PTSD was first introduced in DSM-III, its inclusion being spurred in part by the increasing recognition of posttraumatic conditions in veterans of the Vietnam War. The current DSM-IV-TR criteria for PTSD are presented in Table 11-15. As in DSM-III-R, the disorder continues to be classified with the anxiety disorders, and the major criteria of an extreme precipitating stressor, intrusive recollections, emotional numbing, and hyperarousal have been maintained. The DSM-III-R descriptor of the traumatic event as one "outside the range of usual human experience" was considered rather vague and unreliable and was eliminated. New duration criteria were also established, subdividing the disorder into acute or chronic.

Not all investigators agree that PTSD belongs with the anxiety disorders. Although anxiety is a prominent symptom, so are depression and dissociation. The diagnostic criterion of a precipitating stressor or trauma in PTSD makes this disorder different from other anxiety disorders and is more reminiscent of conditions such as brief reactive psychosis, acute stress disorder, pathological bereavement, and adjustment disorders. The International Classification of Diseases, Tenth Revision (ICD-10; World Health Organization 1992), for example, classifies all such disorders as stress related. In acknowledgment of the spectrum of disorders stemming from severe stress, DSM-IV added acute stress disorder (ASD) to the anxiety disorders. Acute stress disorder is similar to PTSD with regard to the precipitating traumatic event and to symptomatology but is time limited, occurring up to 1 month after the event. In addition, dissociative symptoms figure prominently in the definition of acute stress disorder, whereas they are not addressed in the PTSD description. It has now been well established by a number of studies, including prospective ones, that ASD is a highly reliable predictor of developing PTSD down the road; it may well be that the two should not be defined as discrete disorders. In a study of people who sustained mild traumatic brain injury in motor vehicle accidents, 82% of those who met ASD criteria were diagnosed with PTSD 6 months later (Bryant and Harvey 1998), as opposed to only 11% of those without ASD, and a steady 80% were diagnosed with PTSD 2 years after the accident (Harvey and Bryant 2000). The DSM-IV-TR diagnostic criteria for ASD are presented in Table 11-16.

Beyond the symptoms of PTSD per se, increasing attention has been drawn to an enduring constellation of traits that frequently develop in individuals subjected to chronic trauma as children or adults. Investigators such as Herman and van der Kolk had originally suggested that a discrete entity of complicated posttraumatic syndromes be recognized, otherwise designated as DESNOS (disorders of extreme stress not otherwise specified), characterized by lasting changes in identity, interpersonal relationships, and the sense of life's meaning (Herman et al. 1999; van der Kolk and Sarno 1991). Similar personality changes are recognized in ICD-10 and are classified as "enduring personality change after catastrophic experience." In the past decade, attention has increasingly been focused on the concept of "trauma-spectrum" disorders, which can include admixtures of posttraumatic stress, dissociative, somatoform, and conversion symptoms, and the classification approach to trauma-related conditions is a subject of ongoing debate.

**Clinical Description**

A soldier participates in the torture and murder of civilians. A passenger is the sole survivor of a commercial airliner crash. A woman is raped and severely beaten by an unknown assailant. The characteristic features that may develop after a traumatic event such as these include psychic numbing, reexperiencing of the trauma, and increased autonomic arousal. The trauma is reexperienced in recurrent painful and intrusive recollections, daydreams, or nightmares. Dissociative states may occur, lasting from minutes to days, in which there is a dreamlike, unreal state with hazy memory and a distorted sense of time. Psychic numbing or emotional anesthesia is manifested by diminished responsiveness to the external world, with feelings of being detached from other people, loss of interest in usual activities, and inability to feel emotions such as intimacy, tenderness, or sexual interest. Symptoms of excessive
autonomic arousal may include hyperactivity and irritability, an exaggerated startle response, difficulty concentrating, and sleep abnormalities. Rape or mugging victims sometimes become afraid to venture out alone for variable periods of time. Situations reminiscent of the original trauma may be systematically avoided.

Other symptoms may include guilt about having survived, guilt about not having prevented the traumatic experience, depression, anxiety, panic attacks, shame, and rage. There may be prolonged episodes of intense affect; increased irritability; explosive, hostile behavior; and impulsive behavior. Other accompanying or complicating symptoms associated with PTSD may include substance abuse, self-injurious behavior and suicide attempts, occupational impairment, and interference with interpersonal relationships.

**Epidemiology**

Although there are marked individual differences in how people react to stress, when stressors become extreme, such as in concentration camp situations or in extended combat, the rate of morbidity rapidly increases (Eltinger 1971; Krystal 1968). Posttraumatic syndromes may be found in up to 30% of victims of disasters (Chapman 1962). Long-term physical health effects have been noted in persons 30 years after their having survived concentration camps (Eltinger 1971).

Although this disorder has been more extensively studied in select groups, such as survivors of combat, concentration camps, and natural disasters, the ECA study investigated the occurrence of PTSD in the general population (Helzer et al. 1987). A 1% lifetime prevalence of PTSD was found (0.5% in men and 1.3% in women). The nature of the precipitating trauma differed between the two sexes. Combat and witnessing someone's injury or death were the two traumas identified in men, whereas physical attack or threat accounted for almost half of the traumas in women. In another large, random community survey of young adults, the lifetime prevalence of PTSD was 9.2%, higher than that found in the ECA study (Breslau et al. 1991). As in the ECA study, the prevalence was higher in women (11.3%) than in men (6%). In the more recent National Comorbidity Survey, the lifetime prevalence of PTSD was similarly found to be 7.8%, much higher than in the ECA study, and was more common in women. The most common stressors were combat exposure in men and sexual assault in women (Kessler et al. 1995).

