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Posttraumatic Stress Disorder and Acute Stress Disorder II: *Considerations for Treatment and Prevention*

ABSTRACT

Posttraumatic stress disorder is a common and often chronic and disabling anxiety disorder that can develop after exposure to highly stressful events characterized by actual or threatened harm to the self or others. This is the second of two invited articles summarizing the nature and treatment of PTSD and the associated condition of acute stress disorder (ASD). The present article reviews evidence for the efficacy of psychological and pharmacological treatments for PTSD and ASD. In summary, cognitive behavior therapy (CBT) has been found efficacious in the treatment of chronic PTSD as well as the treatment of ASD/prevention of PTSD. The selective serotonin reuptake inhibitors, sertraline, paroxetine, and fluoxetine, have been found efficacious in the treatment of chronic PTSD, with sertraline and paroxetine receiving the FDA indication for this condition. There is less evidence for efficacious medications in the treatment of ASD/prevention of PTSD. At present, hydrocortisone and propranolol show the greatest promise. Limitations of these treatments, including dropout and a significant number of patients showing no or only partial response, are discussed as well as issues related to selecting among efficacious treatments.

People wade through the flood waters of New Orleans following Hurricane Katrina.

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INTRODUCTION

This is the second of two companion papers on the topic of posttraumatic stress disorder (PTSD) and acute stress disorder (ASD). In the first paper, we focused on issues related to the nature of PTSD and ASD and their implications for clinical assessment.[1] In this second paper, we address issues regarding the treatment of chronic PTSD and the treatment of ASD/prevention of chronic PTSD. Considerable research has been conducted since the introduction of PTSD into DSM-III[2] in 1980 indicating that both cognitive-behavior therapy (CBT) and selective serotonin reuptake inhibitors (SSRIs) can be highly effective in the treatment of chronic PTSD. Additionally, since the inclusion of ASD into DSM-IV,[3] there is a growing evidence for the efficacy of CBT in treatment of ASD/prevention of chronic PTSD, whereas the research on pharmacotherapy is quite limited in this area.

TREATMENT OF CHRONIC PTSD

Cognitive-behavior therapy (CBT). CBT is an umbrella term that covers a number of different psychological interventions designed to reduce the intensity and frequency of distressing negative emotional reactions, challenge and modify maladaptive beliefs, decrease avoidance of safe but feared stimuli, and promote effective coping. CBT is intended to be short-term therapy, with most studies on PTSD providing between 9 to 12 sessions, each typically lasting 90 to 120 minutes, which are administered once or twice weekly. In between sessions, patients are usually assigned homework that involves practicing the specific interventions being used. The interventions most frequently used in the treatment of PTSD are exposure therapy, anxiety management training, and cognitive restructuring. A fourth treatment for PTSD, eye movement desensitization and reprocessing (EMDR),[4] incorporates elements of all three interventions and adds the use of therapist-directed rapid eye movements and other laterally alternating activities (e.g., mentally tracking laterally alternating sounds) during the "desensitization" (i.e., exposure therapy) and "reprocessing" (i.e., cognitive restructuring) phases of treatment.

Exposure therapy. Exposure therapy is itself a class of treatment procedures that are designed to help individuals confront feared but safe thoughts, situations, objects, people, places, or activities that are otherwise avoided for the purpose of reducing the unrealistic anxiety and avoidance elicited by these stimuli. Exposure therapy is a major component of treatment for other anxiety disorders such as phobias, panic disorder and agoraphobia, social anxiety disorder, and obsessive-compulsive disorder.[5]

Applied to the treatment of PTSD, exposure therapy typically includes imaginal exposure to the memory of the trauma and *in-vivo* exposure to stimuli that trigger trauma-related memories and emotional reactions.[6] The term *imaginal exposure* refers to a therapy in which patients are instructed to close their eyes and recall the trauma memory by imagining the event as if it is happening right now, while simultaneously describing out loud what he or she is remembering. Patients are encouraged to provide a detailed description of the memory, including any salient sights, sounds, smells, tastes, or physical sensations they experience, along with their thoughts and emotional reactions that occurred at the time of the trauma. These trauma narratives are repeated several times in the course of a therapy session for 20 to 45 minutes and usually tape-recorded. The patient then repeats listening to the recordings as homework in between therapy sessions.

In-vivo exposure involves first identifying a range of people, places, situations, and activities that have come to trigger anxiety and avoidance as a result of the trauma; second, evaluating the situations for safety and relevance to the patient's normal functioning; and third, repeatedly confronting these situations for prolonged periods of time until there is a significant reduction in the patient's anxiety. Progress with *in-vivo* exposure usually commences along a hierarchy, starting with stimuli that provoke moderate levels of anxiety and then gradually working up the hierarchy as the patient achieves success with the lower items. Often the most fear-provoking stimuli on the hierarchy will need to broken down into smaller, more manageable steps to help patients overcome their avoidance. For example, victims of interpersonal violence perpetrated by a stranger frequently avoid crowded places, such as busy supermarkets, stores, and recreation venues (e.g., theaters, sports arenas), out of fear that they will again be attacked by a stranger. Although the ultimate goal may be to help the patient be able to go shopping alone on the weekend at a crowded, busy shopping mall, the patient may need to begin with easier steps, such as going to a department store during the weekday accompanied by a coach and then gradually increasing the difficulty of the exercise by going at busier times, shifting from a department store to a mall, and fading out the coach's assistance.

