Substance Use Disorders in Patients With Posttraumatic Stress Disorder: A Review of the Literature

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Objective: Alcohol use disorders and other substance use disorders are extremely common among patients with posttraumatic stress disorder (PTSD). This article reviews studies pertaining to the epidemiology, clinical phenomenology, and pathophysiology of comorbid PTSD and substance use disorders.

Method: Studies were identified by means of computerized and manual searches. The review of research on the pathophysiology of PTSD and substance use disorders was focused on studies of the hypothalamic-pituitary-adrenal axis and the noradrenergic system.

Results: High rates of comorbidity suggest that PTSD and substance use disorders are functionally related to one another. Most published data support a pathway whereby PTSD precedes substance abuse or dependence. Substances are initially used to modify PTSD symptoms. With the development of dependence, physiologic arousal resulting from substance withdrawal may exacerbate PTSD symptoms, thereby contributing to a relapse of substance use. Preclinical work has led to the proposal that in PTSD, corticotropin-releasing hormone and noradrenergic systems may interact such that the stress response is progressively augmented. Patients may use sedatives, hypnotics, or alcohol in an effort to interrupt this progressive augmentation.

Conclusions: Vigorous control of withdrawal and PTSD-related arousal symptoms should be sought during detoxification of patients with comorbid PTSD and substance use disorders. Inclusion of patients with comorbid PTSD and substance use disorders in neurobiologic research and in clinical trials will be critical for development of effective treatments for this severely symptomatic patient population.

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Substance use disorders, particularly abuse of and dependence on central nervous system (CNS) depressants, are common in patients with posttraumatic stress disorder (PTSD). This article reviews clinical, epidemiologic, and neurobiologic studies relevant to the problem of comorbid PTSD and substance use disorders and discusses the clinical implications of these findings.

Clinical Phenomenology and Epidemiology

PTSD develops in some people after exposure to a severe traumatic event. The DSM-IV diagnosis of PTSD consists of symptoms in three clusters: 1) reexperiencing symptoms, including intrusive recollections of the trauma that are triggered by exposure to cues symbolizing the trauma; 2) avoidance symptoms, which involve diminished participation in activities and avoidance of thoughts, people, places, and memories associated with the trauma; and 3) arousal symptoms, which include difficulty sleeping, irritability, difficulty concentrating, hypervigilance, and exaggerated startle response.

Although intoxication and withdrawal symptoms vary across abused substances, all substance use disorders share key features. They include a maladaptive pattern of substance use leading to failure to fulfill work, school, or home obligations; legal problems; and substance-related interpersonal problems. Substance dependence further includes tolerance, withdrawal symptoms upon cessation of use, unsuccessful efforts to control use, and continued use despite persistent substance-related physical or psychological problems.

Persons with PTSD have elevated rates of comorbid psychiatric disorders. Studies of both combat veterans and civilians with PTSD have demonstrated that, among men with PTSD, alcohol abuse or dependence is the most common co-occurring disorder, followed by depression, other anxiety disorders, conduct disorder, and nonalcohol substance abuse or dependence (1, 2). Among women with PTSD, rates of comorbid depression and other anxiety disorders are highest, followed by alcohol abuse and dependence (1, 2). High rates of comorbidity of PTSD and substance use disorders were first reported in war-related studies, in which as many as 75% of combat veterans with lifetime PTSD also met criteria for alcohol abuse or dependence (2). Among civilian populations, estimates of the prevalence of lifetime substance use disorders have ranged from 21.6% to 43.0% in persons with PTSD, compared with 8.1% to 24.7% in persons without PTSD (1, 3, 4). Similarly, among substance abusers in the general popula-

tion, the reported rate of PTSD is 8.3% (5). Rates of PTSD appear to be higher among patients in inpatient substance abuse treatment (up to 42.5%) (6) and among pregnant women in residential treatment for substance abuse (62%) (7). Surveys of substance-dependent adolescents have also found rates of PTSD ranging up to 19.2% (8).

