Posttraumatic Stress Disorder

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This article reviews concepts that help synthesize the data on posttraumatic stress disorder (PTSD), a very complex condition in terms of its etiology, psychobiology, epidemiology, comorbidity, and treatment. At least four neurobiologic systems are involved in PTSD: the catecholamine, the hypothalamic-pituitary-adrenocortical, the thyroid, and the endogenous opioid systems. Six other systems are probably or possibly implicated as well. The avoidance and hyperarousal of PTSD distort the patient's appraisal of the world. The symptoms of PTSD can be understood through models of learning and memory, which form the basis of behavioral treatments. The concepts of tonic and phasic alteration and of allostasis versus homeostasis also shed light on PTSD. In addition to PTSD, there may be other identifiable posttraumatic syndromes that might be diagnosed separately, such as "complex" PTSD. Cross-cultural issues may also affect clinical phenomenology and thereby confuse the diagnosis. Comorbid disorders may actually be clues to subtypes of PTSD. The fact that victims of PTSD are also more vulnerable to medical illnesses makes a closer relationship with primary care providers and other specialists mandatory. New approaches to prevention, treatment of chronic PTSD, psychotherapy, pharmacotherapy, and research hold promise of an improved prognosis for patients with PTSD. *(J Clin Psychiatry 1997;58[suppl 9]:33–36)*

COMPLEXITY OF PTSD

Posttraumatic stress disorder (PTSD) is very complex in its etiology, psychobiology, epidemiology, comorbidity, and treatment. It involves many, if not all, of the neurobiologic and psychological mechanisms that have evolved for coping, adaptation, and survival of the species. These factors interact in very complicated ways. By comparison, panic disorder, obsessive-compulsive disorder (OCD), and phobia disorders are so much simpler neurobiologically that it is no wonder that it has been difficult to understand the pathophysiology of PTSD and to develop effective treatments for it. This complexity extends over the entire range of PTSD abnormalities: the dysregulation of many neurobiologic systems, the distortion of the patient's appraisal process, the disruption of learning and memory, the alterations in both tonic and phasic mechanisms, and the difficulties caused by the neurobiologic shift from homeostasis to allostasis.

Neurobiologic Systems

As reviewed by van der Kolk,[1] neurobiologic systems that are definitely dysregulated in PTSD include the catecholamine, the hypothalamic-pituitary-adrenocortical (HPA), the thyroid, and the endogenous opioid systems.

Other systems that are probably involved include the serotonin system, hence the efficacy of the serotonin selective reuptake inhibitors (SSRIs); the gamma-aminobutyric acid (GABA)-benzodiazepine system; and the *N*-methyl-D-aspartate (NMDA) or excitatory amino acid system. Dysregulation of the NMDA system, which mediates learning and memory, may be an important abnormality in dissociative states.

Dysregulation of corticotropin-releasing factor (CRF) may be the most important abnormality in PTSD. CRF is the hypothalamic hormone that releases adrenocorticotropic hormone (ACTH) from the pituitary, which then signals the adrenals to release glucocorticoids; it is also the neurotransmitter in the final common pathway that activates the locus ceruleus and therefore the systemic adrenergic response. Finally, CRF also initiates the immunologic responses to stress.

Possibly also involved in the etiology of PTSD are neuropeptide Y, which inhibits CRF, and neurotensin, a substance that antagonizes dopamine.

The Appraisal Process

PTSD distorts the normal appraisal process: people with the disorder see the world differently. They have great

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difficulty discriminating safety cues and are oversensitive to danger cues. As Foa[2] and coworkers have suggested, this is a consequence of exposure to a stressor that is both uncontrollable and unpredictable.

We are currently monitoring appraisal as a treatment outcome variable in our laboratory. As patients improve, we have predicted that they will begin to see ambiguous situations less as threats and more as challenges. Focusing on distortion in the appraisal process provides greater insight into the clinical phenomenology of PTSD.

Learning and Memory

PTSD may be the psychiatric disorder that best exemplifies classic models of learning and conditioning: fear conditioning, inability to habituate, inability to extinguish learned behavior, inescapable stress, and the fear-potentiated startle response, to name a few. Existing information allows us to better understand these mechanisms in a clinical context. Learning theory provides the basis for many of the cognitive-behavioral approaches, especially the one described by Foa in this supplement.[2]

Memory is also a very rich area, since some PTSD patients can not forget their traumatic experiences while others can not remember them. Research into PTSD has implications as to how memories are encoded, processed, and retrieved. State-dependent learning and conditioned inhibition may be useful psychobiological models for repression. The many animal models in this field give us abundant opportunities to increase our understanding of PTSD.