Symptoms of PTSD, albeit too few in number to meet the full diagnostic criteria, are quite common in the general population. In a Canadian community survey, full PTSD was found in 2.7% of women and 1.2% of men, whereas partial PTSD was found in an additional 3.4% of women and 0.3% of men. Such individuals, seemingly women in particular, may be important to identify, because they experience clinically meaningful distress and functional impairment (M.B. Stein et al. 1997). The gender difference in PTSD prevalence, higher in women, has been consistent across several studies. It appears that women are more likely to develop PTSD than are men with comparable exposure to traumatic events, especially if exposure is before age 15 years (Breslau et al. 1997b). This difference is not well understood and could involve characteristics of both the individuals and the traumatic experiences.

A high rate of comorbid disorders is found in PTSD. In the ECA study, the highest comorbidity was with affective disorders and OCD. Men with PTSD had no increased risk for panic disorder or phobias, whereas women with PTSD had a three- to fourfold increased risk for these disorders (Helzer et al. 1987). In the survey by Breslau et al. (1991), a high comorbidity risk was found for OCD, agoraphobia, panic, and depression, whereas the association with drug or alcohol abuse was weaker. Comorbidity of PTSD with depression is a very consistent finding, although the nature of the relationship between the two conditions is controversial. Epidemiological analyses suggest that in trauma survivors, the vulnerabilities for PTSD and depression are not separate; rather, the risk for depression is highly elevated in just those trauma survivors who manifest PTSD (Breslau et al. 2000). On the other hand, a prospective study of a
large sample of trauma survivors found depression and PTSD to be independent sequelae of trauma (Shaley et al. 1998b). Regardless of causality, it is clear that PTSD in women increases the risk for a new onset of both depression and alcohol use disorder (Breslau et al. 1997a). Individuals with PTSD may be more likely to manifest borderline or self-defeating personality disorder, and it appears that the actual PTSD diagnosis rather than the trauma history accounts for this association (Shea et al. 2000).

Etiology

The Role of the Stressor

The severity of the stressor in PTSD differs in magnitude from that found in adjustment disorder, which is usually less severe and within the range of common life experience. However, this relationship between the severity of the stressor and the type of subsequent symptomatology is not always predictable. For example, studies of bereavement and divorce have found that stressors within the range of usual human experience can also produce a distinctive syndrome of reexperiencing the trauma (Horowitz et al. 1980). In effect, it has generally been underemphasized that in the average community setting, events such as sudden loss of a spouse are a much more frequent cause of PTSD than are assault and violence (Breslau et al. 1998).

Nevertheless, events such as sexual assault or armed robbery, which are interpersonal insults to integrity, self-esteem, and security, are particularly likely to lead to PTSD. When stressors become extreme (e.g., rape, extended combat, torture, concentration camp experiences), the rate of morbidity significantly increases. For example, the ECA study found that in men who had served in Vietnam, 4% of those who were in combat but were not wounded had PTSD, whereas 20% of combat veterans who had been wounded developed PTSD. In even more horrendous conditions, such as those endured by U.S. prisoners of war of the Japanese in World War II, extremely high PTSD incidence rates have been reported: 84% lifetime and 59% decades after (Engdahl et al. 1997). Variable PTSD rates have been found in individuals subjected to major noninterpersonal trauma; for example, reported rates in severely injured accident victims range from a very low 2% (Schnyder et al. 2001) to 32% (Koren et al. 1999). In those sustaining severe traumatic brain injury, a 27% PTSD incidence has been reported (Bryant et al. 2000a). Childhood interpersonal trauma can often result in PTSD, as is widely known clinically and documented by numerous studies. In an inner-city child psychiatry clinic, more than half of the traumatized children had syndromal or subsyndromal PTSD, with experiencing physical abuse or witnessing domestic violence being the strongest contributors (Silva et al. 2000). In a large community sample followed prospectively into young adulthood, about one-third of the children who had suffered substantiated sexual abuse, physical abuse, or neglect had PTSD (Widom 1999). On average, it is estimated that approximately one-fourth of all individuals who experience major trauma develop PTSD (Breslau et al. 1991). In addition, as described by McFarlane, a definite dose–response relationship exists between the impact of the trauma and PTSD. Still, it is rare even for overwhelming trauma to lead to PTSD in more than half of the exposed populations, clearly suggesting that other etiological factors also play a role (McFarlane 1990). A discussion of such predictors follows.

Risk Factors and Predictors

There is general agreement in the literature that a variety of premorbid risk factors predispose to the development of PTSD. Although the disorder can certainly develop in people without significant preexisting psychopathology, a number of biological and psychological variables have been identified that render individuals more vulnerable to the development of PTSD. In one study in a Vietnam veteran outreach center, a prior history of good adolescent friendships was predictive of PTSD, whereas a history of poor adolescent friendships was more likely in those who did not have PTSD. In addition, this study described several patients with good premorbid adjustment, low childhood trauma, and good adolescent
relationships who developed severe PTSD after experiencing prolonged trauma in Vietnam (Lindy et al. 1984). In general, however, previous adversity has been associated with a higher likelihood of developing PTSD.

It has been suggested that the greater the amount of previous trauma experienced by an individual, the more likely he or she is to develop symptoms after a stressful life event (Horowitz et al. 1980). In addition, individuals with previous traumatic experiences may be more likely to become exposed to future traumas, because they can be prone to reenact the original trauma behaviorally (van der Kolk 1989). In a study of Vietnam veterans, individuals with PTSD had higher rates of childhood physical abuse than veterans without PTSD, as well as a significantly higher rate of total traumatic events before entrance into the military (Bremner et al. 1993a).

McFarlane (1989) found that the severity of exposure to disaster was the major determinant of early posttraumatic morbidity, whereas preexisting psychological disorders better predicted the persistence of posttraumatic symptoms over time. A number of psychiatric conditions in probands and their relatives appear to predispose these individuals to develop PTSD. In the ECA sample, a history of childhood conduct problems before age 15 years was predictive of PTSD. Patients with anxious premorbid states and family histories of anxiety may also respond to a trauma with pathological anxiety and develop PTSD (Scrignar 1984). An epidemiological survey identified, albeit retrospectively, different risk factors for becoming exposed to trauma versus developing PTSD after traumatic exposure (Breslau et al. 1991). Risk factors for exposure to trauma were male sex, childhood conduct problems, extraversion, and family history of substance abuse or psychiatric problems. Risk factors for developing PTSD after traumatic exposure were disrupted parental attachments, anxiety, depression, and family history of anxiety. Having an Axis II disorder also increases the risk for chronic PTSD (Ursano et al. 1999). Having a past history of PTSD increases the risk for both acute and chronic PTSD (Ursano et al. 1999). Compared with nonchronic PTSD, chronic PTSD of more than 1 year's duration has been specifically associated with higher rates of comorbid anxiety and depressive disorders and a family history of antisocial behavior (Breslau and Davis 1992).

