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Complications of Chemical Abuse and Dependency

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Substance abuse disorders are a frequent comorbid condition associated with post-traumatic stress disorder (PTSD). Among Vietnam veterans seeking treatment for PTSD, 60%–80% exhibit concurrent diagnosis for drug or alcohol abuse or dependence (1–8). These clinical data are also supported by two major epidemiologic surveys. In the Center for Disease Control's Vietnam Experience Study (9), 39% of veterans meeting criteria for PTSD during the month before examination also meet criteria for alcohol abuse or dependence. Higher rates of comorbidity were found in the National Vietnam Veterans Readjustment Study (10), which revealed that among Vietnam veterans who met criteria for a current or lifetime PTSD diagnosis, 20% and 75%, respectively, met criteria for alcohol abuse or dependence.

On a psychological level, patients with PTSD and substance abusers both suffer because they cannot regulate their emotions, self-esteem, relationships, or behaviors. It has been observed by clinicians that substance abusers resort to using substances to relieve or to control the distress associated with their self-regulation problems. This has led to the self-medication hypothesis developed by Khantzian (11,12) to explain substance abuse behavior. Decades of clinical work with alcoholics and addicts have seemed to support such a viewpoint. As the scientific thinking in psychiatry has changed, in contrast to early psychodynamic formulations that emphasized pleasurable and aggressive drives and the unconscious meanings of drug use, the more contemporary formulations have stressed how drugs and alcohol serve substance abusers as treatment for their affect deficits, troubled self-other relationships, and developmental disabilities. An application of these ideas to PTSD is illustrated by substance use in Vietnam veterans. The Vietnam War focused attention on drug abuse as well as on PTSD in soldiers, and raised concerns that returning veterans would create an epidemic of American heroin addiction. In fact, soldiers who participated in atrocities in Vietnam reported both more severe stress symptoms and more extensive use of heroin (13). They also reported that illicit drug use acutely ameliorated these stress symptoms in Vietnam. Later, back in the United States, when these symptoms recurred as part of PTSD, some veterans again turned to illicit drugs for relief and many turned to alcohol. This phenomenon became understood as an attempt at "self-medication." The self-medication hypothesis of substance abuse provided an initial understanding of the comorbidity of PTSD with substance abuse in light of the effects of ethanol and opioids on central noradrenergic hyperactivity and endogenous opioid function. The hypothesis remains controversial, however, and has limitations especially with respect to treatment approaches that assume substance

abuse is a "secondary" disorder. The self-medication model will be discussed briefly in this chapter.

Regardless of the usefulness of the self-medication model, it is clear that the interaction of PTSD and substance abuse is complex and that the direction of the causal arrow is controversial. Beyond being part of the sequelae of stress disorders, substance abuse can interact with stress in a complex way at multiple levels during both development of stress-related symptoms and subsequent maintenance of these disorders. Furthermore, there is some evidence that substance abuse may contribute to the risk of developing PTSD. Even though the direction of causality is not clearly established, it is clear that both disorders display remarkable overlap in biological systems affected and in models used to explain and investigate them.

One very important way that PTSD and substance abuse disorders converge is that they are both frequently conceptualized as disorders of both psychological and biological regulation. As biological approaches to psychiatric disorders have become increasingly influential and complex, the concept of a biological self-regulation deficit, or disorder in homeostasis, has been invoked to reconcile some of these complexities. The issue of homeostasis as it applies to PTSD is discussed in detail elsewhere in this volume. However, since this concept is also used in explaining substance abuse, it further illuminates the unique connection between these disorders. Furthermore, physiologic, behavioral, and neurochemical systems themselves are similarly affected by stress and substance abuse. Pharmacological agents used in treatment of PTSD also overlap in their biological effects with the substances abused by people with this disorder. These overlapping neurochemical and pharmacological issues will be discussed in this chapter according to specific drugs of abuse.

Since biological models for PTSD and substance abuse are addressed in detail elsewhere in this volume, this chapter will not review in detail biological and behavioral science discussed elsewhere, but will focus on the complexities of the interaction between comorbid PTSD and substance abuse conditions, and the implications that this interaction has for clinical treatment. Finally, pharmacological treatment issues that reflect the interaction of these disorders will be considered.

RISK FACTORS FOR COMORBID PTSD AND SUBSTANCE ABUSE

A variety of risk factors for comorbidity have been identified in the literature. Some clinicians have argued that the high rates of substance abuse are primarily due to the fact that alcohol and other drugs were extremely available to military personnel stationed in Vietnam during the war (14,15). This cannot explain, however, the observation that veterans with higher levels of combat exposure are more likely to abuse alcohol than those who saw considerably less combat (16), since all personnel would be equally exposed to available substances of abuse. Indeed, the latter finding suggests rather that neurobiological or other alterations associated with PTSD itself make affected individuals more susceptible to alcohol and illicit drug use. Several studies in fact suggest that severity of combat trauma exposure is correlated with higher current and lifetime rates of alcohol and drug problems (17,18). This is consistent with evidence from Helzer (19) that severity of trauma is also correlated with PTSD, and tends to also support the hypothesis that severity of substance abuse is correlated with severity of PTSD.

However, there is also evidence that preservice variables may be better predictors of postservice alcohol abuse than combat exposure (19). A variety of specific risk factors have been suggested, including family history and preservice drinking (19), relative youth at the time of combat exposure (18), and a learned helplessness attributional style (20). These issues are extensively reviewed by Kofoed et al. (21).

