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175 Years of Progress in PTSD Therapeutics: Learning From the Past

Murray B. Stein, M.D., M.P.H., Barbara O. Rothbaum, Ph.D., A.B.P.P.

Traumatic stressors have always been a part of the human experience. What is now referred to as posttraumatic stress disorder (PTSD) was first studied in the context of military trauma during the Civil War and World War I but most extensively in World War II. Much of what we know about the medical and psychological management of PTSD has its origins in military psychiatric approaches, and a review of these practices reveals important tenets that should be applied in current treatment for both military and nonmilitary PTSD. These practices include intervention as soon as possible after the traumatic exposure, provision for a safe and supportive therapeutic milieu designed for an individual's relatively rapid return to his or her responsibilities and normal activities, and using a combination of pharmacotherapy and psychotherapy (especially exposure to the traumatic memory). A review of current guidelines for treatment of PTSD reveals that few treatments are endorsed with great certainty, owing in large part to a paucity of clinical trials, particularly of pharmacotherapy. This shortcoming must be addressed to enable translation of promising discoveries in the neuroscience of fear into the therapeutic advances patients need and deserve.

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As we reflect on the 175 years since the inception of the *American Journal of Psychiatry*, we retrace the treatment of trauma—now known as posttraumatic stress disorder (PTSD)—throughout the years. Trauma is not a new phenomenon. We have always lived in a dangerous world and experienced the effects. In *Henry IV*, Part 1, in the observations of Hotspur's wife, Kate, of her husband's behaviors after repeated mortal combat, Shakespeare nearly perfectly described PTSD symptoms as defined in DSM:

> Tell me, sweet lord, what is't that takes from thee
> Thy stomach, pleasure and thy golden sleep?
> Why dost thou bend thine eyes upon the earth,
> And start so often when thou sit'st alone?
> Why hast thou lost the fresh blood in thy cheeks;
> And given my treasures and my rights of thee
> To thick-eyed musing and curst melancholy?
> In thy faint slumbers I by thee have watch'd,
> And heard thee murmur tales of iron wars;
> Speak terms of manage [horsemanship] to thy bounding steed;
> Cry 'Courage! to the field!'
> And thou hast talk'd
> Of sallies and retires, of trenches, tents,
> Of palisadoes, frontiers, parapets,
> Of basilisks, of cannon, culverin,
> Of prisoners' ransom and of soldiers slain,
> And all the currents of a heady fight.
> Thy spirit within thee hath been so at war,
> And thus hath so bestirr'd thee in thy sleep,
> That beads of sweat have stood upon thy brow
> Like bubbles in a late-disturbed stream;
> And in thy face strange motions have appear'd,
> Such as we see when men restrain their breath
> On some great sudden hest. O, what portents are these?

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Remembering Our Past As We Envision Our Future

March 1947: Psychiatric Experience in the War, 1941–1946
Brig. General William C. Menninger

"Another observation which can be made as a result of our experience, is that if intensive treatment was provided early, in an environment in which the expectation of recovery prevailed, remarkable results were obtained."

(Am J Psychiatry 1947; 103:577–586)

What becomes apparent as we look back is the possibility that a great many of our recent therapeutic advances in PTSD were presaged by past practices. In looking back at some of the seminal writings in this area—many of them published in the *American Journal of Psychiatry*—we include here numerous, detailed quotes from many of these papers in order to give the reader a glimpse into the wisdom of our professional

ancestors. The fact that these detailed accounts appeared in print in a prestigious and influential journal also gives us pause to consider how much of the rich narrative of clinical experience is no longer communicated in the modern era of scientific discourse.

THE ERA PRIOR TO DSM

Terminology and Definitions

Until the appearance of DSM-III in 1980 (1), many of the reports of what we would now consider to be PTSD referred to the constellation of symptoms according to the index trauma, for example, "traumatic hysteria from railroad injury" (2) and rape trauma syndrome (3). During the U.S. Civil War, stress reactions were known as Da Costa's syndrome or "irritable heart" (4). During World War I, the terms "shell shock," "soldier's heart" (5, 6), and "effort syndrome" (7) were used, in addition to Da Costa's syndrome, and in the United States specifically, "neurocirculatory asthenia" (8). The British used the nonspecific term "not yet diagnosed, nervous" (9, 10).