Cognitive Behavior Therapy Interventions
Exposure Therapy
Anxiety Management Training
Cognitive Restructuring
Eye Movement Desensitization and Reprocessing (EMDR)

At the core of the theoretical model behind the use of exposure therapy are the ideas that exposure to a traumatic event results in the conditioning of fear and anxiety to cues that were present at the time of the trauma, and that such conditioned reactions are triggered by subsequent exposure to memories and reminders of the trauma. These conditioned fear reactions subsequently motivate attempts to alleviate the intense distress and any cognitive or behavioral responses that accomplish distress reduction are strengthened through the process of negative reinforcement. Whereas the successful avoidance of feared but safe memories and reminders may promote a temporary feeling of relief, such avoidance prevents habituation of the fear reactions that would otherwise occur when the trauma survivor is exposed to the trauma memories and reminders in the absence of actual harm. In addition, exposure to trauma is thought to promote the development of beliefs that the world is a dangerous place and that one's inability to prevent the trauma or cope with one's symptoms in the immediate aftermath of a trauma are evidence of self-incompetence.[7] Successful avoidance similarly prevents the person from acquiring new experiences that would serve to counter or moderate these trauma-related cognitions.

Several different psychological mechanisms are thought to underlie the efficacy of exposure therapy.[7] First, repeated exposure to memories and reminders of the trauma promote habituation of anxiety associated with them, thereby correcting erroneous beliefs that anxiety will not diminish without engaging avoidance or escape strategies. Second, confronting the trauma memories and reminders, rather than avoiding them, blocks the further negative reinforcement of the cognitive and behavioral avoidance. Third, it helps patients to realize that remembering the trauma, although emotionally upsetting, is not dangerous. Fourth, it also helps patients to differentiate between the traumatic event, which was dangerous, and other similar but not dangerous events, thereby allowing them to view the trauma as a specific occurrence rather than an indication that the entire world is dangerous and that the self is completely incompetent. Fifth, success at overcoming their avoidance and confronting these distressing thoughts and feelings will alter patients' perception of their symptoms, from being evidence of their incompetence to indications of personal mastery and courage. In other words, patients learn they can tolerate their symptoms and that having those symptoms does not lead to going crazy or losing control. As a result, individuals may come to see themselves as trauma survivors, rather than trauma victims. And sixth, exposure to the trauma memory helps patients to focus on details of the trauma memory that may otherwise be overshadowed by the more salient threat-related elements of the memory. These other details may help to modify negative cognitions about the dangerousness of the world and the survivor's own competence. For example, an individual feeling guilty about not having done more to resist an assailant may come to the realization that had he or she resisted more, the perpetrator may have further escalated the level of violence.

Anxiety management training. Anxiety management training is another class of treatment procedures, in this case focused on acquiring skills to manage stressful situations and problematic emotional reactions. Meichanbaum's stress inoculation training (SIT)[8] is one specific anxiety management protocol that has been subjected to considerable empirical research, and the only comprehensive anxiety management program that has been studied in the treatment of PTSD. Applied to the treatment of PTSD,[9–11] the SIT program consists of training in controlled breathing, progressive muscle relaxation, guided positive imagery, thought stopping, and cognitive restructuring (discussed in greater detail in the following section). The rationale for SIT in the treatment of PTSD[9] is based on Lang's[12] triple response model in which trauma-related anxiety is conceptualized as comprising three partially independent response systems: cognitive (i.e., thoughts, images, beliefs, perceptions), physiological (arousal), and behavioral (escape and avoidance responses). Because these systems are partially independent, individuals will differ in how they experience and express their anxiety reactions, and one goal for treatment is to match interventions with specific symptoms. For example, controlled breathing and progressive muscle relaxation may be used to target the symptoms of physiological arousal of PTSD. Thought stopping, by contrast, is designed to disrupt intrusive recollections about the trauma or other anxiety provoking thoughts and images (e.g., worry, rumination about current life stressors).

Cognitive restructuring. Cognitive therapy, first developed as a treatment for depression[13] and then extended to the treatment of anxiety,[14] is based on the notion that it is not events *per se* that cause problematic emotional reactions, but one's interpretation of those events. Accordingly, cognitive therapy techniques, of which cognitive restructuring is one of the most basic, are designed to help patients identify and challenge their inaccurate or unhelpful cognitions and replace them with more realistic or helpful ones. Evaluating the accuracy of one's beliefs often involves sys-

tematically reviewing the evidence both for and against the belief or evaluating the pros and cons of maintaining the belief, carefully considering the likelihood or actual cost of feared consequences, investigating possible alternative explanations for difficult or challenging situations, or attempting to view the situation from the perspective of another.

