsychotic medications as add-on treatments, as described in Appendix H; however, that does not affect his agreement with these general statements about the overall inadequacy of the evidence.

of evidence meeting current standards (the committee summarizes clinical practice guidelines developed by others in the face of this scientific uncertainty). This overall conclusion of scientific inadequacy is not a clinical practice recommendation or guideline. It is also not a judgment on the quality of the research in this field using methods acceptable at the time. The overall conclusion also adds urgency to the committee's recommendations for a more strategic research effort that defines the relevant populations and subpopulations; develops and tests treatment modalities alone and in combination, in individual and group formats (for psychotherapy), and of various intensities and durations; uses the latest and most rigorous methods for designing and executing study protocols; and follows all study participants through the end of treatment and for meaningful periods thereafter.

The committee was also struck by the scant evidence exploring some of the possibly unique aspects of PTSD in veterans. For the most part we cannot say whether the treatment of PTSD in veterans should be the same as in civilians, and whether important subpopulations of veterans defined by age, sex, trauma type, socioeconomic status, educational level, comorbidities, and brain injury should be treated the same or differently.

The committee could only conclude that well-designed research is needed to answer the key questions regarding the efficacy of treatment modalities in veterans. Success will depend on the collaboration of VA and other government agencies, researchers, clinicians, and patient and veterans' groups and will further require the continued support and attention of policymakers and the public. The individuals returning from current conflicts and now re-entering civilian life with this disorder deserve no less.

Alfred O. Berg
Chair

Contents

Summary

The Institute of Medicine (IOM) Committee on Treatment of Posttraumatic Stress Disorder (PTSD) was charged by the Department of Veterans Affairs (VA) to review and assess the evidence on the efficacy of pharmacologic and psychologic treatment modalities for PTSD (see Box S-1 for the complete Statement of Task).

The committee was given five major tasks: review the scientific evidence and make conclusions regarding efficacy; note restrictions of the conclusions to certain settings, populations, and so on; comment on gaps and future research; answer several questions related to the goals, timing, and length of treatment; and finally, note areas where the evidence base is limited by inadequate attention or poor quality.

This report contains the committee's conclusions about the strength of the evidence regarding the efficacy of various treatment interventions. There are two important qualifiers of the committee's underlying objective in responding to its charge. First, the committee was not asked to develop clinical practice recommendations, but to reach evidence-based conclusions that would inform policy decisions. Second, concluding that the evidence is inadequate to determine efficacy is not the same as concluding that a treatment modality is inefficacious. In responding to its charge, the committee found the evidence inadequate to determine the efficacy of most treatment modalities (see Statement of Task II.C.3). The committee did not examine the many factors that contribute to recommendations for clinical practice, including clinician and patient preferences, access, safety, availability, cost, alternatives, local practice patterns, medicolegal issues, and ethical concerns. The committee did not conclude that the evidence for any treatment

BOX S-1
Statement of Task

I. The Department of Veterans Affairs has asked the IOM to convene a new committee to review the literature on various treatment modalities (including pharmacotherapy and psychotherapy) and treatment goals for individuals with PTSD.
II. Specifically, the committee will conduct an evidence-based review on best treatment practices and types and timing of specific interventions, and comment on the prognosis of individuals diagnosed with PTSD (and existing comorbidities). As part of its assessment, the IOM committee shall:
   a. Develop descriptive evidence tables including type of study and identify potential bias and generalizations of the study. The committee shall also search for and classify systematic and narrative reviews on the topic of treatment and recovery of individuals with PTSD.
   b. The committee shall examine and classify the existing studies on various treatment modalities for PTSD. The committee will report on the highest levels of evidence available. For each study the committee will consider the quality of design and execution, and will be guided by the following classification:
      I Randomized controlled trial
      II-1 Controlled trial without randomization
      II-2 Cohort or case-control study
      II-3 Time series or uncontrolled experiment
      III Opinion of respected authority, case report, and expert committee
   c. The committee shall consider the following framework to make conclusions about the strength of the available evidence for treatment modalities:
      1. Evidence is sufficient to conclude the efficacy of *X* in the treatment of PTSD. (A qualifier of magnitude may be added if appropriate.)

modality was suggestive that it was ineffective or harmful (see Statement of Task II.C.4 and C.5).

The committee conducted a systematic and comprehensive search of the relevant published literature and identified a total of 2,771 studies, and from that list included only randomized controlled trials (RCTs; placebo-controlled pharmacotherapy trials and wait-list or similar controls in the psychotherapy trials) in its review. The committee identified 37 RCTs on pharmacotherapies and 52 studies on psychotherapies (see Chapter 2 for more details about the committee's methods). The committee excluded

2. Evidence is suggestive but not sufficient to conclude the efficacy of *X* in the treatment of PTSD. (The committee may note inconsistencies in the data.)
3. Evidence is inadequate to determine the efficacy of *X* in the treatment of PTSD.
4. Evidence is suggestive that *X* treatment is ineffective in treating PTSD.
5. Evidence is suggestive that *X* treatment is harmful in the treatment of PTSD.

d. For each of the conclusions above, the restriction of the conclusion regarding the population, provider, setting [of] intervention, or comparator intervention will be noted.

III. As part of its assessment, the IOM committee shall note limitations in the evidence base and make suggestions for further research that could strengthen the evidence or address research gaps in the treatment of PTSD.

IV. In conducting its work, the committee shall consider the following questions in relation to treatment modalities (including pharmacotherapy and psychotherapy) and treatment goals for individuals diagnosed with PTSD.

a. What are the goals of PTSD treatment?
   - What is the definition of *recovery*?
   - For what proportion of patients is recovery possible?
   - Besides recovery, what other outcomes would benefit patients?

b. Does evidence support the value of early intervention?

c. How long should treatment continue?
   - What is the impact of a hiatus in treatment?
   - What is the impact of periodic reexamination for asymptomatic patients?

V. The committee shall note when the evidence base does not allow for responding to these questions due to insufficient research attention or poorly conducted studies.

nonrandomized and uncontrolled studies for several reasons. It is extremely difficult to answer questions of efficacy in an uncontrolled way because of the variability of treatments, outcome measures, disease course, and patient choice. RCTs are the most reliable form of evidence for efficacy, and the committee found that the characteristics of the disorder, its measurement, and its treatment are sufficiently heterogeneous that observational studies were unlikely to provide useful evidence beyond the data available from RCTs. Therefore, per part II.B of the Statement of Task, all studies included in this review are classified as level I evidence.

ISSUES IN PTSD TREATMENT RESEARCH

The committee encountered several noteworthy issues in its review and evaluation of the evidence base. First, there is some suggestion that there may be differences between civilian populations and veteran populations with PTSD in their response to treatment and to various types of treatment (Stein et al., 2006; van der Kolk, 2007).[1] However, the committee cannot comment conclusively on this matter because the evidence neither demonstrates that there are differences between the two populations, nor does it show that the two groups are indistinguishable in their response to treatment. The committee also notes that the populations of veterans with PTSD now returning from Iraq and Afghanistan might be different enough from U.S. veterans from previous wars such that studies of the latter populations (mostly dating back to the Vietnam conflict) may be minimally informative about treatment efficacy in veterans of the recent conflicts.

Second, the committee examined the question of treatment efficacy in PTSD in general populations, not just PTSD in veterans, but found it striking that so few of the studies were conducted in populations of veterans.

Third, the committee found problems in the design and performance of studies, many apparently due to the difficulties of conducting research in this clinical domain (Harvey et al., 2003). Design problems included lack of assessor blinding or assessor independence in the psychotherapy studies, small sample size, and lack of follow-up for individuals who dropped out before the trials ended. The problems of high dropout rates and weak handling of missing data, which have the potential to introduce significant bias, were frequent in both pharmacotherapy and psychotherapy studies and are discussed in Chapter 5 and Appendix D. High dropout rates are a particular problem in this domain, and regardless of how they are handled, they reduce the certainty of study results. Often studies reported data only on those completing therapy, a strategy biased in favor of showing a treatment effect. Those studies incorporating a strategy to deal statistically with the dropouts usually used "last observation carried forward," a method that may bias results in either direction depending on context.

The committee sought to address these issues by taking the following steps:

1. basing conclusions on evidence satisfying basic quality criteria (see Box S-2 and Chapter 2);

[1]The Cochrane systematic review of pharmacotherapy for PTSD notes the following: " . . . combat veterans (this subgroup has been regarded as more resistant to treatment, and is arguably more likely to have more chronic and severe symptoms, to have comorbid depression, and to be male)" (Stein et al., 2006: 7).

BOX S-2
Criteria to Assess a Study's Quality

- Assembly of comparable groups (randomized,** similar distributions of known confounders).
- Maintenance of comparable groups (i.e., minimal attrition, crossovers, or contamination, good adherence). Use of intention to treat (ITT) analysis.
- Measurements equal, valid, and reliable (validated PTSD outcome measure, double masking in pharmacotherapy studies** and assessor blinding or at least assessor independence** in psychotherapy studies).
- Loss to follow-up causing missing outcome data:
  - — Differential loss to follow-up no greater than 15% absolute difference between groups.**
  - — If approximately equal loss to follow-up in each arm, study quality is affected by the analytic methods used to handle missing data:
    - o Up to 10% missing outcome data acceptable without formal missing data methods employed (i.e., may use completer analysis or last observation carried forward [LOCF]).
    - o Between 10% and 40% missing outcome data acceptable depending on validity of missing data analytic method employed (e.g., for lower proportions, single imputation, for higher proportions, likelihood-based methods, multiple imputation, sensitivity analysis).
    - o Use of LOCF decreases study quality as the percentage dropout increases, severely if dropout exceeds 30%. Completer analysis is not acceptable.**
    - o No more than 40% loss to follow-up in any arm.**

**Indicates a criterion that if absent (or if the authors do not disclose) is a major limitation that limited the study's usefulness to the committee in reaching its conclusion regarding efficacy.

2. providing commentary to put the conclusion statements in the broader clinical and research context (see Chapters 3 and 4); and
3. describing opportunities and making recommendations for improving the validity and applicability of future PTSD treatment studies (see Chapter 5).

Third, the committee found that the evidence fails to address the effects of high rates of comorbidity among veterans with PTSD, especially major

depression, traumatic brain injury, and substance abuse. Thus the committee's conclusions regarding efficacy overall may not apply to the substantial proportion of veterans with one or more important comorbidities. Further, the committee notes that the evidence is mostly silent on the acceptability, efficacy, or generalizability of treatment in ethnic and cultural minorities, as few studies stratified results by ethnic background. The committee expects that the psychotherapies in particular might pose special challenges in different cultural groups but was unable to comment because none of the studies addressed it. A recommendation on important subpopulations is provided in Chapter 5 and below.

CONCLUSIONS

Below, the committee's conclusions about each class of treatment are provided, first for the pharmacotherapy modalities and then for psychotherapy modalities. Evidence tables summarizing key data and references are provided in Chapter 3 for pharmacotherapy and in Chapter 4 for psychotherapy.

Pharmacotherapies

The committee reviewed 37 pharmacotherapy studies and divided them by class where the number of studies made that useful, and into more general categories for small numbers of studies for a given class. Head-to-head studies in classes not proven efficacious on the basis of randomized placebo-controlled trials were excluded.

- The committee reviewed two RCTs of alpha-adrenergic blockers. The studies that were excluded were open-label trials, a retrospective chart review, and a study that did not use an overall PTSD outcome measure.
- The committee reviewed eight studies of anticonvulsants and excluded five (all open label, one a maintenance study).
- The committee reviewed 10 RCTs of novel antipsychotics (namely, olanzapine and risperidone) and excluded three studies that were open label or head-to-head.
- The committee included one study of benzodiazepines and excluded all that were open label or did not include an overall PTSD outcome (e.g., focus on sleep only).
- The committee found the literature on selective serotonin reuptake inhibitors (SSRIs) most extensive of all classes of medication. The committee included 14 studies in its review and excluded 15 studies. Of the seven studies judged most informative with

respect to efficacy, four showed a positive effect on primary PTSD outcomes, and three did not. The largest trial conducted in male combat veterans used LOCF with 30% dropout and did not demonstrate an improvement in primary PTSD outcomes.

- The committee's review included four RCTs of MAOIs (monoamine oxidase inhibitors) (two each phenelzine and brofaromine) and excluded four additional studies that were open label, uncontrolled, or for one study, a head-to-head comparison with moclobemide.
- In its review of other antidepressants, the committee identified one RCT each for the following drugs: tricyclic antidepressants imipramine and amitriptyline, mirtazapine, and nefazodone. The committee also reviewed two large RCTs of venlafaxine.
- In the category of "other drugs," the committee reviewed one study of inositol and one study of cycloserine. The committee also made note of one RCT of opioid antagonist naltrexone in patients with alcohol dependence, which did not meet inclusion criteria, that it suggested a benefit to using naltrexone in an important subpopulation.

For the all drug classes and specific drugs reviewed in each of the following classes, the committee concludes that the evidence is inadequate to determine efficacy in the treatment of PTSD:

- *alpha-adrenergic blocker prazosin,*
- *anticonvulsants,*
- *novel antipsychotics olanzapine and risperidone,*[2]
- *benzodiazepines,*
- *MAOIs phenelzine and brofaromine,*
- *SSRIs,*[3]
- *other antidepressants, and*
- *other drugs (naltrexone, cycloserine, or inositol).*

Important comments are appended to the conclusions for alpha-adrenergic blockers, novel antipsychotics, benzodiazepines, and SSRIs. One committee member does not concur with the committee's consensus on two conclusions—on SSRIs and novel antipsychotic medications—and offers alternate conclusions (see Appendix H).

[2]Please refer to Dr. Thomas Mellman's minority opinion on this conclusion in Appendix H.
[3]Please refer to Dr. Thomas Mellman's minority opinion on this conclusion in Appendix H.

Psychotherapies

The committee's search of the psychotherapy literature resulted in 52 studies. The committee organized the psychotherapy treatments into several categories based on how they appeared in the literature; this categorization also enabled the committee to draw meaningful conclusions. The majority of the studies reviewed included one or more cognitive-behavioral therapy (CBT) approaches. The largest proportion of CBT studies included an exposure-based therapy. The committee recognized that exposure is frequently administered in combination with another CBT technique, and that led the committee to group together studies with exposure and exposure plus something else (such as cognitive restructuring or a coping skills training modality [e.g., relaxation]). The next largest category was eye movement desensitization and reprocessing therapy, or EMDR. Although EMDR has a CBT component, the committee evaluated this research separately from exposure and other CBT in recognition of the ongoing debate about the theoretical underpinnings of EMDR and the contribution of various EMDR components in PTSD treatment (Foa et al., 2000; Power et al., 2002). The committee also examined cognitive restructuring studies separately, in cases where the approach was not explicitly combined with exposure. The committee then reviewed coping skills therapies such as relaxation and biofeedback. The committee identified a few other psychotherapies with fairly limited evidence and assessed their results as a group. The "other" category included hypnotherapy and psychodynamic therapy. Finally, the committee reviewed studies employing a group format psychotherapy.

As with the pharmacotherapy studies, the committee first considered studies that compared the intervention of interest to a control. In the case of the psychotherapy studies, the control generally was assignment to a wait list, and less frequently to minimal care or usual care. In some studies, the control was active, and the committee considered those studies next. Finally, head-to-head studies in classes of psychotherapy not proven efficacious on the basis of randomized, wait list, or equivalent-controlled trials were excluded.

The committee reviewed 23 RCTs of exposure-based treatments, some of which included in the same treatment condition (or arm) exposure plus cognitive restructuring or exposure plus coping skills training.

The committee finds that the evidence is sufficient to conclude the efficacy of exposure therapies in the treatment of PTSD.

The committee reviewed a small number of studies comparing exposure to another psychotherapy approach. However, this body of literature was

characterized by many limitations, making it impossible to reach a conclusion regarding the equivalency of exposure and any other psychotherapy.

The committee also reviewed studies of EMDR, cognitive restructuring, coping skills training, and other psychotherapies:

- The committee reviewed 10 RCTs of EMDR compared to wait list and other psychotherapy approaches or wait list alone. Many studies were excluded because they were comparison trials, did not have a comparison group, or only a portion of the sample had diagnosed PTSD.
- The committee reviewed three RCTs of cognitive restructuring.
- The committee reviewed four RCTs of coping skills and excluded one study because it did not have a control or comparison group.

The committee concludes that the evidence is inadequate to determine the efficacy of the following psychotherapy modalities in the treatment of PTSD:

- **EMDR**
- **cognitive restructuring**
- **coping skills training**

In the category of "other psychotherapies", the committee reviewed a total of four RCTs of eclectic psychotherapy (two studies), hypnotherapy, psychodynamic therapy, and brainwave neurofeedback. Based on these single trials, the committee felt that it would be inappropriate to reach a conclusion regarding the efficacy of these treatments.

Finally, the committee reviewed four studies utilizing a group therapy format.

The committee concludes that the evidence is inadequate to determine the efficacy of therapy delivered in group formats in the treatment of PTSD.

FINDINGS AND RECOMMENDATIONS

In response to VA's important questions related to recovery and the length and timing of PTSD treatment, and considering the gaps in the research, the committee makes eight recommendations. More detail is provided in Chapter 5.

Finding 1. The committee found that treatment of PTSD has not received the level of research activity needed to support conclusions about the potential benefits of treatment modalities. Although progress in scientific standards can be observed, and recent studies tend to provide more useful information than older studies, important limitations remain. There are very few large scale, multi-site initiatives of the type that has been directed toward other psychiatric disorders. The studies conducted over the nearly three decades since Diagnostic and Statistical Manual of Mental Disorders (DSM) adoption of the PTSD definition do not form a cohesive body of evidence about what works and what does not. As described elsewhere in this report, studies have used a wide variety of outcome measures and lengths of treatment (for the same treatment). Further, many studies lack basic characteristics of internal validity including high dropout rates handled with weak missing data analyses and high differential dropout among treatment arms. (Other characteristics include follow-up of all patients admitted to the trials, attention to conflict of interest, assessor independence, and length of follow-up.) Although experts in the field (Foa and Meadows, 1997; Harvey and Bryant, 2003) have called for setting research standards that would strengthen methodologic quality and internal validity, more work is needed.

Recommendation 1. The committee recommends that VA and other funders of PTSD research take steps to identify and require investigators to use methods that will improve the internal validity of the research, with particular attention to standardization of treatment and outcome measures, follow-up of individuals dropping out of clinical trials, and handling of missing data.

Finding 2. The committee found that the majority of drug studies were funded by pharmaceutical manufacturers. This is an issue that has received much attention in recent years from the academic research community, government agencies, patient communities, and the editors of major biomedical journals. The committee also found that many of the psychotherapy studies were conducted by individuals who developed the techniques or their close collaborators. It is important to know whether these treatments would show the same effect if implemented in other settings, requiring the confirmation and replication of these research results by other investigators.

Recommendation 2. The committee recommends that VA and other funders of PTSD treatment research seek ways to give opportunities to

a broad and diverse group of investigators to ensure that studies are conducted by individuals and in settings without potential financial or intellectual conflicts of interest.

Finding 3. The committee found that the available research leaves significant gaps in assessing the efficacy of interventions in important subpopulations of veterans with PTSD, especially those with traumatic brain injury, major depression, other anxiety disorders, or substance abuse, as well as ethnic and cultural minorities, women, and older individuals.

Recommendation 3. The committee recommends that VA assist clinicians and researchers in identifying the most important subpopulations of veterans with PTSD and designing specific research studies of interventions tailored to these subpopulations.

Finding 4. The committee found that research on treatment of PTSD in U.S. veterans is inadequate to answer questions about interventions, settings, and lengths of treatment that are applicable in this specific population. The committee recognizes that the successful conduct of research directly applicable to veterans will require close collaboration among funding agencies (Department of Defense, National Institute of Mental Health, National Institute of Alcohol Abuse and Alcoholism, National Institute of Drug Abuse), veterans' groups, and clinical service settings. Specifically veterans groups could make considerable contributions to the design and conduct of high-quality research on the treatment of PTSD.

Recommendation 4. The committee recommends that Congress require and ensure that resources are available for VA and other relevant federal agencies to fund quality research on the treatment of PTSD in veteran populations and that all stakeholders are included in research plans.

Finding 5. The committee found that studies of PTSD interventions have not systematically and comprehensively addressed the needs of veterans with respect to efficacy of treatment and the comparative effectiveness of treatments in clinical use.

Recommendation 5. The committee recommends that VA take an active leadership role in identifying research priorities for addressing the most important gaps in evidence in clinical efficacy and comparative effectiveness.[4] Potential areas for future research include:

- **Comparisons of psychotherapy (e.g., CBT) and medication;**
- **Evaluation of the comparative effectiveness of individual and group formats for psychotherapy modalities; and**
- **Evaluations of the efficacy of combined psychotherapy and medication, compared with either alone, and compared with control conditions.[5] Combined treatment could be tested within study designs like those that have been applied in large studies for other psychiatric conditions.**

Finding 6. The committee found no generally accepted and used definition for recovery in PTSD. Also, many studies used measures of questionable validity and reliability instead of validated, high-quality measures such as the Clinician-Administered PTSD Scale (Foa et al., 2000). The committee places the lack of agreement about recovery in context of a more general concern about identifying appropriate outcomes for PTSD research.

Recommendation 6. The committee recommends that clinicians and researchers work toward common outcome measures in three general domains that relate to recovery: loss of PTSD (DSM) diagnosis, PTSD symptom improvement, and end-state functioning. The committee fur-

[4]The committee has noted with interest research on effectiveness in other areas of mental health. The STAR*D (Sequenced Treatment Alternatives to Relieve Depression) study aimed to reproduce some real-life settings in allowing participants' choice and offering alternatives when a course of treatment did not work, and used an outcome measure of "remission" meaning becoming symptom free. Another study brought to the committee's attention is the CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) Schizophrenia study, which compares newer atypical antipsychotics with each other and with conventional antipsychotics in regard to long-term effectiveness and tolerability, and also in identifying antipsychotics that work for patients who have not had success with that class of drugs. Finally, STEP-BD (Systematic Treatment Enhancement Program for Bipolar Disorder) is a long-term study of manic-depressive illness that studied treatment (both pharmacologic and psychosocial) of affected individuals on two "pathways"—one a naturalistic, best practices pathway that allowed patients and clinicians to choose the best course of treatment, and the other a "randomized care pathway" that involved patients in multi-site randomized controlled trials. Program participation lasted for up to 5 years to facilitate adequate follow-up.

[5]The committee found one study that does this in the work of van der Kolk (2007) and colleagues.

ther recommends the following three principles be considered in the selection of outcome measures:

- **validity in research;**
- **convergence on a core of common outcomes for the purpose of comparability; and**
- **usefulness to clinicians to assess patients over time as symptoms and function change.**

The committee recommends that VA assume a leadership and convening role and work with other relevant federal agencies in developing these common approaches.

Finding 7. The committee was unable to reach a conclusion on the value of intervention early in the course of PTSD based on the treatment literature it reviewed.

Recommendation 7. The committee recommends that VA and other government agencies promote and support specific research on early intervention (i.e., reducing chronicity) in PTSD. The committee further recommends that future research specify both time since trauma exposure and duration of PTSD diagnosis, and that interventions be tested for efficacy at specific clinically meaningful intervals, as interventions might be expected to vary in effectiveness related to time since exposure and duration of diagnosis.

Finding 8. The committee was unable to draw conclusions regarding optimal length of treatment with psychopharmacology or psychotherapy.

Recommendation 8. The committee recommends that VA and other funders call for research on the optimal duration of various treatments. Trials of comparative effectiveness of different treatment lengths for those treatments found efficacious should follow. Finally, studies with adequate long-term (i.e., greater than one year) follow-up should be conducted on treatments of any length found to be efficacious.

CONCLUDING OBSERVATIONS

In this report the committee sought to describe the evidence regarding the efficacy of available treatment modalities for PTSD, identify some of the major issues in the field, and make recommendations to help guide further research in PTSD treatment. The committee's findings, conclusions, and recommendations about the evidence for the treatment modalities reviewed

in this report are not clinical practice guidelines. The committee does not intend to imply that, for example, exposure therapy is the only treatment that should be used in treating individuals with PTSD. The committee recognizes that the transparent presentation and assessment of evidence is just one part of the larger picture of PTSD treatment that includes many other factors. Further, assessing the scientific evidence may reveal areas of uncertainty. The next step in the process toward clinical decisionmaking is making recommendations for clinical practice—a step the committee was not asked to, and did not, take.

The committee applied contemporary standards in evaluating studies, including research dating back to 1980 when PTSD was first formally defined. The principal finding of the committee is that the scientific evidence on treatment modalities for PTSD does not reach the level of certainty that would be desired for such a common and serious condition among veterans. For some modalities, for example novel antipsychotic drugs and SSRIs, the committee debated whether to characterize the body of evidence as "suggestive" or "inadequate." It is important to emphasize that in the larger picture of PTSD treatment, had the debate ended with "suggestive" conclusions (rather than the "inadequate" conclusions the committee finally reached), the core message that better-quality research is needed would not have been rendered less urgent in consequence. The committee reached a strong consensus that additional high-quality research is essential *for every treatment modality*. Applying the general recommendations outlined above to exposure therapy, there is a need for better understanding of the most important and active components of exposure therapy, determining optimal administration and length of treatment, attention to principal subpopulations, and determining whether it can be effectively delivered in group format, presenting a challenging and urgent agenda for researchers and clinicians in the field.

The committee views its more general findings and recommendations regarding further research to be as important as its conclusions regarding the evidence supporting treatment modalities. The committee became aware of the formidable challenges that researchers face in conducting high-quality studies of efficacy and comparative effectiveness. Nonetheless, the committee was able to identify studies that met the highest internationally accepted standards for randomized controlled trials (in assembling populations, administering treatment, measuring outcomes, and following up enrolled subjects), showing that such studies are possible even for such a difficult clinical condition as PTSD. As outlined in the committee's recommendations in Chapter 5, setting a high standard for research on PTSD and delivering on it will require close collaboration between VA and other government agencies, researchers, clinicians, and patient groups. Thus,

the committee's recommendations are its suggestions for setting a framework for the future that can more successfully address the critical needs of veterans who return to civilian life with the diagnosis of PTSD.

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1

Introduction

> There is evidence that the high rates of trauma experienced by those stationed in the Southwest Asia theaters will result in increased demands on the Department of Defense (DoD), the Department of Veterans Affairs (VA), and community health care systems as these service members return, move back to civilian status, and become eligible for VA health benefits. As the number of OIF/OEF[1] veterans grows, their continued care is a national health care concern.
>
> —*Mapping the Landscape of Deployment Related Adjustment and Mental Disorders*, 2006

Mental disorders, including posttraumatic stress disorder (PTSD), constitute an important health care need of veterans, especially those recently separated from service. The Institute of Medicine (IOM) Committee on Treatment of PTSD was charged by the Department of Veterans Affairs (VA) with reviewing and assessing the evidence on PTSD treatment modalities. To prepare this report, the committee undertook a comprehensive, systematic review of the treatment literature dating back to 1980, and included both pharmacologic and psychologic therapies in its review.

The committee was given five major tasks: review the scientific evidence and make conclusions regarding efficacy; note restrictions of the conclusions to certain settings and populations; comment on gaps and future research; answer several questions related to the goals, timing, and length

[1]OIF/OEF: Operation Iraqi Freedom/Operation Enduring Freedom.

BOX 1-1
Statement of Task

I. The Department of Veterans Affairs has asked the IOM to convene a new committee to review the literature on various treatment modalities (including pharmacotherapy and psychotherapy) and treatment goals for individuals with PTSD.
II. Specifically, the committee will conduct an evidence-based review on best treatment practices and types and timing of specific interventions, and comment on the prognosis of individuals diagnosed with PTSD (and existing comorbidities). As part of its assessment, the IOM committee shall:
   a. Develop descriptive evidence tables including type of study and identify potential bias and generalizations of the study. The committee shall also search for and classify systematic and narrative reviews on the topic of treatment and recovery of individuals with PTSD.
   b. The committee shall examine and classify the existing studies on various treatment modalities for PTSD. The committee will report on the highest levels of evidence available. For each study the committee will consider the quality of design and execution, and will be guided by the following classification:
      I Randomized controlled trial
      II-1 Controlled trial without randomization
      II-2 Cohort or case-control study
      II-3 Time series or uncontrolled experiment
      III Opinion of respected authority, case report, and expert committee
   c. The committee shall consider the following framework to make conclusions about the strength of the available evidence for treatment modalities:
      1. Evidence is sufficient to conclude the efficacy of *X* in the treatment of PTSD. (A qualifier of magnitude may be added if appropriate.)

of treatment; and, finally, note areas where the evidence base is limited by insufficient research attention or poorly conducted studies (see Box 1-1 for the complete Statement of Task).

In conducting its search of the literature, the committee excluded studies on patient groups that did not fully meet the *Diagnostic and Statistical Manual of Mental Disorders* definition.[2] Box 1-2 below lists other topics that are not included in this report.

[2]Two exceptions were studies that included a majority of patients with PTSD and a minority of patients with subsyndromal PTSD.

2. Evidence is suggestive but not sufficient to conclude the efficacy of *X* in the treatment of PTSD. (The committee may note inconsistencies in the data.)
3. Evidence is inadequate to determine the efficacy of *X* in the treatment of PTSD.
4. Evidence is suggestive that *X* treatment is ineffective in treating PTSD.
5. Evidence is suggestive that *X* treatment is harmful in the treatment of PTSD.

d. For each of the conclusions above, the restriction of the conclusion regarding the population, provider, setting [of] intervention, or comparator intervention will be noted.

III. As part of its assessment, the IOM committee shall note limitations in the evidence base and make suggestions for further research that could strengthen the evidence or address research gaps in the treatment of PTSD.

IV. In conducting its work, the committee shall consider the following questions in relation to treatment modalities (including pharmacotherapy and psychotherapy) and treatment goals for individuals diagnosed with PTSD.

a. What are the goals of PTSD treatment?
   - What is the definition of *recovery*?
   - For what proportion of patients is recovery possible?
   - Besides recovery, what other outcomes would benefit patients?

b. Does evidence support the value of early intervention?

c. How long should treatment continue?
   - What is the impact of a hiatus in treatment?
   - What is the impact of periodic reexamination for asymptomatic patients?

V. The committee shall note when the evidence base does not allow for responding to these questions due to insufficient research attention or poorly conducted studies.

THE STUDY PROCESS

The committee held five meetings over a period of approximately nine months. The first meeting on January 16–17, 2007, part of which was an information-gathering session open to the public, included presentations from the sponsor, several subject experts, and veterans organizations (this meeting agenda can be found in Appendix F). The following four meetings were held in closed session (the fifth meeting took place via conference call). Additionally, the committee held weekly conference calls to plan the literature search, discuss findings, and formulate conclusions and recommendations.

BOX 1-2
Topics Not Addressed in This Report

- Current clinical practice in the treatment of PTSD, whether in the VA health care system or elsewhere
- Diagnostic and assessment issues (these were the subject of an earlier IOM report in 2006)
- PTSD treatment in the context of compensation, a set of issues addressed in the IOM report entitled *PTSD Compensation and Military Service* (2007b)
- PTSD in children or adolescents
- Feasibility, cost, or cost-effectiveness of various treatment modalities

The committee also received public submissions of material for its consideration at the meetings and by e-mail throughout the course of the study.[3] A Web site (http://www.iom.edu/PTSDtreatment) and e-mail listserv were created to provide information to the public about the committee's work and to facilitate communication with the committee. Materials from the information-gathering meeting are available in electronic format on the project's Web site.

On the pages that follow in this chapter, the committee provides an overview of PTSD, with a special focus on veterans and treatment. Chapter 2 describes the methods the committee used to search for, organize, and evaluate the literature. In Chapters 3 and 4, respectively, the committee presents its assessment of the pharmacotherapy and psychotherapy modalities by describing key data from the included studies (see evidence tables in Chapters 3 and 4), summarizing the evidence, and making conclusions based on the evidence. Chapter 5 contains a discussion of issues in PTSD research identified by the committee, and responses to other questions posed by the Statement of Task. Additional information is provided in the appendixes referred to in the report (Appendix G provides the committee biographies and Appendix E contains the acronyms used in the report).

[3]A list of materials reviewed by the committee (in the form in which they were reviewed), including all submissions of information from the public and many items not cited in this report, can be found in the study's public access file, obtained from the National Academies Public Access Records Office at (202) 334-3543 or http://www8.nationalacademies.org/cp/ManageRequest.aspx?key=48739.

THE DISORDER

PTSD results from exposure to a range of extreme stressors but one of its most common associations has been with war and combat, as described in historic and literary accounts. The name, etiology, cause, diagnosis, and treatment of the disorder all have been subject to considerable debate and controversy over the years (Wilson et al., 2001). PTSD develops in a significant minority (up to a third) of individuals who are exposed to extreme stressors, and symptoms of PTSD almost always emerge within days of the trauma. More information on the prevalence, etiology, and symptomatology of PTSD is provided in an upcoming IOM report, *Gulf War and Health: Physiologic, Psychologic, and Psychosocial Effects of Deployment-Related Stress* (Institute of Medicine, 2007a).

The *Diagnostic and Statistical Manual of Mental Disorders* (DSM) of the American Psychiatric Association (APA) first formally defined PTSD in 1980 in the DSM-III. The definition was revised in 1987 (DSM-III-R) and 1994 (DSM-IV) (APA, 1987, 1994). There was no change in the 2000 DSM-IV-TR (APA, 2000). The DSM-IV defines PTSD by several criteria: experiencing a traumatic stressor ("experienced or witnessed actual or threatened death, injury, or threat to the physical integrity of self or others") reacted to with "intense fear, helplessness, or horror" (Criterion A); intrusive recollections of the traumatic event (Criterion B); avoidance and numbing (Criterion C); and hyperarousal in the form of extreme startle reflex, inability to fall or stay asleep, and so on (Criterion D); the symptoms must be experienced for at least 1 month (Criterion E); and the symptoms cause distress or impairment in various areas of functioning (Criterion F) (APA, 2000). According to the DSM-IV, PTSD may be acute (symptom duration under 3 months) or chronic (symptom duration of 3 months or longer), and its onset may be delayed (occurring at least 6 months after exposure). The definition of PTSD does not recognize subtypes classified by type of trauma, such as combat versus civilian or simple exposure versus repeated exposure.

PTSD is heterogeneous with respect to symptom expression, severity, and chronicity. This heterogeneity may have important implications for response to specific treatments. Those in whom the predominant disturbance is insomnia might require a different treatment than persons in whom the predominant disturbance is avoidance. The course of PTSD may vary in duration of symptoms and level of disability, with a considerable proportion of persons with the disorder experiencing disabling symptoms for years (Kessler et al., 1995).

Epidemiology of PTSD

The most recent estimates of the lifetime prevalence of PTSD in the United States come from the National Comorbidity Survey—Replication (NCS-R), conducted in 2000. The lifetime prevalence of PTSD in the NCS-R is 6.8 percent; 9.7 percent in women and 3.4 percent in men. Current (12 month) prevalence is 3.6 percent, 5.2 percent in women and 1.8 percent in men (Harvard Medical School, 2007). A sex difference in PTSD is a consistent finding in epidemiologic research and is not accounted for by sex differences in overall prevalence of exposure to traumatic events or by sex differences in the prevalence of specific types of traumatic events (e.g., sexual assault).

Military personnel are at elevated risk for exposure to trauma. Estimates from the National Vietnam Veterans Readjustment Survey (NVVRS), a congressionally mandated large survey conducted in the late 1980s, reported that 30.9 percent of all men who had served in Vietnam developed PTSD; prevalence in the late 1980s was 15.2 percent. A recent reanalysis of the NVVRS data gave lower estimates: 18.7 percent for lifetime and 9.1 percent for current (at the time the NVVRS was conducted) (Dohrenwend et al., 2006). The reanalysis used military records and data from the clinical examinations conducted on a subsample. The latter enabled the investigators to (1) distinguish between war-related first onset of PTSD and first onsets that occurred before or after service in Vietnam and (2) take into account level of impairment. Surveys of military personnel returning from the wars in Iraq and Afghanistan have yielded a wide range of estimates, for example, 12.6 percent of U.S. men who fought in Iraq and 6.2 percent of U.S. men who fought in Afghanistan. The estimates of PTSD in British combat and noncombat troops that served in Iraq were 6 percent and 3 percent, respectively (Hotopf et al., 2006).

Comorbidities and Implications

Comorbidity of PTSD with other psychiatric disorders is common in military and civilian epidemiologic samples. In the NVVRS, 98.8 percent of veterans with lifetime PTSD also met criteria for at least one other psychiatric disorder (Kulka et al., 1990). The most common comorbid disorders among male veterans with PTSD were alcohol use disorder and major depression. In civilian samples, comorbidity with other psychiatric disorders occurs in the vast majority of lifetime PTSD cases (>80 percent) (Breslau et al., 1991; Kessler, 1995; Ruzek, 2003). The lifetime prevalence of major depression among men and women with PTSD is nearly 50 percent. Comorbidity is not unique to PTSD; psychiatric disorders are rarely "pure." There is evidence that people with comorbid disorders have greater impairment than those with a single disorder.

Theoretically, comorbidity in PTSD can occur through several alternative (but not mutually exclusive) pathways. Preexisting disorders might increase the risk for exposure to traumatic events or to PTSD following exposure. PTSD might increase the risk for subsequent onset of other disorders (e.g., drug use disorder in persons who use drugs to relieve painful symptoms). PTSD and comorbid disorders might share common vulnerabilities or result from the traumatic experience that precipitated PTSD (Wilson et al., 2001; Yehuda, 1998). The limited empirical evidence from prospective studies suggests different pathways across the comorbid disorders. The possibility that the trauma that precipitated PTSD is the cause of the comorbid disorders is not supported. The incidence of other disorders in victims of trauma is primarily concentrated in the small subset who have developed PTSD. Comorbidity with other diagnoses may create greater complexity in treating PTSD, although there is little research in this area.

Many of the PTSD treatment studies reviewed by the committee excluded cases with comorbid diagnoses, such as depression, other anxiety disorders, and alcohol and substance use disorders. The fact that people with comorbidities are often excluded from treatment efficacy trials necessarily raises questions about the generalizability of study results.

