GUIDELINE WATCH (MARCH 2009): PRACTICE GUIDELINE FOR THE TREATMENT OF PATIENTS WITH ACUTE STRESS DISORDER AND POSTTRAUMATIC STRESS DISORDER

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APA's *Practice Guideline for the Treatment of Patients with Acute Stress Disorder and Posttraumatic Stress Disorder* was published in October 2004. Since that time, a number of well-designed randomized controlled trials of pharmacological and psychotherapeutic interventions for posttraumatic stress disorder (PTSD) have been conducted in various populations exposed to trauma. Numerous case reports, small case series, and open trials have also been reported, but they will not be the focus of this guideline watch. While early intervention studies for acute stress disorder (ASD) are currently in progress, no major research on the treatment of ASD has been completed since publication of the 2004 guideline.

Factors predicting development of ASD or PTSD have still not been established. A 2008 study by Bryant et al. (1) found that ASD was a poorer predictor of getting PTSD than just having PTSD criteria alone in the acute stage.

In response to increased attention on U.S. military veterans returning from combat in Iraq and Afghanistan, the Institute of Medicine has also reviewed and summarized the evidence supporting treatment for PTSD (2). The 2007 report recognizes that there is evidence for the pharmacological treatment of combat-related PTSD but states that this evidence is not as strong as the evidence for treatment of other trauma-related PTSD. In particular, the report states that large randomized controlled trials, consid-

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The American Psychiatric Association's (APA's) practice guidelines are developed by expert work groups using an explicit methodology that includes rigorous review of available evidence, broad peer review of iterative drafts, and formal approval by the APA Assembly and Board of Trustees. APA practice guidelines are intended to assist psychiatrists in clinical decision making. They are not intended to be a standard of care.

The ultimate judgment regarding a particular clinical procedure or treatment plan must be made by the psychiatrist in light of the clinical data presented by the patient and the diagnostic and treatment options available. Guideline watches summarize significant developments in practice since publication of an APA practice guideline. Watches may be authored and reviewed by experts associated with the original guideline development effort and are approved for publication by APA's Executive Committee on Practice Guidelines. Thus, watches represent opinion of the authors and approval of the Executive Committee but not policy of the APA.

ered a standard of evidence in other areas of medicine, are lacking from the evidence base. The report concludes that existing evidence is sufficient only to establish the efficacy of exposure-based psychotherapies in the treatment of PTSD. However, there was disagreement among the report authors about this conclusion, and the report includes a dissenting opinion by one author about the strength of the evidence for pharmacotherapy.

Our review concludes that the best evidence from recent studies bolsters support for exposure-based psychotherapies as well as for pharmacological intervention in many circumstances. Emerging evidence suggests the potential for psychotherapy to be facilitated by at least one recently identified pharmacological agent (d-cycloserine). Recently published studies also suggest that in certain patient populations new pharmacotherapeutic options, such as prazosin, may be more effective than other widely prescribed medications (e.g., selective serotonin reuptake inhibitors [SSRIs]) indicated for PTSD.

As described in the 2004 guideline, the generalizability of findings from available studies on treatments for PTSD is limited by small numbers of subjects, variable inclusion criteria (e.g., patients with treatment-resistant illness, patients receiving multiple treatments), nonstandardized outcome measures, inadequate controls, and lack of replication. These issues also limit meaningful comparison of data for psychopharmacological versus psychotherapeutic approaches. Specific recommendations to improve psychotherapy research for PTSD have been put forward by Schottenbauer et al. (3).

PHARMACOTHERAPIES

ANTIDEPRESSANTS

Selective Serotonin Reuptake Inhibitors for Non-Combat-Related PTSD

Meta-analyses and several randomized controlled trials published since 2004 generally support the superiority of SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs) over placebo for non-combat-related PTSD.

In a 2006 Cochrane meta-analysis, Stein et al. (4) reviewed 35 short-term randomized controlled trials (of 14 or fewer weeks in duration) involving a total of 4,597 participants. In 17 of the trials, symptom severity was significantly reduced in the medication groups relative to placebo. Evidence of efficacy was most convincing for the SSRIs, across all symptom clusters and for co-occurring depression and disability.