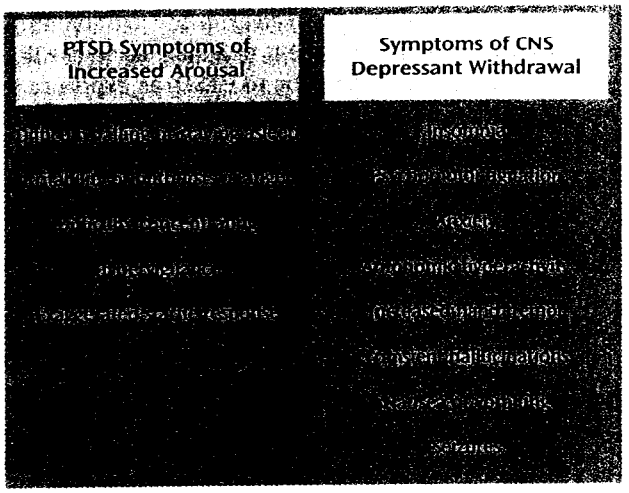
Patients with both PTSD and a substance use disorder have significantly higher rates of comorbid axis I and II disorders, psychosocial and medical problems, substance- or alcohol-related inpatient admissions, and relapse to substance use, compared with patients whose substance use is not complicated by PTSD (4, 9). Furthermore, patients with PTSD and substance use disorders tend to suffer from more severe PTSD symptoms, particularly those in the avoidance and arousal symptom clusters, than do patients with PTSD alone (10). Conversely, one longitudinal study of patients with PTSD and a comorbid substance use disorder found at 6-month posttreatment follow-up that patients whose PTSD symptoms had remitted reported significantly less substance use than did patients with unremitted PTSD (11).

Relationship of Substance Use to PTSD Symptoms

Elevated rates of comorbid depressive and anxiety disorders in patients with PTSD greatly complicate any effort to develop a model of the relationship between PTSD and substance use. High rates of comorbidity suggest that PTSD and substance use disorders are functionally related to one another. Two primary pathways have been described to explain these high rates of comorbidity. In the first, substance abuse precedes PTSD. To sustain their habit, some substance abusers repetitively place themselves in dangerous situations and, as a result, experience high levels of physical and psychological trauma (5). For example, in a study of patients with PTSD and comorbid cocaine abuse, patients whose cocaine abuse developed first later developed PTSD as a result of trauma sustained in the context of procurement and use of cocaine (12). Given that chronic substance use can lead to higher levels of arousal and anxiety as well as to sensitization of neurobiologic stress systems (13), substance abuse may result in a higher level of vulnerability to development of PTSD after exposure to trauma.

In the second pathway, PTSD precedes development of substance use disorders. In this model, the use of substances is a form of self-medication. Patients report that CNS depressants, such as alcohol, cannabis, opioids, and benzodiazepines acutely improve PTSD symptoms (14). Consistent with this, patients with PTSD report that onset and severity of substance abuse parallel the onset and escalation of PTSD symptoms (14). In addition, clinical evidence suggests that the choice of substances of abuse (CNS depressants versus CNS stimulants) may stem from the particular constellation of PTSD symptoms that patients

FIGURE 1. Symptoms of Increased Arousal in PTSD and Symptoms Associated With Withdrawal From CNS Depressants[a]



[a] From the DSM-IV criteria for PTSD, alcohol withdrawal, and sedative, hypnotic, or anxiolytic withdrawal.

experience. For example, PTSD patients with alcohol dependence exhibit significantly more arousal symptoms that do PTSD patients with cocaine dependence (10).

In the second model, withdrawal from substances, particularly CNS depressants, may initiate a cycle that perpetuates relapse and continued substance use. The withdrawal syndromes associated with many CNS depressants overlap extensively with the arousal symptoms of PTSD (15) (Figure 1). Substances may be taken initially to ameliorate PTSD symptoms. As noted earlier, patients with PTSD have reported that CNS depressants acutely provide symptom relief (14). Furthermore, objectively measured startle responses are reduced by alcohol (16). However, the physiologic arousal resulting from substance withdrawal may have an additive effect with arousal symptoms stemming from PTSD. The resulting hyperaroused state may serve as a conditioned reminder of traumatic events and thus precipitate an increase in reexperiencing symptoms. Exacerbation of PTSD symptoms may then prompt relapse to substance use in an attempt to self-medicate. Thus, for the PTSD patient who already has symptoms of arousal, the additional arousal that accompanies withdrawal from substances may be intolerable. Alternatively, substances may be used to cope with the traumatic event itself (17). This pattern may particularly apply when trauma that leads to PTSD occurs during adulthood. The initial calming effects from substance use may cue patients to resume substance use when PTSD symptoms reemerge.

Most published data support the second model, in which substance use follows or parallels traumatic exposure and the development of PTSD (18). In a longitudinal study conducted by Chilcoat and Breslau (19), 1,007 adults were reevaluated 3 and 5 years after an initial assessment.

The researchers found that preexisting substance abuse did not increase subjects' risk of subsequent exposure to trauma or their risk of developing PTSD after exposure to trauma. The relationship between exposure to trauma and increased risk for development of a substance use disorder was found to be specific to PTSD, as exposure to trauma without subsequent development of PTSD did not increase risk for development of a substance use disorder (19). Of note, one study of patients with cocaine dependence and PTSD found that patients in whom PTSD preceded the onset of cocaine use were significantly more likely to suffer from comorbid major depression and to use benzodiazepines and opiates than were patients in whom PTSD developed after the onset of cocaine use (12).