The term "acute combat stress reaction" was used during World War II, as were the synonyms "battle fatigue" and "combat exhaustion" and, among aviation personnel, "operational fatigue" (11). And finally, "posttraumatic stress disorder" became an official diagnosis in DSM-III in 1980, largely in response to the need to classify large numbers of Vietnam veterans who were experiencing this syndrome (1, 2).

World War II: Descriptions of Treatments and Outcomes

A dramatic increase in the number of articles pertaining to trauma has occurred after each war. By World War II, as described in a paper presented at the 99th annual meeting of the American Psychiatric Association (APA), held in Detroit in 1943, the approach to treatment included individual therapy with a psychodynamic stance with a mostly silent doctor, dream analysis, and discussions of transference and ego strength but with several innovations necessitated by the sheer numbers of patients in need (12). An excerpt from this paper is as follows:

> Group therapy also implies a distinction in treatment, the introduction of a didactic element. Many psychiatrists, far from scouting this, would affirm that the power of the intellect has not received sufficient respect in psychotherapy and that it should be more fully exploited.... It was pointed out how nervousness meant feelings, how feelings in wartime meant chiefly fear, how fear prepared the body for defense against attack, and how fear set the adrenalin mechanism governing. Thus analyzed as a physiologic defense apparatus, fear lost much of its implication of moral cowardice for the men, and became acceptable in their minds. (12, p. 128)

This description of early treatment for PTSD, emphasizing the importance of psychoeducation as well as spelling out a role for cognitive interventions, foreshadows several critical elements of current-day trauma-focused psychotherapies.

The 100th annual meeting of the APA, held in Philadelphia in 1944, had a prominent focus on military psychiatry, represented by several papers published in the *American Journal of Psychiatry*. What is common practice in the treatment of PTSD today can clearly be traced back to approaches during World War II that ushered in the more modern era of treatment. At the centenary meeting, our predecessors described the need for faster treatment, with a reliance on pharmacotherapy but also on combination psychotherapy and pharmacotherapy, with an emphasis on helping the patient face the traumatic memory:

> War pressures have forced us all into the search for time-saving techniques in psychotherapy. It was natural in this dilemma that among other therapeutic agents we should seek also greater help from drugs....
>
> From a review of the literature, as well as from our clinical experience, we have concluded that there are three principal methods of attacking the pathology and therefore the symptomatology with drugs. The object, no matter what the means, is to enable the patient to face his traumatic experience and to uncondition him to it.
>
> The three methods of attack are 1) use of sedatives to secure rest; 2) use of intravenous barbiturates to promote mental catharsis, thereby assisting in the recall of a suppressed episode; 3) use of drugs acting directly on the autonomic nervous system. (13, p. 355)

This is strikingly similar to current theoretical and translational models in which PTSD is considered to be a disorder of conditioned fear and avoidance, with subsequent failure of fear extinction (14, 15):

> Several factors contribute to the persistence and intensification of the fear response to the one or more traumatic experiences. The threat to life results in markedly increased production of epinephrine (physiologic response to fear), which causes the physical symptoms described below and also increases irritability to external stimuli. Due to this state of irritability, milder or ordinarily ineffective stimuli result in the liberation of still more epinephrine. Resultant physical symptoms also serve to further increase fear so that both external and internal stimuli act to continue and increase the reaction. (13, p. 355)
>
> The dynamic force is a continuing stimulus at the cortical level in the form of the memory of the traumatic experience. This reaction to his memory is of course fear, with stimulation of the lower autonomic centers. (13, p. 356)

World War II: Sodium Pentothal and Other Approaches to Facilitating Psychotherapy for PTSD

Following the lead of Grinker and Spiegel (16), Heath and Sherman applied a technique in which military patients "relived the battle experience while under the influence of sodium pentathol" (13, p. 357):

> In the treatment of battle reactions narcosynthesis possesses considerable advantage over ordinary sedation. While both reduce sympathetic overactivity, the narcosynthesis permits

> mental catharsis at the same time. Unconditioning is therefore hastened by the fact that revelation of the traumatic incident does not produce the usual great discomfort. (13, p. 357)

This formulation is remarkably close to the current explanation for proposing the use of psychedelic-assisted psychotherapy, such as 3,4-methylenedioxymethamphetamine (MDMA)-assisted therapy (17).