Tonic and Phasic Alterations

At baseline, people with PTSD show many abnormalities, including immunologic suppression, adrenergic dysregulation, low concentrations of corticosteroids, and high concentrations of thyroid hormones.[3] Phasic changes are much more dramatic and clinically significant. Phasic abnormalities can be unmasked by both psychological probes, such as exposure to trauma-related stimuli, or biologic probes, such as yohimbine or dexamethasone.[3] A better understanding of the pathophysiology of PTSD, both in the resting and the provoked state, will improve diagnosis and treatment.

Allostasis and Homeostasis

Allostasis, a term coined by McEwen,[4] describes an abnormal steady state that differs from the homeostatic steady state. For example, a seesaw carrying two 50-pound children, one on each end, is in homeostasis. It is perfectly—homeostatically—balanced. The beam will still be horizontal if forced to support two 5-ton elephants, but such balance is achieved at a great price. Because the seesaw was never designed for such a load, it will be strained, unstable, and easily destroyed. This is an example of allostasis.

In PTSD, the balance is allostatic. Evidence shows that both the HPA and adrenergic systems have achieved an abnormal, allostatic balance. Up-regulated glucocorticoid receptors are in balance with low steady-state cortisol levels, and excessive catecholamine levels cause down-regulation of β- and α_2-adrenergic receptors.[3] The allostasis model helps us understand the price paid neurobiologically and psychologically by the person with PTSD.

DIAGNOSTIC ISSUES

PTSD is not the only result of trauma, and prevalence rates may underestimate its impact, as discussed elsewhere in this supplement by Solomon and Davidson[5] and Brady.[6] Other symptoms are associated with trauma, particularly somatization and dissociation. As shown in the 10th edition of the *International Classification of Diseases*, European mental health professionals pay greater attention to dissociation than we do in America.[7] However, other aspects of PTSD remain unexplored.

Researchers have suggested additional syndromes. "Complex PTSD," a new entity initially proposed by Herman,[8] encompasses other symptoms seen in trauma survivors, especially those traumatized in childhood: affect dysregulation, poor impulse control, dissociation, somatization, self-destructive behavior, preoccupation with the perpetrator, and problems with meaning. Patients with complex PTSD usually have all of the symptoms of PTSD as well. Complex PTSD appears to occur most often in people who have been subjected to prolonged stressful situations, such as victims of childhood sexual abuse or survivors of protracted political torture. The "Stockholm syndrome," in which kidnap victims or hostages begin to identify with their captors, may also be a form of complex PTSD.

Other cultures may have unique equivalents to PTSD. "Ataques de nervios," a response to trauma or loss sometimes seen in Hispanic cultures, is a syndrome encompassing anxiety, demoralization, and somatization. Salvadoran women have "calor," which means heat—a fever induced by traumatic loss. The Euro-American perspective of PTSD is not the only perspective, and it is important to be open to the idioms of posttraumatic distress as expressed in other, more traditional, nonindustrialized societies.[9]

Patients with PTSD very frequently have other DSM-IV diagnoses, especially depression, anxiety, somatization, and dissociation disorders.[5,6] "Comorbidity" may be a misnomer, an artifact of total reliance on the DSM-IV system of phenomenology. For example, PTSD patients who also meet DSM-IV criteria for depression are not dexamethasone nonsuppressors, as in true melancholia, but rather dexamethasone supersupressors.[10] Does this mean they have PTSD plus depression? Or is the depression part of the PTSD? We cannot yet distinguish between these two conditions. Panic disorder, other anxiety syndromes,

and perhaps some of the Axis II disorders may be part of the PTSD syndrome. It is hoped that exclusion criteria will help future differentiation and nosology.

Besides somatization, people with PTSD are at a higher-than-normal risk for medical illness. People who have been traumatized are more likely to seek treatment from primary or specialist medical practitioners than from mental health practitioners.[11] Physiologically, PTSD patients exhibit abnormal cardiovascular function, endocrine dysregulation, and immunosuppression.[3] They also have psychological risk factors related to medical illness: hostility (the cardiovascular risk factor in the type A personality), depression, drug abuse, risk-taking behavior, and poor coping skills.[11] The connection between PTSD and medical illness demands that mental health professionals develop closer working relationships with primary care providers and medical and surgical specialists who must be educated to incorporate a trauma questionnaire into their routine screening procedures. Ideally, development of better screening will lead to timely intervention and referral of undiagnosed PTSD patients who seek treatment outside mental health settings. Psychiatric intervention may reduce medical illness and utilization of resources, thereby promoting more cost-effective care.