Exclusion of Subjects with Co-Occurring Disorders

Psychotherapy studies, specifically prolonged exposure, which is the most extensively researched psychotherapy, have few exclusion criteria. Exposure therapy studies allow certain drugs (such as selective serotonin reuptake inhibitors [SSRIs]) and several comorbid mental disorders (such as major depression and other anxiety disorders). In general, they exclude organic brain syndrome, current (or lifetime) psychoses, high suicide risk, and active substance abuse or dependence. (Some also exclude "severe" major depression.)

Psychopharmacology studies, specifically those of SSRIs, which are the most extensively researched in this category, often have more exclusions. In addition to the exclusions applied in psychotherapy studies, SSRI studies often exclude primary or principal[4] (though not comorbid) major depression and various anxiety disorders to avoid their potentially confounding role, especially when a study is conducted as part of an expected application for a PTSD indication to the Food and Drug Administration (FDA). Some exclude all or primary Axis I disorders, and they also exclude patients on other psychoactive medications. In some, concomitant psychotherapy is an

[4]"Primary" or "principal," referring to depression or other co-occurring disorder, means that onset of the condition preceded or is currently of greater severity or clinical importance than the PTSD.

exclusion criterion (Marshall et al., 2001; Martenyi et al., 2002). An additional reason to exclude subjects with comorbid disorders is to decrease heterogeneity and increase statistical power. Inclusion of subjects with comorbid disorders that also are strong prognostic indicators usually must be managed with a more complex research design, such as prerandomization stratification and recruiting larger samples. The first goal is to show that an experimental treatment has efficacy. Once efficacy is established, effectiveness in populations actually seen (such as those with comorbid conditions) can be addressed, but little treatment research in PTSD has been extended to this question of effectiveness. A few published studies focus on treatment of patients with dual diagnoses, such as PTSD comorbid with substance use disorders (Brady et al., 2005). These studies do not address the broader question of generalizability of findings in the general population or to the veteran population.

PTSD IN THE VETERAN POPULATION

VA provides health care services to approximately 7 million veterans (Department of Veterans Affairs, 2004). According to recent data, PTSD constitutes a substantial proportion of the burden of illness among veterans. In a study of 103,788 Operation Iraqi Freedom and Operation Enduring Freedom (OIF/OEF) veterans seen at VA health care facilities between September 2001 and December 2005, PTSD was the most commonly diagnosed military service-related mental health diagnosis (13,205 cases), accounting for more than half of the veterans receiving a mental health diagnosis and 13 percent of all OIF/OEF veterans in the study (Seal et al., 2007). In their presentation to this committee, VA officials stated that during Fiscal Year (FY) 2006, VA medical center programs served over 346,000 veterans diagnosed with PTSD in specialized outpatient programs and general mental health clinics (Batres and Zeiss, 2007). It is important to note, however, that not all veterans receive care from VA facilities, so the committee was careful to make reference both to the VA and veteran populations in its research and in this report.

The committee's review of the evidence was not restricted to veterans, but included all relevant studies of PTSD treatment in a variety of populations, including veterans. Since such a broad examination of the literature is necessary, it presents an important challenge in the question of applicability of nonveteran research findings to veteran populations. This challenge and how the committee sought to address it is discussed in Chapter 5.

The U.S. veteran population is not homogeneous; there is great variation among veterans, and not only in terms of sex, ethnicity, and socioeconomic and educational status. Veterans of World War II, the Vietnam and Korean conflicts, the Gulf War, and the current OIF/OEF have been

exposed to different types of stressors in considerably different social contexts. This heterogeneity constitutes yet another challenge for evaluation discussed in more detail in Chapter 5.

Special Issues Related to PTSD in the Military

Military sexual assault (sexual assault experienced while in military service[5]) is an additional traumatic stressor that affects military personnel, and subsequently, is identified as an exposure leading to PTSD in some, generally female, veterans. There is evidence that military sexual assault makes PTSD more likely than sexual assault occurring before or after military service (Himmelfarb et al., 2006; Yaeger et al., 2006), and potentiates the risk of developing PTSD from combat exposure (Himmelfarb et al., 2006; Kang et al., 2005).

One of the major challenges of diagnosing and treating PTSD is the stigma associated with it and mental illness in general. Stigma may have a profoundly negative effect on individual self-esteem, care-seeking behaviors, and social interaction (Department of Health and Human Services, 1999; Sartorius, 2002). In the military context, where self-reliance and inner strength are highly valued, mental illness may be considered a sign of weakness or a reason for shame, leading people to deny their illnesses or, once diagnosed, to avoid seeking care. Data on this issue in the veteran population are limited, but a 2003 study of several thousand current members of the Army and Marine Corps before and after deployment explored mental health status, interest in receiving care, and health care service utilization (Hoge et al., 2004). The study's findings were striking, highlighting several common themes, including the role of perceived stigma as a barrier to accessing services, perception of stigma and damage to one's military career, and other negative views of what suffering from a mental health condition and seeking care for it would mean for one's future in the military (Hoge et al., 2004). As a result of stigma, only 23–40 percent of those in need of mental health services actually seek care (Hoge et al., 2004).

TREATMENT OF PATIENTS WITH PTSD

Treatments available for PTSD include a variety of pharmacologic and psychotherapeutic modalities, and they are provided in diverse settings. For veterans, a considerable proportion receive services at both inpatient and outpatient VA facilities. The general population receives services in community clinics (some may specialize in specific types of trauma), from

[5]The IOM report *PTSD Compensation and Military Service* notes that a majority of perpetrators in military sexual assault cases were military peers or supervisors (IOM, 2007b).

private professionals, and in the hospital setting. Providers range from clinicians such as psychiatrists to psychologists, social workers, and other therapists, as well as support and self-help groups. In many areas, including rural and underserved settings, primary clinicians also play a major role in PTSD treatment.

There are two main categories of PTSD treatment examined by the committee, pharmacotherapy and psychotherapy, described below.

Description of the Pharmacotherapies

In its review of the literature the committee found seven main categories (and a miscellaneous category) of pharmacotherapy used to treat PTSD for which there are randomized controlled clinical trials (RCTs). These treatments are listed and briefly described below. The specific studies included in the evidence review by the committee are listed in Chapter 3. The committee also came across several drug therapies for PTSD for which there were either no RCTs (open label, case series, etc.), the population studied did not have diagnosed PTSD, or the main study outcome was not PTSD, so did not meet inclusion criteria (these drug therapies are listed below and inclusion criteria is discussed in Chapter 2).

Alpha-Adrenergic Blockers

Prazosin is an alpha-adrenergic blocker that has been proposed for reducing nightmares and improving sleep in patients with PTSD. Prazosin is currently approved by FDA to treat hypertension. It is hypothesized to work by blocking noradrenergic arousal during sleep. Known potential common side effects of prazosin include dizziness, drowsiness, headache, weakness, nausea, and syncope with sudden loss of consciousness after the first use of the drug.

Anticonvulsants

Anticonvulsants used in treating patients with PTSD include lamotrigine and topiramate. Drugs in this class work in different ways and are used to control epileptic seizures, prevent migraines, and treat other brain disorders. More recently they have also been used as mood stabilizers to treat mania and bipolar disorder. Lamotrigine is a glutamate-inhibiting anticonvulsant with antidepressant properties (Hertzberg et al., 1999) and topiramate enhances GABA[6]-activated chloride channels (Tucker et al., 2007). Lamotrigine is FDA approved to treat seizures and bipolar disorder;

[6]GABA refers to gamma-aminobutyric acid.

topiramate is approved to treat seizures and migraines. Known potential common side effects for anticonvulsants include dizziness, drowsiness, fatigue, nausea, tremor, rash, and weight gain.

Novel Antipsychotic Medications

Novel atypical antipsychotics such as olanzapine and risperidone are known to be used in the treatment of PTSD. Both drugs are hypothesized to work by controlling psychotic symptoms through antagonism (opposing) of selected dopamine and serotonin receptors. Olanzapine is FDA approved to treat the mixed or manic episodes of bipolar I disorder; risperidone is FDA approved to treat schizophrenia, symptoms of bipolar disorder, and in autistic children to treat symptoms of irritability. Known potential common side effects of olanzapine include agitation, behavior problems, difficulty in speaking or swallowing, restlessness, stiffness of arms or legs, and trembling or shaking of hands and fingers. For risperidone, common side effects include extrapyramidal effects (sudden, often jerky, involuntary motions of the head, neck, arms, body, or eyes), dizziness, hyperactivity, tiredness, and nausea.

Benzodiazepines

Benzodiazepines, such as alprazolam, are sometimes used in treating patients with PTSD (APA, 2004; Friedman, 1998; VA/DOD, 2002). Benzodiazepines treat anxiety, insomnia, and irritability. Alprazolam specifically is an antianxiety agent and central nervous system depressant and works by decreasing abnormal excitement in the brain. Benzodiazepines have a known risk of dependency and of withdrawal after abrupt discontinuation; if there is current or past drug abuse or dependence, dependence on this class of drugs is more likely to develop. Other known potential side effects include drowsiness, light-headedness, tiredness, dizziness, irritability, talkativeness, dry mouth, increased salivation, changes in sex drive or ability, changes in appetite, weight changes, and difficulty urinating.

Monoamine Oxidase Inhibitors

Monoamine oxidase inhibitors (MAOIs), such as brofaromine and phenelzine, are another class of drugs used to treat patients with PTSD. MAOIs irreversibly inhibit monoamine oxidase, the enzyme responsible for the degradation of serotonin and related molecules in the central nervous system. Brofaromine is a reversible and selective type-A MAOI that also has serotonin reuptake inhibitory properties. It currently is not available in the United States. Phenelzine is used to treat symptoms of depression includ-

ing feelings of sadness, fear, anxiety, or worry about physical health. It is usually utilized after other antidepressants have been unsuccessful for the patient. Potential common side effects of MAOIs include dizziness, feeling weak or drowsy, sleep problems (insomnia), constipation, upset stomach, dry mouth, decreased urination, and impotence or difficulty achieving an orgasm. Drinking alcohol while taking an MAO inhibitor may also cause serious side effects.

Selective Serotonin Reuptake Inhibitors

SSRIs, such as paroxetine, sertraline, fluoxetine, and citalopram, are a class of antidepressants also used to treat anxiety disorders. SSRIs are hypothesized to relieve symptoms of depression by blocking the reuptake of the neurotransmitter serotonin in certain synapses in the brain. Fluoxetine,[7] paroxetine,[8] and sertraline[9] are all FDA approved to treat depression. Sertraline and paroxetine are the only pharmacotherapies approved by FDA to treat PTSD. The four studies submitted to the FDA to gain approval were included in the literature reviewed by the committee: Brady et al., 2000, and Davidson et al., 2001, for sertraline; and Marshall et al., 2001, and Tucker et al., 2001, for paroxetine. Common side effects of SSRIs include nausea, sexual dysfunction, headache, diarrhea, nervousness, rash, agitation, restlessness, increased sweating, drowsiness, insomnia, and weight gain. Stopping treatment abruptly or missing several doses can cause withdrawal-like symptoms. It should be noted that FDA requires that SSRIs carry a boxed warning on their label about increased risk of suicidality.

Other Antidepressants

Tricyclic Antidepressants

Tricyclic antidepressants (TCAs) also may be used in treating patients with PTSD. TCAs include amitriptyline, imipramine, and desipramine. The pathway through which they improve depression symptoms is not fully understood although it is hypothesized that they increase the activity of norepinephrine or serotonin in the brain.

[7]Also FDA approved to treat depression, obsessive-compulsive disorder, bulimia nervosa, premenstrual dysphoric disorder, and panic disorder.

[8]Also FDA approved to treat social anxiety disorder.

[9]Also FDA approved to treat social anxiety disorder, obsessive-compulsive disorder, panic disorder, and premenstrual dysphoric disorder.

Mirtazapine

Mirtazapine is a noradrenergic and specific serotonergic antidepressant (NaSSA) tetracyclic, FDA approved to treat major depression. How mirtazapine improves depression symptoms is not fully understood although it is hypothesized that it increases the activity of norepinephrine or serotonin in the brain, which helps improve mood. Common known side effects are abnormal dreams and thinking, constipation, dizziness, drowsiness, dry mouth, flu symptoms, increased appetite, weakness, and weight gain.

Venlafaxine

Venlafaxine is a serotonin and norepinephrine reuptake inhibitor (SNRI) that is FDA approved to treat depression and generalized as well as social anxiety disorders, but it is also one of the drugs used in the treatment of patients with PTSD. Potential side effects include anxiety, blurred vision, changes in taste, constipation, sexual dysfunction, dizziness, drowsiness, dry mouth, flushing, headache, increased sweating, loss of appetite, nausea, nervousness, stomach upset, trouble sleeping, vomiting, weakness, and weight loss.

Nefazodone

Nefazodone is another drug used in PTSD treatment that is FDA approved to treat depression. Its mechanism of action, as with other antidepressants, is unknown but clinical trials have shown that it inhibits neuronal uptake of serotonin and norepinephrine. Nefazodone has a boxed warning stating that cases of life-threatening hepatic failure (hepatotoxicity) have been reported in patients treated with nefazodone hydrochloride tablets. Common side effects include abnormal dreams, abnormal skin sensations, changes in taste, chills, confusion, constipation, decreased concentration, decreased sex drive, diarrhea, dizziness, drowsiness, dry mouth, fever, frequent urination, headache, incoordination, increased appetite, and others.

Other Drugs

D-cycloserine and inositol each have been studied to treat PTSD in one randomized controlled trial. D-cycloserine is an antibiotic used in the treatment of tuberculosis. It is also a partial N-methyl-D-aspartic acid (NMDA) agonist that boosts the activity of NMDA in the brain, which is needed for fear extinction. Inositol, specifically myo-inositol, is a second-messenger system constituent that has been investigated in the treatment of anxiety disorders, including PTSD (Freeman et al., 2002).

Other drugs researched in the treatment of PTSD for which there are no published RCTs at the time of this writing include the following:

- Naltrexone and disulfiram (Lubin et al., 2002; Petrakis et al., 2006)
- Tianeptine (Onder et al., 2006)
- Baclofen (Drake et al., 2003)
- Propranolol (alpha-adrenergic blocker) (Pitman et al., 2002)
- Carbamazepine, divalproex, valproate (anticonvulsants) (Berlant and van Kammen, 2002; Clark et al., 1999)
- Quetiapine and levomepromazine (antipsychotics) (Ahearn et al., 2006; Aukst-Margeti et al., 2004)
- Clonazepam (benzodiazipine) (Cates et al., 2004)
- Fluvoxamine (SSRI) (Escalona et al., 2002; Spivak et al., 2006; Tucker et al., 2000)

Description of the Psychotherapies

As with most of the pharmacotherapies, psychotherapies are used to treat a variety of mental health conditions. Several psychotherapeutic interventions are used in the treatment of PTSD, sometimes in combination with medication. These interventions include cognitive behavioral therapies (CBTs). Components of psychotherapy used to treat PTSD include: (1) exposure to trauma-related memories or stimuli used in exposure therapies, such as eye movement desensitization and reprocessing (EMDR); (2) cognitive restructuring used in cognitive therapy and cognitive processing therapy; (3) coping skills training used in stress inoculation training, relaxation, and in social, family, and vocational interventions; (4) hypnosis; and (5) psychodynamic interpretation. Psychotherapy is designed to reduce the intrusion, avoidance, and hyperarousal symptoms of PTSD by some combination of reexperiencing and working through trauma-related memories and associated emotions, and teaching better means of managing trauma-related stressors. Psychotherapy approaches are designed to help patients control and reduce symptoms through either inducing them under controlled circumstances and then modulating them, or by focusing on stress management and nontrauma-related aspects of the person's life.

Behavioral therapy includes approaches such as systematic desensitization, biofeedback, and relaxation. The cognitive and behavioral approaches in CBT may be separated, but "aspects of both are frequently combined, and studies that identify the effective components of these therapies or that distinguish one from another are not available" (APA, 2004). For example, Harvey et al. (2003) described four basic components of CBT: psychoeducation, exposure, cognitive restructuring, and anxiety management

training. The theoretical literature also acknowledges the overlap among these approaches (as well as incomplete understanding of the mechanisms at work when these interventions are used) (APA, 2004; Harvey et al., 2003). Further explanation of the various psychotherapies can be found in Appendix A.

SUMMARY OF THE MAJOR CLINICAL PRACTICE GUIDELINES

To be sure that the committee was aware of all pharmacotherapies and psychotherapies in general clinical use, a search was conducted for clinical practice guidelines developed by major professional organizations. The committee reviewed clinical practice guidelines developed by the Management of Post-traumatic Stress Working Group of VA and the Department of Defense (DoD), the American Psychiatric Association (APA), the British National Institute for Clinical Excellence (NICE), the International Society for Traumatic Stress Studies (ISTSS), and the Australian Centre for Posttraumatic Mental Health of the Australian National Health and Medical Research Council. The committee made no judgments about the quality of these guidelines in the processes used or conclusions reached, but found them useful in defining the domain of clinical PTSD interventions.

The VA/DoD *Clinical Practice Guideline* (2004) classifies four psychotherapy treatments as being of significant benefit: cognitive therapy, exposure therapy, stress inoculation therapy, and EMDR. Treatment modalities considered to offer some benefit include imagery rehearsal therapy, psychodynamic therapy, and PTSD patient education. The guidelines also identified two adjunctive treatments: dialectical behavioral therapy and hypnosis. Among the pharmacotherapy interventions, only one group, the SSRIs, was classified as being of significant benefit. Medications identified as having some benefit include TCAs, MAOIs, sympatholytics, and novel antidepressants. Anticonvulsants, atypical antipsychotics, nonbenzodiazepine hypnotics, and the antianxiety drug buspirone were identified as having unknown benefit. Finally, drugs with no benefit or possible harm include benzodiazepines and typical antipsychotics.

The APA (2004) practice guidelines grouped its recommendations into categories: (I) recommended with substantial clinical confidence; (II) recommended with moderate clinical confidence; and (III) may be recommended on the basis of individual circumstances. SSRIs were the only pharmacotherapy rated as category I, while TCAs and MAOIs were rated category II, and benzodiazepines, anticonvulsants, antipsychotics and adrenergic inhibitors were rated category III. The guidelines found clinical effects in studies with women with chronic PTSD related to rape or assault are particularly noteworthy in the SSRI class. The evidence for MAOIs was limited to male combat veterans. For benzodiazepines, the evidence identified by

the guideline authors was unclear, and the class was recommended only for anxiety and improving sleep, not as monotherapy. Among the antipsychotics, studies of olanzapine and risperidone found some suggestive evidence from preliminary studies in patients with psychotic symptoms. The guideline authors found no controlled studies in alpha 2-adrenergic agonists but found preliminary evidence of possible benefit for prazosin. The psychotherapies reviewed by the APA include CBT and other exposure-based therapies, which demonstrated the strongest evidence, category I (but several studies showed increase in symptoms in some individuals). Stress inoculation, imagery rehearsal and prolonged exposure (which, in this report and elsewhere have been categorized under the CBT heading), psychodynamic therapy, hypnosis (little empirical support, few RCTs for psychodynamic therapy and hypnosis, but usefulness supported by clinical consensus), and EMDR were rated as category II. Finally, the guideline assigned a category III rating to case management, psychoeducation, other supportive interventions, and to group present-centered and trauma-focused therapy.

The NICE guidelines rated interventions on an A through C scale. An A rating means that the evidence comes from "at least one RCT as part of a body of literature of overall good quality and consistency addressing the specific recommendation (evidence level I[10]) without extrapolation." A B rating means that evidence comes from "well-conducted clinical studies but no randomised clinical trials on the topic of recommendation" (evidence levels II or III[11]) or that evidence was extrapolated from level-I evidence. A C rating means evidence came from "expert committee reports or opinions and/or clinical experiences of respected authorities (evidence level IV[12]) or extrapolated from level I or II evidence. This grading indicates that directly applicable clinical studies of good quality are absent or not readily available. Of the psychotherapies, trauma-focused CBT and EMDR were rated A, and relaxation was rated B. The guidelines identified only a short list of pharmacotherapies, including the SSRI paroxetine and the NaSSA mirtazapine for general use, and the TCA amitriptyline and the MAOI phenelzine for use by mental health specialists, both categories to be used in patients unwilling or unable to receive psychotherapy. Hypnotic medication was rated C to be used on a temporary basis, and olanzapine was rated C to be used as an adjunctive. The NICE guidelines also recommended that

[10](I) Evidence obtained from a single randomised controlled trial or a meta-analysis of randomised controlled trials.

[11](IIa) Evidence obtained from at least one well-designed controlled study without randomization; *or* (IIb) evidence obtained from at least one other well-designed quasi-experimental study; *or* (III) evidence obtained from well-designed nonexperimental descriptive studies, such as comparative studies, correlation studies, and case studies.

[12](IV) Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities.

medication be offered if psychological treatments are not effective, but they noted that the former are not as helpful as trauma-focused psychological treatments. Medication is recommended as first line of treatment when the patient prefers not to have psychological treatment, it would be difficult to start psychological treatment because of a threat of further trauma, or if psychological treatment was not helpful. Pharmacotherapy is also recommended as adjunct to psychotherapy in cases with comorbid depression or severe hyperarousal that interferes with psychotherapy.

ISTSS reviewed the evidence base for treatment of PTSD and made recommendations on six "categories of endorsement" in its *2000 Practice Guidelines* (Foa et al., 2000). ISTSS found that CBT and SSRIs are shown to be effective, with some evidence of effectiveness for several additional psychotherapies, including psychodynamic therapy, hypnotherapy, and EMDR. The guideline discusses the evolution of CBT approaches, from the older therapies (systematic desensitization, relaxation training, biofeedback) that are based on learning theory, to the more recent techniques, based on emotional and information processing theories, and which include exposure, cognitive therapy, and cognitive processing therapy. The guideline reviewed eight CBT techniques, three of which are combinations of other techniques: exposure, systematic desensitization, stress inoculation therapy, cognitive processing therapy, cognitive therapy, assertiveness training and biofeedback (both are anxiety management approaches), relaxation training, stress inoculation therapy plus exposure, exposure plus relaxation plus cognitive therapy, and cognitive therapy plus exposure.

At the time of this writing, the Australian government's Centre for Posttraumatic Mental Health had just published its *Australian Guidelines for the Treatment of Adults with Acute Stress Disorder and Posttraumatic Stress Disorder*. The guidelines drew on the British NICE guidelines and U.S. VA/DoD guidelines, and the authors reviewed studies published after the NICE review. The guidelines recommended the use of trauma-focused interventions (namely, trauma-focused CBT or EMDR, in addition to *in vivo* exposure) first, with SSRIs as the first choice in pharmacologic treatment. In regard to the scientific evidence on SSRIs, however, the guidelines found that the four SSRI studies conducted after the publication of the NICE "failed to provide evidence that these drugs were superior to placebo either in the treatment of PTSD symptoms or in the treatment of depression in the context of PTSD." The guidelines also recommended that group CBT therapy "may be provided as adjunctive to" but not as an alternative to individual therapy (Australia Centre for Posttraumatic Mental Health, 2007: xviii).

SUMMATION

In this chapter we reviewed the charge to the committee from VA, the DSM definition of PTSD and epidemiologic information about its prevalence, provided an overview of treatment research for PTSD that has appeared in peer-reviewed journals over the past 30 years, and summarized several major clinical practice guidelines. The following chapter addresses the methods that were developed and used to evaluate the quality of published PTSD treatment research for this report.

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2

Methods

This chapter describes the methods the committee used to search and organize the literature, assess the quality of studies, and reach conclusions about the strength of the evidence regarding efficacy of various treatment modalities for posttraumatic stress disorder (PTSD).

THE LITERATURE SEARCH

An extensive search of the published[1] scientific literature of PTSD treatment was conducted and over 2,000 potentially relevant references were retrieved. The following categories were of primary interest to the committee:

1. Meta-analyses and reviews of effectiveness of drug therapies and psychotherapies in all populations with PTSD
2. Clinical trials and epidemiological studies of drug therapies and psychotherapies for veterans with PTSD and/or anxiety disorders
3. Studies other than meta-analyses, reviews, clinical trials, or epidemiological studies that discuss drug therapies and psychotherapies for veterans with PTSD
4. Studies of treatment outcomes, progression, prognosis, or recovery for veterans with PTSD

[1]National Academies committees are required to make publicly available all material reviewed in the course of their deliberation and used in preparing reports and making recommendations. For this reason, the committee did not use any unpublished material in its review.

The committee's database searches used the National Library of Medicine's Medical Subject Headings (MeSH) keyword nomenclature developed for MEDLINE. Searches included terms for drug interventions, psychotherapy interventions, and study design, and were limited to studies published in English, after 1980,[2] and conducted in adult populations (≥18 years old). The committee also reviewed selected reference lists of relevant review articles, meta-analyses, and books. The committee did not undertake a systematic search for unpublished data. A more detailed explanation of this search can be found in Appendix B. Databases consulted include:

- MEDLINE,
- EMBASE (Excerpta Medica),
- PsycINFO,
- Cochrane Database of Systematic Reviews,
- Cochrane Controlled Trials Register,
- National Technical Information Service (NTIS),
- Social service abstracts, and
- Database of Abstracts of Reviews of Effectiveness (DARE).

The searches identified a total of 2,771 sources. All citations were imported into an electronic database (EndNote). Table 2-1 outlines the sources of the citations.

The committee developed criteria for inclusion and exclusion based on the patient populations and outcome measures (see Box 2-1 for specific criteria). Once the nonrelevant studies were eliminated—including those that were not on treatment (many were on assessment and diagnosis of PTSD, biologic markers for PTSD, or were not in a PTSD population)—each abstract was reviewed for relevance, and the full text was retrieved for all potentially relevant abstracts for further review, with the guidance of all committee members. Decisions to include and exclude studies were made by the committee.

This review focused on adult patients (ages 18 years and older) with PTSD diagnosed by the study investigators according to *Diagnostic and Statistical Manual of Mental Disorders* (DSM) criteria. That is why the committee's search included only studies published beginning in 1980, when the first DSM definition was published. Studies with patients of mixed diagnoses (e.g., some with diagnosed PTSD, others subsyndromal) only were included if results were reported separately for the relevant subgroups.

[2]In 1980 the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) first recognized PTSD as a disorder and provided a definition and symptoms list.

TABLE 2-1 Number of Citations, by Source

Source	Number of Citations
MEDLINE	1554
EMBASE	578
PsycINFO	334
Cochrane Database of Systematic Reviews	11
Cochrane Controlled Trials Register	28
NTIS	151
Social service abstracts	97
DARE	18
Total	2771

BOX 2-1 Inclusion Criteria for Review

- Randomized controlled trial (RCT; randomized comparative trials were only used if RCTs for a given modality demonstrated efficacy)
- PTSD diagnosis based on DSM criteria
- Published between 1980 and June 2007
- Adults ages 18 and older
- PTSD outcome measure included (primary or secondary measure)
- English language

This review also included only primary research and no reanalyses of prior research.[3]

The committee was charged to "report on the highest levels of evidence available." Although the number of studies for some treatment modalities was small, in most cases randomized controlled trials were available for review. (For clarity, it should be noted that in the psychotherapy studies, the control was not placebo, but wait list, usual care, or a type of active control.) Therefore, per part II.B of the Statement of Task, only level-I studies (RCTs) were included in the committee's review. The committee recognizes that study designs other than RCTs can be informative for questions of effectiveness and other outcomes, but did not believe that non-RCTs would inform the core question of treatment efficacy. The committee judged

[3]When there was more than one primary study based on the same data, the study with the most complete data set was used.

that, in general, questions of treatment efficacy are best addressed in high quality RCTs because the variability of treatments, outcome measures, course of the disorder, and patient and provider preferences make studies of other designs unreliable in making causal inferences. The committee further reasoned that the specific characteristics of PTSD (multiple symptom clusters, occurring in various combinations in patients), its measurement (multiple outcome measures, some with several scales), and its treatment (a wide range of pharmacotherapy and psychotherapy options) were of such heterogeneity and fragmentation that observational studies were unlikely to provide sufficiently valid and reproducible evidence to be considered in addition to the RCTs.

Data Abstraction

The committee developed an evidence table template and database for abstracting data from the included studies. Once the evidence table data were abstracted by staff, committee members worked in pairs to check the tables for completeness and to assess the quality of the study as well as its contribution to the evidence regarding efficacy of the treatment. The following information was extracted from all included studies if available: geographical location; setting; study design; interventions (including dose, duration, dose protocol, concurrent interventions, and clinician); population characteristics (including age, sex, race/ethnicity, education, trauma type and duration, concurrent medications, psychotherapies, and comorbidities); study inclusion and exclusion criteria; number screened, number enrolled, and completion rates; funding source; and results for PTSD outcomes as well as outcomes on depression, anxiety, and quality-of-life measures. Additionally, information was abstracted on whether or not adverse events were reported, if meeting diagnostic criteria after treatment was reported, and if the study included veterans.

REACHING CONCLUSIONS REGARDING THE EFFICACY OF TREATMENT MODALITIES

The committee was charged with making conclusions about the strength of the available evidence for treatment modalities according to the following framework:

1. Evidence is sufficient to conclude the efficacy of *X* in the treatment of PTSD.
2. Evidence is suggestive but not sufficient to conclude the efficacy of *X* in the treatment of PTSD.

3. Evidence is inadequate to determine the efficacy of *X* in the treatment of PTSD.
4. Evidence is suggestive that *X* treatment is ineffective in treating PTSD.
5. Evidence is suggestive that *X* treatment is harmful in the treatment of PTSD.

Conclusions 4 and 5 (suggesting and concluding ineffectiveness/harm) are mirror images of conclusions 2 and 1 (suggesting and concluding efficacy). The data extraction and review processes addressed the question of whether there was a body of evidence regarding the effect of a treatment modality in either direction—efficacy or inefficacy. Thus the five conclusions above collapsed into making only three conclusions regarding a treatment modality: evidence sufficient to conclude its effect (positive or negative); evidence suggestive but not sufficient to conclude its effect (positive or negative); and evidence inadequate to conclude its effect (positive or negative). The committee viewed the conclusion of inadequate evidence as a neutral position with respect to efficacy—neither concluding that the modality was effective or ineffective.

Assessing the Literature to Reach Conclusions

The committee made an assessment of both the strength of the individual studies comprising the body of evidence, and the overall sufficiency of that body of evidence for judging treatment efficacy. The assessment of strength of individual studies was based on the degree to which the studies adhered to current scientific standards in design and analysis (see Criteria to Assess a Study's Quality in Box 2-2) as well as the estimated magnitude of effect and precision of that estimate.

In making its conclusions regarding efficacy, the committee found most informative those studies that failed the fewest criteria and that did not have major limitations. The committee further assessed the overall body of evidence for each treatment modality with attention to the volume of studies meeting quality criteria, the consistency of the direction of the effect among studies (e.g., positive, negative, or mixed), the size of the studies (small: <30 participants per treatment condition; moderate: 30–99 per arm; large: >99 per arm), the statistical significance of the findings, the magnitude of the effect (including its clinical significance), and the length of follow-up.

A high-quality study that was small might produce weak evidence because the small size leads to an uncertain estimate of effect, whereas a low-quality large study might also produce weak evidence because the low quality leads to biased estimates of effect. The assessment of overall sufficiency of evidence for judging treatment efficacy depended on the

BOX 2-2
Criteria to Assess a Study's Quality

- Assembly of comparable groups (randomized,** similar distributions of known confounders).
- Maintenance of comparable groups (i.e., minimal attrition, crossovers, or contamination, good adherence). Use of intention to treat (ITT) analysis.
- Measurements equal, valid, and reliable (validated PTSD outcome measure, double masking in pharmacotherapy studies** and assessor blinding or at least assessor independence** in psychotherapy studies).
- Loss to follow-up causing missing outcome data:
  - — Differential loss to follow-up no greater than 15% absolute difference between groups.**
  - — If approximately equal loss to follow-up in each arm, study quality is affected by the analytic methods used to handle missing data:
    - o Up to 10% missing outcome data acceptable without formal missing data methods employed (i.e., may use completer analysis or last observation carried forward [LOCF]).
    - o Between 10% and 40% missing outcome data acceptable depending on validity of missing data analytic method employed (e.g., for lower proportions, single imputation, for higher proportions, likelihood-based methods, multiple imputation, sensitivity analysis).
    - o Use of LOCF decreases study quality as the percentage dropout increases, severely if dropout exceeds 30%. Completer analysis is not acceptable.**
    - o No more than 40% loss to follow-up in any arm.**

**Indicates a criterion that if absent (or if the authors do not disclose) is a major limitation that limited the study's usefulness to the committee in reaching its conclusion regarding efficacy.

strength of the individual studies, the consistency of the effects among studies, and the degree to which the interventions, populations, and outcome measures used in those studies were deemed comparable. This overall sufficiency of the evidence for judging treatment efficacy was classified into the three categories (reflecting, as described above, the collapsed five conclusions listed in the committee's charge): *Sufficient* to conclude the presence of a treatment effect, *Suggestive but not sufficient*, and *Inadequate* (see Box 2-3).

BOX 2-3
Assessments Leading to Conclusions of Efficacy

"Evidence is sufficient . . ."
- High quality of the body of evidence (i.e., more than one study) indicating a clinically meaningful treatment effect
- High confidence in both the presence and magnitude of an effect
- Future research is unlikely to change confidence in the estimate of effect

"Evidence is suggestive but not sufficient . . ."
- Moderate quality of the body of evidence, with the best studies all pointing in the same clinical direction
- Moderate confidence in the presence of an effect, but not confident in the magnitude of the effect
- Further research is likely to have an important impact on confidence in the estimate of the effect and may change the estimate
- Moderate confidence that the effect will hold up in future studies of high quality

"Evidence is inadequate . . ."
- Low quality of the body of evidence (i.e., evidence comes from seriously flawed studies)
- Not confident in the presence of an effect. Any estimate of effect is uncertain
- Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate
- Uncertainty whether future high-quality studies will show an effect

Committee members found certain heuristics useful in thinking about the meaning of those categories (Box 2-3). One approach was to distinguish between the confidence in the presence of a treatment effect and the magnitude of that effect. A body of evidence that produced high confidence in both the presence and size of the effect would be "sufficient"; moderate confidence in the presence of an effect but substantial uncertainty about the size of the effect (e.g., whether it was clinically meaningful) would be "suggestive"; and uncertainty about both the effect and its size would be "inadequate." Another heuristic was to assess the robustness of the current evidence by imagining the impact of a high-quality moderate-size future study: if it were unlikely to impact conclusions about the presence or size of an effect, current evidence would be deemed "sufficient"; if it could meaningfully shift the strength of evidence, the current evidence pointing to an effect would be "suggestive"; and if it would effectively

substitute for the current evidence, then the current evidence would be judged "inadequate."

Although all of these determinations were based on recognized principles and guidelines for evaluating evidence, there is no established algorithmic approach to these classifications and the committee did not use one. Instead, it attempted to be as transparent as possible in describing the foundations of its judgments, and these are reflected both in the evidence tables and in the "Synthesis" paragraphs immediately preceding statement of the conclusion for each treatment modality presented in Chapters 3 and 4. The evidence tables include population descriptors, sample size by arm and total, handling of missing data and dropout rates, information about blinding, PTSD outcome measure change data,[4] loss of PTSD diagnosis data, and finally, a listing of a study's principal limitations.

SUMMARY OF THE LITERATURE REVIEWED IN MAKING CONCLUSIONS

The final set of studies reviewed by the committee consisted of 89 total, with 37 studies of pharmacotherapies and 52 studies of psychotherapies. All studies were randomized controlled trials. Studies ranged in sample size from fewer than 20 to more than 500 and were conducted with a variety of patient populations: male, female, and mixed populations; various traumas (combat- and noncombat-related); more recent onset of the disorder and chronic PTSD; and so on. Studies reviewed also employed a range of PTSD outcome measures, from frequently used, validated measures such as the Clinician Assessment PTSD Scale (CAPS) and the Impact of Events Scale (IES), to more idiosyncratic measures sometimes developed for a specific study. The studies reviewed by the committee included a large number of outcome measures; a summary table of the measures most often encountered in the literature is provided in Appendix C.

SUMMARY OF EXISTING SYSTEMATIC REVIEWS AND META-ANALYSES

In addition to its review of individual research studies, the committee examined a number of systematic and qualitative reviews and meta-analyses. Some reviewed both psychotherapies and pharmacotherapies,

[4]PTSD outcome measure change data were obtained either directly from the study, when provided, or by subtracting data reported at treatment completion (not follow-up data) from baseline data (before treatment began). Average baseline score when reported or when baseline scores for all arms are nearly the same; otherwise, baseline scores listed individually in order of arm.

others focused on a category or class of treatment (e.g., selective serotonin reuptake inhibitors [SSRIs]) and yet others on a specific treatment modality (e.g., sertraline). None of the reviews exactly coincided with the committee's charge or purpose, and none of the reviews used the same inclusion and exclusion criteria, criteria to assess quality, and methods to reach conclusions as did the committee. Many of the reviews did not publish exactly how the literature was identified, assessed, and summarized. Thus the committee found it interesting to see how others have conceptualized the field and conducted reviews, and used the reviews to make sure that the committee's literature search was exhaustive and comprehensive. However, the committee could not use the existing systematic reviews and meta-analyses to directly inform its assessments of the efficacy of specific interventions. The summaries below are presented as general background.[5]

The descriptive reviews included Foa and Meadows (1997), Hembree and Foa (2003), and others. The meta-analyses included two issued by the Cochrane Collaboration (Bisson and Andrew, 2006; Stein et al., 2006). Brief summaries are provided below.

Hembree and Foa conducted a qualitative review of pharmacotherapies and psychotherapies used with crime victims (Hembree and Foa, 2003). They considered a variety of designs, including open-label studies. Findings included significant reduction in symptoms with SSRI treatment, monoamine oxidase inhibitors (MAOIs) were found moderately effective, and tricyclic antidepressants (TCAs) were mildly effective for patients with chronic PTSD. The authors also found equivalent outcomes among exposure; cognitive therapy, stress inoculation training (SIT), and a combination of the two; and eye movement desensitization and reprocessing (EMDR), though they noted that dismantling studies suggest eye movements are not integral. The SSRI studies showed them to be the first-line medication because of their relative safety profile and their efficacy in improving comorbid conditions (depression, panic, obsessive-compulsive disorder).

