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The National Center for PTSD
VA Medical Center (116D)
215 North Main Street
White River Junction
Vermont 05009-0001 USA

(802) 296-5132
FAX (802) 296-5135
Email: ncptsd@va.gov

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Treatments for PTSD: Understanding the Evidence

Psychotherapy

Paula P. Schnurr, Ph.D.
National Center for PTSD

The first practice guideline for PTSD was published in 2000 by the International Society for Traumatic Stress Studies (ISTSS). Guidelines produced by the American Psychiatric Association and the US Departments of Veterans Affairs and Defense followed later, along with guidelines by groups in the United Kingdom and Australia (see Kilpatrick's column, this issue, for information about PTSD treatment guidelines and references for these works). Psychotherapy figures prominently in these guidelines, especially treatments that are based on cognitive-behavioral techniques.

A lot of research has appeared since 2000, so much that the ISTSS is issuing an updated guideline in 2008. This article describes key issues to consider in interpreting the underlying literature on psychotherapy (Schnurr, 2007) and suggests articles for readers who want to read the original sources to find out which techniques are most effective. The focus is on randomized controlled trials (RCTs) and recent publications, although the bibliography includes a few references to older studies as well.

Design Considerations

Unlike medication trials, studies of psychotherapy (and other nonpharmacological interventions) typically cannot utilize a placebo controlled design, widely considered to be the gold standard for evaluating an intervention. Instead, investigators must employ various designs that are appropriate to the state of knowledge about a given treatment. Often the initial stage of research utilizes a randomized waitlist design, in which participants either receive the target treatment or undergo study assessments only for a specified period (e.g., Chard, 2005; Ehlers et al., 2005; Monson et al., 2006; Rothbaum, 1997). If participants are randomized to treatment, waitlist designs are useful for controlling most threats to internal validity and thus permit inferences about

Pharmacotherapy

Matthew J. Friedman, MD, Ph.D.
National Center for PTSD

The last time pharmacotherapy for PTSD was reviewed in the *Research Quarterly* was Winter 2000 (Volume 11, Number 1). At that time, the first multisite trial with the selective serotonin reuptake inhibitor (SSRI) sertraline had just been published, so that review focused primarily on a small number of clinical trials with tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and two small trials of diazepam and propranolol, respectively. Readers are referred to that issue for this older literature.

Since 2000, a total of almost 50 randomized controlled trials (RCTs) have been published. More than half have tested antidepressant agents: SSRIs, venlafaxine, nefazadone, and mirtazepine. Most of these studies have been sponsored by the pharmaceutical industry. There have not been any new trials of TCAs or MAOIs. Since the purpose of this article is a guide to the published results rather than a comprehensive literature review, readers should consider Friedman and Davidson (2007), which discusses the pharmacology of different medications with respect to the unique pathophysiology of PTSD, and Friedman, Davidson, and Stein (in press), which reviews all published RCTs and provides effect sizes for each study.

Another important development since 2000 has been an assessment of the empirical evidence regarding the efficacy of pharmacotherapy (and other PTSD treatments) by a number of organizations including the American Psychiatric Association, the US Institute of Medicine (IOM), The UK National Institute for Clinical Excellence (NICE), a joint practice guideline by the US Department of Veterans Affairs and Department of Defense, the International Society for Traumatic Stress Studies, and others (see Kilpatrick, this issue). All have agreed that cognitive-behavioral treatment (CBT), especially prolonged exposure and cognitive processing therapy, are proven evidence-based treatments for PTSD. On the other hand, there is

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whether treatment is responsible for any changes observed. The disadvantage of waitlist designs is that they do not rule out the possibility that any kind of treatment would be just as effective or even better than the one under investigation. Waitlist controls are also used in studies that compare treatments, and are especially helpful for interpreting the results of a study in which the treatments being compared do not differ from one another (e.g., Foa et al., 1999; Resick et al., 2002).

Nonspecific comparison designs that control for the effects of receiving treatment are the next step. Patients are randomized to receive a target treatment or one that controls for the nonspecific benefits of therapy, such as supportive counseling (Bryant et al., 2003), relaxation training (Taylor et al., 2003), or present-centered therapy (Schnurr et al., 2003; Schnurr et al., 2007). Like waitlist control groups, nonspecific comparison groups may be used if there is more than one target treatment (e.g., Bryant et al., 2003; Taylor et al., 2003).

Although nonspecific comparison designs provide some information about a target treatment's mechanism of action, this question is best addressed by systematically manipulating elements that are thought to be the treatment's active ingredients. In a dismantling design, the treatment is compared to variations in which one or some of the active elements are present (e.g., Cusack & Spates, 1999; Resick et al., 2008). In an additive design, techniques shown to work in isolation are combined and compared to the separate techniques (e.g., Bryant et al., 2003; Foa et al., 1999; Foa et al., 2005); for example, patients may be randomized to exposure, cognitive restructuring, or a combination of the two. In a parametric design, the amount of the active element, e.g., length of exposure sessions or depth of emotional processing, is manipulated from lesser to greater. The fourth class of designs involves the comparison of two different treatments (e.g., Resick et al., 2002; Rothbaum et al., 2005; Taylor et al., 2003).

Regardless of the type of design, investigators need to equate the conditions being compared on factors that might affect treatment response, such as the amount of treatment, therapist expertise, and treatment credibility. Both the type of design and how conditions are equated will affect the size of the treatment effect (Schnurr et al., 2007). The more active the comparison group and the greater the control for nonspecific factors, the smaller the effect will be. It is not possible to directly compare the effect size from a study that used a waitlist design with the effect size from a study that used a nonspecific design. Even nonspecific designs are not necessarily comparable because the effects depend on the therapeutic effectiveness of the comparison treatment and how well the comparison treatment was equated to the target treatment.

Missing data is another important issue to consider when interpreting the results of any clinical trial. Patients who have a poor response to treatment may drop out prematurely; likewise, patients who improve rapidly may drop out because they no longer perceive the need for treatment. Analyzing data from treatment completers only can significantly bias results, but the direction of bias depends on who is dropping out of each condition. The gold standard for treatment research is to analyze data from all patients as randomized—"intention-to-treat analysis"—even if they never receive any treatment. To handle missing data, some investigators use the last available endpoint for a patient to fill in a patient's missing values, a strategy known as "last-endpoint-

carried-forward," but this also results in bias unless dropout is very low (Institute of Medicine, 2007). The best approach to missing data is to attempt to measure all patients regardless of treatment compliance and to use statistical methods that correctly account for missing data, such as hierarchical linear modeling.

Studies of Psychological Treatments

The largest number of studies on psychotherapy for PTSD indicates that cognitive-behavioral treatments, as well as Eye Movement Desensitization and Reprocessing (EMDR), are the most effective types. Both predominantly cognitive treatments (Ehlers et al., 2005; Monson et al., 2006; Resick et al., 2002) and predominantly behavioral treatments (Foa et al., 1999; Foa et al., 2005; Schnurr et al., 2007) are effective, as are cognitive-behavioral treatments combined with other approaches (e.g., Cloitre et al., 2002; Glynn et al., 1999). The Institute of Medicine (2007) recently reported that there was only sufficient evidence for exposure-based treatment, but in my view, the lack of support for cognitive approaches stemmed from the classification of cognitive treatments that include some exposure, such as Cognitive Processing Therapy (Resick et al., 2002), as exposure treatments, which resulted in an insufficient number of studies of cognitive therapies.

Although group therapy is widely used in VA, military, and civilian settings, there have been few RCTs of group therapy and the existing evidence is weak (e.g., Schnurr et al., 2003). However, a combination of group and individual formats for delivering Cognitive Processing Therapy appears promising (Chard, 2005). There is not enough evidence to draw conclusions about other approaches, including creative, dynamic, and complementary and alternative treatments.