Interestingly, parental PTSD is a risk factor for PTSD in offspring, even in the absence of elevated trauma (Yehuda et al. 1998b). Findings with regard to gender are conflicting, in that female gender was found to be associated with chronic PTSD in one study (Breslau and Davis 1992) but with only acute PTSD in another (Ursano et al. 1999a). An additional factor that has been associated with a higher likelihood of developing PTSD is lower premorbid intelligence (Macklin et al. 1998). Neurological compromise, with increased neurological soft signs and a childhood history of neurodevelopmental problems and lower intelligence, is associated with PTSD and could possibly be a predisposing risk factor (Gurvits et al. 2000).

Early predictors of PTSD after a traumatic event have also received great attention, and their potential significance for early intervention and prevention is obvious. As previously stated, the occurrence of ASD in the first month after trauma is a very strong predictor of later PTSD. ASD diagnosis combined with a resting heart rate greater than 90 has a surprisingly high sensitivity, 88%, and specificity, 85%, in predicting development of PTSD (Bryant et al. 2000b). Similarly, high heart rate and decreased cortisol in the acute aftermath of trauma strongly correlate with later PTSD (Yehuda et al. 1998a). Even elevated heart rate, on its own, shortly after trauma is a significant predictor of later PTSD (Shalev et al. 1998a). The importance of the very early reaction to a traumatic event in predicting PTSD cannot be underestimated: early PTSD-type symptoms within 1 week of a traffic accident predict PTSD 1 year later (Koren et al. 1999).

In recent years, increased attention has been given to dissociative phenomena and to their relationship
with posttraumatic symptoms (Spiegel and Cardena 1990). Greater dissociation around the time of the traumatic event is a strong predictor of subsequent development of PTSD (Harmar et al. 1994; Shaley et al. 1996). Individuals with peritraumatic dissociation are 4-5 times more likely than those without such phenomena to develop both acute and chronic PTSD (Ursano et al. 1999b). It may be that early peritraumatic dissociation can serve as a “marker” to identify individuals who will be at high risk of developing PTSD in the future.

Cognitive and Behavioral Theories
A cognitive model proposed to explain the persistence of PTSD symptoms postulates that PTSD becomes persistent when individuals process their trauma in a way that leads to a sense of serious and current threat. Such threat processing consists of excessively negative appraisals of the trauma or its consequences and a disruption in autobiographical memory involving poor contextualization and strong associative memory (Ehlers and Clark 2000).

Behavioral theory suggests that a disturbance of conditioned responses occurs in PTSD. Autonomic responses to both innocuous and aversive stimuli are elevated, with larger responses to unpaired cues and reduced extinction of conditioned responses (Peri et al. 2000). It is proposed that individuals with PTSD have higher sympathetic system arousal at the time of conditioning and therefore are more conditionable than trauma-exposed individuals without PTSD (Orr et al. 2000). Individuals with PTSD also generalize fear-related conditioned responses across stimuli, having been sensitized by stress (Grillon and Morgan 1999).

Recent studies have also revealed a number of disturbances in cognitive processes associated with PTSD. For example, the high incidence of PTSD after severe traumatic brain injury involving loss of consciousness but few traumatic memories suggests that trauma can mediate PTSD in part at an implicit level (Bryant et al. 2000a). Impairments in explicit memory have been associated with PTSD (Bremner et al. 1993b; Jenkins et al. 1998) and may be related to hippocampal toxicity resulting from stress-mediated elevations in norepinephrine (Bremner et al. 1995). In addition, subjects with PTSD may exhibit recall deficits not for trauma-related words, but rather for positive and neutral words, suggesting that avoidance of the encoding of disturbing information does not occur in PTSD (McNally et al. 1998). This appears consistent with the intrusive nature of traumatic memories clinically encountered in the disorder. Indeed, there appears to be an attentional bias toward traumatic stimuli in PTSD (Bryant and Harvey 1997), whereas generalized attentional disturbances have not been found (Golier et al. 1997).

Biological Theories
More than a century ago, Janet described the breakdown in normal adaptation, information processing, and action that can result from overwhelming trauma and noted the automatic emotional and physical overreaction that occurs with reexposure (van der Kolk and van der Hart 1989). Freud (1919/1955) implicated a biological basis to posttraumatic symptoms, in the form of a physical fixation to the trauma. Pavlov (1927/1960) demonstrated chronic change in autonomic nervous system activity level in response to repeated traumatic exposure. Kardiner (1959) comprehensively described the phenomenology of war traumatic neurosis, identifying five cardinal features: 1) persistence of startle response, 2) fixation on the trauma, 3) atypical dream life, 4) explosive outbursts, and 5) overall constriction of personality. He called this condition a physioneurosis, a term implying an interaction of psychological and biological processes, which served as a forerunner of current psychobiological models of PTSD.