In a study reported in 2007, Marshall et al. (5) evaluated the efficacy of paroxetine for treating symptoms and associated features of chronic PTSD. Fifty-two mostly minority adult patients (out of 70 initially enrolled) who were rated as not significantly improved after 1 week of placebo were randomized to receive flexibly dosed paroxetine (maximum 60 mg/day by week 7) or continued placebo. After 10 weeks, significantly more patients treated with paroxetine responded to treatment, as rated by the Clinical Global Impression–Improvement (CGI-I) scale. Patients treated with paroxetine were also observed to have significantly greater reduction in total score on the Clinician-Administered PTSD Scale (CAPS) and the Dissociative Experience Scale; self-reported interpersonal problems were also noted to be significantly decreased. During a 10-week maintenance phase, paroxetine response but not placebo response continued to improve.

In a 2006 reanalysis of two previously published trials, Stein et al. (6) examined 395 adult patients with PTSD who were randomized to double-blind treatment with flexibly dosed sertraline (50–200 mg/day) or placebo. After 12 weeks, sertraline was significantly more effective than placebo on most primary efficacy variables including Part 2 of the CAPS, irrespective of whether the patients had experienced childhood abuse or interpersonal trauma, suggesting the utility of medication treatment in individuals whose precipitating trauma is either childhood abuse in particular or interpersonal trauma in general.

In a 2005 study, Davidson et al. (7) compared the relapse rates of 57 of 62 total patients who responded to 6 months of open-label fluoxetine and who were subsequently blindly randomized to continue receiving fluoxetine (mean dosage = 42.1 mg/day) or placebo. Relapse rates were 22% for fluoxetine compared with 50% for placebo ($p=0.02$); the odds ratio for relapse on placebo relative to fluoxetine was 3.50, and time to relapse on fluoxetine was longer than on placebo ($p=0.02$, log rank statistic).

These newer studies augment the evidence base for SSRI efficacy previously established in samples of predominantly women with PTSD resulting from civilian trauma, including childhood and adult sexual assault, other interpersonal traumas, and motor vehicle accidents.

SSRIs for Combat-Related PTSD

Randomized controlled trials have called into question the efficacy of SSRIs for the treatment of PTSD in com-

bat veterans. Some of this evidence was described in the 2004 guideline, including van der Kolk et al.'s 1994 study (8) of 31 veterans with chronic PTSD randomized to fluoxetine or placebo. In this study, fluoxetine was significantly superior to placebo for symptoms of co-occurring depression as measured by the Hamilton Depression Rating Scale (HAM-D), but change in total PTSD score did not differ between placebo and fluoxetine. In a similar randomization of 88 veterans with PTSD, none of those receiving 8 weeks of fluoxetine treatment achieved an asymptomic state as measured by the CAPS at 6-month follow-up (9). Negative results were reported in a placebo-controlled, randomized controlled trial by Hertzberg et al. (10) of fluoxetine in 12 Vietnam war veterans.

More recently, Friedman et al. (11) completed a multicenter trial of sertraline in 169 combat veterans with PTSD recruited from 10 Veterans Affairs medical centers. After 1 week of placebo, the patients were randomized to receive 12 weeks of flexibly dosed sertraline (mean dosage=156 mg/day among completers) or continued placebo. Total PTSD symptom reduction as measured by the CAPS did not significantly differ between the sertraline (–13.1, +/–3) and placebo (–15.4, +/–3.1) groups, and in both groups, combat-related PTSD was associated with poorer outcome compared with non-combat-related PTSD.

In a 2002 study, Zohar et al. (12) randomized 42 Israeli combat veterans to sertraline (mean dosage=120 mg/day, +/–60 mg) or placebo. At 10 weeks, no significant differences were noted in total score on the CAPS-2 or on any of the three CAPS symptom cluster scores.

These findings stand in contrast to a 2006 randomized controlled trial by Martenyi and Soldatenkova (13) of 144 combat veterans of the Balkan Wars recruited at eight sites in Bosnia-Herzegovina and Croatia and randomized to fluoxetine (20–80 mg/day) or placebo for both a 12-week acute phase and 24-week relapse prevention phase. In the acute phase, fluoxetine was superior to placebo as measured by total score on the Treatment Outcome PTSD (TOP-8) scale (–9.05 compared with –5.20; $p=0.001$), total score on the CAPS (–31.12 compared with –16.07; $p<0.001$), all CAPS subscores, and total score on the Davidson Trauma Scale (DTS). Fluoxetine was also more effective for depression as measured by the Montgomery-Åsberg Depression Rating Scale (MADRS) and for anxiety symptoms as measured by the Hamilton Anxiety Scale. In the relapse prevention phase of the trial, fluoxetine was superior to placebo in sustaining improvement in TOP-8 and CAPS scores, and the risk of relapse was significantly greater in the placebo arm than in the fluoxetine arm (log rank test $\chi^2=4.9$, df=1, $p=0.048$). The veterans of the Balkan Wars were younger than the Israeli and American combat veterans (mean age=36), somewhat more recently traumatized (although mean duration from index trauma was 6–7 years), and had likely received less treatment for their symptoms prior to study entry. It is possible that negative results with older combat veterans (in contrast to positive results with fluoxetine among younger veterans of the Balkan Wars) may be due to the chronicity of their PTSD (and co-occurring disorders) rather than a unique resistance to SSRI treatment among individuals with combat-related PTSD.