Head-to-head comparisons between types of effective treatments typically show no substantive differences (e.g., Resick et al., 2002; Rothbaum et al., 2005), with few exceptions (e.g., Taylor et al., 2003) that are not consistent across the range of studies. Results of additive studies are similarly mixed (e.g., Bryant et al., 2003; Foa et al., 1999; Foa et al., 2005). For example, Bryant et al. (2003) found that cognitive restructuring added to exposure was superior to exposure alone, whereas Foa et al. (2005) found that cognitive restructuring conferred no additional benefit to the effects of exposure.

Statistical power is one possible explanation for the lack of differences among active treatments. Because differences between the effects of effective treatments are likely to be small, very large samples are needed to attain sufficient statistical power to detect these small differences. The effects of power are illustrated in a recent dismantling study of Cognitive Processing Therapy, which includes both cognitive and written exposure components (Resick et al., 2008). Even though the sample was large compared with many treatment studies—there were approximately 50 patients in each of three conditions—differences among treatments were detected only according to a longitudinal method that increased power (by examining trajectories of change). The cognitive component alone resulted in faster improvement than the written component alone, with the effects of standard Cognitive Processing Therapy falling between the effects of its components.

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Looking Toward the Future

Although research on new treatments continues to emerge, interest has shifted to other questions: specifically, how to make existing treatments more efficient and how to maximize the delivery of treatment through telehealth strategies. This work includes the use of virtual reality for exposure therapy (Difede et al., 2007) and therapist-assisted Internet delivery (Litz et al., 2007). There also is increasing interest in combining medication and psychotherapy to treat patients who fail to respond to treatment adequately. For example, Rothbaum et al. (2006) found that Prolonged Exposure improved outcomes in partial responders to an SSRI, although the converse may not be true: Simon et al. (2008) found that an SSRI did not improve outcomes in partial responders to Prolonged Exposure.

An additional topic that has received little systematic attention in PTSD is treatment matching. At present, effective treatments appear to be more similar than dissimilar. Our challenge for the future is how to determine the optimal treatment for each patient.

References

Schnurr, P.P. (2007). **The rocks and hard places in psychotherapy outcome research.** *Journal of Traumatic Stress, 20*, 779-792.

ABSTRACTS *Psychotherapy*

Bryant, R.A., Moulds, M.L., Guthrie, R.M., Dang, S.T., & Nixon, R.D.V. (2003). **Imaginal exposure alone and imaginal exposure with cognitive restructuring in treatment of posttraumatic stress disorder.** *Journal of Consulting and Clinical Psychology, 71*, 706-712. This study investigated the extent to which providing cognitive restructuring (CR) with prolonged imaginal exposure (IE) would lead to greater symptom reduction than providing IE alone for participants with PTSD. Fifty-eight civilian survivors of trauma with PTSD were randomly allocated to IE/CR, IE, or supportive counseling (SC). Treatment involved 8 individual weekly sessions with considerable homework. Independent assessments were conducted pretreatment, posttreatment, and at 6-month follow-up. IE/CR and IE resulted in reduced PTSD and depression compared with SC at posttreatment and follow-up. Further, IE/CR participants had greater reductions in PTSD and maladaptive cognitive styles than IE participants at follow-up. These findings suggest that providing CR in combination with IE may enhance treatment gains.

Cloitre, M., Koenen, K.C., Cohen, L.R., & Han, H. (2002). **Skills training in affective and interpersonal regulation followed by exposure: A phase-based treatment for PTSD related to childhood abuse.** *Journal of Consulting and Clinical Psychology, 70*, 1067-1074. Fifty-eight women with PTSD related to childhood abuse were randomly assigned to a 2-phase cognitive-behavioral treatment or a minimal attention wait list. Phase 1 of treatment included 8 weekly sessions of skills training in affect and interpersonal regulation; Phase 2 included 8 sessions of modified prolonged exposure. Compared with those on wait list, participants in active treatment showed significant improvement in affect regulation problems, interpersonal skills deficits, and PTSD symptoms. Gains were maintained at 3- and 9-month follow-up. Phase 1 therapeutic alliance and negative mood regulation skills predicted Phase 2 exposure success in reducing PTSD, suggesting

the value of establishing a strong therapeutic relationship and emotion regulation skills before exposure work among chronic PTSD populations.

Ehlers, A., Clark, D.M., Hackmann, A., McManus, F., & Fennell, M.J.V. (2005). **Cognitive therapy for post-traumatic stress disorder: Development and evaluation.** *Behaviour Research and Therapy, 43*, 413-431. The paper describes the development of a cognitive therapy (CT) program for PTSD that is based on a recent cognitive model. In a consecutive case series, 20 PTSD patients treated with CT showed highly significant improvement in symptoms of PTSD, depression and anxiety. A subsequent randomized controlled trial compared CT ($N = 14$) and a 3-month waitlist condition (WL, $N = 14$). CT led to large reductions in PTSD symptoms, disability, depression and anxiety, whereas the waitlist group did not improve. In both studies, treatment gains were well maintained at 6-month follow-up. CT was highly acceptable, with an overall dropout rate of only 3%. The intent-to-treat effect sizes for the degree of change in PTSD symptoms from pre- to post-treatment were 2.70-2.82 (self-report), and 2.07 (assessor-rated). The controlled effect sizes for CT versus WL post-treatment scores were 2.25 (self-report) and 2.18 (assessor-rated). As predicted by the cognitive model, good treatment outcome was related to greater changes in dysfunctional post-traumatic cognitions. Patient characteristics such as comorbidity, type of trauma, history of previous trauma, or time since the traumatic event did not predict treatment response; however, low educational attainment and low socioeconomic status were related to better outcome.

Foa, E.B., Hembree, E.A., Cahill, S.P., Rauch, S.A.M., Riggs, D.S., Feeny, N.C., & Yadin, E. (2005). **Randomized trial of prolonged exposure for posttraumatic stress disorder with and without cognitive restructuring: Outcome at academic and community clinics.** *Journal of Consulting and Clinical Psychology, 73*, 953-964. Female assault survivors ($N = 171$) with chronic PTSD were randomly assigned to prolonged exposure (PE) alone, PE plus cognitive restructuring (PE/CR), or wait list (WL). Treatment, which consisted of 9-12 sessions, was conducted at an academic treatment center or at a community clinic for rape survivors. Evaluations were conducted before and after therapy and at 3-, 6-, and 12-month follow-ups. Both treatments reduced PTSD and depression in intent-to-treat and completer samples compared with the WL condition; social functioning improved in the completer sample. The addition of CR did not enhance treatment outcome. No site differences were found: Treatment in the hands of counselors with minimal cognitive behavioral therapy (CBT) experience was as efficacious as that of CBT experts. Treatment gains were maintained at follow-up, although a minority of patients received additional treatment.

Litz, B.T., Engel, C.C., Bryant, R.A., & Papa, A. (2007). **A randomized, controlled proof-of-concept trial of an internet-based, therapist-assisted self-management treatment for posttraumatic stress disorder.** *American Journal of Psychiatry, 164*, 1676-1683. *Objective:* The authors report an 8-week randomized, controlled proof-of-concept trial of a new therapist-assisted, Internet-based, self-management cognitive behavior therapy versus Internet-based supportive counseling for PTSD. *Method:* Service members with PTSD from the attack on the Pentagon on September 11th or the Iraq War were randomly

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assigned to self-management cognitive behavior therapy ($N = 24$) or supportive counseling ($N = 21$). *Results:* The dropout rate was similar to regular cognitive behavior therapy (30%) and unrelated to treatment arm. In the intent-to-treat group, self-management cognitive behavior therapy led to sharper declines in daily log-on ratings of PTSD symptoms and global depression. In the completer group, self-management cognitive behavior therapy led to greater reductions in PTSD, depression, and anxiety scores at 6 months. One-third of those who completed self-management cognitive behavior therapy achieved high-end state functioning at 6 months. *Conclusions:* Self-management cognitive behavior therapy may be a way of delivering effective treatment to large numbers with unmet needs and barriers to care.

