Published in final edited form as:
Psychiatr Clin North Am. 2009 September ; 32(3): 687–704. doi:10.1016/j.psc.2009.06.001.

Posttraumatic Stress Disorder (PTSD) and Stress Related Disorders

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Synopsis

Post-traumatic Stress Disorder (PTSD) is a prevalent anxiety disorder. PTSD typically follows a psychologically traumatic event, and thus has a recognizable point of onset. PTSD symptoms are present shortly after an exposure to a traumatic event, abate with time in the majority of those who initially express them, and leave a significant minority with chronic PTSD. PTSD may be treated with pharmacotherapy or psychotherapy. The treatment of the early expressions of disorder constitutes a separate domain of theory and research. The treatment of chronic PTSD often stabilizes the condition, but rarely produces stable remission. This chapter reviews the empirical evidence on the treatment of acute and chronic PTSD, outlines similarities and differences between PTSD and other Axis I disorders, evaluates new therapeutic approaches, and discusses the implications of current knowledge for the forthcoming DSM V.

Keywords

stress-disorder posttraumatic; anxiety disorders; therapy (pharmacological); therapy (psychological)

Introduction

Numerous studies have established the frequent occurrence of post-traumatic stress disorder (PTSD) among individuals exposed to traumas including wars, disasters, terrorist attacks, road traffic accidents and interpersonal violence (1–5). The estimated lifetime prevalence of PTSD in the U.S. population is about 10% (6,7). Lower prevalence rates were found in Europe, along with lower frequency of trauma exposure (8,9). The conditional probability of developing PTSD is more stable across continents, but varies between types of traumatic events and genders: the lifetime prevalence of PTSD is higher in women, although it remains unclear whether this can be explained by the more frequent occurrence of gender-related incidents (i.e., rape; assault; e.g., 9,10).

The validity of the diagnosis of PTSD has been challenged, with particularly critical emphasis on the implied etiological role of the traumatic event (10–13). However, a reevaluation of the prevalence of PTSD among Vietnam veterans, with independent corroboration of combat

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exposure (1), yielded somewhat smaller but still impressive lifetime (18.7%) and point prevalence (11.1%) of the disorder in this population.

Studies that examine the construct validity of the syndrome, as defined in DSM IV, have generally confirmed its current latent structure, with some suggestions for the possible separation of DSM IV Avoidance/Numbing diagnostic criterion into 'effortful avoidance' and 'emotional numbing' components (14–16). The latter (i.e., diminished interest in significant activities; feeling of detachment or estrangement from others; restricted range of affect, and sense of a foreshortened future) resemble symptoms of depression, and might explain part of the observed co-morbidity of the two conditions. However, unlike other anxiety disorders where the onset of depression tends to follow that of anxiety, the co-ocurrence of PTSD and depression exist from the very beginning of the disorder (17).

The high prevalence of PTSD among deployed servicemen of current wars (e.g., 24% of US reservists of the Iraq and Afghanistan campaigns, one year after homecoming; 4,18) continues to be worrisome. The degree of functional disability and quality-of-life impairments in patients with PTSD is comparable with, and in many instances greater than, those of other anxiety and mood disorders (e.g., 19,20).

Longitudinal studies (reviewed in 21) indicate that PTSD symptoms appear shortly after the traumatic event, subside in many survivors, and persist in others in the form of chronic PTSD. Accordingly, PTSD might be seen as a 'disorder of recovery' from the early responses to psychologically traumatic events (22). In an epidemiological study (6) about 40% of survivors with early PTSD had diagnosable PTSD six years later (6). Importantly, 95% of those who recover do so within the year that followed the traumatic event. On the basis of the extant therapies, Kessler et al., (6) questioned the advantage of administering treatment with the purpose of reducing the long-term prevalence of PTSD.

Chronic PTSD most often co-occurs with mood, anxiety and substance use disorders. It is highly reactive to environmental reminders of the traumatic event and to renewed life-stressors, and thus may have a fluctuating course (23).

The implications for treatment of these particularities are important. The saliency of the traumatic event and the early expression of typical symptoms create an opportunity for preventive interventions. The treatment of chronic PTSD, on the other hand, should set realistic goals (e.g., stabilization versus remission) and evaluate the relative merit of properly therapeutic efforts versus rehabilitation. Similarities between PTSD and emotional learning have lead to novel therapeutic attempts to affect the acquisition, the extinction and the reconsolidation of fear responses, in this disorder.