Van Etten and Taylor (1998) reviewed both pharmacotherapy and psychotherapy for PTSD. Inclusion criteria were patients diagnosed based on DSM criteria, studies where N≥5, and outcome measures were reliable and valid (including nonrandomized, uncontrolled) (van Etten and Taylor, 1998). The authors included 38 studies and 1,029 completers. Psychotherapy studies had lower dropout rates than pharmacotherapy studies (14 percent versus 32 percent), and psychotherapies were more effective in reducing symptoms. Both pharmacotherapy and psychotherapy were more effective versus controls. The greatest effect size in pharmacotherapy studies

[5]The committee considered including effect size or weighted means differential data for each meta-analysis summarized, but it concluded that relaying such results alone in the absence of other data is not particularly useful for the interested reader.

was found in SSRI studies and the one carbamazepine study. The greatest effect size in psychotherapy studies was in behavior therapy and EMDR, but EMDR used significantly fewer sessions and took less time.

Foa and Meadows (1997) reviewed psychotherapy studies. They found the evidence for efficacy of exposure and SIT most robust, the evidence on cognitive processing therapy promising, and the evidence on EMDR mixed and "inundated with methodological flaws." Their assessment of studies of hypnotherapy and psychodynamic was that the research in this area lacked rigor (studies were mostly case reports) or had methodological problems. Furthermore, they found that combined therapies, such as SIT with prolonged exposure, did not appear to be superior to their components, and without studies dismantling them it was not possible to discern which components were most active.

The committee reviewed the Cochrane systematic review of psychotherapies (Bisson and Andrew, 2006) that examined 26 RCTs of interventions they divided into four categories: trauma-focused cognitive-behavioral therapy (CBT), stress management (or nontrauma-focused CBT, roughly equivalent to the committee's category of coping skills training therapies), other therapies (supportive therapy, nondirective counseling, psychodynamic therapy, and hypnotherapy), and group CBT. (The review did not include EMDR; the authors expected to add and reissue the review early in 2007, but no update was available at the time of this writing.) The meta-analysis found both trauma-focused CBT and stress management significantly better than wait list or usual care. There was no significant difference between trauma-focused CBT and stress management, and both were better than other therapies, and those, in turn, were not significantly different from wait list or usual care. Group trauma-focused CBT was also found to be significantly better than wait list or usual care.

Bradley et al. (2005) conducted a meta-analysis of psychotherapy RCTs with more than 10 subjects published between 1980 and 2003. The treatments reviewed include exposure, CBT, exposure plus CBT, and EMDR. The meta-analysis included 26 studies and 1,535 patients. The authors found no significant difference in comparing treatment against wait list or standard care.

Harvey et al. (2003) conducted a descriptive review of the CBT literature and organized their findings by type of trauma. They found strong support for CBT interventions, but identified methodologic weaknesses in many of the studies they reviewed. Harvey and colleagues also briefly described some of the evidence and some key issues (e.g., methodologic problems) in EMDR research.

Sherman (1998) evaluated 17 controlled studies of psychotherapy, 11 of which were in populations with combat-related trauma. This meta-analysis

found support for exposure therapy both in populations with combat and noncombat-related trauma.

Shepherd et al. (2000) reviewed 16 RCTs comparing EMDR to another psychotherapy, to EMDR variants, or to delayed EMDR. The authors found that the studies varied in methodologic quality, and were generally small, most lacked assessor blinding, and had high rates of loss to follow-up. Fifteen of 16 studies showed positive treatment effects for EMDR.

Maxfield and Hyer (2002) reviewed the EMDR literature. Their analysis included calculated effect sizes and evaluating methodology using Foa and Meadows' (1997) gold standards (the authors assigned scores of 0, 0.5, or 1 on a scale of seven items). Their review included 12 RCTs remaining, 9 of which were above 5.5 mean on the quality evaluation, and they all found EMDR effective.

Davidson and Parker (2001) reviewed 34 studies of EMDR and conducted a meta-analysis. They found great variation in methodologic quality, and found evidence of an effect in pre-post comparisons, and when EMDR was compared to psychotherapeutic approaches that excluded exposure.

The Cochrane systematic review of pharmacotherapies for PTSD (Stein et al., 2006) included 35 short (14 weeks or less) randomized controlled trials, with a total of 4,597 participants. The reviewers found that a significantly greater proportion of patients responded to treatment compared to placebo (59.1 percent versus 38.5 percent), with the largest trials showing SSRI efficacy, including long-term efficacy. However, the authors noted,

> The current evidence base of RCTs is unable to demonstrate superior efficacy or acceptability for any particular medication class. Although some have suggested that the SSRIs are more effective than older antidepressants (Dow and Kline, 1997; Penava, 1996), class membership did not contribute significantly to the variation observed in symptom severity outcomes between trials, while the confidence intervals for the summary statistic of responder status on the seven SSRI trials overlapped with that of the MAOI and TCA trials.

Comer and Figgitt (2000) reviewed the sertraline literature. They selected only large, well-controlled studies with appropriate statistical methodology. They identified five multicenter, double-blind RCTs with a total of 4,075 participants. The authors found significant effect in two of three civilian studies and in one of two veteran studies.

Mooney et al. (2004) conducted a review of sertraline RCTs, open-label and uncontrolled studies, case series, and case reports. Twelve studies with a total of 1,159 subjects were included. Only 5 of the 12 studies were RCTs, and only these were included in the meta-analysis, which supported the use of sertraline (Mooney et al., 2004).

In addition to the peer-reviewed literature, *Effective Treatments for PTSD* (Foa et al., 2000), the *Practice Guidelines from the International Society for Traumatic Stress Studies*, includes several descriptive reviews (most were systematic) of the PTSD treatment literature: pharmacotherapy, CBT, EMDR, group therapy, psychodynamic therapy, and hypnosis. Summaries of these are provided below.

First, Rothbaum et al. (2000) reviewed "empirical studies" of CBT, focusing on eight identified techniques including exposure and cognitive therapy, and several combined approaches. The authors used Foa and Meadows' gold standard ratings and the Agency for Health Care Policy and Research (AHCPR)[6] A–F ratings to review approximately 40 controlled and uncontrolled studies. Rothbaum and colleagues found the evidence of effectiveness for exposure conclusive, and also found evidence of effectiveness for SIT and cognitive processing therapy. They found combined CBT approaches (such as exposure plus SIT) were neither better nor worse than their components.

Friedman (2000), in Foa et al. (2000), conducted a review of RCTs, open trials, and case reports. Their review gave greater weight to RCTs and also used the AHCPR A–F rating. The studies reviewed included a number of RCTs on SSRIs, benzodiazepines (one study), TCAs, and MAOIs. There were no RCTs, only other types of studies for antipsychotics, anticonvulsants, antiadrenergics and serotonergics, nefazodone, and traxodone. The evidence was strongest for TCAs, MAOIs, and SSRIs, but they were weak or mixed for serotonergic, alpha-adrenergic drugs, anticonvulsants, benzodiazepines, and antipsychotics.

Chemtob et al., also in Foa et al. (2000), reviewed seven published RCTs of EMDR that found EMDR more efficacious than controls (wait list, routine care, and active treatment), but recommended further research to address the limitations of existing research.

The systematic review of group therapy literature by Foy et al. (in Foa et al., 2000) identified 20 studies, only two of which were randomized. Most studies reported positive treatment outcomes, but most studies were characterized by methodologic limitations. The review of psychodynamic therapy (Kudler et al., also in Foa et al., 2000) described a literature that does not fit the RCT-oriented paradigm. The bulk of psychodynamic research consists of rich and interesting case studies, but extremely few employ randomization or controls. Similarly, the hypnosis literature reviewed by Cardena et al. consisted of only one controlled study, but the review noted that other clinical reports in the literature have shown that hypnosis may be useful as an adjunct to other PTSD therapy.

[6]Now the Agency for Healthcare Research and Quality (AHRQ).

EVALUATING THE EVIDENCE

In the chapters that follow, the committee applies the methods and background knowledge described in the present chapter to assess the available evidence on PTSD treatment modalities, first pharmacotherapy (Chapter 3) then psychotherapy (Chapter 4). The narrative for each modality describes the committee's assessments of individual studies and summarizes the body of evidence. The chapters include abbreviated evidence tables with key information about studies that contributed to reaching conclusions about the evidence regarding the efficacy of each treatment modality.

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KEY for Tables 3-1 through 3-11:

Arm = treatment condition
DO = dropout rate
ITT = intent-to-treat analysis
LOCF = last observation carried forward
Misc = miscellaneous
N/A = not available
NR = not reported
NS = not significant
PL = placebo
PTSD outcome measures—refer to list of acronyms in Appendix E for full name of measure
S&NS assault or abuse = sexual and nonsexual assault or abuse
Tx = treatment

3

Evidence and Conclusions: Pharmacotherapy

The committee included 37 studies of pharmacotherapy in their review (reasons for exclusion are listed in the individual sections below). Of the included studies, 14 had no major limitations and were judged most informative to the committee's conclusions regarding the efficacy of a treatment modality. Brief descriptions of the studies and evidence tables of key data provided are provided on the pages that follow. The committee identified 22 individual drugs that are organized below in seven classes and a miscellaneous "other drugs" category. Trauma types in these studies included combat (both former American and international troops), sexual abuse, physical assault, accidental injury, witnessing (e.g., acts of genocide) and motor vehicle accidents.

When analyzing the studies by sex, population, or trauma type, the committee categorized each study as being "predominantly" one type of sex, population, or trauma if 80 percent of the study population or more were of one type of sex, population, or trauma. The committee labeled the study as "mixed" if 79 percent or less of the study population were of one type of sex, population, or trauma. Twelve studies had a predominantly male population (7 for female population, 14 for mixed), 13 studies were predominantly in veteran populations whose primary trauma was combat, 10 studies in civilian populations predominantly included victims of sexual abuse, and 14 studies had a mixed trauma type.[1] The committee found that, in most cases, if the study was predominantly in a veteran population, the participants were mostly male, and if the study was predominantly in

[1]Some studies did not include sex and/or trauma type.

a sexually abused population, participants were mostly female although there are instances where this is not the case. For studies in populations with mixed trauma type, the sex was also generally mixed.

ALPHA-ADRENERGIC BLOCKERS

The committee identified a small number of studies examining the effects of prazosin, an alpha-adrenergic blocker, on posttraumatic stress disorder (PTSD). Only two studies met inclusion criteria, and in neither was PTSD the primary outcome. Trauma for participants in both studies was combat-related (primarily from the Vietnam War). The mean age of participants was approximately 55 years. Neither study directly reported the duration of illness but clearly time of exposure was during the war the participant was involved in. In the study that reported race/ethnicity, 73 percent of participants were white (Raskind et al., 2007). The length of treatment in the two studies was 9 and 8 weeks, respectively.

The single randomized trial meeting inclusion criteria was small and focused on nightmares and sleep disturbance as the primary outcomes (Raskind et al., 2007), demonstrating improvement in those completing treatment. Total Clinician Administered PTSD Scale (CAPS) scores were not significantly different between treatment and control patients at the end of the trial. There also was a small (n = 10) crossover study (Raskind et al., 2003) that focused on sleep disturbance with similar results.

Synthesis: The committee found the studies on alpha-adrenergic blockers to be limited in number, and not focused on overall PTSD outcomes. Thus the committee judged the overall body of evidence to be scant and low quality. The committee is uncertain about the presence of an effect, and believes that future well-designed studies will have an important impact on confidence in the effect and the size of the effect.

Conclusion: The committee concludes that the evidence is inadequate to determine the efficacy of prazosin in the treatment of PTSD.

Comment

Although the committee judged the evidence inadequate to determine the efficacy of prazosin as a treatment of PTSD in general populations for overall PTSD outcomes, there are two small studies suggesting efficacy for combat-related nightmares and sleep disturbance in veterans.

Exclusion Notes

All open-label trials were excluded, as was a retrospective chart review (Raskind et al., 2002) and a study that did not use an overall PTSD outcome measure (Taylor et al., 2006).[2] See Table 3-1 for a summary of the two included clinical trials.

ANTICONVULSANTS

The committee identified a small number of studies examining the effects of anticonvulsants such as topiramate, tiagabine, and lamotrigine on PTSD. Most studies were excluded because they were open label or uncontrolled. Participants in the anticonvulsant studies suffered a variety of traumas including combat-related, sexual and physical abuse and/or assault, witnessing, and serious accident or injury. The mean age of study participants was 43 years old with a range from late-20s to mid-50s. One study reported the duration of illness to be an average of 13 years, and duration of illness and time since trauma was not reported in the other studies (Davidson et al., 2007). In one study ethnicity was not reported, and the others had predominantly black (71 percent) and white (90 percent) populations, respectively.

All studies were double-blinded and included a placebo control. Treatment length was 12 weeks for all studies. Only one study conducted follow-up after completion of treatment (1-year follow-up) (Hertzberg, 1999). All studies measured adverse events associated with the treatment condition. The main PTSD outcome measures used in the selective serotonin reuptake inhibitors (SSRIs) studies were CAPS-Total and SI-PTSD.

Of the three randomized controlled trials (RCTs), two had major limitations including high differential and total dropout rates (Davidson et al., 2007; Tucker et al., 2007) and neither showed a positive effect on a primary PTSD outcome. The third qualifying RCT showed a positive effect of treatment with lamotrigine, but the trial was too small (a total of 15 patients) to reach statistical significance or estimate an effect size (Hertzberg et al., 1999).

Synthesis: The committee found the overall body of evidence regarding anticonvulsants to be scant and low quality. The committee is uncertain about the presence of an effect, and believes that future well-designed studies will have an important impact on confidence in the effect and the size of the effect.

[2]This study looked at daytime psychological stress, and used an E-Stroop test (word lists) to evaluate outcomes.

TABLE 3-1 Alpha-Adrenergic Blockers

Study	Population[a]	Arm (N)	Handling of Dropouts and % Completed Tx by Arm	PTSD Outcome Measure
Raskind et al., 2007[c]	Male, combat	Total (34)[d] Prazosin (17) PL (17)	LOCF[e] 90.0% 92.5%	CAPS-Total
Raskind et al., 2003 Crossover Study	Male, combat	Total (10)[f] Prazosin (5) PL (5)	LOCF 100%[g] 100%	CAPS-Total

[a]In the population column, male alone or female alone denotes that at least 80% of the study population was male or female. If only one trauma type is listed, at least 80% of the study population reported that type of trauma.

[b]PTSD outcome measure change data were obtained either directly from the study, when provided, or by subtracting data reported at treatment completion (not follow-up data) from baseline data (before treatment began). Average baseline score when reported or when baseline scores for all arms are nearly the same; otherwise, baseline scores listed individually in order of arm.

[c]Study focus was sleep and nightmares.

Conclusion: The committee concludes that the evidence is inadequate to determine the efficacy of anticonvulsants in the treatment of PTSD.

Exclusion Notes

Several open-label trials with anticonvulsants have been completed (Berlant, 2004; Berlant and van Kammen, 2002; Clark et al., 1999; Lipper et al., 1986), none of which were included. The committee identified one maintenance study (Connor et al., 2006) on tiagabine that was not included in its assessment of efficacy. This study was an open-label discontinuation study with 29 patients in the open-label portion following 18 responders who were randomized to either treatment or placebo. Patients in the maintenance phase who were randomized to tiagabine generally maintained the benefits obtained during the open-label portion although there was a 40 percent dropout rate compared to a 12.5 percent dropout rate in the placebo group. See Table 3-2 for a summary of the three included clinical trials.

Double-Blind?	Baseline[b] and Change in PTSD Measure	Statistically Significant? (versus control)	Loss of Diagnosis or Clinical Improvement (%)	Principal Limitations
Yes	~77		N/A	No major limitations
	–13	No		
	–7	—		
Yes	~82		N/A	No major limitations
	21.8	Yes		
	2.9	—		

[d]Study began with 40 patients, 6 failed to complete any scheduled outcome assessment (after randomization) because of protocol discontinuation.

[e]It is not clear if this was for all measures or just CAPS nightmare item scores.

[f]Seven were receiving one or more of the following medications for PTSD: selective serotonin reuptake inhibitors (N = 5), trazodone (N = 2), benzodiazepines (N = 4), anticonvulsants (N = 2), hydroxyzine (N = 2), and risperidone (N = 1). Medications and psychotherapy were maintained unchanged during the study.

[g]Results for first half of study before crossover.

NOVEL ANTIPSYCHOTIC MEDICATIONS

The committee identified seven trials of novel antipsychotics olanzapine or risperidone in the treatment of individuals with PTSD (Bartzokis et al., 2005; Butterfield et al., 2001; Hamner et al., 2003; Monnelly et al., 2003; Padala et al., 2006; Reich et al., 2004; Stein et al., 2002). The participants in these studies had suffered from several traumas including combat (mostly U.S. participants) and sexual and physical abuse and/or assault. The mean age in these studies was approximately 45 years, with a range of 19–68 years. None of the studies reported duration of illness or time since trauma. Most studies provided information about ethnicity of the participants. In most studies the majority of the patients were white with a smaller number of studies reporting non-white participants at approximately 10 percent to 29 percent. More than half (54 percent) of one study's population was comprised of black participants.

All studies were double-blinded and included a placebo control. The treatment period ranged from 5–16 weeks, and only one study conducted follow-up after completion of treatment (3-month follow-up) (Bartzokis et

TABLE 3-2 Anticonvulsants

Study	Population[a]	Arm (N)	Handling of Dropouts and % Completed Tx by Arm	PTSD Outcome Measure
Davidson et al., 2007	Female (66%) and Male; S&NS assault (53%), witnessing, accident	Total (232) Tiagabine (116) PL (116)	NR (ITT) 66% 55%	CAPS-Total
Tucker et al., 2007	Female, mixed abuse	Total (40)[c] Topiramate (20) PL (20)	LOCF 70% 80%	CAPS-Total
Hertzberg et al., 1999	Male and Female, combat (71%)	Total (15) Lamotrigine (11) PL (4)	LOCF 83% 80%	SI-PTSD[d]

[a]In the population column, male alone or female alone denotes that at least 80% of the study population was male or female. If only one trauma type is listed, at least 80% of the study population reported that type of trauma.

[b]PTSD outcome measure change data were obtained either directly from the study, when provided, or by subtracting data reported at treatment completion (not follow-up data) from baseline data (before treatment began). Average baseline score when reported or when baseline

al., 2004). All studies measured adverse events associated with the treatment condition. The main PTSD outcome measures used in these studies were CAPS-Total, Patient Checklist for PTSD-Military Version (PCL-M), and Structured Interview for PTSD (SI-PTSD).

One of these studies, a trial of risperidone, included only PTSD patients with "comorbid psychotic features" (Hamner et al., 2003). Three of the studies described participants as being treatment resistant in the following terms: "probably treatment resistant" (Bartzokis et al., 2005), "somewhat treatment refractory" (Hamner et al., 2003), and "SSRI-resistant" (Stein et al., 2002). One of the olanzapine studies was small with high dropouts and failed to show a benefit (Butterfield et al., 2001). The second olanzapine study was also small with a high rate of dropout and used last observation carried forward (LOCF) to adjust for missing values, but showed a statistically significant improvement in CAPS scores (Stein et al., 2002). Of the five studies of risperidone, it was the primary treatment rather than an add-on to other therapy in only one trial (Padala et al., 2006), and that study

Double-Blind?	Baseline[b] and Change in PTSD Measure	Statistically Significant? (versus control)	Loss of Diagnosis or Clinical Improvement (%)	Principal Limitations
Yes	~82.5 –30.7 –30.2	 No —	CAPS-Total <20 (remission) 16% 14%	Dropout between 45% and 34%; handling of missing data unclear
Yes	~88 –52.7 –42	 No —	CAPS scores <20 (remission) 42% 21%	Dropout between 30% and 40% using LOCF
Yes		—[e] —	Duke Global Rating 50% 25%	Dropout 17% and 20% using LOCF; trial too small to estimate effect size

scores for all arms are nearly the same; otherwise, baseline scores listed individually in order of arm.

[c]ITT population is reported at 38, with 19 in each treatment condition.

[d]Only individual scores were given (no means or analysis were calculated) for SI-PTSD.

[e]Trial too small to reach statistical significance or estimate an effect size.

was judged weakly informative with respect to efficacy because handling of missing values was not reported. In the three risperidone trials judged by the committee to be most informative with respect to efficacy, the drug had small positive effects, but dropout rates were close to 30 percent, with LOCF used to manage missing values in all but one of the studies (Bartzokis et al., 2005; Reich et al., 2004; Stein et al., 2002), raising concern about the precision of the point estimate of benefit. In all three studies, risperidone was an adjunctive or augmenting therapy (although only half of the patients in Reich were on other psychotropics), and of the three, two had populations that included treatment-resistant patients (Bartzokis et al., 2005; Stein et al., 2002).

Synthesis: The committee found the studies on novel antipsychotics to be limited. The number of studies was small, and several had major limitations in study design. All but one were small (fewer than 30 subjects per treatment condition), and the size of the effect was small (e.g., decrease in

CAPS ~ 10) in those that were statistically significant. Most of the studies focused on a population of patients with PTSD that had some special feature, such as treatment refractory or psychotic symptoms. Thus the committee judged the overall body of evidence to be low quality. The committee is not confident that the effect is present; and further high-quality research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Conclusion: The committee concludes that the evidence is inadequate to determine the efficacy of the novel antipsychotics olanzapine and risperidone in the treatment of PTSD.[3]

Comment

Although the committee judged the evidence inadequate to determine the efficacy of risperidone as a treatment of PTSD in general populations, there are three studies suggesting efficacy for the adjunctive use of risperidone in individuals inadequately responsive to other therapy.

Exclusion Notes

No open-label studies were included (Ahearn et al., 2006; Aukst-Margeti et al., 2004)[4]. There was one head-to-head trial comparing olanzapine and fluphenazine, but because the efficacy for both of these drugs has not yet been proven, it was not considered in this review (Pivac et al., 2004). See Table 3-3 for a summary of the seven included clinical trials.

BENZODIAZEPINES

The committee identified only one placebo-controlled RCT of alprazolam with a primary PTSD outcome, which showed that the drug was ineffective. The participants in the study suffered from three different trauma types: combat-related (40 percent), motor vehicle accident, or accidental serious injury. The mean age was 37 years, with a range of 19–56 years. Duration of illness and time since exposure were not reported, nor was race/ethnicity. This study was double-blinded and included a placebo control. The treatment lasted 5 weeks and had no post-treatment follow-up. The outcome measure used was the PTSD Scale which consists of each of the 12 items that make up *Diagnostic and Statistical Manual of Mental Disorders* (DSM)-III criteria. However, the trial was very small (fewer than

[3]Please refer to Dr. Thomas Mellman's minority opinion on this conclusion in Appendix H.
[4]This study also used sleep as its primary outcome.

10 subjects per treatment condition), had a high dropout rate, and did not address missing values (Braun et al., 1990).

Synthesis: The committee found the overall body of evidence regarding benzodiazepines to be scant and low quality. The committee is uncertain about the presence of an effect, and believes that future well-designed studies will have an important impact on confidence in the effect and the size of the effect.

Conclusion: The committee concludes that the evidence is inadequate to determine the efficacy of benzodiazepines in the treatment of PTSD.

Comment

The available evidence is uninformative for the primary use of benzodiazepines in patients with PTSD. The absence of a robust body of evidence regarding benzodiazepines is remarkable in that they are commonly prescribed for patients with PTSD, perhaps as a treatment for anxiety symptoms, while many clinical guidelines recommend against using them at all in this setting (APA, 2004; VA/DOD, 2004). The committee did not examine the evidence regarding the benefits or harms of using benzodiazepines in treating specific symptoms in patients with PTSD.

Exclusion Notes

There are several open-label studies on benzodiazepines, none of which were included, as well as one case-series and one nonrandomized small trial where the patients were treated within approximately 6.7 days after the trauma (range of 2–18 days) so could not have had diagnosed PTSD (Gelpin et al., 1996). There were two trials that focused only on sleep and did not include an overall PTSD outcome that were excluded (Cates et al., 2004; Randall et al., 1995). See Table 3-4 for a summary of the one included clinical trial.

MONOAMINE OXIDASE INHIBITORS

The committee identified four RCTs examining the effects of the monoamine oxidase inhibitors (MAOIs) phenelzine or brofaromine (a selective MAOI not available in the United States) compared with a placebo control (Baker et al., 1995; Katz et al., 1994; Kosten et al., 1991; Shestatzky et al., 1988). Participants in studies had suffered a variety of traumas including combat-related (mostly American former troops), sexual and physical abuse or assault, serious injury, and motor vehicle accidents. The ages in

TABLE 3-3 Novel Antipsychotic Medications

Study	Population[a]	Arm (N)	Handling of Dropouts and % Completed Tx by Arm	PTSD Outcome Measure
Padala et al., 2006	Female, S&NS abuse	Total (20) Risperidone (11) PL (9)	LOCF 82% 67%	CAPS-Total
Bartzokis et al., 2004	Male, combat	Total (65) Risperidone[d] (33) PL (32)	Mixed model and ITT 67% 81%	CAPS-Total
Reich et al., 2004	Female, mixed abuse	Total (21) Risperidone (12) PL (19)	Random effects time modeling and LOCF in some cases 75% 78%	CAPS-2
Hamner et al., 2003	Male, combat	Total (40) Risperidone (20[e]) PL (20[f])	LOCF 58% 66%	CAPS-Total
Monnelly et al., 2003[g]	Male, combat	Total (16) Risperidone (8) PL (8)	Not clear 87.5% 100.0%	PCL-M[b]
Stein et al., 2002[i]	Male, combat	Total (19) Olanzapine (10) PL (9)	LOCF 70% 78%	CAPS-Total
Butterfield et al., 2001	Female, sexual assault, combat (20%)	Total (15) Olanzapine (10) PL (5)	LOCF 70% 80%	SI-PTSD

[a]In the population column, male alone or female alone denotes that at least 80% of the study population was male or female. If only one trauma type is listed, at least 80% of the study population reported that type of trauma.

[b]PTSD outcome measure change data were obtained either directly from the study, when provided, or by subtracting data reported at treatment completion (not follow-up data) from baseline data (before treatment began). Average baseline score when reported or when baseline scores for all arms are nearly the same; otherwise, baseline scores listed individually in order of arm.

Double-Blind?	Baseline[b] and Change in PTSD Measure	Statistically Significant? (versus control)	Loss of Diagnosis or Clinical Improvement (%)	Principal Limitations
Yes	~87[c] –30 –7	 Yes —	N/A	Dropout 18% and 33% using LOCF with a 15% differential
Yes	~100 –14.3 –4.6	 Yes —	N/A	Dropout 33% and 19%
Yes	~64 –29.6 –18.6	 Yes —	N/A	No major limitations
Yes	~90 –9 –10.1	 No —	N/A	Dropout 42% and 33% using LOCF
Yes	~71 –10 –0.5	 Yes —	N/A	Dropout 12.5% in one arm; handling of missing data unclear
Yes	~85 –14.8 –2.67	 Yes —	N/A	Dropout 30% and 22% using LOCF
Yes	~52 –20.5	 No —	N/A	Dropout 30% and 20% using LOCF

[c]Actual numbers not given—read off of a line graph.
[d]Adjunctive to stable psychotropic Rx regimen.
[e]19 evaluable.
[f]18 evaluable.
[g]The main focus of this study was anger but measured overall PTSD as well. Adjunctive to stable psychotropic Rx regimen.
[b]Patient Checklist for PTSD-Military Version-self report.
[i]Adjunctive to stable psychotropic Rx regimen.

TABLE 3-4 Benzodiazepines

Study	Population[a]	Arm (N)	Handling of Dropouts and % Completed Tx by Arm	PTSD Outcome Measure
Braun et al., 1990 Crossover Study	Sex NR, combat (40%), accidental injury	Total (16) Alprazolam (7) PL (9)	Not clear 57% 67%	PTSD Scale

[a]In the population column, male alone or female alone denotes that at least 80% of the study population was male or female. If only one trauma type is listed, at least 80% of the study population reported that type of trauma.

[b]PTSD outcome measure change data were obtained either directly from the study, when

these trials ranged from 26 to 73 years. One study reported duration of illness, which ranged from 2 to 12 years (Shestatzky et al., 1988). Duration of illness and time since exposure was not reported in the other studies. Race/ethnicity was only reported in one study, and participants were predominantly white (88 percent) (Kosten et al., 1991).

The treatment period for these studies ranged from 5 weeks to 14 weeks. None of the studies conducted follow-up after completion of treatment. Two studies measured adverse events associated with the treatment condition (Baker et al., 1995; Katz et al., 1994). The main PTSD outcome measures used in the MAOI studies were CAPS-Total, Impact of Events Scale (IES), and the PTSD Scale.

One of the phenelzine trials failed to show a significant benefit, but it was extremely small, and dropouts were high with weak treatment of missing values (Shestatzky et al., 1988). The second study of phenelzine was larger and showed significant benefit, but dropouts approached 50 percent with weak treatment of missing values (Kosten et al., 1991). The two studies of brofaromine (Baker et al., 1995; Katz et al., 1994) had a primary PTSD outcome, and both failed to show a beneficial effect. However, because study designs were weak in the treatment of missing values to address the substantial dropout rates, the committee could not conclude that brofaromine was ineffective.

Synthesis: The committee found the overall body evidence regarding MAOIs to be scant and low quality. The committee is uncertain about the presence of an effect, and believes that future well-designed studies will have an important impact on confidence in the effect and the size of the effect.

Double-Blind?	Baseline[b] and Change in PTSD Measure	Statistically Significant? (versus control)	Loss of Diagnosis or Clinical Improvement (%)	Principal Limitations
Yes	~30 –4.3 –1.2	 No —	N/A	Dropout 43% and 33%; handling of missing data unclear

provided, or by subtracting data reported at treatment completion (not follow-up data) from baseline data (before treatment began). Average baseline score when reported or when baseline scores for all arms are nearly the same; otherwise, baseline scores listed individually in order of arm.

Conclusion: The committee concludes that the evidence is inadequate to determine the efficacy of the MAOIs phenelzine and brofaromine in the treatment of PTSD.

Exclusion Notes

There are several open-label trials or trials in MAOIs with no comparison group, none of which were included (Davidson et al., 1987; Lerer et al., 1987; Neal et al., 1997). There was one head-to-head study comparing moclobemide and tianeptine. The efficacy of either of these drugs has not been proven, so this trial was excluded from the committee's review. See Table 3-5 for a summary of the four included clinical trials.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

The committee found that the literature on SSRIs was the most extensive for any of the pharmacotherapies, identifying 14 studies meeting inclusion criteria (Brady et al., 2000; Connor et al., 1999; Davidson et al., 2001a, 2006b; Friedman et al., 2007; Hertzberg et al., 2000; Marshall et al., 2001, 2007; Martenyi et al., 2002a; Tucker et al., 2001, 2003; van der Kolk et al., 1994, 2007; Zohar et al., 2002). The studies examined different drugs (sertraline, fluoxetine, paroxetine, and citalopram) and dosage regimens for varying periods of time and differed in dropout rates (which were generally in the range of 30 percent), and many studies handled missing values with LOCF or conducted the analysis only on those completing treatment.

Participants in the SSRI studies had suffered a variety of traumas including combat-related (U.S. and international participants), sexual and

TABLE 3-5 MAOIs

Study	Population[a]	Arm (N)	Handling of Dropouts and % Completed Tx by Arm	PTSD Outcome Measure
Baker et al., 1995	Male (78%), combat, sexual assault	Total (118) Brofaromine (56) PL (58)	LOCF 70.3% overall NR NR	CAPS-Total
Katz et al., 1995	Male (76%), physical assault, injury	Total (64) Brofaromine (33) PL (31)	LOCF 70% 71%	CAPS-Total
Kosten et al., 1991	Male, combat	Total (60) Phenelzine (19) Impramine[c] (23) PL (18)	LOCF 51.6% overall	IES[d]
Shestatzky et al., 1988 Crossover Study	Sex NR, combat, car accident	Total (13) Phenelzine (7) PL (6)	Not clear 77% overall NR NR	PTSD Scale

[a]In the population column, male alone or female alone denotes that at least 80% of the study population was male or female. If only one trauma type is listed, at least 80% of the study population reported that type of trauma.

[b]PTSD outcome measure change data were obtained either directly from the study, when provided, or by subtracting data reported at treatment completion (not follow-up data) from baseline data (before treatment began). Average baseline score when reported or when baseline

physical abuse and/or assault, witnessing, and serious accident or injury. The age range of study participants was from 18 to late 60s, with most studies reporting a mean age between the mid-30s and mid-40s. Three studies reported durations of illness that were approximately 6, 12, and 18 years (Brady et al., 2000; Connor et al., 1999; Friedman et al., 2007). Six studies reported time since trauma that ranged from about 13 to 24 years (Brady et al., 2000; Davidson et al., 2001a; Friedman et al., 2007; Marshall et al., 2001; Tucker et al., 2001; van der Kolk et al., 2007). One study reported the percent of participants who had their first trauma as a child vs. first trauma as an adult (van der Kolk et al., 1994) and one study reported the trauma type as the Vietnam war for the entire study populations so it could be inferred that was the time of trauma (Hertzberg et al., 2000). Five studies did not report any information on either duration of illness or time

Double-Blind?	Baseline[b] and Change in PTSD Measure	Statistically Significant? (versus control)	Loss of Diagnosis or Clinical Improvement (%)	Principal Limitations
Yes	~80 –27.18 –24.68	 Yes —	N/A	Dropout data aggregated with 30% overall dropout using LOCF
Yes	~81 –41.6 –30.2	 No —	N/A	Dropout ~30% using LOCF
Yes	~33.5 –13.6 –9.1 –1.7	 Yes Yes —	N/A	Dropout data aggregated with 48% overall dropout using LOCF
Yes	~20[e] –7 –6.8	 No —	N/A	Dropout data aggregated with 33% overall dropout with unclear handling of missing data

scores for all arms are nearly the same; otherwise, baseline scores listed individually in order of arm.

[c]Trycyclic antidepressant.

[d]Impact of Events Scale.

[e]Only results from first randomization are included here.

since trauma (Davidson et al., 2006b; Marshall et al., 2007; Martenyi et al., 2002a; Tucker et al., 2003; Zohar et al., 2002). All but three studies provided information about the race/ethnicity of participants. In most studies the majority of participants were white, with a smaller number of studies reporting percentages of non-white participants to be approximately 10–33 percent. In two studies participants were mostly minorities, with 25 percent white in one (Marshall et al., 2007) and 42 percent white in another (Hertzberg et al., 2000).

Most of the studies had a 2-week washout period before treatment and did not allow other prescription medications to be used during the study period. All studies were double-blinded and included a placebo control. The treatment period for most studies was 12 weeks but some were 5, 8, or 10 weeks. Only one study conducted follow-up after completion of treatment

(van der Kolk et al., 2007). All but two studies measured adverse events associated with the treatment condition (Connor et al., 1999; Zohar et al., 2002). The main PTSD outcome measures used in the SSRI studies were CAPS, CAPS-2, CAPS-SX, and Duke Global Rating.

Of the 14 trials, 7 were judged weakly informative with respect to efficacy because of study limitations such as high differential and/or total dropout rates and weak or absent treatment of missing values (Connor et al., 1999; Davidson et al., 2006b; Hertzberg et al., 2000; Marshall et al., 2001, 2007; Tucker et al., 2001; van der Kolk et al., 1994). Further, the 14 studies were not all statistically significant in showing a positive effect: 7 demonstrated a benefit and 7 demonstrated no benefit (although some of these may have been too underpowered to detect a benefit). Among the 7 studies with the fewest design limitations, 4 demonstrated a benefit (Brady et al., 2000; Davidson et al., 2001a; Martenyi et al., 2002a; Tucker et al., 2003) and 3 demonstrated no benefit (Friedman et al., 2007; van der Kolk et al., 2007; Zohar et al., 2002). The most recent, largest, and best-designed trial in predominantly male combat veterans showed no benefit in primary PTSD outcomes (Friedman et al., 2007), but had a high differential dropout rate between treatment and control conditions and used LOCF to account for missing values.

Given the extensive literature for this class, the committee also organized the 7 studies with the fewest limitations by population/trauma type into three groups: 2 of 2 studies in veterans are negative (Friedman et al., 2007; Zohar et al., 2002); 3 of 4 studies in civilians are positive (Brady et al., 2000; Davidson et al., 2001a; Tucker et al., 2003), 1 negative (van der Kolk et al., 2007); and 1 study in a mixed (close to evenly divided) population is positive (Martenyi et al., 2002a). The committee did not formally consider whether a quantitative meta-analysis would be possible with the 7 most informative studies, and could not determine whether there was an association between population type and outcome.

The committee also noted that virtually all of the trials were industry sponsored. Publication of the largest multicenter, industry-sponsored trial of sertraline demonstrating no effect on PTSD outcomes (Friedman et al., 2007) was delayed more than 10 years, leading to concern about publication bias.

Synthesis: The committee found that the body of evidence regarding SSRIs presented unusual challenges. Many studies were excluded because of weaknesses in design. Although the overall body of evidence might be characterized as moderate quality, the best studies did not consistently point in the same clinical direction demonstrating benefit. The committee believes that it is uncertain whether future high-quality studies will show an effect. Thus the committee is not confident in the presence of an effect

and believes that any estimate of effect is uncertain, including in relevant subpopulations (such as veterans). Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.

Conclusion: The committee concludes that the evidence is inadequate to determine the efficacy of SSRIs in the treatment of PTSD.[5]

Comment

The committee concluded that the evidence is inadequate to determine the efficacy of SSRIs in the treatment of PTSD based on weaknesses in study designs and inconsistency of results. The committee also observed that SSRIs are widely prescribed, have a good safety profile, and might often find indications for use in veterans with PTSD because of comorbid major depression and anxiety disorders.

The committee's conclusion about the SSRI literature was difficult to reach. Several consensus clinical practice guidelines recommend SSRIs as a first line of pharmacologic treatment for PTSD. The committee distinguished between the principles used in developing guidelines and its own task of evaluating the evidence for efficacy. The former task, i.e., making clinical practice guidelines (and treatment decisions based on them), can be accomplished even when the scientific evidence is not definitive.

The committee believes that the weight of the scientific evidence is insufficient to determine the efficacy of SSRIs. The most recent studies continue to be divided in their findings regarding the efficacy of SSRIs. Therefore the committee's conclusion echoes those of other recent evidence-based assessments such as that of the Cochrane systematic review (Stein et al., 2006) and the 2007 *Australian Guidelines for the Treatment of Adults with Acute Stress Disorder and Posttraumatic Stress Disorder*.[6] While recognizing that

[5]Please refer to Dr. Thomas Mellman's minority opinion on this conclusion in Appendix H.