Monson, C.M., Schnurr, P.P., Resick, P.A., Friedman, M.J., Young-Xu, Y., & Stevens, S.P. (2006). **Cognitive processing therapy for veterans with military-related posttraumatic stress disorder.** *Journal of Consulting and Clinical Psychology, 74*, 898-907. Sixty veterans (54 men, 6 women) with chronic military-related PTSD participated in a wait-list controlled trial of cognitive processing therapy (CPT). The overall dropout rate was 16.6% (20% from CPT, 13% from waiting list). Random regression analyses of the intention-to-treat sample revealed significant improvements in PTSD and comorbid symptoms in the CPT condition compared with the wait-list condition. 40% of the intention-to-treat sample receiving CPT did not meet criteria for a PTSD diagnosis, and 50% had a reliable change in their PTSD symptoms at posttreatment assessment. There was no relationship between PTSD disability status and outcomes. This trial provides some of the most encouraging results of PTSD treatment for veterans with chronic PTSD and supports increased use of cognitive-behavioral treatments in this population.

Resick, P.A., Galovski, T.E., Uhlmansiek, M.O., Scher, C.D., Clum, G.A., & Young-Xu, Y. (2008). **A randomized clinical trial to dismantle components of cognitive processing therapy for posttraumatic stress disorder in female victims of interpersonal violence.** *Journal of Consulting and Clinical Psychology, 76*, 243-258. The purpose of this experiment was to conduct a dismantling study of cognitive processing therapy in which the full protocol was compared with its constituent components - cognitive therapy only (CPT-C) and written accounts (WA) - for the treatment of PTSD and comorbid symptoms. The intent-to-treat (ITT) sample included 150 adult women with PTSD who were randomized into 1 of the 3 conditions. Each condition consisted of 2 hours of therapy per week for 6 weeks; blind assessments were conducted before treatment, 2 weeks following the last session, and 6 months following treatment. Measures of PTSD and depression were collected weekly to examine the course of recovery during treatment as well as before and after treatment. Secondary measures assessed anxiety, anger, shame, guilt, and dysfunctional cognitions. Independent ratings of adherence and competence were also conducted. Analyses with the ITT sample and with study completers indicate that patients in all 3 treatments improved substantially on PTSD and depression, the primary measures, and improved on other indices of adjustment. However, there were significant group differences in symptom reduction during the course of treatment whereby the CPT-C condition reported greater improvement in PTSD than the WA condition.

Rothbaum, B.O. (1997). **A controlled study of eye movement desensitization and reprocessing in the treatment of posttraumatic stress disorder sexual assault victims.** *Bulletin of the Menninger Clinic, 61*, 317-334. Eye movement desensitization and reprocessing (EMDR) is a new method developed to treat PTSD. This study evaluated the efficacy of EMDR compared to a no-treatment wait-list control in the treatment of PTSD in adult female sexual assault victims. 21 subjects were entered and 18 completed. Treatment was delivered in 4 weekly individual sessions. Assessments were conducted pre- and posttreatment and 3 months following treatment termination by an independent assessor kept blind to treatment condition. Measures included standard clinician- and self-administered PTSD and related psychopathology scales. Results indicated that subjects treated with EMDR improved significantly more on PTSD and depression from pre- to posttreatment than control subjects, leading to the conclusion that EMDR was effective in alleviating PTSD in this study.

Rothbaum, B.O., Cahill, S.P., Foa, E.B., Davidson, J.R.T., Compton, J.S., Connor, K.M., Astin, M.C., & Hahn, C.-G. (2006). **Augmentation of sertraline with prolonged exposure in the treatment of posttraumatic stress disorder.** *Journal of Traumatic Stress, 19*, 625-638. The present study was designed to determine whether augmenting sertraline with prolonged exposure (PE) would result in greater improvement than continuation with sertraline alone. Outpatient men and women with chronic PTSD completed 10 weeks of open label sertraline and then were randomly assigned to five additional weeks of sertraline alone ($n = 31$) or sertraline plus 10 sessions of twice-weekly PE ($n = 34$). Results indicated that sertraline led to a significant reduction in PTSD severity after 10 weeks but was associated with no further reductions after five more weeks. Participants who received PE showed further reduction in PTSD severity. This augmentation effect was observed only for participants who showed a partial response to medication.

Schnurr, P.P., Friedman, M.J., Foy, D.W., Shea, M.T., Hsieh, F.Y., Lavori, P.W., Glynn, S.M., Wattenberg, M., & Bernardy, N.C. (2003). **A randomized trial of trauma-focused group therapy for posttraumatic stress disorder: Results from a Department of Veterans Affairs Cooperative Study.** *Archives of General Psychiatry, 60*, 481-489. *Background:* Department of Veterans Affairs Cooperative Study 420 is a randomized clinical trial of 2 methods of group psychotherapy for treating posttraumatic stress disorder (PTSD) in male Vietnam veterans. *Methods:* Vietnam veterans (360 men) were randomly assigned to receive trauma-focused group psychotherapy or a present-centered comparison treatment that avoided trauma focus. Treatment was provided weekly to groups of 6 members for 30 weeks, followed by 5 monthly booster sessions. Severity of PTSD was the primary outcome. Additional measures were other psychiatric symptoms, functional status, quality of life, physical health, and service utilization. Follow-up assessments were conducted at the end of treatment (7 months) and at the end of the booster sessions (12 months); 325 individuals participated in 1 or both assessments. Additional follow-up for PTSD severity was performed in a subset of participants at 18 and 24 months. *Results:* Although posttreatment assessments of PTSD severity and other measures were significantly improved from baseline, intention-to-treat analyses found no overall differences between therapy groups on

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any outcome. Analyses of data from participants who received an adequate dose of treatment suggested that trauma-focused group therapy reduced avoidance and numbing and, possibly, PTSD symptoms. Dropout from treatment was higher in trauma-focused group treatment. Average improvement was modest in both treatments, although approximately 40% of participants showed clinically significant change. *Conclusions:* This study did not find a treatment effect for trauma-focused group therapy. The difference between the effectiveness and adequate dose findings suggests the possible value of methods to enhance the delivery of cognitive-behavioral treatments in clinical practice settings.

Schnurr, P.P., Friedman, M.J., Engel, C.C., Foa, E.B., Shea, M.T., Chow, B.K., et al. (2007). **Cognitive behavioral therapy for posttraumatic stress disorder in women: A randomized controlled trial.** *Journal of the American Medical Association, 297, 820-830.* *Context:* The prevalence of PTSD is elevated among women who have served in the military, but no prior study has evaluated treatment for PTSD in this population. Prior research suggests that cognitive behavioral therapy is a particularly effective treatment for PTSD. *Objective:* To compare prolonged exposure, a type of cognitive behavioral therapy, with present-centered therapy, a supportive intervention, for the treatment of PTSD. *Design, Setting, and Participants:* A randomized controlled trial of female veterans ($n = 277$) and active-duty personnel ($n = 7$) with PTSD recruited from 9 VA medical centers, 2 VA readjustment counseling centers, and 1 military hospital from August 2002 through October 2005. *Intervention:* Participants were randomly assigned to receive prolonged exposure ($n = 141$) or present-centered therapy ($n = 143$), delivered according to standard protocols in 10 weekly 90-minute sessions. *Main Outcome Measures:* PTSD symptom severity was the primary outcome. Comorbid symptoms, functioning, and quality of life were secondary outcomes. Blinded assessors collected data before and after treatment and at 3- and 6-month follow-up. *Results:* Women who received prolonged exposure experienced greater reduction of PTSD symptoms relative to women who received present-centered therapy (effect size, 0.27; $P = .03$). The prolonged exposure group was more likely than the present-centered therapy group to no longer meet PTSD diagnostic criteria (41.0% vs 27.8%; odds ratio, 1.80; 95% confidence interval, 1.10-2.96; $P = .01$) and achieve total remission (15.2% vs 6.9%; odds ratio, 2.43; 95% confidence interval, 1.10-5.37; $P = .01$). Effects were consistent over time in longitudinal analyses, although in cross-sectional analyses most differences occurred immediately after treatment. *Conclusions:* Prolonged exposure is an effective treatment for PTSD in female veterans and active-duty military personnel. It is feasible to implement prolonged exposure across a range of clinical settings.