Additional possibilities in the causal interaction would be substance abuse behavior or vulnerability as a risk factor for PTSD, as well as the possibility that certain premorbid traits may predispose individuals to both PTSD and substance abuse disorders.

Most data on PTSD-substance abuse comorbidity is obtained from studies of Vietnam veterans with PTSD; therefore, conclusions are lim-

ited concerning possible risk of acquiring PTSD in primary substance abuse patients. There are however, some data suggesting that abusers of cocaine and opiates are more likely than other substance abusers to suffer from PTSD, and that problems with drugs and alcohol in general appear to increase the risk of PTSD.

Working on the Epidemiologic Catchment Area survey, Cottler et al. (22) reported new information on the relationship between trauma and the use of drugs and alcohol. They asked 2,663 men and women in the St. Louis area about traumatic events in their lives and symptoms of PTSD—nightmares, jumpiness, trouble concentrating, feelings of shame, and a need to avoid reminders of the traumatic event. Interviewees were also asked how much alcohol they drank and which drugs they had taken more than five times for nonmedical purposes. The PTSD was more than twice as common among the drug and alcohol users, but mainly because they had had more traumatic experiences. After a trauma, only 2% of marijuana users developed PTSD; under those circumstances they were actually slightly less vulnerable than comparison subjects who did not use drugs at all. The authors suggest that people who use illicit drugs but succeed in limiting that use to marijuana have a higher-than-average capacity to cope with stress. Cocaine/opiate users on the other hand were nearly three times more likely to have experienced a traumatic event, with physical assault the chief cause. The lifetime prevalence rate for PTSD itself was 8.3% among cocaine/opiate users versus 0.3% among comparison subjects.

Another recent study (23) supports a high prevalence of civilian PTSD in an outpatient substance abuse population. In a 6-week period, 39 of 46 patients completed the Mississippi Scale for civilian PTSD (24). Seventy-two percent of those scored 86 or greater of a 39–195 score range indicating "generalized distress." Eighteen percent scored over 120, the cutoff score for PTSD.

There is also other evidence suggesting an elevated frequency of dissociative symptoms in the substance abuse population. A study reported by Dunn et al. (25) focused on veteran patients with substance abuse problems and was designed to: 1) evaluate the base rate of self-reported dissociative experiences, and 2) assess the impact of demographic and clinical variables on scores obtained with the 28-item Dissociative Experiences Scale (26). In a cohort of 265 subjects, 41.5% had a score of 15 or more on the Dissociative Experiences Scale, which suggests that dissociative experiences are common in this population. The authors suggest that screening for dissociative disorders should be considered in chemically dependent subjects.

Although this study did not discriminate between primary dissociative symptoms with secondary substance abuse and substance abuse as a risk factor for development of dissociative symptoms, the study by Cottler et al. (22) reported that, in general, the onset of substance abuse preceded the onset of post-traumatic symptoms, suggesting that substance abuse predisposes people to exposure to traumatic events or vulnerability to PTSD after such exposure.

In the Cottler study, when other variables, including antisocial behaviors, were controlled, female gender also predicted PTSD. Women may therefore form a subpopulation especially prone to trauma and the consequences of substance abuse itself. In addition to the Cottler study, a survey of metropolitan areas carried out at the National Institute of Mental Health revealed that drug abuse/dependence was the second most common psychiatric disorder among women aged 18–24 (27). Female alcoholics may suffer a higher mortality rate than male alcoholics (28), and women opiate addicts experience poorer long-term adjustment than their male counterparts (29,30,31).

In addition to sequelae of opiate abuse, women also are more vulnerable to problems associated with cocaine abuse. A study by Mendelson et al. (32) of hospitalized cocaine abusers reported notable differences between men and women. Women began using cocaine earlier than men and entered treatment at a younger age after having used cocaine for a shorter period. Men had better overall social adjustment, including better employment and living situations. Cocaine was more likely to make men feel more guilty and to reduce guilt in women. Men had a higher incidence of antisocial personality disorder, and women were more likely to have major depression. Although men and women were

almost equally depressed at admission, men improved more rapidly, according to the 24-item Hamilton Depression Rating Scale (33). The possibility of gender differences in PTSD vulnerability and in vulnerability to PTSD/substance abuse comorbidity remains an important area for future investigation.

SELF-MEDICATION MODEL AND PTSD, SUBSTANCE ABUSE, AND COMORBID CONDITIONS

The concept of "self-medication" is commonly seen in the general dual diagnosis (11,34) as well as the PTSD/substance abuse literature. Those clinicians treating patients with substance abuse and PTSD have generally assumed self-medication to be the etiology of the substance abuse (35–37). This hypothesis suggests that substance use relieves specific dysphoric symptoms of PTSD and reinforces further use. The hypothesis also touches on the controversy within the field of substance abuse concerning the relative roles of positive (e.g., drug-induced euphoria) versus negative (relief from distress) reinforcement in maintaining substance abuse behavior. This concept, espoused and developed over the years by Wikler (38,39), emphasizes physical dependence, the abstinence syndrome, correlated environmental stimuli, and primarily aversive correlates of opiate use. Currently, in most cases the role of positive reinforcement is considered to be most important in maintaining substance abuse behavior, but negative reinforcement also plays an influential role and is especially important in maintaining opiate dependence (40). Similarly, the self-medication model that can be considered a diagnosis or symptom-specific modification of more general "tension reduction" models, although widely used and popular among clinicians, has fallen out of favor in scientific literature. For example, as reviewed by Volpicelli (41), evidence for tension reduction models of substance abuse is mixed and inconsistent. A later review by Kofoed et al. (21), specifically of PTSD and substance abuse, also finds the self-medication model of little help for planning therapeutic approaches.