This chapter separately addresses the treatment of the early forms of PTSD (Acute Stress Disorder and Acute PTSD) and that of chronic PTSD. Psychopharmacology and psychotherapy are addressed in each section. Each section starts by pointing to relevant treatment targets, and ends by discussing novel therapies and future directions.

The treatment of PTSD has been the object of recent meta-analyses and critical reviews (24–33). Treatment guidelines have been published by several professional and national agencies, (e.g., the US Institute of Medicine; 34; the American Psychiatric Association; 35; the UK National Institute of Clinical Excellence; 36; The World Federation of Societies of Biological Psychiatry; 37; the Australian National Center for PTSD; 38; and the British Association for Psychopharmacology; 39). This chapter is informed by these publications, as well as by the re-evaluation of PTSD within the revision of DSM (DSM V).

Acute Stress Disorder and Acute PTSD

Converging evidence from basic and clinical studies suggests that there is a window of opportunity to help those vulnerable to develop chronic PTSD in the early aftermath of trauma (e.g., 40–45). There is also convincing evidence that preventing chronic PTSD is imperative, because chronic PTSD can be pernicious and disabling for many across the lifespan (e.g., 1, 6,46). Even more alarming, when individuals with chronic PTSD overcome various personal, familial, cultural, economic, and logistical barriers and obtain care, they may still not get the care they need (e.g., 4,47), their problems may be so entrenched that they fail to benefit from formal treatment (e.g., 48), or they may drop out of treatment prematurely (49,50). Finding early interventions that effectively prevent chronic PTSD is perceived as critical public health mandate (34,51).

Brewin et al.'s meta-analysis of risk factors for PTSD (52) suggests that adversity and lack of social support after the traumatic event contribute significantly to the maintenance of PTSD symptoms. The duration of expressing early PTSD symptoms may have an independent pathogenic effect, in that it repeats and strengthens the association between reminders of the traumatic event and alarm responses. This idea is subsumed under Antelman's (53) "time-dependent sensitization" model, Post's (54) kindling model and McEwen's (55,56) allostatic stress model. These models predict the occurrence of irreversible changes to the central nervous system within a critical period, during which a triggering event is followed by repeated reinforcements. The persistence of external stressors, but also the continuation of inner states of hypervigilence (57) or repeated and distressing recall of the traumatic event can be seen as such reinforcements. This view predicts that early interventions could have an inherent advantage to the degree that they prevent the repeated reinforcements of the responses to the traumatic event.

Targets for early Intervention

The main target of early intervention is the prevention of chronic PTSD. Effective prevention requires accurate case identification, accessible services, acceptance of care by survivors at risk and efficacious interventions.

Defining candidates for early intervention is the first challenge. Historically, the most popular preventive intervention for PTSD was psychological debriefing, provided to groups of exposed survivors, regardless of initial symptoms. However, systematic reviews and meta-analyses (e.g., 58–60) have failed to confirm the efficacy of this technique. Moreover, Mayou et al., (61) reported adverse long-term effects of debriefing. A review of other "Interventions for all," such as Education (e.g., 62), Collaborative Care (63,64) and Trauma Focused Counseling (65) similarly concluded that those are unlikely to have a clinically important effect on subsequent PTSD (36, pp.84, 66). The collapse of the scientific basis for using trauma-exposure as risk indicator underscores the need better identify the factors that put an individual at high risk and use this information to selectively offer services to those survivors at high risk before offering therapies.

Acute stress disorder (ASD) has been identified as one potential identifier. The essential feature ASD is the expression of PTSD and dissociation symptoms within a month of trauma exposure. Up to 80% of ASD patients develop chronic PTSD (for review see 67). However, the majority of those who develop PTSD do not have diagnosable ASD. Consequently, ASD cannot be used to exclusively define the risk group in need of treatment. Acute PTSD (that is PTSD developing between one and three months of the traumatic event) can supplement ASD in defining high-risk survivors.

Pharmacotherapy for Acute Stress Disorder or Acute PTSD

Because medications can be easily dispensed and delivered (e.g., in disaster-prone areas or war zones), developing pharmacological prevention of PTSD is of particular interest. At this point, however, there is no good evidence that pharmacological interventions can prevent the development of PTSD. Furthermore, the number and the qualities of current studies are limited.