[6]From the Cochrane systematic review (Stein et al., 2006): "The current evidence base of RCTs is unable to demonstrate superior efficacy or acceptability for any particular medication class. Although some have suggested that the SSRIs are more effective than older antidepressants (Dow, 1997; Penava, 1996), class membership did not contribute significantly to the variation observed in symptom severity outcomes between trials, while the confidence intervals for the summary statistic of responder status on the seven SSRI trials overlapped with that of the MAOI and TCA [tricyclic antidepressant] trials. . . . Nevertheless, the SSRI trials constitute the bulk of the evidence for the efficacy of medication in treating PTSD, both in terms of the number of studies and their size. The finding of the effectiveness of the SSRIs were also more robust to differences in the particular summary statistic employed than was the case for either the amitryptiline or mirtazapine trials. It is therefore reasonable to support the expert consensus (Ballenger, 2000, 2004; Foa, 1999) that SSRIs constitute the first-line medication choice in PTSD."

some studies are suggestive of benefit in general civilian (i.e., nonveteran) populations, the committee noted that there are important limitations in study designs and inconsistent results even in the civilian studies.

Finally, the committee noted that sertraline and paroxetine are approved by the Food and Drug Administration (FDA) to treat PTSD. The four studies submitted to FDA to gain approval[7] were included in the literature reviewed by the committee (Brady et al., 2000, and Davidson et al., 2001a, for sertraline; Marshall et al., 2001, and Tucker et al., 2001, for paroxetine). The committee's review had a different purpose than the regulatory one at the core of FDA's approval process. The committee was also able to review a larger number of studies and used different criteria to judge study quality and the overall body of evidence than did FDA in its review.

Exclusion Notes

The committee did not include any open-label trials in its review. The committee also did not include any studies for which PTSD was not the primary outcome of the trial. Of these studies, one focused on co-occurring alcohol dependence (Brady et al., 2005), one utilized quality-of-life measures (Rapaport et al., 2002), and one was a psychometric study on the Davidson Trauma Scale (Davidson, 2004). There were also eight head-to-head trials comparing one SSRI to another, SSRIs to cognitive behavioral therapy (CBT), and SSRIs to drugs in other drug classes (Chung et al., 2004; Frommberger et al., 2004; McRae et al., 2004; Onder et al., 2006; Otto et al., 2003; Saygin et al., 2002; Smajkic et al., 2001; Spivak et al., 2006). See Table 3-6 for a summary of the 14 included clinical trials.

The committee also identified four maintenance studies using SSRIs (Davidson et al., 2001b, 2005; Londborg et al., 2001; Martenyi et al., 2002b). Martenyi et al. (2002b) used data from another Martenyi et al., (2002a) trial—a 12-week randomized controlled trial included in the committee's review—and was a relapse prevention trial. Responders[8] from the initial trial were randomized to either continued treatment (N = 69) or to placebo (N = 62) for 6 months. The sample size in the initial trial was 226. An analysis of time to relapse showed that the treatment (fluoxetine) was statistically significantly superior to placebo in relapse prevention. Of the treatment group, 82.6 percent completed the relapse prevention phase compared to 66.1 percent of the placebo group.

[7]FDA granted approval to sertraline in 1999 and paroxetine in 2001 to treat PTSD.

[8]Defined as participants who responded to treatment by a 50 percent decrease in the eight-item Treatment Outcome PTSD Scale (TOP-8) score from baseline, a Clinical Global Impression Severity Scale (CGI-S) score of 42, and not meeting the DSM-IV diagnostic criteria for PTSD.

The Davidson et al., 2005, trial was an open-label discontinuation study. The first 6 months were open-label only (N = 123), then responders[9] were randomized to either treatment (fluoxetine) (N = 30) or placebo (N = 32)[10] and treated over the next 6 months. Three patients in the treatment group and two in the placebo group dropped out of the study early, and LOCF was employed for missing data. Rates of relapse were 22 percent for treatment versus 50 percent for placebo (P = .02), and time to relapse on treatment was longer than for placebo (P = .02, log-rank statistic) on Clinical Global Impressions (CGI). No other measures showed statistical significance.

The Davidson et al., 2001b, trial was designed differently than the 2005 study. The study began with a 12-week randomized treatment period (acute phase) (N = 380 with 275 completers) followed by a 24-week open-label for all acute-phase completers regardless of responder status (N = 252 with 155 completers). The final phase was a 28-week double-blind, placebo-controlled treatment for responders[11] to continuation treatment (139 were eligible with 96 randomized—46 to sertraline and 50 to placebo). Of the treatment group, 82.6 percent completed the final phase of the study, while 92 percent of the placebo group completed the final study phase. Sertraline demonstrated a significant advantage over placebo in prevention of PTSD relapse (sertraline: 5.3 percent; placebo: 26.1 percent) and in sustaining improvement in PTSD symptoms.

Longborg et al. (2001) is a continuation study of which the first phase of the study consisted of 12 weeks with a placebo control. The subjects were pooled from two identical RCTs conducted in 24 centers in the United States. Patients who completed those studies were eligible to take part in a 24-week open-label continuation study within 3 days of their last visit. Two hundred and fifty patients were entered into the continuation phase, of which approximately 50 percent had been in each the treatment and placebo conditions in the initial study. Only the 128 patients who had been in the treatment condition (sertraline) were analyzed in the study. All 925 responders in the initial phase maintained their response during the 6 months of continuation treatment. Fifty-four percent of acute-phase non-responders[12] became responders during continuation therapy. High baseline PTSD scores (CAPS-2 score greater than 75) significantly predicted a longer time to respond to treatment.

[9]Defined as "minimal improvement."

[10]Approximately 31 percent of the sample in the second phase were veterans.

[11]Defined as participants who responded to treatment by a Clinical Global Impression Improvement Scale (CGI-I) score of less than or equal to 2 (much or very much improved) and a 30 percent or greater improvement in the total severity score in part 2 of the CAPS-PTSD Scale.

[12]Defined as participants who responded to treatment by at least a 30 percent decrease in the CAPS-2 total severity score and a CGI score of 1 or 2.

TABLE 3-6 SSRIs

Study	Population[a]	Arm (N)	Handling of Dropouts and % Completed Tx by Arm	PTSD Outcome Measure
Friedman et al., 2007	Male, combat (71%), S&NS assault	Total (169) Sertraline (86) PL (83)	LOCF 70% 83%	CAPS-2
Marshall et al., 2007[c]	Male and Female, mixed assault	Total (52) Paroxetine (25) PL (27)	Mixed efffects models and LOCF/ITT 68% 48%	CAPS-Total
van der Kolk et al., 2007	Female, S&NS abuse, injury	Total (88) Fluoxetine (30) EMDR (29) PL (29)	LOCF 87% 83% 90%	CAPS-Total
Davidson et al., 2006b	Male and Female, S&NS abuse, 9% combat	Total (538)[d] Venlafaxine[e] (179) Sertraline (173) PL (179)	LOCF and observed cases analysis are endpoint 65% overall NR NR NR	CAPS-SX
Tucker et al., 2003	Female (74%), S&NS abuse	Total (58) Citalopram (25) Sertraline (23) PL (10)	LOCF 80% 74% 70%	CAPS-Total
Martenyi et al., 2002a	Male, witnessing, combat (48%) (international)	Total (301) Fluoxetine (226) PL (75)	LOCF Mean exposure to treatment[f] 80 days of 84 79 days of 84	CAPS-Total
Zohar et al., 2002	Male, combat (Israeli)	Total (42) Sertraline (23) PL (19)	LOCF 73.9% 73.7%	CAPS-2
Davidson et al., 2001a	Female (77%), S&NS abuse	Total (208) Setraline (100) PL (108)	LOCF 70% 73%	CAPS-2

Double-Blind?	Baseline[b] and Change in PTSD Measure	Statistically Significant? (versus control)	Loss of Diagnosis or Clinical Improvement (%)	Principal Limitations
Yes	~72 –13.1 –15.4	 No —	≥30% CAPS-2 reduction 34.5% 42.7%	Dropout 30% and 17% using LOCF
Yes	~83 –25.7 –6.3	 Yes —	N/A	Dropout 32% and 52% with a 20% differential
Yes	NR –33.23 –39.15 –30.95	 No No —	Loss of PTSD diagnosis 73% 76% 59%	No major limitations
Yes	~82 –41.51 –39.44 –34.17	 Yes No —	CAPS-SX ≤ 20 (remission) 30.2% 24.3% 19.6%	Dropout data aggregated with 35% overall dropout using mainly LOCF
Yes	~90 –30.72 –41.82 –13.6	 Yes Yes —	N/A	Dropout of 20%, 36%, and 30% using LOCF
Yes	~80.5 –34.6 –26.8	 Yes —	≥50% reduction in TOP-8 and CGI-S of 1 or 2 59.9% 43.8%	Actual dropout rates not provided; used LOCF
Yes	~92 –18.7 –13.5	 No —	≥30% CAPS-2 reduction and CGI-I of 1 or 2 41% 20%	Dropout ~26% using LOCF
Yes	~80 –33 –26.2	 Yes —	≥30% CAPS-2 reduction and CGI score of 1 or 2 60% 38%	Dropout 30% and 33% using LOCF

continued

TABLE 3-6 Continued

Study	Population[a]	Arm (N)	Handling of Dropouts and % Completed Tx by Arm	PTSD Outcome Measure
Marshall et al., 2001	2:1 Female, mixed trauma (no combat)	Total (563) Paroxetine 20 mg (188) Paroxetine 40 mg (187) PL (188)	LOCF and general linear models in some cases 67% 62% 65%	CAPS-2
Tucker et al., 2001	Female (66%), S&N assault, witness, injury	Total (307) Paroxetine (151) PL (156)	LOCF 61.6% 60.3%	CAPS-2
Brady et al., 2000	Male (73%), S&NS abuse, misc (including combat)	Total (187) Setraline (94) PL (93)	LOCF 69.1% 72.0%	CAPS-2
Hertzberg et al., 2000	Male, combat	Total (12) Fluoxetine (6) PL (6)	Completer analysis 83.3% 100.0%	DTS
Connor et al., 1999	Female, S&NS abuse	Total (53) Fluoxetine (27) PL (26)	LOCF 77.7 % 57.7%	Duke Global Rating
van der Kolk et al., 1994	Male (65%), combat (48%), S&NS abuse	Total (64) Fluoxetine (33) PL (31) Fluoxetine TC[g] Fluoxetine VA[h] PL TC PL VA	No treatment of missing values[i] 63.6% 86.7%	CAPS-Total

[a]In the population column, male alone or female alone denotes that at least 80% of the study population was male or female. If only one trauma type is listed, at least 80% of the study population reported that type of trauma.

[b]PTSD outcome measure change data were obtained either directly from the study, when provided, or by subtracting data reported at treatment completion (not follow-up data) from baseline data (before treatment began). Average baseline score when reported or when baseline scores for all arms are nearly the same; otherwise, baseline scores listed individually in order of arm.

[c]The results presented in this table are for the randomized acute phase of this study only,

Double-Blind?	Baseline[b] and Change in PTSD Measure	Statistically Significant? (versus control)	Loss of Diagnosis or Clinical Improvement (%)	Principal Limitations
Yes	~75 –39.6 –37.9 –25.3	 Yes Yes —	Global improvement score 1 = very much improved, 2 = much improved 62% 54% 37%	Dropout 33%, 38%, and 35% using LOCF
Yes	74.3, 73.2 –35.5 –24.7	 Yes —	<20 CAPS score = remission 30% 20%	Dropout ~38% and 40% using LOCF
Yes	~75 33 23.2	 Yes —	>30% decrease in CAPS-2 score and CGI-I of 1 or 2 53% 32%	Dropout 31% and 28% using LOCF
Yes	~108 –3 –9	 No —	Duke Global Rating 17% 33%	Dropout ~17% in one arm with a ~17% differential dropout; completer analysis only
Yes	Baseline NR Score of 1: 59% 19%	 Yes	Responder (Duke cutoff of 1–2) 85% 62%	Dropout ~22% and ~42% with a 20% differential using LOCF
Yes	~82 –35 –12 –17 –3	 Yes No — —	N/A	Dropout ~36% and ~13% with a 23% differential and no handling of missing data

and not the maintenance phase, which only included patients who were "much improved" or "very much improved."

[d]Seven dropped out before receiving study drug.

[e]Antidepressant.

[f]Martenyi (2002a) does not report actual dropout rates, only average length of treatment, which may be considered rough to completer rates, but it may conceal important information.

[g]23 patients total from a trauma clinic (TC).

[h]24 patients total from a VA site.

[i]Data were reported by intake site: trauma clinic (nonveterans) and VA site.

OTHER ANTIDEPRESSANTS

The committee identified three RCTs of the tricyclic antidepressants imipramine, desipramine, and amitriptyline that included placebo controls (Davidson et al., 1990; Kosten et al., 1991; Reist, 1989). Participants in the tricyclic antidepressant studies all suffered from combat-related trauma (all U.S.). Age was reported in two of the three studies and ranged from 28 to 64 years with a mean age of about 38 years. None of the studies reported duration of illness or time since exposure. Race/ethnicity was only reported in one study and participants were predominantly white (88 percent) (Kosten et al., 1991).

The treatment period for these studies ranged from 4 to 6 weeks. None of the studies conducted follow-up after completion of treatment. One study measured adverse events associated with the treatment condition (Davidson et al., 1990). The main PTSD outcome measures used in the tricyclic antidepressant studies was IES. All three trials used a weak study design. The studies analyzed only those who completed treatment and suffered from high dropout rates; thus the committee found it impossible to judge whether the modest improvements were valid.

The committee identified one RCT of mirtazapine, showing a modest benefit of treatment; but the study was small and did not use a robust method for handling the dropout rates and managing missing values (Davidson et al., 2003). The committee identified one RCT of nefazodone, showing a modest benefit of treatment; but the study was small, of short duration, and did not use a robust method for handling dropouts and managing missing values (Davis et al., 2004). Finally, the committee identified two large RCTs of venlafaxine. However, both had dropout rates exceeding 30 percent with weak treatment of missing values (LOCF) and showed very small changes in CAPS, although they were statistically significant (Davidson et al., 2006a, 2006b).

Synthesis: The committee found that the overall body of evidence regarding other antidepressants to be low quality because of study limitations and a small number of studies for each drug. The committee is not confident in the presence of an effect and believes that any estimate of effect is uncertain. Further research is very likely to have an important impact on confidence in the estimate of effect of any of these agents and is likely to change the estimate.

Conclusion: The committee concludes that the evidence is inadequate to determine the efficacy of other antidepressants in the treatment of PTSD.

Exclusion Notes

No open-label trials were included on tricyclic antidepressants. There were two prior RCTs comparing phenelzine and impramine to placebo (Frank et al., 1988; Kosten et al., 1992), but those were superseded by the updated and more complete1991 study by Kosten and colleagues so only that study was included. See Table 3-7 for a summary of the three included clinical trials.

Open trials of mirtazepine were not included (Kim et al., 2005). One study was excluded because it was not randomized (Connor and Sutherland et al., 1999). One study was excluded because it was a comparative trial (Chung et al., 2004) (compared mirtazapine and sertraline). See Table 3-8 for a summary of the one included clinical trial.

Open trials of nefazodone were not included (Garfield et al., 2001). There were two head-to-head trials comparing nefazodone to sertraline that were not included (McRae et al., 2004; Saygin et al., 2002). See Table 3-9 for a summary of the one included clinical trial.

Open trials of venlafaxine were not included nor was the one head-to-head trial comparing venlafaxine to sertraline and paroxetine (Smajkic et al., 2001). See Table 3-10 for a summary of the two included clinical trials.

OTHER DRUGS

The committee identified studies of naltrexone, cycloserine, and inositol, but not all met inclusion criteria. An RCT of naltrexone, an opioid antagonist, was conducted in patients with alcohol dependence, approximately one-third of whom also had PTSD, finding reductions in alcohol intake and improvements in CAPS scores (Petrakis et al., 2006). The committee found the single study difficult to interpret with respect to the overall treatment of PTSD, while recognizing that the study suggests a benefit to using naltrexone in an important subpopulation.

The participants in the single study of D-cycloserine had suffered from work or traffic accidents, terrorist attacks, and physical abuse. The age range was 22 to 61 years. Duration of illness ranged from 1 to 20 years. Race/ethnicity was not reported. This was a double-blind study with a placebo control and a crossover study design. Treatment lasted 12 weeks, and the study did not have post-treatment follow-up. The PTSD outcome measure used in this study was CAPS-Total (Heresco-Levy et al., 2002).

The participants in the inositol study suffered trauma from combat, serious accidents, and physical assault. The mean age was 40 years, with a range from 25 to 56 years. Time since trauma ranged from 6 months to 28 years. Race/ethnicity was not reported. This was a double-blind study

TABLE 3-7 Tricyclic Antidepressants

Study	Population[a]	Arm (N)	Handling of Dropouts and % Completed Tx by Arm	PTSD Outcome Measure
Kosten et al., 1991	Male, combat	Total (60) Phenelzine[c] (19) Impramine (23) PL (18)	LOCF 51.6% overall Not clear	IES
Davidson et al., 1990	Male, combat	Total (46) Amitriptyline (25) PL (21)	No treatment of missing values, completer analysis 71% completed 8 weeks overall NR NR	IES
Reist et al., 1989 Crossover Study	Male, combat	Total (27)[d] Desipramine (NR) PL (NR)	Completer analysis only 77.7–66.6%[e] NR NR	IOE, intrusion (I) and avoidance (A)

[a]In the population column, male alone or female alone denotes that at least 80% of the study population was male or female. If only one trauma type is listed, at least 80% of the study population reported that type of trauma.

[b]PTSD outcome measure change data were obtained either directly from the study, when provided, or by subtracting data reported at treatment completion (not follow-up data) from baseline data (before treatment began). Average baseline score when reported or when baseline

TABLE 3-8 Mirtazapine

Study	Population[a]	Arm (N)	Handling of Dropouts and % Completed Tx by Arm	PTSD Outcome Measure
Davidson et al., 2003	Sex NR, mixed	Total (29) Mirtazapine (17) PL (9)	LOCF 69% overall NR NR	SPRINT

[a]In the population column, male alone or female alone denotes that at least 80% of the study population was male or female. If only one trauma type is listed, at least 80% of the study population reported that type of trauma.

[b]PTSD outcome measure change data were obtained either directly from the study, when

Double-Blind?	Baseline[b] and Change in PTSD Measure	Statistically Significant? (versus control)	Loss of Diagnosis or Clinical Improvement (%)	Principal Limitations
Yes	~33.5 –13.6 –9.1 –1.7	 Yes Yes —	N/A	Dropout data aggregated with ~48% overall dropout using LOCF
Yes	~34 4 wks: –5.7 8 wks: –6.8 4 wks: –2.7 8 wks: –2.9	 No — 	N/A	Dropout data aggregated with 39% overall dropout; no handling of missing data; completer analysis
Yes	A: ~27 I: ~28 A: –0.4 I: –0.9 A: –0.1 I: –0.4	No No — —	N/A	Dropout data aggregated; no handling of missing data; completer analysis; total IOE score not provided, only subscales

scores for all arms are nearly the same; otherwise, baseline scores listed individually in order of arm.

[c]MAOI.

[d]21 continued to crossover period.

[e]Not clear if patients dropped out before or after crossover.

Double-Blind?	Baseline[b] and Change in PTSD Measure	Statistically Significant? (versus control)	Loss of Diagnosis or Clinical Improvement (%)	Principal Limitations
Yes	~22 –7 –7	Yes —	Response rate 67% 22%	Dropout data aggregated with 31% overall dropout using LOCF

provided, or by subtracting data reported at treatment completion (not follow-up data) from baseline data (before treatment began). Average baseline score when reported or when baseline scores for all arms are nearly the same; otherwise, baseline scores listed individually in order of arm.

TABLE 3-9 Nefazodone

Study	Population[a]	Arm (N)	Handling of Dropouts and % Completed Tx by Arm	PTSD Outcome Measure
Davis et al., 2004	Male, combat	Total (42) Nefazodone (27) PL (15)	LOCF 52% 60%	CAPS-Total

[a]In the population column, male alone or female alone denotes that at least 80% of the study population was male or female. If only one trauma type is listed, at least 80% of the study population reported that type of trauma.

[b]PTSD outcome measure change data were obtained either directly from the study, when

TABLE 3-10 Venlaflaxine

Study	Population[a]	Arm (N)	Handling of Dropouts and % Completed Tx by Arm	PTSD Outcome Measure
Davidson et al., 2006a	Male and Female, mixed trauma (12% combat)	Total (329) Venlaflaxine (161) PL (168)	LOCF 70% 67%	CAPS-SX
Davidson et al., 2006b	Male and Female, S&NS abuse, 9% combat	Total (538)[c] Venlafaxine (179) Sertaline[d] (173) PL (179)	LOCF and observed cases analysis are endpoint 65% overall NR NR NR	CAPS-SX

[a]In the population column, male alone or female alone denotes that at least 80% of the study population was male or female. If only one trauma type is listed, at least 80% of the study population reported that type of trauma.

[b]PTSD outcome measure change data were obtained either directly from the study, when provided, or by subtracting data reported at treatment completion (not follow-up data) from

with a placebo control and a crossover study design. Treatment lasted 4 weeks, and the study did not have post-treatment follow-up. The PTSD outcome measure used in this study was IES (Kaplan et al., 1996).

The studies of inositol and cycloserine were small, used a weak crossover design, and failed to show improvement in overall PTSD measures (Heresco-Levy et al., 2002; Kaplan et al., 1996).

Double-Blind?	Baseline[b] and Change in PTSD Measure	Statistically Significant? (versus control)	Loss of Diagnosis or Clinical Improvement (%)	Principal Limitations
Yes (2:1 design)	~82 –19.1 –13.5	 Yes —	≥30% improvement in CAPS-Total 47% 42%	Dropout of 48% and 40% using LOCF

provided, or by subtracting data reported at treatment completion (not follow-up data) from baseline data (before treatment began). Average baseline score when reported or when baseline scores for all arms are nearly the same; otherwise, baseline scores listed individually in order of arm.

Double-Blind?	Baseline[b] and Change in PTSD Measure	Statistically Significant? (versus control)	Loss of Diagnosis or Clinical Improvement (%)	Principal Limitations
Yes	~82 –51.8 –44.8	 Yes —	CAPS ≤20 50.9% 37.5%	Dropout of 30% and 33% using LOCF
Yes	~82 –41.51 –39.44 –34.17	 Yes No —	CAPS-SX ≤20 (remission) 30.2% 24.3% 19.6%	Dropout data aggregated with 35% overall dropout using mainly LOCF

baseline data (before treatment began). Average baseline score when reported or when baseline scores for all arms are nearly the same; otherwise, baseline scores listed individually in order of arm.

[c]Seven dropped out before receiving study drug.

[d]SSRI.

Synthesis: The committee found that the overall body of evidence regarding other drugs to be low quality because of study limitations and a small number of studies for each drug. The committee is not confident in the presence of an effect and believes that any estimate of effect is uncertain. Further research is very likely to have an important impact on confidence in the estimate of effect of any of these agents and is likely to change the estimate.

TABLE 3-11 Other Rx Treatments

Study	Population[a]	Arm (N)	Handling of Dropouts and % Completed Tx by Arm	PTSD Outcome Measure
Heresco-Levy et al., 2002 Crossover Study	Male, accident, physical abuse	Total (11) D-cycloserine (6) PL (5)	64% overall NR NR	CAPS-Total
Kaplan et al., 1996 Crossover Study	Male and Female, mixed trauma	Total (17) Inositol (NR) PL (NR)	Completer No treatment of missing values	IES

[a]In the population column, male alone or female alone denotes that at least 80% of the study population was male or female. If only one trauma type is listed, at least 80% of the study population reported that type of trauma.

[b]PTSD outcome measure change data were obtained either directly from the study, when provided, or by subtracting data reported at treatment completion (not follow-up data) from

Conclusion: The committee concludes that the evidence is inadequate to determine the efficacy of naltrexone, cycloserine, or inositol in the treatment of PTSD.

Exclusion Notes

Several case studies or series, open-label trials, uncontrolled trials, and RCTs have been conducted on various pharmacotherapies not included in the classes outlined above. Several other studies were excluded, and the reasons are briefly described here. In one RCT only 36 percent of the sample was diagnosed with PTSD so was excluded (Petrakis et al., 2006). One study compared tianeptine with fluoxetine and moclobemide, but had no placebo group so was excluded (Onder et al., 2006). Dow and Kline (1997) was excluded because it used several different drugs, had no comparison group or blinding, adverse events were not distinguished from efficacy failures, and it had many uncontrolled variables. A study examining sildenafil was excluded, because it only focused on erectile dysfunction (Orr et al., 2006). A study on naloxone was excluded, because it only looked at pain and not overall PTSD (Pitman et al., 1990). Another study by Pitman and colleagues that was excluded examined PTSD outcomes but the treatment

Double-Blind?	Baseline[b] and Change in PTSD Measure	Statistically Significant? (versus control)	Loss of Diagnosis or Clinical Improvement (%)	Principal Limitations
Yes	~59 –4.4 –6.8	 No —	N/A	Dropout data aggregated with 36% overall dropout; no handling of missing data
Yes	~35 –3.8[c] 0.4	 No —	N/A	Dropout data NR; completer analysis only

baseline data (before treatment began). Average baseline score when reported or when baseline scores for all arms are nearly the same; otherwise, baseline scores listed individually in order of arm.

[c]Results at 4 weeks.

(propranolol) began within 6 hours after the traumatic event so the subjects could not have been diagnosed with PTSD (Pitman et al., 2002). See Table 3-11 for a summary of the two included RCTs.

SUMMATION

Based on its assessment of the medications for which randomized controlled trials were available—alpha-adrenergic blockers, anticonvulsants, novel antipsychotic medications, benzodiazepines, MAOIs, SSRIs, and other antidepressants—the committee found the evidence for all classes of drugs reviewed inadequate to determine efficacy for patients with PTSD. Important comments are appended to the conclusions for alpha-adrenergic blockers, novel antipsychotics, benzodiazepines, and SSRIs.

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KEY for Tables 4-1 through 4-9:

BEP = brief eclectic psychotherapy
CBT = cognitive behavior therapy
CS = coping skills; examples:
CS-B = biofeedback
DO = dropout rate
E = exposure
E+CR = exposure plus cognitive restructuring
E+CS = exposure plus coping skills
EMDR = eye movement desensitization and reprocessing
F = female
ITT = intent-to-treat analysis
LOCF = last observation carried forward
MC = minimum care
MVA = motor vehicle accident
N/A = not available
NR = not reported
ns = not significant
OT = other therapy
PCT = present-centered therapy (active control)
PE = prolonged exposure
PTSD outcome measures—refer to list of acronyms in Appendix E for full name of measure
S&NS assault = sexual and nonsexual assault
Ss = subjects
SSRI = selective serotonin reuptake inhibitor
Tx = treatment
UC = usual care
WL = wait list

4

Evidence and Conclusions: Psychotherapy

Psychotherapeutic interventions for posttraumatic stress disorder (PTSD) vary in their emphasis on reexposure to trauma-related memories and stimuli, cognitive restructuring of the trauma experience, expression and management of emotion, training in stress management (including relaxation training), and general social and vocational support. Although a number of these treatments emphasize one of these components, many combine more than one either implicitly or by design, and relatively few studies dismantled effective components of the psychotherapy. A more complete description of psychotherapy is provided in Appendix A.

The committee noted that virtually all of the recent literature on psychotherapies for PTSD examines interventions that some experts consider components of cognitive-behavioral therapy (CBT). For example, Harvey et al. (2003) describe four basic components of CBT: psychoeducation, exposure, cognitive restructuring, and anxiety management training. The theoretical literature also acknowledges the overlap among these approaches as well as incomplete understanding of the mechanisms at work when these interventions are used (Foa and Meadows, 1997; Foa et al., 2000; Harvey et al., 2003). Nonetheless, the committee found that the psychotherapeutic approaches studied in the literature are segmented into CBT components alone and in various combinations. In presenting the summaries below, the committee has grouped therapies based on its understanding of the psychotherapeutic literature and for convenience of exposition, but is aware that others have and may organize the literature differently. The committee identified the following categories of psychotherapies (as used in a treatment condition or "arm"): exposure, cognitive restructuring, coping skills

training, exposure plus cognitive restructuring, exposure plus coping skills, eye movement desensitization and reprocessing (EMDR), other psychotherapies, and group format psychotherapy. Exposure refers to several closely related techniques such as prolonged exposure, direct exposure therapy, and multiple channel exposure therapy, and they are evaluated here as one category, both alone and in combination with other approaches. The category of coping skills training includes stress inoculation therapy, relaxation, biofeedback, and so on. The category of cognitive restructuring refers to psychotherapies designed to help individuals with PTSD alter their understanding of the meaning of their traumatic experiences, for example, by considering their adaptive responses to the trauma as well as the helplessness inflicted by it. The treatment modalities assessed in this chapter were individually administered with a few exceptions where psychotherapy was administered in a group format.

The majority of psychotherapy studies compared one or more active treatments to a wait-list control. Less frequently, the control was usual care (such as non-PTSD specific care) or minimum care (such as phone counseling). A smaller proportion of the psychotherapy studies compared active treatment to an active control such as a coping skills training program (e.g., relaxation) or present-centered therapy.

The committee included 52 studies of psychotherapies (reasons for exclusion are listed in the individual sections below). Of the included studies, 18 had no major limitations and thus were most informative to the committee's conclusions regarding efficacy of a treatment modality (see evidence tables following each treatment for a summary of these studies), but such studies were considered in the context of the body of evidence for each treatment modality. Trauma types in these studies included combat (within the United States and internationally), sexual abuse, physical assault, accidental injury, motor vehicle accidents (MVAs), natural disaster, witnessing (death or genocide), being a victim of crime, and being a refugee.

When analyzing the studies by sex, population, or trauma type, the committee labeled the study as being "predominantly" one type of sex, population, or trauma if 80 percent of the study population or more was of one type of sex, population, or trauma. The committee labeled the study as "mixed" if 79 percent or less of the study population was of one type of sex, population, or trauma. Eleven studies had a predominantly male population, 25 had a female population, and 15 had a mixed (male and female) population. Ten studies were in veteran populations, 17 included victims of sexual or physical abuse, and 23 had a mixed or other trauma type.[1] The committee found that in the psychotherapy literature, as in the pharmacotherapy literature, with few exceptions, when a veteran

[1]Some studies did not include sex or trauma type.

population predominated, the participants were mostly male, and when the majority of cases had been sexually abused or assaulted, participants were mostly female although there are instances when that is not the case. With mixed trauma type, the sex ratios were more equally divided.

EXPOSURE THERAPIES

The committee found a substantial number of randomized controlled trials (RCTs) comparing exposure therapies (alone or with some other component) to wait-list or usual care controls. The category of exposure comprised exposure therapies alone and several different combinations of exposure with cognitive restructuring or coping skills training. The large number of studies of exposure therapy comprises the range of features found in the rest of the psychotherapy studies, with regard to length of treatment, variety of trauma, age of participants, training of clinicians, and so on.

Participants in the exposure therapy studies had suffered a variety of traumas, including combat-related, sexual abuse and/or assault, civil war, and motor vehicle accident. The mean age of study participants ranged from early-20s to the 50s, with most studies reporting a mean age between the mid-30s and mid-40s. Few studies reported duration of illness, but many provided information about the time since trauma, which ranged from several months in studies with rape survivors to more than two decades in studies with veterans. Some studies, such as those in survivors of sexual assault, included only female participants, while many others had a mix of men and women, and studies in people traumatized by combat had all male participants. Some, but not all, studies provided information about the race/ethnicity of participants. In most studies, participants were white, with a smaller number of studies reporting percentages of non-white participants at approximately 20 percent, 30 percent, and in a few cases, nearly 50 percent.

Exposure therapy included psychoeducation, breathing retraining, and relaxation, in addition to exposure (specifically imaginal and in vivo exposure, flooding, directed therapeutic exposure, etc.). Some exposure therapy programs also required completing homework, generally repeated exposure to a trauma tape or other record of the trauma narrative. Exposure studies, like other psychotherapy studies, are lengthy and require considerable investment of time, emotion, and effort. Most studies administered exposure and usually also the comparison treatments for at least several weeks (e.g., 4.5, 9–12, 30 weeks). Only a small number of studies provided treatment in one session or for a short time: one 60-minute session in Basoglu et al. (2005), one session in Basoglu et al. (2007), two 90-minute sessions in Boudewyns et al. (1993).

Most studies reported that study therapists had at least master's level training and frequently held doctorates in psychology, clinical psychology, or clinical social work. Only one study used therapists with less then graduate training but considerable counseling experience, and a few studies used graduate students. Most studies used psychologists, but several studies also used marriage and family counselors (MFCCs), licensed clinical social workers, and one study also used nurses. The majority of studies reported that study therapists were trained and supervised.

The majority of exposure therapy studies did not report on or measure adverse events associated with their treatment condition. Only Monson et al. (2006), Foa et al. (2005), Schnurr et al. (2007), and Chard (2005) measured adverse events.

Many studies conducted follow-up after the completion of treatment. The earliest timing of follow-up assessments was 1 month, and the latest was between 1 and 2 years after treatment. Some studies took follow-up measures at 3, 6, and 9 months post-treatment.

Of the 23 studies in this category, 16 had major limitations including high dropout rates,[2] absent or weak treatment of missing values, lack of assessor independence, not conducting an intention to treat analysis, or failure to report a critical characteristic (Blanchard and Hickling, 2004; Boudewyns et al., 1993; Classen et al., 2001; Cloitre et al., 2002; Falsetti et al., 2001; Foa et al., 1991, 1999, 2005; Glynn et al., 1999; Keane et al., 1998; Kubany et al., 2003, 2004; McDonagh et al., 2005; Power et al., 2002; Resick et al., 2002; Rothbaum et al., 2005). Eight studies met most or all of the quality criteria outlined in Chapter 2 (the main shortcoming in two of these studies was in the handling of substantial dropout rates with less robust statistical methods and or assessor blinding or independence) (Basoglu et al., 2005, 2007; Chard, 2005; Fecteau and Nicki, 1999; Hinton et al., 2005; Keane et al., 1989; Monson et al., 2006; Rothbaum et al., 2005). All eight of these studies demonstrated a statistically significant improvement with treatment to a primary PTSD scale or to the loss of PTSD diagnosis. One of these studies with no major limitations in male veterans with chronic PTSD showed both reductions in a primary PTSD scale and the loss of PTSD diagnosis with cognitive processing therapy (a combination of exposure and cognitive restructuring) (Monson et al., 2006).

The committee identified eight additional RCTs comparing exposure therapies to an active control (coping skills training program or present-centered therapy). Four of the studies had major limitations, such as high dropout rates and either presenting only a completer analysis or using last observation carried forward (LOCF) despite dropout rates of up to

[2]The APA (2004) review of the literature identifies high rate of dropout as a challenge of exposure therapies.

40 percent (Boudewyns et al., 1990; Marks et al., 1998, 2007; Taylor et al., 2003; Vaughan et al., 1994). Four studies had few or no limitations. One small study conducted among mostly female victims of abuse or MVA found substantial decrease in Clinician Administered PTSD Scale (CAPS) scores and loss of diagnosis (Bryant et al., 2003). One was conducted in male veterans with chronic PTSD showing no benefit of trauma-focused therapy administered in groups compared with present-centered therapy (Schnurr et al., 2003). Another study among female veterans with PTSD, 70 percent of whom nominated sexual assault as their index (worst) trauma, showed a benefit of individually administered exposure therapy (Schnurr et al., 2007). A single small study of female victims of sexual assault showed significant improvements in both a global PTSD scale and in loss of diagnosis (Echeburua et al., 1997). The committee found it difficult to judge the validity of the results comparing exposure therapy to a coping skills training program or present-centered therapy overall because four of the eight studies had major limitations, but the remaining studies support the overall conclusion that exposure therapy is efficacious.

Synthesis: The committee judged that the quality of the overall body of evidence supporting exposure therapies is moderate to high, with the best studies all pointing in the same direction with an important clinical benefit. The committee is confident in both the presence of a positive effect and in its clinical significance. Further research is likely to refine estimates of the effect in different settings and populations, but is unlikely to change confidence in the overall estimate of effect.

Conclusion: The committee finds that the evidence is sufficient to conclude the efficacy of exposure therapies in the treatment of PTSD.

Comment

The evidence for efficacy of exposure therapy in veterans—especially in males with chronic PTSD—is less consistent than the general body of evidence.

Also, it should be noted that, as described above and in Appendix A, exposure therapies (e.g., prolonged exposure), as delivered often contain components of other CBT approaches, such as cognitive restructuring and coping skills training. Thus the conclusion that the evidence supports the efficacy of exposure therapy should not be interpreted too narrowly.

Head-to-Head Comparisons

Because the committee judged the evidence sufficient to establish efficacy of exposure therapies, it also reviewed the literature where an

exposure therapy was compared with some other intervention.[3] If evidence strongly supported equivalency of the other therapy compared with exposure therapy, it would add support for the other therapy. We identified seven such studies, but only one—a comparison of exposure therapy with cognitive restructuring in a mixed trauma population (Tarrier et al., 1999)—had no major limitations and it showed that the two therapies were equivalent. The study was small, however, so the committee could not judge whether it had adequate power to detect a clinically significant difference, and thus did not reach a conclusion regarding the equivalency of the two treatments.

Exclusion Notes

Several exposure trials were excluded because they were not randomized (or only partially randomized) (Brady et al., 2001;[4] Cloitre and Koenen, 2001;[5] Cooper and Clum, 1989;[6] Humphreys et al., 1999;[7] Monson et al., 2005[8]). Trials that did not include a comparison or control group were also excluded (Basoglu et al., 2003;[9] Forbes et al., 2002;[10] Frommberger et al., 2004;[11] Najavits et al., 1998). Three trials included participants not formally diagnosed with PTSD, or only part of the sample was diagnosed so were excluded (Foa et al., 1995;[12] Lubin et al., 1998;[13] Valentine and Smith, 2001). There were also two studies where PTSD was not the main

[3]After this report was released an additional head-to-head study was brought to the committee's attention (Ironson et al., 2002). Because of lack of clarity regarding inclusion criteria, the randomization protocol, and the treatment actually delivered, the study was uninformative regarding the principal comparison of PE to EMDR.