One argument against the self-medication model is that much of what is found in non-PTSD literature examining diagnosis/drug preference combinations seems counter-intuitive (for instance, increased rates of stimulant abuse in schizophrenic samples) (34). However, this particular example could be explained by possible relief of negative symptoms by stimulant abuse in these patients.

Another argument is that there is little specificity of drug choice in PTSD, rendering the self-medication hypothesis too nonspecific to be helpful (21). Since the main biological abnormality associated with PTSD most likely to generate susceptibility to chemical abuse/dependency is sympathetic nervous system hyperarousal and chronic lowering of endogenous opioid levels, it would be predictable that PTSD patients might successfully ameliorate intolerable symptoms with heroin, methadone, and other opiates. (Kosten and Krystal (35) have reviewed the biological basis for PTSD symptoms and substance abuse.) This is consistent with clinical experience since PTSD patients generally prefer alcohol, marijuana, central depressants or opiates, and cocaine and stimulant users with PTSD are usually also dependent on alcohol, marijuana, and opiates (8). Nevertheless, the wide range of substances used, even if understandable in terms of PTSD biology, does limit the usefulness of the self-medication hypothesis. In the section that follows, some biological grounds for use of specific substances will be mentioned.

Although the self-medication model has intuitive appeal and may be useful in understanding the etiology and persistence of comorbid PTSD/substance abuse if it is not applied too rigidly, it is certainly a misuse of this model to conclude that treating the "primary" disorder (PTSD) will lead to resolution of the "secondary" disorder. As eloquently reviewed by Kofoed et al. (21), this position has little support, and most evidence confirms the clinical necessity of simultaneous treatment of both disorders.

The self-medication hypothesis is certainly not useful if a simple one-to-one correspondence is expected between a specific comorbid psychiatric diagnosis and specific substances abused. It may be more useful if specific symptoms and affected biological systems are considered with

respect to particular drugs of abuse that relieve or exacerbate those symptoms. The next section will consider specific drugs of abuse with respect to their self-medication potential for PTSD, as well as paradoxical ways in which the self-medication attempt can result in worsening of the disorder.

SPECIFIC SUBSTANCES OF ABUSE AND IMPLICATIONS FOR STRESS DISORDERS

Opiates

Opiate abuse and dependence can influence PTSD symptoms at multiple biological levels. Opiates impinge on a particular vulnerability in PTSD patients. As discussed elsewhere, PTSD is associated with abnormality in endogenous opioid systems. Most notably, plasma beta-endorphin levels have been observed to be low in PTSD patients (42). In general, acute opiate use diminishes PTSD symptoms, while chronic opiate abuse and opiate withdrawal states exacerbate such symptoms. In fact, opiate withdrawal and acute PTSD symptoms can be so similar that some authors have called PTSD a withdrawal state (43). Van der Kolk and associates (43) have also proposed that the animal model of learned helplessness in the face of inescapable shock may be directly applicable to PTSD. They hypothesize that long-term potentiation of locus coeruleus pathways to the hippocampus and amygdala may produce the hyperarousal, traumatic nightmares, and flashbacks that characterize PTSD. Such a theory also suggests that fluctuations in endogenous opioid levels will affect the response to traumatic stimuli, since the locus coeruleus is inhibited by opioids. The inescapable shock theory offers a neurobiological rationale for stress-induced analgesia, and for the "action junkie" behavior that is sometimes considered secondary to PTSD and thus has implications for opiate addiction.

Much of the interaction between PTSD and opiate abuse can be related to the adrenergic abnormalities discussed elsewhere in this volume. Kosten and Krystal (35) have suggested that adrenergic inhibition of corticotropin-releasing hormone (CRH) may account for a disturbance in the endogenous opioid system associated with PTSD. The CRH promotes release of adrenocorticotropic hormone (ACTH) from the pituitary; ACTH is coreleased with beta-endorphin, which influences the activity level of the endogenous opioid system. Therefore, Kosten and Krystal postulate that inhibition of CRH by excessive sympathetic arousal also produces an endogenous opioid deficiency in patients with PTSD. This prediction is consistent with previously mentioned clinical reports of lowered pain thresholds in PTSD patients (44) and of a possible link between chronic pain and PTSD (45,46).

Opiate withdrawal, which has been demonstrated to have an important adrenergic component (47), has even been reported to present as PTSD (48). Detoxification from opiates therefore represents a special problem in PTSD patients. Withdrawal syndromes associated with these drugs of abuse increase central noradrenergic activity and may worsen PTSD symptoms (47,49,50). Methadone-maintained patients are a special group in which chronic opiate medication may facilitate PTSD treatment in dually diagnosed patients but also ironically maintain vulnerability for adrenergic hyperactivity. Some recent evidence suggests that opiate addicts treated with methadone experience withdrawal-like symptoms when given drugs that stimulate the adrenergic system, such as cocaine (51) or yohimbine (52) (Stine et al., unpublished data).