The 2004 guideline recommends the SSRIs as a first-line medication treatment for patients with PTSD. The trials reviewed above suggest that the SSRIs may no longer be recommended with the same level of confidence for veterans with combat-related PTSD as for patients with non-combat-related PTSD. Further research is needed to answer why these populations have been shown to have differential responses to SSRI treatment.

Other Antidepressants

Since publication of the 2004 guideline, several randomized, placebo-controlled trials of venlafaxine, one trial of mirtazapine, one trial of nefazodone, and one trial of bupropion have been reported, as well as several head-to-head comparisons of these medications with SSRIs.

In a 2006 study, Davidson et al. (14) randomly assigned 329 adult outpatients from 56 sites who had a primary diagnosis of PTSD with symptom duration of 6 months or longer and CAPS scores of 60 or greater to receive venlafaxine, extended release (37.5–300 mg/day), or placebo. At 24 weeks, mean changes in total CAPS score from baseline were –51.7 for the venlafaxine group compared with –43.9 for the placebo group ($p=0.006$); improvement was significantly greater for the venlafaxine group in symptom cluster scores for reexperiencing ($p=0.008$) and avoidance/numbing ($p=0.006$) but not for hyperarousal. Remission rates (defined as a CAPS score of 20 or lower) were found to be 50.9% for venlafaxine and 37.5% for placebo ($p=0.01$). A 12-week, multicenter double-blind trial (15) compared venlafaxine extended release (37.5–300 mg/day) to sertraline (25–200 mg/day) or placebo in adult outpatients with PTSD. Mean changes from baseline scores on the CAPS-SX17 (an abbreviated version of the CAPS) were –41.8, –39.4, and –33.9 for venlaxine, sertraline, and placebo, respectively, with only venlafaxine separating from placebo in a statistically significant manner ($p<0.05$).

In a 2007 study, Becker et al. (16) found no between-group differences in 30 patients with civilian- or military-related PTSD who were randomized to placebo or bupropion, sustained release, in addition to usual pharmacological care. About half of these patients were already receiving an SSRI at the time of randomization.

In a 2004 study, Davis et al. (17) randomized 41 predominantly male combat veterans with PTSD to nefazodone or placebo. After 12 weeks, they found significant improvement in percentage change of total CAPS score from baseline in those receiving nefazodone compared with those receiving placebo in a repeated analysis of variance with last observation carried forward ($p=0.04$, effect size = 0.6).

Finally, in a double-blind, randomized, placebo-controlled trial of 29 patients with PTSD reported in 2003 by Davidson et al. (18), mirtazapine (up to 45 mg/day) was found to be more effective than placebo on the Global Improvement item of the Short PTSD Rating Interview (SPRINT; but not on total SPRINT score, nor on DTS total score), as well as on the Structured Interview for PTSD and anxiety subscale of the Hospital Anxiety and Depression Scale.

Head-to-Head Comparisons of Antidepressants

As described in the 2004 guideline, no significant differences among antidepressants, including the SSRIs, were found in the few head-to-head studies then available. Since that time, studies have been published comparing nefazodone and sertraline (19), venlafaxine and sertraline (15), the SNRI reboxetine and fluvoxamine (20), and fluoxetine, moclobemide, and tianeptine (21). These studies have generally demonstrated the superiority of antidepressants to placebo but have done little to clarify the relative utility of these different antidepressants.

In total, these data build on the relatively robust evidence basis for pharmacological treatment with antidepressant medications (particularly SSRIs and SNRIs for noncombat PTSD) as compared with other classes of medications. However, the data also suggest that more effective pharmacological treatments must be identified, particularly for veterans with combat-related PTSD. It is also important to note that comparison of other pharmacotherapies with the SSRIs and SNRIs is complicated by methodological differences in the available studies. While the SSRIs and SNRIs have mostly been studied in rigorous trials compared with placebo, other agents have been studied against "treatment as usual" conditions or as augmentation agents in patients with refractory illness.