Pathophysiology

Our review of the literature on the pathophysiologic basis of comorbid PTSD and addiction selectively focuses on studies of the hypothalamic-pituitary-adrenal (HPA) axis and the noradrenergic system, as these have been most extensively studied in PTSD. It must be emphasized that many other neurobiological systems are involved in both the acute and chronic adaptation to stress and to substance use. These systems include the dopaminergic, γ-aminobutyric acid, benzodiazepine, and serotonergic systems, as well as the thyroid axis. Interactions among these systems in patients with comorbid PTSD and substance dependence are enormously complex. Thus, the potential relationships we discuss between the HPA axis, the noradrenergic system, and symptoms in patients with comorbid PTSD and substance use disorders should be viewed as one part of a far more complex whole.

HPA Axis in PTSD and Addiction

In humans and animals, acute stress elicits a cascade of neurohormonal events, including increased turnover of norepinephrine in terminal projection regions of the locus ceruleus and liberation of hypothalamic corticotropin-releasing hormone (CRH) into the pituitary portal system, which stimulates release of ACTH from the pituitary, which in turn triggers release of cortisol (human) or corticosterone (rat) from the adrenals (20). Animal and human research has implicated this cascade in the pathophysiology of both substance use disorders and PTSD.

Humans with substance dependence most frequently identify stress and negative mood states as reasons for relapse and ongoing substance abuse (21). Recently, a personalized stress imagery task was shown to reliably increase cocaine craving and salivary cortisol in cocaine-dependent patients (22). Animal studies have shown that stress induces relapse to heroin and to cocaine self-administration in rats trained to self-administer these substances and then subjected to a prolonged drug-free period (23, 24). Similarly, in animals naive to illicit substances, a large range of stressors increases the proclivity toward drug self-administration (25). Initial work on the pathophysiology of this phenomenon indicated that stress-induced or stress-enhanced drug self-administration is mediated by corticosterone (26).

Evidence has accumulated to support a role for CRH in mediating the effects of stress on drug self-administration. Central, but not peripheral, administration of CRH has been shown to induce a long-lasting enhancement (sensitization) of the locomotor response to d-amphetamine (27), and pretreatment with a CRH antagonist has been shown to block the development of stress-induced sensitization to d-amphetamine (28). Indeed, central administration of anti-CRH antibody or the CRH receptor antagonist α-helical CRH has been found to block the locomotor hyperactivity induced by cocaine (29).

Withdrawal from chronic cocaine or alcohol administration in rats produces anxiety-like behavior and decreased exploration that is associated with selective increases in CRH in the hypothalamus, amygdala, and basal forebrain (30, 31). Pretreatment with anti-CRH immunoserum or α-helical CRH, blocking the effects of CRH, completely prevents the development of these withdrawal-associated behaviors (30). Consistent with these observations, CSF CRH is elevated in humans in acute alcohol withdrawal and then normalizes or decreases below normal levels with extended abstinence and resolution of withdrawal symptoms (32). Shaham and colleagues (33) found that intracerebroventricular injection of CRH reinstated heroin seeking after extinction in rats trained to self-administer the drug. In addition, α-helical CRH attenuated the reinstatement effect of footshock stress (33). Neither adrenalectomy nor chronic or acute exposure to the corticosterone synthesis inhibitor metyrapone interfered with the reinstatement effects of priming injections of heroin or of footshock stress. A potent, selective CRF1 receptor antagonist, CP-154,526, has been found to attenuate reinstatement of drug seeking induced by footshock stress after up to 14 days of extinction in rats trained to self-administer heroin or cocaine (34).

Findings from both animal and human studies of the effects of chronic stress or of PTSD on HPA axis function vary depending on the experimental paradigm used or the population studied. In patients with PTSD, elevated (35), reduced (36), and normal (37) levels of cortisol secretion have been reported. A series of studies performed by Yehuda and colleagues demonstrated that patients with PTSD have an elevated number of lymphocyte glucocorticoid receptors (38), enhanced suppression of cortisol after administration of dexamethasone (39), a greater than normal decrease in the number of lymphocyte glucocorticoid receptors after administration of dexamethasone (39), and higher than normal increases in ACTH after metyrapone blockade of cortisol synthesis (40). All of these findings suggest that glucocorticoid negative feedback is enhanced in PTSD.