Taylor, S., Thordarson, D.S., Maxfield, L., Fedoroff, I.C., Lovell, K., & Ogrodniczuk, J.S. (2003). **Comparative efficacy, speed, and adverse effects of three PTSD treatments: Exposure therapy, EMDR, and relaxation training.** *Journal of Consulting and Clinical Psychology, 71, 330-338.* The authors examined the efficacy, speed, and incidence of symptom worsening for 3 treatments of PTSD: prolonged exposure, relaxation training, or eye movement desensitization and reprocessing (EMDR; $N = 60$). Treatments did not differ in attrition, in the incidence of symptom worsening, or in their effects on numbing and hyperarousal symptoms. Compared with EMDR and relaxation training, exposure therapy (a) produced significantly larger reductions in avoidance and reexperiencing

symptoms, (b) tended to be faster at reducing avoidance, and (c) tended to yield a greater proportion of participants who no longer met criteria for PTSD after treatment. EMDR and relaxation did not differ from one another in speed or efficacy.

CITATIONS *Psychotherapy*

Chard, K.M. (2005). **An evaluation of cognitive processing therapy for the treatment of posttraumatic stress disorder related to childhood sexual abuse.** *Journal of Consulting and Clinical Psychology, 73, 965-971.* Women with PTSD and histories of child abuse were recruited from the community and randomized to Cognitive Processing Therapy ($n = 36$) or a minimal attention condition ($n = 36$). The active treatment group, which received both individual and group therapy, showed significant improvements over time, whereas the control group did not. Effect sizes were large.

Cusack, K., & Spates, C.R. (1999). **The cognitive dismantling of eye movement desensitization and reprocessing (EMDR) treatment of posttraumatic stress disorder (PTSD).** *Journal of Anxiety Disorders, 13, 87-99.* The authors addressed the role of the cognitive reprocessing component of EMDR Treatment for PTSD. The 27 participants, who had PTSD related to a range of events, were randomized to standard EMDR or EMDR without reprocessing (EMD). No difference between conditions was detected.

Difede, J., Cukor, J., Jayasinghe, N., Patt, I., Jedel, S., Spielman, L., et al. (2007). **Virtual reality exposure therapy for the treatment of posttraumatic stress disorder following September 11, 2001.** *Journal of Clinical Psychiatry, 68, 1639-1647.* Virtual reality (VR) as a method of exposure therapy was tested in a sample of direct victims of a terrorist attack, all of whom had PTSD. Participants assigned to VR ($n = 10$) showed greater improvement over time than did waitlist controls ($n = 8$). The authors provide a useful description of the novel treatment.

Foa, E.B., Dancu, C.V., Hembree, E.A., Jaycox, L.H., Meadows, E.A., & Street, G.P. (1999). **A comparison of exposure therapy, stress inoculation training, and their combination for reducing posttraumatic stress disorder in female assault victims.** *Journal of Consulting and Clinical Psychology, 67, 194-200.* To test the idea that the combination of prolonged exposure (PE) and stress-inoculation training (SIT) would produce better results than either alone, the authors compared three active treatments (PE, SIT, PE+SIT). In intention-to-treat analyses, PE was superior to the other active treatments, as well as to the waitlist control group. The effect may have been attributable to the lower drop-out rate in the PE condition.

Glynn, S.M., Eth, S., Randolph, E.T., Foy, D.W., Urbaitis, M., Boxer, L., et al. (1999). **A test of behavioral family therapy to augment exposure for combat-related posttraumatic stress disorder.** *Journal of Consulting and Clinical Psychology, 67, 243-251.* The authors believed that symptoms of avoidance and numbing might be targeted by behavioral family therapy (BFT) offered in combination with exposure therapy (DTE). Male veterans ($n = 42$) were randomized to DTE, DTE+BFT, or waitlist. No differences between the two active treatments were detected. Issues of BFT drop-out and dose were discussed.

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Resick, P.A., Nishith, P., Weaver, T.L., Astin, M.C., & Feuer, C.A. (2002). **A comparison of cognitive-processing therapy with prolonged exposure and a waiting condition for the treatment of chronic posttraumatic stress disorder in female rape victims.** *Journal of Consulting and Clinical Psychology, 70*, 867-879. Cognitive processing therapy was compared to prolonged exposure and a minimal attention condition in a randomized controlled trial conducted with 171 female rape victims with PTSD. Both active treatments produced significant improvements but did not differ from each other on primary outcome measures.

Rothbaum, B.O., Astin, M.C., & Marsteller, F. (2005). **Prolonged exposure versus eye movement desensitization and reprocessing (EMDR) for PTSD rape victims.** *Journal of Traumatic Stress, 18*, 607-616. Prolonged Exposure (PE) and Eye Movement Desensitization and Reprocessing (EMDR) therapies were compared to each other and to a waitlist control in a randomized trial involving 74 female rape victims with PTSD. Careful attention to monitoring therapist fidelity to the PE and EMDR models facilitated validity of comparisons. Improvements were comparable in the two active treatments; both conditions improved more than waitlist controls.

Simon, N.M., Connor, K.M., Lang, A.J., Rauch, S., Krulewicz, S., LeBeau, R.T., et al. (2008) **Paroxetine CR augmentation for posttraumatic stress disorder refractory to prolonged exposure therapy.** *Journal of Clinical Psychiatry, 69*, 400-405. Patients who remained symptomatic after prolonged exposure (PE) therapy were randomized to receive paroxetine CR ($n = 9$) or placebo ($n = 14$), along with additional PE. The two groups did not differ, both showing minimal further improvement.

disagreement whether pharmacotherapy should be considered a first-line treatment for PTSD. IOM and NICE have argued to the contrary, while others have maintained a favorable opinion on the efficacy of SSRIs and a few other medications. Although it is beyond the scope of this review to discuss this disagreement in depth, it is clear that CBT has consistently proven more effective than pharmacotherapy. Furthermore, when you consider that over twenty different medications have been tested on different populations in approximately fifty studies, there really haven't been too many replications of either positive or negative results.

A few words are in order about dosage and control groups. Although each reviewed study reports the prescribed dose of a given medication, it's not always clear how much medication was received by each study participant for two reasons. First, there are often differences in patient compliance (e.g. how well they followed the dosing directions). Second, patients who receive the same dose of a given medication may have different blood levels of that medication because of individual differences in metabolic capacity. Some, but not most, of these studies attempt to address these concerns by measuring medication blood levels, the number of pills that were taken, or both blood levels and pill counts. On the other hand, most studies do not do this sort of monitoring. So it's something to keep in mind when considering each report.

As for control groups, most of these studies have used an inactive placebo, so you might expect that it would be easy for both clinicians and participants to distinguish whether they are on an active medication or not. Usually, neither patients nor clinicians can tell the difference because complaints about side effects are frequently voiced by those on placebo as well as those on active agents.

Since it is impossible to cite all relevant RCTs on pharmacotherapy, this current *Research Quarterly* will provide a sampler of the major areas of research. Readers are referred to Friedman and Davidson (2007) and Friedman et al. (in press) for a comprehensive review of this expanding literature. Here, we mention exemplars of specific clinical trials.

Antidepressants

SSRIs have received the most attention. Two medications, sertraline and paroxetine, have received approval by the US Food and Drug Administration as indicated treatments for PTSD. In large multisite industry-sponsored trials with mostly civilian participants, positive findings have been obtained with sertraline (Brady et al., 2000; Davidson et al., 2001) and paroxetine (Marshall et al., 2001; Tucker et al., 2001). A large study with the SSRI fluoxetine, with military veterans (Martenyi, Brown, Zhang, Prakash, & Koke, 2002), was also positive. On the other hand, negative findings have been reported in a multisite trial of sertraline among US veterans in VA hospital settings (Friedman et al., 2007), and an RCT with fluoxetine among mostly civilian women was also negative (Martenyi et al., 2007). The effect sizes for successful SSRI trials have generally been in the medium range, compared to large effect sizes for CBT studies (see Friedman, Davidson, & Stein, in press). Finally, Rothbaum et al. (2006) showed that SSRI partial responders achieved further improvement after medication treatment was augmented by prolonged exposure therapy.