Noradrenergic system
The neurobiological response to acute stress and trauma involves the release of various stress hormones that allow the organism to respond adaptively to stress. These releases include heightened secretion of catecholamines and cortisol. When PTSD develops under severe or repeated trauma, the stress response
becomes dysregulated and chronic autonomic hyperactivity sets in, manifesting itself in the "positive" symptoms of PTSD—that is, the hyperarousal and intrusive recollections. A wide range of data support this hypothesis. The noradrenergic system, originating in the locus coeruleus, regulates arousal (Southwick et al. 1999). Animals exposed to inescapable shock initially show evidence of increased turnover of norepinephrine, with subsequent depletion of central norepinephrine (Anisman et al. 1980). Animals that have experienced previous inescapable shock are more sensitive to norepinephrine depletion. In patients with PTSD, heightened physiological responses to stressful stimuli, such as blood pressure, heart rate, respiration, galvanic skin response, and electromyographic activity, have been consistently documented (Kolb 1987; Pitman et al. 1987). Long-standing increases in the urinary catecholamines norepinephrine and epinephrine have been found in patients with PTSD (Kosten et al. 1987; Spivak et al. 1999), as well as elevated plasma norepinephrine (Spivak et al. 1999). Agents that stimulate the arousal system, such as lactate (Rainey et al. 1987) and yohimbine (Southwick et al. 1992, 1997), induce flashbacks and increases in core PTSD symptoms. Clinical improvement in intrusive recollections and hyperarousal during open treatment with adrenergic-blocking agents, such as clonidine or propranolol, also suggests adrenergic hyperactivity (Kolb et al. 1984). A decrease in the number and sensitivity of α2-adrenergic receptors, possibly as a consequence of chronic noradrenergic hyperactivity, has been reported in PTSD (Perry et al. 1987). Downregulation of the α2-adrenergic receptor is also supported by one case report of a PTSD patient with a blunted GH response to clonidine, which normalized after behavioral treatment (Hansen et al. 1991).

**Endogenous opioid system**

Whereas affective numbing was understood, in the past, primarily as a psychological defense against overwhelming emotional pain, more recent research has suggested a biological component to the "negative" symptoms of PTSD. van der Kolk et al. (1984) proposed that animal models of inescapable shock may parallel the development of PTSD in humans. Animals prevented from escaping from severe stress develop a syndrome of learned helplessness (Maier and Seligman 1976) that resembles the symptoms of constricted affect, withdrawal, amotivation, and decline in functioning associated with PTSD.

Animals exposed to prolonged or repeated inescapable stress develop analgesia, which appears to be mediated by release of endogenous opiates and which is blocked by the opiate antagonist naloxone (Kelly 1982; Maier et al. 1980). Similarly, it is suggested that in humans who have experienced prolonged or repeated trauma, endogenous opiates are readily released with any stimulus that is reminiscent of the original trauma, leading to analgesia and psychic numbing (van der Kolk et al. 1984). Pitman et al. (1990) compared pain intensity in response to thermal stimuli in Vietnam veterans with PTSD and veterans without PTSD who were watching a war videotape. PTSD patients, but not control subjects, had a 30% analgesic effect (i.e., decreased pain intensity) when pretreated with a placebo injection; this analgesia was eliminated with naloxone pretreatment. On the basis of such findings, the concept of trauma addiction has been proposed (van der Kolk et al. 1984). After a transient opioid burst on reexposure to traumatic stimuli, accompanied by a subjective sense of calm and control, opiate withdrawal may set in. This withdrawal may then contribute to the hyperarousal symptoms of PTSD, leading the individual into a vicious cycle of traumatic reexposures to gain transient symptomatic relief.

The noradrenergic and opiateergic systems of the brain interact and may serve reciprocal functions. Clonidine, an α2-adrenergic agonist, has been shown to suppress opiate withdrawal symptoms in opiate addiction (Gold et al. 1980). Open treatment with clonidine in Vietnam veterans with PTSD demonstrated substantial decreases in hyperreactivity (Kolb et al. 1984).

**Serotonergic system**

The serotonergic system has also been implicated in the symptomatology of PTSD (van der Kolk and
Saporta 1991), although such work is still in its infancy. The septohippocampal brain system contains serotonergic pathways and mediates behavioral inhibition and constraint. The role of serotonergic deficit in impulsive aggression has been studied extensively. In animals, repeated inescapable shock can lead to serotonin depletion. Thus, the irritability and outbursts seen in patients with PTSD may be related to serotonergic deficit. The partial serotonin agonist m-CPP induces an increase in PTSD symptoms suggestive of serotonergic sensitization; interestingly, the PTSD subjects showing this response appear to constitute a separate subgroup from the ones exhibiting noradrenergic sensitization (Southwick et al. 1997). Decreased plasma serotonin levels have been found in PTSD (Spivak et al. 1999). A blunted prolactin response to fenfluramine challenge is similarly supportive of central serotonergic dysregulation in PTSD (Davis et al. 1999). The efficacy of SSRIs in PTSD is indirectly supportive of dysregulated serotonergic modulation in PTSD.

**Hypothalamic-pituitary-adrenal axis**

A number of findings in PTSD have implicated a chronic dysregulation of HPA axis functioning that is highly characteristic of this disorder and distinct from that seen in other psychiatric disorders such as depression. The findings include elevated CSF corticotropin-releasing hormone (D.G. Baker et al. 1999; Bremner et al. 1997a), low urinary cortisol concentrations (J.W. Mason et al. 1986) and an elevated urinary norepinephrine-cortisol ratio (J.W. Mason et al. 1988), a blunted ACTH response to CRF (Smith et al. 1989), enhanced suppression of cortisol in response to dexamethasone administration, and a decrease in lymphocyte glucocorticoid receptor number. All of these findings are consistent with a model of a highly sensitized HPA axis that is hyperresponsive to stress and the effects of cortisol (Yehuda et al. 1993, 1995a).

