REPORTS OF VIOLENCE, INJURY, AND DEATH APPEAR DAILY ON HEADLINE news. More than 70% of adults worldwide experience a traumatic event at some time in their lives, and 31% experience four or more events.1 Post-traumatic stress disorder (PTSD) is the most prevalent psychopathological consequence of exposure to traumatic events. The lifetime prevalence of PTSD varies according to social background and country of residence, ranging from 1.3 to 12.2%, and the 1-year prevalence is 0.2 to 3.8%.2 The core features of PTSD are the persistence of intense, distressing, and fearfully avoided reactions to reminders of the triggering event, alteration of mood and cognition, a pervasive sense of imminent threat, disturbed sleep, and hypervigilance. This report outlines our current understanding of the diagnosis, prevalence, neurobiologic characteristics, and treatment of PTSD, as well as the clinical implications of this knowledge.

DEFINITION AND DIAGNOSIS

The diagnostic criteria for PTSD have been substantially updated in the fifth edition of the American Psychiatric Association’s Diagnostic and Statistical Manual of Mental Disorders (DSM-5),3 as compared with the fourth edition (DSM-IV-TR)4 (Table 1). PTSD now belongs to a new category, called “Trauma- and Stressor-Related Disorders”; avoidance has been added as one of the required “diagnostic clusters,” negative cognitions are highlighted, and traumatic events are not defined by an initial reaction of fear, horror, or helplessness. In contrast, the World Health Organization’s forthcoming International Classification of Diseases, 11th Revision (ICD-11), retains six PTSD-specific symptoms and eliminates those shared by other disorders (Table 1).

The results of these modifications are clinically significant.5 Recent field studies have shown only a 55% overlap between persons identified as having PTSD according to the DSM-IV criteria and those meeting DSM-5 criteria, with a meager 30% overlap among the three nosologies (DSM-IV, DSM-5, and ICD-11).6 Moreover, research in previous decades used DSM-IV diagnostic criteria, and the extent to which previous findings are still valid with the use of DSM-5 criteria is unclear.

The new diagnostic criteria highlight PTSD-related negative cognitions, self-denigration, and negative worldviews and encourage clinicians to consider these features in their assessments and interventions. Discrepancies between diagnostic templates should alert clinicians to the fundamental difference between diagnostic criteria, which are meant to index disorders, and the fuller array of symptoms in patients.7 Until the broader implications of changes in the definition of PTSD become clear, clinicians should be careful not to disallow treatment or insurance and disability benefits for persons who cease to meet PTSD diagnostic criteria in the transition from earlier to later definitions (Table 1).
Table 1. Diagnostic Criteria for Post-Traumatic Stress Disorder.