Animal studies examining the effects of uncontrollable stress on HPA axis function have reported initial increases of corticosterone secretion, followed by normalization of corticosterone secretion with ongoing chronic stress (41). However, some investigators have failed to demonstrate normalization of corticosterone secretion with chronic uncontrollable stress (42), particularly in animals that have been reared under stressful conditions (43) or when levels of chronic stress are high (44). In a pattern similar to that found in humans with PTSD, animals subjected to a single episode of prolonged stress and then briefly restressed after a stress-free period showed enhancement of glucocorticoid negative feedback (45).

Although both animal and human studies have suggested that glucocorticoid negative feedback may be enhanced in PTSD, the implications of these observations for CRH secretion in this disorder are unclear. As noted earlier, CRH-producing cells and CRH receptors exist both in the hypothalamus and in extrahypothalamic sites. Findings from some studies have suggested that hypothalamic and extrahypothalamic CRH-producing cells may respond differently to corticosterone. Specifically, corticosterone appears to restrain hypothalamic CRH-producing cells while stimulating extrahypothalamic CRH-producing cells, particularly those in the amygdala (46). Replacement of corticosterone in adrenalectomized rats decreases CRH production in the parvocellular nucleus of the hypothalamus while increasing CRH production in the central nucleus of the amygdala (47). This region-specific pattern of regulation is also seen in adrenally intact rats treated with high-stress levels of corticosterone for extended periods of time (48). Thus, while glucocorticoid feedback may decrease CRH production and release in the hypothalamus, it may stimulate CRH production and release in other brain regions, including the amygdala. This possibility has been addressed in two studies of patients with PTSD, one that examined CSF concentrations of CRH at a single time point (49) and one that examined CSF concentrations of CRH at serial time points over a 6-hour period (37). Both found significantly higher levels of CSF CRH in patients with PTSD than in normal comparison subjects. However, although elevated CSF CRH suggests that brain CRH may be elevated, the specific brain tissues producing CRH elevations cannot be determined from CSF data alone.

The possibility that brain CRH levels are elevated in PTSD is of great interest because of a rich preclinical literature indicating that elevated levels of CRH in the brain, particularly in the amygdala, potentiate fear-related behavioral responses, including the startle response (50). These anxiogenic effects of CRH are reversed by administration of CRH antagonists (50). As noted earlier, findings from animal and human studies have supported a role for CRH in mediating some effects of drugs of abuse, including stress- or priming-induced relapse to drug self-administration and symptoms of withdrawal (27, 28, 32–34). Thus, elevated levels of CRH in the brain in PTSD may mediate both the symptoms of hyperarousal as well as the increased risk for substance abuse and dependence seen in this disorder. More specifically, elevated levels of CRH in the brain in PTSD may enhance the euphorigenic properties of certain drugs, such as stimulants, and may worsen the severity of withdrawal symptoms, thereby prompting patients to relapse to drug use. Conversely, brain CRH elevations induced by withdrawal from substance use may exacerbate symptoms of hyperarousal, which could trigger other symptoms of PTSD, prompting relapse to substance use.

Noradrenergic System in PTSD and Addiction

During chronic uncontrollable stress, norepinephrine turnover increases in specific brain regions, including the locus ceruleus, hypothalamus, hippocampus, amygdala, and cerebral cortex (51). Evidence for noradrenergic dysregulation in patients with PTSD has included elevated 24-hour urinary epinephrine and norepinephrine excretion, a lower than normal number of platelet α_2-adrenergic receptors, elevated 24-hour plasma norepinephrine, and exaggerated cardiovascular and 3-methoxy-4-hydroxyphenylglycol (MHPG) (a norepinephrine metabolite) responses to intravenous yohimbine (52). Noradrenergic dysregulation has also been reported during states of withdrawal from chronic self-administration of alcohol and other abused substances. The levels of noradrenaline, norepinephrine, and MHPG in both plasma and CSF have been found to be increased and the number of platelet α_2-adrenergic receptors decreased in alcoholics during acute withdrawal (53, 54). The severity of alcoholic withdrawal symptoms has been positively correlated with the concentration of MHPG in CSF (54). Evidence for noradrenergic dysregulation in opiate withdrawal has included findings of elevated plasma MHPG in humans and elevated plasma and brain MHPG in animals (55, 56). In animals, the level of noradrenergic activity was significantly correlated with the severity of withdrawal symptoms (56). These findings have prompted the use of the α_2-adrenergic receptor agonist clonidine in the treatment of both opiate withdrawal symptoms and PTSD (57, 58).