**Brain circuitry and neuroimaging findings**

A number of neuroimaging findings, both structural and functional, in PTSD studies over the past several years have begun to delineate a model suggestive of limbic sensitization and diminished cortical inhibition in PTSD, with specific dysfunction in brain areas involved in memory, emotion, and visuospatial processing (Bremner et al. 1999a). Functional deficits in verbal memory have been correlated with decreased hippocampal volume on MRI in combat-related PTSD (Bremner et al. 1995). Similarly, a decrease in hippocampal volume has been found in adult survivors of childhood abuse (Bremner et al. 1997b). PET imaging with PTSD symptom provocation via audiotaped traumatic scripts revealed activation of the right limbic and paralimbic systems and of the visual cortex (Rauch et al. 1996). PET imaging during auditory exposure to traumatic scripts has shown that abuse memories are associated with decreased blood flow in the medial prefrontal cortex, hippocampus, and visual association cortex (Bremner et al. 1999a). When mental images of combat-related pictures are generated by PTSD veterans, blood flow increases in the amygdala and anterior cingulate and decreases in Broca's area. These patterns may relate to the nonverbal emotional visual imagery involved in the reexperiencing of PTSD symptoms (Shin et al. 1997). Enhanced amygdalar responses to general negative stimuli (not specifically related to trauma) have been found in PTSD and appear to be dissociated from higher cortical influences (Rauch et al. 2000). Indeed, exposure of subjects with PTSD to traumatic stimuli results in decreased blood flow in the medial prefrontal cortex, an area responsible for the regulation of emotional response via inhibition of the amygdala (Bremner et al. 1999b). There is evidence, based on case reports, that successful treatment of PTSD with eye movement desensitization and reprocessing (EMDR) may result not in reduced limbic activity but rather in increased cingulate and prefrontal activity, which enhances the ability to differentiate real threat (Levin et al. 1999).

**Genetics**

A large study of Vietnam veteran twins found that genetic factors accounted for 13%-34% of the variance in liability to the various PTSD symptom clusters, whereas no etiological role was found for
shared environment (True et al. 1993). Molecular genetic studies of PTSD are sparse. An initial study found an association between PTSD and a polymorphism of the dopamine D₂ receptor (Comings et al. 1996); however, this finding was not replicated in a later study (Gelernter et al. 1999).

Course and Prognosis
Scoggin (1984) divided the clinical course of PTSD into three stages. Stage I involves the response to trauma. Nonsusceptible persons may experience an adrenergic surge of symptoms immediately after the trauma but do not dwell on the incident. Predisposed persons have higher levels of anxiety and dissociation at baseline, an exaggerated response to the trauma, and an obsessive preoccupation with the trauma after the trauma has occurred. If symptoms persist beyond 4–6 weeks, the patient enters stage II, or acute PTSD. Feelings of helplessness and loss of control, symptoms of increased autonomic arousal, reliving of the trauma, and somatic symptoms may occur. The patient's life becomes centered around the trauma, with subsequent changes in lifestyle, personality, and social functioning. Phobic avoidance, startle responses, and angry outbursts may occur. In stage III, chronic PTSD develops, with disability, demoralization, and despondency. The patient's emphasis changes from preoccupation with the actual trauma to preoccupation with the physical disability resulting from the trauma. Somatic symptoms, chronic anxiety, and depression are common complications at this time, as are substance abuse, disturbed family relations, and unemployment. Some patients may focus on compensation and lawsuits.

A retrospective study examined patterns of treatment length in PTSD and compared characteristics of short-term patients (i.e., those who were successfully treated within 3 months) with those of long-term patients (i.e., those who received treatment for more than 12 months) (Burstein 1986). All patients were treated with medication and psychotherapy. No difference was found between the two groups with regard to type of stressor, reported symptom distress, possible financial compensation factors, length of time from trauma to intervention, and various demographic features. In this study, the number of patients who were treated successfully in a brief period was almost equal to the number of patients who underwent a prolonged course of treatment. Compared with the patients who were treated over a short period, the patients who required long-term treatment needed higher daily doses of imipramine and may have been more depressed after the first 3 months of treatment. This study did not relate imipramine effects to presence of panic attacks.

In another study, it was found that the rate of full remission from chronic PTSD over a 5-year prospectively studied period was only 18%, highlighting the frequent chronicity of the illness. Histories of alcohol abuse and childhood trauma were associated with less remission (Zlotnick et al. 1999). Even when studies correct for comorbid psychiatric or medical disorders, people with PTSD are found to manifest significant impairment in major domains of living, such as physical limitations, unemployment, poor physical health, and diminished well-being. Thus, in multiply afflicted patients, it may be crucial to specifically target and treat PTSD if present (Zatzick et al. 1997).

Diagnosis
The diagnosis of PTSD is usually not difficult if there is a clear history of exposure to a traumatic event, followed by symptoms of intense anxiety lasting at least 1 month, along with arousal and stimulation of the autonomic nervous system, numbing of responsiveness, and avoidance or reexperiencing of the traumatic event. However, a wide variety of anxiety, depressive, somatic, and behavioral symptoms for which the relationship between their onset and the traumatic event is less clear-cut may easily lead to misdiagnosis.

Differential Diagnosis
Organic Mental Disorders
Following acute physical traumas, head trauma, or concussion, an organic mental disorder must be ruled out, because this diagnosis has important treatment implications. Mild concussions may leave no immediate apparent neurological signs but may have residual long-term effects on mood and concentration. A careful evaluation of the nature of the head trauma, including a review of medical records and witnesses' observations, followed by mental status evaluation and neurological examination, and, if indicated, laboratory examinations, is essential in a diagnostic workup. Malnutrition may occur during prolonged stressful periods and may also lead to organic brain syndromes. Survivors of death camps may have symptoms of an organic mental disorder such as failing memory, difficulty concentrating, emotional lability, headaches, and vertigo. Other causes of organic mental disorder may occasionally mimic PTSD if anxiety, depression, personality changes, or abnormal behaviors are present. Abnormalities of cognition, memory, altered sensorium or level of consciousness, or focal neurological signs would suggest an organic mental disorder.

Organic mental disorders that could mimic PTSD include organic personality syndrome, delirium, amnestic syndrome, organic hallucinosis, and organic intoxication and withdrawal states. In addition, patients with PTSD may cope with their disorder through excessive use of alcohol, drugs, caffeine, or tobacco and thus may present with a combination of organic and psychological factors. In such cases, each concomitant disorder should be diagnosed.