When the first study that used D-cycloserine to facilitate the extinction of fear in humans by using exposure therapy was published (18), a reviewer of the study commented that it was "a paradigm shift in psychiatry." However, the idea of combining pharmacotherapy and psychotherapy for trauma-related disorders has been in existence longer than the use of monotherapies:

> With these well known concepts in mind we feel that successful treatment must be directed essentially toward reconditioning the patient to the traumatic episode so that exposure to it does not produce the great autonomic imbalance.... Drug therapy, in order to be successful, must be directed toward correction of these specific alterations of physiology, thereby making more rapid reconditioning possible. Specific therapy saves time and discouragement in contrast to hit and miss therapy. (13, p. 356)

World War II: Deconditioning and Other Precursors of In Vivo Exposure Therapy for PTSD

The research by Heath and Sherman (13) and other work published around the same time (19–22) describe what is known today as in vivo exposure (and could be considered a forerunner to virtual reality–assisted therapy):

> In this connection we have used a short movie of an actual torpedoing to great advantage. (13, p. 358)

> Audio-visual aids—motion pictures—are extremely useful adjuncts to group treatment and training. (19, p. 496)

Modern-day residential programs, including "deconditioning," were described in another paper presented at the 100th APA annual meeting. The residential programs discussed encompassed occupational therapy, physical activities, educational courses, vocational rehabilitation, group recreational activities, and sleep records. Furthermore, "most encouraging is the use of visio-auditory stimulation in the 'deconditioning' process of combat experience" (20, p. 498). Excerpts from this paper are presented below:

> Briefly, films of actual combat scenes, graded in order of intensity of stimulation are shown, followed or accompanied by a record of battle sounds. (20, p. 498)

> When the technique of group discussion has been established, actual combat films of bombings, strafings, and some captured Japanese films are shown with the battle sounds.... After these films, pulses and blood pressures are taken. This is followed by group discussion with the psychiatrist acting as a moderator.... Patients are given simple explanations of the conditioned reflex illustrated by Pavlov's experiments with dogs. (20, p. 499)

During the World War II period, several authors invoked conditioning to explain the symptoms of PTSD, although this did not preclude the use of hypnosis and abreaction (21). In one of the earliest descriptions of desensitization, the authors describe gradually increasing the intensity of war movie screenings of actual battle scenes for 15 minutes per day: "At first the scenes are shown silently. Only gradually is the sound introduced. Day by day the sound is increased until full volume is reached" (22, p. 477). The authors report good results in 12 showings and generalization of results; they refer to "extinction" of a conditioned reflex (22, p. 477) "in all but one of 14 cases" (22, p. 478).

World War II: Tenets of Military Psychiatry—Immediacy, Proximity, and Expectancy

The tenets of immediacy of treatment and psychological first aid were described in World War II military psychiatry papers, referring to the "first aid treatment of neurosis" (23):

> [T]he keynote of treatment of all acute neuroses is promptness, and the longer the delay in treatment, the less chance is there of a patient returning to duty or of regaining his former state of health. (23, p. 600)

> Forward treatment was first tried out in this war by Brigadier James and Major Palmer during the N. Africa campaign and a ward of 100 beds was set aside for psychiatric cases.... The average length of stay in hospital was under one week and the percentage of those returning to duty was quite high. (23, p. 602)

> For the anxiety cases or those suffering from severe exhaustion resulting from fatigue and battle stress, continuous narcosis is the method of treatment. By this means, the patient is cut from all external stimuli, the memory of the battle experience is removed and the patient is given complete rest of mind and body. He should be nursed in a quiet darkened room, and owing to the shortage of single rooms for this purpose in this hospital, small dormitories are set aside where 4 or 5 patients can be treated together.... The hours of sleep are recorded on a chart and the aim should be to keep the patient asleep for about 20 hours out of the 24. The treatment may be continued from 3 to 12 days. (23, pp. 602–603)

