Abbreviations

POST-TRAUMATIC STRESS DISORDER

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Learning Objectives

1. Diagnose post-traumatic stress disorder (PTSD) using the three symptom clusters.
2. Design a plan to initiate pharmacotherapeutic interventions for managing PTSD.
3. Apply current research to augment therapy for a patient with residual or refractory symptoms of PTSD.
4. Compose a patient education strategy to treat PTSD, including the effects of substance abuse.
5. Develop a monitoring plan for both therapeutic effects and adverse effects for treating PTSD with antidepressants.

Introduction

The term, post-traumatic stress disorder (PTSD), is relatively new, although allusions to the condition in early classical writings indicate historical endurance. The term "PTSD" was coined in the early 1980s by clinicians seeking a descriptor for the pathological sequelae to the stressor of war. Much of what currently is understood about PTSD was formulated through the treatment of Vietnam conflict veterans. "Soldier's Heart", "Shell Shock", and "War Neurosis" are among the defunct terms previously used to describe PTSD. Although the large numbers of symptomatic war veterans fueled early PTSD research, later studies examining the prevalence of traumatic events in the general population revealed that PTSD can result from a wide range of traumatic experiences, such as rape, assault, natural disaster, or the sudden, tragic death of loved ones.

Epidemiology

The lifetime prevalence of traumatic exposure (e.g., criminal, domestic, or sexual violence; war; natural disasters; and serious accidents) is estimated to be 40–90%, whereas the lifetime prevalence of PTSD is estimated to be 1–9%. What prompts the development of PTSD symptoms in select individuals and not in others who have experienced similar traumas remains unknown. Serial trauma is known to increase the probability of developing PTSD with exposure to subsequent traumas. For example, a childhood sexual abuse survivor will have a lower threshold for development of PTSD compared with a nonabused peer. There is a positive correlation between exposure to previous traumas and symptom severity, chronicity, and comorbidity. People who fail to integrate and accurately store details of a traumatic event in their memory during the event are at increased risk for developing PTSD, as are people who experience peritraumatic dissociation.

Clinical Presentation

Patients initially presenting for treatment of PTSD often report feeling overwhelmed by frequent, distressing memories or nightmares of their trauma. They report dreading sleep for fear of recurring nightmares of the trauma, and describe themselves as sleep-deprived, irritable, and "jumpy". They fear alienating their social support systems as a result of anger outbursts or chronic irritability. Patients often develop an isolative stance to avoid physically or emotionally harming others.

In addition to chronic reliving of the traumatic event, patients with PTSD often present with clinical depression. Symptoms of appetite disturbance, sleeplessness, apathy,

Halligan SL, Michael T, Clark DM, Ehlers A. Posttraumatic stress disorder following assault: the role of cognitive processing, trauma memory and appraisals. J Consult Clin Psychol 2002;71:419–31.

Jaycox L, Marshall GN, Orlando M. Predictors of acute distress among young adults injured by community violence. J Trauma Stress 2003;16:237–45.

Abbreviations in this Chapter

5-HT	Serotonin	GABA	Gamma-aminobutyric acid
ACTH	Adrenocorticotropic hormone	HPA	Hypothalamic-pituitary-adrenal (axis)
CAPS	Clinician Administered PTSD Scale	IES	Impact of Events Scale
CGI	Clinical Global Impressions (scale)	MAOI	Monoamine oxidase inhibitor
CGI-I	Clinical Global Impressions Scale for Improvement	MVA	Motor vehicle accident
		PTSD	Post-traumatic stress disorder
CGI-S	Clinical Global Impressions Scale for Severity	Q-LES-Q	Quality of Life Enjoyment and Satisfaction Questionnaire
CRF	Corticotropin releasing factor	REM	Rapid eye movement
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision	SSRI	Selective serotonin reuptake inhibitor
		TCA	Tricyclic antidepressant
		TOP-8	Treatment Outcome PTSD Scale
FDA	Food and Drug Administration		

lethargy, and hopelessness are common. Patients who have avoided seeking treatment often "self-medicate" through the use of alcohol, marijuana, prescription anxiolytics, or narcotic pain relievers. Substance abuse is common among patients with PTSD.

About 90% of patients with PTSD have at least one other psychiatric disorder. It is unknown whether PTSD causes psychological fragility, or whether inherent psychological vulnerability predisposes people to PTSD on trauma exposure. The most commonly occurring concomitant diagnoses are alcohol and/or substance abuse and/or dependence, and major depressive disorder. Chronic substance abuse obscures accurate diagnosis and precludes treatment. When substance abuse is discovered during the PTSD assessment process, it typically is addressed as the first phase of treatment.

Diagnosis

It is important to understand that PTSD is not a normal response to an abnormal event. The diagnostic interview allows for the differentiation between the self-limited distress experienced after exposure to trauma and the severe maladaptive behavior associated with PTSD.

According to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR), PTSD is an enduring condition that manifests in reaction to an extreme traumatic stressor. The three symptom clusters are reexperiencing, avoidance, and increased arousal. The hallmark symptom is unwelcome, persistent reexperiencing of a traumatic event through nightmares, flashbacks, or intrusive memories. Trauma nightmares are recurring and tend to be replicas or close representations of the trauma. Flashbacks are dissociative states lasting several minutes to several hours in which traumatic memories are experienced as reality. People having PTSD flashbacks may behave as though they are experiencing the actual trauma. Flashbacks can manifest in reaction to trauma-reminiscent stimuli (i.e., sights, sounds, or smells that trigger memories of the trauma). Intrusive memories are recurring, distressing, recollections of the trauma. Reexperiencing symptoms also are referred to collectively as intrusive symptoms.

People with PTSD experience avoidant symptoms. They withdraw socially and avoid idiosyncratic trauma-reminiscent stimuli (e.g., war movies, fireworks, and gunfire). Patients with PTSD report emotional numbing and may be amnestic about details of their ordeal. Symptoms of hyperarousal are sleep disturbance, hypervigilance, irritability, exaggerated startle response, and decreased concentration.

Accurate diagnosis of PTSD requires that the combination of persistent and intractable reexperiencing of a definite trauma, avoidance of trauma reminders, and psychobiologic arousal be present to a degree sufficient to impede social, occupational, or other areas of functioning. Because the manifestation of one or more PTSD symptoms is a common initial reaction to trauma (i.e., acute stress reaction), the condition does not meet DSM-IV-TR criteria until symptoms have persisted for more than 1 month.

Differential diagnosis is especially salient to PTSD assessment because PTSD shares symptoms with many other psychiatric conditions. The emotional numbing, social avoidance, concentration impairment, and irritability of PTSD can be misdiagnosed as depression unless a history of trauma is elicited. Sleeplessness and anger dyscontrol often associated with PTSD can be mistaken for similar symptoms associated with bipolar disorder. Hypervigilance may resemble paranoia, and flashbacks may be misinterpreted as tactile, auditory, or visual hallucinations, leading to an erroneous diagnosis of schizophrenia. An understanding of the "voices and visions" associated with PTSD requires a teasing out of the origin of these experiences and should not be assumed to represent psychosis. The social avoidance aspect of PTSD may be misinterpreted as schizoid or avoidant personality disorder.

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. Washington, D.C.: American Psychiatric Press, 2000.

Prognosis

Although PTSD is a treatable condition, there is no known cure. Researchers are exploring ways to mediate psychological reaction to trauma as a means of decreasing the development of PTSD after trauma exposure. Critical Stress Incident Debriefing, a process during which trauma survivors are encouraged to discuss the trauma with other survivors soon after the event, shows promise. Though it is unclear whether Critical Stress Incident Debriefing prevents PTSD, clinical wisdom supports debriefing as a means of mitigating traumatic sequelae.

Prognosis is influenced by many factors, including severity of traumatic stressor, duration of traumatic event, preexisting mental illness, use of illicit substances, premorbid coping skills, and strength of support systems. In general, serial trauma (e.g., long-term childhood sexual abuse) is linked to poorer prognosis. Similarly, preexisting mental illness, substance abuse, and insufficient support systems challenge the recovery process. Anecdotal evidence indicates that untreated PTSD may worsen in old age when historical trauma memories eclipse more immediate memories as short-term memory declines. Similarly, retirement may increase vulnerability in people who were traumatized earlier in life but learned to use work as a distraction from PTSD symptoms.

Pathophysiology

The pathophysiology of PTSD is complex and not completely understood. Many changes in the neuroendocrine, immunological, and neurochemical systems are reported, but a comprehensive theory incorporating these findings has yet to be developed.

One of the fundamental aspects of the biology of PTSD is the "fight or flight" response (i.e., the acute stress response) that mobilizes the sympathetic nervous system to ensure survival. The "fight or flight" response is initiated when the hypothalamus releases corticotropin releasing factor (CRF) subsequent to a perceived emotional or physical threat. Corticotropin releasing factor activates the locus ceruleus, which contains about 70% of the brain's adrenergic neurons. The release of norepinephrine from the locus ceruleus triggers the peripheral sympathetic nervous system to produce the familiar arousal symptoms of the "fight or flight" response: increased heart and respiration rates, increased blood pressure, and diaphoresis.