Specific serotonin inhibitors (SSRIs) have been recommended for use in chronic PTSD (see below) but their effect on acute stress disorder is virtually unexplored. A randomized controlled study of escitalopram for acute PTSD (68) found no positive effect of that drug over placebo or wait list control. The small study sample, however, (22 in each arm) calls for larger replications.

Minor tranquilizers are often used to abate anxious responses to life stressors. However, studies of benzodiazepines in recent trauma survivors showed either no beneficial effect (69) or a higher likelihood of subsequent PTSD (70). Again, these studies are limited by sample size and design, and require large-scale replications.

A retrospective, chart review of the anti-psychotic risperidone, given five days after a traumatic event (71), suggests that this agent can reduce sleep disturbances, nightmares and hyperarousal. However, these results should be interpreted with caution given the lack of randomized studies.

Several theory–driven, exploratory studies of early interventions have been published. Theory suggests that blocking the adrenergic responses to a traumatic event might prevent its long-term encoding as a fear response (see below). In a randomized, double blind controlled study Pitman and colleagues' (42) administered the beta-adrenergic blocking agent proporanolol to trauma survivors who had elevated initial heart-rate within hours of a traumatic event. The treatment failed to decrease the intensity of PTSD symptoms three months later. Similarly, Stein et al., (72) found that neither propranolol, nor the anti-convulsive agent gabapentin could reduce PTSD symptoms when administered within 48 hours of a traumatic injury.

Promising, yet preliminary result were obtained in the Schelling et al (73) study, in which injured trauma survivors who received stress doses of cortisol showed lower levels of PTSD symptoms at follow-up. Other small studies and case series have been published – yet the most pertinent observation is that the pharmacological prevention of PTSD is pretty much unexplored.

Psychological Interventions for Acute Stress Disorder or Acute PTSD

Systematic reviews and meta-analyses have established the efficacy of early, trauma-focused, exposure-based cognitive behavioral therapy (CBT) in preventing chronic PTSD (66,74–77). There is, however, significant heterogeneity between studies as follows: Studies that found a beneficial effect of exposure-based CBT include the following.

- Foa et al., (78) compared four CBT sessions (n=10) with repeated assessments of trauma-related psychopathology (n=10). The active treatment significantly reduced the prevalence of PTSD (10% vs. 70%) and the intensity of PTSD symptoms.
- Echeburua et al. (79) compared five one hour sessions of Cognitive Therapy (CT) and coping skills training (n=12) with progressive muscle relaxation (n=12) in treatment-seeking sexual assault survivors within three months of the assault. Survivors in the CT arm had lower level of PTSD symptoms one year later.
- A series of studies by Bryant et al (74–77) has shown a relative advantage of early exposure-based CBT, relative to supportive counseling at six months and four years intervals from the traumatic event. The addition of anxiety management techniques

to exposure-based CBT did not increase its efficacy. The effects were maintained at a 3-year follow-up.

- Ehlers et al. (80) compared twelve weekly sessions of cognitive therapy with a self-help booklet and repeated assessments in MVA survivors. The treatment started approximately four months after the traumatic event. Cognitive therapy was superior to both control conditions.
- Bryant, et al. (81) compared CBT, CBT + hypnosis and SC. Both active treatment modalities were better than the comparator. Hypnosis did not add to the already substantial effect of CBT.
- Bryant et al., (76) found that exposure-based CBT is superior to cognitive restructuring in reducing PTSD symptoms among survivors with acute stress disorder
- Shalev et al., (68) compared exposure-based CBT with cognitive therapy and waitlist control and found that the two active treatments were similarly effective in reducing the prevalence of PTSD (respectively 20% and 22% versus 56% in the control group), and the intensity of PTSD and symptoms.
- Other studies have failed to show a beneficial effect of early CBT:
- Bisson et al. (82) compared four one-hour CBT sessions to no-intervention in individuals endorsing at least moderate PTSD symptoms 1–3 weeks after mild to moderate physical injury. There were no statistical differences between the treatment groups.
- Van Emmerik et al., (83) have failed to find a difference between five 1.5 hours sessions of CBT and Structured Writing Therapy among trauma survivors with ASD.
- Foa et al (83) compared 4 weekly two hours of CBT with social counseling and repeated assessments in women survivors of sexual and physical aggression within four weeks of the assault. The results did not differentiate the CBT from the assessment only. The authors suggested that downplaying the necessity of in-vivo exposure and homework-based imaginal exposure in this trial may have attenuated the effects of the CBT.
- Sijbrandij et al. (84) evaluated the effect of four sessions of brief CBT (n=79) relative to waitlist control (n=64) provided within three months of a traumatic event and found a transient beneficial effect of the active treatment group (one week following treatment completion), which was not evident any more four months later.