> In wartime there is little time for detailed psychotherapy to unearth conflicts and short cuts to this end are necessary. (23, p. 604)

World War II: Introduction of Hypnosis to Treatment

The use of hypnosis in the treatment of acute combat reactions was proposed because of the need for rapid therapy and the fact that early drug treatments were not helpful. Both the importance of recounting and recall (24, p. 631) and a post-hypnotic suggestion for sleep (24, p. 634) were emphasized, as well as what could be described as the art and science of protocol therapy (24, p. 631). Group psychotherapy for persons diagnosed with "severe and acute anxiety states" (25, p. 637) was recommended in 12 sessions over 4 weeks (25, p. 640). One of the earliest follow-up studies described the outcomes of treatment:

> During the first year of operation (July 1, 1944 to July 1, 1945) ...we treated about 240 veterans of World War II who had been discharged because of neuropsychiatric disabilities. Psychotherapy, usually weekly interviews, was often supplemented by group therapy, pentothal and by social and environmental "therapy," including coordination with various community resources. (26, p. 259)

The authors contacted by letter 178 of the 240 veterans they had treated during the first year, with 83 veterans responding (26). Among the 83 respondents, 55% had improved.

Another follow-up report, "Traumatic War Neuroses Five Years Later" (27), provides a nearly exact description of our current criteria for PTSD, including the following symptoms:

> Intense anxiety, recurrent battle dreams, startle reaction to sudden or loud noises, tension, depression, guilt, and a tendency to sudden, explosive, aggressive reactions... a tendency to avoid people, fear of exposure to any type of criticism, difficulty in making decisions, and various types of sleep disturbances. (27, p. 401)

In this same follow-up report, the authors detail how the experience of combat-related trauma transfers into civilian life:

> Upon his return to civilian life the patient constantly re-experiences the feelings engendered in combat. The threat of annihilation and destruction that was very real and imminent under combat conditions is carried over into civilian life.... Thus the patient reacts to seemingly minor stimuli and seemingly innocuous situations in civilian life as if he were still under combat conditions. (27, p. 401)

In a prescient nod to the future, the authors describe what we understand now as a gene-by-environment interaction. They go on to delineate what we know today as exposure therapy and indicate that about 20 sessions were usually required:

> [I]t is apparently necessary to have a combination of accidental circumstances superimposed upon a receptive soil in order to precipitate an overt, chronic traumatic war neurosis. (27, p. 402)

> Because of the importance of the establishment of a firm, deep relationship between patient and therapist, the use of intravenous narcosis and hypnosis has gradually diminished in our clinic. We have found that abreaction of traumatic events occurs without intravenous narcosis or hypnosis in the course of regular interviews. (27, p. 405)

Korean War: Advances in Combat Psychiatry

In a paper presented at the 108th APA annual meeting, held in Atlantic City, N.J., in 1952, the authors asserted that the Korean War and combat psychiatry continued "the concept developed in both world wars that combat fatigue should be treated as near the scene of combat, and as quickly as possible.... As far forward in the division as practicable, fatigue is dealt with by proper rest with or without sedation" (28, p. 252). The authors engaged in an interesting discussion of the dilemma of sending service members back to the front:

> Perhaps one of the greatest difficulties in combat psychiatry lies within the physician himself, and this difficulty increases with his personal distance from combat. The physician is the victim of his own attitudes, motivations for the practice of medicine, training, and ego ideal.... It is easier to say, "This man should never have been drafted," than to help him adjust to his duties. It is easier to send a frightened young soldier, who reminds one of one's self or one's own son, to the rear than to return him to combat duty.... One's own feelings of guilt over returning another to combat duty, more dangerous and arduous than one's own duty, make it difficult for the psychiatrist to function effectively and without anxiety. It is quite necessary that the psychiatrist work these things through so that he may effectively and happily carry out his chosen work—or the work that has been chosen for him. (28, p. 253)

> It may seem unkind to require further duty of a person who is anxious and uncomfortable, but the greatest psychiatric mishandling, and the greatest possible unkindness, is the medical evacuation of a patient who has not yet performed with the degree of honor required of him by both his superego and the community as he sees it, aiding him to burn his bridges behind him and making his guilt irrevocable. (28, p. 254)

In a review article published in the *American Journal of Psychiatry* in 1954, Glass (11) summarized four state-of-the-art basic principles of military psychiatry: treatment should be as near the battlefront as possible; treatment should combine simplicity and brevity; psychiatric staff should create a therapeutic atmosphere that reflects positive motivation; and the psychiatrist should identify with the needs of the combat group, rather than the individual.