<table>
<thead>
<tr>
<th>DSM-IV-TR Criteria</th>
<th>DSM-5 Criteria</th>
<th>ICD-11 Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. The person has been exposed to a traumatic event in which both of the following were present:</strong></td>
<td><strong>A. Exposure to actual or threatened death, serious injury, or sexual violence in one (or more) of the following ways:</strong></td>
<td><strong>Exposure to an extremely threatening or horrific event or series of events</strong></td>
</tr>
<tr>
<td>1. The person experienced, witnessed, or was confronted with an event that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others.</td>
<td>1. Directly experiencing the traumatic event(s).</td>
<td><strong>Intrusion symptoms:</strong> Re-experiencing the traumatic event or events in the present in the form of vivid intrusive memories, flashbacks, or nightmares. Re-experiencing accompanied by strong and overwhelming emotions such as fear or horror and strong physical sensations, feelings of being overwhelmed or immersed in the same intense emotions that were experienced during the traumatic event.</td>
</tr>
<tr>
<td>2. The person’s response involved intense fear, helplessness, or horror. Note: In children this may be expressed, instead, by disorganized or agitated behavior.</td>
<td>2. Witnessing, in person, the event(s) as it occurred to others.</td>
<td><strong>Avoidance:</strong> Avoidance of thoughts and memories of the traumatic event(s).</td>
</tr>
<tr>
<td><strong>B. The traumatic event is persistently re-experienced in one (or more) of the following ways:</strong></td>
<td><strong>B. Presence of one (or more) of the following intrusion symptoms associated with the traumatic event(s), beginning after the traumatic event(s) occurred:</strong></td>
<td><strong>Avoidance:</strong> Avoidance of activities, situations, or people reminiscent of the event or events.</td>
</tr>
<tr>
<td>1. Recurrent and intrusive distressing recollections of the event, including images, thoughts, or perceptions.</td>
<td>1. Recurrent, involuntary, and intrusive distressing memories of the traumatic event(s).</td>
<td><strong>Avoidance:</strong> Avoidance of thoughts and memories of the event or events.</td>
</tr>
<tr>
<td>2. Recurrent distressing dreams of the event.</td>
<td>2. Recurrent distressing dreams in which the content and/or affect of the dream are related to the traumatic event(s).</td>
<td><strong>Avoidance:</strong> Avoidance of activities, situations, or people reminiscent of the event or events.</td>
</tr>
<tr>
<td>3. Acting or feeling as if the traumatic event were recurring (includes a sense of reliving the experience, illusions, hallucinations, and dissociative flashback episodes, including those that occur on awaking or when intoxicated).</td>
<td>3. Dissociative reactions (e.g., flashbacks) in which the individual feels or acts as if the traumatic event(s) were recurring. (Such reactions may occur on a continuum, with the most extreme expression being a complete loss of awareness of present surroundings.)</td>
<td><strong>Avoidance:</strong> Avoidance of activities, situations, or people reminiscent of the event or events.</td>
</tr>
<tr>
<td>4. Intense psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event.</td>
<td>4. Intense or prolonged psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).</td>
<td><strong>Avoidance:</strong> Avoidance of activities, situations, or people reminiscent of the event or events.</td>
</tr>
<tr>
<td>5. Physiological reactivity on exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event.</td>
<td>5. Marked physiological reactions to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).</td>
<td><strong>Avoidance:</strong> Avoidance of activities, situations, or people reminiscent of the event or events.</td>
</tr>
<tr>
<td><strong>C. Persistent avoidance of stimuli associated with the trauma and numbing of general responsiveness (not present before the trauma), as indicated by three (or more) of the following:</strong></td>
<td><strong>C. Persistent avoidance of stimuli associated with the traumatic event(s), beginning after the traumatic event(s) occurred, as evidenced by one or both of the following:</strong></td>
<td><strong>Avoidance:</strong> Avoidance of activities, situations, or people reminiscent of the event or events.</td>
</tr>
<tr>
<td>1. Efforts to avoid thoughts, feelings, or conversations associated with the trauma.</td>
<td>1. Avoidance of or efforts to avoid distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s).</td>
<td><strong>Avoidance:</strong> Avoidance of activities, situations, or people reminiscent of the event or events.</td>
</tr>
<tr>
<td>2. Efforts to avoid activities, places, or people that arouse recollections of the trauma.</td>
<td>2. Avoidance of or efforts to avoid external reminders (people, places, conversations, activities, objects, situations) that arouse distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s).</td>
<td><strong>Avoidance:</strong> Avoidance of activities, situations, or people reminiscent of the event or events.</td>
</tr>
<tr>
<td>3. Inability to recall an important aspect of the trauma.</td>
<td>3. Inability to recall an important aspect of the traumatic event(s).</td>
<td><strong>Avoidance:</strong> Avoidance of activities, situations, or people reminiscent of the event or events.</td>
</tr>
<tr>
<td>4. Markedly diminished interest or participation in significant activities.</td>
<td>4. Markedly diminished interest or participation in significant activities.</td>
<td><strong>Avoidance:</strong> Avoidance of activities, situations, or people reminiscent of the event or events.</td>
</tr>
<tr>
<td>5. Feeling of detachment or estrangement from others.</td>