[4]This study also looked at dual diagnosis (PTSD and cocaine addiction) and had a high dropout rate greater than 50 percent.

[5]This was a naturalistic study where treatment was interpersonal process group therapy in patients with and without bipolar disorder.

[6]Randomization was not 100 percent. Patients were assigned to standard treatment or standard treatment plus imaginal flooding.

[7]Program evaluation.

[8]This was a preliminary program effectiveness study that compared two variations of CBT in a veteran population.

[9]Modified behavioral treatment given to N = 231 earthquake survivors; duration of treatment and improvement of symptoms were outcomes.

[10]Longitudinal trial examining predictors of response versus treatment efficacy.

[11]This trial compared paroxetine treatment (10–50 mg dosages given) versus CBT treatment (exposure and cognitive restructuring). PTSD and depression symptomatology were outcome variables.

[12]Subjects diagnosed with PTSD per *Diagnostic and Statistical Manual of Mental Disorders,* 3rd edition (DSM-III), but mean duration of illness was 15 days (9.40 for control), corresponding to the current definition for acute stress disorder.

[13]Patients only had PTSD symptoms, not PTSD diagnosis.

study outcome, and neither study included overall PTSD outcome measures (Boudewyns and Hyer, 1990; Chemtob et al., 1997[14]). Falsetti et al. (2003) was excluded because it is an additional analysis of Falsetti et al. (2001) that does not include PTSD outcome data (although it includes other data for the complete sample, unlike the 2001 publication, which was preliminary). See Tables 4-1, 4-2, and 4-3 for a summary of included studies.

EYE MOVEMENT DESENSITIZATION AND REPROCESSING

The committee identified a diverse literature of 10 randomized trials of EMDR compared with various other therapies and wait list or alone compared with wait-list control. The mean age in these studies was in the 30s to the 40s (with a wider range for civilian studies, typically including participants from age 18 to the 70s, and a narrower range for studies in veterans, generally of the Vietnam War). The sex of participants varied in a pattern similar to that described in Chapter 3—in four studies where the trauma was combat, most or all participants were male; participants in the two studies with sexual assault/abuse victims were all female, and participants with a variety of trauma types included a mix of men and women. Approximately half of the studies provided race/ethnicity data, with the range of white participants from 54 to 68 percent. Most studies reported duration of PTSD diagnosis or exposure to index trauma with a range from approximately 1 year in a study of occupational witnessing man-under-train accidents to two decades in the case of veterans. Treatment length ranged from 2 sessions to 10 weekly sessions, and duration of sessions was generally 90 minutes. Most studies provided information about therapists administering the treatment, and they typically were reported as being licensed, trained at master's level or above, and having received EMDR training (some had level II training). Most therapists also were supervised. Some studies did not conduct follow-up after the completion of treatment, while others conducted follow-up at 3, 6, 12, or 15 months.

Six trials had major limitations such as lack of assessor blinding or independence, high dropout rates, or weak (or no) treatment of missing values (Boudewyns et al., 1993; Jensen, 1994; Marcus et al., 1997; Power et al., 2002; Rothbaum, 1997; Silver et al., 1995). Four studies had few or no major limitations, and of those, two showed statistically significant improvement in CAPS score or a significant difference in loss of diagnosis in the treated group (Carlson et al., 1998; Hogberg et al., 2007; Rothbaum et al., 2005; van der Kolk et al., 2007). The study by Carlson and colleagues was a small trial in male veterans, and it showed no effect post-treatment. The study by van der Kolk and colleagues was an RCT comparing EMDR,

[14]Anger is main outcome. This trial was done with Vietnam War veterans.

TABLE 4-1 Exposure

Study	Population[a]	Arm (N)	Handling of Dropouts and % Completed Tx by Arm	PTSD Outcome Measure
Basoglu et al., 2007	Female, nat. disaster	Total (31) E (16) WL (15)	100%	CAPS
Monson et al., 2006	Male, combat	Total (60) E+CR (30) WL (30)	ITT (random regression) 80% 87%	CAPS
Basoglu et al., 2005[c]	Female, nat. disaster	Total (59) E+CR (31) WL (28)	100%	CAPS
Chard, 2005	Female, sexual abuse	Total (71) E+CR (36) MC (35)	ITT (LOCF) 83.3% 80.0%	CAPS
Foa et al., 2005	Female, S&NS abuse	Total (179) E (79) E+CR (74) WL (26)	ITT (BOCF)[d] 59% 66% 96%	PSS-I
Hinton et al., 2005	Mixed sex, witness genocide	Total (40) E+CR WL, then E+CR[e]	None No dropouts	CAPS
McDonagh et al., 2005	Female, sexual abuse	Total (74) E+CR (29) CS (22) WL (23)	ITT (LOCF) 59% 91% 87%	CAPS
Rothbaum et al., 2005	Female, sexual abuse, assault	Total (72) E (23) EMDR (25) WL (24)	ITT (but only completer reported) 83.3% total 87.0% 80.0% 83.3%	CAPS

Assessor Blinded?	Baseline[b] and Change in PTSD Measure	Statistically Significant? (versus control)	Loss of Diagnosis (%)	Principal Limitations
Yes				No major limitations
	–32.9	Yes		
	–13.2			
Yes	76.73, 79.10	Yes		No major limitations
	–24.59			
	–3.07		40%	
			3%	
Yes		Yes	NR	No major limitations
	–23.4			
	–5.8			
Yes	65.46, 68.30	Yes	93%	No major limitations
	–56.5		26%	
	–5.3			
Yes	35.1, 30, 35.5		NR	High dropout handled with BOCF, high differential dropout
	–16.1			
	–13.7	Yes		
	–6.5	Yes		
Yes	74.85, 75.91	Yes	60%	No major limitations
	–35.60	(compared to	0%, then	
	–2.86, then	delayed WL	50%	
	–28.00	group, no after WL treated)		
Yes	69.9, 67.7, 72.0			High attrition handled with LOCF, high differential dropout
	–16.8	Yes	27.6%	
	–20.5	Yes	31.8%	
	–6.5		17.4%	
Yes	M(SD) NR			Treatment of missing data not reported
		Yes	95%	
		Yes	75%	
			10%	

continued

TABLE 4-1 Continued

Study	Population[a]	Arm (N)	Handling of Dropouts and % Completed Tx by Arm	PTSD Outcome Measure
Blanchard et al., 2004	Mixed sex, MVA	Total (98) E+CR (36) CS (37) WL (25)	ITT (reanalysis incl. dropouts) 75.0% 72.9% 96.0%	CAPS
Kubany et al., 2004	Female, abuse	Total (125) E+CR-I[f] (63) E+CR-D[f] (62)	ITT[g] 73.1% 56.5%	CAPS
Neuner, 2004	Female, mixed	Total (43) E (17) CS (14) MC (12)	Restricted maximum likelihood procedure 94% 86% 100%	PTSD diagnosis per PDS
Kubany et al., 2003	Female, assault	Total (37) E+CR-I[f] (19) E+CR-D[f] (18)	ITT (LOCF) 94.7% 77.7%	CAPS
Cloitre et al., 2002	Female, S&NS abuse	Total (58) E+CS (31) WL (27)	ITT (LOCF) 71% 89%	CAPS
Power et al., 2002	Mixed sex, MVA, other	Total (105) EMDR (39) E+CR (37) WL (29)	None 70% 59% 83%	IOE[j]
Resick et al., 2002	Female, sexual abuse, assault	Total (121) E+CR (41) E (40) MC (40)	ITT (LOCF) 73.2% 72.7% 85.1%	CAPS

Assessor Blinded?	Baseline[b] and Change in PTSD Measure	Statistically Significant? (versus control)	Loss of Diagnosis (%)	Principal Limitations
Yes	68.2, 65.0, 65.8			High dropout handled with LOCF and high differential dropout
		Yes	76.2%	
	–44.5	Yes	44.4%	
	–24.9			
	–11.8			
Yes	72.9, 71.9[h]			High dropout handled with LOCF and high differential dropout
	–57.1	Yes	91%	
	–5.6, then –49.8	No, then yes	80%	
Yes	25.2, 2.0, 19.5		(at 1-year follow-up)	No major limitations
	–6.1	Yes[i]		
	–2.2	No	71%	
	+1.7		21%	
			20%	
Yes	80.9, 79.1			High dropout handled with LOCF and high differential dropout
	–70.8	Yes	94%	
	–3.0, then –67.5	Yes	93%	
Yes	69		NR	High dropout handled with LOCF and high differential dropout
	–38	Yes		
	–7			
Yes		Yes	NR	High dropout, no treatment of missing data, high differential dropout
	–23.3			
	–13.5			
	–3			
Yes				Relatively high dropout handled with LOCF
	–35.68	Yes	53%	
	–31.71	Yes	53%	
	–0.59		2%	

continued

TABLE 4-1 Continued

Study	Population[a]	Arm (N)	Handling of Dropouts and % Completed Tx by Arm	PTSD Outcome Measure
Classen et al., 2001	Female, sexual abuse	Total (55)[k] E+CR (14) CS (7) WL (34)	NR Unclear	TSC-40[l]
Falsetti, et al. 2001	Female, mixed trauma	Total (22) E (7) WL (15)[m]	NR Unclear	CAPS
Fecteau and Nicki, 1999	Female, MVA	Total (23) E+CR (12) WL (11)	NR 83% 91%	CAPS
Foa et al., 1999	Female, mixed assault	Total (96) E (25) CS (26) E+CS (30) WL (15)	ITT (LOCF) 92% 73% 73% 100%	PSS-I
Glynn et al., 1999	Male, combat	Total (42) E (12) E+CS[n] (17) WL (13)	 100% 65% 100%	CAPS NR; positive (+)/ negative (–) symptom factor score
Boudewyns et al., 1993	Male, combat	Total (20) EMDR (9) E (6) MC (5)	NR	CAPS
Foa et al., 1991	Female, sexual assault	Total (55) CS-SIT (17) E (14) CS (SC) (14) WL (10)	Completer 82.4% 71.4% 78.6% 100.0%	PTSD severity rating

Assessor Blinded?	Baseline[b] and Change in PTSD Measure	Statistically Significant? (versus control)	Loss of Diagnosis (%)	Principal Limitations
NR	NR –8.1 (both Tx groups) –3.8	 No	NR	High dropout handled with LOCF and high differential dropout, non-standard PTSD measure; assessor blinding or independence not reported
Yes	M(SD) NR	 Yes	 91.7% 33.3%	Dropout or completer numbers not reported
Yes	70.9, 77.3 –33.4 –2.7	 Yes	50% 0%	No major limitations
Yes	~30 –17.8 –16.5 –16.4 –6.0	 Yes Yes Yes —	 60% 42% 40% 0%	High dropout handled with LOCF, high differential dropout
Yes	Unclear	No	NR	High dropout and differential, key data not reported
NR	NR (only physiological measures given)	No	NR	No reporting of dropout or completer numbers, no reporting of blinding or independence, CAPS data not reported (other data not relevant)
Yes	~24–25 –13.41 –10.34 –6.30 –4.93	(Pre-Tx vs. follow-up) Yes Yes No	50% 40% 90% 100%	High dropout, completer analysis only, high differential dropout

continued

TABLE 4-1 Continued

Study	Population[a]	Arm (N)	Handling of Dropouts and % Completed Tx by Arm	PTSD Outcome Measure
Keane et al.,1989	Male, combat	Total (24) E (11) WL(UC) (13)	N/A 100% 100%	MMPI-PTSD

[a]In the population column, male alone or female alone denotes that at least 80% of the study population was male or female. If only one trauma type is listed, at least 80% of the study population reported that type of trauma.

[b]PTSD outcome measure change data were obtained either directly from the study, when provided, or by subtracting data reported at treatment completion (not follow-up data) from baseline data (before treatment began). Average baseline score when reported or when baseline scores for all arms are nearly the same; otherwise, baseline scores listed individually in order of arm.

[c]This study did not have a typical endpoint, because the treatment was a single session, and the "endpoint" was the 6-week post-treatment assessment.

[d]Pre-Tx scores for dropouts.

[e]Immediate vs. delayed E+CR groups; 2nd group served as control, then began Tx after group 1 completed 12 sessions.

[f]I = immediate; D = delayed.

TABLE 4-2 Exposure Studies Using an Active Control Only

Study	Population[a]	Arm (N)	Handling of Dropouts and % Completed Tx by Arm	PTSD Outcome Measure
Schnurr et al., 2007	Female, mixed, combat	Total (284) E (141) PCT (143)	ITT (multiple imputation)[c] 62% 79%	CAPS
Bryant, 2003	Female (Male), abuse, MVA	Total (58) E (20) E+CR (20) CS[d] (18)	ITT (LOCF) 75.0% 75.0% 83.3%	CAPS Intensity (I) and Frequency (F)[e]

Assessor Blinded?	Baseline[b] and Change in PTSD Measure	Statistically Significant? (versus control)	Loss of Diagnosis (%)	Principal Limitations
No	~36 –7.6 –4.6	No	NR	No assessor blinding or independence

[g]The investigators (Basoglu et al., 2005) conducted intent-to-treat analyses on the data by evaluating outcomes for all participants who were randomly assigned, using pre-treatment data scores for post-treatment scores for nonstarters and non-completers.

[b]The delayed group had two pre-therapy assessments: 77.5 and 71.9 CAPS, coinciding with the post-therapy assessment for the immediate group.

[i]Analysis reported for 1-year follow-up only, not reported post-test (change at 1 year: 9.2, –1.1, –4.4).

[j]CAPS subscales are primary study outcome measure.

[k]The investigators reported that 3 of 58 dropped out before beginning of treatment, but apparently after randomization. However, they were not included in the actual reported dropout figure. Also, the number of patients in the control arm was calculated by subtracting 14 + 7 from 55.

[l]Trauma Symptom Checklist 40 (Elliott and Briere, 1991, 1992).

[m]This was a preliminary analysis. Five of WL group were crossed over to treatment—data breakdown was not reported. A further analysis of the completed study was in press after the release of this IOM report, so it could not be included in the committee's review.

[n]Behavioral family therapy.

Assessor Blinded?	Baseline[b] and Change in PTSD Measure	Statistically Significant? (versus control)	Loss of Diagnosis (%)	Principal Limitations
Yes	–24.7 –17.8	Yes	41.0% 27.8% (odds ratio 1.8)	38% dropout handled appropriately; 17% differential dropout
Yes	~32 (I) 36.80/36.00/ 38.33 (F) –16.07, –20.8 –22.4, –25.07 –8.14, –13.13	 Yes, no Yes, yes	 50% 65% 33%	No major limitations

continued

TABLE 4-2 Continued

Study	Population[a]	Arm (N)	Handling of Dropouts and % Completed Tx by Arm	PTSD Outcome Measure
Schnurr et al., 2003	Male, combat	Total (360) E+CR (180) CS: PCT (180)	Mixed model 66% 75%	CAPS
Taylor et al., 2003	Female, mixed	Total (60) E (22) EMDR (19) CS (19)	ITT (LOCF) 68% 79% 79%	CAPS
Marks et al., 1998	Male (Female), mixed	Total (87) E (23) CR (19) E+CR (24) CS (21)	ITT (LOCF) 57% 63% 54% 67%	CAPS
Echeburua et al., 1997	Female, sexual assault, abuse	Total (20) E+CR (10) CS (10)	100%	Global scale of PTSD (0–51)
Vaughn et al., 1994	Female (Male), mixed	Total (36) EMDR (12) E (IHT[f]) (13) CS (11)	100%	SI-PTSD
Boudewyns and Hyer, 1990	Male, combat	Total (58) E (26) PCT (32)	NR	VETS

[a]In the population column, male alone or female alone denotes that at least 80% of the study population was male or female. If only one trauma type is listed, at least 80% of the study population reported that type of trauma.

[b]PTSD outcome measure change data were obtained either directly from the study, when provided, or by subtracting data reported at treatment completion (not follow-up data) from baseline data (before treatment began). Average baseline score when reported or when baseline

Assessor Blinded?	Baseline[b] and Change in PTSD Measure	Statistically Significant? (versus control)	Loss of Diagnosis (%)	Principal Limitations
Yes	80.41, 82.01 –6.41 –5.98	No	≥10 pts CAPS ↓ 38.8% 37.5%	No major limitations (34% dropout well handled)
Yes	NR	Yes No	2 standard deviations decrease in score but reported by symptom category	32% dropout handled with LOCF
Yes	NR –30 –36 –38 –14	 Yes Yes Yes	NR 25% 35% 37% 45%	Dropout from 33% to 46% handled with LOCF
Yes	32.5 –19.8 –11.3	 Yes	 90% 10%	No major limitation
Yes	–8.0 (E and EMDR groups) –1.7	No	All subjects 78% baseline 47% endpoint	Data for active treatment arms aggregated
NR	NR	Unclear	NR	No dropout or completer numbers reported, no outcomes or effect data reported

scores for all arms are nearly the same; otherwise, baseline scores listed individually in order of arm.

[c]With Markov chain Monte Carlo method.

[d]Supportive therapy and counseling.

[e]Total CAPS scores not reported.

[f]Image habituation training.

TABLE 4-3 Head-to-Head Exposure Studies, No Control (Exposure)

Study	Population[a]	Arm (N)	Handling of Dropouts and % Completed Tx by Arm	PTSD Outcome Measure
Van Minnen and Foa, 2006	Mixed sex, domestic and job violence, sexual assault	Total (92) E(PE) (60) E (32)	ITT (LOCF) 77% 84%	PSS-I
Hembree, 2004	Female, S&NS assault	Total (75) E (41) E+CR (34)	NR	PSS-I
Otto et al., 2003	Female, genocide, war (all on clonazepam)	Total (10) SSRI (5) SSRI+CBT (5)	NR	CAPS
Lee et al., 2002	Mixed sex, NR	Total (24)[c] EMDR (12) E+CS (12)	NR, unclear 76.9 or 71.4 84.6 or 78.6	SI-PTSD
Paunovic and Ost, 2001	Mixed sex, refugees	Total (16) E (8) E+CR (8)	NR 80%	CAPS total severity
Devilly and Spence, 1999	Mixed sex, mixed trauma	Total (32) E+CR (15) EMDR (17)	NR 80% 65%	PSS-SR
Tarrier et al., 1999	Mixed sex, crime, accidents, other	Total (72) CR (37) E (35)	NR 89% 83%	CAPS

[a]In the population column, male alone or female alone denotes that at least 80% of the study population was male or female. If only one trauma type is listed, at least 80% of the study population reported that type of trauma.

[b]PTSD outcome measure change data were obtained either directly from the study, when provided, or by subtracting data reported at treatment completion (not follow-up data) from baseline data (before treatment began). Average baseline score when reported or when baseline

Assessor Blinded?	Baseline[b] and Change in PTSD Measure	Statistically Significant?	Loss of Diagnosis (%)	Principal Limitations
NR	25.9, 27.2 –11.1 –12.9	No (shows 30 min E as effective as 60 min E)	NR	Assessor blinding or independence not reported
NR	NR	NR	Not reported by arm	No dropout or completer numbers reported; assessor blinding or independence not reported
NR	57.2, 64.6 +4.6 –14	Unclear (no *P* values), but combined had "dramatic" effect compared to modest effect of SSRI alone	NR	No dropout or completer numbers reported; assessor blinding or independence not reported; very small sample size
No[d]	37.58, 42.25 –20.58 –17.17	No (yes compared to 2nd assessment during wait-list period)	83% 75%	No method of handling dropout reported; assessor blinding or independence not reported
No	98.4, 95.1 –52.4 –56.1	Yes Yes	25%	Dropout data aggregated for both arms; assessor blinding or independence not reported
NR	36.25, 35.09 –21.83 –10.45	Yes (superior)	58.33% 27.27%	35% dropout without adequate treatment; 15% dropout differential; assessor blinding or independence NR
Yes	77.76, 71.14 –26.94 –22.9	No	42% 59%	No major limitations

scores for all arms are nearly the same; otherwise, baseline scores listed individually in order of arm.

[c]It is unclear from the authors' reporting how many people were randomized. 29 were screened, 2 dropped out before randomization, and the authors report that 3 patients dropped out of treatment—one from E+CS, one from EMDR, and one "went to prison." The treatment condition of the patient who went to prison is unclear.

[d]But, the authors note, self-reported data were consistent with interview data.

fluoxetine, and placebo, and failed to show significant improvement despite the LOCF treatment of missing values that in this case should have biased the study toward showing a positive outcome.

The committee also identified two RCTs comparing EMDR with a coping skills training therapy, namely, applied muscle relaxation and relaxation training (Taylor et al., 2003; Vaughan et al., 1994). However, both studies had major limitations such as high dropouts or uninterpretable aggregation of data, and in any case neither demonstrated a statistically significant benefit.

The committee noted that some experts have questioned whether the eye movement component adds benefit to the reprocessing component, but the committee identified no adequately designed studies testing the hypothesis and so was unable to reach a conclusion.

Synthesis: The committee found the overall body of evidence for EMDR to be low quality to inform a conclusion regarding treatment efficacy. Four studies, three of medium and one of small sample size, had no major limitations, but only two showed a positive effect for EMDR. The committee is uncertain about the presence of an effect, and believes that future well-designed studies will have an important impact on confidence in the effect and the size of the effect.

Conclusion: The committee concludes that the evidence is inadequate to determine the efficacy of EMDR in the treatment of PTSD.

Exclusion Notes

Three trials that did not include a comparison or control group were excluded (Ironson et al., 2002; Raboni et al., 2006; Rogers et al., 1999) as were comparison studies (Cusack and Spates, 1999; Devilly and Spence, 1999; Lee et al., 2002; Pitman et al., 1996). Many trials included participants not formally diagnosed with PTSD, or only part of the sample was diagnosed so were excluded (Devilly et al., 1998;[15] Renfrey and Spates, 1994;[16] Sanderson and Carpenter, 1992;[17] Scheck et al., 1998;[18] Wilson et

[15]War veterans with PTSD "symptomatology."

[16]Patients "were screened positive for traumatic events as defined by the DSM-III-R, and experienced current intrusive symptoms as similarly defined." This trial evaluated active components of EMDR, standard EMD, a variant of EMD in which eye movements were engendered with light tracking task, and a variant of EMD with fixed visual attention.

[17]The patient sample from this trial only included those with phobias, and a subgroup of phobias that "nearly resemble" PTSD.

[18]PTSD diagnosis was not a requirement for study inclusion. In addition this sample included patients ages16–25, so did not meet the committee's criteria for only adult populations.

al., 1995, 1997[19]). The committee also identified a progress report for an ongoing 3-year study with selected results; only preliminary findings were available so it was not included on the review (Boudewyns and Hyer, 1996). See Tables 4-4 and 4-5 for a summary of included studies.

COGNITIVE RESTRUCTURING

The committee identified three RCTs of cognitive restructuring compared with coping skills training or an educational booklet. One study suffered high dropout rates (up to 46 percent) and used LOCF to address missing data. Another study with no major limitations showed no difference between cognitive restructuring and exposure-focused therapy, but had no control group (Tarrier et al., 1999). A second trial with no major limitations conducted in individuals who had experienced a motor vehicle accident had a modest dropout rate handled by LOCF, and showed significant improvement on CAPS and loss of diagnosis (Ehlers and Clark, 2003). However, the committee was reluctant to judge cognitive restructuring on the basis of this single trial in victims of motor vehicle accidents.

Synthesis: The committee judged the overall body of evidence on cognitive restructuring in the treatment of PTSD to be moderate quality, but there were important limitations. Although the three studies identified were all of medium size and two were reasonably well-conducted, one of the two did not find an effect and the other found a large effect. The committee is uncertain about the presence of an effect, and believes that future well-designed studies will have an important impact on confidence in the effect and the size of the effect.

Conclusion: The committee concludes that the evidence is inadequate to determine the efficacy of cognitive restructuring in the treatment of PTSD.

Exclusion Notes

The committee did not identify any studies on cognitive restructuring alone to exclude. See Table 4-6 for a summary of included studies.

[19]Less than half of the 2005 study participants met PTSD diagnosis. Separate results for those with and without PTSD not provided except for one supplemental analyses for those with PTSD. The 1997 follow-up study did analyze PTSD versus non-PTSD patients separately, however there was no longer a control group so the study is uninformative with regard to the core question of efficacy.

TABLE 4-4 EMDR

Study	Population[a]	Arm (N)	Handling of Dropouts and % Completed Tx by Arm	PTSD Outcome Measure
Hogberg et al., 2007	Male, witnessing	Total (24) EMDR (13) WL (11)	100%	GAF and loss of diagnosis (SCID)
van der Kolk et al., 2007	Female, S&NS abuse, injury	Total (88) SSRI (30) EMDR (29) PL (29)	ITT (LOCF) 87% 83% 90%	CAPS
Rothbaum et al., 2005	Female, sexual abuse	Total (72) E (23) EMDR (25) WL (24)	ITT (NR) 87.0% 80.0% 83.3%	CAPS
Power et al., 2002	Mixed sex, MVA, other	Total (105) EMDR (39) E+CR (37) WL (29)	None 70% 59% 83%	IOE[d]
Carlson et al., 1998	Male, combat	Total (35) EMDR (10) CS (13) UC (12)	NR 100% 92.3% 100%	IES
Marcus et al., 1997[e]	Female, S&NS abuse	Total (67) EMDR (33 or 34) SC (34 or 33)	Not clear	IES
Rothbaum, 1997	Female, sexual assault	Total (21)[g] EMDR (10) WL (8)	Completer total 85.7%	PSS-I
Silver et al., 1995	Male, combat	Total (83) EMDR (13) CS-R (9) CS-B (6) MC (55)	NR	PRF

Assessor Blinded?	Baseline[b] and Change in PTSD Measure	Statistically Significant? (versus control)	Loss of Diagnosis (%)	Principal Limitations
Yes	~64[c] –14.5 –1.9	Yes	 67% 11%	No major limitations
Yes	NR –33.23 –39.15 –30.95	No	 73% 76% 59%	No major limitations
Yes	M(SD) NR 	 Yes Yes 	 95% 75% 10%	No major limitations (but outcome data not reported)
Yes	35.1, 32.7, 32.6 –23.3 –13.5 –3	 Yes Yes	NR	41% dropout; no treatment of missing data
Yes	~52 –17.3 –8.4 –14.1	 No No	(at 3-month follow-up) 77.77% (of 9) 22.22% (of 9)	No major limitations
Yes[f]	46.09, 49.70 –28.2 –14.7	 Yes	 77% 50%	Dropout or completer numbers not clear
Yes	33.3, 39 –19 –4	 Yes	 90% 12%	No breakdown of dropout rates[g]
NR	No single measure, 8 symptom scales	Yes (on 5 of 8 PRF scales)	NR	No dropout or completer data reported; assessor blinding or independence not reported; nonstandard outcome measure and uninterpretable data

continued

TABLE 4-4 Continued

Study	Population[a]	Arm (N)	Handling of Dropouts and % Completed Tx by Arm	PTSD Outcome Measure
Jensen, 1994	Male, combat	Total (25) EMDR (13) WL (12)	100%	SI-PTSD
Boudewyns et al., 1993	Male, combat	Total (20) EMDR (9) E (6) MC (5)	NR	CAPS

[a]In the population column, male alone or female alone denotes that at least 80% of the study population was male or female. If only one trauma type is listed, at least 80% of the study population reported that type of trauma.

[b]PTSD outcome measure change data were obtained either directly from the study, when provided, or by subtracting data reported at treatment completion (not follow-up data) from baseline data (before treatment began). Average baseline score when reported or when baseline scores for all arms are nearly the same; otherwise, baseline scores listed individually in order of arm.

[c]Higher Global Assessment of Functioning (GAF) scores mean improvement, so the change was 64.0 to 78.9 for the treatment group, and 64.9 to 66.8 for the WL group.

TABLE 4-5 EMDR Studies Where Coping Skills Are the (Only) Control

Study	Population[a]	Arm (N)	Handling of Dropouts and % Completed Tx by Arm	PTSD Outcome Measure
Taylor et al., 2003	Female, assault, accidents	Total (60) E (22) EMDR (19) CS (19)	ITT (LOCF) 68% 79% 79%	CAPS
Vaughn et al., 1994	Mixed sex, mixed trauma[c]	Total (36) EMDR (12) E (IHT[d]) (13) CS (11)	100%	SI-PTSD

[a]In the population column, male alone or female alone denotes that at least 80% of the study population was male or female. If only one trauma type is listed, at least 80% of the study population reported that type of trauma.

[b]PTSD outcome measure change data were obtained either directly from the study, when provided, or by subtracting data reported at treatment completion (not follow-up data) from baseline data (before treatment began). Average baseline score when reported or when baseline scores for all arms are nearly the same; otherwise, baseline scores listed individually in order of arm.

Assessor Blinded?	Baseline[b] and Change in PTSD Measure	Statistically Significant? (versus control)	Loss of Diagnosis (%)	Principal Limitations
NR	29.92, 37.08 –5.77 –9.88	No	NR	Assessor blinding or independence not reported
NR	NR	No	NR	No dropout or completer numbers reported; no outcome

[d]IOE is Impact of Events Scale (also known as IES). The three CAPS subscales were the primary study outcome measure.

[e]Follow-up in the Marcus et al., 1997, study was further analyzed in Marcus et al., 2004.

[f]Blind assessment was affected by client revelations.

[g]The numbers randomized to each arm are unclear, but may be deduced to be either 11 or 10 for either, meaning that with completer numbers of EMDR 10 and WL 8, the respective dropout rates were either 0 for EMDR (100% completed) and 3 for WL (73% completed), or 1 for EMDR (91% completed) and 2 for WL (80% completed). The article states that two of the three patients who dropped out were assigned to WL, so one could conclude that the third patient that dropped out was probably assigned to EMDR. If that is true, the dropout rates would have been 91% and 80% for EMDR and WL, respectively.

Assessor Blinded?	Baseline[b] and Change in PTSD Measure	Statistically Significant? (versus control)	Loss of Diagnosis (%)	Principal Limitations
Yes	NR	Yes No	2 standard deviations decrease in score but reported by symptoms category	32% dropout handled with LOCF
Yes	NR –8.0 (E and EMDR groups) –1.7	No	All subjects 78% baseline 47% endpoint	Outcome data aggregated, uninterpretable

[c]At entry to the study all patients satisfied DSM-III-R Category B (reexperiencing/intrusive) and Category D (hyperarousal) criteria for PTSD. However 22% failed to qualify for a diagnosis of PTSD because they had less than the three required Category C (avoidance, numbing) symptoms. "This is a symptom pattern common in community samples (Creamer, 1989; Solomon and Canino, 1990) and has promoted moves to reduce the number of Category C criteria from three to two in DSM-IV (Davidson and Foa, 1993)" (Vaughn et al., 1994).

[d]Image habituation training.

TABLE 4-6 Cognitive Restructuring

Study	Population[a]	Arm (N)	Handling of Dropouts and % Completed Tx by Arm	PTSD Outcome Measure
Ehlers et al., 2003	Sex NR, MVA	Total (85)	ITT	CAPS frequency (F) and intensity (I) scores[e,f]
		CR (28)	100%	
		MC[c] (28)	89%	
		MC[d] (29)	93%	
Tarrier, et al., 1999[b]	Mixed sex, crime	Total (72)	NR	CAPS
		CR (37)	89%	
		E (35)	83%	
Marks et al., 1998[i]	Mixed sex, mixed trauma	Total (87)	ITT (LOCF)	CAPS
		E (23)	57%	
		CR (19)	63%	
		E+CR (24)	54%	
		CS (21)	67%	

[a]In the population column, male alone or female alone denotes that at least 80% of the study population was male or female. If only one trauma type is listed, at least 80% of the study population reported that type of trauma.

[b]PTSD outcome measure change data were obtained either directly from the study, when provided, or by subtracting data reported at treatment completion (not follow-up data) from baseline data (before treatment began). Average baseline score when reported or when baseline scores for all arms are nearly the same; otherwise, baseline scores listed individually in order of arm.

COPING SKILLS THERAPIES

The committee found 10 RCTs of coping skills training compared to minimum care, or compared to another treatment modality and minimum care. Most of the trials had major limitations including high rates of dropout, inadequate handling of missing values, high differential dropout among arms, and lack of assessor blinding or independence. Only 2 of 10 studies had no noteworthy limitations, but neither found an effect (Carlson et al, 1998; Neuner et al., 2004). Most of the remaining studies (six of eight) (Blanchard et al., 2004; Foa et al., 1999; Hien et al, 2004; McDonagh et al., 2005; Silver et al., 1995; Zlotnick et al., 1997) showed an effect, but had major limitations that severely weakened confidence in the results.

Synthesis: The committee judged that the overall body of evidence on coping skills training was low quality to inform a conclusion regarding efficacy. The committee is uncertain about the presence of an effect, and believes

Assessor Blinded?	Baseline[b] and Change in PTSD Measure	Statistically Significant? (versus control)	Loss of Diagnosis (%)	Principal Limitations
Yes	F I		per PDS[g]	No major limitations
	~32[f] ~26			
	20.5 16.5	Yes	85.7%	
	9.7 7.1		21.4%	
	7.2 3.5		27.6%	
Yes	77.76, 71.14			No major limitations
	–26.94	No	42%	
	–22.9		59%	
Yes	NR		NR	Dropout from 33% to
	–30	Yes	75%	46% handled with LOCF
	–36	Yes	65%	
	–38	Yes	63%	
	–14		55%	

[c]Self-help booklet.
[d]Repeated assessments.
[e]CAPS frequency and intensity scores were reported, but no CAPS total provided.
[f]In Ehlers et al., 2003, the 3-month follow-up was considered the post-treatment point (p. 1029).
[g]Posttraumatic Diagnostic Scale.
[b]No control.
[i]CS is the only control.

that future well-designed studies will have an important impact on confidence in the effect and the size of the effect.

Conclusion: The committee concludes that the evidence is inadequate to determine the efficacy of coping skills therapies in the treatment of PTSD.

Exclusion Notes

The committee excluded one study comparing three different coping skills with no control group (Watson et al., 1997). See Table 4-7 for a summary of included studies.

OTHER PSYCHOTHERAPIES

The committee identified four individual trials of other psychotherapies—eclectic psychotherapy, hypnotherapy, psychodynamic therapy, and

TABLE 4-7 Coping Skills

Study	Population[a]	Arm (N)	Handling of Dropouts and % Completed Tx by Arm	PTSD Outcome Measure
McDonagh, 2005	Sex NR, sexual abuse	Total (74) E+CR (29) CS (22) WL (23)	ITT (LOCF) 59% 91% 87%	CAPS
Blanchard et al., 2004	Mixed sex, MVA	Total (98) E+CR (36) CS (37) WL (25)	ITT (reanalysis incl. dropouts) 75.0% 72.9% 96.0%	CAPS
Hien et al., 2004	Female, interpersonal violence	Total (107) CS (41)[c] CS (34)[d] MC (32)	ITT (LOCF+)[e] 61% 71% 100%	CAPS
Neuner et al., 2004	Mixed sex, war refugees	Total (43) E (17) CS (14) MC (12)	Restricted maximum likelihood 94% 86% 100%	PTSD diagnosis per PDS
Classen et al., 2001	Female, sexual abuse	Total (55)[g] E+CR (14) CS (7) WL (34)	NR Unclear	TSC-40[b]
Foa et al., 1999	Female, mixed assault	Total (96) E (25) CS (26) E+CS (30) WL (15)	ITT (LOCF) 92% 73% 73% 100%	PSS-I

Assessor Blinded?	Baseline[b] and Change in PTSD Measure	Statistically Significant? (versus control)	Loss of Diagnosis (%)	Principal Limitations
Yes	69.9, 67.7, 72.0	Yes	27.6%	41% dropout handled with LOCF; 28% differential dropout
	–16.8	Yes	31.8%	
	–20.5		17.4%	
	–6.5			
Yes	68.2, 65.0, 65.8, DO 69.2			27.1% dropout rate; 21% differential dropout
		Yes	76.2%	
	–44.5	Yes	44.4%	
	–24.9			
	–11.8			
No	~72		NR	
	–15.02			39% dropout handled with LOCF and mean replacement; 39% differential dropout; no assessor blinding or independence
	–19.17	Yes		
	–5.88	Yes		
Yes	25.2, 2.0, 19.5		(at 1-year follow-up)	No major limitations
	–6.1	Yes[f]		
	–2.2	No	71%	
	+1.7		21%	
			20%	
NR	NR	No	NR	Dropout or completer numbers not reported; no assessor blinding or independence not reported; outcomes reported aggregated for treatment groups
	–8.1 (both Tx groups)			
	–3.8			
Yes	~30			27% dropout handled with LOCF; 27% differential dropout
	–17.8	Yes	60%	
	–16.5	Yes	42%	
	–16.4	Yes	40%	
	–6.0	—	0%	

continued

TABLE 4-7 Continued

Study	Population[a]	Arm (N)	Handling of Dropouts and % Completed Tx by Arm	PTSD Outcome Measure
Carlson et al., 1998	Male, combat	Total (35)	NR	IES
		EMDR (10)	100%	
		CS (13)	92.3%	
		UC (12)	100%	
Zlotnick, 1997	Female, childhood sexual abuse	Total (48)[i]	Completers	DTS
		CS (17)	71%	
		WL (16)	75%	
Silver et al., 1995	Male, combat	Total (83)	NR	PRF
		EMDR (13)		
		CS-R (9)		
		CS-B (6)		
		MC (55)		
Foa et al., 1991	Female, sexual assault	Total (55)	NR	PTSD severity rating
		CS-SIT (17)	82.4%	
		E (14)	71.4%	
		CS (SC)[j] (14)	78.6%	
		WL (10)	100%	

[a]In the population column, male alone or female alone denotes that at least 80% of the study population was male or female. If only one trauma type is listed, at least 80% of the study population reported that type of trauma.

[b]PTSD outcome measure change data were obtained either directly from the study, when provided, or by subtracting data reported at treatment completion (not follow-up data) from baseline data (before treatment began). Average baseline score when reported or when baseline scores for all arms are nearly the same; otherwise, baseline scores listed individually in order of arm.

[c]Seeking-safety therapy.