ADRENERGIC AGENTS

Beta-blockers

As described in the 2004 guideline, a potential role for propranolol in preventing PTSD was suggested by a pilot study reported in 2002 by Pitman et al. (22), in which 32 emergency department patients received a 10-day course of propranolol or placebo, beginning within 6 hours of a trauma. Propranolol treatment did not change CAPS scores at 1 month but did decrease physiological response to script-driven imagery 3 months after the trauma. However, a 14-day randomized controlled trial reported in 2007 by Stein et al. (23) of propranolol compared with gabapentin compared with placebo failed to demonstrate the superiority of either medication over placebo.

Prazosin

Among the most promising advances in the pharmacological treatment of PTSD have been a series of placebo-controlled augmentation trials demonstrating the efficacy of the α-adrenergic antagonist prazosin for the treatment of trauma-related nightmares and sleep disruption (24–26). In these trials, patients were allowed to continue maintenance medications, including SSRIs, as the primary outcome variables were related to sleep disturbance rather than daytime PTSD symptoms. However, the studies also assessed total PTSD symptoms using either the CAPS or the PTSD Checklist–Civilian Version (PCL-C).

The first study, reported in 2003 by Raskind et al. (24), was a double-blind, crossover trial in which 10 Vietnam combat veterans with PTSD received placebo or prazosin (mean dosage = 9.6 mg/night) over a 3-week dose-titration phase and a 6-week maintenance phase. Prazosin was significantly superior to placebo in reducing nightmares (CAPS "recurrent distressing dreams" item) and sleep disturbance (CAPS "difficulty sleeping" item) and in improving global clinical status (Clinical Global Impression of Change [CGIC]), with effect size $z>1.0$ on all measures. Change in total CAPS score and scores on all three CAPS cluster items was also significantly greater with prazosin than with placebo.

The second study, reported in 2007 by Raskind et al. (25), was a parallel-group trial in 40 veterans with chronic PTSD, most of whom experienced combat-related trauma in Vietnam. Patients received placebo or prazosin (mean dosage = 13.3 mg/night) during a 4-week dose-titration phase and an 8-week maintenance phase. Similar improvements were observed in nightmares, sleep disturbance, and CGIC scores (effect size = 0.9). A numerically greater reduction in total CAPS score was observed with prazosin, but this did not reach statistical significance.

Finally, in a double-blind, placebo-controlled crossover study of 13 civilians with trauma-related PTSD, reported in 2008 by Taylor et al. (26), prazosin was rapidly titrated to 3 mg/night during each 3-week treatment phase. Along with clinical outcomes, sleep time and sleep latency were recorded in the final 3 nights of the treatment phase. Total sleep time was 94 minutes longer with prazosin than with placebo (374 +/–86 minutes compared with 280 +/–

105 minutes, $p<0.01$, effect size=0.98), and total rapid eye movement (REM) sleep and mean REM duration were also longer with prazosin. Once again, reductions in trauma nightmares, total PTSD symptoms (using the PCL-C) and CGIC scores were significantly changed compared with placebo.

Further investigation may clarify an optimal dosage and titration for prazosin, which based on the above studies appears to be effective in a range of 3–15 mg/night. Clinically, a low dose could be tried and then increased if response is inadequate. Long-term efficacy has not been established.

Second-Generation (Atypical) Antipsychotic Medications

In 2006, Padala et al. (27) reported the results of a small pilot study in which 20 women ages 19–94 years with PTSD from sexual and domestic abuse were randomized during the acute phase to receive risperidone or placebo. A significant difference was observed between baseline and subsequent visit TOP-8 total scores beginning in week 6 and persisting through the 12th week of the study. This response pattern was also observed in the secondary outcome measures of CAPS, the HAM-D, and the Hamilton Anxiety Scale.

Risperidone was also studied in an 8-week randomized controlled trial reported in 2004 by Reich et al. (28) of 19 women who met DSM-III-R criteria related to childhood abuse. Significant differences in reduction from baseline total CAPS-2 score ($z=-2.44$, $p=0.015$) and significant reductions in CAPS-2 intrusive ($z=-5.71$, $p<0.001$) and hyperarousal ($z=-2.74$, $p=0.006$) subscores were associated with flexible dosing (0.5–8 mg/day) of risperidone. In 2008, Rothbaum et al. (29) randomized 25 adult PTSD patients whose symptoms did not remit (<70% decrease in symptoms, as measured by the CAPS) with 8 weeks of open-label sertraline to augmentation with risperidone compared with placebo for an additional 8 weeks. Patients receiving placebo and risperidone did not differ in their continued improvement in symptoms of depression or PTSD over the 8 weeks of augmentation (both groups improved), although those who received risperidone showed more improvement on the DTS sleep item on post hoc analysis.