**Mood and Anxiety Disorders**

**Major depression**
There is much overlap between PTSD and major mood disorders. Symptoms such as psychic numbing, irritability, sleep disturbance, fatigue, anhedonia, impairments in family and social relationships, anger, concern with physical health, and pessimistic outlook may occur in both disorders. In some veteran outreach populations, 70%-80% of patients meet diagnostic criteria for both disorders. Major depression is a frequent complication of PTSD; when it occurs, major depression must be treated aggressively, because comorbidity carries an increased risk of suicide. If major depression develops secondary to PTSD, both disorders should be diagnosed. Dysthymic symptoms are frequently secondary to PTSD, but if they are of sufficient severity, the additional diagnosis of dysthymic disorder should be made.

**Phobic disorders**
After a traumatic event, patients may be aversively conditioned to the surroundings of the trauma and may develop a phobia of objects, surroundings, or situations that remind them of the trauma itself. Phobic patients experience anxiety in the feared situation, whereas avoidance is accompanied by anxiety reduction that reinforces the avoidant behavior. In PTSD, the phobia may be symptomatically similar to specific phobia, but the nature of the precipitant and the symptom cluster of PTSD distinguish this condition from simple phobia.

**Generalized anxiety disorder**
The symptoms of GAD, such as motor tension, autonomic hyperactivity, apprehensive expectation, and vigilance and scanning, are also present in PTSD. However, the onset and course of the illness differ: GAD has an insidious or gradual onset and a course that fluctuates with environmental stressors, whereas PTSD has an acute onset often followed by a chronic course. Phobic symptoms, which are absent in GAD, are often present in PTSD. DSM-IV does not allow for the diagnosis of GAD if PTSD is present.

**Panic disorder**
Patients with PTSD may also experience panic attacks. In some patients, panic attacks predate the PTSD or do not occur exclusively in the context of stimuli reminiscent of the traumatic event. In other patients,
however, panic attacks develop after the PTSD and are cued solely by traumatic stimuli.

**Adjustment disorder**
Adjustment disorders are maladaptive reactions to identifiable psychosocial pressures. Signs and symptoms may include a wide variety of disturbances and emerge within 3 months of the stressful event. If symptoms are of sufficient severity to meet other Axis I criteria, the diagnosis of adjustment disorder is not made. Adjustment disorder differs from PTSD in that the stressor in adjustment disorder is usually less severe and within the range of common experience and the characteristic symptoms of PTSD, such as reexperiencing the trauma, are absent. The prognosis of full recovery in adjustment disorder is usually excellent.

**Compensation neurosis (factitious disorder and malingering)**
Both factitious disorder and malingering involve conscious deception and feigning of illness, although the motivation for each condition differs. Factitious disorder may present with physical or psychological symptoms, the feigning of symptoms is under voluntary control, and the motivation is to assume the "patient" role. Chronic factitious disorder with physical symptoms (i.e., Munchausen syndrome) involves frequent doctor visits and surgical interventions. PTSD differs from this disorder by absence of fabricated symptoms, acute onset after a trauma, and absence of a bizarre pretraumatic medical history.

Malingering involves the conscious fabrication of an illness for the purpose of achieving a definite goal such as obtaining money or compensation. Malingers often reveal an inconsistent history, unexpected symptom clusters, a history of antisocial behavior and substance abuse, and a chaotic lifestyle, and there is often a discrepancy between history, claimed distress, and objective data.

**Postconcussion syndrome**
Mental disorders secondary to head injury are influenced by physiological, psychological, and environmental factors. Psychological symptoms are extremely common after mild closed-head injuries, even when the injuries do not involve loss of consciousness. The so-called postconcussion syndrome encompasses the symptoms of headache, dizziness, irritability, and emotional lability after head injury with concussion. Depression and lethargy are the affective symptoms that occur most commonly. These symptoms bear no relation to the degree of physical injury.

**Treatment**

**Pharmacotherapy**
A variety of different psychopharmacological agents have been used in the treatment of PTSD by clinicians and reported in the literature as case reports, open clinical trials, and controlled studies. A summary of the pharmacological treatment of PTSD is presented in Table 11–17. In the past few years, SSRIs and other serotonergic agents have emerged as the first-line pharmacological treatment of PTSD.

**Adrenergic blockers**
Kolb et al. (1984) treated 12 Vietnam veterans with PTSD in an open trial of the ß-blocker propranolol over a 6-month period. Dosage ranged from 120 to 160 mg/day. Eleven patients reported a positive change in self-assessment at the end of the 6-month period, with less explosiveness, fewer nightmares, improved sleep, and a decrease in intrusive thoughts, hyperalertness, and startle response. Another open pilot study by this group (Kolb et al. 1984) using clonidine, an noradrenergic α₂ agonist, was conducted in nine Vietnam veterans with PTSD. Daily doses of 0.2–0.4 mg of clonidine were administered over a 6-month period. Eight patients reported reduced explosiveness and improvement in their capacity to control their emotions, and a majority reported improvements in sleep and nightmares; lowered startle response, hyperalertness, and intrusive thinking; and psychosocial improvement. These findings

support the role of noradrenergic hyperactivity in the maintenance of autonomic arousal symptoms in PTSD. In a retrospective treatment review of Cambodian patients with PTSD, Kinzie and Leung (1989) found that most benefited from the combination of clonidine and a TCA, as opposed to either medication taken alone. Controlled studies of adrenergic blockers in PTSD are needed.

**Tricyclic antidepressants**

Until about a decade ago, most reports on the pharmacotherapy of PTSD involved the use of TCAs. A retrospective study by Bleich et al. (1986) of 25 patients with PTSD treated with a variety of different antidepressants, including TCAs and MAOIs, reported good or moderate results in 67% of the patients treated. Response was not clearly related to the presence of somatization symptoms, depression, or panic attacks. Antidepressants appeared to be more useful than major tranquilizers. Although antidepressants improved intrusion-type symptoms, their most prominent impact was decreased insomnia and an overall sedative effect. Antidepressants also were found to have a positive impact on psychotherapy in 70% of cases.