Another recent example of overlap between PTSD and substance abuse was reported by Southwick et al. (53). In that study, a subgroup of patients with PTSD were observed to experience yohimbine-induced panic attacks (70% [14/20]) and flashbacks (40% [8/20]). In addition, in the patients with PTSD, yohimbine induced significant increases in core PTSD symptoms such as intrusive traumatic thoughts, emotional numbing, and grief.

Since yohimbine has also been reported to precipitate opiate withdrawal-like symptoms in methadone-maintained patients, it is to be expected that dually diagnosed PTSD/opiate-dependent patients have a special vulnerability to PTSD relapses. In addition to being more susceptible to adrenergic-opioid system interac-

tions, PTSD patients are at greater risk of opiate dependence, since heroin not only dampens adrenergic hyperarousal but may also serve to replenish an endogenous opioid system that has been depleted because of the pathophysiology of PTSD.

Interestingly in this context, Pitman and associates (54) have shown that exposing Vietnam veterans with PTSD to combat scenes from the movie *Platoon* produces a naloxone-reversible 30% decrease in pain responses. This important finding of stress-induced analgesia suggests not only that PTSD is associated with dysregulation of the endogenous opioid system, but also that a possible baseline opioid deficiency might be dramatically reversed when PTSD patients are exposed to traumatic stimuli. These dramatic fluctuations of activity of the endogenous opioid system could mimic and promote the experience of opiate abuse.

Stimulants

Stimulants like cocaine and amphetamines exert their effects on the brain by increasing extracellular concentrations of dopamine (DA), noradrenaline (NA), and 5-hydroxytryptamine (5-HT). Although both cocaine and amphetamines are equally effective in blocking the reuptake of monoamines, amphetamine is more potent than cocaine in that it also promotes release (55–57).

Most studies have focused on the effects of stimulants on dopaminergic systems, due to the high correlation of this system with the rewarding efficacy and abuse liability of these drugs (58–60). Very little is known about the effects of chronic stimulant usage on other brain monoamine systems.

As mentioned earlier, PTSD has striking similarity to stimulant abuse in the way that brain neurobiology is affected. In animal research, the forebrain DA neurons show an augmented response to repeated stress, as well as to repeated administration of psychostimulants such as cocaine and amphetamines. Previous exposure to stress increases the subsequent locomotor response, subserved by DA systems of the striatum, to cocaine challenge (61–64). Thus, stress and psychostimulants can, under certain conditions, cross-sensitize. Clinical reports of severe anxiety and depression following stimulant withdrawal (65) suggest that (66,67) chronic stimulant usage may influence PTSD symptom severity through brain noradrenergic systems.

A recent study (68) in rats demonstrated that chronic exposure to amphetamine, cocaine, and the tricyclic antidepressant DMI increased activity in the noradrenergic neurons of the locus coeruleus. After 2 weeks' exposure, cells from animals in all three drug-treated groups showed a significant increase in sensitivity to the acute effects of cocaine and amphetamine. These animals also had a significant increase in behavioral stimulation (stereotypy). Autoreceptors on monoamine neurons have been reported to become subsensitive following chronic exposure to stimulants (69–71) and DMI (72,73). In the Harris and Williams study (68), there was also a significant increase in the behavioral sensitivity of the drug-treated animals to the sedative effects of clonidine.

Although a similar effect has not been demonstrated directly in humans or PTSD patients, these findings have implications for clinical observations in drug-abusing patients. Because central stimulants facilitate sympathetic hyperarousal (which would be predicted to exacerbate PTSD symptoms), PTSD patients would also be expected to exhibit less cocaine and amphetamine abuse. In fact, Friedman (8) reports that "PTSD patients do not like the heightened emotional state produced by cocaine, amphetamines, and other stimulants." It would also be expected that risk of developing PTSD and the severity of ongoing PTSD would be increased in those patients who do abuse stimulants. In fact, an epidemiological study of substance abusers discussed previously did support increased risk for development of PTSD in this population. In that study (22), cocaine/opiate users were the only group especially vulnerable to PTSD once they were exposed to trauma, thus providing interesting indirect evidence for this hypothesis. Eight percent of all cocaine/opiate users and 19% of those experiencing a trauma had the symptoms. In addition to illicit stimulant abuse, caffeine and other psychostimulants, including some found in common over-the-counter decongestant medica-

tions, also may present a risk for patients prone to anxiety disorders.

Opiate/Stimulant Interactions

The concurrent use of opiates and cocaine by addicts has interesting implications for PTSD patients because of the interaction of heroin and cocaine on opiate withdrawal. Opiate withdrawal symptoms precipitated by naloxone challenge may be attenuated in opiate-dependent individuals who have a recent history of cocaine abuse, but are not currently intoxicated with cocaine (74). This symptom relief may explain some cocaine use by patients on low doses of methadone (25–40 mg daily) and why cocaine use increases in some opiate-abusers after onset of methadone maintenance (75). However, cocaine use may also be reduced by sufficiently high doses of methadone (76). A potential mechanism for these apparently contradictory findings involves the $alpha_2$ adrenergic system. The antagonist yohimbine (which causes indirect stimulation of noradrenergic neurons of blocking feedback inhibition at the presynaptic autoreceptor) can precipitate opiate withdrawal when administered acutely (52), but it also attenuates development of withdrawal symptoms when administered chronically and repeatedly in rats dependent upon opiates (77). If cocaine-induced noradrenergic stimulation acutely precipitates or exacerbates opiate withdrawal symptoms (or adrenergic symptoms sufficiently similar to be interpreted as withdrawal), chronic cocaine use may attenuate subsequent naloxone-precipitated withdrawal in a fashion analogous to the effect of repeated yohimbine administration.