Despite heterogeneity between studies the weighted evidence (e.g., 25,35,36,38) seems to suggests that exposure-based trauma focused CBT is efficacious in the early aftermath of traumatic event. The case for cognitive therapy without exposure is still uncertain. The number of treatment sessions needed to achieve an effect is unknown. Indeed, rather than specify the number of sessions, one could use treatment outcome, in each case, as an indication to either stop or continue treatment: patients may differ in their ability to learn and practice CBT. There is no knowledge about “booster sessions” and other means to enhance or maintain the effect of an initial intervention. Most importantly, the effectiveness of preventive CBT in large groups has not been explored.

Challenges to early interventions

Challenges to early interventions include the lack of an accurate threshold criteria for selecting survivors for treatment and the time lag between the traumatic event and the beginning of therapy.

With regard to threshold criteria, a recent review of early psychological interventions (33) suggests that survivors who do not meet the full diagnostic criteria for acute PTSD recover with or without treatment and thus may not need treatment. Similarly Shalev et al., (68) randomized controlled study of CBT, Cognitive therapy and an SSRI, found that survivors with partial PTSD fared as well with or without treatment at five and eight months after the traumatic event.

The time lag between the traumatic event and the onset of treatment has been examined in Shalev et al., study (68), in which participants of the waitlist control group (n=60) started an exposure-based CBT upon completion of the early phase of the study. At the study's completion (eight months) there was no difference between the early and the late treatment group in prevalence of PTSD (19 vs. 22%) and in the severity of PTSD symptoms. One can conclude that early treatment should start within the first five months after exposure, include survivors with full PTSD and must consist of trauma-focused CBT

Additionally there are significant barriers to receiving early care among trauma-exposed civilians and military personnel (3,85–87). In the Shalev et al., (68) study 49% of 1501 civilian survivors who were assessed by telephone interviews and found to have distressing ASD symptoms declined an offer to see a clinician, and 27% of those seen by clinicians, and diagnosed as having acute PTSD declined an offer to begin treatment.

To further confound the picture, recent studies of combat veterans from the Iraq and Afghanistan wars (e.g., 4,18) have shown an increase in the prevalence of PTSD in the years following their homecoming. Although the true incidence of delayed-onset PTSD is considered to be rare (e.g., 88), the saliency of early symptoms might be limited by survivors' need to cope with ongoing stressors (e.g., injury), continue to perform under stress (e.g., in war zone) or otherwise dampen their emotionality. The presence of a 'delayed onset', or a 'mute' form of early PTSD reduces the number of survivors who will seek or accept early care.

Even if the previous barriers were overcome, early psychological interventions would be frustrated by the availability of adequate resources and the dissemination of treatment skills. Skilled cognitive behavioral therapists are rare in developed countries, and virtually inexistent in the developing world. Even when they exist, the demand for such services will often exceed the supply (e.g., in mass casualty events). Disseminating CBT skills to professionals and non-specialists, and possibly modifying face-to-face techniques are major future challenges (89, 90). On a positive note, a recent implementation of a very short CBT protocol, in earthquake survivors in Turkey (91) significantly reduced the prevalence and the severity of PTSD. Efforts to simplify, test, and disseminate CBT deserve further attention.

Chronic PTSD

Formally defined as having more than three months duration, chronic PTSD is often much longer: epidemiological studies have shown that the average duration of PTSD episode is more than seven years (e.g., 19). This longer form of PTSD is often co-morbid with other disorders, and difficult to treat. The US Institute of Medicine (34) found that the scientific evidence on treatment modalities for PTSD was "below the level of certainty that would be desired for such a common and serious disorder". The IOM has identified but one treatment component of CBT – Exposure Therapy – to have convincing evidence behind it. The evidence for other treatment modalities, including pharmacological therapies have been found to be inadequate.