Noradrenergic System/HPA Axis Interactions

Evidence that brain CRH and noradrenergic systems modulate each other has been reported. Stress has been shown to increase CRH levels in the locus ceruleus (59), a primary source of noradrenergic projections to all cortices as well as to the thalamus and hypothalamus, while intraventricular administration of CRH has been found to increase the discharge rates of locus ceruleus neurons and to increase norepinephrine turnover in hippocampus, hypothalamus, and prefrontal cortex (60–62). Conversely, stress-induced activation of the locus ceruleus has been blocked by administration of CRH antagonists (63). Similar evidence exists for the interaction of the CRH and nor-

adrenergic systems in the hypothalamus (64) and the amygdala, where stress induces increases in both CRH and norepinephrine (65). Furthermore, norepinephrine in the amygdala appears to stimulate release of CRH (66).

These observations have prompted the proposal by Koob (20) that interactions of the CRH and noradrenergic systems in the brain may, under some conditions, function as a feed-forward system, leading to the progressive augmentation of the stress response with repeated stress exposure that is characteristic of PTSD. This progressive augmentation of response with repeated stress has previously been conceptualized as kindling (67). A feed-forward interaction between the CRH and noradrenergic systems may represent one neurobiologic underpinning of both PTSD and substance use disorders. More specifically, stress, including stress related to self-administration of or withdrawal from substances, may stimulate CRH release in the locus ceruleus, leading to activation of the locus ceruleus and release of norepinephrine in the cortex, which in turn may stimulate the release of CRH in the hypothalamus and amygdala (20). Such an interaction between the brain noradrenergic and CRH systems may mediate the symptoms of hyperarousal seen in PTSD, including exaggerated startle response. The proclivity toward misuse of CNS depressants by patients with PTSD may reflect an attempt to interrupt this feed-forward interaction by suppressing activity of the locus ceruleus with these agents (68).

Conclusions

Clinical and epidemiologic studies confirm that comorbidity of PTSD with substance use disorders is common and that the symptoms of patients with this comorbidity tend to be more severe and more refractory to treatment than those of patients suffering from either disorder alone. Despite the frequency with which patients with both diagnoses present for treatment, no systematic treatment approach of proven efficacy has been developed for this population. Furthermore, little is known about the impact on substance use disorder outcomes of the medications and psychosocial interventions commonly used to treat PTSD, or vice versa.

These limitations notwithstanding, the research conducted to date can inform both clinical practice and future clinical and preclinical research. For example, clinical research suggests that PTSD patients with substance dependence, particularly those who are addicted to CNS depressants, may find the physiologic arousal resulting from substance withdrawal intolerable due to additive effects with preexisting arousal symptoms related to PTSD. Successful detoxification of these patients may thus require inpatient admission to permit vigorous control of withdrawal and PTSD-related arousal symptoms.

Neurobiologic research indicates that high levels of CRH in the brain, particularly in the amygdala, may be common to both PTSD and to substance withdrawal states. Further, CRH antagonists reduce both the anxiety and the enhanced response to illicit substances (sensitization) that are induced by higher levels of brain CRH. These observations suggest that CRH antagonists could potentially have a role in the treatment of patients with PTSD and comorbid substance dependence. Although at present no CRH antagonist has been approved for human use, a series of CRH antagonists that can be administered peripherally have been developed and have been shown to cross the blood brain barrier (34, 69). These agents will be important tools for further defining the potential role of CRH antagonism in the treatment of patients with PTSD and substance dependence and will hopefully lead to development of orally active preparations.

Evidence of noradrenergic dysregulation in both PTSD and in withdrawal from CNS depressants has prompted the use of the α_2-adrenoceptor agonist clonidine in both disorders (57, 58). Data from both preclinical and clinical research suggest that this agent, as well as the selective α_2-adrenoceptor agonist guanfacine, would be effective in reducing noradrenergic hyperactivity in patients with PTSD and comorbid substance dependence. Guanfacine, given its greater selectivity, may offer a more favorable side effect profile. Given the dearth of established treatments for this patient population, controlled clinical trials to establish the efficacy of these agents are clearly indicated.

Finally, although preclinical work has resulted in considerable progress toward delineating the contributions of the HPA axis and noradrenergic systems to the pathophysiologic underpinnings of PTSD with comorbid substance dependence, few neurobiologic studies have been conducted in this patient population. The inclusion of subjects with this comorbidity may render such studies more complicated, but the data emerging from this work would better inform the clinical management of the difficult-to-treat symptoms of these frequently encountered patients. At the minimum, patients who participate in studies of PTSD or of substance dependence must be thoroughly evaluated for the presence of this comorbidity to permit adequate control of the effects of the comorbid condition on the neurobiologic processes under study.

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