[d]Relapse prevention therapy (a substance abuse treatment was used as a comparator, not as PTSD treatment).

brainwave neurofeedback. The usefulness of one of the two trials of eclectic psychotherapy was severely limited by a 42 percent dropout rate handled with LOCF (Lindauer et al., 2005); the other, conducted among police officers (Gersons et al., 2000), had no major limitations and showed a significant difference in loss of PTSD diagnosis (Gersons et al., 2000; Lindauer et al., 2005). The trial of hypnotherapy and psychodynamic therapy had only one major limitation and showed a significant decrease

Assessor Blinded?	Baseline[b] and Change in PTSD Measure	Statistically Significant? (versus control)	Loss of Diagnosis (%)	Principal Limitations
Yes	~52		(at 3-month follow-up)	No major limitations
	–17.3	No	77.77% (of 9)	
	–8.4	No	22.22% (of 9)	
	–14.1			
No (self-report)	66.88, 74.69			
	–21.12	Yes	87%	29% dropout rate with completers analysis
	–1.63		41%	
NR	No single measure, 8 symptom scales	Yes (on 5 of 8 PRF scales)	NR	Dropout or completer numbers not reported; non-standard, multiple scale PTSD measure and no total reported
Yes	~24–25	(Pre-Tx vs. follow-up)	50%	28.6% dropout; method of handling missing data not reported; no adequate treatment of missing data; 28.6% differential dropout
	–13.41	Yes	40%	
	–10.34	Yes	90%	
	–6.30	No	100%	
	–4.93			

[e]The authors report that they also tested "mean replacement" to address missing data, yielding results no different from LOCF.

[f]Analysis reported for 1-year follow-up only, not reported post-test (change at 1 year: 9.2, –1.1, –4.4).

[g]The investigators reported that 3 of 58 dropped out before beginning treatment but after randomization. However, these were not included in the actual reported dropout figure. Also, the number of patients in the control arm was calculated by subtracting 14 + 7 from 55.

[b]Trauma Symptom Checklist-40.

[i]Fifteen dropped out.

[l]In this study CS was used as an active control, not as a treatment arm.

in change from baseline to post-treatment measures for each treatment arm (Brom et al., 1989). The trial of brainwave neurofeedback in Vietnam veterans with chronic PTSD used the Minnesota Multiphasic Personality Inventory (MMPI)-PTSD lacked assessor blinding or independence (Peniston and Kulkosky, 1991). Based on this extremely limited body of evidence, the committee believes that it would be inappropriate to reach a conclusion regarding the efficacy of any of these treatments.

Exclusion Notes

Several case studies and series, uncontrolled trials, and RCTs have been conducted on various psychotherapies not included in the classes outlined above. Several other studies were excluded, and the reasons are briefly described here. Three trials were excluded because they were not randomized (or only partially randomized) (Ragsdale et al., 1996[20]) or did not include a comparison or control group (Forbes et al., 2003;[21] Zayfert et al., 2005[22]). Many trials included participants not formally diagnosed with PTSD, or only part of the sample was diagnosed so were excluded (Classen et al., 2001; Igreja et al., 2004;[23] Krakow et al., 2000, 2001;[24] Lange et al., 2001, 2003;[25] Solomon et al., 1992;[26] Zatzick et al., 2004[27]). In one study, PTSD was not the primary study outcome, and the study did not include an overall PTSD outcome measure (Ouimette et al., 1997[28]). The committee also identified two program reviews that were not included in this review (Hammarberg and Silver, 1994;[29] Johnson et al., 1996[30]). See Table 4-8 for a summary of included studies.

GROUP THERAPY

The committee noted that any psychotherapy can be administered in a group format, and was aware that group formats are commonly used in

[20]Trial examined short-term specialized inpatient treatment for war-related PTSD (adventure-based counseling and psychodrama).

[21]This was a pilot study using imagery rehearsal as the treatment.

[22]Assessed rates of exposure therapy (ET) and completed CBT for PTSD in a clinical setting and looked at predictors of completion. Illustrated therapeutic challenges in real-world clinical practice (as opposed to in the context of a study).

[23]Trial used a testimony method intervention in rural community survivors of war; case and noncase group; "case" group randomly divided into testimony method or control.

[24]Patients had PTSD symptoms coupled with clear criterion A trauma link(s). Treatment was sleep-imagery rehearsal.

[25]Patients had mild to severe posttraumatic stress (not PTSD diagnosis). Treatment was Interapy or Internet therapy, vs. a wait-list control condition.

[26]This was a cohort study where some patients had combat stress reaction, some PTSD. It compared veterans who participated in the Koach program vs. veterans who did not. Koach used behavior therapy (flooding) with a focus on functioning in a military-type setting that exposed veterans to anxiety-provoking stimuli.

[27]Mixed diagnosis—PTSD symptomatology (but not actual PTSD) and/or depression. Subjects were trauma patients receiving medical care immediately after the trauma, and although some were acutely stressed, diagnosis of PTSD was not made until the 3-month follow-up.

[28]Impact on PTSD symptoms not assessed, and main treatment was for substance abuse (substance abuse and psychosocial outcomes examined 1 year after VA inpatient substance abuse treatment).

[29]Treatment involved multiple modalities.

[30]Program evaluation of a three-phase inpatient program.

veteran populations. Ideally there would be evidence regarding the comparative effectiveness of a given therapy in individual and group formats, with some indication of the population or subpopulation characteristics that would make one or the other more effective. However, only four studies examining group formats, and all using CBT approaches[31] met the committee's inclusion criteria, combining various components of exposure, restructuring, and coping skills training. They are discussed below.

In general, studies of exposure (including studies of exposure plus cognitive restructuring and exposure plus coping skills training) administered the treatment in individual, rather than group sessions. Exceptions include Schnurr et al. (2003), Falsetti et al. (2001), and Chard et al. (2005), which are discussed in more detail below. The committee also identified a fourth study that employed a group therapy comparing affect management (a type of coping skills training) used as an adjunct to ongoing psychotherapy and pharmacotherapy to wait list (Zlotnick et al., 1997). This study found a benefit to group therapy, but had dropout rates of 25 and 29 percent handled only with completers analysis. The authors further acknowledge that the lack of standardization in concurrent treatment (including drugs administered) limited the validity of the study.

Schnurr el al. (2003), Falsetti et al. (2001), and Chard et al. (2005) showed mixed effect of various types of group therapy on PTSD symptoms. The large and well-conducted Schnurr et al., 2003, study in veterans compared group trauma-focused to group present-focused therapy. Although post-treatment assessments of PTSD severity significantly improved from baseline, there were no differences between treatment groups for any outcome. The Falsetti et al. (2001) study had a small sample size, was conducted in a population with mixed trauma, and showed an effect but was a preliminary analysis (study was not complete) and included a control-then-treatment group. The medium-size Chard et al. (2005) study did not have major limitations and found an effect, but it alternated individual and group therapy (9 weeks of both, 7 weeks of group therapy, and the final week of individual therapy) in its treatment arm, making it difficult to ascertain which component of the therapeutic approach was efficacious. In addition to the Schnurr et al. (2003) study in a veteran population, the committee made note of another large study (Creamer et al., 2006) in veterans that showed mixed effect on PTSD symptoms, but the Creamer study was a large case-series without a control (so was not included in the committee's review). Schnurr et al. (2003) found no significant differences in outcome between the two types of group intervention (analysis of patients receiving

[31]Foa et al. (2000) describe two other types of group therapy for which the committee did not find RCTs: group psychodynamic therapy and supportive group therapy.

TABLE 4-8 Other Psychotherapies

Study	Population[a]	Arm (N)	Handling of Dropouts and % Completed Tx by Arm	PTSD Outcome Measure
Lindauer et al., 2005	Mixed sex, mixed trauma	Total (24) OT (BEP)[c] (12) WL (12)	ITT 58% 92%	PTSD diagnosis per SI-PTSD
Gersons et al., 2000	Mixed sex, police work	Total (42) OT (BEP) (22) WL (20)	NR 100% 95%	PTSD symptoms[d] (SI-PTSD data NR)
Peniston and Kulkosky, 1991	Male, trauma type NR	Total (29) OT (BN)[f] (15) UC[g] (14)	 100%	MMPI-PTSD
Brom et al., 1989	Mixed sex, mixed trauma	Total (112) E (31) OT (H)[b] (29) OT (P)[i] (29) WL (23)	NR 90.3% 89.7% 89.7% 86.9%+	IES Total

[a]In the population column, male alone or female alone denotes that at least 80% of the study population was male or female. If only one trauma type is listed, at least 80% of the study population reported that type of trauma.

[b]PTSD outcome measure change data were obtained either directly from the study, when provided, or by subtracting data reported at treatment completion (not follow-up data) from baseline data (before treatment began). Average baseline score when reported or when baseline scores for all arms are nearly the same; otherwise, baseline scores listed individually in order of arm.

[c]Brief eclectic psychotherapy, a combination of CBT and psychodynamic approaches including relationship and work issues.

what was considered an adequate dose of 80 percent of treatment sessions). See Table 4-9 for a summary of included studies.

Synthesis: The committee judged the overall body of evidence regarding group therapy formats to be low quality to inform a conclusion regarding efficacy because of the lack of well-designed studies comparing group and individual formats and including appropriate controls. The committee is uncertain about the presence of an effect, and believes that future well-designed studies will have an important impact on confidence in the effect and the size of the effect.

Assessor Blinded?	Baseline[b] and Change in PTSD Measure	Statistically Significant? (versus control)	Loss of Diagnosis (%)	Principal Limitations
Yes	100.0% –83.3% –25.0%	Yes	Same as baseline and change	42% dropout
Yes (but broken in 4 Ss)	11.5[e] –8 –3	Yes	91% 50%	No major limitations
No	31, 36 –21 –0	Yes	No relapse at 30 months 80% 0%	No assessor blinding or independence
NR	19.4 17.1 13.6 4.6	Yes Yes Yes	NR	Assessor blinding or independence not reported

[d]Outcome measure was "recovery proportions," including no PTSD and fewer than six symptoms (SI-PTSD used to determine both).

[e]Data not provided; figures estimated based on visual inspection of a bar graph, with the help of a ruler.

[f]Brainwave neurofeedback.

[g]Usual care.

[h]Hypnosis.

[i]Psychodynamic therapy.

Conclusion: The committee concludes that the evidence is inadequate to determine the efficacy of group therapy formats in the treatment of PTSD.

SUMMATION

Based on its assessment of the psychotherapy approaches for which randomized controlled trials were available—exposure, EMDR, cognitive

TABLE 4-9 Group Therapy

Study	Population[a]	Arm (N)	Handling of Dropouts and % Completed Tx by Arm	PTSD Outcome Measure
Chard et al., 2005	Female, sexual abuse	Total (71) E+CR (36) MC (35)	ITT (LOCF) 83.3% 80.0%	CAPS
Falsetti, et al. 2001	Female, mixed trauma	Total (22) E (7) WL (15)[m]	NR Unclear	CAPS
Schnurr et al., 2003	Male, combat	Total (360)	Mixed model	CAPS
		E+CR (180) CS (PCT) (180)	66% 75%	
Zlotnick, 1997	Female, childhood sexual abuse	Total (48)[c] CS (17) WL (16)	Completers 71% 75%	DTS

[a]In the population column, male alone or female alone denotes that at least 80% of the study population was male or female. If only one trauma type is listed, at least 80% of the study population reported that type of trauma.

[b]PTSD outcome measure change data were obtained either directly from the study, when

restructuring, coping skills training, other therapies, and psychotherapies administered in a group format—the committee found the evidence for all but one psychotherapeutic approach inadequate to reach a conclusion regarding efficacy. The evidence was sufficient to conclude the efficacy of exposure therapies in treating patients with PTSD.

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Assessor Blinded?	Baseline[b] and Change in PTSD Measure	Statistically Significant? (versus control)	Loss of Diagnosis (%)	Principal Limitations
Yes	65.46, 68.30 –56.5 –5.3	Yes	93% 26%	No major limitations
Yes	M(SD) NR	Yes	91.7% 33.3%	Dropout or completer numbers not reported
Yes	80.41, 82.01 –6.41 –5.98	No	≥10 pts drop on CAPS 38.8% 37.5%	No major limitations (34% dropout well handled)
No (self-response)	66.88, 74.69 –21.12 – 1.63	Yes	87% 41%	29% dropout rate with completers analysis

provided, or by subtracting data reported at treatment completion (not follow-up data) from baseline data (before treatment began). Average baseline score when reported or when baseline scores for all arms are nearly the same; otherwise, baseline scores listed individually in order of arm.

[c]Fifteen dropped out.

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5

Issues in PTSD Treatment Research

In its review of the evidence—pharmacotherapy and psychotherapy randomized controlled trials—in Chapters 3 and 4, the committee identified several issues that warrant examination. The first part of this chapter discusses these issues and makes recommendations to address the challenges they present. The second part of the chapter seeks to respond to several issues raised in the Statement of Task, specifically pertaining to posttraumatic stress disorder (PTSD) recovery, early intervention, and length of treatment.

ISSUES IDENTIFIED IN REVIEWING THE EVIDENCE

In its review of the PTSD treatment literature, a number of common themes and important questions emerged. These include: methodological problems, especially attrition and subsequent handling of missing data; funding of pharmacotherapy studies by pharmaceutical companies, raising concern about publication bias and investigator independence; applicability of the PTSD treatment outcome studies in civilian populations to the Department of Veterans Affairs (VA) and veteran populations (including the fact that there is neither evidence to show that PTSD in the two populations is different, nor that it is the same); research gaps in regard to special veteran populations; length of follow-up (discussed in conjunction with length of treatment in the latter part of this chapter); and apparent divergence between the committee's conclusion and the Food and Drug Administration (FDA)'s regulatory determination on the evidence regarding two selective serotonin reuptake inhibitors (SSRIs).

A Challenge to Internal Validity

The available evidence on PTSD treatment is limited in that relatively few high-quality randomized controlled (by placebo, wait list, or equivalent) trials, or RCTs, have been performed for most modalities. The committee excluded a large volume of studies that were case reports and case-series, and controlled studies without randomization. The remaining studies varied in their adherence to current standards of design quality, had problems with sample size, assessor blinding or independence, high dropout rates, and had short or no follow-up after treatment concluded.

A characteristic of most studies of PTSD reviewed by the committee is a high degree of attrition of participants from assigned treatment, whether pharmacologic or psychotherapeutic. This may be due to the underlying condition and patient characteristics that may make adherence to any form of therapy difficult, or it may be due to improvement or worsening of symptoms. High degrees of dropout are common in studies of a broad range of psychological conditions. In a review of studies by Khan (2001a, b), dropout rates in trials of antidepressants averaged 37 percent, similar between treatment and placebo arms, and were in the 50 to 60 percent range for trials of antipsychotics, somewhat greater in treatment than in placebo, and intermediate among active controls.

A particularly difficult challenge is the assessment of efficacy in the face of different rates of dropout for different study treatments. As an illustration of this challenge (Figure 5-1), consider a study of an intervention with identical 50 percent remission rates in the intervention and control arms. Assume that 25 percent of patients who undergo the treatment but who are not improving fail to return for follow-up evaluation (perhaps due to treatment side effects) versus 5 percent among nonimproving control subjects. When the analysis focuses only on those with follow-up evaluations, this ineffective intervention will appear effective (67 percent remission rate versus 53 percent for controls). The point of the illustration is not that a study with dropouts is invalid, but rather, that an improper analysis (in this case, among completers only) in the face of differential dropout rates that are related to the clinical course can produce a biased result.

If outcome data are not obtained from patients who drop out from treatment, outcome data from those participants will be missing. It is critical to recognize that dropout from treatment does not necessarily mean that outcome data "must" be missing. With aggressive and systematic follow-up procedures, outcome data can still be obtained from many subjects who discontinue treatment. This was demonstrated in studies by Schnurr and colleagues (2003, 2007) where outcomes were successfully measured in a high proportion of participants who discontinued treatment. The committee viewed missing outcome data partly as a result of choices made in study

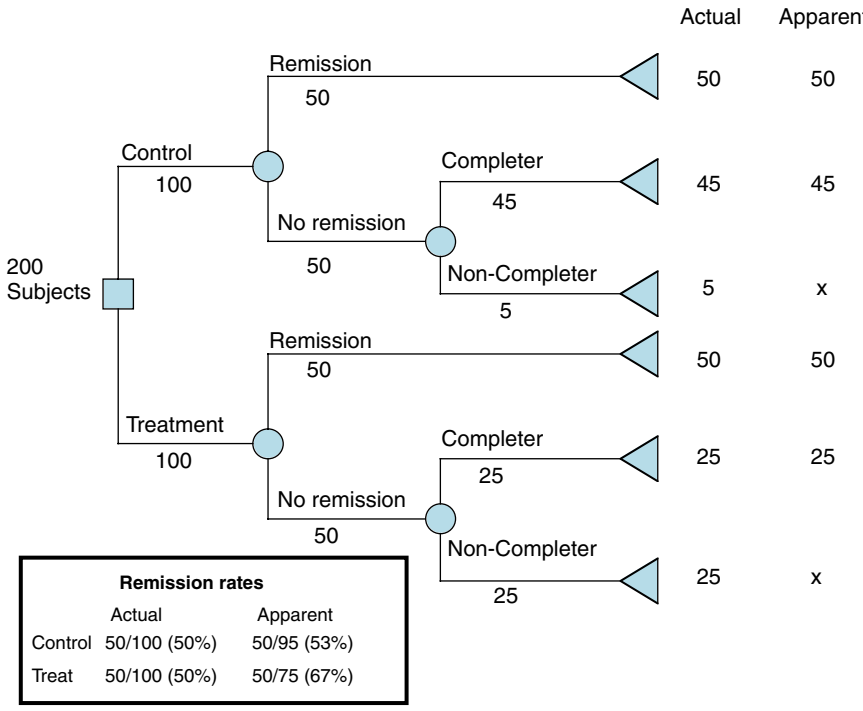

FIGURE 5-1 Potential impact of attrition: illustrating the importance of proper analysis.

design and not an inevitable result of the condition, treatment, or behavior. Unfortunately, few of the studies examined by the committee obtained outcome information after a patient stopped treatment or during post-treatment follow-up. Because a very high percentage of patients—typically 20 to 50 percent—typically dropped out of these studies, large fractions of outcome data were missing.

Over the past three decades, analytic approaches to handling missing data have matured, with multiple imputation and mixed-model repeated measurement (MMRM) and similar approaches being implemented in standard software and commonly used by biostatisticians in many fields (Little and Rubin, 2002; Molenberghs and Kenward, 2007). Unfortunately, the most common way missing data were handled in the literature reviewed was to use the last recorded outcome as the final outcome in a patient who dropped out—also known as the "last observation carried forward"

(LOCF) approach. As explained in detail in Appendix D, the LOCF approach has long been recognized as a poor method for handling missing data (in some cases introducing a conservative and other cases an anti-conservative bias, and always overstating precision), requiring that results based on LOCF analyses must be scrutinized very closely.

The committee notes that at least one major peer-reviewed journal, the *Journal of the American Medical Association,* requires that study authors provide flow diagrams of study participation, including loss to follow-up and reasons (JAMA, 2007).

Finding 1. The committee found that treatment of PTSD has not received the level of research activity needed to support conclusions about the potential benefits of treatment modalities. Although progress in scientific standards can be observed, and recent studies tend to provide more useful information than older studies, important limitations remain. There are very few large-scale, multi-site initiatives of the type that have been successfully applied to other psychiatric disorders. The studies conducted over the nearly three decades since *Diagnostic and Statistical Manual of Mental Disorders* (DSM) adoption of the PTSD definition do not form a cohesive body of evidence about what works and what does not. As described elsewhere in this report, studies have used a wide variety of outcome measures and lengths of treatment for the same treatment modality. Further, many studies lack basic characteristics of internal validity including suffering from high dropout rates handled with weak missing data analyses, and high differential dropout among treatment arms. Other important characteristics that the committee found lacking included follow-up of all patients admitted to the trials, attention to conflict of interest, assessor independence, and length of follow-up. Although experts in the field (Foa and Meadows, 1997; Harvey et al., 2003) have called for setting research standards that would strengthen methodologic quality and internal validity, more work is needed.

Recommendation 1. The committee recommends that VA and other funders of PTSD research take steps to identify and require investigators to use methods that will improve the internal validity of the research, with particular attention to standardization of treatment and outcome measures, follow-up of individuals dropping out of clinical trials, and handling of missing data.

Investigator Independence

The psychotherapy studies were often conducted by the individuals who developed the techniques, and some did not include blind or independent

assessment of outcomes. The committee also was concerned about the possibility of publication bias in this domain, especially the effect of industry sponsorship of the majority of the drug studies.

Finding 2. The committee found that the majority of drug studies were funded by pharmaceutical manufacturers. This is an issue that has received much attention in recent years from the academic research community, government agencies, patient communities, and the editors of major biomedical journals. The committee also found that many of the psychotherapy studies were conducted by individuals who developed the techniques or their close collaborators. It is important to know whether these treatments would show the same effect if implemented in other settings, requiring the confirmation and replication of these research results by other investigators.

Recommendation 2. The committee recommends that VA and other funders of PTSD treatment research seek ways to give opportunities to a broad and diverse group of investigators to ensure that studies are conducted by individuals and in settings without potential financial or intellectual conflicts of interest.[1]

Special Veteran Populations

PTSD Comorbid with Traumatic Brain Injury (TBI)

A high percentage of returning soldiers with PTSD also have sustained concussive TBI (Seal et al., 2007). Moreover, the diagnosis of either condition may be complicated by the number of symptoms that are identical for PTSD and the chronic postconcussion syndrome. These overlapping symptoms include noise sensitivity, fatigue, anxiety, insomnia, poor concentration, poor memory, irritability and anger, and depression. PTSD patients with concussive TBI may have more prominent postconcussive symptoms (e.g., problems with concentration, dizziness, fatigue, headaches, and visual disturbances), suggesting that PTSD can exacerbate cognitive and other symptoms in TBI (Lezak et al., 2004).

Psychological treatment of patients with TBI and PTSD may be complicated by cognitive impairments due to concussive TBI. Such impairments can interfere with a patient's abilities to focus attention and deflect distractions, grasp spoken statements fully, and communicate easily, all of which

[1]Some ways to do this include: developing designs with an eye to balancing investigator interests and potential biases, and organizing studies in a way that ensures independent data collection and analysis (e.g., forming a coordinating center for all studies).

are necessary for cognitive behavior therapies to be effective. The committee did not identify any PTSD treatment research that recognizes these potential factors in veterans currently returning from Iraq and Afghanistan.

PTSD Comorbid with Major Depression and Substance Abuse

The committee noted that major depression, other anxiety disorders, and substance abuse are common among patients with PTSD, and yet some research systematically excludes such patients from the clinical trials. The result is that the literature is almost completely uninformative about how best to treat the substantial proportion of veterans who have an important comorbid condition.

PTSD in Special Populations

The committee noted that the literature also is almost entirely silent on the efficacy of treatment in discrete ethnic and cultural minorities, and on related issues of potential subgroup differences in their acceptance of treatment modalities and tolerability of distinct types of medications. These concerns are also pertinent to subgroup differences by sex, degree and types of physical impairment, socioeconomic status, education, age, and by veteran cohorts with diverse trauma experiences.

Finding 3. The committee found that the available research leaves significant gaps in assessing the efficacy of interventions in important subpopulations of veterans with PTSD, especially those with traumatic brain injury, major depression, other anxiety disorders, or substance abuse, as well as ethnic and cultural minorities, women, and older individuals.

Recommendation 3. The committee recommends that VA assist clinicians and researchers in identifying the most important subpopulations of veterans with PTSD and designing specific research studies of interventions tailored to these subpopulations.

Applicability to VA and Veteran Populations

The committee found a lack of information elucidating how the great heterogeneity in triggering stressors (e.g., combat-related versus civilian, frequent and continuous exposure versus one-time exposure) may affect the effectiveness of different treatments. For example, is PTSD in male veterans different from PTSD in civilian female rape survivors?—just to name two of the major trauma types in the literature. The committee examined

the question of treatment efficacy in PTSD in general populations, not just PTSD in veterans, but found it striking that so few of the studies were conducted in populations of veterans. The committee understands the position that effects of PTSD treatment may be similar in all populations, but it is not clear from the available evidence that findings about victims of a natural disaster will apply equally well to veterans. Although the literature includes some suggestion that there may be differences in how the civilian and veteran populations respond to treatment (for example, meta-analyses that have found higher effect sizes in civilians compared to veterans), there is no conclusive evidence that shows that PTSD in the two populations is different, nor that it is the same. The committee also notes that the populations of veterans with PTSD now returning from Iraq and Afghanistan might be different enough from U.S. veterans from previous wars such that studies of the latter populations (mostly dating back to the Vietnam conflict) may be minimally informative about treatment efficacy in veterans of the recent conflicts. Acknowledging the heterogeneity of trauma types associated with cases of PTSD, and the question of applicability of evidence regarding treatments for PTSD across different contexts, the current report considers the range of contexts, highlighting the evidence of applicability to the veteran population where it is possible to do so.

The studies reviewed by the committee required that eligibility be based on DSM PTSD criteria. (Most studies since 1980 have used this eligibility criterion.) Many recent studies also required a specified level of severity to exclude mild cases. Strictly speaking, a study's results are generalizable to the population that the sample "represents." Theoretical arguments or clinical experience might also be relevant to the applicability question. There is no *a priori* basis for limiting the potential applicability of findings on treatment of PTSD by sample characteristics such as trauma type, gender, or chronicity. If a body of evidence is judged to be inadequate for concluding that a treatment is either efficacious or inefficacious, it is also inadequate for concluding that it is applicable or inapplicable to populations of patients other than the population "represented" by the sample. Conflicting findings across studies that test a class of PTSD treatments are difficult to resolve. Results do not form a consistent pattern that might suggest that efficacy depends on type of trauma, chronicity, or gender. However, there are some suggestions from the literature and the experience of clinicians that responsiveness to specific treatments varies among PTSD populations possibly as a function of chronicity, sex, and other factors.

Generalizability

Because the number of well-conducted studies in veterans was small, the committee was concerned about generalizing the evidence to veterans

overall, and to the newest veterans from the conflicts in Iraq and Afghanistan in particular. The committee understands the argument that treatments proven effective on any group of individuals with PTSD should generalize to all who share the diagnosis, but there is no evidence to support this hypothesis or its converse. The committee noted that type of trauma, recurrence or frequency of trauma (as in current combat situations), gender, ethnicity and cultural differences, comorbidities (especially substance abuse and depression), presence of TBI, and compensation issues are likely to be highly relevant to populations of veterans, and observed that the literature is (to varying degrees) uninformative on many of these considerations.

> Finding 4. The committee found that research on treatment of PTSD in U.S. veterans is inadequate to answer questions about interventions, settings, and lengths of treatment that are applicable in this specific population. The committee recognizes that the successful conduct of research directly applicable to veterans will require close collaboration among funding agencies (Department of Defense, National Institute of Mental Health, National Institute of Alcohol Abuse and Alcoholism, National Institute of Drug Abuse), veterans groups, and clinical service settings. Specifically, veterans' groups could make considerable contributions to the design and conduct of high-quality research on the treatment of PTSD.

> **Recommendation 4. The committee recommends that Congress require and ensure that resources are available for VA and other relevant federal agencies to fund quality research on the treatment of PTSD in veteran populations and that all stakeholders are included in research plans.**

Selection of Interventions Appropriate for Study

In general the committee believes that studies should provide an evidence base for current practice patterns in addition to stimulating novel research. The committee observed discrepancies between research and clinical practice. For example, the committee understands that benzodiazepines are commonly used in patients with PTSD (APA, 2004; VA/DOD, 2004), but found virtually no directly applicable evidence on primary PTSD outcomes. Further, the committee understands that clinicians and investigators are divided on whether it would be useful or even ethical to conduct further research on benzodiazepines in patients with PTSD. As another example, the committee found that research conducted on some drugs or psychotherapies may not correspond to actual use of the therapies in clinical practice with respect to dosage regimen, length of treatment, or follow-up. There is little current incentive (or funding) for researchers to conduct studies on older

drugs (for example, psychopharmacologic agents available in generic form) or psychotherapies. Researchers and their funding sources tend to be more inspired by novelty, leading to a certain inertia about actual treatments in use that are not investigated empirically (Branscomb et al., 2001: 51). Some studies test head-to-head comparisons of interventions that clinicians find irrelevant to actual practice, especially for veterans. Finally, the population of veterans is heterogeneous, including older veterans with chronic PTSD and younger returning veterans; they also include women and members of various ethnic and racial groups. Little is known from systematic research on the potential response to various treatments or the acceptability of various treatment modalities across the groups identified. VA is in a unique position to help bring order and direction to the research enterprise regarding PTSD.

Finding 5. The committee found that studies of PTSD interventions have not systematically and comprehensively addressed the needs of veterans with respect to efficacy of treatment and the comparative effectiveness of treatments in clinical use.

Recommendation 5. The committee recommends that VA take an active leadership role in identifying research priorities for addressing the most important gaps in evidence in clinical efficacy and comparative effectiveness.[2] Potential areas for future research include:

- **Comparisons of psychotherapy (e.g., CBT) and medication**
- **Evaluation of the comparative effectiveness of individual and group formats for psychotherapy modalities**
- **Evaluations of the efficacy of combined psychotherapy and medication, compared with either alone, and compared with**

[2]The committee has noted with interest research on effectiveness in other areas of mental health. For example, the STAR*D (Sequenced Treatment Alternatives to Relieve Depression) study aimed to reproduce some real-life settings in allowing participants choice and offering alternatives when a course of treatment did not work, and used an outcome measure of "remission" meaning becoming symptom free. Another study brought to the committee's attention is the CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) Schizophrenia study, which compares newer atypical antipsychotics with each other and with conventional antipsychotics in regard to long-term effectiveness and tolerability, and also in identifying antipsychotics that work for patients who have not had success with that class of drugs. Finally, STEP-BD (Systematic Treatment Enhancement Program for Bipolar Disorder) is a long-term study of manic-depressive illness that studied treatment (both pharmacologic and psychosocial) of affected individuals on two "pathways"—one a naturalistic, best practices pathway that allowed patients and clinicians to choose the best course of treatment, and the other a "randomized care pathway" that involved patients in multi-site randomized controlled trials. Program participation lasted for up to 5 years to facilitate adequate follow-up.

control conditions.[3] Combined treatment could be tested within study designs like those that have been applied in large studies for other psychiatric conditions.

The Evidence on SSRI Efficacy

A final issue identified in the process of assessing the evidence pertains to what may be perceived as a surprising divergence between the committee's conclusion in regard to the body of evidence on SSRIs and FDA's approval of the SSRIs sertraline and paroxetine (in 1999 and 2001, respectively), previously approved for treating depression, for treating PTSD. FDA's determination was of a regulatory nature, and its focus was risk-benefit analysis. The committee considered the published RCTs available on SSRIs and made its conclusion on the basis of what emerged as a very mixed picture on efficacy. Further, at present, FDA generally does not reconsider its regulatory decisions except in cases where new safety data emerges. Reviews of the empirical evidence such as the one contained in this report take into consideration studies and data emerging over years and even decades.

ISSUES DEFINED IN THE STATEMENT OF TASK

In addition to assessing the quality and direction of the empirical evidence on various PTSD treatment modalities, the committee discussed the following issues, as requested by the sponsor:

- What are the goals of PTSD treatment?
  - What is the definition of "recovery"?
  - For what proportion of patients is recovery possible?
  - Besides recovery, what other outcomes would benefit patients?
- Does evidence support the value of early intervention?
- How long should treatment continue?
  - What is the impact of a hiatus in treatment?
  - What is the impact of periodic reexamination for asymptomatic patients?

[3]The committee found one study that does this in the work of van der Kolk and colleagues, 2007.

Recovery

The committee reviewed the literature on PTSD treatment for definitions of the term *recovery*, finding that the term is used inconsistently and is not clinically meaningful in the same way that it is in other clinical domains (e.g., as in acute illnesses). PTSD can be chronic and can also remit and relapse over a patient's lifetime (Wilson et al., 2001). No longer meeting PTSD diagnostic criteria is a common way to define recovery when inventory or questionnaire scores fall below an important threshold in the condition's trajectory. However, the studies that constitute the evidence base on the efficacy of treatment modalities for PTSD use a variety of terms to denote a change for the better in PTSD status: improvement (significant improvement, reliable improvement, improvement in functioning), remission, therapeutic success, loss of PTSD diagnosis, symptom reduction or improvement, trauma recovery, good or high end-state functioning, treatment response, clinically meaningful change, and so on, while the term *recovery* is used in only three studies (Davidson et al., 1990; Gersons et al., 2000; McDonagh et al., 2005). In most cases, these terms simply describe the primary outcomes chosen in the individual study leading to a positive, negative, or neutral conclusion regarding efficacy. See Box 5-1 for three definitions of recovery (two pertain to mental health recovery in general, and one relates to PTSD specifically).

The studies the committee reviewed employed a range of specific definitions for "recovery" terms. These definitions may be divided into three categories: (1) absence or loss of PTSD diagnosis, (2) multiple domain measures used to determine good or high end-state functioning, and (3) a clinically meaningful threshold for "symptom improvement." Not all studies seeking to show symptom improvement also reported PTSD diagnostic status, but almost all studies reporting loss of diagnosis did so by showing changes on PTSD symptom measures such as the Clinician administered PTSD Scale (CAPS), the Structured Interview for PTSD (SI-PTSD), and the Structured Clinical Interview for DSM-IV (SCID).

In the first category, studies that had as an outcome absence of or loss of PTSD diagnosis, defined recovery by a decrease in percentage or two standard deviations (SDs) improvement in CAPS score, by decrease or disappearance of a number of symptoms or an entire symptom cluster,[4] by change in SI-PTSD scores, or by loss of the diagnosis using DSM criteria. The *X* percent or 2 SDs decrease are appropriate criteria for loss of diagnosis in many cases. However, a patient with a high score on a measure (>2 SDs above the mean for the PTSD population on which the measure

[4]The DSM-IV definition of PTSD includes three symptom clusters: reexperiencing, avoidance, and hyperarousal.

BOX 5-1
Some Definitions of Recovery

In its final report, the President's New Freedom Commission on Mental Health (PNFCMH) defined recovery (not specific to PTSD, but referring to mental health in general) as

> *the process in which people are able to live, work, learn, and participate fully in their communities. For some individuals, recovery is the ability to live a fulfilling and productive life despite a disability. For others, recovery implies the reduction or complete remission of symptoms. Science has shown that having hope plays an integral role in an individual's recovery. (PNFCMH, 2003, 5)*

From the National Consensus Conference on Mental Health Recovery and Mental Health Systems Transformation (December 2004):

> *Mental health recovery is a journey of healing and transformation enabling a person with a mental health problem to live a meaningful life in a community of his or her choice while striving to achieve his or her full potential.*

This definition is noteworthy because it includes an elaboration of 10 fundamental components of recovery that illustrate the meaning of recovery for the individual. These components or dimensions include: self direction, individualized and person-centered, empowerment, holistic, nonlinear, strengths-based, peer support, respect, responsibility, and hope (Department of Health and Human Services [DHHS], Substance Abuse and Mental Health Services Administration, and Center for Mental Health Services, 2004).

The recent Institute of Medicine (IOM) report, *PTSD Compensation and Military Service* stated the following:

> *Recovery can be defined in various ways. In the context of this report, the committee considered recovery to be a reduction in the frequency and intensity of symptoms accompanied by an increase in social and occupational function. The research reviewed and cited in this section often used return to work as the specific measure of recovery. (IOM, 2007)*

was normed, or ≥86th percentile) may report significant improvement in a post-treatment score drop of 2 SDs or 50 percent (to the 36th percentile, for example) while still troubled by PTSD symptoms, albeit in a milder form. Should many patients in a study have a severe form of the condition, these criteria would mask their continuing dysfunction and invalidate a positive conclusion based on these criteria, meaning, in these cases, the statistical

BOX 5-2
Examples of Domain Measures

PTSD specific:

- CAPS (total score lower than 19 points)
- SI-PTSD (at least 50% decrease)
- PTSD Symptom Scale (PSS), both interviewer and self-report
- Modified PSS-I (less than 20)
- Posttraumatic Diagnostic Scale (PDS)
- Distressing Events Questionnaire (score of 25 or less)
- Davidson Trauma Scale (score less than 18)

criteria do not provide accurate documentation of absence or loss of PTSD diagnosis.

Studies in the second category, those with the outcome of good or high end-state functioning, defined recovery by specific levels on multiple domain measures, including one or more PTSD specific measures (such as CAPS; other examples from the literature reviewed by the committee are provided below) in combination with specific levels on other types of measures of depression (Hamilton Rating Scale for Depression and Beck Depression Inventory), anxiety scales (Hamilton Rating Scale for Anxiety, Beck Anxiety Inventory, and State-Trait Anxiety Inventory), and multidimensional measures (Clinical Global Impressions [CGI] Scale and Symptom Checklist-90). See Box 5-2 for examples of domain measures.

The third category of studies, those that sought to identify a clinically meaningful threshold for symptom improvement, defined recovery as a change in CAPS (≥10 point decrease, ≥30 percent decrease, or two standard deviations below pretreatment level); a change in Impact of Events Scale (IES), Short PTSD Rating Interview (SPRINT), or SI-PTSD scores; change in Clinical Global Impressions rating (to 1, very much improved, or 2, much improved); change in Davidson Trauma Scale score (≤17); or significant improvement in the Mississippi Scale for Combat-Related PTSD (M-PTSD) score.

Finding 6. The committee found no generally accepted and used definition for recovery in PTSD. Also, many studies used measures of questionable validity and reliability instead of validated, high-quality

measures such as CAPS (Foa and Meadows, 1997). The committee places the lack of agreement about recovery in context of a more general concern about identifying appropriate outcomes for PTSD research.

Recommendation 6. The committee recommends that clinicians and researchers work toward common outcome measures in three general domains that relate to recovery: loss of PTSD (DSM) diagnosis, PTSD symptom improvement, and end state functioning. The committee further recommends the following three principles be considered in the selection of outcome measures:

- **validity in research;**
- **convergence on a core of common outcomes for the purpose of comparability; and**
- **usefulness to clinicians to assess patients over time as symptoms and function change.**

The committee recommends that VA assume a leadership and convening role and work with other relevant federal agencies in developing these common approaches.

Early Intervention

The statement of task asks "Does evidence support the value of early intervention?" (Statement of Task IV-B, see Summary, Box S-1). *Early intervention* may refer either to a time before the onset of PTSD or early in the course of PTSD. The committee assumes the latter represents VA's intent in this question, because intervention before the diagnosis of PTSD is outside the committee's understanding of its charge. In this context, the goal of early intervention is reducing the chronicity of PTSD through early treatment.