Vietnam War: Combat Psychiatry in the Face of Overwhelming Mental Health Needs

During the Vietnam War (1955–1975), the three principles of immediacy, proximity, and expectancy were continued in the practice of combat psychiatry. Bloch (29) asserted that the combat veteran "should be treated as soon as possible after he develops incapacitating symptoms, he should be treated as close to his own unit and comrades as possible, and his treatment is undertaken and maintained with the expectation that he will respond favorably and return to duty" (29, p. 289). However, at that time the capacity of mental health personnel was inadequate to meet the needs of the military, with fewer than 20 Army psychiatrists and few social workers, and fewer personnel still for the Navy, Marines, and Air Force:

> A combat soldier who breaks down in battle or a noncombat soldier who develops symptoms in an outlying area is taken to the nearest of these outposts, where one of the specially trained medics ministers to him. He usually takes him to a quiet place, urges him to review the traumatic events, reassures him, lets him sleep overnight after a hot meal when possible, recommends medications to the general medical physicians there when appropriate, and then returns the man to duty the next morning. (29, p. 290)

Rape Trauma Syndrome

In 1974, continuing in the pre-DSM-III tradition of describing posttrauma reactions in a trauma-specific manner, a

revolutionary article on rape trauma syndrome was published. On the basis of a qualitative analysis of interviews with 92 adult female rape survivors, Burgess and Holmstrom (3) identified three reactions and different treatment for each reaction. For the survivor with typical rape trauma syndrome, they recommended crisis intervention counseling, which was clearly not considered psychotherapy. For women with compounded reactions, additional professional counseling was recommended. They went on to assert that providers treating survivors who did not disclose the rape, termed "silent rape reaction," must be "alert to indications of the possibility of rape having occurred" (3, p. 981). They defined rape as an act of violence rather than a sexual act, which was deemed revolutionary at the time. "The long-term process: reorganization" stage was characterized by almost one-half of the women who were changing residences and seeking social support but also experiencing more PTSD-like symptoms of nightmare and "traumatophobia." (Sandor Rado coined the term traumatophobia to define the phobic reaction to a traumatic situation [3, p. 984].)

THE DSM ERA OF TREATMENT OF PTSD

The designation of PTSD as an official diagnosis in DSM-III (1) ushered in the modern era of PTSD treatment. Psychodynamic conceptualizations and treatment continued, but controlled clinical trials testing them were (and continue to be) rare. Cognitive-behavioral therapy (CBT) quickly became one of the first-line treatments for PTSD. CBT was well suited for PTSD: PTSD is characterized by anxiety, avoidance, and cognitive distortions, and CBT has well-delineated techniques with proven efficacy for such problems (30). CBT is generally short term, problem focused, and readily manualized for teaching and dissemination.

Development of Trauma-Focused Psychotherapies for PTSD

One of the first post-DSM treatments developed for survivors of rape with PTSD was stress inoculation training (31), which is a package of anxiety management techniques and became the basis for cognitive processing therapy (32). However, these early studies aimed to alleviate fear and anxiety in rape survivors rather than PTSD specifically. Cognitive processing therapy was later adapted for active-duty and veteran military patients with PTSD.

Techniques in which patients were assisted in confronting the memory of a traumatic event in a therapeutic manner were some of the first tested in randomized controlled trials for PTSD, which naturally grew out of the conceptualizations of PTSD (30). Possibly the first randomized controlled trial published that actually referred to patients as having PTSD (33) applied these techniques to Vietnam veterans, and this study was soon followed by a study of female rape survivors (34). This approach was used in the development of one of the first published treatment manuals specifically for PTSD, although initially with a focus on rape survivors (35) and later for PTSD more broadly (36).