Eye movement desensitization and reprocessing (EMDR). Although treatment with EMDR is formally described as consisting of eight phases,[4] as the name implies, two major components are brief imaginal exposure to trauma-related thoughts, images, and memories (desensitization) and a form of cognitive restructuring, called reprocessing. During the desensitization phase, patients are instructed to generate a mental image that represents the targeted traumatic event and to think about a specific trauma-related cognition that they would like to change. For example, the patient may come to hold the belief that he or she is worthless as a result of repeated instances of domestic violence. The therapist then induces a series of rapid left-to-right eye movements by instructing the patient to follow the therapist's hand as it is moves back and forth across the patient's visual field (approximately 24 complete cycles taking approximately 30 seconds to complete), followed by the instruction to "blank out" the image and then a query about "What do you get now?" This process is repeated with the new thought or image until there is a substantial decline in the patient's self-reported distress. After successful desensitization, the process is repeated, except this time, the patient holds in mind both the original trauma image and an alternative positive cognition the patient would like to believe (e.g., "I am a worthwhile person"); these are called installation trials. The sets of rapid eye movements are again induced and repeated until the patient reports a high level of belief in the new cognition. In some cases, the rapid eye movements are replaced by other laterally alternating stimuli (e.g., tones) or responses (e.g., hand taps).

Much of the initial research on EMDR suffered from significant methodological limitations, which have been thoroughly discussed in the literature (for critical reviews, see Acierno, et al.,[15] Herbert and Meuser,[16] and Lohr, et al.,[17–19]). However, more recent research has since established the basic efficacy of EMDR in adequately conducted randomized, controlled trials for the treatment of PTSD, although dismantling studies have repeatedly failed to find superior outcome for EMDR treatment that includes the use of the rapid eye movements compared to a range of control condition, including conducting EMDR while having patients close their eyes or focus on a set point.[20] In addition, the one study that has investigated the role of installation by comparing the standard EMDR treatment with a treatment in which installation trials were replaced by additional desensitization trials failed to find any group differences.[21] Thus, neither of the procedures that most differentiate EMDR from other combined CBT programs have been found to significantly contribute to treatment outcome.

Efficacy of CBT. The efficacy of CBT in the treatment of PTSD has now been demonstrated in a number of randomized, controlled studies. For example, a recently published meta-analysis contained 26 studies, yielding a total of 44 active treatment conditions and 21 control conditions (waitlist, relaxation, or supportive counseling).[22] Across all active treatments, the mean within-group effect size was 1.43 in contrast to 0.35 for waitlist control conditions and 0.59 for active control conditions (relaxation and supportive counseling). The mean between-group effect sizes for studies comparing active treatment with waitlist and active controls were 1.11 and 0.83, respectively. Among studies that reported diagnostic status at post-treatment, 67 percent of patients completing active treatment no longer met criteria for PTSD compared to 16 percent in waitlist conditions and 39 percent in active control treatments. Rather than attempt an exhaustive review or simply summarize the Bradley, et al., meta-analysis, we provide a more select review to illustrate some of the emerging trends and issues relevant to treatment considerations and future research. Unless specifically noted otherwise, all of the studies of CBT for PTSD reviewed below utilized random assignment of participants to a minimum of two conditions and all studies utilized accepted measures of PTSD with demonstrated reliability and validity.

1. Trauma populations. The efficacy of these various CBT interventions has been demonstrated across a wide range of specific adult trauma populations, including female victims of physical and sexual assault perpetrated in adulthood[11,23] and sexual assault perpetrated in childhood;[23–25] male combat veterans;[26,27] male and female victims of motor vehicle accidents;[28,29] male and female refugees;[30] and female victims of domestic violence;[31,32] as well as several mixed gender/mixed trauma samples comprising mostly victims of violent crime and motor vehicle accidents.[33–37] In addition, these studies have also shown quite consistently that treatment of PTSD results in the concomitant improvement on measures of depression (for some specific examples, see studies by Foa, et al.;[10,11,23] for a more inclusive meta-anlytic summary, see Van Etten and Taylor[76]) and general anxiety (for some specific examples, see

studies by Foa, et al.;[10,11] for a more inclusive metal-analytic summary, see Van Etten and Taylor[76]). Studies that have included follow-up assessments, ranging between three months and two years post-treatment, indicate that treatment gains are generally maintained.

2. Comparisons between treatments. Several studies have been conducted directly comparing the efficacy of exposure therapy with other treatments, including SIT,[10,11] variations of cognitive therapy,[34,36,38] and EMDR.[35,37] The general pattern of results for these direct comparisons has been that treatments are generally comparable to one another and that small differences found within individual studies do not reliably replicate across studies. This general comparability of treatments extends not just to treatment outcome on measures of PTSD, but also to depression and general anxiety. At present, there are no published studies directly comparing cognitive therapy, SIT, or EMDR with one another.

3. Combined treatments. Five studies have investigated whether combining separately efficacious treatments yields better treatment than the individual treatments. One study[11] investigated whether the combination of exposure therapy plus SIT resulted in better outcome than either treatment alone. In a similarly designed study, Marks, et al.,[34] investigated whether the combination of exposure therapy plus cognitive restructuring resulted in better outcomes than either alone. Neither of these studies found evidence for the superiority of combined treatment over the constituent treatments. Consistent with Marks, et al.,[34] Paunovic and Ost[30] and Foa, et al.,[23] also found comparable outcome between exposure therapy alone and exposure therapy combined with cognitive restructuring. By contrast, Bryant, et al.,[33] found that adding cognitive restructuring enhanced the efficacy of exposure therapy. Whereas exposure therapy in the study by Bryant, et al.,[33] was limited to imaginal exposure, the studies that did not find augmentation of exposure therapy with the addition of either SIT[11] or cognitive restructuring[23,30,34] employed both imaginal and *in-vivo* exposure. Thus, one possibility is that the effects of imaginal exposure alone are enhanced by the addition of either *in-vivo* exposure or cognitive restructuring, but the combination of imaginal plus *in-vivo* exposure is not further enhanced by the addition of cognitive restructuring or SIT.