The increased baseline heart rate and diastolic blood pressure noted in patients with PTSD are not replicated in either nontraumatized individuals, or those who have undergone trauma but did not develop PTSD. A possible predictive relationship between cardiovascular reactivity and the potential for developing PTSD may exist. Preliminary research indicates that increased heart rate 1 week after a motor vehicle accident (MVA) predicted PTSD severity, but increased heart rate 1 month later was not related to more severe symptoms.

Firing of the locus ceruleus stimulates the amygdala and the hippocampus to ensure cognitive activation and emotional reactivity. The amygdala processes feelings of fear and anxiety and plays a role in regulating changes in heart rate associated with emotional stimulation. The hippocampus is responsible for processing, assimilating, and storing information. It coordinates memories received from multiple senses and connects visual memories with smells and sounds.

Studies demonstrate increased levels of epinephrine and norepinephrine and decreased platelet α_2-adrenergic receptor sites in combat veterans with PTSD, but not in those with other psychiatric diagnoses. This suggests a down-regulation of α_2-receptors secondary to chronically elevated catecholamine levels.

Another aspect of the acute stress response involves the Hypothalamic-pituitary-adrenal (HPA) axis that is activated by CRF. Release of CRF from the hypothalamus stimulates the pituitary to secrete adrenocorticotropic hormone (ACTH) which then stimulates the adrenal glands to release cortisol. Cortisol fuels the "fight or flight" response by increasing glucose levels. Studies demonstrated lower baseline levels of cortisol and increased glucocorticoid receptors in patients with PTSD compared with normal controls. It is hypothesized that PTSD is not a manifestation of a chronic stress response, but rather a disorder in which the neuroendocrine system is unable to regulate its response to stress. Rather than being an alteration subsequent to prolonged stress, decreased cortisol concentrations may actually predispose people to develop PTSD.

Brain imaging studies indicate that chronic stress results in decreased hippocampal volume. The precise clinical manifestations of these changes are not known. As with other neurochemical and neuroendocrine changes associated with PTSD, it is not clear if these changes are subsequent to the trauma or are a risk factor for PTSD.

Functional imaging studies of the brain reveal heightened sensitivity of the amygdala and limbic structures. The increased sensitivity of the amygdala translates clinically into increased fear conditioning and is accompanied by a decreased response of the anterior cingulate and inhibition of amygdala activity. These changes may contribute to the inability to extinguish the fear response or to produce habituation.

The acute stress response is attenuated by serotonergic transmission, which occurs through the inhibitory effects of serotonin (5-HT) on the HPA system and the locus ceruleus. The increased activation of the HPA noted in PTSD produces an up-regulation of presynaptic 5-HT_2-receptors. This up-regulation leads to decreased serotonergic output and allows for the "flight or flight" response to go unchecked. The reduced number of postsynaptic 5-HT_{1A}-receptors does not allow for the available 5-HT to serve its inhibitory role. Well established clinical symptoms of decreased serotonergic transmission also are manifest in PTSD: aggression, depression, impulsivity, panic, and obsessive thoughts.

Hageman I, Anderson HS, Jorgensen MB. Post-traumatic stress disorder: a review of psychobiology and pharmacotherapy. Acta Psychiatr Scand 2001;104:41–22.

Assessment Measures

There are two broad types of PTSD measures: self-report and clinician-administered. Clinician-administered measures require that a mental health clinician query the patient about PTSD symptomatology and document responses. Both types of measures ultimately rely on patient self-report and, therefore, are vulnerable to overreporting of symptomatology because of a desire for compensation, or underreporting of symptomatology because of shame or to misunderstanding of terminology (e.g., the therapist's definition of "sexual abuse" may differ from the patient's).

The Clinician Administered PTSD Scale (CAPS) uses a validated structured interview format to gather information about symptom frequency and intensity. It consists of two measures: CAPS-1 and CAPS-2. The CAPS-1 is a diagnostic tool used to assess current or lifetime PTSD symptomatology. The CAPS-2 is used to assess changes in symptom severity during treatment. The CAPS-2 is a 17-item, observer-rated scale that assesses the frequency and intensity of PTSD symptoms on a 5-point scale. Severe PTSD is indicated by a score of more than 60. The CAPS-2 also contains two items that measure occupational and social impairment, which can be used to assess functioning of patients with PTSD.

The Impact of Events Scale (IES) is a short, self-report measure used by researchers. It assesses intrusive and avoidant, but not hyperarousal symptoms of PTSD. Although it was used commonly in early PTSD research, it has been supplanted by the CAPS-2. The IES should be used as a screening tool for intrusive and avoidant symptoms of PTSD.

The Treatment Outcome PTSD Scale (TOP-8) is an eight-item, clinician-rated instrument that measures the presence and severity of PTSD symptoms. Although it assesses the presence of symptoms from each domain, it only assesses eight symptoms. Each item is rated on a scale of 0–4, with higher numbers indicating increased severity.

The Duke Global Rating for Post-Traumatic Stress Disorder is an anchored, 7-point scale that measures both severity and improvement of PTSD symptoms. It is an interviewer-rated scale that assesses each of the three PTSD symptom domains. A high score on the severity scale indicates more severe symptoms, whereas a high score on the improvement scale indicates greater response to treatment.

General measures are used to assess quality of life and level of functioning in PTSD; it is common practice to pair these measures with PTSD-specific measures. The short form of the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) is a self-reported measure used to assess an individual's quality of life and life satisfaction across various domains. The quality of life score is based on 14 items that are ranked on a 5-point scale. The maximum score is 70, but scores often are reported as a percentage of the total possible score.

Finally, an overall impression of the patient's status can be captured by the Clinical Global Impressions (CGI) scale. There are two variations of the CGI: the CGI for Severity (CGI-S) and the CGI for Improvement (CGI-I). The CGI-S assesses the severity of overall symptomatology on a 7-point Likert scale that ranges from not ill at all (score of 1) to ill (score of 7). The CGI-I also is a 7-point Likert scale rating overall patient status from very much improved (a score of 1) to very much worse (a score of 7).

Therapeutic Approaches

Psychotherapeutic Treatment

Therapists from many different schools of psychology treat PTSD, and no one school has developed a PTSD treatment paradigm that is effective in all cases. In practice, practitioner qualities of empathy, compassion, and sensitivity, supported by sound PTSD knowledge and awareness of the idiosyncrasies of specific traumatic stressors (e.g., torture), have a greater impact on treatment outcome than does any specific psychotherapeutic approach. Educating family members, as well as the patient, about the signs, symptoms, causes, and course of PTSD can improve outcome. Educated family members can reduce exposure to traumatic stressors (e.g., war movies) and provide informed reassurance to patients experiencing flashbacks or hypervigilance.

Cognitive behavioral therapy is the best researched psychotherapeutic approach to treating PTSD. Most psychotherapists use treatment methods and information gleaned from several different constructs as an adjunct to the critically important therapeutic relationship. Absent a trust-based therapeutic relationship, even solidly research-based PTSD treatment techniques are ineffective. Reestablishing trust in humans is especially germane to treating human-wrought trauma, such as war and rape. The length of time needed to develop a trusting rapport is variable, and is a major factor in determining both efficacy and time course of treatment. Typically, patients with PTSD participate in weekly individual or group psychotherapy sessions for the first few months of treatment. Once they become proficient in PTSD symptom management skills, bimonthly sessions, followed by monthly sessions are appropriate. Patients who have benefited maximally from psychotherapy are graduated, though they can return on an as-needed basis when symptom severity worsens because of intervening stressors. Patients with complex or protracted courses of PTSD may require psychotherapy for several years before achieving maximal response.

The foundation of PTSD psychotherapeutic treatment is to teach the patient symptom management skills. Once

Shear MK, Feske U, Brown C, Clark DB, Mammen O, Scotti J. Anxiety disorders measures. In: Handbook of Psychiatric Measures. Washington, D.C.: American Psychiatric Press, 2000:549–90.

Rabkin J, Wagner G, Griffin KW. Quality of life measures. In: Handbook of Psychiatric Measures. Washington, D.C.: American Psychiatric Press, 2000:135–50.

coping skills are firmly in place, and if the patient is amenable and cognitively able, the trauma material is verbalized and emotionally processed at a pace that is tolerable to the patient. In cases where oral processing is prohibited (e.g., cognitive impairment and psychological fragility), a supportive, nonexplorative approach is taken. Regardless of the approach, the goals of psychotherapy are to reduce and manage symptoms, and improve quality of life.

A possible side effect of psychotherapy treatment is retraumatization (e.g., talking about a trauma can produce increased memories of the event). Nightmares and flashbacks may increase as the traumatic material is made more conscious. Aggravated intrusive symptoms can have a cascading effect on other symptom domains. Social avoidance may intensify in defense of increased reexperiencing of trauma. Impaired sleep may worsen irritability and concentration. The stress of revisiting trauma may exacerbate exaggerated startle response. Such an exacerbation of symptoms would necessitate diverting the focus of therapy back to strengthening coping skills.