This opens the door to many complex, although speculative, interactions with the biology of PTSD, but it is clear that the attempt to self-medicate PTSD with both opiates and stimulants can both ameliorate and exacerbate PTSD symptoms.

Alcohol and Benzodiazepines

The relationship between PTSD and alcoholism may be especially important; one survey by Sierles et al. (6) showed that PTSD was highly associated with other concurrent psychiatric illnesses, particularly alcohol abuse. In a later study by Davidson et al. (78), alcohol abuse and nonbipolar depression were the most frequently noted diagnoses (41% each) in PTSD. Nonalcoholic substance abuse (16%) was also quite common. Not only is alcoholism a common diagnosis in the lifetime assessment of PTSD patients, but it is also present in more than 50% of first-degree relatives of probands with this disorder (78). Drug abuse and alcohol abuse considered together were the most common of all diagnoses in relatives of PTSD probands (60%) (79). The relative specificity of the connection is supported by the observation that alcohol and drug abuse were also significantly more common in the relatives of patients with PTSD (60%) than in relatives of patients with depression (26%) and generalized anxiety (38%).

Alcoholism also influences the neurobiologic findings of PTSD studies, and clinical experience suggests that comorbid diagnoses influence treatment response. Low platelet monoamine oxidase (MAO) activity has been suggested as a psychopathological risk factor for many conditions, including alcoholism (80–82). Davidson et al. (79) reported that the platelet MAO activity of veterans suffering from chronic PTSD was lower than that of control subjects. Patients were grouped according to whether or not they had a history of alcohol abuse and whether or not they had a concurrent diagnosis of major affective disorder. Nine patients reported a positive history and 14 patients reported a negative history for alcohol abuse. The alcohol-abusing PTSD patients also had significantly lower platelet MAO activity than the nonalcoholic PTSD patients.

All patients in the Davidson et al. (78) study had experienced another psychiatric disorder at some time in their lives. Many times these were of long duration and led to considerable morbidity, with hospitalization, loss of job, and disrupted interpersonal relationships. The authors speculate that one diagnosis sustains the other. Thus, the ability of PTSD to resolve will be hindered by a coexisting depression or other major psychiatric illness, especially substance abuse.

GENERAL OBSERVATIONS IMPLICATIONS FOR TREATMENT

General Treatment Issues

Not only do PTSD and substance abuse disorders overlap in their acute and chronic effects and influence each other at all levels—both disorders also can influence the resilience of the fundamental psychological and biological systems themselves. This results in disorders of self-regulation and compromises a patient's ability to benefit from treatment. Thus, treatment of the dually diagnosed patient must be firmly based simultaneously in both PTSD and substance abuse theory and technique.

Treatment specifically for PTSD is discussed in detail elsewhere in this volume, so this chapter will focus on the role of substance abuse treatment and its interaction with PTSD treatment. A brief mention of the history of substance abuse treatment may be useful. Dating back to the late 1960s, psychodynamic studies by investigators such as Weider and Kaplan (83), Milkman and Frosch (84), Wurmser (85), Krystal (86), Khantzian (11,12), Wilson et al. (87), Luborsky et al. (88), and Dodes (89) have indicated that substance abusers' difficulties stem from developmental handicaps and psychological deficits. Khantzian (11,12) describes four areas of self-regulation problems that predispose addicts to become dependent on and relapse to substances of abuse: 1) affect life; 2) self-esteem; 3) relationships; and 4) self care. Although the treatment of substance abuse disorders through psychodynamic methods is controversial, this formulation has been fruitful for clinicians. Other psychological approaches such as the learning model have contributed enormously in recent years as a basis for empirical research and treatment development. Learning models also deal with elements of self regulation (e.g., identifying and extinguishing automatic and impulsive responses to drug-associated cues).

Currently, most substance abuse treatment involves group or individual psychotherapy based on twelve-step programs such as Alcoholics Anonymous or relapse prevention therapies, a type of cognitive/behavioral therapy developed by Marlatt (90) and extended by others (91). Although it has been repeatedly stated that the high comorbidity of PTSD/substance abuse (91% according to Boudewyns et al. (92)) and the "inextricably intertwined" nature of these disorders require simultaneous treatment of both, there are few articles describing such a combined treatment. As reviewed by Kofoed (21), clinicians generally have combined group and individual therapies for PTSD with aspects of substance abuse treatment such as the twelve-step approach. Authors such as Abueg (93) and Jellinek (94) generally prepose a multiple-stage approach in which a stabilization and motivational period is followed by more focused PTSD and substance abuse treatment, often in a group format.

Comparisons of different therapies on outcome immediately posttreatment and at longer follow-up intervals have been limited. The Abueg (93) study suggests that relapse prevention training during a residential PTSD treatment program is superior to residential treatment alone, but that this differential effect is lost at 9 months posttreatment. This is consistent with clinicians' general assessment that treatment must be long-term, including inpatient and outpatient services.

Another study in a group of patients undergoing residential alcohol treatment (95) suggests no difference in abstinence rates for a heavy combat exposure group treated with additional readjustment group therapy and a light combat exposure group receiving no additional treatment. However, this study is limited by a nonrandomized design and no controls (21).