4. Partial responders, dropouts, and extending treatment. We previously highlighted the efficacy of CBT in the treatment of chronic PTSD by contrasting the percent of patients continuing to have PTSD following treatment and control conditions summarized in the Bradley, et al.,[22] meta-analysis. However, the finding that, on average, 67 percent of patients receiving CBT no longer met criteria for PTSD also means that 33 percent of them continued to meet criteria for PTSD. Thus, although many patients clearly benefit from treatment, many patients are left with significant residual symptoms. In addition, an average of 21 percent of patients dropped out of active treatment compared to 11 percent for active control treatments and 12 percent for waitlist control conditions. As we reviewed in Points 2 and 3 above, different forms of CBT yield similar outcomes, and attempts to improve efficacy by combining separately effective treatments have generally not been successful. These findings extend also to dropout rates. Bradley, et al.,[22] found dropout rates for exposure therapy alone, cognitive therapy alone, and EMDR were 24, 17, and 16 percent, respectively, compared to 32 percent for exposure therapy combined with other treatments (see Hembree, et al.,[39] for a similar analysis). A second strategy for improving efficacy that has been evaluated in one study involves extending treatment for partial responders. Foa, et al.,[23] provided exposure therapy alone or combined with cognitive restructuring to female assault victims with chronic PTSD. Patients who demonstrated a reduction in self-reported PTSD severity of 70 percent or greater by Session 8 were scheduled to terminate treatment at Session 9. Patients who did not achieve this criterion were provided with up to a total of 12 therapy sessions. Fifty-eight percent of patients who completed at least eight sessions went on to receive one or more extension sessions because they did not meet the criteria for early termination. Results for this group indicated that further improvement was achieved during the extension period. The average treatment gain from pretreatment to Session 8 for these patients was a 31-percent reduction in PTSD severity. After completion of the extension sessions, the average reduction in PTSD severity compared to pretreatment was 60 percent. Thus only a few additional sessions nearly doubled their treatment gains.

Comment. The most frequently used control group in published treatment studies of CBT for PTSD has been waitlist or minimal attention. Compared to this standard, the cumulative evidence is quite strong that the various CBT programs described above are all efficacious, and by contrast, as noted in Points 2 though 4 above, there is little cumulative evidence to support any particular CBT over another.

A more rigorous standard, but less frequently used, is to compare the target CBTs with a non-specific control treatment, such as supportive counseling (e.g., Foa, et al.,[10] Blanchard, et al.,[28] Bryant, et al.[33]), or relaxation (e.g., Marks, et

al.,[34] Taylor, et al.[37]). In these studies, the target CBT interventions have uniformly had numerically superior outcome to the control treatment, but have not always achieved statistical significance. The pattern of consistent numerical superiority but occasional lack of statistical superiority is likely due to two related factors. First, there is some evidence that non-specific treatments may provide at least some benefit relative to wait-list,[28] thereby reducing the magnitude of the difference between the target CBT and the non-specific control treatment. Second, most studies of CBT for PTSD have used relatively small sample sizes. These two factors, in combination with other instances in which one or more of the target CBTs did achieve statistically superior results compared to the nonspecific treatment, suggest the instances in which CBT was not superior to nonspecific treatment is more likely to reflect low statistical power to detect a difference, rather than a true lack of difference. However, future research should make greater use of non-specific control groups and ensure adequate sample sizes to detect meaningful differences in order to resolve this issue and further improve the efficacy of psychotherapy for PTSD.

Medication. The earliest studies of medication for the treatment of PTSD investigated the efficacy the tricyclic antidepressants amitriptyline,[40] desipramine,[41] and imipramine;[42] the monoamine oxidase inhibitor (MAO-I) phenelzine,[42,43] and the benzodiazpine alprazolam,[44] finding little evidence of either a placebo effect or a significant medication effect. As a group, many of these studies suffered numerous methodological limitations, such as small sample sizes with predominately veteran samples and short duration of treatment (4–8 weeks). Two later trials of the rapidly reversible MAO-I brofaramine utilizing treatment trials of 10[45] and 14[46] weeks duration in large samples that included a mix of civilian and military PTSD found evidence of a strong placebo response, but failed to find significantly greater improvement in the medication condition.

More recently, a growing number of well-conducted, large-scale, placebo-controlled trials have been published demonstrating the efficacy of the serotonin reuptake inhibitor (SRI) medications sertraline,[47,48] paroxetine,[49,50] and fluoxetine,[51,52] two of which (sertraline and paroxetine) have received the FDA indication for the treatment of PTSD. Across these six similarly designed studies, a significantly greater percent of patients receiving active treatment were judged to be treatment responders (53–85%) compared to patients receiving pill placebo (32–44%). The mean doses of sertraline at endpoint for completers in the Brady, et al.,[47] and Davidson, et al.,[48] studies were 151.3 (SD=51.2) and 146.3 (SD=49.3) mg/day, respectively; the median final fluoxetine dose in the Connor, et al.,[51] study was 30 (first and fourth quartiles were 20 and 50) mg/day and the mean endpoint dose in the Martneyi, et al., study[52] was 57mg/day; and the mean paroxetine dose at endpoint in the Tucker, et al.,[50] study was 27.6 (SD=6.72) mg/day. Marshall and colleagues[49] directly compared two fixed doses of paroxetine and found comparable efficacy for 20 and 40mg/day.