Two multisite trials with the selective serotonin/norepinephrine

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reuptake inhibitor, venlafaxine, have also been reported in which the medication was significantly more effective than placebo (Davidson et al., 2006a, 2006b). In other RCTs, nefazadone performed as well as sertraline and better than placebo in three clinical trials, while mixed results have been found with mirtazepine (see Friedman, Davidson, & Stein, in press).

Antiadrenergic Agents

Interest in antiadrenergic agents dates back to the mid-1980s. Unfortunately, no RCTs with such medications have been carried out until recently. Given the adrenergic dysregulation associated with PTSD, such trials have been awaited with great anticipation. Prazosin, an alpha-1 post-synaptic receptor antagonist, has shown consistent efficacy in preventing traumatic nightmares and inconsistent success in reducing PTSD symptoms (possibly because it was only administered once a day, at bedtime) (Raskind et al., 2007). A large multisite replication is currently in progress. In a small pilot RCT, propranolol, a post-synaptic beta receptor antagonist, has shown promise in preventing PTSD-related psychophysiological arousal but not PTSD among emergency room patients who received the medication within six hours of their traumatic event (Pitman et al., 2002). The theoretical rationale was to prevent posttraumatic adrenergic-mediated hyperarousal and consolidation of traumatic memories. Another provocative pilot study among individuals with chronic PTSD indicated that administration of propranolol after reactivation of traumatic memories reduced physiological arousal during subsequent mental imagery of the event (Brunet et al., 2007). These results are consistent with the hypothesis that propranolol prevented reconsolidation of traumatic memories after they had been elicited during the experimental protocol. Finally, guanfacine, the alpha-2 presynaptic agonist, was ineffective, compared to placebo, among Vietnam veterans treated within a VA setting (Neylan et al., 2006). These intriguing findings are exciting from both a theoretical and practical standpoint. Therefore, it is gratifying that further studies with these three different adrenergic agents are in progress.

Atypical Antipsychotic Agents

As noted earlier, SSRI treatment is not always effective, especially with chronic patients. Several small RCTs, mostly in VA clinical settings, have administered the atypical antipsychotic agents risperidone and olanzapine to antidepressant/SSRI non-responders (Bartzokis et al., 2004; Reich et al., 2004; see Friedman & Davidson, 2007; and Friedman et al., in press, for additional references). In all cases, patients exhibited a favorable response. A large multisite replication study is currently in progress.

D-Cycloserine

A classical Pavlovian fear conditioning model has provided a very useful heuristic for understanding the pathophysiology of PTSD. Within this context, amelioration of conditioned fear is accomplished through extinction. Extinction occurs because new responses are learned to conditioned stimuli so that fearful (or traumatic) stimuli no longer elicit the conditioned fear response (or expression of PTSD symptoms). In recent years, animal researchers have shown that extinction of fear responses can be accelerated by administering d-cycloserine (DCS). Acting as a partial agonist at the glutamatergic NMDA receptor (which mediates learning and memory), DCS enhances extinction of fear responses. Prolonged exposure, which

is based on a fear conditioning model, is the very successful CBT approach designed to promote the new learning that leads to extinction of PTSD symptoms. Combining exposure therapy with DCS has led to faster extinction than with exposure therapy alone in acrophobia and social phobia. Research currently in progress will determine whether a similar approach will benefit PTSD patients. Davis et al. (2006) provide an excellent review of theory and research concerning DCS.

Benzodiazepines and Mood Stabilizers

There are theoretical reasons to postulate that medications that enhance neurotransmission of inhibitory GABAergic neurons would be effective treatments for PTSD. Unfortunately, that has not proven to be the case with the benzodiazepine alprazolam (Braun et al., 1990) or with two mood stabilizers that enhance GABA activity. Large RCTs with tiagabine and valproate have both had negative results (Davidson et al., 2007; Davis et al., 2008). In short, there is little current evidence suggesting that GABA receptors are a useful target for PTSD pharmacotherapy.

Summary

The good news is that clinical investigators are moving beyond the testing of conventional antidepressants and considering medications that might be expected to ameliorate the psychobiological abnormalities associated with PTSD. Much more research is needed, especially with anti-adrenergic agents, DCS, and other medications currently under development.

ABSTRACTS *Pharmacotherapy*

Brady, K., Pearlstein, T., Asnis, G.M., Baker, D., Rothbaum, B., Sikes, C.R., et al. (2000). **Efficacy and safety of sertraline treatment of posttraumatic stress disorder: A randomized controlled trial.**

Journal of the American Medical Association, 283, 1837-1844.

Despite the high prevalence, chronicity, and associated comorbidity of PTSD in the community, few placebo-controlled studies have evaluated the efficacy of pharmacotherapy for this disorder. To determine if treatment with sertraline hydrochloride effectively diminishes symptoms of PTSD of moderate to marked severity, a 12-week, double-blind, placebo-controlled trial followed a 2-week, single-blind placebo lead-in period. Participants were 187 outpatients with a DSM-III-R diagnosis of PTSD and a Clinician Administered PTSD Scale Part 2 (CAPS-2) total severity score of at least 50 at baseline. Patients were randomized to acute treatment with sertraline hydrochloride in flexible daily dosages of 50 to 200 mg/d, following 1 week at 25 mg/d ($n = 94$); or placebo ($n = 93$). Sertraline treatment yielded significantly greater improvement than placebo on 3 of the 4 primary outcome measures (mean change from baseline to end point for CAPS-2 total score, -33.0 vs -23.2), with the fourth measure, the IES total score, showing a trend toward significance. Using a conservative last-observation-carried-forward analysis, treatment with sertraline resulted in a responder rate of 53% at study end point compared with 32% for placebo. Significant efficacy was evident for sertraline from week 2 on the CAPS-2 total severity score. Sertraline was well tolerated, with insomnia the only adverse effect reported significantly more often than placebo (16.0% vs 4.3%). Our data suggest that sertraline is a safe, well-tolerated, and effective treatment for PTSD. [Abstract Adapted]

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Brunet, A., Orr, S.P., Tremblay, J., Robertson, K., Nader, K., & Pitman, R.K. (2007). **Effect of post-retrieval propranolol on psychophysiologic responding during subsequent script-driven traumatic imagery in posttraumatic stress disorder.** *Journal of Psychiatric Research, 42*, 503-506. The β -adrenergic blocker propranolol, given within hours of a psychologically traumatic event, reduces physiologic responses during subsequent mental imagery of the event. Here we tested the effect of propranolol given after the retrieval of memories of past traumatic events. Subjects with chronic PTSD described their traumatic event during a script preparation session and then received a one-day dose of propranolol ($n = 9$) or placebo ($n = 10$), randomized and double-blind. A week later, they engaged in script-driven mental imagery of their traumatic event while heart rate, skin conductance, and left corrugator electromyogram were measured. Physiologic responses were significantly smaller in the subjects who had received post-reactivation propranolol a week earlier. [Abstract Adapted]

Davidson, J.R.T., Rothbaum, B.O., Van der Kolk, B.A., Sikes, C.R., & Farfel, G.M. (2001). **Multicenter, double-blind comparison of sertraline and placebo in the treatment of posttraumatic stress disorder.** *Archives of General Psychiatry, 58*, 485-492. Outpatients with a DSM-III-R diagnosis of moderate-to-severe PTSD were randomized to 12 weeks of double-blind treatment with either sertraline ($N = 100$) in flexible daily doses in the range of 50 to 200 mg or placebo ($N = 108$). Primary outcome measures consisted of the Clinician-Administered PTSD Scale (CAPS-2) total severity score, the patient-rated Impact of Event Scale (IES), and the Clinical Global Impression-Severity (CGI-S) and -Improvement (CGI-I) ratings. Mixed-effects analyses found significantly steeper improvement slopes for sertraline compared with placebo on the CAPS-2, the IES, the CGI-I score, and the CGI-S score. An intent-to-treat end-point analysis found a 60% responder rate for sertraline and a 38% responder rate for placebo. Sertraline treatment was well tolerated, with a 9% discontinuation rate because of adverse events, compared with 5% for placebo. Adverse events that were significantly more common in subjects given sertraline compared with placebo consisted of insomnia (35% vs 22%), diarrhea (28% vs 11%), nausea (23% vs 11%), fatigue (13% vs 5%), and decreased appetite (12% vs 1%). The results of the current study suggest that sertraline is a safe, well-tolerated, and significantly effective treatment for PTSD. [Abstract Adapted]