Pharmacotherapy

The pharmacotherapy of PTSD can be considered to be in its nascent stages. Most every pharmacological modality has been attempted. Clinically, the incomplete knowledge of the underlying pathophysiology of PTSD has prevented a more focused research approach to pharmacotherapy. A review of the current pharmacological literature provides a lesson in the evolving study methodology in this area. The earlier studies often used rating scales that were not specific to PTSD or failed to encompass all the symptom clusters. Often, studies measured outcomes based on improvement of concomitant depression, or overlooked the possibility of delayed response. As knowledge of the field develops, the use of psychotropics and the assessment of therapeutic benefits should make the pharmacotherapy of PTSD less overwhelming for the clinician and more encouraging for the patient.

Antidepressants

The initial use of antidepressants to treat PTSD was guided, in part, by the high depressive comorbidity. Antidepressants also are expected to decrease distressing nightmares based on suppression of rapid eye movement (REM) sleep. Until a few years ago, there were relatively few well-designed studies assessing antidepressants to treat PTSD. Today, the antidepressants are the main area of focus for treating PTSD pharmacologically.

Monoamine Oxidase Inhibitors

The earliest controlled trials in the field of PTSD were conducted to assess the potential benefits of the monoamine oxidase inhibitors (MAOIs). Unfortunately, the rapid and impressive results suggested by some case studies were not substantiated in controlled trials. Of the five studies conducted to date, none has provided evidence of efficacy salient enough to recommend it as a first- or second-line agent.

Two of these studies assessed the use of phenelzine in a small sample of survivors of combat trauma. Although both studies demonstrated preferential improvement in intrusive symptoms, the IES (the only PTSD measure used) did not allow for the assessment of hyperarousal symptoms.

Another study assessing phenelzine, and two others assessing brofaromine were completed in patients who had experienced trauma from varying sources. Phenelzine and brofaromine did not show improvement in PTSD symptoms compared with placebo. Although the phenelzine study can be criticized for its small sample size, one brofaromine study enrolled more than 100 patients, and patients who responded to placebo were excluded before randomization.

The second brofaromine study enrolled a small number of patients of varying sources of trauma and used the CAPS to assess response to drugs. Brofaromine was more effective than placebo in relieving PTSD symptoms. Brofaromine is a selective, reversible inhibitor of monoamine A that is associated with a lower potential for drug-drug and drug-food interactions and is not available in the United States.

Tricyclic Antidepressants

Numerous case reports of questionable responses to the tricyclic antidepressants (TCAs) led to four placebo-controlled studies. Two of the previously mentioned phenelzine studies conducted in combat veterans included an imipramine arm. Although both studies showed greater response to imipramine than to placebo on the IES, phenelzine was more effective than imipramine, achieving twice the decrease in IES score. In a separate trial, neither desipramine nor amitriptyline demonstrated better response than placebo on the IES after an 8-week trial in combat veterans.

The TCAs have a less “patient-friendly” side effect profile (i.e., blurred vision, constipation, drowsiness, dry mouth, and urinary retention) compared with more recently available antidepressants. Given the wisdom of avoiding anticholinergic side effects in patients older than 65 years of age (i.e., current Korean and World War II veterans), the TCAs are not recommended for treating PTSD.

Selective Serotonin Reuptake Inhibitors

The selective serotonin reuptake inhibitors (SSRIs) are the drugs of choice for the pharmacotherapy of PTSD. Many well-designed trials assessing the effects of sertraline, paroxetine, and fluoxetine in this patient population are published.

Acute Treatment. ***Sertraline.*** Sertraline was the first antidepressant to receive a Food and Drug Administration (FDA) labeled indication for treating PTSD. The indication was based on two randomized, clinical trials of patients with a primary diagnosis of severe PTSD. The studies were comprised primarily of women who were survivors of sexual or physical assault. Based on these studies, sertraline 150 mg/day is expected to decrease the frequency and severity of all symptom clusters of PTSD as assessed by the CAPS-2 by at least 40% within 12 weeks. Using the CGI-I, at least 50% of patients were “much” or “very much” improved by week 12. Response may be noted as early as week 2 of treatment.

Paroxetine. Paroxetine is the other SSRI with an FDA labeled indication to treat PTSD. The results from two pivotal trials replicate those obtained with sertraline, and were performed in similar treatment populations. The mean therapeutic dose of paroxetine is 30 mg/day, although a dose-response relationship is not clear. The CAPS-2 scores were decreased by at least 48%, and at least 69% of patients achieved "much "or "very much" improvement on the CGI-I at week 12. Improvement was statistically significant at week 2.

Fluoxetine. The response rate for fluoxetine is similar to that reported with sertraline and paroxetine, although the largest fluoxetine trial predominantly enrolled men who were combat veterans. Fluoxetine 60 mg/day can be expected to decrease the TOP-8 total score by at least 50%. When response is assessed using the CGI-I, 60% of patients achieved "much" or "very much" improvement within 12 weeks. Significant improvement was first noted at week 6. This later response compared with the sertraline and paroxetine studies may reflect a more gradual dose titration to the therapeutic dose with fluoxetine.

Continuation Treatment. ***Sertraline.*** Based on results from a 24-week, open-label continuation study with sertraline, lack of response at week 12 does not denote treatment resistance. Continued treatment led to response in 50% of patients who previously gained no benefit. Ninety-two percent of patients who had derived positive benefit from sertraline continued to experience improvement in symptoms.

Relapse Prevention. The use of maintenance therapy is beneficial in decreasing the risk of relapse and recurrence for major depressive disorder and various anxiety disorders. Most PTSD studies concentrate on the acute phase of treatment. Two studies addressed treatment duration and rate of relapse. Patients whose symptoms improved after 36 weeks of treatment with sertraline maintained response over a 28-week period with continued therapy. The rate of relapse in the placebo group was 4 times that observed in the sertraline group. Patients whose PTSD responded to fluoxetine who were randomized to continue fluoxetine treatment experienced half the rate of relapse compared with placebo.

Quality of Life. ***Sertraline.*** The extent to which PTSD affects quality of life necessitates that the impact of treatment also be assessed using measures of functioning and life satisfaction. After 12 weeks of treatment with sertraline, 58% of patients whose symptoms improved achieved a normalization of Q-LES-Q scores (defined as being within 10% of community norms) compared with placebo. Improvement in Q-LES-Q and emotional functioning continued over the next 36 weeks during the continuation phase of treatment and results were maintained during the relapse prevention phase. Quality of life evaluations using different assessment measures of occupational functioning, and social and family life demonstrated a 40% improvement over placebo during the acute phase of treatment with paroxetine. Vitality, social functioning, and mental health also were enhanced with fluoxetine to a significantly greater extent than placebo.

Other SSRIs. Two small open-label studies of predominantly civilian-related PTSD suggest improvement in overall PTSD symptoms with citalopram. Fluvoxamine was not effective in two open-label trials.

Bupropion

There are no randomized trials assessing the efficacy of bupropion in patients with PTSD.

Mirtazapine

Mirtazapine demonstrated a significantly higher response rate (65%) in PTSD symptoms compared with placebo (20%) in 29 patients after 8 weeks of treatment with 45 mg/day. The rating scale used in this trial was the Short Posttraumatic Stress Disorder Rating Interview Global Improvement measure.

Venlafaxine

There are no randomized trials assessing the efficacy of venlafaxine in PTSD.

Antiadrenergic Drugs

Adrenergic blockers have not been studied extensively to treat PTSD, but case reports and open-label trials suggest both preventive and therapeutic roles. If the ingraining of traumatic memories can be prevented, the development of PTSD may be averted. Two placebo-controlled studies evaluating the potential of β-adrenergic blockade have yielded disparate results.

Adrenergic blockers serve an adjunctive role in PTSD treatment by decreasing nightmares as noted in open-label studies of clonidine and guanfacine. A small 20-week, placebo-controlled, cross-over study of prazosin in 10 Vietnam combat veterans demonstrated a significant decrease in recurrent distressing dreams and difficulty initiating or maintaining sleep. Prazosin 10 mg/day

Londborg PD, Hegel MT, Goldstein S, et al. Sertraline treatment of posttraumatic stress disorder: results of 24 weeks of open-label continuation treatment. J Clin Psychiatry 2001;62:325–31.

Martenyi F, Brown EB, Zhang H, et al. Fluoxetine v. placebo in prevention of relapse in post-traumatic stress disorder. Br J Psychiatry 2002;181:315–20.

Rapaport MH, Endicott J, Clary CM. Posttraumatic stress disorder and quality of life: results across 64 weeks of sertraline treatment. J Clin Psychiatry 2002;63:59–65.

Davidson JR, Weisler RH, Butterfield MI, et al. Mirtazapine vs. placebo in posttraumatic stress disorder: a pilot trial. Biol Psychiatry 2003;53:188–91.

Reist C, Duffy JG, Fujimoto K, Cahill L. β-Adrenergic blockade and emotional memory in PTSD. Int J Neuropsychopharmacol 2001;4:377–83.

Pitman RK, Sanders KM, Zusman RM, et al. Pilot study of secondary prevention of posttraumatic stress disorder with propranolol. Biol Psychiatry 2002;51:189–92.

produced mild orthostasis and dizziness that subsided with continued treatment.

Although much work has to be completed to elucidate the potential role of β-adrenergic blockade in decreasing the development of PTSD symptoms after trauma, this class of drugs may have utility in decreasing nightmares and improving overall sleep. Further research is warranted.