Another second-generation (atypical) antipsychotic trial of note is a randomized, placebo-controlled augmentation study of 73 combat veterans reported in 2005 by Bartzokis et al. (30). This trial demonstrated risperidone's superiority to placebo in increasing response to SSRIs. These findings are consistent with the limited evidence from previous small randomized controlled trials of risperidone (31) and olanzapine (32).

In summary, these data are encouraging for adjunctive treatment with a second-generation antipsychotic in patients who have partially responded to an SSRI or an SNRI, including for co-occurring psychotic symptoms. As recommended in other APA practice guidelines (33), patients receiving an antipsychotic medication should be monitored for side effects including weight gain and metabolic changes.

Anticonvulsants

Randomized controlled trials of anticonvulsant medications remain extremely limited in number and have shown mixed results. In a study reported in 2007 by Tucker et al. (34), 38 civilian patients with PTSD were randomized to placebo or flexibly dosed topiramate (25–400 mg/day); there were no significant differences in total CAPS scores or total Clinical Global Impression Scale scores, although patients treated with topiramate demonstrated clinically significant decreases in TOP-8 total score and CAPS re-experiencing symptoms subscale score.

In a continuation study reported in 2006 by Connor et al. (35), 29 patients with PTSD who completed an open-label trial of tiagabine and demonstrated at least minimal improvement were randomized to continued tiagabine or placebo. Benefits of treatment were maintained in the tiagabine group, and tiagabine was associated with a greater trend toward remission, but there was no statistically significant difference in remission rates, nor was there a change in rate of relapse in comparison with the placebo group.

In 2007, Davidson et al. (36) also evaluated the efficacy of tiagabine (2–4 mg/day in divided doses) in a 12-week randomized, placebo-controlled, multisite trial of 232 adult patients with PTSD. They found neither a statistically significant change from baseline CAPS score in either group nor a significant difference in any other outcome measure including CGIC, TOP-8, Davidson Trauma scale, or MADRS. Thus, while the small, open-label trial of Connor et al. (35) suggested efficacy of tiagabine, this larger randomized controlled trial failed to confirm this.

Most recently, Davis et al. (37) randomized 85 older male military veterans with PTSD to an 8-week trial of divalproex compared with placebo. No difference in outcomes was noted for either group, and no improvement was noted.

Despite the fact that anticonvulsant medications have been well tolerated in all studies and despite the promising results of some open-label studies, limited evidence of efficacy precludes any recommendations for change in practice.

PSYCHOTHERAPIES

Nearly all of the randomized controlled trials of psychotherapy published since 2004 have examined interventions that many experts consider to be components of cognitive-behavioral therapy (CBT). As described in the 2007 report of the Institute of Medicine (2), therapeutic approaches and techniques overlap across psychotherapies, and there is no consensus on how these psychotherapies should be categorized. This review follows the approach of the Institute of Medicine report, grouping approaches and techniques as follows: CBTs that include elements of exposure, eye-movement desensitization and reprocessing (EMDR), other psychotherapies, and group psychotherapy. Research published since 2004 supports, in particular, exposure-based CBTs such as cognitive processing therapy and prolonged exposure therapy as effective treatments for PTSD when delivered in individual formats.

EXPOSURE-BASED CBTs

Trials of exposure-based CBTs conducted in the last several years generally included components of psychoeducation, breathing, and relaxation training. By definition, these exposure therapies also incorporated into the therapy sessions some form of reexposure to past traumatic experience (e.g., imaginal, in vivo, directed therapeutic, written, verbal, or taped narrative recountings). In addition, homework was often included. The generalizability of the results of many of these studies to typical clinical populations is limited by high dropout rates, lack of intention-to-treat analysis, and lack of clarity regarding blinding of assessors. Nevertheless, several well-designed studies augment prior knowledge.

In 2006, Monson et al. (38) reported the results of a waitlist-controlled study of cognitive processing therapy in 60 combat veterans. The overall dropout rate was 16.6% (20% from cognitive processing therapy, 13% from waitlist), but random regression analyses of the intention-to-treat sample revealed significant improvements in both PTSD and co-occurring depressive symptoms in the treatment group compared with the waitlist group. At completion of the study, 40% of those in the intention-to-treat group receiving cognitive processing therapy no longer met criteria for a PTSD diagnosis, and 50% had a reliable decrease in their PTSD symptoms.