In addition to the more conventional SRIs, recent research suggests that nefazedone and mirtrazepine may hold promise. Davis and colleagues[53] conducted a small study of nefazedone and found that it resulted in more rapid reduction in PTSD severity compared to placebo. After four weeks of treatment, 42 percent of patients receiving nefazodone compared to zero percent of patients receiving placebo were judged to be treatment responders, a difference that narrowed to 47 percent of patients receiving nefazodone and 42 percent of patients receiving placebo after 12 weeks of treatment. In a second small study, McRae, et al.,[54] directly compared nefazodone with sertraline. Both treatments showed significant reductions in PTSD severity, but there were no differences between groups. Davidson, et al.,[55] conducted a small placebo-controlled study that found a significantly greater percent of patients receiving mirtrazapine (65%) were treatment responders

DRUG KEY
Alprazolam (Xanax®)
Amitripityline (Elavil®)
Desipramine (Norpramin®)
Fluoxetine (Prozac®)
Imipramine (Imavate®, Janimine®, Tofranil®...)
Mirtrazipine (Remeron®)
Nefazedone (Serzone®)
Olanzapine (Zyprexa®)
Paroxetine (Paxil®)*
Phenelzine (Nardil®)
Risperidone (Belivon®, Rispen®, Risperdal®)
Sertraline (Zoloft®)*

* FDA-indicated for PTSD; All other drugs listed above are considered off-label for PTSD or would be used for a comorbid condition (e.g., depression).

compared to placebo (22%). Future research with larger sample sizes should be conducted to determine whether these early results are replicable.

As with CBT, although the majority of patients treated with one of these SRI medications were found to be treatment responders, a significant minority (approximately 30%) of patients dropped out of treatment, and as high as 15 to 47 percent of patients receiving active medication failed to achiever responder status. Londborg, et al.,[56] investigated the effects of 24 weeks of open-label sertraline continuation among patients who previously received sertraline in a 12-week, placebo-controlled trial. Results indicated that 92 percent of patients who had responded to the medication in the initial 12-week trial maintained their gains over the 24-week continuation period and eight percent relapsed during that period. In addition, 54 percent of patients who had not responded to the medication during the initial 12-week trial became responders during the continuation period. Thus, by the end of 36 weeks of treatment, 54 percent of the total sample were responders within the initial 12 weeks of treatment and maintained their gains during the 24-week continuation phase, another 22 percent of patients achieved responder status during the 24-week continuation phase, and five percent of their total sample achieved responder status during the initial 12-week trial but relapsed during continuation. The remaining 19 percent of the sample never achieved responder status during the 36 weeks of active medication. One developing area of research involves the use of neuroleptics, such as olanzapine[57] and risperidone,[58] in the treatment of PTSD, either as a primary medication or as an augmentation to SRI medication. This literature was recently reviewed by Adetunji, et al.,[59] in the same issue of *Psychiatry 2005* in which our initial paper[1] appeared and therefore will not be repeated here.

Two studies have investigated the effect of medication discontinuation on relapse. Davidson, et al.,[60] studied patients that had completed the previously described 24-week, open-label continuation study of sertraline by Londborg, et al.[56] Patients who were found to be responders at both of the last two study visits of the Londborg study were randomly assigned to a 28-week continuation phase either continuing on sertraline or shifting to placebo under double-blind conditions. Results revealed that 26 percent of the patients who were shifted to placebo relapsed, compared to only five percent of those who were maintained on sertraline, and nearly as many more of the placebo-treated patients discontinued the study due to clinical deterioration that was not severe enough to meet the criteria for formal relapse. In all, 46 percent of patients shifted to placebo either relapsed or discontinued due to deterioration, most of which occurred within 12 weeks of the shift, compared to 16 percent of patients maintained on sertraline. Martenyi, et al.,[61] randomly assigned medication responders from a previously mentioned 12-week placebo controlled study of fluoxetine[52] to continue for 24 additional weeks on fluoxetine or shift to placebo under double-blind conditions. As in the sertraline discontinuation study, shifting to placebo was associated with a significantly higher rate of relapse (16%) than continuation on fluoxetine (6%). In total, 44 percent of patients shifted to placebo either relapsed or discontinued participation in the study, compared to 17 percent of patients maintained on fluoxetine.

As with CBT, although the majority of patients treated with one of these SRI medications were found to be treatment responders, a significant minority (approximately 30%) of patients dropped out of treatment, and as high as 15 to 47 percent of patients receiving active medication failed to achiever responder status.

TREATMENT OF ASD/PREVENTION OF CHRONIC PTSD

As discussed in our previous article,[1] ASD was introduced into DSM-IV[3] for the explicit purpose of identifying within the first month following exposure to trauma those individuals who, without intervention, are most likely to develop chronic PTSD. Moreover, we reviewed some of the empirical evidence supporting the utility of the ASD diagnosis in predicting subsequent PTSD. Here we turn to the question of whether brief interventions initiated shortly after the trauma can prevent the development of chronic PTSD.