Antipsychotic Drugs

Antipsychotic drugs were used to treat PTSD before the formulation of diagnostic criteria, when many of these patients were misdiagnosed with schizophrenia. When the diagnostic criteria for PTSD were published in 1980, a better understanding of the illness and the risks of exposing these patients to tardive dyskinesia made this therapeutic class less appealing. The subsequent availability of the atypical antipsychotic drugs and incomplete response to more thoroughly studied treatment modalities have fueled resurgence in the use of antipsychotic drugs in this patient population.

Two small double-blind, placebo-controlled studies evaluated the use of atypical antipsychotic drugs as adjunctive treatments to SSRI therapy in combat veterans whose PTSD was resistant to antidepressants. One study evaluated olanzapine, and the other evaluated risperidone.

Olanzapine demonstrated a significantly greater reduction in PTSD symptoms on the CAPS-2 compared with placebo after 8 weeks of treatment (mean daily dose 15 mg). Improvement in sleep as assessed by a self-reported measure also was significantly improved with olanzapine.

The risperidone study was completed in combat veterans with significant irritability and aggression. The mean daily dose of risperidone at completion of the 6-week study was 0.57 mg. Patients demonstrated decreased irritability and intrusive thoughts.

Based on another placebo-controlled study, risperidone also is effective when used adjunctively to manage comorbid psychosis in patients with PTSD. The use of olanzapine as a single agent to treat PTSD was not effective in one placebo-controlled study. One open-label study demonstrated improvement in PTSD symptoms with quetiapine (mean dose 100 mg/day) in combat veterans with symptoms resistant to other therapeutic interventions.

The use of atypical antipsychotic drugs in the clinical setting far exceeds the research evidence supporting use. Because atypical antipsychotic drugs are associated with weight gain, hypertriglyceridemia, and diabetes, they should not be used indiscriminately. These agents should only be considered after an adequate trial of an SSRI is completed. Psychotic target symptoms should be assessed before and during treatment to minimize unnecessary antipsychotic drug exposure, and the patient should be monitored for metabolic changes.

Anxiolytics

Benzodiazepines

The gamma-aminobutyric acid (GABA)-transmitted inhibitory activity of the benzodiazepines, in theory, suggest their usefulness in treating PTSD, but their use is not substantiated by well-designed studies. Current research indicates no significant benefit of benzodiazepines in treating PTSD symptoms or preventing the development of PTSD symptoms when used immediately after trauma.

These findings may be explained by differences in the pathophysiology between PTSD and other anxiety disorders in the GABA system. Flumazenil, a benzodiazepine antagonist, provoked panic attacks in patients with panic disorder but did not produce panic symptoms or exacerbate PTSD symptoms in patients with PTSD.

A recent single photon emission computed tomography study suggests that the lack of efficacy of the benzodiazepines in PTSD may be secondary to decreased benzodiazepine receptor binding in the prefrontal cortex. On the other hand, this may suggest an etiology for PTSD symptomatology.

Buspirone

Theoretically, the 5-HT_{1A} partial agonist, buspirone is a more favorable alternative than the benzodiazepines because buspirone lacks the potential for tolerance or dependence. The currently published studies of buspirone in PTSD lack rigorous design but indicate response.

One open-label study assessing buspirone as the primary therapeutic modality for PTSD reported improvement in all PTSD symptom clusters. Two open-label trials assessing buspirone as adjunctive treatment for PTSD also demonstrated global improvement in PTSD symptoms. Although it is difficult to recommend buspirone based on the currently available data, it does appear to be a better alternative than the benzodiazepines.

Cyproheptadine

Cyproheptadine produces histamine and 5-HT blockade. Doses of 2–28 mg at bedtime decreased nightmares and improved overall sleep in patients with PTSD based on six published case reports. Controlled studies assessing the use of this agent in PTSD are lacking.

Raskind MA, Peskind ER, Kanter ED, et al. Reduction of nightmares and other PTSD symptoms in combat veterans by prazosin: a placebo-controlled study. Am J Psychiatry 2003;160:371–3.

Stein MB, Kline NA, Matloff JF. Adjunctive olanzapine for SSRI-resistant combat-related PTSD: a double-blind, placebo-controlled study. Am J Psychiatry 2002;159:1777–9.

Monnelly EP, Ciraulo DA, Knapp C, Keane T. Low-dose risperidone as adjunctive therapy for irritable aggression in posttraumatic stress disorder. J Clin Psychopharmacol 2003;23:193–6.

Braun P, Greenberg D, Dasberg H, Lerer B. Core symptoms of posttraumatic stress disorder unimproved by alprazolam treatment. J Clin Psychiatry 1990;51:236–8.

Gelpin E, Bonne O, Peri T, Brandes D, Shalev AY. Treatment of recent trauma survivors with benzodiazepines: a prospective study. J Clin Psychiatry 1996;57:390–4.

Table 1-1. Antidepressant Options Based on Controlled Trials

Drug	Starting Dose (mg/day)	Titration Schedule	Target Dose (mg/day)
First-line Agents			
Fluoxetine	10	Increase by 10 mg/day every week	40–60
Paroxetine	20	Increase by 20 mg/day every 3 weeks	30
Sertraline	25	Increase by 25 mg/day every week	150
Second-line Agent			
Mirtazapine	15	Increase by 15 mg/day every week	45

Mood Stabilizers

The prominent irritability and aggressive symptoms in patients prompted the investigation of mood stabilizers in PTSD, as these symptoms are shared symptoms of bipolar disorder. It also is thought that the autonomic arousal associated with traumatic memories may result in a kindling effect that leads to the persistent and intense reexperiencing symptoms of PTSD. Mood stabilizers are thought to inhibit the kindling effect associated with bipolar disorder. There are no controlled studies of mood stabilizers in PTSD published to date.

Carbamazepine

Three open-label studies evaluated the use of carbamazepine as either adjunctive or monotherapy for PTSD; two studies were completed in combat veterans, the other in children who experienced sexual abuse. The three studies enrolled a total of 56 patients. The studies completed in the veteran population used carbamazepine as single-agent therapy for PTSD. These studies demonstrated improved impulse control and decreased violent and angry outbursts at carbamazepine plasma concentrations between 8 mcg/ml and 12 mcg/ml. The children received carbamazepine adjunctively. Seventy-nine percent became asymptomatic when dosed to achieve carbamazepine plasma concentrations of 10.0–11.5 mcg/ml.

Divalproex Sodium

Two open-label studies evaluated a total of 27 combat veterans who received divalproex sodium either as an adjunctive or single agent. Significant improvement was noted in overall PTSD symptoms in 18 of these patients. The average dose was 1250 mg/day.

Implementing a Therapeutic Plan

The PTSD treatment modality selected depends on symptom severity and the patient's ability to process traumatic memories. Mild cases of PTSD may respond to psychotherapy alone. Survivors of repeated trauma or patients with long-standing PTSD symptoms are likely to benefit most from both psychotherapy and pharmacotherapy.

Choice of Agent

The current research, along with treatment guidelines, supports the use of sertraline, paroxetine, or fluoxetine as first-line treatment for PTSD (see Table 1-1). As is common practice when treating other anxiety disorders, the initial dose should be lower than that used for depression. This practice minimizes the risk of activation effects, and can promote compliance. Doses should be increased gradually to a minimum of 150 mg/day for sertraline, 30 mg/day for paroxetine, and 60 mg/day for fluoxetine, keeping in mind that most studies were not fixed-dose. Suggested titration schedules are listed in Table 1-1. The risk of SSRI side effects does not appear to be increased significantly compared with treatment in other patient populations. Common adverse effects that may occur during therapy with SSRIs are listed in Table 1-2.

The PTSD literature does not address the question of switching SSRIs. Based on the depression literature, it is logical to treat with an alternative SSRI should response not be achieved with the initial agent. The use of mirtazapine may be considered "second-line therapy" (see Table 1-1).

Time to Response

The onset of therapeutic response occurs within 2 weeks with sertraline and paroxetine; benefits with fluoxetine can occur at 6 weeks. Whether this difference in rate of response is drug-specific or because of the gradual dose titration in the fluoxetine studies is not clear. Nonetheless, continued improvement with SSRIs can be appreciated beyond the 12-week acute treatment phase. Although it may be difficult to convince a patient to continue treatment beyond 12 weeks when no considerable improvement is achieved, about half of patients who derive no benefit within 12 weeks will eventually experience improvement in symptoms with continued treatment.

Initially, patients should be monitored every 2 weeks. Once treatment tolerability is ensured, monthly monitoring is appropriate. It is important to have a flexible monitoring approach to accommodate possible clinical decline, depending on the progress of psychotherapy. As psychotherapy progresses, it is not unusual for symptoms to worsen as memories become more frequent and intense. Although this does not necessitate a change in drug regimen, patients often are reassured by knowing that their symptom exacerbation is not evidence that they have grown "tolerant" or "immune" to the drug. They should be assured that the drug is still at work and symptoms will resolve as progress

Table 1-2. Adverse Effects for Monitoring during SSRI Therapy (in Descending Order of Frequency)

Nausea
Insomnia
Dry mouth
Headache
Diarrhea
Somnolence
Asthenia
Abnormal ejaculation
Fatigue
Decreased appetite

is made in psychotherapy. Once response is attained, maintenance treatment is beneficial in decreasing risk of relapse. Current studies support continued use of antidepressants for at least 1 year.