A 2008 Institute of Medicine report (37) established that trauma-focused treatments had more evidence for their efficacy in the treatment of PTSD than any other intervention, including two medications approved by the Food and Drug Administration (FDA) (sertraline and paroxetine). Soon after the publication of the report, the U.S. Department of Veterans Affairs (VA) began the first national dissemination effort to initiate empirically supported treatments for PTSD, training VA providers nationwide in two evidence-based (38) trauma-focused therapies: prolonged exposure therapy and cognitive processing therapy. Recent research has shown that although cognitive processing therapy can be delivered in a group format, its efficacy is better when administered individually (39). Virtual reality exposure therapy (40), which is a higher-tech version of the techniques showing films of combat, as described by Schwartz (20), was first administered to Vietnam veterans experiencing PTSD in the late 1990s in order to provide a potent stimulus for exposure therapy in this population, which comprises many individuals with treatment-resistant PTSD (41). Virtual reality therapy has since shown efficacy among veterans of the wars in Iraq and Afghanistan (42).

Health Service Delivery for PTSD

In the VA health care system, specialized PTSD clinical teams were established for outpatient service delivery (43). These PTSD clinical teams have typically included a multidisciplinary group of clinicians and other relevant professionals (e.g., psychiatrists, psychologists, social workers, and chaplains) capable of providing a broad set of treatments and services—more recently, evidence-based treatments—to patients with PTSD. Although there has been some research assessing the duration and intensity of this type of outpatient specialty care (44), to the best of our knowledge there is no evidence showing that this specialized care is superior to or more cost efficient than general mental health outpatient care for PTSD, although the fact that PTSD clinical teams are equipped to deliver evidence-based psychotherapies argues in favor of retaining this structural organization and the associated therapeutic expertise of its team members. Recent examples of specialized PTSD mental health programs in the private sector include the Cohen Military Family Clinics and the Wounded Warrior Project Warrior Care Network.

In the active-duty military setting, the Army adopted structural changes in 2010 that harken back to World War II practices of providing care geographically and temporally proximate to the battlefield (11, 43). In addition to increasing the number of mental health personnel and standardizing the services they provide, the Army has been "embedding small teams of mental health professionals within all operational (combat) brigades, fostering enhanced access and greater coordination with unit leaders" (45). In an interesting long-term follow-up of a study of combat stress-reaction casualties from the 1982 Lebanon war, Israeli soldiers who received frontline treatment fared better 20 years later than those who did not receive treatment on the frontline (46). A key lesson from these

observations is that not every "new" intervention must be followed by years of outcomes research before it can be considered actionable. Careful examination of the utility (or lack thereof) of similar interventions deployed in previous eras may be sufficiently informative to permit practice changes to occur in real time, although once implemented these changes should be evaluated prospectively as recommended in a 2014 Institute of Medicine report (47).

As Winston Churchill noted, the better one understands history, the more one can project into the future.

Pharmacotherapy for PTSD

Most pharmacotherapies studied for PTSD have been antidepressants, tried partly on the basis of the high comorbidity between PTSD and major depression but also partly on the basis that antidepressants were almost the only credible drug candidates available for clinical trials for PTSD. Early published research suggested possible utility of the tricyclic antidepressant desipramine (48) and monoamine oxidase inhibitors (49), but evidence was scant, and use of these drugs for PTSD had not become prevalent by the time selective serotonin reuptake inhibitors (SSRIs) entered the market in the mid- to late 1980s. Some have argued that these medications—possibly tricyclic antidepressants and desipramine in particular—deserve further study as treatments for PTSD (50).

As a result of the first large-scale randomized controlled trials for PTSD drug treatment, the FDA approved sertraline and paroxetine for PTSD in 1999. These were the first—and last—drugs to obtain FDA approval for the treatment of PTSD (51, 52). Many other drugs were studied, mostly in relatively small-scale studies, although some of these studies were bona fide randomized controlled trials. A 2006 Cochrane Review reported that 35 randomized controlled trials had been conducted, involving 4,597 participants (51). The report concluded that SSRIs could be considered first-line agents in the treatment of PTSD but that there was a "need for more effective agents" (51). More recent reviews have been more sanguine, pointing toward a modest effect of SSRIs and serotonin-norepinephrine reuptake inhibitors for PTSD and the "need for more research in this area" (52). With the exception of venlafaxine, for which there is solid evidence of efficacy for PTSD (although without FDA approval), no substantial evidence of efficacy exists for any drugs subsequently studied.