NEW APPROACHES

Prevention

Moving from the molecular realm to society at large, efforts to prevent and treat PTSD should include public policy to reduce the risk of trauma. The abolition of war, rape, child abuse, or urban violence, or the passage of legislation such as the Brady bill to promote gun control would constitute universal preventive interventions.

Selective intervention involves early detection and treatment for people at high risk of PTSD. As Foa[2] has demonstrated with rape victims, if people at high risk are treated as soon as possible, we may be able to forestall the later development of PTSD. Psychoeducation—teaching people what to expect after traumatic events—has demonstrated powerful efficacy after disasters.[2] Critical incident stress debriefing may also be an effective selective intervention.[12]

Treatment matching could greatly improve the effectiveness of selective intervention. We need to determine who will benefit from cognitive-behavioral therapy, pharmacotherapy, or other PTSD treatment approaches.

Chronic PTSD

We need new approaches for chronic PTSD. Work with homeless women and veterans living in shelters indicates that PTSD is the largest diagnostic entity among these populations.[13,14] Smith,[13] Rosenheck,[14] and their coworkers have indicated that many patients in the public-sector mental health system may have been misdiagnosed. In the VA and state hospital systems and in community mental health centers, many patients currently diagnosed with schizophrenia or some other chronic mental illness actually have severe end-stage PTSD. This can be detected if they are asked about their history of traumatic events, but such questions are rarely asked. These patients are indistinguishable in other respects from patients with chronic schizophrenia or chronic affective disorders. For this reason, we must consider utilizing case-manager or residential treatment approaches, which have been effective in treating other patients with chronic mental illnesses.[15] We need ways to recognize who will benefit from these approaches, since it may be too late to offer such patients medication, cognitive behavioral therapy, or psychotherapy.

Psychotherapy

The most comprehensive data available involve cognitive behavioral therapy. Only one randomized clinical trial has dealt with short-term psychodynamic treatment[16,17]—not an adequate test. Group therapy is currently under systematic investigation for the first time. Other unproved approaches include eye movement desensitization and reprocessing (EMDR), which has been endorsed by some seasoned therapists on the basis of their clinical experience, rather than findings from controlled clinical trials.[18]

Intriguing evidence comes from a recent article on cognitive behavioral therapy of OCD.[19] Positron emission tomography scans of patients who had successful cognitive behavioral treatment for OCD showed reduced blood flow in the right thalamus and head of the caudate nucleus, indicating that cognitive behavioral treatment may act on some level as a biologic therapy.[19] One might argue that behavioral therapy constitutes the best access to biologic systems because it can affect all of these systems at once, rather than affecting one or two neurotransmitters at a time, as is the case with many pharmacologic agents.

Pharmacotherapy

More randomized, controlled clinical trials of currently available and new treatments are needed.[16] The existing agents—SSRIs, monoamine oxidase inhibitors, and tricyclics—were developed for depression and only later tried in PTSD. Although the SSRIs have achieved impressive results,[20] they do not affect abnormalities like the startle response.[1] New directions for pharmacotherapy may include investigation of CRF antagonists and agonists of neuropeptide Y. The hypotheses of kindling and behavioral sensitization as mechanisms underlying PTSD suggest that certain anticonvulsants may be promising for further study, and research into NMDA receptor modulators might therapeutically address the learning and memory abnormalities associated with PTSD.

Research

Theory must drive future experimental agendas. With good animal models for experimentation, we need more

basic research on stress, pathophysiology of PTSD, and the impact of trauma on psychopathology. How might trauma cause other clinical sequelae? Are there different subtypes of PTSD? A depressive subtype? A serotonergic versus an adrenergic subtype? Are there other syndromes associated with these subtypes?

We must apply laboratory paradigms to clinical assessment. Work on dexamethasone supersuppression,[10] startle responses,[1] and neurohormonal profiling[21] has shown how psychobiologic techniques might improve the diagnostic assessment of PTSD. Techniques to distinguish PTSD from depression should be used when indicated. The impact of PTSD on physical health must also be investigated.

Finally, the best treatment for PTSD is prevention of trauma. It is therefore clinically appropriate to attempt to influence public policy and thus reduce the likelihood that men, women, and children will be exposed to traumatic events that might precipitate PTSD.

Drug names: dexamethasone (Decadron and others), dopamine (Dopastat, Intropin), yohimbine (Yocon and others).

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