<td>5. Feeling of detachment or estrangement from others.</td>
<td><strong>Avoidance:</strong> Avoidance of activities, situations, or people reminiscent of the event or events.</td>
</tr>
<tr>
<td>6. Restricted range of affect (e.g., unable to have loving feelings).</td>
<td>6. Restricted range of affect (e.g., unable to have loving feelings).</td>
<td><strong>Avoidance:</strong> Avoidance of activities, situations, or people reminiscent of the event or events.</td>
</tr>
<tr>
<td>7. Sense of a foreshortened future (e.g., does not expect to have a career, marriage, children, or a normal life span).</td>
<td>7. Sense of a foreshortened future (e.g., does not expect to have a career, marriage, children, or a normal life span).</td>
<td><strong>Avoidance:</strong> Avoidance of activities, situations, or people reminiscent of the event or events.</td>
</tr>
<tr>
<td><strong>D. Negative alterations in cognition and mood associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by two (or more) of the following:</strong></td>
<td><strong>D. Negative alterations in cognition and mood associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by two (or more) of the following:</strong></td>
<td><strong>Avoidance:</strong> Avoidance of activities, situations, or people reminiscent of the event or events.</td>
</tr>
<tr>
<td>1. Inability to remember an important aspect of the traumatic event(s) (typically due to dissociative amnesia and not to other factors such as head injury, alcohol, or drugs).</td>
<td>1. Inability to remember an important aspect of the traumatic event(s) (typically due to dissociative amnesia and not to other factors such as head injury, alcohol, or drugs).</td>
<td><strong>Avoidance:</strong> Avoidance of activities, situations, or people reminiscent of the event or events.</td>
</tr>
<tr>
<td>2. Persistent and exaggerated negative beliefs or expectations about oneself, others, or the world (e.g., “I am bad,” “No one can be trusted,” “The world is completely dangerous,” “My whole nervous system is permanently ruined”).</td>
<td>2. Persistent and exaggerated negative beliefs or expectations about oneself, others, or the world (e.g., “I am bad,” “No one can be trusted,” “The world is completely dangerous,” “My whole nervous system is permanently ruined”).</td>
<td><strong>Avoidance:</strong> Avoidance of activities, situations, or people reminiscent of the event or events.</td>
</tr>
<tr>
<td>3. Persistent, distorted cognitions about the cause or consequences of the traumatic event(s) that lead the individual to blame himself/herself or others.</td>
<td>3. Persistent, distorted cognitions about the cause or consequences of the traumatic event(s) that lead the individual to blame himself/herself or others.</td>
<td><strong>Avoidance:</strong> Avoidance of activities, situations, or people reminiscent of the event or events.</td>
</tr>
<tr>
<td>4. Persistent negative emotional state (e.g., fear, honor, anger, guilt, or shame).</td>
<td>4. Persistent negative emotional state (e.g., fear, honor, anger, guilt, or shame).</td>
<td><strong>Avoidance:</strong> Avoidance of activities, situations, or people reminiscent of the event or events.</td>
</tr>
<tr>
<td>5. Markedly diminished interest or participation in significant activities.</td>
<td>5. Markedly diminished interest or participation in significant activities.</td>
<td><strong>Avoidance:</strong> Avoidance of activities, situations, or people reminiscent of the event or events.</td>
</tr>
<tr>
<td>6. Feelings of detachment or estrangement from others.</td>
<td>6. Feelings of detachment or estrangement from others.</td>
<td><strong>Avoidance:</strong> Avoidance of activities, situations, or people reminiscent of the event or events.</td>
</tr>
<tr>
<td>7. Persistent inability to experience positive emotions (e.g., inability to experience happiness, satisfaction, or loving feelings).</td>
<td>7. Persistent inability to experience positive emotions (e.g., inability to experience happiness, satisfaction, or loving feelings).</td>
<td><strong>Avoidance:</strong> Avoidance of activities, situations, or people reminiscent of the event or events.</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>DSM-IV-TR Criteria</td>
<td>DSM-5 Criteria</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>D. Persistent symptoms of increased arousal (not present before the trauma), as indicated by two (or more) of the following:</strong></td>
<td>1. Difficulty falling or staying asleep.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Irritability or outbursts of anger.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Difficulty concentrating.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4. Hypervigilance.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5. Exaggerated startle response.</td>
<td></td>
</tr>
<tr>
<td><strong>E. Marked alterations in arousal and reactivity associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by two (or more) of the following:</strong></td>
<td>1. Irritable behavior and angry outbursts (with little or no provocation) typically expressed as verbal or physical aggression toward people or objects.</td>
<td>2. Reckless or self-destructive behavior.</td>
</tr>
<tr>
<td></td>
<td>3. Hypervigilance.</td>
<td>4. Exaggerated startle response.</td>
</tr>
<tr>
<td></td>
<td>5. Problems with concentration.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6. Sleep disturbance (e.g., difficulty falling or staying asleep or restless sleep).</td>
<td></td>
</tr>
<tr>
<td><strong>F. Duration of the disturbance (symptoms in Criteria B, C, D) is more than 1 month.</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>G. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Specify if:**