Cognitive-behavior therapy. Foa and colleagues[62] investigated the efficacy of a brief CBT program in the prevention of PTSD among recent female assault victims who met all criteria for PTSD except the duration criteria, as patients entered the study on average 15 days after the trauma. The CBT program consisted of four weekly 90-minute therapy sessions and contained elements of imaginal and *in-vivo* exposure plus training in anxiety management skills modeled after the SIT program.[10,11] Relative to a no-treatment comparison group, significantly fewer patients in the CBT condition met criteria for PTSD immediately after treatment (10%) compared to those in the comparison condition who were assessed after a comparable period of time (70%), although this difference disappeared at a follow-up assessment occurring approximately six months after the assault (11% and 22%, respectively). One limitation of this study is that comparison participants, although matched with treatment patients on several key PTSD and demographic features, were drawn from a longitudinal study of trauma reactions. Therefore, the study lacks the random assignment necessary to draw strong conclusions.

The initial promising results from the Foa, et al.,[62] pilot study have been systematically extended in a series of four randomized, controlled studies conducted by Richard Bryant and colleagues. Patients in three of these studies were men and women with no indications of brain injury who met criteria for ASD following motor vehicle accidents,[63-65] industrial accidents,[63] non-sexual assault,[64,65] and other non-military traumas.[65] Patients in the fourth study[66] were men and women with mild brain injury and ASD following motor vehicle accidents and non-sexual assaults. All four studies included a five-session CBT condition that combined imaginal and *in-vivo* exposure with SIT, modeled after the work of Foa and colleagues,[62] and a five-session supportive counseling (SC) control condition. In addition, one study included an exposure therapy only condition[64] and a second study included a condition that combined CBT with hypnosis to enhance the in-session imaginal exposure.[65]

In summary, results of all four studies by Bryant, et al., revealed that significantly fewer patients completing CBT were found to meet criteria for PTSD immediately following treatment (8–20%) and at six-month follow-up (15–23%) compared to SC (46–83% at posttreatment, 58–67% at follow-up). In addition, CBT was effective in reducing depression and general anxiety. Results of the study in which patients had minimal brain injury and ASD[66] were highly similar to results from the remaining studies in which minimal brain injury was a rule-out condition. As with the treatment of chronic PTSD, the combination of exposure therapy plus SIT was not more effective than exposure therapy alone.[64] The addition of hypnosis to CBT resulted in greater reductions on re-experiencing symptoms than CBT alone, but these two conditions did not differ on avoidance symptoms, total PTSD severity, or incidence of PTSD either immediately after treatment or at six-month follow-up.[65]

Subsequently, Bryant, et al.,[67] were able to obtain four-year follow-up data from approximately 50 percent of patients receiving CBT or SC in two of their earlier studies.[63,64] Among patients who completed the four-year assessment, eight percent of those who received CBT met criteria for PTSD compared to 25 percent of those who received SC.

Medication. In our previous article,[1] we briefly mentioned biological factors that may be involved in the development of PTSD, in particular the ideas that low levels of cortisol at the time or in the immediate aftermath of trauma may result in a more intense or sustained stress response to the trauma[68,69] and that intensity of the biological stress response to the trauma, indicated by an elevated heart rate,[70] may be a determinant of who recovers and who develops chronic PTSD. In line with such thinking, Schelling and colleagues have reported results from two randomized studies investigating the prophylactic use of intravenous hydrocortisone to raise cortisol levels among medical patients to prevent the development of chronic PTSD. In the first study,[71] a subgroup of patients enrolled in a randomized, placebo-controlled study of the hemodynamic effects of hydrocortisone during septic shock were evaluated for PTSD an average (median) of 31 months after discharge from the intensive care unit. Significantly fewer patients receiving hydrocortisone (11%) met criteria for PTSD at the follow-up assessment than patients receiving placebo (63%). In their second study,[72] patients undergoing cardiac surgery were randomly assigned to receive during the perioperative period either hydro-

cortisone or placebo and were followed up six months post-surgery. Results revealed that patients receiving hydrocortisone had significantly lower PTSD severity scores compared to placebo.

Based on the hypothesis that elevated levels of epinephrine at the time of the trauma results in an overly strong emotional memory and conditioning of fear that leads to chronic PTSD, Pitman and colleagues[73] conducted a small study to test the hypothesis that administration of the B-adronergic blocker propronolol, which is known to cross the blood-brain barrier, shortly after the trauma (within 6 hours) would prevent the overconsolidation of the trauma memory in patients with elevated heart rates (>80 BPM) and thereby reduce the incidence of PTSD one and three months later. Results indicated that 18 percent of patients receiving propranolol and 30 percent of those receiving placebo met criteria for PTSD at the one month follow-up assessment (not statistically different). At the three-month assessment, the corresponding rates of PTSD were 11 percent and 13 percent. Assessment of skin conductance at the three-month follow-up in response to tape-recorded narratives of the trauma found lower levels of arousal in the propranolol condition. Vaiva and colleagues[74] offered treatment with propranolol to patients seeking medical help in a hospital emergency room 2 to 20 hours after a motor vehicle accident or physical assault and whose heart rate was >90 BPM. At a follow-up assessment two months later, fewer patients that accepted treatment with propranolol met criteria for PTSD (9%) than patients who refused it (38%).