As discussed earlier, women present particular treatment challenges. Women remain a subgroup of noncombat substance abusers at risk for PTSD. In a recent study of women substance abusers with and without PTSD, women with PTSD were more likely to have been victims of sexual and physical abuse, had higher scores on the psychological problems and substance abuse areas of the Addiction Severity Index, and were more likely to have comorbid affective disorder. They also had lower compliance with aftercare (96). The authors recommend screening women substance abusers for victimization and PTSD

in order to provide more aggressive PTSD treatment and improve treatment retention.

Clearly, more controlled studies with attention to treatment-matching issues are needed. Some progress has been made in this direction by McLellan and colleagues, who found that global severity as measured by the Addiction Severity Index (ASI) was a powerful prognostic variable (97). Psychiatric severity as measured by the ASI differentially predicted treatment response in both retrospective (98) and prospective studies (99), with low severity generally predicting greater response to treatment. Other studies have also found that psychiatric severity can predict treatment results in substance abusers, with specific diagnoses such as depression associated with differential response to specific therapies (100,101). However, no studies have examined this issue specifically in PTSD patients.

PHARMACOLOGICAL TREATMENT

Psychological techniques can be complemented by pharmacological treatment, and these pharmacological treatments can themselves constitute a psychological tool. Just as behavioral techniques have proved useful in extinguishing some of the conditioned-alarm aspects in PTSD, combined pharmacological-behavioral approaches may assist in disrupting conditioned cues that promote drug abuse. Disulfiram has been used successfully to extinguish ethanol use by negatively reinforcing its abuse. Methadone maintenance was intended to extinguish opiate abuse by blocking the rewarding properties of self-administration through cross-tolerance (102,103). Opiate maintenance may also provide some protection against PTSD symptoms. However, maintenance on opiate agonists postpones eventual detoxification, and detoxification may revive PTSD symptoms. The opiate antagonist naltrexone might extinguish previous conditioned, abuse-promoting stimuli, and although naltrexone may release peripheral catecholamines and antagonize central gamma-aminobutyric acid (GABA) systems, thereby exacerbating both PTSD and conditioned withdrawal phenomena, this occurs at much higher doses than routinely used (104).

A biological approach may complement psychological diagnostic and treatment techniques. With regard to treatment, almost every type of psychotropic agent has reported efficacy in PTSD. However, very few double-blind therapeutic trials have been published. Successful pharmacotherapy appears to diminish DSM-III-R intrusive recollections and hyperarousal, but not avoidant symptoms (8). Current information suggests that drug treatment alone is not sufficient to relieve the suffering in PTSD, but is often useful as an adjunct to psychotherapy.

Many medications have been reported helpful in treatment of PTSD, but most reports are of open treatment studies. The status of the pharmacological treatment of PTSD has been recently reviewed by Friedman (105). Controlled studies are few but have reported efficacy for tricyclic antidepressants (TCAs) (106–108), monoamine oxidase inhibitors (106,109), the beta-adrenergic antagonist propranolol (110), and alprazolam (111). Open trails have supported a possible role for the medications just mentioned, as well as carbamazepine, lithium, neuroleptics (8,112,113, 114) (see review by ver Ellen and van Kammen (115)). Other medications studied in more recent open trials are buspirone, fluoxetine, cyproheptadine, alprazolam, valproate, and TCA/clonidine combination therapy (reviewed by Friedman (105)). Most controlled studies report that successful pharmacotherapy for PTSD results in attenuation of DSM-III-R intrusive recollections (especially nightmares) and arousal (especially insomnia, startle, and irritability) symptoms, while avoidant/numbing symptoms usually do not respond to medication (8). An exciting preliminary result in this regard, however, is that fluoxetine may reduce the severity of avoidant/numbing as well as the other PTSD symptoms (see next paragraph) (116,117).

A variety of open studies has suggested the usefulness of selective serotonin reuptake inhibitors (SSRIs) in PTSD treatment (116,118–121). There is also a considerable body of evidence for the role of serotonin in the pathophysiology of PTSD. (see Chapter 26 for a more detailed review.) The only controlled trial with SSRIs, reported by van de Kolk et al. (122), confirmed the effectiveness of fluoxetine in reducing

arousal and numbing but not avoidance symptoms. Fluoxetine has also been suggested as a potential pharmacotherapy for substance abuse, specifically for cocaine abuse. Fluoxetine reduces intravenous cocaine self-administration in rats (123) and has been clinically shown to reduce cocaine abuse in an open trial in opiate-dependent patients who were in methadone maintenance treatment (124).

Other pharmacological agents suggested for treatment of substance abuse also have some overlap with medications used in PTSD treatment. While there are specific medications for opiate dependence (e.g., maintenance treatment with agonists such as methadone, LAAM, and buprenorphine as well as the antagonist naltrexone), the state of the art for cocaine abusers is quite different. Similar to PTSD treatment studies, there are many encouraging open trials (e.g., medications that have appeared effective for cocaine abuse in open trials include disulfiram but not naltrexone (125), amantadine (126), bromocriptine (127), pergolide (128), methylphenidate (129), flupenthixal (130), and mazindol (131), as well as buproprion (132) and fluoxetine (124)). However, few of these pharmacological agents have been confirmed as effective in controlled trials. One medication that has shown some effectiveness for cocaine dependence in a controlled trial is desipramine (130). Although later attempts to replicate this finding have been negative or mixed (133–135), this medication may have effectiveness for a depressed subgroup (136). It may be that since desipramine has been useful for PTSD symptoms, it would be an effective medication for PTSD/cocaine abuse patients. Such specific pharmacological studies for comorbid PTSD/substance abuse patients have not yet been reported.