There are also examples in which drugs widely used and thought to be beneficial for some aspects of PTSD were subsequently shown to be ineffective for global PTSD symptoms when amelioration of these symptoms was the primary outcome. Probably the best example is the VA Cooperative Study of Risperidone for PTSD (53), wherein risperidone failed to achieve efficacy on the primary outcome (total score on the Clinician-Administered PTSD Scale) but showed benefits for hyperarousal and reexperiencing symptoms, as well as for insomnia (54). Another—but more perplexing—example involves prazosin in the treatment of nightmares. Prazosin not only performed well in small randomized controlled trials and was used extensively in VA facilities and elsewhere (expanding nationwide from its origins in the VA Puget Sound Health Care System [55]), but in an iconic study of active-duty personnel with PTSD it outperformed placebo to the extent that the study was halted early (56). Yet in one VA cooperative study, prazosin failed to outperform placebo (57). Reasons for these discrepant outcomes may have more to do with the characteristics of the patients included in the VA Cooperative studies (e.g., high illness chronicity and prior drug treatment failures) than with the properties of the drugs themselves, highlighting the importance of stratifying by such clinical characteristics in future PTSD trials. Another imperative is the need to test the efficacy—in randomized controlled trials—of drugs that are currently widely used for PTSD (e.g., trazodone) without any empirical basis (58).

Combination Pharmacotherapy and Psychotherapy

Again, harkening back to the treatment recommendations made at the 100th APA annual meeting in 1944, many patients with PTSD are treated with combined pharmacotherapy and psychotherapy. Yet randomized controlled trials of combination therapies have rarely shown them to be more effective than monotherapy. Combining sertraline and prolonged exposure was only more effective than sertraline alone among patients with weak medication responses (59). Similarly, adding paroxetine to prolonged exposure therapy was shown to be no more effective than adding placebo to prolonged exposure therapy (60). To our knowledge, there has been only one randomized controlled trial in which combination with an SSRI was more effective than placebo plus prolonged exposure therapy, and this was among individuals who experienced PTSD after surviving the September 11, 2001, attack on the World Trade Center (61). Combining more novel compounds with psychotherapy has had mixed results. D-cycloserine has generally shown a weak effect when added to psychotherapy for PTSD (62). There is some evidence and enthusiasm for combining MDMA and psychotherapy for PTSD (63)—again very similar to what was described almost 75 years ago (13)—but confirmative results from randomized controlled trials are pending.

Treatment Guidelines

The American Psychiatric Association "Practice Guideline for the Treatment of Patients With Acute Stress Disorder and Posttraumatic Stress Disorder" (64) was published in 2004, with a Guideline Watch (65) published in 2009, but the guidelines have not been further updated—and should be. The most recently updated treatment guidelines for PTSD are the American Psychological Association 2017 "Clinical Practice Guideline for the Treatment of PTSD" (66) and the VA/Department of Defense 2017 "Clinical Practice Guideline for the Management of Posttraumatic Stress Disorder and Acute Stress Disorder" (version 3.0) (67).

The American Psychological Association guidelines strongly recommend a variety of cognitively and behaviorally oriented psychotherapies, including CBT, cognitive processing therapy, cognitive therapy, and prolonged exposure therapy, acknowledging that the Guideline Development Panel for the Treatment of PTSD did not evaluate trauma-focused therapies separately from those that are not trauma focused. The panel suggested (a lower level of endorsement than "strongly recommend") the use of brief eclectic psychotherapy, eye movement desensitization and reprocessing, and narrative exposure therapy. The panel also suggested the following drug treatments: fluoxetine, paroxetine, sertraline, and venlafaxine.

The VA/Department of Defense guidelines strongly recommend individualized, manualized trauma-focused psychotherapy as first-line treatment and non-trauma-focused psychotherapy or medication (sertraline, paroxetine, fluoxetine, or venlafaxine) when the former is not readily available or preferred. These are the only two strong recommendations.