Davidson, J.R.T., Rothbaum, B.O., Tucker, P., Asnis, G., Benattia, I., & Musngung, J.J. (2006a). **Venlafaxine extended release in posttraumatic stress disorder: A sertraline- and placebo-controlled study.** *Journal of Clinical Psychopharmacology, 26*, 259-267. This 12-week, double-blind, multicenter trial evaluated the efficacy of venlafaxine extended release (ER), sertraline, and placebo in adult outpatients ($N = 538$) with a primary diagnosis of PTSD, as defined in DSM-IV, symptoms for 6 months or more, and 17-item Clinician-Administered PTSD Scale (CAPS-SX17) score of 60 or more. Patients were randomly assigned to receive placebo or flexible doses of venlafaxine ER (37.5-300 mg/day) or sertraline (25-200 mg/day) for 12 weeks or less. The primary outcome was the baseline-to-end-point change in total CAPS-SX17 score (last observation carried forward). Secondary measures included CAPS-SX17 symptom cluster scores for reexperiencing/intrusion, avoidance/numbing, and hyperarousal; frequency of remission (CAPS-SX17 ≥ 4 20); and changes in Davidson Trauma Scale total score and symptom cluster

scores for avoidance/numbing, hyperarousal, and reexperiencing/intrusion. Week 12 remission rates were venlafaxine ER 30.2% ($P < 0.05$ vs. placebo), sertraline 24.3%, and placebo 19.6%. Both treatments were generally well tolerated. Study results suggest that venlafaxine ER is effective and well tolerated in the short-term treatment of PTSD. [Abstract Adapted]

Davidson, J.R.T., Baldwin, D.S., Stein, D.J., Kuper, E., Benattia, I., Ahmed, S., et al. (2006b). **Treatment of posttraumatic stress disorder with venlafaxine extended release: A 6-month randomized, controlled trial.** *Archives of General Psychiatry, 63*, 1158-1165. To evaluate the efficacy of venlafaxine extended release (ER), a serotonin norepinephrine reuptake inhibitor, in PTSD, a 6-month, double-blind, placebo-controlled trial was conducted at 56 sites with 329 adult outpatients with a primary diagnosis of PTSD as defined in the DSM-IV, symptoms for 6 months or longer, and a 17-item Clinician-Administered PTSD Scale (CAPS) score of 60 or higher. Patients were randomly assigned to receive flexible doses of venlafaxine ER (37.5-300 mg/day) or placebo for 24 weeks. Mean changes from baseline in CAPS total scores at end point were -51.7 for venlafaxine ER and -43.9 for placebo. Improvement was significantly greater for the venlafaxine ER group than for the placebo group in cluster scores for reexperiencing and avoidance/numbing, but not for hyperarousal. Remission rates were 50.9% for venlafaxine ER and 37.5% for placebo. The venlafaxine ER group also showed significantly greater improvement at end point than the placebo group on all other reported outcome measures. The mean maximum daily dose of venlafaxine ER was 221.5 mg/day. Withdrawal rates were similar between groups with no significant difference in dropouts attributable to adverse events. In this study, venlafaxine ER was effective and well tolerated in short-term and continuation treatment of patients with PTSD. [Abstract Adapted]

Davis, M., Ressler, K., Rothbaum, B.O., & Richardson, R. (2006). **Effects of D-cycloserine on extinction: Translation from preclinical to clinical work.** *Biological Psychiatry, 60*, 369-375. Administration of benzodiazepines and serotonin reuptake inhibitors in combination with behavior therapy for the treatment of many anxiety disorders has generally led to only modest gains. In this article we suggest that pharmacotherapy aimed not at treating the symptoms of anxiety but instead aimed at improving the learning that takes place in exposure therapy might actually improve the effectiveness of exposure therapy. This was verified in a small clinical study showing that DCS facilitated exposure therapy for fear of heights in a well-controlled virtual reality environment. [Abstract Adapted]

Friedman, M.J., Marmar, C.R., Baker, D.G., Sikes, C.R., & Farfel, G.M. (2007). **Randomized, double-blind comparison of sertraline and placebo for posttraumatic stress disorder in a Department of Veterans Affairs setting.** *Journal of Clinical Psychiatry, 68*, 711-720. To evaluate the efficacy of sertraline in the treatment of combat-related PTSD, 169 outpatients with a DSM-III-R diagnosis of PTSD and who scored 50 or higher on Part 2 of the Clinician-Administered PTSD Scale (CAPS-2) at the end of a 1-week placebo were studied. Patients recruited from 10 VA medical centers were randomly assigned to 12 weeks of flexibly dosed sertraline (25-200 mg/day) ($N = 86$), or placebo ($N = 83$). The primary efficacy measures were the mean change in CAPS-2 total severity score from baseline to endpoint, in the total score from the Impact of Event Scale, and in the Clinical Global Impressions - Severity of Illness and

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Improvement scales. There were no significant differences between sertraline and placebo on any of the primary or secondary efficacy measures at endpoint. Sertraline was well tolerated, with 13% of patients discontinuing due to adverse events. Sertraline was not demonstrated to be efficacious in the treatment of PTSD in the VA clinic settings studied. [Abstract Adapted]

Marshall, R.D., Beebe, K.L., Oldham, M., & Zaninelli, R. (2001). **Efficacy and safety of paroxetine treatment for chronic PTSD: A fixed-dose, placebo-controlled study.** *American Journal of Psychiatry, 158*, 1982-1988. This study evaluated the efficacy and safety of paroxetine for the treatment of patients with chronic PTSD. Outpatients with chronic PTSD according to DSM-IV criteria and a score of 50 or more on the Clinician-Administered PTSD Scale, part 2, were randomly assigned to take placebo ($N = 186$), 20 mg/day of paroxetine ($N = 183$), or 40 mg/day of paroxetine ($N = 182$) for 12 weeks. Efficacy was assessed by examining the change in total score from baseline to endpoint on the Clinician-Administered PTSD Scale, part 2, and rates of response (“very much improved” or “much improved”) for global improvement on the Clinical Global Impression scale. Paroxetine-treated patients in both dose groups demonstrated significantly greater improvement on primary outcome measures compared to placebo-treated patients in the intent-to-treat analysis. Both doses were well tolerated. Doses of 20 and 40 mg/day of paroxetine are effective and well tolerated in the treatment of adults with chronic PTSD. [Abstract Adapted]

Martenyi, F., Brown, E.B., Zhang, H., Prakash, A., & Koke, S.C. (2002). **Fluoxetine versus placebo in posttraumatic stress disorder.** *Journal of Clinical Psychiatry, 63*, 199-206. This study was designed to address the efficacy and tolerability of fluoxetine in patients with PTSD as diagnosed using the Structured Clinical Interview for DSM-IV Axis I Disorders and the Clinician-Administered PTSD Scale (CAPS). The patient population included both civilians and combat veterans. This was a double-blind, randomized, placebo-controlled study conducted in Europe, Israel, and South Africa, primarily in war-torn countries. Patients were randomly assigned to 12 weeks of acute treatment with fluoxetine, 20 to 80 mg/day ($N = 226$), or placebo ($N = 75$). The primary efficacy measurement was the mean change from baseline in the Treatment Outcome PTSD rating scale (TOP-8) total score, which was analyzed using a repeated measures analysis of variance. Secondary assessments included the CAPS, the Davidson Trauma Scale, the Clinical Global Impressions-Severity of Illness Scale (CGI-S), the CGI-Improvement Scale (CGI-I), the Montgomery-Asberg Depression Rating Scale (MADRS), the Hamilton Rating Scale for Anxiety (HAM-A), and the Hopkins 90-Item Symptom Checklist-Revised. Fluoxetine was associated with a greater improvement from baseline in total TOP-8 score than was placebo. This difference was statistically significant by week 6 of treatment through the end of the acute phase of the study. Compared with placebo, fluoxetine was also associated with significantly greater improvement in CAPS total score and in CGI-S, CGI-I, HAM-A, and MADRS scores. There were no clinically significant safety differences. Fluoxetine is effective and well tolerated in the treatment of PTSD. Most PTSD patients will respond satisfactorily at doses in the upper normal range for the usual antidepressant doses of fluoxetine. [Abstract Adapted]