The effectiveness of cognitive processing therapy was also examined in a controlled study reported in 2005 by Chard (39) of 71 adult sexual abuse survivors with PTSD. The control was a minimal-attention waitlist group. Participants were assessed pretreatment, immediately after treatment, 3 months after treatment, and 1 year after treatment using the CAPS and a variety of other clinician-administered rating scales. Analysis demonstrated that cognitive processing therapy was superior to waitlist in reducing PTSD symptoms and that reductions were maintained for at least 1 year.

A recent study by Resick et al. (40) attempted to dismantle the components of cognitive processing therapy and determine their relative contributions to treatment efficacy. In this study, 150 adult women with PTSD were randomized into one of three conditions: 1) full cognitive processing therapy, which included both exposure (i.e., writing and reading a detailed account of the trauma) and cognitive therapy (i.e., challenging patient assertions about the meaning of the trauma and the implications for the patient's life); 2) cognitive therapy without the writing and reading component; and 3) the writing and reading component without cognitive therapy. All conditions included 2 hours of therapy per week for 6 weeks. Patients were assessed for PTSD (using CAPS) and depression in a blinded manner weekly, 2 weeks after the last session of therapy, and at 6 months. At the conclusion of the study, all treatment completers still met criteria for PTSD. However, substantial improvement was observed in all three treatment groups on primary PTSD and depression outcomes as well as on secondary measures of anxiety, guilt, and shame. Cognitive therapy without exposure was associated with greater improvement than the exposure-only condition, suggesting that the cognitive component of this therapy (i.e., altering the meaning of the traumatic event) may be an active treatment mechanism that may occur without repeated and explicitly evoked fear memories. It also suggests that cognitive processing therapy might be characterized as a more cognitive than exposure-based therapy. Similar dismantling studies are under way and will be important to further clarify the active components of various psychotherapies for PTSD. Research questions include how cognitive components as compared with exposure components may be variably effective depending on factors such as the stage of the disorder (e.g., early compared with late), the presence of particular symptoms (e.g., dissociation, high levels of arousal, avoidance), and, of course, therapist variables.

Prolonged exposure therapy was studied in a randomized controlled trial reported in 2007 by Schnurr et al. (41) of female veterans (N=277) and active duty personnel

(N=7) across 12 sites specializing in medical treatment for military veterans, including nine Veterans Affairs hospitals, two Veterans Affairs counseling centers, and one military hospital. Patients were randomly assigned to receive prolonged exposure therapy (N=141) or present-centered therapy (N=143) delivered in 10 weekly 90-minute sessions. Blinded assessors collected data before and immediately after treatment and 3 and 6 months after treatment. Immediately after treatment, the prolonged exposure group was more likely than the present-centered therapy group to no longer meet PTSD criteria (41% compared with 27.8%, odds ratio [OR]=1.80, confidence interval [CI]=95%) and more likely to achieve full remission (15.2% compared with 6.9%, OR=2.43, CI=95%). These results were maintained at 3- and 6-month follow-up. It should be noted that although this was a study of military personnel and veterans, 70% of participants indicated sexual trauma as their index (worst) traumatic experience, and there was a 17% differential dropout rate between prolonged exposure and present-centered therapy, with more participants dropping out of the prolonged exposure arm.

A controlled study reported in 2005 by Rothbaum et al. (42) evaluated the relative efficacy of prolonged exposure therapy and EMDR. In this study, 74 adult female rape victims (index rape occurring either in adulthood or childhood) were randomized into 9-session prolonged exposure, EMDR, and waitlist control groups. Dropout rates across the groups were not significantly different (13% prolonged exposure, 20% EMDR, 16.7% waitlist). Immediately following treatment, the groups receiving prolonged exposure and EMDR both demonstrated statistically significant improvement across three outcome measures, including a 50% or more decrease from baseline in CAPS score ($p=0.001$). Posttreatment, 95% of participants who received prolonged exposure therapy and 75% of participants who received EMDR no longer met criteria for PTSD, and individuals who received both treatments showed significantly reduced depressive symptoms and dissociative symptoms immediately and at 6 months. Results were maintained at 6-month follow-up for the prolonged-exposure group across PTSD, depressive, and dissociative symptoms but maintained to a significantly lesser extent for the EMDR group with regard to PTSD.