Other practice guidelines (35,92,93) recommended the use of exposure-based, trauma focused CBT as well as SSRIs. The British National Institute for Clinical Excellence (NICE) practice guidelines, however (36), found the evidence about pharmacotherapy to be tentative, and

recommended that medication be offered if psychological treatments are not effective or in the case of co-morbid depression or severe hyper arousal that interferes with psychotherapy.

Pharmacotherapy

Many PTSD patients receive pharmacological treatment. For example, 80% of US Veteran's Administration PTSD patients received psychotropic medication during the year 2004 (a total of 274,297 prescriptions); 89% of those were prescribed antidepressants, 61% had anxiolytics/sedative-hypnotics, and 34% received antipsychotics (94). Although some of this compunds might have been prescribed for co-morbid conditions, these numbers are still in sharp contrast with the empirical evidence of drug efficacy in PTSD, reviewed below.

Early pharmacological studies focused on the tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors. More recent work addressed selective serotonin reuptake inhibitors (SSRIs) and newly introduced antidepressants (Nefazodone, venlafaxine, mirtazapine). Fewer studies evaluated the role of anti-convulsive, atypical neuroleptics and prazosin, an adrenergic-inhibiting agent (see below).

Large-scale RCTs have found that SSRIs are effective in reducing PTSD and associated symptoms (95–98). Research support to date is particularly strong for Paroxetine (97,98) Sertraline (95,96), and Fluoxetine (99, but see a negative study in 100). Consequently, SSRIs have been considered to be a first-line pharmacological treatment for the disorder (101). As noted by Friedman and colleagues (101), SSRIs also have a potential use for co-occurring conditions such as depression, other anxiety disorders, and impulsivity. Several SSRIs were approved by the FDA (sertraline, paroxetine) and the EMEA (sertraline) for the treatment for PTSD.

A systematic review of pharmacotherapy for PTSD (32) concluded that selective serotonin reuptake inhibitors (SSRIs) are effective in treating PTSD on both a short (14 weeks) and a longer-term (e.g., one year) basis. More cautiously, Zhang and Davidson's review (102) proposes that the "Existing pharmacologic agents produce meaningful results and bear the advantage of treating depression and other co-morbid disorders, yet still fall short of being ideal due to limited response and remission rates and tolerability issues".

This statement truly summarizes the state of facts: SSRIs may produce clinically meaningful alleviation of suffering, but the magnitude of the response leaves many patients with partial PTSD. Specifically, the response rates of SSRIs rarely exceed 60%, and less than 20–30% of the patients achieve remission (103).

Non-SSRI antidepressants (venlafaxine, nefazodone, trazodone and mirtazapine) have been evaluated in open-label trials and case studies and cannot be recommended for systematic use in PTSD. Several of the older anti-depressants, and MAO inhibitors have inconsistent effects, and most of them were abandoned with the advent of SSRIs (for review see 105).

The atypical anti-psychotic olanzapine has been evaluated as single agent or adjunct to SSRIs with positive, yet preliminary results (e.g., 106,107). Pae et al., (107) recommended caution in interpreting the current evidence, given the quality and availability of the data.

One single-blind study, and three case reports evaluated the effect of the anti-epileptic compound valproate in PTSD symptoms and showed statistically significant reduction of some PTSD symptoms (108). Preliminary studies have also evaluated the effect of other anti-convulsant (lamotrigine, carbamazepine, clonidine) in PTSD, but the evidence does not amount to clear clinical recommendation (e.g., 35)

Finally, prazosin, an adrenergic-inhibiting agent, has been evaluated for its effects of nightmares and insomnia and would seem to produce a beneficial effect (109, reviewed in 110).

One way to understand the gap between prescribing routines and the empirical evidence of efficacy in PTSD is the discrepancy between the criteria used in clinical trials (mainly symptoms reduction) and what patients and treating psychiatrists may try to achieve in a real world practice (e.g., stabilization, better sleep, better controllability of emotional reactions, reduction of self-medication with alcohol or substances of abuse). Many PTSD patients continue to receive medication despite their limited effect. Furthermore, the lack of accepted criteria of 'success' and 'remission' (34) leaves clinicians without clear indication about stopping medication, switching to other compounds or using augmentation techniques. For many practitioners, the pharmacological treatment of the chronic PTSD patient is experienced as a long struggle with the boundaries of their professional ability to help. Reliable information about the patients' perspective is lacking, yet it likely that even smaller effects of medication would be viewed as helpful.