In its review of the literature, including clinical guidelines and recent publications, the committee found that all or most mentions of "early intervention" refer to antecedent events on the disorder continuum, before a PTSD diagnosis can be made, and generally these refer to treatment modalities such as crisis intervention and psychological debriefing (Harvey et al., 2003; Hembree and Foa, 2003). The committee focused on secondary prevention—reducing the prevalence of PTSD by shortening the duration of the disorder and reducing chronicity, and tertiary prevention—reducing the symptom burden and disability associated with the disorder.

The data abstracted from the literature reviewed by the committee are informative about one data element relating to the timing of intervention, namely, time since exposure to the trauma. In most studies the length of time a participant had been diagnosed with PTSD before entering the

study is not provided. Sometimes a study specifically used duration of diagnosis as part of the inclusion/exclusion criteria (e.g., including chronic PTSD patients only). In those cases, only the minimum or maximum duration required for study inclusion is provided, but not the average duration. Often, the time since exposure to the trauma is provided and/or the number of different traumas they have been exposed to. It cannot be assumed that PTSD developed soon following the trauma, so time since trauma is not informative regarding how long patients have been diagnosed with PTSD. Three of the psychotherapy studies reported durations of illness with a range from 7.8 to 11.6 years (Devilly and Spence, 1999; Paunovic and Ost, 2001; Taylor et al., 2003) and four pharmacotherapy studies with a range of 11 to 30 years (Brady et al., 2000; Davis et al., 2004; Friedman et al., 2007; Rapaport et al., 2002). Time since exposure varied greatly by study, ranging from 4 months to 21.7 years in the psychotherapy studies,[5] and 6 months to 25 years in the pharmacotherapy studies.

Finding 7. The committee was unable to reach a conclusion on the value of intervention early in the course of PTSD based on the treatment literature it reviewed.

Recommendation 7. The committee recommends that VA and other government agencies promote and support specific research on early intervention (i.e., reducing chronicity) in PTSD. The committee further recommends that future research specify both time since trauma exposure and duration of PTSD diagnosis, and that interventions be tested for efficacy at specific clinically meaningful intervals, as interventions might be expected to vary in effectiveness related to time since exposure and duration of diagnosis.

Length of Treatment

The committee divided the question of length of treatment into three phases: (1) for a given treatment does treatment of any length have efficacy; (2) if so, how does length of the treatment affect outcome (requiring comparative trials); and (3) what are the long-term (greater than 1 year) effects of treatment at follow-up? The literature reviewed by the committee was limited in the information it provided about optimal length of PTSD treatment. Obviously, there would be differences between medication and psychotherapy, but none of the reviewed studies considered length of treatment as a dependent variable in their research design. Efficacy associated

[5]Only includes numbers actually reported in the studies. If exposure type was given (e.g., Vietnam) but the actual months or years were not provided, it is not included here.

with a drug cannot be expected to be maintained after treatment stops, as in other chronic psychiatric and physical conditions. In major depression, the bulk of which is recurrent, there is evidence supporting long maintenance of pharmacotherapy to prevent recurrence. The committee reviewed four maintenance studies (four SSRIs and one anticonvulsant), but they had methodological problems (results discussed in Chapter 3). These studies offer the only data the committee identified as potentially relevant to the question of hiatus in treatment.

The impact of periodic reexamination for asymptomatic patients is also difficult to ascertain from the literature reviewed by the committee. Although a number of pharmacotherapy and psychotherapy studies conducted follow-up after the completion of treatment, most of the studies did not assess patients' symptom status specifically, but rather, identified scores on various measures, such as measures of PTSD, depression, and anxiety.

Of the ones that assessed symptom status, they generally measured improvement in symptoms on the Impact of Events Scale (much improved, very much improved, etc.), but none found patients to be completely symptom free. Therefore, the committee is unable to draw a conclusion about the impact of reexamining patients who no longer show symptoms of PTSD.

Length of treatment in the pharmacotherapy studies reviewed by the committee ranged in length from 5 to 6 weeks (5 studies) to 5 to 7 months (4 studies). The majority of the studies provided treatment for between 8 to 16 weeks (28 studies). Length of treatment in the psychotherapy studies varied even more, from a single treatment session to multiple sessions conducted over a period of many months (5–7), and in one case, for up to 1 year. Some studies reported a mean number of sessions when the "dose" was flexible (therapy was concluded when the patient and therapist agreed the patient had improved); others described fixed numbers of sessions administered. Approximately 15 studies provided treatment for less than 8 weeks, about 22 studies (the majority) treated subjects for 8–16 weeks, and another 8 studies provided treatment for longer than 16 weeks (including two that reported a 16–20 week range). Several studies were unclear about the length of treatment and reported only the number of sessions administered.

Compounding the difficulty in assessing the effect of length of treatment, there was also great heterogeneity of the studies in terms of the modalities used, dosage regimens for drugs, and standardization of psychotherapies (despite manualization in some cases). Generally short length of follow-up (in no studies was follow-up longer than 1 year, many did not report follow-up) also made it difficult for the committee to assess the effect of length of treatment on PTSD, which is known for its variable course, with or without treatment. The committee was unable to find a correlation between length of treatment and outcome across the studies meeting

inclusion criteria. The committee also notes that there may be a need for the development and evaluation of efficient adaptations of standard psychotherapies for PTSD, such as prolonged exposure. A course of treatment, delivered in a shorter period of time (less than the typical 10–12 weeks), in more frequent and fewer sessions, might have the added benefit of increasing the rate of treatment completion.

Finding 8. The evidence base contained studies that varied greatly on length of treatment and other variables, therefore, the committee was unable to draw conclusions regarding optimal length of treatment with psychopharmacology or psychotherapy.

Recommendation 8. The committee recommends that VA and other funders call for research on the optimal duration of various treatments. Trials of comparative effectiveness of different treatment lengths for those treatments found efficacious should follow. Finally, studies with adequate long-term (i.e., greater than 1 year) follow-up should be conducted on treatments of any length found to be efficacious.

Length of Follow-Up

Ideally, improvements during treatment endure long after treatment is complete. Evaluation of treatment effectiveness should include follow-up over a sufficient period to determine whether improvement is maintained, continued, or declines. Treatments for which improvements are not maintained provide short-term relief but may have long-term consequences as symptoms recur. Patients may be reluctant to try again, or may remain dependent on the treatment, which may be impractical or costly. When improvement is maintained or continues after treatment concludes, one can infer that these patients have acquired permanent positive changes that enable them to function more effectively or comfortably independent of treatment.

The literature examined by the committee was limited in providing long-term follow-up. The committee understands that follow-up beyond treatment is uncommon in drug studies aimed at addressing efficacy, regardless of clinical condition, but nonetheless observed that only 11 of 36 drug studies followed patients beyond treatment cessation, and none longer than 6 months. Thus, in general, the committee could not address what occurs when medications are discontinued. The evidence on longer-term follow-up is somewhat more extensive for psychotherapy. Of 52 psychotherapy studies, 43 reported follow-up data: 14 for 3 months or less, 18 for 6 to 9 months, 6 for 12 months, and 5 for 15 or more months. The evidence becomes scant, however, for effectiveness beyond 15 months, with the

longest follow-up 2 years post-treatment in studies examined by the committee. Many of these studies reassessed their subjects two or three times after treatment concluded.

CONCLUDING OBSERVATIONS

In this report the committee sought to describe the evidence regarding the efficacy of available treatment modalities for PTSD, identify some of the major issues in the field, and make recommendations to help guide further research in PTD treatment. The committee's findings, conclusions, and recommendations about the evidence for the treatment modalities reviewed in this report are not clinical practice guidelines. The committee does not intend to imply that, for example, exposure therapy is the only treatment that should be used in treating individuals with PTSD. The committee recognizes that the transparent presentation and assessment of evidence is just one part of the larger picture of PTSD treatment that includes many other factors. Further, assessing the scientific evidence may reveal areas of uncertainty. The next step in the process toward clinical decisionmaking is developing recommendations for clinical practice—a step the committee was not asked to, and did not, take. Such recommendations must propose strategies in the face of scientific uncertainty that are informed by clinician and patient preferences, access, safety, cost, alternatives, local practice patterns, medicolegal issues, ethical concerns, and other factors.

The committee applied contemporary standards to evaluate research, including research dating back to 1980 when PTSD was first defined. The principal finding of the committee is that the scientific evidence on treatment modalities for PTSD does not reach the level of certainty that would be desired for such a common and serious condition among veterans. For some modalities, for example, novel antipsychotic drugs and SSRIs, the committee debated whether to characterize the body of evidence as "suggestive" or "inadequate." It is important to emphasize that in the larger picture of PTSD treatment, had the debate ended with "suggestive" conclusions (rather than the "inadequate" conclusions the committee finally reached), the core message that better-quality research is needed would not have been rendered less urgent in consequence. The committee reached a strong consensus that additional high-quality research is essential *for every treatment modality*. This extends equally to the one treatment modality—exposure therapies—for which the committee found the evidence to be the strongest. As outlined in the recommendations above, better understanding of the most important and active components of exposure therapy, determining optimal administration and length of treatment, attention to principal subpopulations, and determining whether group therapies can be made as

effective present a challenging and urgent agenda for researchers and clinicians in the field.

The committee views its more general findings and recommendations regarding further research to be as important as its conclusions regarding the evidence supporting treatment modalities. The committee became aware of the formidable challenges that researchers face in conducting high-quality studies of efficacy and comparative effectiveness. The committee was able to identify studies that met the highest internationally accepted standards for randomized controlled trials (in assembling populations, administering treatment, measuring outcomes, and following up enrolled subjects), showing that such studies are possible even for such a difficult clinical condition as PTSD. As outlined in the committee's recommendations in this chapter, setting a high standard for research on PTSD and delivering on it will require close collaboration between VA and other government agencies, researchers, clinicians, and patient groups. Thus, the committee's recommendations are its suggestions for setting a framework for the future that can more successfully address the critical needs of veterans who return to civilian life with the diagnosis of PTSD.

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Appendix A

PTSD Psychological Interventions

I. TRAUMA-FOCUSED THERAPY

Trauma-focused therapies are a general class of therapies, not a specific intervention. They may be administered as group or individual therapy. They encourage clients to explore traumatic material in depth, gaining mastery over traumatic memories and taking control of their own lives. This class of therapies includes techniques from various therapeutic approaches, including cognitive-behavioral and psychodynamic (Friedman, 2003).

II. SUPPORTIVE THERAPY

Supportive therapy refers to a general class of therapies, rather than to a specific intervention. Unlike trauma-focused therapy, supportive therapy does not encourage exploration of traumatic material, instead promoting problem solving and adaptive coping in the present "here and now" context (Friedman, 2003). Supportive therapy can be delivered in individual or group therapy formats, which are intended to maintain interpersonal comfort and orient members toward coping (Foa et al., 2000).

III. COGNITIVE-BEHAVIORAL THERAPY (CBT) COMPONENTS

CBT is administered either in the group or individual context. It is generally short-term, lasting 8–12 sessions, meeting once or twice weekly. CBT utilizes principles of learning and conditioning to treat disorders and includes components from both behavioral and cognitive therapy. CBT components,

which may be used in the treatment of posttraumatic stress disorder (PTSD) either alone as "types" of CBT or used in combination include exposure, cognitive restructuring, various coping skills or anxiety management, and psychoeducation (Foa et al., 2000; Friedman, 2003, Harvey et al., 2003).

Exposure

Exposure is a treatment that involves confrontation with frightening stimuli and is continued until anxiety is reduced. Types of exposure include *imaginal exposure,* which involves exposure to traumatic event through mental imagery, either memory constructed through client's own narrative or scene presented by therapist based on provided information (Foa et al., 2000), and *in vivo*, where a client confronts the actual scene or similar events in life. Most salient in this type of exposure is the "correction of erroneous probability estimates of danger and habituation of fearful responses to trauma-relevant stimuli" (Foa et al., 2000).

In exposure therapy, the client and clinician may create a "fear hierarchy," rating feared situations in order of anxiety response; clients may be exposed to the *most* distressing situation or trigger (flooding) or *moderately* anxiety-provoking situations first (Foa et al., 2000). Anxiety management techniques are usually taught (e.g., relaxation, psychoeducation), but more time and attention are given to exposure proper (Foa et al., 2000). The client is exposed to trauma-related stimuli (imaginal or in vivo) with interruptions during which the client reports his or her anxiety level using Subjective Units of Distress Scale (SUDS) (10 [no distress] to 100 [most fear]) (Friedman, 2003). The aim is to extinguish the conditioned emotional response to traumatic stimuli (learn that nothing "bad" will happen in traumatic events), which eventually reduces or eliminates avoidance of feared situations. Exposure therapy has received the strongest evidence for PTSD, and clinical practice guidelines recommend it as the first line of treatment unless reasons exist for ruling it out (e.g., patients who were perpetrators of harm) (Foa et al., 2000).

Cognitive Restructuring

Cognitive therapy (CT) was originally developed by Aaron Beck in 1976 to treat depression, and subsequently developed as a treatment for anxiety (Foa et al., 2000). Beck's (1976) theory holds that it is the *interpretation* of the event, rather than the event itself, that determines an individual's mood; therefore, overly negative interpretations lead to negative mood states. CT uses *cognitive restructuring* techniques aimed at facilitating relearning thoughts and beliefs generated from a traumatic event and increasing awareness of dysfunctional thoughts contributing to anxiety response in

inappropriate situations. CT sessions help individuals identify automatic thoughts related to trauma (e.g., I will never be normal again; I'm going to die) and correct or replace dysfunctional thoughts with more rational ones (e.g., I will get better, but it will take time; I *feel* scared, but I am safe). This often requires the clients to record their thoughts and emotions during stressful or fearful situations between sessions (homework).

Various Coping Skills

Several coping skills training or anxiety management components are described below. Assertiveness training centers on replacing anxiety response to a reminder of the trauma with an assertive response, and may be delivered either in a group or individual context. This approach helps clients be assertive rather than passive or aggressive in discussing their traumas, asking for help and correcting misunderstandings (Foa et al., 2000). Assertiveness training is mainly viewed as a *component* of treatment for PTSD, rather than a stand-alone intervention (Foa et al., 2000).

Biofeedback is another anxiety management technique. Its aim is to facilitate client awareness of physiological responses, such as continuous feedback on heart rate or muscle tension. The goal is to help the client learn to control such processes.

Relaxation training also is an anxiety management technique. It involves teaching a client how to create a sense of relaxation, eventually in response to reminders of trauma, through diaphragmatic breathing, progressive muscle relaxation, imagery, and other techniques that induce muscle relaxation (and inhibit anxiety response). Relaxation training may induce anxiety in some patients (Foa et al., 2000).

Psychoeducation

Psychoeducation is either administered as a group or individual therapy. Practitioners aim to help clients understand the nature of PTSD and its effect on them. The approach is largely didactic (e.g., explaining origin and nature of emotional and physiological symptoms, normalizing experience, describing prognosis and appropriate expectations).

IV. COGNITIVE-BEHAVIORAL THERAPY APPROACHES[1]

CBT approaches utilize the components listed above either alone or as a "package" in specific clinical investigations or trials. Approaches themselves may be used in combination.

[1]Some may also be used independently or as a part of other interventions.

Prolonged Exposure

Consists primarily of exposure (imaginal and in vivo), combined with psychoeducation (Department of Health and Human Services et al., 2003).

Cognitive Processing Therapy (CPT)

CPT incorporates elements of cognitive restructuring and exposure and focuses on emotional *and* cognitive consequences of trauma (Foa et al., 2000). The client is asked to write a thorough account of traumatic experiences. The client reads the account to their therapist and at home (exposure component) and determines "stuck points," or moments during the trauma that are particularly difficult to accept and require more attention during cognitive therapy (Foa et al., 2000). CPT targets negative *beliefs* by confronting distorted traumatic memories, and attempts are made to change or modify the erroneous beliefs and subsequently inappropriate emotions.

Stress Inoculation Training (SIT)

SIT involves anxiety management techniques to handle anxiety that was conditioned at the time of the trauma and generalizes to many situations (Foa et al., 2000) and is designed to increase coping skills for current situations. SIT may include education, muscle relaxation training, breathing retraining, role playing, covert modeling, guided self-dialogue, and thought stopping (Foa et al., 2000).

Systematic Desensitization

This is a form of exposure typically involving exposure in vivo and/or imaginal exposure *and* relaxation training (Foa et al., 2000). The approach also includes anxiety management techniques, namely relaxation, aimed at disassociating fear and anxiety from trauma memories through behavioral interventions. Systematic desensitization stems from theory of conditioned fear and operant avoidance of feared stimuli (Foa et al., 2000). Client and clinician often create a "fear hierarchy," rating feared situations in order of anxiety response, then exposure begins with *least* fear-inducing situation (e.g., seeing picture of a spider) and progress to *most* feared situation (e.g., spider crawling up arm). The client is exposed to trauma-related stimuli with interruptions during which relaxation techniques are practiced (client reports anxiety level during interruption using SUDS rating). *Habituation* occurs through repeated presentation of trauma-related cues paired with relaxation. Evidence suggests that relaxation during exposure does not

enhance treatment effectiveness, so exposure alone has gained more relative support than systematic desensitization (Foa et al., 2000).

V. EYE MOVEMENT DESENSITIZATION AND REPROCESSING (EMDR)

As originally designed, EMDR includes saccadic eye movements (quick, jumping from one point of fixation to another) believed to reprogram brain function so emotional impact of trauma can be resolved (Friedman, 2003).[2] In the EMDR process, the client is instructed to imagine a traumatic memory and negative cognition and articulates an incompatible positive cognition (e.g., personal worth). The clinician asks the client to contemplate memory while focusing on rapid movement of clinicians' fingers. After 10–12 eye movements (back and forth) clinician asks client to rate strength of memory and his or her belief in *positive* cognition.

VI. PSYCHODYNAMIC THERAPY

Explores psychological meaning of a traumatic event (Foa et al., 2000). Focus is on bringing unconscious traumatic memories into conscious awareness so that the PTSD symptomatology (which are presumed to be a result of these unconscious processes and memories) can be reduced. Treatment is given in weekly sessions 50 minutes in length, traditionally lasting from 12 sessions to more than 7 years (Friedman, 2003). Few empirical investigations with randomized designs, controlled variables, and validated outcome measures have been reported; case reports constitute the bulk of the literature (Foa et al., 2000). Brief psychodynamic psychotherapy (BPP) is typically conducted in 12 sessions and up to 20, and focuses on the traumatic event itself (Foa et al., 2000; Friedman, 2003).

VII. HYPNOSIS

Hypnosis may be used as an adjunct to psychodynamic, cognitive-behavioral, or other therapies, and has been shown to significantly enhance their efficacy for many clinical conditions; however, there is a lack of quality evidence on use of hypnosis with PTSD patients. Hypnosis requires professional training (Foa et al., 2000).

[2]There is some controversy as to whether the eye movements or the cognitive processing of the traumatic event account for effectiveness of EMDR.

VIII. MARITAL AND FAMILY THERAPIES

Marital and family therapy is often used in combination with other therapies (Foa et al., 2000; Friedman, 2003). These approaches focus on symptom relief through increasing help and understanding in the family unit and fostering communication and support, or by treating marital or family disruption (Foa et al., 2000). Marital and family therapy approaches are typically time-limited, problem-focused interventions with courses of treatment varying depending on format of therapy (Foa et al., 2000).

IX. PEER COUNSELING

Peer counseling is not a psychotherapy, but rather a supportive group approach. Voluntary group members convene, without an authority figure or expert, to give to and receive assistance from one another through honest disclosure and response (Friedman, 2003).

X. PSYCHOSOCIAL REHABILITATION

Psychosocial rehabilitation is currently suggested only as an adjunct to other forms of treating PTSD, since it is not typically trauma focused (Foa et al., 2000). Techniques are effective, but none listed here have been studied with PTSD patients using randomized, controlled trials (Foa et al., 2000). Techniques include health education and psychoeducational techniques, self-care and independent-living skills training, supported housing, family skills training, social skills training, vocational rehabilitation, and case management.

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Appendix B

Search Strategy

Search 1—Meta-analyses or reviews
((Anxiety Disorders) OR PTSD) AND Veterans AND Drug therapies AND (Meta-analyses OR Reviews)

Search 2—Meta-analyses or reviews
(((Anxiety Disorders) OR PTSD) AND Veterans AND Psychotherapies AND (Meta-analyses OR Reviews))

Search 3—Clinical trials or epidemiological studies
((Anxiety Disorders) OR PTSD) AND Veterans AND Drug therapies AND (Clinical trials OR Epidemiological Studies)

Search 4—Clinical trials or epidemiological studies
((Anxiety Disorders) OR PTSD) AND Veterans AND Psychotherapies AND (Clinical trials OR Epidemiological Studies)

Search 5—Studies other than meta-analyses, reviews, clinical trials or epidemiological studies
(((Anxiety Disorders) OR PTSD) AND Veterans AND Drug therapies) NOT (Results from Search 1 OR Search 3)

Search 6—Studies other than meta-analyses, reviews, clinical trials or epidemiological studies
(((Anxiety Disorders) OR PTSD) AND Veterans AND Psychotherapies) NOT (Results from Search 2 OR Search 4)

Search 7—Treatment outcomes, prognosis, disease progression or recovery
((Anxiety Disorders) OR PTSD) AND Veterans AND (Treatment Outcomes)

DETAILED DESCRIPTION OF EACH SET EMPLOYED IN THE SEARCHES OUTLINED ABOVE

All databases were searched via the OVID database gateway. OVID command-line syntax:

- Exp [explode] – automatically includes all narrower subject heading from the thesaurus or controlled vocabulary for any given database
- Forward slash [/] – forces OVID to search in the subject headings or controlled vocabulary
- Adj – adjacency or proximity operator
- Pt=publication type; ti=title; ab=abstract ; sh=subject heading ; fs=floating sub-heading ; dt=drug therapy sub-heading ; th=therapeutic interventions other than drug therapies, subheading

Anxiety Disorders and Traumatic Stress Disorders Set

(exp Anxiety Disorder?/ or (anxiety disorder? or post-traumatic stress or posttraumatic stress or PTSD).ti,ab. or combat experience/)) [NOTE: exploding (exp) Anxiety Disorders automatically includes all types of Traumatic Stress Disorders to include PTSD]

Veterans or Military Set

(veteran? or veterans, hospitals/ or military medicine/ or military psychiatry/ or military personnel/ or exp War/ OR World War I/ or World War II/ or Korean War/ or vietnam conflict/ or Gulf War/ OR (army or navy or air force or marines or soldier)
veterans/ or exp military phenomena/ or soldier/ or battle injury/)

Drug Therapies or Pharmacotherapies Set

(exp drug therapy/ or (drug therap$ or pharmacotherap$).ti,ab. or exp serotonin uptake inhibitors/ or exp serotonin agents/ or (selective serotonin reuptake inhibitors or SSRI?) OR exp Monoamine Oxidase Inhibitors/ OR MAOI? OR exp Antidepressive Agents, Tricyclic/ OR ((TCA? and antidepress$) or anti depress$) OR exp Stress Disorders, Traumatic/dt or exp

Anxiety Disorders/dt OR (exp stress disorders, traumatic/ and dt.fs.) OR (exp Anxiety Disorders/ and dt.fs.) OR exp adrenergic antagonists/ OR exp adrenergic uptake inhibitors/ OR Guanfacine/ OR guanfacine.ti,ab. OR exp anti-anxiety agents/ or exp antipsychotic agents/ OR exp Anticonvulsants/ OR exp Serotonin Reuptake Inhibitors/ or exp Tricyclic Antidepressant Drugs/ or Adrenergic Blocking Drugs/ or exp neuroleptic Drugs/ or exp Anticonvulsive Drugs/)

Psychotherapies Set

(exp psychotherapy/ or psychotherap$.ti,ab. OR exp Stress Disorders, Traumatic/th or exp Anxiety Disorders/th OR (exp stress disorders, traumatic/ and th.fs.) or (exp Anxiety Disorders/ and th.fs.) OR exp Behavior Therapy/ OR (cognit$ behav$ therapy or exposure therapy or cognitive processing therapy or «biofeedback and relaxation training» or systematic desensitization or assertiveness training or stress innoculation training) OR psychodynamic psychotherapy OR («eye movement desensitization and reprocessing» or EMDR) OR social rehabilitat$ therap$ OR exp psychotherapy, group/ OR family therapy/ or marital therapy/)

Reviews and Meta-Analyses Set

(systematic review$.ti,ab,sh,pt. OR systematic literature review$.ti,ab,sh. OR meta-analysis.pt,ti,ab,sh. or (meta-analy$ or metaanaly$).ti,ab,sh. OR ((methodol$ OR systematic$ or quantitativ$) adj3 (review$ or overview$ or survey$)).ti,ab,sh. OR (Medline or Embase or Index Medicus).ti,ab,sh. OR ((pool$ or combined or combining) adj (data or trials or studies or results)).ti,ab. OR review literature/ or review.pt,sh.)

Clinical Trials or Epidemiological Studies Set

((randomized controlled trial or controlled trial).pt. OR randomized controlled trials/ or controlled clinical trials/ OR random$.ti,ab. or Double-blind method/ or Random allocation/ OR single blind method/ OR ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)) OR clinical trial.pt. OR clinical trials/ OR (clinical adj trial$).ti,ab. OR placebos/ OR placebo$.ti,ab. OR research design/ OR Comparative Study/ or comparative stud$.ti,ab. OR exp evaluation studies/ or follow-up studies/ or follow up.ti,ab. or prospective studies/ OR (control$ or prospectiv$ or volunteer$).ti,ab.)

Prognosis, Recovery, Rehabilitation Set

(disease progression/ OR prognosis/ or disease-free survival/ or medical futility/ or exp treatment outcome/ or treatment failure/ OR (recovery or rehabilitat$).ti,ab. or rehabilitation/ OR "recovery (disorders)"/)

Appendix C

Measures Used in the Assessment of Posttraumatic Stress Disorder

Table begins on next page.

Measure	Description	Scales/Factors
Anxiety Disorders Interview Schedule-Revised (ADIS-R) (DiNardo and Barlow, 1988)	• Assesses anxiety and affective disorders • Structured diagnostic interview • Likert rating scales	
Clinician Administered PTSD Scale (CAPS) (Blake et al., 1990)	• Most widely used measure of PTSD (Weathers et al., 2001) • Assesses all DSM-IV PTSD symptoms, impact on functioning, response validity, lifetime diagnosis, and overall PTSD severity • Original version, based on DSM-III-R criteria: *CAPS-1* (current and lifetime diagnosis, symptoms over *past*, or *worst month since trauma*) *CAPS-2* (symptoms over *past week* for repeated assessments) • DSM-IV revision with user feedback incorporated: *CAPS-1* renamed *CAPS-DX* (diagnostic version) and *CAPS-2* renamed *CAPS-SX* (symptom status version) • Current version, *CAPS,* combined *CAPS-1* and *CAPS-2* • Structured interview • 45–60 minute administration by trained (para)professionals • 34 items (17 items on frequency, 17 items on intensity) • Dichotomous (diagnosis present/absent) and continuous assessment • Five-point Likert ratings of symptom severity (0–4) • Time frames for assessment include: *past week*, *month*, or *worst month since trauma* • Initially validated on combat veterans, subsequently applied in a wide variety of trauma populations including victims of rape, crime, motor vehicle accidents, incest, torture, and cancer (Weathers et al., 2001)	• Confirmatory factor analyses supported fit of two-factor structure (Buckley et al., 1998): • *Intrusion and avoidance, hyperarousal, and numbing* • Confirmatory factor analyses comparing solutions suggested an oblique 4-factor, first-order solution as the best fit to data (King et al., 1998): • *Reexperiencing, effortful avoidance, emotional numbing, hyperarousal*

Psychometric Properties	Scoring and Interpretation Guidelines
Sensitivity: 1.0 (Blanchard et al., 1986) *Specificity:* .91 (Blanchard et al., 1986) • Inconsistent findings from two studies, better statistics in combat veterans than community-based study (Keane et al., 2000)	
Sensitivity: >.8, often >.9 (Weathers et al., 2001) *Specificity:* >.8, often >.9 (Weathers et al., 2001) *Kappa:* >.7 (criterion: SCID; Weathers et al., 2001) *Internal consistency (alpha):* typically .8–.9 for three clusters and for entire syndrome (Weathers et al., 2001) *Test-retest reliability:* .9–.98 (Weathers et al., 1992) *Interrater reliability:* ≥.9 (continuous); comparable, up to 100% (diagnosis) (Weathers et al., 2001) • ≥.7 (typically .8–.9) correlations with self-report PTSD measures (Mississippi, Impact of Event Scale [IES], PTSD Checklist [PCL], Davidson Trauma Scale [DTS], Minnesota Multiphasic Personality Inventory [MMPI-2] Keane Scale, Structured Clinical Interview for PTSD [SCID-PTSD]) (for review: Weathers et al., 2001)	• Frequency scores: 0–68 • Intensity scores: 0–136 • Rating scales summed to create 9-point (0–8) severity score for each symptom • *Total Severity Score:* **0–19:** asymptomatic/few symptoms **20–39:** mild PTSD/subthreshold **40–59:** moderate PTSD/threshold **60–79:** severe PTSD symptoms **≥80:** extreme PTSD symptoms • Clinically significant change: ≥15 pt change in CAPS total severity score • *Symptom Endorsement Scoring Rules:* **F1/I2:** freq. ≥"1", inten. ≥2 **Rule of 2:** severity ≥2 **Rule of 3:** severity ≥3 **Rule of 4:** severity ≥4 • Diagnostic Rules "B" ≥1, "C" ≥3, "D" ≥2 TSEV65: total severity ≥65 • Nine diagnostic scoring rules yield different prevalence rates (research setting: 26–49%, clinical: 47–82%) (Weathers et al., 1999) • F1/I2 most lenient in clinical sample, second in research, clinician rating-based rules most stringent (Weathers et al., 1999) • Explicit reporting and use of several scoring rules recommended • Lenient rules recommended for screening purposes, while stringent rules appropriate for confirming diagnosis or creating case groups (Weathers et al., 1999)

continued

Measure	Description	Scales/Factors
Clinical Global Impression (CGI) (Guy, 1976)	• Assesses treatment response in psychiatric patients • 5-minute administration by trained rater or clinician • 3-item scale • Clinician rates severity of illness at time of assessment (severity of illness), how much the patient's illness has improved/worsened since baseline (global improvement) and compares patient's baseline condition with a ratio of current therapeutic benefit to severity of side effects (efficacy index) • Administered at initial assessment and at least once after treatment is initiated • Clinical Global Impression Improvement Scale (CGI-I) • Clinical Global Impression Severity Scale (CGI-S)	
Diagnostic Interview Schedule (DIS) (Robins et al., 1981)	• Assesses DSM III-R/IV symptomatology • Primarily used in community settings (Newman et al., 1996) • Semistructured interview • 15-minute administration by trained lay interviewer • Dichotomous (yes/no) symptom ratings • Does not assess symptom severity, can be used for diagnosis • Requires patient to associate each symptom with a specific traumatic event	• PTSD section
Davidson Trauma Scale (DTS) (Davidson et al., 1997)	• Assesses DSM-IV PTSD criteria (B–D) • Self-report questionnaire • 17 items, 5-point (1–4) Likert rating scales • <10 minute administration	• Principal components factor analysis yielded a 2-factor solution for general sample and a 6-factor solution with PTSD population (Davidson et al., 1997)

Psychometric Properties	Scoring and Interpretation Guidelines
	• **Item 1. Severity of Illness:** 7-point scale (1 = normal to 7 = extremely ill) • **Item 2. Global Improvement:** 7-point scale (1 = very much improved to 7 = very much worse) • **Item 3. Efficacy Index:** 4-point scale ("none" to "outweighs therapeutic effect")
Sensitivity: community .22; clinical .81–.89, .23–.89 *Specificity:* community .98, clinical .92–.94, .92–.98 (Kulka et al., 1991)	
Diagnostic accuracy: 83% *Internal consistency (alpha):* .99 (Davidson et al., 1997) *Test-retest reliability:* .73–.93 (Wildes, 2007) • Low to strong correlations with measures of similar constructs • Effect sizes equal to or greater than those found for IES, CAPS, and SI-PTSD (Davidson et al., 2002) • Strong association with SCID-DSM-III-R diagnosis (Wildes, 2007)	• Frequency: 0–68 • Severity: 0–68 • Total: 0–136 • *Diagnostic cutoff score*: 40 (Davidson et al., 1997)

continued

Measure	Description	Scales/Factors
Impact of Event Scale-Revised (IES-R) (Horowitz et al., 1979; Weiss and Marmar, 1997)	• Assesses 14/17 DSM-III-R and DSM-IV PTSD criteria (B–D) • Widely used PTSD-related scale across trauma populations (Newman et al., 1996) • Self-report questionnaire • 15 items, 4-point (0–5) Likert rating scales	• Intrusion, avoidance, hyperarousal • CFA
Los Angeles Symptom Checklist (LASC) (King et al., 1995)	• Assesses for PTSD symptoms and associated features including signs of distress and functional problems • Self-report questionnaire • 43 items, Likert scales • Dichotomous and continuous assessment • Studied across populations (e.g., males, females, various traumas) (Keane et al., 2000)	• 17-item PTSD index
Minnesota Multiphasic Personality Inventory, Keane PTSD Scale (PK) (Keane et al., 1984; Lyons and Keane, 1992)	• Originally composed of 29 items, revised for MMPI-2 by deleting 3 item repetitions • Self-report questionnaire • 46 MMPI items • Norms available for different populations	
Mississippi Scale for Combat-related PTSD (M-PTSD) (Keane et al., 1988)	• Assesses DSM-III combat-related PTSD and related features (e.g., suicidality, depression, substance abuse) • Self-report questionnaire • 35 items, 5-point Likert scale • 10–15 minute administration • Civilian Mississippi Scale for PTSD version	• Principal components factor analysis (Keane et al., 1988): *Factor 1* (9 items): Intrusive memories and depressive symptomatology *Factor 2* (5 items): Interpersonal adjustment problems *Factor 3* (3 items): Lability of affect and memory *Factors 4* and *5* (3 items each): Ruminative features *Factor 6* (2 items): Sleep problems

Psychometric Properties	Scoring and Interpretation Guidelines
Internal consistency (alpha): .75–.93 (Wildes) *Test-retest reliability:* .87 *Split-half reliability:* .86 (Wildes, 2007) • Low to moderate correlations with measures of similar constructs, strong correlation with CAPS	• Total score: 0–75 • Two scoring systems available (Green, 1991)
Sensitivity: .74 (PTSD index; King et al., 1995) *Specificity:* .77 (PTSD index, King et al., 1995) *Internal consistency (alpha):* .88–.95 (King et al., 1995) *Test-retest reliability:* .9–.94	
Sensitivity: .57–.90 (Newman et al., 1996) *Specificity:* .55–.95 (Newman et al., 1996) *Diagnostic accuracy:* 82% (Keane et al., 1984; Watson et al., 1986) *Internal consistency (alpha):* .85–.87 (Graham, 1990); .95–.96 (combat, Newman et al., 1996) *Test-retest reliability:* .86–.94 (combat, Newman et al., 1996)	• *Optimal cutoff score*: 8.5–30 across populations and studies (Newman et al., 1996)
Sensitivity: .77–.93 (Newman et al., 1996) *Specificity:* .83–.89 (Newman et al., 1996) *Diagnostic Accuracy:* .9 (Keane et al., 1988) *Internal consistency (alpha):* .94 *Split-half:* .93 *Test-retest reliability:* .97 (Keane et al., 1988) • Low to strong correlations with measures of similar constructs • Predictive of SCID-DSM-III-R diagnosis (McFall et al., 1990)	• Total: 35–175 • *Diagnostic cutoff score*: 107 (Keane et al., 1988)

continued

Measure	Description	Scales/Factors
Penn Inventory for Posttraumatic Stress (Hammerberg, 1992)	• Self-report questionnaire • 26 items • Primarily used with male patients, including accident victims, veterans, and general psychiatric patients (Keane et al., 2000)	
Posttraumatic Diagnostic Scale (PTDS) (Foa et al., 1997)	• Assesses DSM-IV PTSD criteria • Self-report questionnaire • 17 questions, including 12-item checklist of traumatic events • 4-point Likert rating for frequency of PTSD symptoms in the *past month* and self-ratings of impairment across nine areas of functioning • Validated across several populations, including combat veterans and sexual and nonsexual-assault survivors (Keane et al., 2000)	
PTSD Checklist (PCL) (Weathers et al., 1993)	• Assesses DSM PTSD diagnostic criteria • Self-report questionnaire • 10 minute administration • 17 items, 5-point (0–4) Likert rating for *past month* • PTSD Checklist-Military version (PCL-M)	• Principal components analysis indicated 1-factor solution (Wildes, 2007)
PTSD Interview (Watson et al., 1991)	• Structured clinical interview • Dichotomous and continuous assessment • Patient given a copy of scale to read along with interviewer and asked to give subjective ratings for each symptom	

Psychometric Properties	Scoring and Interpretation Guidelines
• Sensitivity comparable to Mississippi scale, specificity slightly lower (Keane et al., 2000)	
Sensitivity: .89 *Specificity:* .75 *Kappa:* .65 (criterion: SCID) *Internal consistency (alpha):* .92 *Test-retest reliability:* .74 (diagnosis), .83 (symptom severity)	
Sensitivity: .82 *Specificity:* .83 *Overall diagnostic efficiency:* .9 (criterion: CAPS) (Blanchard et al., 1996) *Internal consistency (alpha):* .97 (Weathers et al., 1993) *Test-retest reliability:* .96 (Weathers et al., 1993) • Moderate to strong correlations, r > .75, with measures of similar constructs (Mississippi, PK, IES, CAPS) (Blanchard et al., 1996; Weathers et al., 1993) • Reductions in diagnostic accuracy as symptoms improve and approach threshold for diagnostic criteria (Forbes et al., 2001)	• Individual symptom score: 0–8 • *Symptom endorsement cutoff:* 3 or 4 (Blanchard et al., 1995; Forbes et al., 2001) • Total severity: 17–85 • *Diagnostic cutoff score*: 50 in veteran population (Blanchard et al., 1996; Forbes et al., 2001)
Sensitivity: .89 *Specificity:* .94 *Kappa:* .82 (Criterion: DIS) (Watson et al., 1991) *Internal consistency (alpha):* .92 *Test-retest reliability:* .95	

continued

Measure	Description	Scales/Factors
PTSD Symptom Scale Interview (PSS-I) (Foa et al., 1993)	• Assesses DSM criteria of PTSD • Semistructured interview • 20–30 minute administration • Self-report questionnaire version (PSS-S): 10 minute administration • Likert rating scales for criterion symptoms • Dichotomous and continuous assessment • 2-week time frame	• Subscales: *reexperiencing* (5 items) *avoidance* (7 items) *arousal* (5 items)
Symptom Checklist-90-R (SCL-90-R) (Derogatis, 1977)	• Assesses a broad range of psychological problems, symptoms of psychopathology, patient progress, and treatment outcomes • Self-report questionnaire • 12–15 minute administration • 90 items, 5-point Likert rating • Global Severity Index: summary of test	• 9 primary symptom dimensions, 3 global indices • 28-item *Crime-Related PTSD Scale* (Saunders et al., 1990) • 12-item *PTSD Subscale for Disaster Survivors* (Green, 1991) • 25-item *War-Zone-Related PTSD Scale* (Weathers et al., 1996)
Structured Clinical Interview (SCID) PTSD Module (Spitzer et al., 1990)	• Assesses prevalence, absence, and subthreshold presence of PTSD • Used across trauma populations • Semistructured interview • 25 minute administration • Permits only dichotomous rating (present/absent) of symptoms, does not assess severity of symptoms	

Psychometric Properties	Scoring and Interpretation Guidelines
Sensitivity: .88 (PSS-I), .62 (PSS-S) *Specificity:* .96 (PSS-I) (Criterion: DIS; Foa et al., 1993) *Internal consistency (alpha):* .86 (PSS-I-total), .65–.74 (PSS-I subscales) (Foa and Tolin, 2000) *Test-retest reliability:* Strong (Foa et al., 1993) *Interrater reliability:* 98.3% (Foa and Tolin, 2000) • Good agreement with CAPS and SCID (Foa and Tolin, 2000)	
• War-Zone-Related PTSD Scale is only SCL-90 PTSD scale that has greater predictive validity than the Global Severity Index (Green, 1991)	
Sensitivity: .81 *Specificity:* .98 *Kappa:* .68 (Keane et al., 1998) • Agreement across lifetime, current, and never PTSD 78% (Keane et al., 1998) • Highly correlated with other measures of PTSD	

continued

Measure	Description	Scales/Factors
Structured Interview for PTSD (SI-PTSD or SIP) (Davidson et al., 1989)	• Assesses DSM PTSD criteria (re-experiencing, avoidance and numbing, and hyperarousal) and functional impairment • Structured interview, including initial probes, behavioral observations and follow-up questions • 20 minute administration • Severity and frequency of symptoms rated on 5-point (0–4) Likert scale • Dichotomous and continuous assessment • Assesses lifetime PTSD by "worst ever" symptomatology	• Treatment Outcome PTSD Scale (TOP-8) (Connor and Davidson, 1999; Davidson and Colket, 1997) assesses treatment response: 8 items endorsed frequently and responded to treatment over time, drawn from 3 symptom clusters

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Sensitivity: .96 *Specificity:* .8 (Davidson et al., 1989)	• *Diagnostic cutoff score*: 20

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Appendix D

Analysis and Interpretation of Studies with Missing Data

A characteristic of virtually all studies of posttraumatic stress disorder (PTSD), and of many psychiatric conditions, is a high degree of attrition of participants from assigned treatment, whether that treatment be pharmacologic or psychotherapeutic. This can be caused by the underlying condition and patient characteristics, which makes adherence to any form of therapy difficult, or it can be caused by improving or worsening of symptoms. High degrees of dropout are common in studies of a broad range of psychologic conditions. In a review of studies by Khan (2001a,b), dropout rates in trials of antidepressants averaged 37 percent, similar between treatment and placebo, and were in the 50–60 percent range for trials of antipsychotics, somewhat greater on treatment than on placebo, and intermediate among active controls.