Burstein (1984), in administering imipramine at daily doses of 50–350 mg to 10 patients with recent-onset PTSD, observed significant improvement in intrusive recollections, sleep and dream disturbance, and flashbacks. Similar improvement in intrusive symptomatology was reported with an open trial of desipramine (Kauffman et al. 1987). A positive effect of imipramine on posttraumatic night terrors was reported by J.R. Marshall (1975).

Although controlled studies of TCAs in PTSD were subsequently conducted, they were unable to replicate the earlier trials’ success in decreasing posttraumatic symptoms. In a 4-week, double-blind crossover study of desipramine and placebo in 18 veterans with PTSD, only depressive symptoms improved; anxiety, intrusive symptoms, and avoidance did not change with desipramine therapy (Reist et al. 1989). Davidson et al. (1990) conducted a 4- to 8-week double-blind comparison of amitriptyline and placebo in 46 veterans with PTSD. Although depression and anxiety decreased with amitriptyline therapy, the decrease in intrusive and avoidant symptoms was apparent only in the subgroup of patients who completed weeks 6 of amitriptyline therapy and was marginal. At the end of the study, roughly two-thirds of patients in both treatment groups still met the criteria for PTSD.

**Monoamine oxidase inhibitors**

An early study of MAOIs described five patients with "traumatic war neurosis" in whom phenelzine, at doses of 45–75 mg/day, improved traumatic dreams, flashbacks, startle reactions, and violent outbursts (Hogben and Cornfield 1981). Panic attacks were also described in all of the patients in this study. Positive effects of phenelzine on intrusive posttraumatic symptoms have been reported in subsequent small open trials (Davidson et al. 1987; van der Kolk 1983).

An 8-week randomized double-blind trial subsequently compared phenelzine (71 mg), imipramine (240 mg), and placebo in 34 veterans with PTSD (Frank et al. 1988). Both antidepressants resulted in some overall improvement in patients’ posttraumatic symptoms, and phenelzine tended to be superior to imipramine. The most marked improvement was the decrease in intrusive symptoms in patients receiving phenelzine, with an average reduction of 60% on the intrusion scale measure.

**Serotonin reuptake inhibitors**

Earlier on, multiple open trials with SSRIs suggested that these medications had at least modest efficacy for the treatment of PTSD, and in the past few years SSRIs have become the medications of choice for this disorder. Several initial open trials of fluoxetine reported marked improvement in PTSD symptoms at a wide range of doses (Davidson et al. 1991; McDougle et al. 1991b; Shay 1992). Subsequently, in a double-blind trial comparing fluoxetine and placebo, fluoxetine led to a significant reduction of PTSD symptomatology, especially for arousal and numbing symptoms (van der Kolk et al. 1994). An initial
open trial of sertraline (Brady et al. 1995) also claimed benefit for PTSD. Sertraline is now FDA approved for the treatment of PTSD, in the wake of two large controlled trials that recently documented its efficacy. In a 12-week, multicenter, placebo-controlled trial, sertraline at doses of 50–200 mg/day resulted in significant benefits that began to appear by week 2. The response rate was over 50%, and improvement in both numbing and arousal symptoms, although not in reexperiencing, was significantly greater than with placebo (Brady et al. 2000). Comparable results were reported in another large sertraline study with very similar design (Davidson et al. 2001), with a 60% response rate by conservative intent-to-treat analysis. Open trials of other SSRIs, such as fluvoxamine (De Boer et al. 1992) and paroxetine (R.D. Marshall et al. 1998), suggest that these medications have similar efficacy in PTSD, despite the lack of controlled trials.

**Mood stabilizers and anticonvulsants**

In a small open trial of lithium treatment of PTSD, van der Kolk (1983) reported improvement in intrusive recollections and irritability in more than half of the patients treated. However, there have been no controlled trials. In an open trial of carbamazepine in 10 patients with PTSD, Lipper et al. (1986) reported moderate to great improvement in intrusive symptoms in 7 patients. Wolf et al. (1988) reported decreased impulsivity and angry outbursts in 10 veterans who were also treated with carbamazepine; all patients had normal EEGs. Valproate was initially reported to decrease irritability and angry outbursts in two veterans with PTSD (Szymanski and Olympia 1991). More recently, in an open trial of 16 patients treated with valproate for 8 weeks, a significant decrease in symptoms of hyperarousal and intrusion, but not of numbing, was reported (Clark et al. 1999b). In a very small, placebo-controlled trial of lamotrigine at doses up to 500 mg/day, more patients appeared to respond to lamotrigine than to placebo (Hertzberg et al. 1999), a finding warranting larger studies.

**Other medications**

Several open trials have described benefits with nefazodone treatment. A 12-week study using a mean dose of 430 mg/day showed improvement in all three symptom clusters in patients with previously treatment-refractory PTSD (Zisook et al. 2000). An 8-week open trial reported similar improvements in patients with chronic PTSD (Davis et al. 2000), whereas another report found a 60% response rate in treatment completers (Davidson et al. 1998), and yet another described improvement in all 10 patients treated (Hertzberg et al. 1998). Thus, nefazodone appears very promising in treating PTSD and a controlled trial is warranted.

A small open trial of buspirone reported that seven out of eight patients experienced a significant reduction in PTSD symptoms; there are no controlled studies (Duffy and Malloy 1994). In a small open trial, triiodothyronine was reported to result in significant clinical improvement in four out of five PTSD patients who had only partial responses to SSRIs; however, it remains unclear whether this was not primarily an antidepressant response (Agid et al. 2001). Cyproheptadine has been reported to greatly decrease the nightmares characteristic of PTSD (Clark et al. 1999a; Gupta et al. 1998). An open trial of bupropion in PTSD reported global improvement secondary to decreased depression, but PTSD symptoms remained mostly unchanged (Canive et al. 1998).

**Psychotherapy**

It is generally agreed that some form of psychotherapy is necessary in the treatment of posttraumatic pathology. Crisis intervention shortly after the traumatic event is effective in reducing immediate distress, possibly preventing chronic or delayed responses, and, if the pathological response is still tentative, may allow for briefer intervention.