Expected Outcome

The extent of improvement appears to be at least a 40% reduction in the frequency and severity of PTSD symptoms by week 12 based on the CAPS-2. This assessment tool, requiring about 45 minutes to complete, often is not practical in a clinical setting because of time constraints and lack of provider familiarity with PTSD rating scales. The CGI-I is a more practical means of measuring response. The CGI-I is designed to approximate extent of improvement and at least 50% of patients can be expected to improve "much" or "very much". Therapeutic decisions should not be based on the expectation of complete symptom resolution.

Adjunctive Therapy

The most recent therapeutic guidelines agree on the use of SSRIs as agents of choice, but do not clearly delineate second-line treatment if the anticipated 40% decrease in symptoms is not achieved. Based on the current understanding of the pathophysiology of PTSD, the use of antiadrenergic agents is most logical. It is postulated that the consolidation of traumatic memories achieved by noradrenergic transmission in the amygdala leads to the development of PTSD symptoms. In addition, the activation of peripheral adrenergic receptors at the time of the trauma stimulates the formation of traumatic memories through the vagal pathways to the brainstem. The antiadrenergic agents may be effective agents that have not received research attention because of their nonproprietary status. At this time, prazosin is the only agent supported by controlled studies. Its use requires gradual dose titration and monitoring for dizziness and orthostatic hypotension.

The use of atypical antipsychotic drugs for treating PTSD is rapidly increasing, although the current literature contains only two controlled studies. Olanzapine or risperidone may be considered adjunctively to reduce intrusive symptoms and decrease irritability. The potential for significant metabolic side effects that can produce clinically significant consequences must be considered in each individual patient.

Treatment guidelines are clear that the use of benzodiazepines is not substantiated in the literature, either as single-agent therapy or as adjuvant therapy. It also is important to consider the high substance abuse/dependence comorbidity in this patient population.

Perhaps a better approach to using adjunctive agents to treat PTSD is to consider concomitant diagnoses or the most persistent or resistant symptoms (see Figure 1-1 and Table 1-3). About 90% of patients with PTSD have another psychiatric diagnosis that should be treated maximally regardless of PTSD symptomatology. Using such an approach can lead to a synergistic effect and benefits beyond focusing on one diagnosis exclusively. The issue of external validity is a major clinical hindrance when reviewing the current literature. Most efficacy studies included patients with a primary diagnosis of PTSD and excluded patients with concurrent psychotic disorders, bipolar disorders, cognitive disorders, or substance abuse/dependence issues. Although this is necessary to answer the question of efficacy in a scientifically sound manner, the high rate of comorbidity in PTSD makes the clinical application of these studies somewhat difficult.

Pharmacoeconomic Considerations

Although there are no published pharmacoeconomic studies in PTSD, it is important to consider the treatment costs for patients who may not have medical insurance. The use of fluoxetine that is available in generic form can be expected to produce equivalent therapeutic outcomes compared the more costly SSRIs (i.e., sertraline and paroxetine). Adjunctive therapy with antiadrenergics is a cost-conscious means of treating residual hyperarousal symptoms compared to the more costly atypical antipsychotic drugs.

Table 1-3. Adjunctive Therapies Based on Open Trials

Drug	Starting Dose (mg/day)	Titration Schedule	Dosing
Prazosin	1	2 mg/day every week	10 mg/day[b]
Carbamazepine	400	200 mg/day weekly	8–12 mcg/ml[a]
Risperidone	0.5	0.5 mg/day every 2 weeks	0.5–2 mg/day[b]
Olanzapine	10	10 mg/day every 2 weeks	15 mg/day[b]
Buspirone	10	10 mg/day every 2 weeks	60 mg/day[b]
Valproic Acid	250	250 mg every 2–3 days	70 mcg/ml[a]

[a]Plasma concentration.
[b]Daily doses.

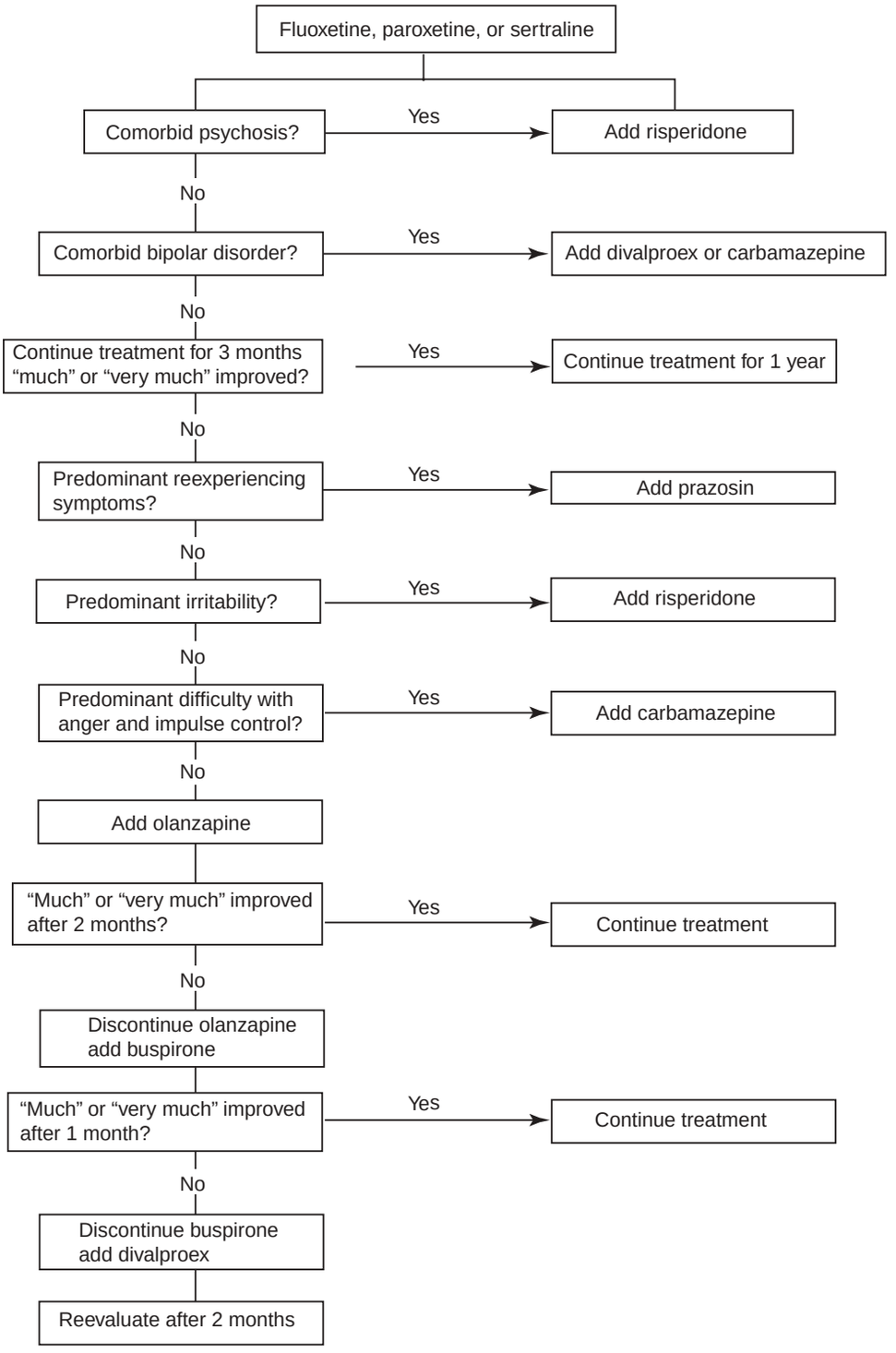

Figure 1-1. Algorithm for augmentation therapy.

It also is important to consider the indirect costs of the illness in terms of vocational productivity, family relationships, and quality of life. When more expensive therapies are viewed in that light, their associated increase in quality of life and functioning may be the impetus to accept treatment.

Research Needs

Although much significant research was completed in the past several years, many questions remain unanswered. The prevailing clinical notion is that combat veterans' symptoms did not improve significantly with any pharmacotherapeutic approach. Although the multinational study of combat-related trauma does not support this contention, it may be criticized on the basis that the trauma was relatively recent (5 years) compared to veterans of World War II, Korea, or Vietnam.

Another unresolved question is the possible discrepancy in response between women and men. This is difficult to establish because the majority of recent studies included significantly more women than men. On the other hand, this seeming enrollment bias reflects the clinical prevalence of this disorder. Rather than indicating that PTSD in women responds better to SSRIs, it may suggest a difference in response based on type and duration of trauma (sexual/physical abuse versus combat trauma).

Although the literature has a notable scarcity of data supporting the use of psychotherapy along with pharmacological therapies, it often is the clinical standard. The significant impact on various areas of functioning associated with PTSD often results in interpersonal difficulties in various life domains. Furthermore, if the lack of adequate coping skills predisposes the individual to PTSD or allows the symptoms to continue unchecked, the use of psychotherapeutic interventions would provide the individual with skills that could be helpful in all areas of functioning.