Martenyi, F., Brown, E.B., & Caldwell, C.D. (2007). **Failed efficacy of fluoxetine in the treatment of posttraumatic stress disorder: Results of a fixed-dose, placebo-controlled study.** *Journal of Clinical Psychopharmacology, 27*, 166-170. A multicenter, double-blind, 12-week, placebo-controlled trial of 411 randomized patients, predominantly women diagnosed with PTSD, failed to show a difference between either dose of fluoxetine treatment and placebo. The mean changes from baseline (SD) measured by the Clinician-Administered PTSD Scale scores were -42.9 (23.1), -42.8 (27.9), and -36.6 (25.7) in the 20-mg fluoxetine, 40-mg fluoxetine, and placebo arms, respectively. Placebo response rate was substantially higher in this study than in a previously published fluoxetine trial of PTSD.

Pitman, R.K., Sanders, K.M., Zusman, R.M., Healy, A.R., Cheema, F., Lasko, B., et al. (2002). **Pilot study of secondary prevention of posttraumatic stress disorder with propranolol.** *Biological Psychiatry, 51*, 189-192. Preclinical considerations suggest that treatment with a beta-adrenergic blocker following an acute psychologically traumatic event may reduce subsequent PTSD symptoms. This pilot study addressed this hypothesis. Patients were randomized to begin, within 6 hours of the event, a 10-day course of double-blind propranolol ($n = 18$) versus placebo ($n = 23$) 40 mg four times daily. These pilot results suggest that acute, post-trauma propranolol may have a preventive effect on subsequent PTSD. [Abstract Adapted]

Raskind, M.A., Peskind, E.R., Hoff, D.J., Hart, K.L., Holmes, H.A., Warren, D., et al. (2007). **A parallel group placebo controlled study of prazosin for trauma nightmares and sleep disturbances in combat veterans with post-traumatic stress disorder.** *Biological Psychiatry, 61*, 928-934. Excessive brain responsiveness to norepinephrine appears to contribute to PTSD, particularly at night. Prazosin, a brain active alpha-1 adrenergic receptor antagonist, significantly reduced trauma nightmares and sleep disturbance in 10 Vietnam War combat veterans in a previous placebo-controlled crossover study. The current parallel group trial in a larger sample of veterans evaluated prazosin effects on trauma nightmares, sleep quality, global clinical status, dream characteristics, and comorbid depression. Forty veterans (mean age 56 ± 9) with chronic PTSD and distressing trauma nightmares and sleep disturbance were randomized to evening prazosin (13.3 ± 3 mg/day) or placebo for 8 weeks. In the evaluable sample ($n = 34$), primary outcome measures demonstrated that prazosin was significantly superior to placebo for reducing trauma nightmares and improving sleep quality and global clinical status with large effect sizes. Prazosin shifted dream characteristics from those typical of trauma-related nightmares toward those typical of normal dreams. Blood pressure changes from baseline to end study did not differ significantly between prazosin and placebo. Prazosin is an effective and well-tolerated treatment for trauma nightmares, sleep disturbance, and global clinical status in veterans with chronic PTSD. [Abstract Adapted]

Tucker, P., Zaninelli, R., Yehuda, R., Ruggiero, L., Dillingham, K., & Pitts, C.D. (2001). **Paroxetine in the treatment of chronic posttraumatic stress disorder: Results of a placebo-controlled, flexible-dosage trial.** *Journal of Clinical Psychiatry, 62*, 860-868. The objective of this double-blind, placebo-controlled study was to investigate the efficacy and safety of paroxetine in outpatients with PTSD. Outpatients who met DSM-IV criteria for PTSD and had baseline scores of 50 or greater on the Clinician Administered

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PTSD Scale (CAPS-2) were randomly assigned to treatment with paroxetine (20-50 mg/day) or placebo for 12 weeks. The primary efficacy variables were the change from baseline to the 12-week endpoint in the CAPS-2 total score and the proportion of responders on the Clinical Global Impressions-Global Improvement scale (CGI-I). Three hundred seven patients constituted the intent-to-treat population. At week 12, compared with the placebo group ($N = 156$), the paroxetine group ($N = 151$) showed significantly greater reduction of PTSD symptoms on both of the primary and all of the secondary outcome measures. Significantly greater improvement on the CAPS-2 total score was observed for paroxetine compared with placebo from week 4 and significantly greater proportions of paroxetine-treated patients achieved response and remission by week 12. Functional improvement at the study endpoint was significantly greater in the paroxetine group in all 3 domains (work, social life, family life). Treatment with paroxetine was well tolerated, with the frequency and type of adverse events recorded for the paroxetine group corresponding to the known safety profile of this medication. Paroxetine in doses of 20 to 50 mg once daily is effective as a treatment for chronic PTSD and is associated with significant reduction in disability after 12 weeks of treatment. [Abstract Adapted]

CITATIONS *Pharmacotherapy*

Bartzokis, G., Lu, P.H., Turner, J., Mintz, J., & Saunders, C.S. (2004). **Adjunctive risperidone in the treatment of chronic combat-related posttraumatic stress disorder.** *Biological Psychiatry*, *57*, 474-479. Forty-eight male Vietnam veterans with chronic PTSD who remained symptomatic after a stable psychotropic medication regimen were randomized to 16 weeks of augmentation treatment with risperidone or placebo. The risperidone group exhibited significantly greater improvement in PTSD and anxiety symptoms.

Becker, M.E., Hertzberg, M.A., Moore, S.D., Dennis, M.F., Bukenya, D.S., & Beckham, J.C. (2007). **A placebo-controlled trial of bupropion SR in the treatment of chronic posttraumatic stress disorder.** *Journal of Clinical Psychopharmacology*, *27*, 193-197. Thirty predominantly male veterans with PTSD maintained on their current medications were randomized to bupropion SR vs. placebo in a 2:1 ratio. Although both groups showed some improvement, there was no difference between treatments.

Braun, P., Greenberg, D., Dasberg, H., & Lerer, B. (1990). **Core symptoms of posttraumatic stress disorder unimproved by alprazolam treatment.** *Journal of Clinical Psychiatry*, *51*, 236-238. Ten male and female patients with PTSD participated in a random-assignment, double-blind crossover trial comparing benzodiazepine, alprazolam, and placebo. Symptoms of PTSD were not altered, although there was modest improvement in anxiety symptoms.

Davidson, J.R.T., Brady, K.T., Mellman, T.A., Stein, M.B., & Pollack, M.H. (2007). **The efficacy and tolerability of tiagabine in adult patients with posttraumatic stress disorder.** *Journal of Clinical Psychopharmacology*, *27*, 85-88. Two hundred thirty-two male and female civilian patients with PTSD participated in a 12-week RCT comparing the mood stabilizer, tiagabine and placebo. There was no difference between treatments and neither group exhibited improvement.

Davis, L.L., Davidson, J.R.T., Ward, L.C., Bartolucci, A.A., Bowden, C.L., & Petty, F. (2008). **Divalproex in the treatment of posttraumatic stress disorder: A randomized, double-blind, placebo-controlled trial in a veteran population.** *Journal of Clinical Psychopharmacology*, *28*, 84-88. Eighty-five older male military veterans with PTSD were randomized to an eight-week trial of the mood stabilizer divalproex or placebo. There was no difference between treatments and neither group exhibited improvement.