**Acute:** If duration of symptoms is less than 3 months.

**Chronic:** If duration of symptoms is 3 months or more.

**With delayed onset:** If onset of symptoms is at least 6 months after the stressor.

**Specify whether:** With dissociative symptoms: The individual’s symptoms meet the criteria for posttraumatic stress disorder, and in addition, in response to the stressor, the individual experiences persistent or recurrent symptoms of either of the following:

1. Depersonalization: Persistent or recurrent experiences of feeling detached from, and as if one were an outside observer of, one’s mental processes or body (e.g., feeling as though one were in a dream; feeling a sense of unreality of self or body or of time moving slowly).

2. Derealization: Persistent or recurrent experiences of unreality of surroundings (e.g., the world around the individual is experienced as unreal, dreamlike, distant, or distorted).

**Note:** To use this subtype, the dissociative symptoms must not be attributable to the physiological effects of a substance (e.g., medication, alcohol) or another medical condition.

**Specify if:** With delayed expression: If the full diagnostic criteria are not met until at least 6 months after the event (although the onset and expression of some symptoms may be immediate).

*Diagnostic criteria are reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR), and fifth edition (DSM-5), and adapted with permission from the forthcoming International Classification of Diseases, 11th Revision (ICD-11; http://apps.who.int/classifications/icd11/browse/1-m/en#).
Epidemiologic Features of PTSD

Prevalence and Conditional Probability

The most frequently reported traumatic events in the United States are physical and sexual assaults (52% lifetime prevalence) and accidents or fires (50%). Worldwide, accidents and injuries are reported most frequently (36% lifetime prevalence).1 Higher rates of PTSD have been documented among socially disadvantaged persons, younger persons, women, military personnel, police officers, firefighters, and first responders to disasters and mass trauma.2,6 The conditional probability that PTSD will develop varies according to sex and the type of trauma; for example, the respective probabilities for men and women are 65% and 46% after rape, 2% and 22% after physical assault, and 6% and 9% after an accident.8 The probability is higher in high-income countries than in lower-income countries.5 These differences probably reflect the roles of sex and social and situational factors in the development, expression, and persistence of PTSD symptoms. Physical assault, for example, might be perceived differently by men and women, and combatants trained to persevere during action may not readily express fear, helplessness, or horror.

Coexisting Disorders and Mortality

In more than 50% of cases, PTSD co-occurs with mood, anxiety, or substance-use disorders.9 It is associated with serious disability, medical illness, and premature death.10 Data on physical illness in patients with PTSD encompass subjectively reported health status and diagnosed diseases in all categories.11 In a nationally representative sample of Vietnam veterans,10 PTSD was associated with an increase in age-related mortality by a factor of 2; the leading causes of death were neoplasms affecting the respiratory tract and ischemic heart diseases.10,11

PTSD is also associated with suicidal behavior,12 but the relationship is neither specific nor simple. The relative risk of a suicide attempt among civilians with PTSD (2.0) is similar to the relative risk of generalized anxiety disorder (2.3) or alcohol dependence (2.5) and is lower than that of depression (4.8).13 Recent studies of active military personnel did not show an association between suicide and war-zone deployment14 or exposure to combat.15 Thus, elevated suicide rates among veterans may reflect protracted PTSD, cumulative life stressors, loneliness, or alienation, all of which are valid targets for intervention.