Patient Education

Providing information on the biological basis of PTSD, the symptomatology, and the treatment goals is essential for PTSD patients. Many patients feel overwhelmed and powerless to change the enormous impact of the trauma that has befallen them. Simply discussing the biological changes in terms that the patient can understand makes the illness less ominous. The average person is likely to feel inadequate and overwhelmed if the numerous neurochemical components of the acute stress response are presented to them, but most people are able to relate to the feeling of having adrenaline course through their bodies. An understanding of the body experiencing a "chronic state of adrenaline" and its associated symptomatology (e.g., poor sleep, jitteriness, feeling on guard, and startling easily) often helps them realize that their symptoms have a chemical basis. Many patients feel that their symptoms reflect a loss of both physical and mental control. Demonstrating compassion and empathy during the patient education process also will convey an understanding that these biological changes are associated with emotional difficulties for the patient.

Explaining that pharmacotherapy will not erase the memories of the trauma or may not restore their premorbid health is an important therapeutic principle for the patient to understand. If forgetting the traumatic event is the patient's understanding of improvement, he or she will anticipate a mood-altering solution and minimize the importance of psychotherapy. Knowing the therapeutic expectation for drug therapy will help the patient maintain realistic expectations.

Delineating PTSD symptoms from other concomitant psychiatric symptoms also allows the patient to better assess response to pharmacotherapy. Although health care providers may feel inept when informing patients that their symptoms are expected to improve by 40%, it is important not to provide false expectations. The extent of improvement can be less disappointing if it is put in more tangible terms: 50% fewer nightmares, 50% less jitteriness, and 50% less emotional numbing. Most patients look forward to 50% fewer symptoms and prefer having this goal than being disappointed by receiving an overly optimistic goal of "being all better".

Drug side effects must be discussed before initiating therapy. Many patients with PTSD have delayed obtaining treatment. The addition of side effects may be more than they are willing to endure if they do not have an understanding of what to do if side effects occur or that response is delayed and requires prolonged compliance. Most patients can better tolerate side effects if they are aware of the side effects' self-limiting nature. A good way of putting side effects into perspective is to ask patients if they can tolerate this degree of side effect for 2 weeks. If this appears to be onerous for the patient, it is best to choose an alternate therapy.

The sharing of current data about quality of life and social/occupational functioning also is important. Often, patients are unaware of the impact of their illness beyond the everyday symptomatology. It may be challenging for them to consider that they are able to do things they had long given up as no longer possible.

Finally, it also is important to encourage patients to participate actively in psychotherapy and other non-pharmacological modalities. Patients should understand that psychotherapy is a method for intellectually capable people to develop coping skills to help them with current symptomatology. Explain that psychotherapy is "keeping in style" with their adaptive strategies rather than an indicator of emotional inadequacy or lack of intelligence. If applicable, encourage patients to attend substance abuse/dependence counseling and support groups and educate them that substance abuse/dependence as an ineffective and potentially harmful means of coping. Psychotherapeutic modalities cannot be assimilated when the patient is "under the influence of alcohol or illicit drugs". Likewise, substance abuse/dependence does not allow for full therapeutic effect to take place.

This area of study is continually developing and it is encouraging to see more well-designed studies guide clinical practice. As the underlying pathophysiology of PTSD is more completely understood, the research process is honed and patients are given hope.

Annotated Bibliography

1. PTSD Treatment Guidelines Task Force. Guidelines for treatment of PTSD. J Trauma Stress 2000;13:539–88.

   These guidelines represent the culmination of the review of clinical and research literature by a task force established by the International Society for Traumatic Stress Studies. These are the most recent treatment guidelines in the area of post-traumatic stress disorder (PTSD), and represent a condensation of material presented in Effective Treatments for PTSD: Practice Guidelines from the International Society for Traumatic Stress Studies (Keane TM, Foa EB, Friedman MJ, eds. New York, NY: Guilford Press, 2000). This is an extensive review incorporating the numerous psychosocial approaches to PTSD, including psychotherapies, pharmacotherapeutics, family therapy, and art therapy. The task force was created to reflect the multidisciplinary approach to the ideal treatment of PTSD. The task force applied the rating system used by the Agency for Health Care Policy and Research to indicate the strength of evidence supporting a particular therapy. The section on pharmacotherapy is concise but no longer reflects the current literature, especially in terms of the selective serotonin reuptake inhibitors (SSRIs).

2. Davidson JR, Rothbaum BO, van der Kolk BA, Sikes CR, Farfel GM. Multicenter, double-blind comparison of sertraline and placebo in the treatment of posttraumatic stress disorder. Arch Gen Psychiatry 2001;58:485–92.

   This was a randomized, double-blind, placebo-controlled study of 208 patients. About 66% of the patients were women whose index traumatic event was physical or sexual assault. The mean duration of illness was 12 years. The mean daily dose of sertraline at end point was 146 mg. Insomnia, diarrhea, nausea, fatigue, and decreased appetite occurred more often with sertraline than with placebo. Nine percent of patients treated with sertraline discontinued early because of adverse effects, whereas 2% of the placebo group discontinued early. The sertraline group had a significantly greater response (65%) than the placebo group (35%). All primary end point measures indicated significantly greater improvement in the sertraline group than the placebo group, respectively: Clinician Administered PTSD Scale (CAPS) Part 2, Impact of Events Scale (IES), Clinical Global Impressions Scale for Severity (CGI-S), and CGI for Improvement (CGI-I). All symptom clusters decreased in severity by 40–50% on the CAPS-2, with 70% of the total improvement attained by week 4.

3. Brady K, Pearlstein T, Asnis GM, et al. Efficacy and safety of sertraline treatment of posttraumatic stress disorder: a randomized controlled trial. JAMA 2000;283:1837–44.

   This 12-week, double-blind study randomized 187 outpatients to sertraline or placebo. This is one of two studies on which the Food and Drug Administration (FDA) indication for using sertraline in PTSD was obtained. It incorporated a good study design and assessment measures, but can be criticized for enrolling mostly women who experienced sexual trauma. About 66% of patients were women; the most frequent source of trauma was physical or sexual assault (61%). The mean duration of symptoms was 12 years.

   The mean dose of sertraline at study completion was 133 mg/day. Insomnia was the only side effect that occurred significantly more often with sertraline than with placebo (16% vs. 4.3%), respectively. Five percent of patients treated with sertraline discontinued the study early because of adverse effects, compared to 2% of the placebo group. The response rate was 53% and 32% in the sertraline and placebo groups, respectively. The sertraline group achieved greater response than the placebo group on all assessments: CAPS-2, CGI-S, and CGI-I. The difference between groups was significant at week 2 and was maintained throughout the remainder of the trial. A 40–50% improvement in symptoms on the CAPS-2 was achieved on all symptom clusters.

4. Davidson J, Pearlstein T, Londborg P, et al. Efficacy of sertraline in preventing relapse of posttraumatic stress disorder: results of a 28-week double-blind, placebo-controlled study. Am J Psychiatry 2001;158:1974–81.

   This study was the first to address relapse prevention in PTSD. This multicenter, double-blind, placebo-controlled study assessed the efficacy of maintenance treatment with sertraline in patients who had responded to a 6-month trial. At the completion of the 28-week study, 5% of the sertraline group had relapsed versus 26% of the placebo group. Although only 96 patients were included, the results suggest that PTSD is best treated by using a maintenance approach.

5. Marshall RD, Beebe KL, Oldham M, Zaninelli R. Efficacy and safety of paroxetine treatment for chronic PTSD: a fixed-dose, placebo-controlled study. Am J Psychiatry 2001;158:1982–8.

   This 12-week, double-blind study enrolled 551 patients with severe PTSD. Patients were randomized to receive placebo, paroxetine 20 mg, or paroxetine 40 mg. The study included twice as many women as men, and the most common source of trauma was physical or sexual assault (48%). Seven percent of patients had combat-related trauma. The index trauma occurred an average of 15 years previously. Adverse effects that occurred in at least 10% of patients and were present at a rate at least twice that of placebo were asthenia, diarrhea, abnormal ejaculation, impotence, nausea, and somnolence. The dropout rate because of adverse effects was 11% in the paroxetine group. The total CAPS-2 scores decreased by 33% in the placebo group and 50% in the paroxetine group. All symptom domains were improved compared with placebo. Improvement was significant at week 4 and remained significant throughout the completion of the study.

6. Tucker P, Zaninelli R, Yehuda R, et al. Paroxetine in the treatment of chronic posttraumatic stress disorder: results of a placebo-controlled, flexible-dosage trial. J Clin Psychiatry 2001;62:860–8.

   This 12-week, double-blind study randomized 307 patients with severe PTSD to receive placebo or paroxetine. Physical or sexual assault was the most common source of trauma (50%); the mean time since trauma was 15 years. About 66% of the patients were women. The mean dose of paroxetine at study completion was 28 mg/day. Nausea, somnolence, dry mouth, asthenia, and abnormal ejaculation occurred in at least 10% of the paroxetine group and at a rate at least twice that of placebo. Twelve percent of patients treated with paroxetine dropped out early because of adverse effects. Improvement was statistically greater in the paroxetine group than the placebo group, with significant improvement noted at week 4. The total CAPS-2 scores were decreased by 34% in the

placebo group, and 48% in the paroxetine group. All symptom clusters were improved with paroxetine.