FUTURE DIRECTIONS FOR PTSD THERAPEUTICS

We hope for a future in which PTSD is the subject of many more trials and larger trials—trials large enough to support strong therapeutic recommendations. The field is not only in dire need of comparative efficacy trials of existing treatments (perhaps a Sequenced Treatment Alternatives to Relieve PTSD study) but also trials of novel therapeutics (58, 68). We should study older drugs that held promise (e.g., desipramine and MDMA) but were insufficiently studied at the time, and we should follow up on drugs that are marketed for other indications and have some theoretical rationale for utility and preliminary promise of efficacy (e.g., methylphenidate [69]). Although the benefit of adding D-cycloserine to augment exposure therapy for PTSD and other anxiety-related disorders has been determined to be very modest at best (62), there is considerable reason for hope that alternative pharmacological approaches to boosting the effect of exposure-based therapies will prove to be useful.

Clearly, we need to understand better the neurobiology of PTSD to develop new compounds that specifically target these neurobiological mechanisms and to determine for whom particular treatments are most likely to be efficacious. In the past decade or so, there have been remarkable advances in preclinical and clinical neurosciences with translational promise for PTSD (14, 15). Although beyond the scope of this article, we point in particular to increased understanding of the molecular biology of fear learning and fear extinction as an extremely promising gateway to drug development for the treatment of PTSD (70, 71).

Furthermore, we need to develop new treatments or modify existing treatments (pharmacological and psychological) that are effective and acceptable to patients with PTSD. A promising method for the delivery of care for veterans with PTSD from the wars in Iraq and Afghanistan is the intensive outpatient program model that is being implemented across the Warrior Care Network funded by the Wounded Warrior Project (https://www.woundedwarriorproject.org/programs/warrior-care-network). Patients are treated daily for 2 or 3 weeks in a cohort model, receiving intensive evidence-based treatment (either prolonged exposure therapy or cognitive processing therapy) in daily individual and group sessions. Again, this is not actually an innovative concept, since a similar type of program was described by Schwartz (20) in 1944. To date, the response and retention rates for this model are impressive and exceed the rates reported for any published clinical trial: approximately 95% of patients with PTSD complete the program, with approximately 20-point decreases in scores on the PTSD Checklist for DSM-5 (72). However, randomized controlled trials are needed to demonstrate superiority to other less intensive programs and modes of service delivery.

Because PTSD occurs after onset of an identifiable traumatic event, secondary prevention is a goal of ongoing and future research. We should pay heed to lessons of the past that emphasize the need to intervene early. Whereas the data are somewhat stronger for early psychological interventions (except "critical incident stress debriefing," which has been shown to be ineffective and, for some individuals, even harmful [73]) than for early pharmacological interventions (e.g., early escitalopram, hydrocortisone, or oxytocin administration) (74–76), the evidence base for both needs to be expanded for them to be appropriately applied in clinical practice. Propranolol studied to prevent PTSD was a disappointment (77, 78), although it has shown some promise when used as a putative reconsolidation blocker during trauma memory reactivation (79). Because aspects of PTSD can be modeled and mapped to increasingly better-understood neuronal mechanisms (e.g., learning and memory and conditioned fear), PTSD has the potential to lead the way in the understanding and development of mechanistically based treatments and preventive interventions for mental disorders (14, 15, 80).

AUTHOR AND ARTICLE INFORMATION

From the Departments of Psychiatry and Family Medicine and Public Health, University of California, San Diego, La Jolla; the VA San Diego Healthcare System, San Diego; and the Department of Psychiatry, Emory University School of Medicine, Atlanta.

Address correspondence to Dr. Stein (mstein@ucsd.edu).

Dr. Stein owns equity in Resilience Therapeutics, which aspires to develop treatments for posttraumatic stress disorder; he is a shareholder with Oxeia Biopharmaceuticals; he has served as a consultant to Actelion, Alkermes, Aptinyx, Bionomics, Dart Neuroscience, Janssen, and Neurocrine; and he receives compensation for editorial work for the journals *Biological Psychiatry* and *Depression and Anxiety* and for the evidence-based physician reference *UpToDate*. Dr. Rothbaum owns equity in Virtually Better, which creates virtual reality products.

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