Natural Course, Prediction, and Risk Factors

Transient symptoms of PTSD are frequently observed shortly after traumatic events, and most cases of chronic PTSD follow an early onset of symptoms. A delayed expression of PTSD, most frequently seen among deployed military personnel, accounts for 25% of chronic cases.16 In most trauma-exposed persons (e.g., 78% of those exposed to combat17), PTSD does not develop after the exposure. Among those in whom the disorder does develop, the severity of symptoms fluctuates over time, with periods of greater severity probably reflecting sensitivity to co-occurring stressors, illness, and life transitions.

The intensity of the trauma and individual susceptibility interact to influence the likelihood of PTSD. Factors associated with increased susceptibility include female sex, childhood trauma, fewer years of schooling, prior mental disorders, exposure to four or more traumatic events, and a history of exposure to interpersonal violence.18 The intensity of the traumatic exposure is also related to the risk of PTSD, and the risk is increased with exposure to death, injury, torture, or bodily disfigurement; traumatic brain injury19; and a traumatic experience that is unexpected, inescapable, or uncontrollable. Physiological and neuroendocrine predictors of PTSD include elevated heart and respiration rates and a low plasma cortisol level.20

Biologic Features of PTSD

Biologic Correlates

Arguably the most important developments in the biologic understanding of PTSD are efforts to organize various findings into functionally integrated mechanistic models. The peripheral biologic correlates of PTSD to date (reviewed by Pitman et al.21) encompass genes,22 epigenetic regulation,23 neuroendocrine factors,24 inflammatory markers,25 autonomic risk and resilience,26 and sleep disturbances.27 Some biologic features constitute preexposure vulnerability factors (e.g., a polymorphism in the FKBP5 gene28 and heart-rate variability29), whereas others might reflect trauma-induced alterations (e.g., immune changes, neuroinflammation,25 and postexposure epigenetic regulation21). The multiplicity and interdepen-
dence of biologic correlates, their variable distribution among affected persons, their contribution to other disorders in addition to PTSD, and the small effect of each one limit their current use as biomarkers for PTSD. The pressing need for diagnostic, prognostic, and therapeutic biomarkers calls for large-scale research initiatives that use advanced bioinformatics to derive new knowledge about the pathogenesis of PTSD and treatment targets (e.g., the initiative described by Logue et al.29).

NEUROBIOLOGIC MODELS

Functional neural systems thought to have a prominent role in the pathophysiology of PTSD include fear learning, threat detection, executive function and emotion regulation, and contextual processing. Abnormalities in these sets of interconnected regions (often referred to as circuits) mediate the acquisition of fear responses in PTSD, avoidance of trauma reminders, impaired regulation of emotions (manifested as irritability, anger, or reckless behavior), and the persistence of defensive responses once safety has been restored. Abnormalities of declarative memory21 and dysfunctional reward processing (manifested as anhedonia and motivational deficits30) are shared by PTSD and other disorders (Fig. 1).

Fear Learning

Abnormal fear learning has been a prime candidate for explaining the pathophysiology of PTSD. Studies have localized fear-related memory formation to the amygdala,31 and its subsequent modulation to a complex interplay between various nuclei and cell types in the basolateral complex of the amygdala. The persistence of fear responses in patients with PTSD has been attributed to abnormalities in extinction of fear, in safety learning,32 and in retaining the fact that extinction of associative learning has occurred (known as extinction recall).31 The fear-learning model of PTSD has inspired some of the common therapies for the disorder, such as exposure-based cognitive behavioral therapy, which is reviewed below.

Threat Detection

Dysfunctional threat detection may underlie preferential attention to threatening stimuli, hypervigilance, heightened threat anticipation, and exaggerated reactivity to salient stimuli in patients with PTSD. Functional neuroimaging studies have identified a network of brain regions that identify threat and salience in general, including the amygdala, the dorsal anterior cingulate cortex, and the insula or operculum.34 PTSD has been associated with overreactivity in the insula,35 amygdala, and dorsal anterior cingulate cortex36 and with hyperconnectivity of brain networks that detect salient stimuli in the environment.37