7. Martenyi F, Brown EB, Zhang H, Prakash A, Koke SC. Fluoxetine versus placebo in posttraumatic stress disorder. J Clin Psychiatry 2002;63:199–206.

A 12-week, double-blind, placebo-controlled study assessed the benefits of fluoxetine in patients diagnosed with PTSD based on Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR), criteria. Patients were from various countries who had either recently participated in or were victims of war. Patients were initiated on fluoxetine 20 mg/day, with 20-mg/day dose increments allowed every 3 weeks. The maximum daily dose of fluoxetine was 80 mg. The primary outcome measure was the change from baseline in the Treatment Outcome PTSD Scale (TOP-8).

Three hundred one patients were randomized to treatment (fluoxetine n=226; placebo n=75). Patients were predominantly men (81%) with a mean age of 37 years. The mean fluoxetine dose at study completion was 57 mg/day. Three percent of patients treated with fluoxetine discontinued early because of adverse effects. The TOP-8 total score decreased by 10 points in patients treated with fluoxetine compared with a mean decrease of 8 points in patients receiving placebo. Significance was first noted at week 6.

Abbreviations

SELF-ASSESSMENT QUESTIONS

Questions 1–3 pertain to the following case.
D.H., a 53-year-old man, is a veteran of the Vietnam conflict who comes to the mental health outpatient clinic with complaints of difficulty sleeping, persistent intrusive memories of Vietnam traumas, extreme irritability with anger outbursts, and intolerance of television war coverage. On further questioning, D.H. also indicates he has a decreased appetite, low energy, loss of interest in hobbies, nightmares accompanied by night sweats, and uncontrollable crying; he also startles easily and has been isolating himself to his room. D.H. reports feeling this way when he first was discharged from the military, but says these symptoms were under control until 2 years ago when he retired because of significant cardiac problems. D.H. says he drinks about a six-pack of beer daily and smokes marijuana several times per week to help him sleep. D.H. has not previously sought treatment for these symptoms. He currently takes an aspirin daily along with atenolol 100 mg every morning.

1. Which one of the following sets of D.H.'s symptoms satisfies the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR), criteria for each of the post-traumatic stress disorder (PTSD) symptom clusters?
   A. Difficulty sleeping, recurrent thoughts of Vietnam, and inability to work.
   B. Night sweats, use of marijuana, and difficulty sleeping.
   C. Recurrent nightmares, exaggerated startle response, and anhedonia.
   D. Uncontrollable crying, irritability, and social isolation.

2. Which one of the following is the best pharmacotherapeutic plan for D.H. at this time?
   A. Start haloperidol 5 mg at bedtime and increase the dose to 10 mg in 2 weeks.
   B. Start diazepam 2 mg 3 times/day and increase the dose to 15 mg/day in 1 week.
   C. Start fluoxetine 10 mg every morning and increase daily dose by 10 mg every week.
   D. Start amitriptyline 50 mg at bedtime and increase the dose gradually to 200 mg at bedtime.

3. Which one of the following is important for D.H. to know about how his alcohol use can impact his diagnosis and treatment?
   A. Alcohol can make the drugs more effective.
   B. Alcohol can cause the drugs to be eliminated from the body more quickly.
   C. Moderate use of alcohol promotes relaxation and enables socialization.
   D. Alcohol decreases the benefit of psychotherapy and interferes with the effects of PTSD drugs.

Questions 4 and 5 pertain to the following case.
M.A. is a 31-year-old woman with PTSD who goes to see her mental health provider with complaints of anger and "losing control". She has been treated with sertraline 200 mg every morning for the past 6 months after a car jacking 1 year earlier. Since having started sertraline, she notes decreased nightmares, decreased intrusive memories, and can now drive her car by herself.

4. Which one of the following is the best adjunctive drug for M.A.?
   A. Carbamazepine.
   B. Chlorpromazine.
   C. Clonazepam.
   D. Cyproheptadine.

5. Which one of the following is the goal of pharmacotherapy for M.A.?
   A. To alleviate associated depressive symptoms.
   B. To diminish intensity of PTSD symptoms.
   C. To uncover traumatic memories.
   D. To unmask concomitant psychiatric disorders.

Questions 6 and 7 pertain to the following case.
E.M. recently turned 16 years old and obtained a driver's license. Last week, she backed into a car in the school parking lot, doing little damage to either vehicle. There were no injuries. Since the accident, she is afraid to drive and has been irritable with her family and friends. Last night, she dreamed that she drove a bus into a crowd of people. Her mother believes that she has PTSD.

6. Which one of the following is E.M.'s diagnosis?
   A. Post-traumatic stress disorder.
   B. Acute stress disorder.
   C. Generalized anxiety disorder.
   D. Panic disorder.

7. Which one of the following statements represents the best treatment approach for E.M.?
   A. E.M. does not require psychotropic drugs at this time.
   B. E.M. requires hypnosis to help her forget the accident.
   C. A long-acting benzodiazepine should be prescribed for E.M. to prevent PTSD.
   D. E.M. should begin an selective serotonin reuptake inhibitor (SSRI) to treat anxiety symptoms.

Questions 8 and 9 pertain to the following case.
J.A. served in the United States Navy during World War II. When another United States ship sank after enemy attack, J.A.'s ship attempted to rescue the survivors. However, the drowning, bleeding sailors attracted sharks. After the war, J.A. married, became an accountant, and raised five children. He worked long hours because he had discovered that immersing himself in work kept his war memories at bay. J.A. functioned well until he retired and volunteered at a local hospital. He found that working at the hospital evoked memories of his traumatic war experience. He had particular difficulty whenever he was in the area of the emergency department, or other areas where he could see or smell blood. J.A. also noted that he was becoming nervous and irritable even when he was away from the hospital. His wife became concerned that he no longer wanted to participate in activities at the Veterans of Foreign Wars club.

8. Which one of the following best describes J.A.'s diagnosis?
   A. Post-traumatic stress disorder.
   B. Social phobia.
   C. Major depressive disorder.
   D. Acute stress disorder.

9. J.A. is quite disturbed by his memories of the sinking ship and decides to discuss these events with a mental health counselor. Which one of the following is how the counselor should state the purpose of psychotherapy?
   A. Psychotherapy will increase distressing memories and emotions and provide J.A. an opportunity to learn how to cope appropriately.
   B. Psychotherapy will assist J.A. in accepting the events of the past as well as the consequences of what he witnessed.
   C. Psychotherapy will help J.A. to understand his current symptoms and provide skills to help him cope.
   D. Psychotherapy will reduce J.A.'s current symptoms by helping him to forget the traumatic events of the past.

Questions 10 and 11 pertain to the following case.
J.U. is a 29-year-old teacher. She has many friends, belongs to a health club, makes pottery, and is a gourmet cook. Six months ago, J.U. was sexually assaulted on her walk home from work. Since then, she has avoided socializing, has lost interest in making pottery, and rarely cooks. In addition, her work performance has been declining. She is nervous, tearful, and is having difficulty sleeping for fear that somebody will break into her home and harm her. She keeps a baseball bat by her bed for protection and is always on edge.

10. J.U. is suffering from which one of the following sets of PTSD symptoms?
    A. Appetite disturbance, social avoidance, and low self-esteem.
    B. Flashbacks, anhedonia, and sense of foreshortened future.
    C. Hypervigilance, poor concentration, and social estrangement.
    D. Nightmares of her trauma, irritability, and restricted affect.

J.U. continues to avoid leaving the house, has stopped going to the health club, and has not made any pottery. Her friends convince her to seek help, and she agrees to discuss this with her primary care provider.

11. Which one of the following is the best pharmacotherapy plan to recommend for J.U.?
    A. A benzodiazepine should be prescribed for J.U. to help with anxiety and insomnia. After a 4-week trial, the dose should be tapered.
    B. An SSRI should be prescribed for J.U. to reduce hyperarousal and avoidance. Improvement in symptoms should occur within 12 weeks.
    C. An atypical antipsychotic should be prescribed for J.U. for symptoms of paranoia. Expect reduction in symptoms in 4–6 weeks.
    D. An adrenergic agent should be prescribed for J.U. to improve sleep disturbance. Symptoms will improve in 1–2 weeks.

Questions 12 and 13 pertain to the following case.
D.A. is a 76-year-old man who served in Korea as a combat medic. He was shot in the leg during combat and received treatment at a field hospital. For the past several years, D.A. has experienced chronic leg pain refractory to treatment with nonsteroidal anti-inflammatory drugs. His pain is being treated with propoxyphene 130 mg every 6 hours as needed and gabapentin 600 mg 3 times/day. D.A. has started taking more propoxyphene than prescribed and often drinks a pint of whiskey to help him sleep and to relieve the pain. He has called the physician's office twice in the past 6 months to report that he had lost his propoxyphene. His wife complains that he is restless during his sleep and often yells out as though being attacked. He started avoiding his friends, and often makes excuses not to attend social events. D.A. also has been experiencing significant anger and crying spells, of which he is ashamed. He is being pressured by his wife to discuss these symptoms with his primary care provider.