Psychotherapies

Trauma focused CBT has the largest research base of well designed randomized controlled studies (RCTs), systematic reviews (e.g., 111) and meta-analyses (e.g., 33,112). The latter has addressed 25 randomized control studies and found (a) a significant reduction of clinician rated symptoms (14 studies; 649 subjects Standardized Mean Difference (SMD) = 1.4; CI −1.89 to −0.91) (b) significant reduction in patient self-rated PTSD symptoms (9 studies, n=428, SMD= −1.7 95% CI −2.1 to −1.24), (c) significant decrease in PTSD diagnoses (Relative risk = 0.44, 95% CI 0.37 – 0.57). Withdrawal rates were higher in the waitlist group.

The components of CBT that have been associated with the largest effects in the treatment of PTSD are cognitive therapy (CT) and prolonged exposure (PE). Cognitive therapy mainly addresses trauma-related cognitive distortions regarding the dangerousness of the world, the imminence of harm, and the limitations of one's own resources. Prolonged exposure relies on exposing patients, during sessions and in homework practices, to inner (psychological) and external reminders of the traumatic event in ways that reduce their avoidance and the associated fearfulness (fear structure) Marks et al., (113) found equivalent reductions in PTSD symptoms in CT alone, prolonged exposure (PE) alone, and CT-PE combined. Similarly, Tarrier and colleagues (114) found equivalent reductions in PTSD symptoms in imaginal exposure and a CT. Resick et al. (115) found equivalent reductions in PTSD symptoms in cognitive processing therapy and PE. Foa and colleagues (116) compared PE to stress inoculation training (containing CT) and found no difference between the treatments in reduction of PTSD severity.

Treatment guidelines have consistently recommended trauma focused CBT for chronic PTSD. Several treatment protocols have been published (e.g., 117,118) and are available to clinicians. Several studies have examined the effect of a variant of trauma-focused CBT – the eye movement desensitization and reprocessing treatment (EMDR) – a technique that combined imaginal exposure to trauma reminders with repeated lateral eye movements (119–122). Critics of this procedure cite evidence suggesting that the procedural components that purportedly differentiate it from exposure (i.e., the guided eye movement) are inactive. Nevertheless, as a treatment package (i.e., eye movement and exposure) EMDR has been effective in several well controlled studies.

Bisson et al., (112) systematic review and meta analysis also evaluated twelve studies of eye movement desensitization and reprocessing (EMDR), seven studies of stress management techniques and six studies of other therapies. EMDR was better than waitlist in reducing PTSD symptoms, and there was some evidence that both CBT and EMDR were better than supportive/

non-directive therapies. The authors have noted the absence of data on side effects and early withdrawal from treatment (intent-to-treat analyses).

New approaches

These include theory-driven and enhanced therapies. The disorder's fear conditioning theory postulates that PTSD has, at its core, an acquired (conditioned) fear response in which the traumatic event serves as conditioning stimulus (CS), the immediate reaction to the event is an unconditioned response (UCR) and the disorder consists of an abnormal conservation of strong associative link between reminders of the CS and fear responses (Conditioned responses or CRs). The determining event in PTSD is, accordingly, the conservation, and the subsequent generalization, of fear (or alarm) responses over time, as opposed to their expected decline via extinction. Much of the current research in PTSD concerns the conditions that interfere with the extinction of traumatic memories. Hypothesis-driven therapies of PTSD are based on hypotheses driven from this model.

Attempts to manipulate the strength of the initial learning, by modifying the endocrine modulators of emotional learning (cortisol and nor-epinephrine) have lead to the above-mentioned studies of propranolol and cortisol (22,72,73). Attempts to enhance glutamatergic transmission, by d-cycloserine, which, in theory, could enhance a cortical (predominantly glutamatergic) control over midbrain fear circuits (123) is another theory driven trial. This particular study did not separate active treatment from placebo. Unpublished studies are evaluating the ability of d-cycloserine to enhance the effect of cognitive behavioral therapy, with the same rationale.