Executive Function and Emotion Regulation

Flexibility in emotional responding requires holding information in mind, resisting distractors, planning, and switching tasks (i.e., the integrity of working memory, attention, inhibition, and task-shifting components of executive function). Emotion regulation relies on the integrity of executive function; thus, impaired executive function and emotion regulation in PTSD may underlie memory and concentration deficits, poorly controlled emotional responses, irritability, and impulsivity. Impaired connectivity in the frontoparietal regions, within and between executive-function networks, has been observed in patients with PTSD, providing evidence of dysfunctional executive-function and emotion-regulation circuits.37

Contextual Processing

Proper processing of contextual information allows one to freeze, flee, or enjoy a situation, as appropriate (e.g., an alligator in one’s backyard is seen as threatening, whereas an alligator in a zoo is seen as exciting). PTSD is characterized by hypervigilance that is inappropriate to the situation and the misreading of cues as threatening despite a safe context (e.g., a response to trauma reminders in a movie as if the event were recurring). Appropriate contextual processing depends on good signaling in the medial prefrontal cortex and the hippocampus.38 Hippocampal changes have been reported in patients with PTSD.21,39 Diminished signaling in the medial prefrontal cortex in affected patients has been linked to impaired extinction recall,40 abnormal processing of contextual information,41 and impaired safety-signal learning, implicating contextual processing circuitry in the pathophysiology of PTSD.

Such neurobehavioral models can account for many of the peripheral biologic findings in PTSD. Neuroendocrine alterations have been linked with altered activity in the amygdala. Noradrenergic
hyperreactivity has been linked to diminished frontal-lobe activity, which mediates executive function. Updates of contextual information occur during rapid-eye-movement (REM) sleep, require a “turning off” of the locus ceruleus, and could be impaired by PTSD-associated hyperadrenergic states. Several innovative therapies (e.g., transcranial magnetic stimulation and neurocognitive modulation training) directly address components of the neural circuitries noted above.

## Treatment
Therapies for PTSD include psychological, pharmacologic, and innovative interventions. Treatment goals, techniques, and effects in the early aftermath of trauma differ from those in cases of protracted PTSD and are therefore reviewed separately. Successful implementation of treatment requires careful assessment, as outlined in the subsequent discussion of clinical practice.

### Interventions for Steady-State, Protracted PTSD
Trauma-focused cognitive behavioral therapy is the best-supported psychological intervention for PTSD. Cognitive behavioral therapy revisits distressing elements of the traumatic events and consequent avoidance and cognitive distortions. Specific cognitive behavioral therapy protocols can be grossly divided into exposure therapies (e.g., prolonged exposure) and nonexposure therapies (e.g., cognitive processing). In exposure therapies, distressing and fearfully avoided memories of traumatic events are engaged in a safe environment. For example, a patient is first trained in self-regulating techniques, such as deep breathing, and is taught to quantify and communicate current distress. The patient then progressively recalls fearfully avoided elements of the traumatic event while keeping distress at tolerable levels with the use of deep breathing and with support from the therapist. The sequence is repeated until the memories no longer trigger intolerable responses and are not avoided. In eye-movement desensitization and reprocessing therapy, the patient recalls traumatic images while engaging in horizontal eye movement. Cognitive processing therapy explores the patient’s dysfunctional post-traumatic beliefs and cognitions (e.g., that the world is dangerous, uncontrollable, and unpredictable and that the patient is ineffectual, helpless, or guilty) and challenges them in a Socratic dialogue.

Nonexposure therapies include present-centered therapy, which focuses on dysfunction in current relationships and life challenges; interpersonal therapy, focusing on interpersonal conflicts and role transitions, which was shown to be similar to prolonged exposure as a treatment for PTSD and slightly better for patients with both PTSD and major depressive disorder; and mindfulness, which refocuses the patient’s attention on bodily and sensory experiences occurring in the present moment. Critical reviews and treatment guidelines emphasize the relative advantage of cognitive behavioral therapy over nonexposure therapies. However, a recent review suggests that present-centered therapy might be similarly beneficial in war veterans. Indeed, a recent comparison of treatment protocols by the investigators who developed them suggests that “branded” interventions have many common components (e.g., psychoeducation and a focus on emotion regulation, cognitive processing, and meaning making). Psychological therapies that target specific PTSD symptoms (e.g., insomnia) offer alternatives to pharmacologic treatment.