Finally, Gelpin and colleagues[75] conducted a small study comparing either clonazepam or alprazolam with a matched control group that received placebo. Treatment began an average of one week after the trauma, and follow-up assessment occurred one and six months after the trauma. Contrary to expectations, 63 percent of patients receiving a benzodiazepine met criteria for PTSD six months after the trauma in contrast to only 23 percent of patients receiving placebo.

SUMMARY AND ISSUES IN THE SELECTION AND ADMINISTRATION OF TREATMENT

The existence of multiple effective treatments for PTSD raises the question how to decide among the possibilities in the treatment of a particular patient. Unfortunately, at the present time, there is little in the way of empirical research to provide guidance in this process. Here we discuss issues for consideration when developing a treatment plan.

Treatment of chronic PTSD

Summary. As the research described in this paper clearly shows, CBT and SRI medication can be effective in the treatment of chronic PTSD and associated depression and anxiety. Within the CBT category, efficacious treatments include exposure therapy, alone or in combination with other CBT treatments; anxiety management training, in particular stress inoculation training; cognitive restructuring and variations of cognitive therapy; and EMDR. These treatments have all been found to produce significant benefits relative to waitlist controls, and a small number of studies have found certain CBT treatment superior to non-specific control treatments, such as relaxation and supportive counseling. Direct comparisons between active CBT treatments generally find similar outcomes with few statistically significant differences in efficacy. Within the medication category, SRI medications have been found superior to placebo and two of these medications, sertraline and paroxetine, have received FDA indication for treatment of PTSD. Fluoxetine, mirtrazepine, and nefazedone have also received some support for their efficacy but have not received the FDA indication for PTSD. The only study to compare fixed doses of paroxetine found no difference between 20 and 40mg/day and another found no difference between nafazedone and sertraline.

Although these treatments can be efficacious, it is important to acknowledge that many patients drop out from these treatments and that, among patients who complete treatment, a significant minority continues to experience substantial symptoms of PTSD. In the case of medication, there is also significant relapse among treatment responders upon discontinuation of the medication. Attempts to improve the efficacy of CBT by combining separately effective treatments, such as the combination of exposure therapy plus anxiety management training or exposure therapy plus cognitive therapy, have generally not yielded better outcome than the individual treatments. By contrast, extending treatment for partial responders has been associated with additional gains for both CBT and medication.

CBT vs. medication vs. CBT plus medication. To date, there are no published studies directly comparing any form of CBT with any kind of medication. In the absence of such studies, Van Etten and Taylor[76] conducted a meta-analysis in which they computed effect sizes based on pre- to post-treatment change and then aggregated effect sizes according to the type of treatment. They found the average effect size for SRI medication on PTSD severity (1.43 for observer-rated and 1.38 for self-reported PTSD severity) that was similar to those for CBT (1.89 and 1.27, respectively) and EMDR (0.69 and 1.24, respectively) as were dropout rates (36% for SRI medication, 15% for CBT, and

14% for EMDR; see also our discussion of dropout rates for medication and CBT above). By contrast, the average effect sizes for supportive counseling were 0.92 for observer-rated and 0.34 for self-reported PTSD severity. Thus, at present, there are no strong empirical grounds for preferring CBT or SRI medication, although it would seem both would be preferred over supportive counseling.

There are also at present, no published studies evaluating the efficacy of medication combined with CBT compared to the individual treatments for PTSD. Questions about the relative efficacy of CBT and medication and the potential benefits of combined CBT plus medication relative to monotherapies have been addressed in studies of other anxiety disorders, such as panic disorder,[77] obsessive-compulsive disorder,[78] and social anxiety disorder.[79] In general, CBT and medication monotherapies tend to produce similar acute treatment outcomes, and combined CBT plus medication seldom results in superior acute treatment outcome.[80] At drug-free follow-up, however, there is some evidence that the addition of CBT to medication helps to prevent relapse relative to medication alone.[77,80] There is a possible methodological explanation for why combined treatments (e.g., exposure therapy plus cognitive restructuring in the treatment of PTSD; CBT plus medication in the treatment of social anxiety) frequently have not yielded substantially better outcome than the constituent treatments. Specifically, combined treatments would not be expected to result in greater benefits among patients who respond well to either of the individual treatments. Thus, when each individual treatment is generally efficacious, it becomes difficult to see an effect of combined treatments started simultaneously without having extremely large sample sizes. The benefits of combined treatments may be more easily detected in studies that provide treatments sequentially (e.g., medication followed by medication plus CBT vs. medication followed by medication plus control therapy; CBT followed by CBT plus medication vs. CBT followed by CBT plus pill placebo), with the second treatment being added for patients that have had no response or only a partial response to the initial treatment. Such sequentially designed studies may not only be better able to detect combined treatment effects if they exist, but also provide a better test of how treatments are often implemented in the clinic. In other words, a second treatment is usually only initiated if a first course of treatment has not yielded satisfactory results.

Availability of resources and patient preference. Given that there are no data strongly supporting the superiority of one class of treatment for PTSD over the other, other factors may be taken into consideration in designing a treatment plan. One factor weighing in favor of medication as a first line treatment for PTSD is the wider availability of medication management relative to CBT. Whereas any physician and certain other medical healthcare providers can write prescriptions for psychiatric medications, few mental health professionals are trained in CBT for PTSD.[81] Indeed, the availability of therapists trained in CBT is generally restricted to larger cities and those cities with universities or medical schools.