Friedman, M.J., & Davidson, J.R.T. (2007). **Pharmacotherapy for PTSD.** In M.J. Friedman, T.M. Keane, & P.A. Resick (Eds.). *Handbook of PTSD: Science and practice* (pp. 376-405). New York: Guilford Press. This is a comprehensive chapter on pharmacotherapy for PTSD that has both a theoretical and empirical focus. It reviews psychobiological abnormalities associated with PTSD, mechanisms of action of medications used to treat PTSD, a review of the growing literature on clinical trials, the generalizability of current findings, and challenges for the future.

Friedman, M.J., Davidson, J.R.T., & Stein, D.J. (in press). **Pharmacotherapy for PTSD.** In E.B. Foa, T.M. Keane, M.J. Friedman, & J.A. Cohen (Eds.). *Effective treatments for PTSD: Practice guidelines from the International Society for Traumatic Stress Studies* (2nd ed.). New York: Guilford Press. This chapter on pharmacotherapy focuses primarily on RCTs. It contains a table of all published RCTs that includes both between-group and within-group effect sizes for all studies.

Martenyi, F., Brown, E.B., Zhang, H., Koke, S.C., & Prakash, A. (2002). **Fluoxetine v. placebo in prevention of relapse in posttraumatic stress disorder.** *British Journal of Psychiatry*, *181*, 315-320. Following successful treatment with fluoxetine, 131 PTSD patients were re-randomized to 24 weeks of treatment with either fluoxetine or placebo. Patients in the fluoxetine group were significantly less likely to relapse than those who received placebo.

Neylan, T.C., Lenoci, M., Samuelson, K.W., Metzler, T.J., Henn-Haase, C., Hierholzer, R.W., et al. (2006). **No improvement of posttraumatic stress disorder symptoms with guanfacine treatment.** *American Journal of Psychiatry*, *163*, 2186-2188. Sixty-three male veterans with PTSD who were either medication-free or receiving stable pharmacotherapy were randomized to the alpha-2 pre-synaptic adrenergic agonist guanfacine, or placebo. After an eight-week trial, neither group exhibited clinical improvement.

Reich, D.B., Winternitz, S., Hennen, J., Watts, T., & Stanculescu, C. (2004). **A preliminary study of risperidone in the treatment of posttraumatic stress disorder related to childhood abuse in women.** *Journal of Clinical Psychiatry*, *65*, 1601-1606. Twenty-one women with PTSD due to childhood sexual abuse were randomized to the atypical antipsychotic risperidone, or placebo. Approximately half of the women were medication-free, while the other half were on a stable dose of antidepressants. PTSD symptoms were significantly reduced in the risperidone, but not in the placebo, group.

Rothbaum, B.O., Cahill, S.P., Foa, E.B., Davidson, J.R.T., Compton, J., Conner, K.M., et al. (2006). **Augmentation of sertraline with prolonged exposure in the treatment of posttraumatic stress disorder.** *Journal of Traumatic Stress*, *19*, 625-638. Following 10 weeks of open label sertraline treatment, 31 men and women were randomized to five more weeks of medication, while 34 were assigned to sertraline plus 10 sessions of exposure therapy. Among partial (but not full) responders to initial SSRI treatment, augmentation with exposure therapy led to further reduction of PTSD symptoms.

PTSD Treatment Guidelines—continued from back page

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Departments of Veterans Affairs and Defense. (2003). *VA/DoD Clinical practice guideline for the management of post-traumatic stress.* Washington, DC: Veterans Health Administration, Department of Veterans Affairs and Health Affairs, Department of Defense.

Foa, E.B., Davidson, J.R.T., Frances, A., Culpepper, L., Ross, R., Ross, D. (Eds.). (1999). **The expert consensus guideline series: Treatment of posttraumatic stress disorder.** *Journal of Clinical Psychiatry*, *60* (Suppl. 16), 4-76.

Foa, E.B., Keane, T.M., & Friedman, M.J. (Eds.). (2000). *Effective treatments for PTSD: Practice guidelines from the International Society for Traumatic Stress Studies.* New York: Guilford Press.

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Dean Kilpatrick, PhD, is Director of the National Crime Victims Research and Treatment Center at the Medical University of South Carolina.

UNDERSTANDING PTSD TREATMENT GUIDELINES

Dean G. Kilpatrick, Ph.D.

National Crime Victims Research and Treatment Center

Numerous treatments for PTSD exist, encompassing a broad array of psychosocial and pharmacological approaches. All of these treatments have proponents who advocate their use. Stakeholders need accurate information to help them evaluate conflicting claims about PTSD treatments and identify the most appropriate treatments. These stakeholders include clinical practitioners, researchers, and policy makers who want to know which treatments work best as well as the costs and benefits of providing various treatments. The most important stakeholders are individuals with PTSD who need to know which treatments are most likely to help them.

The use of evidence-based medicine is a major trend in the health-care field. This approach: 1) identifies treatments with the best evidence for efficacy, effectiveness, and safety; 2) disseminates this information to stakeholders; and 3) develops practice or treatment guidelines encouraging use of treatments that have the best support. Over the past decade, eight major clinical practice and/or treatment guidelines for PTSD have been developed by the American Psychiatric Association (2004); Australian Centre for Posttraumatic Mental Health (2007); the International Society for Traumatic Stress Studies (Foa et al., 1999; in press); the National Institute for Clinical Excellence (2005); the National Crime Victims Research and Treatment Center (Saunders et al., 2003); and the Departments of Veterans Affairs and Defense (2003). Also, the Institute of Medicine (2007) recently published a report evaluating the evidence on PTSD treatment. These PTSD treatment guidelines all reviewed the extant research literature for PTSD treatments and determined the level of support for treatments based on effectiveness and/or safety. Although randomized clinical trials (RCTs) are not perfect, they are widely regarded as providing the highest level of evidence about whether or not treatments are effective. Testimonials without any systematic evaluation can provide no evidence of treatment efficacy, although they can help identify treatments that should be evaluated.

It is impossible to review the methodology, findings, and recommendations of all these treatment guidelines given our space limitations, but here are a few summary points. First, PTSD treatment

outcome research has expanded considerably over the past decade, so more recent guidelines are based on much more data than earlier guidelines. Second, guidelines differ with respect to the number of levels of support they use to classify treatments, as well as how levels of support are labeled. Third, some guidelines are much more rigorous than others in terms of the level of support they require to state that a treatment is well-supported by evidence. For example, the recent IOM report discarded the results of many well-designed RCTs that were very good but not perfect methodologically. Given that the IOM used what some have called excessively rigorous standards for establishing evidence of treatment efficacy (e.g., Mellman, 2007), it is not surprising that other recent treatment guidelines found many more PTSD treatments to be effective than did the IOM (e.g., ACPMH, 2007; Foa et al., in press; NICE, 2005). Fourth, although there are some differences in which treatments achieved the highest level of evidence-based support in various guidelines, a consistent finding is that some PTSD treatments meet the highest standards for evidence-based effectiveness (see Schnurr's and Friedman's articles in this issue).

Stakeholders should find the new ISTSS guidelines particularly useful. The second edition of *Effective Treatments for PTSD* (Foa et al., in press) has several things to recommend it. First, it is based on the most current review of relevant research. Second, it has expanded coverage of important topics such as treatment of PTSD in children and treatment of PTSD when it is comorbid. Third, it addresses limitations in extant research and identifies areas in which more research is needed. Fourth, it provides useful information about how to implement what we know about effective treatments into real-world clinical practice. Fifth, the guidelines have been reviewed rigorously and approved by the ISTSS Board of Directors, a group with unexcelled knowledge, experience, and expertise about PTSD. Finally, it is impossible to review these PTSD treatment guidelines without concluding that effective treatments for PTSD exist. Critics of treatment guidelines may focus on the fact that PTSD treatments aren't perfect and do not work for everyone, but a more encouraging view is that we have made real progress and now have effective treatments to offer stakeholders.

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National Center for PTSD
VA Medical Center (116D)
215 North Main Street
White River Junction, VT 05009-0001