Most patients with PTSD (e.g., 74% of affected war veterans) receive some form of pharmacologic treatment, including antidepressant agents, anxiolytic or sedative-hypnotic agents, and antipsychotic agents (prescribed, respectively, for 89%, 61%, and 34% of those receiving pharmacotherapy). Paroxetine and sertraline are approved by the Food and Drug Administration for the treatment of PTSD. In addition, venlafaxine and nefazodone have been recommended for PTSD; mirtazapine, trazadone, and prazosin have been used for insomnia and nightmares; and topiramate has been used in patients with PTSD and alcohol use disorder. However, unpublished results of a large, randomized, placebo-controlled study of prazosin (Prazosin and Combat Trauma PTSD [PACT]; ClinicalTrials.gov number, NCT00532493) have failed to show a beneficial effect on insomnia, nightmares, PTSD symptoms, or general distress. Effect sizes for antidepressants in patients with PTSD are relatively small. These agents alleviate symptoms but rarely induce remission, and there is a substantial risk of relapse on discontinuation. Maintaining a full therapeutic dose for 6 to 12 months...
and gradually tapering the dose over a period of several months reduces the risk of relapse. Group-based estimates, however, obscure significant response heterogeneity, and clinicians are encouraged to evaluate the responses in the individual patient and manage treatment accordingly.

Figure 1. Brain Regions Implicated in the Pathophysiology of Post-Traumatic Stress Disorder (PTSD).
Shown are the known connectivity paths within four dysfunctional circuits that play a part in the psychopathology of PTSD: emotion regulation and executive function, threat detection, contextual processing, and fear learning.
INTERVENTIONS IN THE EARLY AFTERMATH OF TRAUMATIC EVENTS

Interventions administered shortly after exposure to trauma encompass stress management and psychological and pharmacologic approaches. The first stress management approach was psychological debriefing, a one-session intervention in which survivors’ experiences during a traumatic event are reviewed and discussed shortly after the event. As a result of studies, reviews, and meta-analyses showing that debriefing does not prevent PTSD and might have harmful consequences, this technique is not recommended. In contrast, there is evidence that problem-based, patient-supportive care reduces the severity of PTSD symptoms after traumatic injury and identifies patients for “stepped” referral to cognitive behavioral therapy.

Early cognitive behavioral therapy is currently the mainstay of preventive psychological intervention. It is most effective in patients who meet the diagnostic criteria for PTSD, it is equally effective when administered 1 month or 6 months after the traumatic event, and the results are maintained for years. It nonetheless is ineffective in numerous survivors.

Studies of pharmacologic prevention of PTSD have been negative for propranolol, escitalopram, temazepam, and gabapentin. Preliminary evidence suggests that hydrocortisone administered shortly after exposure to trauma may reduce subsequent PTSD symptoms. Observational and retrospective studies suggest that morphine may reduce the prevalence of PTSD among injured survivors of trauma. A small, randomized, placebo-controlled trial showed that intranasal oxytocin reduced anxiety, irritability, and intrusive recollections in trauma survivors. In contrast, controlled studies and a recently completed large study (PTSD Prevention Using Escitalopram, NCT00300313) showed no preventive effect of selective serotonin-reuptake inhibitors and showed a paradoxical increase in fear-driven behavior and PTSD symptoms with benzodiazepines (diazepam, clonazepam, alprazolam, and temazepam). The latter agents should be avoided in the early aftermath of a traumatic event.

INNOVATIVE AND EXPERIMENTAL THERAPIES

A growing number of studies investigate innovative therapies for PTSD. Neurofeedback trains patients to regulate PTSD-associated brain dysfunction by exposing them to malleable real- time displays of brain activity (mostly electroencephalographic displays). Preliminary studies show that changing brain-wave activity or connectivity on functional magnetic resonance imaging with the use of neurofeedback alleviates PTSD symptoms. Transcranial magnetic stimulation is a noninvasive brain-stimulation procedure that can alter neuronal activity through the administration of magnetic pulses to dedicated brain areas. Preliminary studies suggest that transcranial magnetic stimulation of the right dorsolateral prefrontal cortex has a positive effect.