The numbers in the PTSD literature studied here were comparable. The median follow-up in the 37 PTSD pharmacotherapy studies was 74 percent (10th–90th percentiles 58–90 percent), with one not reporting follow-up. The median differential follow-up (treatment-placebo) was –3 percent (10th–90th percentiles 19 percent to +15 percent). For the psychotherapy studies, in the 79 active treatment arms used in 56 studies, the median follow-up was 80 percent (10th–90th percentiles 61–100 percent). The median follow-up in the 32 minimal care and wait-list arms was 94 percent (10th–90th percentiles 79–100 percent). The median differential follow-up among the 13 trials without a minimal care arm was zero (interquartile range –6 percent to +11 percent). Among the 32 studies with a minimal care or wait-list arm, the median differential follow-up (treatment-minimal care) was –6 percent (10th–90th percentiles, –26 percent to +3 percent).

If outcome data is not obtained from patients who drop out from treatment, that participant's outcome data will be missing. It is critical to recognize that dropout from treatment does not have to produce missing outcome data. Outcome data can still be obtained from subjects who discontinue treatment, so missing data is partly produced by study design (e.g., a failure to follow up patients who stop treatment), and is not an inevitable result of a condition, treatment, or behavior (Lavori, 1992). This was shown in studies of PTSD treatment by Schnurr et al. (2003, 2007) that successfully obtained outcomes measurements from a large fraction of participants who discontinued treatment. Very few of the studies examined here obtained outcome information after a patient stopped treatment or during post-treatment follow-up. Because a very high percentage of patients, from 20 percent to 50 percent, typically dropped out of these studies, large fractions of outcome data were therefore missing. The most common way this is handled in the literature reviewed was to use the last recorded outcome as the final outcome from a patient who dropped out—the "last observation carried forward" (LOCF) approach.

The motivation for this statistical approach is understandable: to include as many patients as possible in the final analysis, and to use as much information as possible from every patient. Unfortunately, the LOCF approach, while it uses "all available data," does so in a way that typically produces improper answers. For that reason, it has long been rejected as a valid method of handling missing data by the statistical community, even as its use has remained prevalent in various domains of research. Statisticians recommend a wide array of more appropriate, albeit technically more complex, methods that have been in existence for decades and can now be implemented in standard software (Schafer and Graham, 2002; Mallinckrodt et al., 2003; Molenberghs et al., 2004; Leon et al., 2006; Little and Rubin, 2002).

PROPERTIES OF MISSING DATA: REASONS FOR MISSINGNESS

The basic principles of how missing data should be handled depend partly on the reasons for that missingness, as reflected in the statistical relationships between the missing data and the observed data used in the analytic model. Technically, there are three types of missing data: missing completely at random (MCAR), missing at random (MAR), and missing not at random (MNAR); the latter two are also known as "nonignorable" or "informative" missingness.

The first type—MCAR—means that the missingness of the outcome data *Y* does not depend on either the observed (Y_{obs}) or unobserved (Y_{miss}) outcomes, after taking into account the other variables included in the analytic model. The mechanism by which this would be produced might

be some administrative or conduct process, wherein the discontinuation of treatment, or the failure to gather data, has nothing to do with a subject's clinical course. Under this scenario, complete case analysis is unbiased, as complete cases constitute a representative sample of the study population. However, complete case analysis is inefficient in that it does not make use of the interim information from subjects without final outcome data. Interestingly, even in this situation where completers represent a completely random representative sample, LOCF is generally biased, because of its assumption that disease severity remains unchanged from its last recorded value (Molenberghs, 2004).

The second kind of missing data (MAR) occurs when data are missing at random if, conditional upon the independent variables in the analytic model, the missingness depends on the observed values of the outcome being analyzed (Y_{obs}) but does *not* depend on the unobserved values of the outcome being analyzed (Y_{miss}). It is thus similar to MCAR, except that a subject's observed disease severity affects the likelihood of subsequent dropout. It assumes that the average future behavior of all individuals with the same characteristics and clinical course up to a given time will be the same, regardless of whether their outcome data is missing after that time. The best approach to this kind of missing data involves forms of data imputation or modeling that take into account all the observed data up to the point where it is missing. These techniques include mixed model repeated measurement (MMRM) and multiple imputation, random regression or hierarchal regression models (Molenberghs et al., 2004; Schafer and Graham, 2002). Both complete case and LOCF perform suboptimally in this situation, the former because it doesn't use the information from patients with incomplete data at all, and LOCF because it does not utilize that information properly.

Finally, data that are missing "not at random" (MNAR) is data whose value is not predictable from the observed data of other patients that completed the trial and from the data on the patient in question up until the point of dropout. An example of this is a patient who drops out due to an unrecorded relapse after apparently doing well, or a patient who drops out because of side effects, whose tolerance might be reduced when their PTSD is worse. Because missingness of the data is related to the value of the unobserved data, this kind of data is called "informatively" or "nonignorably" missing. This condition by definition cannot be ascertained from the observed data, yet most missing data methods take as their assumption that it does not exist. The higher proportion of outcome data that are missing, the more the validity of any analysis rests on this unverifiable assumption, and the less reliable the results from any method. It can be dealt with only via sensitivity analysis, or better, by learning something about the reasons for the dropouts using information external to the data in hand. If the data allows, studying the characteristics and intermediate outcomes of patients

with different patterns of dropout can also be informative (Mallinckrodt et al., 2004; Schafer and Graham, 2002).

Several key points arise from these definitions. Most importantly, the characterization of the missingness mechanism does not rest on the data alone; it involves both the data and the model used to analyze the data. Consequently, missingness that might be MNAR given one model could be MAR or MCAR given another. Therefore, statements about the missingness mechanism cannot be interpreted without reference to what other variables are included in the analytic model.

Such subtleties can be easy to overlook in practice, leading to misunderstanding about missing data and its consequence. For example, when dropout rates differ by treatment group, then it can be said that dropout is not random. But it would be incorrect to conclude that the missingness mechanism giving rise to the dropout is MNAR and that analyses assuming MCAR or MAR would be invalid. Although dropout is not completely random in the simplest sense, if dropout depends only on treatment, and treatment is included in the analytic model, the mechanism giving rise to the dropout would be MCAR.

ISSUES WITH LAST OBSERVATION CARRIED FORWARD APPROACHES TO MISSING DATA

We will focus here on the problems created by using the LOCF approach to handling missing data, which is the most widely used approach in the literature reviewed. The problems with the LOCF approach are severalfold, deriving from a variety of unlikely assumptions (Molenberghs et al., 2004):

(1) A patient's outcome value would not have changed between the time of its last recorded value and the time of last possible follow-up (the "constant profile" assumption).
   - This has the effect not only of possibly misrepresenting what that final outcome would have been, but making it appear as though we can be as certain about the missing outcomes of dropouts as we are about those subjects whose outcome are measured. This makes the precision of the final estimates higher than is justified by the data.

(2) There is nothing about the patient or their course preceding the dropout that is informative about their course after the point of dropout.
   - It is quite often the case that those who drop out differ from those who remain, either at baseline or in their subsequent course. Because LOCF ignores this information, its predictions

are more likely to be wrong than other methods that take that data into account. In this sense, LOCF does not actually use "all the data."

(3) The dropout itself is not informative about a patient's ultimate outcome.
   - This occurs when patients who are either responding, or not responding, preferentially drop out, and that this difference is not reflected in anything already measured about the patient (e.g., occurring when patient is feeling better, or worse, right before they dropped out).

These three factors—false certainty about the missing outcome, ignoring relevant information about the missing outcome, and assuming that dropout itself is not related to outcome—conspire to make LOCF a misleading statistical approach to handling missing data. There is an extensive treatment of this subject in the statistical, medical, and psychiatric literature going back decades (Gueorguieva and Krystal, 2004; Lavori, 1992; Leon et al., 2006; Little and Rubin, 2002; Mallinckrodt et al., 2003; Schafer and Graham, 2003). We summarize here the background for our judgments about the difficulties in deriving inferences from studies that used LOCF in the presence of high proportions (e.g., greater than 30 percent) of missing data.

Although it is sometimes stated that an LOCF analysis will be "conservative," meaning biased towards a null effect, this is not true generally. This approach can introduce a bias in any direction, depending on the trajectory of disease severity in arms being compared, the reasons for and degrees of dropout, and the other factors included in the models. All of these components interact, so neither the magnitude nor direction of bias can be easily predicted. Also, the precision of any estimated effect is always overstated even when no bias is introduced into the estimate of effect. Mallinckrodt et al. (2003) described conditions that produce bias.

Holding all other factors constant, LOCF approaches will:

- overestimate a drug's advantage when dropout is higher in the comparator and underestimate the advantage when dropout is lower in the comparator;
- overestimate a drug's advantage when the advantage is maximum at intermediate time points and underestimate the advantage when the advantage increases over time; and
- have a greater likelihood of overestimating a drug's advantage when the advantage is small.

In scenarios in which the overall tendency is for patient worsening, the above biases are reversed.

LOCF analyses can be biased under all reasons for missingness; the bias generally increases as the dropout rate increases and becomes more differential between groups. The artificially high precision of LOCF estimates also becomes more serious as the dropout rate increases. This does not mean that analyses with LOCF are "invalid" in a binary sense, but rather that the quality of the evidence they provide becomes weaker as dropout rates rise and as its underlying assumptions become harder to confirm from the data.

It is difficult to quantify in a simple manner the relationship between dropout rate and the degree of bias introduced by LOCF, since that bias depends on a number of things besides the dropout rate: the clinical course of untreated patients over time, the time course of the therapeutic effect, the relationship between the interim measurement and the final measurement, and the nature of the outcome measurement (e.g., percentage of "success" versus disease severity). In a comprehensive treatment of the subject, Molenberghs et al. (2004) present equations that allow us to calculate the degree of bias produced by LOCF in a continuous measure of disease severity in the simple situation where each subject is assessed once halfway through treatment, and again at the end. It is assumed that everyone has an intermediate measurement, but that a certain percentage in each group drops out before a final value is measured. Table D-2 shows the degree of bias for the scenarios presented in Table D-1, under equal dropout rates, which is generally the most favorable scenario for the use of LOCF.

We see from these tables that both the degree and direction of bias caused by LOCF is not immediately apparent from underlying treatment effects and trends, and that this bias increases as the follow-up rate decreases (i.e., the dropouts increase). What is not included here are simulations related to the overstated precision of estimates; it is possible that even if the effect size is understated the statistical significance is overstated, if the standard error decreases proportionally by more than the effect size.

These scenarios are merely demonstrative and not meant to be representative of the literature studied herein, although many are plausible PTSD treatment patterns. It is calculations such as these and more intensive and detailed simulations that lead statisticians to view LOCF as problematic for most situations (Cook et al., 2004; Mallinckrodt et al., 2004; Molenberghs et al., 2004), particularly so when the rate of missingness exceeds 30–40 percent. With proper methods such as MMRM or multiple imputation, to the extent that the MAR assumption is met, there is minimal bias. However, at high levels of dropout even these methods become more heavily dependent on the unverifiable MAR assumption. Not all of the scenarios reported in Table D-1 follow a MAR pattern.

TABLE D-1 Various Hypothetical Patterns of PTSD Scores (CAPS-2) in an Idealized Study with Two On-Treatment Measures; One Interim, One Final

	Baseline	Interim Effect	Final Effect	Natural Disease Course
Scenario 1 **Completers:** Interim benefit, sustained **Dropouts:** Interim benefit, nonsustained benefit **LOCF bias:** 0–100% *over*stated benefit				
Completers	75	–15	–15	0
Dropouts	75	–15	0	0
Scenario 2 **Completers:** Interim benefit, increasing **Dropouts:** Interim, decreasing benefit **LOCF bias:** 0–25% *over*stated benefit				
Completers	75	–10	–15	0
Dropouts	75	–10	–5	0
Scenario 3 **Completers:** Early sustained benefit **Dropouts:** Deferred benefit, equal to completers **LOCF bias:** 0–50% *under*stated benefit				
Completers	75	–10	–10	0
Dropouts	75	0	–10	0
Scenario 4 **Completers:** Less severe than dropouts. Interim, increasing benefit. **Dropouts:** Identical benefit **LOCF bias:** 0–33% *under*stated benefit				
Completers	75	–5	–15	0
Dropouts	90	–5	–15	0
Scenario 5 **Completers:** Steadily increasing benefit, with equal natural improvement **Dropouts:** Identical to completers **LOCF bias:** 0–25% *under*stated benefit				
Completers	75	–5	–10	–5
Dropouts	75	–5	–10	–5
Scenario 6 **Completers:** Early large benefit, sustained **Dropouts:** No effect, some early benefit **LOCF bias:** 0–33% *over*stated benefit				
Completers	75	–15	–15	0
Dropouts	75	–5	0	0

NOTE: True underlying patterns for completers and non-completers are listed. "Natural disease course" is the temporal trend in both groups. Negative values represent improvement.

TABLE D-2 Degree of Bias Induced by LOCF Analysis Under Above Scenarios

Follow-up	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5	Scenario 6
1	0	0	0	0	0	0
.9	–11	–4	10	7	5	–4
.8	–25	–8	20	13	10	–8
.7	–43	–13	30	20	15	–14
.6	–67	–18	40	27	20	–22
.5	–100	–25	50	33	25	–33

NOTE: Follow-up is equal in each group. Negative bias represents overstatement of the observed effect, since lower CAPS-2 scores represent clinical improvement. These biases are percentages of the true final effect size. For example, if a therapy had on average a 15-point reduction in the CAPS score, an estimate based on LOCF of a 10-point reduction would represent a bias of 33%, and an estimated 30-point reduction would produce a bias of –100%.

It is for the kinds of reasons that reviews and consensus papers from researchers with academic affiliations (Gueorhuieva and Krystal, 2004; Lieberman et al, 2005), consensus papers from a mix of academic and industry researchers (Leon et al., 2006; Mallinckrodt et al., 2004), and statistics text books (Little and Rubin, 2002; Molenberghs and Kenward, 2007; Verbeke and Molenherghs, 2000) have all recommended that analyses of longitudinal clinical trial data move away from simple methods such as LOCF or observed-case analysis to more principled approaches, such as multiple imputation or the likelihood-based family in which MMRM resides.

These are the foundations of our recommendations that the analytic treatment of missing data and the effort to gain outcome information from subjects who drop out of PTSD treatment studies, need to be greatly strengthened. They have also guided us in our assessment of the quality of studies: if the dropout rate was high (particularly exceeding 30 percent), the differential dropout between arms was high (particularly exceeding 15 percent); and if LOCF was used to address dropouts, then the evidence from otherwise well-designed or well-executed studies was considered lower in quality.

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Appendix E

Acronyms

The list of general acronyms is followed by a list of outcome measure acronyms.

GENERAL ACRONYM LIST

AHCPR	Agency for Health Care Policy and Research
AHRQ	Agency for Healthcare Research and Quality
APA	American Psychiatric Association
BEF	brief eclectic psychotherapy
BOCF	baseline observation carried forward
BPP	brief psychodynamic psychotherapy
CBT	cognitive-behavioral therapy
CPT	cognitive processing therapy
CT	cognitive therapy
DARE	Database of Abstracts of Reviews of Effectiveness
DoD	Department of Defense
DSM	*Diagnostic and Statistical Manual of Mental Disorders*
EMD	eye movement desensitization
EMDR	eye movement desensitization and reprocessing
ET	exposure therapy

FDA	Food and Drug Administration
IOM	Institute of Medicine
ISTSS	International Society for Traumatic Stress Studies
LOCF	last observation carried forward
MAOI	monoamine oxidase inhibitor
MeSH	Medical Subject Heading
MMRM	mixed-model repeated measurement
MVA	motor vehicle accident
NaSSA	noradrenergic and specific serotonergic antidepressant
NCS-R	National Comorbidity Survey-Replication
NICE	National Institute for Clinical Excellence
NMDA	N-methyl-D-aspartic acid
NVVRS	National Vietnam Veterans Readjustment Survey
NTIS	National Technical Information Service
OIF/OEF	Operation Iraqi Freedom and Operation Enduring Freedom
PTSD	Posttraumatic Stress Disorder
RCT	randomized controlled trial
REM	rapid eye movement
SD	standard deviation
SIT	stress inoculation training
SNRI	serotonin and norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitors
TBI	traumatic brain injury
TCA	tricyclic antidepressant
VA	Department of Veterans Affairs

MEASURE ACRONYM LIST

ADIS-IV	Anxiety Disorders Interview Schedule—DSM-IV
ASI	Anxiety Sensitivity Index
ASI	Addiction Severity Index
BAI	Beck Anxiety Inventory

BDI	Beck Depression Inventory
BSI	Brief Symptom Inventory
CADSS	Clinician Administered Dissociative States Scale
CAPS	Clinician Administered PTSD Scale
CGI	Clinical Global Impressions
CGI-I	Clinical Global Impression Improvement Scale
CGI-S	Clinical Global Impression Severity Scale
CMS	Civilian Mississippi Scale for PTSD
DEQ	Distressing Event Questionnaire
DES	Dissociative Experiences Scale
DIS	Diagnostic Interview Schedule
DTS	Davidson Trauma Scale
GAF	Global Assessment of Functioning
GAS	Global Assessment Scale
HAM-A	Hamilton Rating Scale for Anxiety
HAM-D	Hamilton Rating Scale for Depression
HDRS	Hamilton Depression Rating Scale
HRSA	Hamilton Rating Scale for Anxiety
IES	Impact of Events Scale
IES-R	Impact of Events Scale-Revised
IES/IOE	Impact of Events Scale
IIP	127-item Inventory of Interpersonal Problems
LASC	Los Angeles Symptom Checklist
MADRS	Montgomery Asberg Depression Rating Scale
MMPI-2	Minnesota Multiphasic Personality Inventory
MPTSD	Modified PTSD Scale
M-PTSD	Mississippi Scale for Combat-Related PTSD
PANSS	Positive and Negative Syndrome Scale
PCL	PTSD Checklist
PDS	Posttraumatic Stress Diagnostic Scale
Penn	Penn Inventory for Posttraumatic Stress
PGI	Patient Global Impression
PSS-I	PTSD Symptom Scale—Interview
PSS-SR	PTSD Symptom Scale Self Report
PTDS	Posttraumatic Diagnostic Scale
PTSD-I	Posttraumatic Stress Disorder Interview

QLES	Quality of Life Enjoyment and Satisfaction Scale
SCID-I	Structured Clinical Interview for DSM-IV
SCID-P	Structured Clinical Interview for DSM-III-R, Patient Edition
SCL-90	Symptom Checklist-90
SCL-90-R	Symptom Checklist-90-R
SDS/SHEEHAN	Sheehan Disability Scale
SI-PTSD	Structured Interview for PTSD
SIP	Structured Interview for PTSD
SPRINT	Short PTSD Rating Interview
STAI	State-Trait Anxiety Inventory
STAS	State-Trait Anger Scale
STAXI	State-Trait Anger Expression Inventory
STI	Standard Trauma Interview
SUDS	Subjective Units of Disturbance Scale
TOP-8	Treatment Outcome PTSD Scale
TSC-40	Trauma Symptom Checklist-40
VETS	Veterans Adjustment Scale

Appendix F

Agenda for Public Meeting Held by the Committee on Treatment of PTSD

PUBLIC MEETING

Tuesday, January 16, 2007
National Academy of Sciences Building
2101 Constitution Ave, NW
Washington, DC

10:00 am	**Welcome, Opening Remarks and Introduction** *Alfred O. Berg*, Committee Chair
10:10–10:20 am	**Charge to the Committee** *Joseph Francis* Acting Deputy Chief Research and Development Officer Department of Veterans Affairs
10:20–10:30 am	**Committee Questions**
10:30–11:00 am	**Treatment of PTSD in VA Facilities and Programs** Readjustment Counseling Services *Alfonso Batres,* Chief Officer Department of Veterans Affairs

	Mental Health Services *Antonette Zeiss*, Deputy Chief Department of Veterans Affairs
11:00–11:20 am	**Committee Questions**
11:20–11:25 am	**Comment from the Veterans' Disability Benefits Commission** Commissioner Rick Surratt Veterans' Disability Benefits Commission
11:25–11:30 am	**Committee Questions**
11:30 am–12:00 pm	**State of the Research— Pharmacotherapy** *Jonathan Davidson*, Professor Department of Psychiatry and Behavioral Sciences Duke University Medical Center
12:00–12:15 pm	**Committee Questions**
12:15–12:45 pm	**State of the Research—Psychotherapy** *Rachel Yehuda*, Professor Department of Psychiatry Director, Traumatic Stress Studies Division Mount Sinai School of Medicine and Bronx Veterans Affairs Medical Center
12:45–1:00 pm	**Committee Questions**
1:00–2:00 pm	Lunch
2:00–2:20 pm	**Clinical Perspectives** *Douglas Zatzick*, Associate Professor Department of Psychiatry and Behavioral Science University of Washington School of Medicine
2:20–2:35 pm	**Committee Questions**

2:35–2:55 pm	**Treating PTSD in Veterans: Challenges and Opportunities** *Robert Ursano*, Professor and Chair Department of Psychiatry Director, Center for the Study of Traumatic Stress Uniformed Services University of Health Sciences
2:55–3:10 pm	**Committee Questions**
3:10–3:30 pm	**Public Comment**
3:30 pm	**Adjourn**

Appendix G

Committee Member Biographies

Alfred O. Berg, M.D., M.P.H., is a professor in the Department of Family Medicine at the University of Washington School of Medicine, Seattle, where he served as department chair from 1998 to 2007. Dr. Berg received his professional education at Washington University, St. Louis, University of Missouri, and the University of Washington. He is board certified in Family Medicine and in General Preventive Medicine and Public Health. Dr. Berg's research has focused on clinical epidemiology in primary care settings. He has been active on several expert panels using evidence-based methods to develop clinical guidelines, including chairmanship of the United States Preventive Services Task Force, cochair of the otitis media panel convened by the Agency for Health Care Policy and Research (now the Agency for Healthcare Research and Quality), chair and moderator of the Centers for Disease Control and Prevention (CDC) STD Treatment Guidelines panel, member of the American Medical Association (AMA)/CDC panel producing Guidelines for Adolescent Preventive Services, and member of the Institute of Medicine's Immunization Safety Review Committee. Dr. Berg is a member of the Institute of Medicine.

Naomi Breslau, Ph.D., is a professor in the Department of Epidemiology, Michigan State University College of Human Medicine. Dr. Breslau received her L.L.B. at Hebrew University in Jerusalem, her M.A. at New York University (NYU), and her Ph.D. at Case Western Reserve University. She is a psychiatric epidemiologist and sociologist who has contributed to the epidemiological study of numerous psychiatric conditions and behavioral disturbances, most prominently posttraumatic stress disorder and tobacco

dependence. She has conducted large-scale longitudinal epidemiologic studies, including on PTSD, low birthweight, and migraine headaches in relation to psychiatric comorbidity. The American Association for the Study of Headache honored her work on the prospective relationship between major depression and migraine with the Wolf Award. She has had continued National Institutes of Health (NIH) grant support from 1980. Additionally, for a period of 10 consecutive years, from 1982 to 1992, she was supported by National Institute of Mental Health (NIMH) KO2 Research Scientist Development Awards. She is rated as Highly Cited in the ISIHighlyCited.com indexing service. Since 1980, Dr. Breslau has served on numerous NIH review committees. She was a member of the NIMH Consensus Development Panel for ADHA, the DSM-IV Work Group on GAD Mixed Anxiety-Depression. She served on the Test Committee Behavioral Science, Part I, the National Board of Medical Examiners. From 1982 to 1986, she served as coeditor of *Medical Care*. She is currently associate editor of two scientific journals, *Nicotine and Tobacco Research* and the *International Journal of Methods in Psychiatric Research* and is a member of the Editorial Board of *Archives of General Psychiatry*.

Steven Goodman, M.D., M.H.S., Ph.D., is an Associate Professor of Oncology, Pediatrics, Biostatistics, and Epidemiology at the Johns Hopkins Schools of Public Health and Medicine. He trained in medicine at NYU, in pediatrics at Washington University, and in epidemiology and biostatistics at Johns Hopkins University. His main expertise is in evidence synthesis, clinical trial analysis and design, and foundations of inference. He is editor of the journal *Clinical Trials: Journal of the Society for Clinical Trials*, and has been statistical editor for the *Annals of Internal Medicine* since 1987. He was a co-director of the Hopkins Evidence-Based Practice Center and the doctoral program in epidemiology. He is the scientific advisor for the National Blue Cross/Blue Shield Technology Assessment Program, was a member of the Medicare Coverage Advisory Commission, and he has participated in a wide range of Institute of Medicine panels and committees: the Committee on Immunization Safety Review, the Health Effects in Vietnam Veterans of Exposure to Herbicides (Second Biennial Update), Review of Evidence Regarding Link Between Exposure to Agent Orange and Diabetes, Alternative Models to Daubert Standards, and the IOM Workshop on Estimating the Contribution of Lifestyle-Related Factors to Preventable Death.

Muriel D. Lezak, Ph.D., is a neuropsychologist and Professor Emerita in the Department of Neurology at the Oregon Health and Science University School of Medicine. Dr. Lezak has many publications on cognitive, emotional, and social consequences of traumatic brain injury (TBI). She has

conducted numerous workshops and seminars nationally and internationally on TBI—its nature, assessment, remediation, and social ramifications. She had a Department of Veterans Affairs (VA) grant for a longitudinal study on the neuropsychological consequences of brain injury in a veteran (mostly Vietnam) population. Dr. Lezak has also been a participant of, or consultant to, many committees and study groups concerned with TBI and TBI rehabilitation including the California State Athletic Commission (developing an examination for boxers), the NIH Coma Data Bank Project, and the Conseil Québécois de la Recherche Sociale (developing a data bank for TBI due to motor vehicle accidents). Dr. Lezak was Honorary Visiting Professor, West China University of Medical Sciences in 1996, was a recipient of the Annual Award for outstanding service to the brain injured from the Department of Rehabilitation of the Medical College of Virginia, and the Clinical Service Award from the National Head Injury Foundation. Dr. Lezak earned her bachelor degree in general studies and master's degree in human development from the University of Chicago. Her Ph.D. in clinical psychology is from the University of Portland. She has also served as a member of the Institute of Medicine Committee on Traumatic Brain Injury.

David Matchar, M.D., is director of the Center for Clinical Health Policy Research, and professor, Department of Medicine, Duke University. After completing his undergraduate degree in statistics at Princeton University, Dr. Matchar earned his medical degree from the University of Maryland. He then completed a research fellowship in general internal medicine at Duke University Medical Center in 1983, and was awarded an A.W. Mellon Fellowship at New England Medical Center in 1984. Dr. Matchar focuses his work on evaluation of clinical practice based on "best evidence" and implementation and evaluation of innovative strategies to promote practice change. For 10 years, he directed the Duke Evidence-based Practice Center, one of 12 such centers designated by AHRQ. Matchar served as a member of the Institute of Medicine Committee on Gulf War and Health: A Review of the Medical Literature Relative to the Gulf War Veterans Health. Dr. Matchar focuses his research on evidence synthesis to support informed clinical and policy decisions, and on the implementation and evaluation of innovative strategies to promote practice change.

Thomas A. Mellman, M.D., is professor and vice-chair for research, Department of Psychiatry, Howard University, and associate program director for the Howard University General Clinical Research Center. Dr. Mellman received his medical degree from Case Western Reserve, School of Medicine, in 1982. During his 11 years on the faculty at the University of Miami, School of Medicine, Department of Psychiatry and Behavioral Sciences, he

led the development of a VA Medical Center and university-based clinical research program on anxiety disorders and PTSD. In 1999, Dr. Mellman joined the faculty of Dartmouth Medical School, Department of Psychiatry. Much of his research and publications have addressed the role of sleep disturbance in the pathogenesis and treatment of PTSD. His current research studies patients who are being treated for traumatic injuries and includes early sleep recordings and longitudinal assessment of PTSD. This work has led to several recent publications of sleep-related and other predictors of the early development of PTSD. This includes an article in the *American Journal of Psychiatry* that reports and discusses the implications of a relationship between fragmented patterns of rapid eye movement sleep and the development of PTSD. Dr. Mellman contributed to the recent revision of the *Diagnostic and Statistics Manual of Mental Disorders* (DSM), 4th edition, text revision, and the International Society for Traumatic Stress Studies *Treatment Guidelines*. He recently completed service as a member of the National Institute of Mental Health, Interventions, Initial Review Group, and prior to that served on the Violence and Traumatic Stress Review Committee.

David Spiegel, M.D., is the Jack, Lulu & Sam Willson Professor in the School of Medicine, Associate Chair of Psychiatry & Behavioral Sciences, Director of the Center on Stress and Health, and Medical Director of the Center for Integrative Medicine at Stanford University School of Medicine. He is past president of the American College of Psychiatrists. He has published 10 books, 277 scientific journal articles, and 137 chapters on psychosocial oncology, stress, trauma, hypnosis, and psychotherapy. Dr. Spiegel collaborated in the inclusion of Acute Stress Disorder in the DSM-IV. His research is supported by the National Institute of Mental Health, the National Cancer Institute, the National Institute on Aging, the John D. and Catherine T. MacArthur Foundation, the Fetzer Institute, the Dana Foundation for Brain Sciences, and the Nathan S. Cummings Foundation, among others. Dr. Spiegel was a member of the Institute of Medicine Committee on Health and Behavior.

William A. Vega, B.A., M.A., Ph.D., is currently a professor in the Department of Family Medicine at the David Geffen School of Medicine at University of California, Los Angeles. Until July 2007 he was professor of psychiatry at the Robert Wood Johnson Medical School-University of Medicine and Dentistry of New Jersey and director of research, Behavioral Research and Training Institute, University Behavioral Health Care. Dr. Vega has conducted field and clinical research projects on health, mental health, drug abuse, and behavior problems in various regions of the United States and Latin America. His specialty is ethnic subgroup comparative

research, and his work has been supported by numerous public and private grants. He was cited (2006) in the ISIHighlyCited.com indexing service for inclusion in the top one-half of 1 percent of the most cited researchers worldwide in the social sciences over the past 20 years. Dr. Vega received his undergraduate degree in sociology, his master's and doctoral degree in criminology, and his Ph.D. in criminology from the University of California, Berkeley. He has been, and is currently, a member of various boards, committees, and councils of the Institute of Medicine, National Institutes of Health, and private foundations.

Appendix H

Minority Opinion of Dr. Thomas Mellman

I do not concur with the committee's consensus on two conclusions and the comments that accompany those conclusions. My disagreement with the two conclusions is informed by three issues. I disagree with the committee's decision to meet the study charge by making a general conclusion about each intervention, followed by a separate notation about "the restriction of the conclusion regarding the population, provider, setting of intervention, etc." I believe that for the selective serotonin reuptake inhibitor (SSRI) class in particular, the effect of the medication in civilian and specific veteran subpopulations must be noted as separate conclusions. I also disagree with the degree of emphasis the committee placed on the effect of the "last observation carried forward" (LOCF) method for treating missing data on study outcomes (i.e., the fact that use of LOCF is considered a major limitation).[1] Finally, I believe that the distinction the committee makes between its evidence-based conclusions intended to inform policymaking and clinical practice guidelines (such as those developed by the International Society for Traumatic Stress Studies or the American Psychiatric Association) is ultimately not meaningful to practicing clinicians.

The following text reflects my restatement of the conclusions and comments pertaining to SSRIs and novel antipsychotic medications.

[1]Refer to Chapter 5 and Appendix D for the committee's discussion of dropouts and methods for handling missing data, including LOCF.

SSRI Conclusion

The evidence is suggestive but not sufficient to conclude efficacy of SSRIs in general populations with PTSD. The available evidence is further suggestive that SSRIs are not effective in populations consisting of predominantly male veterans with chronic PTSD.

Comment: If one divides the SSRI studies into categories that include combat veterans with chronic PTSD (Friedman et al., 2007; Hertzberg et al., 2000; and van der Kolk et al., 1994) and veterans with more recent exposure to war (Martenyi et al., 2002; Zohar et al., 2002) (all of these male or predominately male) then the 3 studies with male veterans with chronic PTSD have negative results and the preponderance of the studies with civilian populations (9 of 11) are positive (Brady et al., 2000; Connor et al., 1999; Davidson et al., 2001; Marshall et al., 2001, 2007; Martenyi et al., 2002; Tucker et al., 2000, 2001; van der Kolk et al., 1994), and the 2 non-positive studies (Davidson et al., 2006; van der Kolk et al., 2007) show nonsignificant trends favoring the SSRI (sertraline in one study, fluoxetine in the other). (This analysis counts van der Kolk's 1994 study with veteran and civilian groups as 2 studies.)

Limitations (e.g., high dropout rates) warrant "suggestive but not sufficient to conclude the efficacy" rather than "sufficient to conclude the efficacy" of SSRIs. The positive studies tend to be large and well conducted by all criteria other than dropout rates and use of LOCF to address missing data. Three of the larger, well-conducted positive studies have dropout rates that do not exceed 31 percent per group and the rates are similar in the treatment groups. The assumption that LOCF provides a conservative estimate in medication studies is supported by the extant short-term and long-term medication treatment trajectory data that shows continuing improvement over time. Additional evidence that predominantly male veteran populations with chronic PTSD are less responsive to treatments in general comes from Schnurr et al. (2003), which is one of the few studies to not find an advantage of exposure-based cognitive-behavioral therapy over an active control. The Cochrane systematic review (Stein et al., 2006) that utilized meta-analysis (and is referred to in the report in Chapter 3, section on SSRIs) also supports the efficacy of SSRIs for PTSD in the general population.

Novel Antipsychotic Medications Conclusion

There is evidence that is suggestive but not sufficient to conclude the efficacy of new generation antipsychotic medications as add-on or adjunctive for the treatment of PTSD.

Comment: This evidence comes from studies where most of the participants had risperidone or olanzapine added to other medication regimens to which they had not adequately responded. Veterans with chronic PTSD are well represented in these studies.

The fact that this literature highlights severely affected, treatment refractory veterans would seem of particular interest to VA. Although it would not be advisable to make clinical recommendations for the use of novel antipsychotic medications as a first-line therapy because of the nature of the evidence and concerns regarding their tolerability, it should be noted that three of the studies with few major limitations had positive results, and the remaining with a negative result had a very small total N (15) and should be considered separately as it evaluated olanzapine as a monotherapy.

Thomas A. Mellman, MD

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