A second factor that should be taken into consideration is patient preference. At least among female assault victims, there appears to be a strong preference for psychotherapy over medication.[82] However, because of the limited availability of CBT, this preference may lead patients with PTSD to seek general counseling as an alternative to medication. While there is evidence that SC can be helpful in the treatment of PTSD, it has been found less effective than CBT, and comparisons across

Within the CBT category, efficacious treatments include exposure therapy, alone or in combination with other CBT treatments; anxiety management training, in particular stress inoculation training; cognitive restructuring and variations of cognitive therapy; and EMDR.

studies suggest SC would also be less effective than medication.[76] Thus, when CBT is not readily available, it is possible that a patient's preference for therapy over medication could lead to the patient choosing a less effective treatment. Physicians and other medical health professionals may none-the-less be helpful to their patients with PTSD who have a strong preference for psychotherapy over medication in several ways. First, they can provide their patients with accurate information about the nature and efficacy of CBT, so that patients will be educated consumers of psychotherapy services. Related to this, medical health professionals can develop a referral network of therapists trained in CBT for PTSD so that they can assist their patients in finding appropriate treatment. And finally, they can continue to monitor their patients' progress in recovering from trauma and if, after a reasonable period of time in psychotherapy (2–3 months), a patient has made limited gains, the medical health professional can revisit the issue of medication for that patient's PTSD.

Treatment of ASD/prevention of chronic PTSD. Although there is less available research on the treatment of ASD/prevention of PTSD, the existing research on CBT yields a very similar pattern of results as the research on CBT for PTSD. Specifically, treatment that combines elements of imaginal and *in-vivo* exposure with anxiety management training has been repeatedly found to be more effective than SC on measures of PTSD, depression, and anxiety. These treatment gains are generally maintained at follow-up, but treatment with the full CBT package is not more effective than treatment with the exposure therapy elements alone. The primary differences between CBT for ASD compared to CBT for chronic PTSD are that treatment for ASC typically commences approximately 2 to 4 weeks after the trauma, during the normal window in which natural recovery is most likely to occur and, perhaps as a result, fewer sessions (4–5 vs. 9–12) are required.

There is even less available evidence for the efficacy of medication for the treatment of ASD/prevention of PTSD. At the present, there is only one intervention that has shown replicable differences between treatment and placebo conditions, which is the administration of IV hydrocortisone among medical in-patients for the purpose of raising cortisol. There is no research on how efficacious or practical this intervention would be if initiated within hours after more typical traumas, such as sexual and non-sexual assaults and motor vehicle accidents. A second approach showing some promise is the administration of propranolol initiated within a few hours of the trauma. The use of benzodiazepines to prevent PTSD has not been demonstrated and in fact may be contraindicated.

When to offer treatment. In our earlier paper,[1] we reviewed evidence showing that individuals meeting full criteria for ASD approximately two weeks after a motor vehicle accident were highly likely to develop chronic PTSD, perhaps as high as 78 percent of them, whereas individuals who failed to meet symptom criteria for at least two symptom clusters ("subclinical" ASD) were highly unlikely to develop chronic PTSD, less than 20 percent of them.[83] In these two cases, it would appear the decision of whether to offer treatment seems pretty clear: patients meeting criteria for ASD should be provided with treatment, whereas those who do not meet criteria for even subclinical ASD should be monitored to ensure that natural recovery occurs, but more intensive intervention would not seem warranted unless the person was showing clear signs of dysfunction or they meet criteria for chronic or subclinical PTSD (meets symptom criteria for all but the avoidance cluster) three months after the trauma. More challenging is making recommendations for individuals who meet criteria for subclinical ASD. Although a significant percent of these patients will develop chronic PTSD without treatment, perhaps as high as 60 percent, a substantial percentage of them will recover without any need for intervention. We previously suggested that either course of action, offering treatment or arranging for systematic monitoring to determine whether the patient is shows a pattern of natural recovery, would seem reasonable in these intermediate cases.

Within the medication category, SRI medications have been found superior to placebo, and two of these medications, sertraline and paroxetine, have received FDA indication for treatment of PTSD.

Selecting treatment. Based on the relatively small and homogeneous database on efficacious treatments for ASD, CBT clearly seems to be the treatment of choice. Yet, as we noted earlier in our discussion of PTSD, access to qualified therapists with training in this form of intervention is quite limited. The comparison condition in the series of studies by Bryant and colleagues[63–66] was SC, and no additional waitlist group was utilized. Thus, it is difficult to know the extent to which the improvement observed in the SC condition in these studies was due to an effect of SC or natural recovery. The rates of chronic PTSD six months after treatment with SC across the four Bryant, et al., studies[63–66] (58–67%) were somewhat lower than the rate of chronic PTSD found in their previously cited longitudinal study of motor vehicle accident victims with ASD (78%),[83] suggesting that SC may have some beneficial effect. However, because this involves comparisons across studies, there is no random assignment and thus we cannot draw strong conclusions. Providing some additional support for the utility of SC when CBT is not available is the finding that SC was more effective than waitlist among patients with chronic PTSD, although SC was less effective than CBT.[28]

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