Brief dynamic psychotherapy has been advocated both as an immediate treatment procedure and as a way of preventing chronic disorder. The therapist must establish a working alliance that allows the
patient to work through his or her reactions.

The literature has suggested that persons with disrupted early attachments or abuse, who have been traumatized earlier in their lives, are more likely to develop PTSD than are those with stable backgrounds. The occurrence of psychic trauma in a person's past may psychologically and biologically predispose him or her to respond excessively and maladaptively to intense experiences and affects (Herman et al. 1989; Krystal 1968; van der Kolk 1987b). Therefore, attempting to modify preexisting conflicts, developmental difficulties, and defensive styles that render the person especially vulnerable to traumatization by particular experiences is central to the treatment of traumatic syndromes.

The "phase oriented" treatment model suggested by Horowitz (1976) strikes a balance between initial supportive interventions to minimize the traumatic state and increasingly aggressive "working through" at later stages of treatment. Establishment of a safe and communicative relationship, reappraisal of the traumatic event, revision of the patient's inner model of self and world, and planning for termination with a reexperiencing of loss are all important therapeutic issues in the treatment of PTSD. Herman et al. (1989) emphasized the importance of validating the patient's traumatic experiences as a precondition for reparation of damaged self-identity.

Embry (1990) outlined seven major parameters for effective psychotherapy in war veterans with chronic PTSD: 1) initial rapport building, 2) limit setting and supportive confrontation, 3) affective modeling, 4) defocusing on stress and focusing on current life events, 5) sensitivity to transference-countertransference issues, 6) understanding of secondary gain, and 7) therapist's maintenance of a positive treatment attitude.

Group psychotherapy can also serve as an important adjunctive treatment, or as the central treatment mode, in traumatized patients (van der Kolk 1987a). Because of past experiences, such patients are often mistrustful and reluctant to depend on authority figures, whereas the identification, support, and hopefulness of peer settings can facilitate therapeutic change.

Drug treatment has been impressionistically reported to have a beneficial effect on psychotherapy in 70% of cases, with improvements in symptom severity leading to a more positive and motivated approach to psychotherapy and an enhanced accessibility to uncovering and working through (Bleich et al. 1986).

**Cognitive and Behavioral Therapies**

A variety of cognitive and behavioral techniques have gained increasing popularity and validation in the treatment of PTSD. People involved in traumatic events such as accidents frequently develop phobias or phobic anxiety related to or associated with these situations. When a phobia or phobic anxiety is associated with PTSD, systematic desensitization or graded exposure has been found to be effective. This is based on the principle that when patients are gradually exposed to a phobic or anxiety-provoking stimulus, they will become habituated or deconditioned to the stimulus. Variations of this treatment include using imaginal techniques (i.e., imaginal desensitization) and exposure to real-life situations (i.e., in vivo desensitization). Prolonged exposure (i.e., flooding), if tolerated by a patient, can also be useful and has been reported to be successful in the treatment of Vietnam veterans (Fairbank and Keane 1982).

Relaxation techniques produce the beneficial physiological result of reducing motor tension and lowering the activity of the autonomic nervous system, effects that may be particularly efficacious in PTSD. Progressive muscle relaxation involves contracting and relaxing various muscle groups to induce the relaxation response. This technique is useful for symptoms of autonomic arousal such as somatic symptoms, anxiety, and insomnia. Hypnosis has also been used, with success, to induce the relaxation response in PTSD.
Cognitive therapy and thought stopping, in which a phrase and momentary pain are paired with thoughts or images of the trauma, have been used to treat unwanted mental activity in PTSD. A recent randomized trial compared imaginal exposure and cognitive therapy in 72 patients with chronic PTSD (Tarrier et al. 1999). Both treatments resulted in comparable significant improvement, although not complete remission, of symptoms. Another controlled study in 87 patients with chronic PTSD compared exposure therapy, cognitive restructuring, their combination, and simple relaxation techniques (Marks et al. 1998). Both the behavioral and the cognitive treatment resulted in marked improvement, with gains maintained after 6 months; in contrast, their combination was of no additional benefit, and relaxation yielded only modest improvement. In another study, exposure therapy, stress inoculation training, their combination, and a waiting-list control condition were compared in women with chronic PTSD who had experienced an assault (Foça et al. 1999). The three active treatments produced comparable improvement, and the gains were maintained through 1-year follow-up. In another study that attempted to boost the effects of individual exposure therapy by adding family behavioral interventions, the latter rendered no additional benefit (Glynn et al. 1999).

Another approach, affect management, also appears to be beneficial. In a randomized study of adult women with PTSD and a history of childhood sexual abuse who were already receiving individual psychotherapy and pharmacotherapy, those who underwent a 3-month course of group affect-management treatment demonstrated significantly fewer PTSD and dissociative symptoms after the treatment (Zlotnick et al. 1997).

These psychotherapies appear to be highly beneficial for children and adolescents as well, although they have been less rigorously studied in those populations. In an open trial of CBT in 17 elementary school and junior high school students with PTSD, more than half no longer met disorder criteria after treatment, and were doing even better at 6-month follow-up (March et al. 1998a).

**Other Treatments**

EMDR is a relatively new technique that has been applied to the treatment of trauma-related pathology in the past decade. There continues to be controversy in the literature regarding EMDR’s efficacy as well as the underlying mechanisms of its action. In a 5-year follow-up study of a small group of veterans who had initially been treated with EMDR with modest benefits, all benefit had disappeared at follow-up (Macklin et al. 2000). Although EMDR has been found to be superior to relaxation in treating PTSD (Carlson et al. 1998), relaxation is not considered one of the first-line treatments for this disorder. A recent randomized study comparing EMDR with CBT found that CBT was significantly more effective and that its superiority was even more apparent at 3-month follow-up (Devilly and Spence 1999).

Transcranial magnetic stimulation was found to have some transient efficacy in decreasing core PTSD symptoms in 10 patients treated openly, and thus may warrant more investigation in PTSD (Grisaru et al. 1998).