The effectiveness of brief exposure therapy has been demonstrated in two recent studies reported in 2005 and 2007 by Basoglu et al. (43, 44). In the first study, 59 earthquake survivors with PTSD assessed by CAPS were randomized to a single-session exposure-based behavioral therapy intervention (in which the intensity of simulated trauma was adjusted in accordance with the patient's personal feelings of comfort) or to a waitlist (43). At 6, 12, and 24 weeks posttreatment, as well as at 1–2 years posttreatment, the treatment group was observed to have significant decreases in CAPS score, Beck Depression Inventory (BDI) score, and other patient self-measures of fear, anxiety, or overall impression. With regard to CAPS, effect sizes were considerable (Cohen's d=0.7–1.4), and improvement rate rose from 49% at week 6 to over 80% at other assessment points.

In the second study (44), 31 earthquake survivors with PTSD were randomized to a single-session exposure-based behavioral therapy (N=16) or to repeated assessments (N=15). Participants were assessed at 4, 8, 12, and 24 weeks posttreatment and again after 1–2 years. Again, significant between-group treatment effects were observed in PTSD (assessed by CAPS) and assessor-rated global improvement (Global Improvement Scale–Assessor [GIS–A]), with significant between-group treatment effects observed in both outcome measures at week 8. Improvement rates of 40% at week 4 rose to 80% by week 24 and at 1–2 year follow-up, with large effect sizes (Cohen's d=0.9–1.7) noted across primary measures at week 8.

EMDR

EMDR continues to be examined as a treatment for victims of trauma; however, many of the studies published since 2004 include participants without a formal PTSD diagnosis. An exception is a study reported in 2007 by van der Kolk et al. (9), in which 88 patients with PTSD were randomly assigned to 8 weeks of EMDR, fluoxetine, or placebo. Symptoms were assessed using the CAPS and BDI-II immediately posttreatment and at 6 months. At 6-month follow-up, 75% of the adult-onset (compared with 33% of the childhood-onset) patients receiving EMDR achieved remission as compared to none of the patients receiving fluoxetine. Neither treatment produced complete symptom remission in the majority of the patients with childhood-onset PTSD. It should be noted that fluoxetine was discontinued at termination of the 8-week treatment phase, so the poor SSRI outcomes at 6 months should not be surprising.

Another exception is a study reported in 2007 by Högberg et al. (45) of 24 transportation workers who had either been assaulted or who had witnessed a person-under-train accident and who met DSM-IV criteria for PTSD. Participants were randomized to either five sessions of EMDR or to a waitlist. After treatment, eight of 13 patients receiving EMDR (67%) no longer met criteria for PTSD compared with one of 11 (11%) patients on the waitlist ($p=0.02$). Significant differences were also observed in Global Assessment of Functioning and HAM-D scores.

Neither of these studies dismantled the effects of exposure compared with eye-movement components of the

treatment. Previous studies (summarized in the 2004 guideline) have shown the eye movements not to be critical to the treatment effect. These small studies suggest efficacy of brief EMDR in sexual assault victims and witnesses to vehicular accidents but cannot be generalized to combat veterans.

OTHER PSYCHOTHERAPIES

Since publication of the 2004 guideline, studies of other types of psychotherapy, including coping skills therapy, eclectic psychotherapy, psychodynamic psychotherapy, cognitive restructuring, and brainwave neurofeedback, have also been published, but the utility and generalizability of conclusions from these studies are limited by methodological issues such as lack of formalized diagnostic procedures, inclusion of non-PTSD patients, very high dropout rates, unspecified handling of dropouts or missing data, and lack of blinding of assessors. A study reported in 2004 by Neuner et al. (46) of coping skills therapy in 43 war refugees was methodologically sound but failed to demonstrate a differential effect of treatment. As noted in the 2004 guideline, although controlled studies of psychodynamic psychotherapy are lacking, clinical consensus reflects the idea that a psychodynamic approach is useful in helping the patient integrate past traumatic experience(s) into a more adaptive or constructive schema of risk, safety, prevention, and protection, thereby reducing core symptoms of PTSD.

Case reports (47, 48) have recently suggested that exposure-based therapy may be facilitated through the use of computerized audio-visual simulations of a traumatic combat environment. The effectiveness of this facilitated CBT—termed "virtual reality therapy"—in disaster workers with PTSD has also been demonstrated in a small controlled trial. In 2007, Difede et al. (49) assigned 21 September 11 terrorist attack workers to either virtual reality treatment (N=13) or waitlist control (N=8). The treatment group showed a significant decline in CAPS scores compared with the waitlist group. While these reports are encouraging, larger randomized controlled trials must replicate such findings before virtual reality therapy can be recommended with the highest levels of confidence.