Other attempts to enhance the effect of therapies refer to the ability of virtual reality to enhance the patient's engagement in re-living and exploring previously traumatic experiences (e.g., 124). Recently a "Virtual Iraq" has been designed as an aid to exposure therapy of war veterans (125). Recently, Germain et al., (126) compared the efficacy of CBT via video conference with that of face-to-face sessions and found that the two produced similar reduction in PTSD symptoms.

Recent animal research (e.g., 45) has shown that an experimental re-activation of conditioned fear responses is followed by their forgetfulness when protein synthesis is inhibited. The process that enables retention, after recall, has been referred to as reconsolidation. The requirement of such re-writing of memories after recall is at the origin of novel and experimental research, in which drugs that interfere with re-consolidation are administered during deliberate recall of traumatic memories, with the hope to somehow dissolving them (127,128). This line of experiments is worth following.

Finally, current efforts are directed towards circumventing the problem of service delivery, e.g., by using web-based CBT (e.g., 129). The results of these efforts should be followed with great interest.

Active Ingredients of therapies (why do they work?)

Current evidence consistently supports the efficiency of CBT, and less consistently that of pharmacological treatment. There are many ways to interpret the relative success of CBT and the limited performance of medication in PTSD. With regard to medication, it might be true that the nature of PTSD – a learned fear response can be particularly resistant to pharmacological manipulations. PTSD patients show uncontrollable emotional and physiological responses to reminders of the trauma (130). These responses specifically involve an activation of the amygdala – the locus of fear-driven learning. Therefore, the parsimonious interpretation of the relatively limited effect of medications, most of which affect the brain's

distributed modulatory systems (such as the serotonin, dopamine, norepinephrine and GABA-ergic systems) is that these modulatory systems cannot affectively modified this type of learned responses, or cannot affect them to the extent that they do in disorders driven by emotionality (e.g., depression, anxiety disorders). As emotional learning is a natural, normal and absolutely necessary process in all humans, it is robust and resistant to change (131) – and thus may only be marginally affected by modifying its serotonergic or adrenergic environment. Implicit learning – such as that of skills, habits, and conditioned responses – defies forgetting and age. Instead, its alteration essentially requires corrective learning. In that sense, PTSD may resemble several other disorders that involve over-learning or over-reinforcement of an initially normal response (e.g., dieting in anorexia, drinking or using substances for pleasure in the various addictions, and many of the anxiety disorders). Indeed, the extent to which PTSD resists the current pharmacological manipulation resembles the relative resistance of eating or addictive disorders to pharmacological therapies, when used as single agents.

It might be true that pharmacotherapy should be used to create conditions that enable psychological changes in PTSD (as is the case with some anorectic patients, where SSRIs reduce some of the craving for thinness, and the redundant rumination about weight and calories). Unfortunately there are currently no controlled studies of combined pharmacotherapy and psychotherapy in PTSD.

More mundane explanations of the relative poor performance of pharmacological agents in PTSD suggest that, with the exception of SSRIs – nothing has been tried systematically and on a large enough scale. Moreover, most SSRIs have been tried for short periods of time, and there is no systematic study of pharmacological augmentation techniques, combination of medication or other means of modulating CNS responses.

Finally one should remember that current pharmacological therapies, despite their imperfections, have major stabilizing effect on the patient's life. Stabilizing a chronic PTSD patient is a valuable treatment goal that should not be overlooked.

Towards DSM V

Reactive disorders?—Currently classified among the anxiety disorders, PTSD differs by virtue of the fact that it is linked with a triggering event. The latter is both the point of onset of symptoms and their essential reference (e.g., the even appears in the content of nightmares and intrusive recollections, places and situations are avoided that resemble the event). PTSD is at the same time similar to other anxiety disorders because of the clear presence of anxiety within the disorder, which is also the disorder-defining feature of other the other anxiety disorders (e.g. obsessions, phobias, panic attacks). However, the association of the syndrome with a triggering external event, and the continuous reactivity to environmental stimuli, which exists in PTSD, might argue for the inclusion of this disorder in a wider category of stress-reactive disorders. Along with PTSD, one could see dissociative identity disorders, reactive psychoses and adjustment disorders as possible members of this group. The extent to which creating a new category will better inform the study of each disorder is currently unclear. Moreover, the existence of common pathogenic, and patho-physiological mechanisms, behind the 'reactive disorders' remains hypothetical.