Cycloserine, a partial agonist of the glutamatergic N-methyl-D-aspartate (NMDA) receptor, has been evaluated for its capacity to enhance extinction learning (i.e., a reduction in a learned response) during cognitive behavioral therapy, with conflicting results. There is also considerable interest in endocannabinoid modulators. Preliminary studies suggest that cannabinoids may decrease PTSD-related insomnia, nightmares, and hyperarousal. Patients with PTSD frequently use cannabis, and PTSD is an approved condition for medicinal marijuana in some states. However, large-scale trials of cannabis use have not been performed, and clinicians must consider the risk of addiction, psychosis, and mood disorders and carefully monitor the treatment response. Finally, preliminary data suggest that intravenous ketamine, a glutamate NMDA receptor antagonist, rapidly reduces the severity of PTSD symptoms, but further evidence is required to substantiate its clinical use.

LIMITATIONS AND PREDICTION OF TREATMENT OUTCOMES

Despite decades of intensive research, finding an effective treatment for a patient with PTSD is challenging. Responses to treatment differ substantially between individual patients, nonresponse rates are high across treatment approaches, and treatment most often attenuates PTSD symptoms without inducing remission. In an effort to improve the prediction of treatment outcomes, emerging studies are evaluating biomarkers of treatment efficacy. These studies suggest that predictors of a poor response to cognitive behavioral therapy, for example, include memory deficits, impaired connectivity of the neuronal net-
work (Etkin A: personal communication), the Val66Met polymorphism in brain-derived neurotropic factor,71 the short allele of the serotonin transporter gene,72 and diminished activity in neural circuits that regulate emotions.73 These new leads await corroboration and point-of-care assessment tools.

**Implications for Clinical Practice**

**Assessment**

Two recently validated,74 short questionnaires have improved clinical screening for PTSD: the 4-item Primary Care PTSD Screen (PC-PTSD)75 and the 17-item PTSD Checklist (PCL).76 The PCL also quantifies the severity of symptoms and can be used to monitor the response to treatment. To better target the intervention, the clinician should assess the interference of symptoms with the patient’s daily life, memory, concentration, sleep, and self-care. The patient should also be assessed for concurrent depression, suicidal ideation, alcohol and drug use, and ongoing environmental pressures.

**Optimizing Interventions**

As a step toward recommending an intervention, the clinician should clarify the patient’s priorities and treatment goals. Treatment recommendations may then be tailored to the preferences of the patient and clinical resources. Among the available options, interventions with the strongest supportive evidence should be given priority (e.g., cognitive behavioral therapy, sertraline, or venlafaxine), along with those that target the patient’s most disturbing symptoms (e.g., insomnia and irritability). If exposure-based cognitive behavioral therapy is being considered for a patient with emotion-regulation difficulties (i.e., angry outbursts, panic, or dissociation), preliminary skills training in emotion regulation may prevent an adverse response and early discontinuation of treatment.77

**Addressing Treatment Challenges**

Clinicians should acknowledge that approved therapies leave many patients unwell, that a patient may have a preferential response to one of many interventions, and that many patients with PTSD receive off-label medications and might be overmedicated. Stabilizing patients’ lives, reducing self-destructive behavior, and addressing pervasive loneliness and despair are high-priority goals.

Dr. Liberzon reports receiving grant support and consulting fees from ARMGO Pharmaceuticals, grant support and honoraria from Cohen Veterans Bioscience, and consulting fees from Sunovion Pharmaceuticals. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

**References**


40. Milad MR, Wright CI, Orr SP, Pitman RK, Quirk GJ, Rauch SL. Recall of fear extinction in humans activates the ventromedial prefrontal cortex and hippocampus in concert. Biol Psychiatry 2007;62:446-54.


Copyright © 2017 Massachusetts Medical Society.

The Journal welcomes consideration of new submissions for Images in Clinical Medicine. Instructions for authors and procedures for submissions can be found on the Journal’s website at NEJM.org. At the discretion of the editor, images that are accepted for publication may appear in the print version of the Journal, the electronic version, or both.