Carbamazepine and related medications represent a particularly interesting potential pharmacotherapy for both PTSD as well as substance abuse. The theoretical usefulness of this medication is based on the kindling model that has been independently suggested to be useful in understanding substance abuse (137) as well as PTSD (112,113). Briefly, according to this model discussed in a detailed fashion elsewhere, chronic central sympathetic arousal in PTSD, mediated by the locus coeruleus, sensitizes limbic nuclei, thereby producing a longlasting facilitation of continued abnormal arousal. As Friedman (8) comments, kindling would also explain the chronic nature of PTSD, which can continue for decades if untreated (138). Carbamazepine and valproate are two antikindling agents with reported efficacy in treatment of PTSD. The use of carbamazepine in PTSD has been reviewed by Friedman (105) and is supported by two open trials (139, 140). The usefulness of valproate in PTSD has also been supported by open trial (141) and case report (142) evidence.

Carbamazepine has also been investigated for treatment of cocaine dependence, with inconclusive results. In a short (20-day) double-blind crossover study in 32 nonmotivated crack users, carbamazepine improved early cocaine treatment retention and treatment effectiveness (143). Serum carbamazepine levels of 4 ng/ml or more were associated with greater improvement in that study. A subsequent 12-week controlled study of 183 randomized outpatients by these authors supported the usefulness of this medication (144).

Other 8-week (145) and 12-week (146) treatment studies have not replicated this effect. It is tempting to speculate that carbamazepine and related drugs may have special efficacy in a comorbid population, but this hypothesis has not been tested.

Thus, it is apparent that the options in pharmacotherapy are diverse and no treatment is a clear cure. Furthermore, increased understanding of the complex neurobiology of PTSD and substance abuse argues against the likelihood of the future discovery of any single specific pharmachotherapy for these disorders. Increased controlled clinical trials are therefore necessary to develop better approaches to matching subpopulations of patients to treatment in order to fully benefit from the recent advances in this area.

TREATMENT OF WITHDRAWAL STATES—A SPECIAL CHALLENGE

Pharmacological treatment is particularly important for certain acute problems associated

with PTSD/substance abuse. As discussed earlier, drug withdrawal states, perhaps through a common noradrenergic pathway, often exacerbate post-traumatic stress syndromes. Opiate, benzodiazepine, and ethanol withdrawal are associated with central noradrenergic activation and subjective alarm states perhaps similar to that hypothesized for PTSD. These clinical states of drug withdrawal might have additive effects with PTSD on central noradrenergic function and, as a result, worsen the clinical presentation. Alcohol and opiate withdrawal alternating with abuse of these substances causes repeated adrenergic arousal, which can trigger a conditioned emotional response associated with PTSD symptoms (35). Thus, the treatment for chemical dependency, already complex, can precipitate and exacerbate PTSD symptoms, presenting a formidable combination. In other words, the normal difficulties of treating chemical dependency are multiplied by the complex risk of exacerbating PTSD symptoms. A related phenomenon during withdrawal from benzodiazepines and ethanol may be polysensory hallucinations that take the form of post-traumatic flashbacks. Clinical experience suggests that treatment of the drug withdrawal also alleviates components of the exacerbated PTSD symptoms. One could hypothesize that drug abuse whose intended purpose was to alleviate withdrawal might serve a similar protective function of reducing PTSD symptom exacerbations.

Opiate detoxification can present similar problems in PTSD patients. One approach to opiate detoxification already proving useful is to combine clonidine-assisted opiate detoxification with naltrexone in order to minimize central noradrenergic activation during the detoxification and antagonist-initiation phases of treatment (147–150). A compromise solution to minimize symptoms might be achieved through new mixed agonist-antagonist drugs such as buprenorphine (151). During maintenance phases, buprenorphine's agonist actions may suppress conditioned noradrenergic activation, while its antagonist action minimizes the severity of abstinence phenomena and may make the transition to a complete antagonist, such as naltrexone, more tolerable. This approach has been recently reviewed by Stine and Kosten (152).

Somewhat paradoxically, pure opiate antagonists may prove useful in PTSD treatment and substance abuse treatment. Intriguing preliminary results reported by Glover (153) support the potentical usefulness of this approach. In this open study of the effect of the opiate antagonist nalmefene on 18 combat veterans with PTSD, both positive and negative symptoms were observed to improve in 8 subjects. Interestingly, numbing was seen to decrease initially, while anxiety was intensified, as would be predicted in acute antagonist administration. Later responses at higher doses were improvements in both positive and negative PTSD symptoms; this is consistent with a possible protective and normalizing effect of opiate antagonists from cyclical disturbances in endogenous neurotransmission. Another report of the use of naltrexone in PTSD (to reduce flashbacks) has also been published in a brief case history of two patients (154). The use of opiate antagonist is especially interesting in light of the recent reports of naltrexone in treatment of alcoholics (155,156). Thus, naltrexone may be especially useful in patients with PTSD/alcohol abuse comorbidity.