12. Which one of the following is the best course of action for D.A. at this point?
    A. Referral to a substance abuse program.
    B. Initiation of citalopram 10 mg every day.
    C. Increase gabapentin to 900 mg 3 times/day.
    D. Recommend a course of psychotherapy.

D.A. is referred to the mental health clinic for drug therapy. A psychiatrist assesses his symptoms and makes the diagnosis of polysubstance abuse and PTSD. The provider is aware that D.A.'s acceptance of the treatment plan is necessary for a successful outcome.

13. Which one of the following is the best way to discuss D.A.'s treatment plan with him?
    A. Acknowledge that D.A. is using narcotics and alcohol to self-medicate his PTSD symptoms. Encourage substance abuse counseling to allow for successful treatment of PTSD when he is drug- and alcohol-free.
    B. Allow D.A. to decide the right time to stop abusing alcohol and prescription drugs. Enroll him in group psychotherapy so he can obtain the support from other veterans that he will need to progress in his treatment.
    C. Convey to D.A. the importance of successfully treating his pain because it is a trigger for his PTSD symptoms. Treatment of his PTSD symptoms will not be successful until the trigger is removed.
    D. Inform D.A. that narcotics were prescribed for him inappropriately. Advise him to seek another primary care provider to manage his pain issues, and start him on an SSRI for his PTSD symptoms.

Questions 14 and 15 pertain to the following case.
J.O. is a 32-year-old man who suffered neglect and physical abuse for the first 13 years of his life. He frequently relives his traumatic beatings through nightmares. He sometimes has flashbacks when he sees men that resemble his father. J.O. served in Desert Storm as a supply clerk. He never participated in combat. However, he and some friends went searching for casualties one day and discovered two decaying Iraqi soldier corpses. J.O. found the experience traumatic. He has had nightmares and occasional flashbacks about the corpses for many years.

14. Which one of the following is the most accurate statement about the etiology of J.O.'s diagnosis of PTSD?
    A. J.O. had generalized anxiety disorder before serving in Iraq.
    B. J.O.'s symptoms of PTSD are acute because they have existed less than 3 months.
    C. J.O.'s war experience could not produce PTSD because his job did not involve combat or traumatic events.
    D. J.O.'s childhood trauma may have lowered his threshold so that his experiences in Iraq caused PTSD symptoms.

15. J.O. is diagnosed with PTSD and sertraline is started at 25 mg every morning. After 4 weeks of treatment, his symptoms persist. Which one of the following is the best alternative?
    A. Switch to cyproheptadine 12 mg at bedtime.
    B. Augment with olanzapine 15 mg at bedtime.
    C. Increase sertraline to 150 mg every morning.
    D. Wait for another 8 weeks for maximum results.

Questions 16–19 pertain to the following case.
B.B. is a 56-year-old man who served as a door gunner in the Vietnam conflict. He presents with complaints of nightmares of his experiences of combat, guilt for what he had to do as a soldier, increased startle response, and sleeping with a gun under his pillow. B.B. also avoids all Asian people and refuses to watch war movies. He reports doing fine until about 3 years ago when he was injured in a car accident and was unable to return to work. B.B. has a history of alcohol abuse but quit drinking when his wife threatened to leave him. He comes to your pharmacy with a prescription for paroxetine 20 mg at bedtime and asks how a drug could make him well.

16. Which one of the following is the best way to explain how paroxetine can help B.B.?
    A. Paroxetine increases the levels of serotonin (5-HT) and decreases the norepinephrine levels in the brain.
    B. Paroxetine is a sedating antidepressant that was prescribed to help him sleep.
    C. Paroxetine works on the hypothalamic-pituitary-adrenal (HPA) axis to completely resolve symptoms in 3 months.
    D. Paroxetine will improve his mood, but his nightmares and startle response will continue to exist.

17. B.B. is compliant with the paroxetine, and notes some improvement in his symptoms. A month later, when he stops by the pharmacy to pick up his refill, he reports

that he actually felt better while he was drinking. He asks if he could drink moderately with the drug, hoping to feel better, but not drink excessively such that his wife becomes upset. Which one of the following is the best way to answer B.B.'s question?

A. Advise B.B. not to drink with paroxetine because it can cause excessive sedation, which may be dangerous or even fatal.
B. Advise B.B. that his alcohol use was masking his symptoms and encourage him to seek psychotherapy.
C. Advise B.B. that if he is going to drink, he should reduce the dose of paroxetine to 10 mg/day.
D. Advise B.B. to ask his physician for another agent that works better than paroxetine.

18. B.B. returns to the pharmacy with a prescription for risperidone in addition to paroxetine. He reports his physician told him that it would help with his symptoms of PTSD. Which one of the following should you tell B.B. regarding the efficacy of risperidone in PTSD?

A. Risperidone can decrease irritability and anger.
B. Risperidone increases the levels of paroxetine.
C. Risperidone reduces the psychosis associated with PTSD.
D. Risperidone improves all symptom clusters of PTSD.

19. Which one of the following should B.B. be told to expect from his drug regimen?

A. Tell B.B. that his symptoms will respond completely to treatment. It is possible that he may improve within a few weeks after having started drug.
B. Tell B.B. that he may experience side effects to the drugs before he notices any improvements in symptoms. He should discuss side effects with his provider and not discontinue treatment on his own.
C. Tell B.B. that improvement in his symptoms can only be assessed using clinical rating scales. He should be informed he needs to undergo testing to assess any possible improvement in symptoms.
D. Tell B.B. that his symptoms may not respond to drugs alone. He should receive psychotherapy to give the drug a better chance to work.

Questions 20–22 pertain to the following case.

A.L. is a 52-year-old woman who survived a plane crash 1 year ago. She helped carry the wounded to safety, but 30 people died. Since the crash, she has had regular nightmares. She refuses to fly and avoids airports. The sound of sirens, screams, or airplanes can trigger flashbacks of the crash. She feels detached from her social support system and constantly feels jittery. Her family accuses her of either being angry or having no feelings.

20. Which one of the following best describes A.L.'s diagnosis?

A. Acute stress disorder.
B. Post-traumatic stress disorder.
C. Psychosis not otherwise specified.
D. Panic disorder with agoraphobia.

21. A.L. is started on fluoxetine for her symptoms. Which one of the following is an appropriate starting dose and titration schedule?

A. Start fluoxetine 5 mg/day and increase by 5 mg/day every 3 weeks.
B. Start fluoxetine 10 mg/day and increase by 10 mg/day every 3 days.
C. Start fluoxetine 20 mg/day and increase by 20 mg/day every 3 weeks.
D. Start fluoxetine 40 mg/day and increase by 5 mg/day every 2 weeks.

22. A.L. returns to the pharmacy for a refill and reports feeling somewhat better. Her physician has prescribed temazepam 30 mg at bedtime to help her sleep. Which one of the following should you tell A.L. about temazepam?

A. Temazepam can increase blood concentration of fluoxetine.
B. Temazepam may cause dizziness and morning sedation.
C. Temazepam will decrease side effects of fluoxetine.
D. Temazepam will make fluoxetine ineffective.

Questions 23–25 pertain to the following case.

L.G. is a 39-year-old woman who is being treated for PTSD, hypertension, and adult-onset diabetes mellitus. She currently is receiving paroxetine 40 mg/day, lisinopril 10 mg/day, and glyburide 5 mg 2 times/day prescribed by her primary care physician. She continues to experience insomnia, an increased startle response, and hypervigilance. Her blood pressure is 145/98 mm Hg; blood glucose = 118–132 mg/dl; weight is 70 kg; and height is 5'2".

23. Her physician asks for your assistance in achieving better control of L.G.'s PTSD symptoms. Which one of the following is the best plan?

A. Add divalproex 250 mg 3 times/day to L.G's current regimen to help with PTSD symptoms.
B. L.G.'s regimen does not need to be altered because full response is rarely ever attained when treating PTSD.
C. Change lisinopril to prazosin to decrease hyperarousal symptoms of PTSD.
D. Add olanzapine 15 mg at bedtime to help with nightmares.

24. Her physician asks you which one of the following is a quick assessment scale to monitor L.G.'s response to therapy?

A. Clinician Administered PTSD Scale Part 1.
B. Clinical Global Impressions Scale for Improvement.
C. Impact of Events Scale.

D. Treatment Outcome PTSD Scale.

25. L.G. reports that she does not like to take drugs. She asks whether the inconvenience of taking drugs will be overcome by the therapeutic effects. Which one of the following is the best way to address her concerns?

A. Tell L.G. that her social and occupational functioning will improve with drug therapy, thereby allowing her to make an informed decision about therapy.
B. Tell L.G. about the significant side effect burden of drug therapy so she can weigh the risks and benefits of started drug therapy.
C. Tell L.G. that the improvement in PTSD symptoms often is not clinically significant and that she may not wish to undertake the inconvenience of drug therapy.
D. Tell L.G that strict compliance with drugs is not necessary and that she can take the drugs when she feels her symptoms are most bothersome.