Place of Criterion 'A' (the traumatic event)—The diagnosis of PTSD requires an exposure to a traumatic event (DSM-IV PTSD criterion A). A number of studies have shown that those who develop PTSD are significantly more likely to report intense levels of fear, helplessness or horror during the traumatic event than those who did not (17,44,67). Other studies have shown that PTSD more likely follows an initial bodily and emotional response [132,67]. Other initial emotions such as guilt or anger have also been linked with the development of PTSD (134). However, in a large epidemiological study the conditional

probability of developing PTSD following a traumatic event was not substantially affected by the inclusion or the omission of A2 among survivors who were exposed to a traumatic event (for recent discussion see 135). This might be explained, however by the small proportion of those survivors who experienced fear, helplessness or horror that subsequently develops PTSD (67). The epidemiological perspective differs here from that of clinicians, for whom the existence of a traumatic event clearly marks the onset of an often-chronic condition.

From the clinical point of view, the discussion concerning the appropriateness of Criterion A has two weaknesses. The first concerns the place of the traumatic event in the complex causation of PTSD. The second has to do with the wish to identify specific events as 'traumatic.'

Like many other disorders the etiology of PTSD is complex, and involves vulnerability, triggering and maintaining factors (e.g., 136). In such complex causation, any single contributing factor can only account for a small portion of the total causation. This does not mean, however, that one or several critical factors cannot have a decisive role, in which case they become necessary but not sufficient to explain the occurrence of the disorder. The traumatic event is such a critical factor. Moreover, this critical factor will only trigger PTSD in the presence of other contributing conditions and predisposing factors, such as the following: biographical vulnerability factors (e.g., prior mental illness, child abuse/neglect or prior trauma); psychological factors (e.g., co-occurring loss or loneliness); biological (e.g., inherited vulnerability); appraisal of the traumatic event (including appraisal by the group, scapegoating), and the quality of the recovery environment). Consequently, even the most dramatic events are only 'potentially traumatic,' in that they will lead to PTSD only under specific conditions. Much of the current debate concerning criterion 'A,' therefore, reflects confusion between the traumatic event's critical role in the etiology of PTSD with its relative contribution to the total causation of the disorder.

The second problem stems from DSM IV preferential use of descriptive criteria, which forces a focus on well-defined events behind PTSD. It is possible, however, that psychological dimensions within specific events (e.g., perceived intensity, controllability, escape or self-efficacy) determine their potential to generate PTSD. For example, the presence, during an event, of grotesqueness, or incongruous- incomprehensible novelty may trigger a redundant cycle of ruminative elaboration that is typical of PTSD – even in the absence of threat (e.g., as among body handlers, or rescue workers). Thus, attempt to define specifically 'traumatic' events should be replaced by delineating specific 'traumatic' elements of events - and their aftermath.

Conclusions

The study of PTSD has made major progress during the last decade. The disorder's defining symptoms have been re-evaluated and found to be robust and consistent across populations and traumatic events. The disorder's natural course is better known, and fosters attempts at early prevention. Many of the neurobiological mechanisms of PTSD (e.g., fear conditioning, memory consolidation, re-consolidation) have been explored in animal studies, and several have been translated into preliminary human studies. Despite criticism, PTSD has gained increasing acceptance and recognition by clinicians and researchers. Knowledge about the disorder's therapies has converged into a few well-studied interventions.

Progress made in understanding the therapy of PTSD, however, has already shown a ceiling effect of both pharmacotherapy and psychological therapies. At presence, therefore, many PTSD patients continue to suffer despite treatment. Moreover effective psychotherapies for PTSD require resources that are not available in most places. Studies of more sophisticated pharmaco-therapies (e.g., via augmentation of association with psychological therapies) are

badly missing. There is currently no efficient way to prevent the disorder under its naturally occurring circumstances.

Despite advances in knowledge, therefore, PTSD remains prevalent, chronic, disabling and costly. Nonetheless the emergence of theory-driven biological therapies, designed to alter the longitudinal course of the disorder is encouraging, particularly when such therapies are applied during the disorder's 'critical' first few months.

Acknowledgments

This work was supported by a US PHS Grant No. MH71651 to Dr. Shalev

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