Group Psychotherapy

The majority of psychotherapies may be delivered in either individual or group formats. Of the studies reviewed above, the 2005 study by Chard (39) comparing cognitive processing therapy to minimal attention waitlist used both individual and group therapy formats (participants in the treatment group received both individual and group therapy in the first 9 weeks, followed by 7 weeks of group therapy, then one session of individual therapy). Effects of group therapy compared with individual therapy were not clearly demonstrated in this study. While there is a substantial descriptive literature for group therapy for PTSD, well-designed studies of cognitive processing therapy and other psychotherapies delivered in group formats are needed in the future in order to validate the efficacy of this method of delivery.

PSYCHOLOGICAL FIRST AID

The 2004 guideline described the failure of psychological debriefing as an effective strategy for preventing the later development of PTSD. There is hope that a new preventive approach for disaster survivors, called "psychological first aid," will prove effective (50). The essential principles of psychological first aid, including fostering safety, calmness, self- and community efficacy, social connectedness, and optimism in the aftermath of disaster, are supported by considerable empirical evidence, comprehensively summarized in 2007 by Hobfoll et al. (51). However, questions remain regarding how a public health intervention such as psychological first aid should be delivered, including which format and which type of responder (clinician responder compared with emergency responder compared with community leader) would be optimal (52). Thus, at the present time, psychological first aid must be considered an evidence-informed rather than evidence-based intervention. Further research is needed.

NEUROBIOLOGY OF PTSD: IMPLICATIONS FOR TREATMENT

In addition to the intervention studies reviewed here, other recently published studies and articles are noteworthy for advancing our understanding of the neurobiology of the traumatic stress response and PTSD as they relate to the processes of emotional memory and impairment of extinction learning (53–56). These studies provide a theoretical basis for the mechanism of action of exposure-based CBTs as interventions that promote reprocessing and reconsolidation of emotionally laden memories of traumatic experiences and facilitate the extinction of conditioned responses to reminders of these experiences. Studies also point to the involvement of *N*-methyl-D-aspartate (NMDA) receptors in the process of extinction learning, suggesting a potential role for NMDA agonists as enhancers of exposure-based psychotherapies (57, 58). Trials under way at this time may augment the emerging data from pilot studies that suggest the possible benefits of NMDA agonist treatment in combination with exposure-based psychotherapies (59). However, to date there have been no published studies of using d-cycloserine or any other pharmacological agent to enhance response to psychotherapy in patients with PTSD.

CONCLUSION

Since publication of the 2004 guideline, increasing research attention has been focused on the assessment and treatment of PTSD, but much work remains to be done. The studies highlighted in this watch suggest that future psychotherapy research must rely on increasingly standardized mechanisms for addressing treatment dropouts and missing data, as well as standardized definitions of treatment outcome and remission. For generalizability to clinical populations, studies inclusive of co-occurring conditions—particularly other mood and anxiety disorders—and more studies addressing cross-cultural and multiethnic populations are necessary. Further studies may help to clarify the effects of psychological trauma occurring in childhood and adolescence, not only as this pertains to the treatment of PTSD but also with regard to other aspects of psychological functioning (including personality) in adulthood. Although recent studies suggest that exposure-based psychotherapies may be effective for returning combat veterans, effectiveness studies also remain necessary in populations with co-occurring substance abuse or with other general medical and mental disorders (particularly traumatic brain injury). One study of collaborative care suggests that care management in combination with evidence-based psychotherapy and medication treatment may diminish PTSD symptoms in acutely injured trauma survivors (60).

With the exception of the α-adrenergic antagonist prazosin, the evidence base for pharmacological intervention in combat-related PTSD has not been significantly augmented by recent studies. Indeed, these studies suggest that SSRIs may not be recommended with the previous level of confidence for the treatment of PTSD in this particular population. Recent data point more to the need for replication of previous studies in typical clinical populations, the use of more standardized measures of outcome, and the need to identify alternative pharmacological strategies and to clarify the possibility that existing types of psychotherapy might be specifically augmented by novel pharmacological agents or other forms of intervention.

Finally, as epidemiological studies continue to demonstrate that there are increasing numbers of disaster victims and returning combat veterans with PTSD, it is crucial to support and expand efforts to identify effective delivery methods that can increase access to care, including group therapies, Internet- and self-help-based treatments, and treatments integrated into primary care practice environments (61–64). Further epidemiological studies will help identify risk factors and clarify the natural course of the illness, the impact of early intervention on the trajectory of illness, and the relationship between ASD and PTSD.

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