In some chronically relapsing opiate addicts who are not good candidates for detoxification and abstinence, one might choose to medicate PTSD symptoms during opioid maintenance phases. Because of the risk for abuse in these individuals, one might choose tricyclics over benzodiazepines in this population. Reports in depressed opiate abusers suggest that proper psychopharmacological treatment may assist some individuals in maintaining abstinence from illicit drugs and relieving depressive symptoms (157,158). Control of symptoms associated with PTSD may facilitate drug abuse treatment in a parallel fashion.

An example of the synergism between PTSD and alcohol withdrawal phenomena was described by Kosten and Krystal (35). Symptoms were controlled through benzodiazepine-assisted alcohol detoxification, control of panic attacks with alprazolam, and neuroleptic administration. Control of these symptoms ultimately permitted the patient to share some of his vivid memories in therapeutic settings.

After acute treatment of intoxication and withdrawal states, longer-term relapse prevention

treatment also requires that attention be paid to both PTSD and substance abuse pathology, particularly learned responses related to withdrawal phenomena. Mild protracted withdrawal as well as conditioned withdrawal symptoms in response to specific cues may exacerbate PTSD, even after detoxification from addicting substances. Individuals withdrawn from opioids and ethanol often experience withdrawal symptoms and craving for the drug of abuse when exposed to reminders of the drug abuse setting. These conditioned symptoms may reflect central noradrenergic activation and be misattributed to PTSD symptoms (47). Misattribution of the source and significance of conditioned arousal states potentially exacerbates both PTSD symptoms and drug abuse, because individuals with either PTSD or substance abuse have great difficulty labeling and expressing their feelings (159,160). Henry Krystal (161) noted that such individuals tend to experience dysphoric arousal in an undifferentiated global manner, suggesting that those with both disorders may confuse or misattribute conditioned PTSD and withdrawal phenomena. Many stimuli evoke both war experiences and prior drug use; thus, individuals may present with both drug withdrawal and PTSD symptoms. Misattributing the source of arousal, individuals might attempt to alleviate their pseudowithdrawal state rather than seek treatment for PTSD. Recognizing this overlap, the clinician can more accurately develop a treatment plan for these dually diagnosed patients. The patient who presents to drug abuse units and ignores PTSD as contributing to his symptoms, as well as the patient who presents to PTSD-oriented outreach programs and minimizes drug abuse problems, will have inadequate treatment without concurrent management of these two problems.

Benzodiazepines in PTSD/Substance Abuse Treatment

The use of alprazolam described by Kosten and Krystal in the previous section (35) leads us to consider the role of benzodiazepines in PTSD and substance comorbidity. Even the therapeutic use of benzodiazepines remains controversial. Alcoholics represent a special population within the larger PTSD/substance abuse population that may have particular problems with benzodiazepine treatment.

Benzodiazepines are frequently used transitionally to help alcoholics withdraw from alcohol. For patients withdrawing from habitual alcohol use, withdrawal itself may be anxiogenic. But for those suffering from an anxiety disorder, it may be tempting to continue benzodiazepine use indefinitely. Ciraulo et al. (162) concluded that "alcoholics as a group may be more susceptible to benzodiazepine abuse than are nonalcoholics." Also, Ciraulo et al. (163) suggest that the sons of alcoholics may be at higher risk to abuse benzodiazepines. Furthermore, even when benzodiazepines are used therapeutically and appropriately for PTSD patients, they may be problematic for patients who abuse alcohol and other drugs.

The PTSD patients may be unusually sensitive to alprazolam or its withdrawal reaction. In the case of alprazolam, these concerns are augmented by the additional risk of rebound anxiety and severe withdrawal symptoms (164,165). In fact, Risse et al. (166) reported on eight Vietnam veterans who experienced severe exacerbation of their PTSD symptoms during alprazolam withdrawal. The patients exhibited anxiety, sleep disturbance, rage reactions, hyperalertness, increased nightmares, intrusive thoughts, and homicidal ideation. Disappointing results also emerged from a trial of alprazolam in PTSD conducted by Braun and others in Israel (111). Sixteen patients entered this double-blind, random-assignment, placebo-controlled crossover trial; 10 completed 5 weeks of treatment with both alprazolam and placebo. Alprazolam demonstrated significant ($P=.02$) advantage over placebo for anxiety symptoms, but not for symptomatology specific to the PTSD syndrome itself. Although they do not provide details, the authors refer to withdrawal effects in patients who received alprazolam before placebo.

Benzodiazepines can also complicate cognitive effects of PTSD. Anthenelli et al. (167) assessed the ability of 103 healthy young white men, none of whom totally abstained from alco-

hol to recall information. The investigation reported a significant dose-dependent decrement in word recall during even acute diazepam challenges (P<.0001).

There are certainly some good arguments in favor of the use of benzodiazepines as well. As reviewed by Friedman (105), benzodiazepines in general are excellent anxiolytics, and alprazolam, in particular, has potent anxiolytic/antipanic actions. Furthermore, the kindling model of PTSD offers a theoretical reason to consider these drugs, since limbic kindling is associated with increased benzodiazepine receptor binding (168–170). There are two published reports on alprazolam in PTSD treatment. Feldman (171) conducted an open trial and found that 16 of 20 veterans with PTSD treated with alprazolam showed reduced insomnia, anxiety, irritability, and hyperarousal. Evidence for benzodiazepine-induced emotional disinhibition is indicated, however, by Feldman's report that four of these patients showed an increase in outbursts of anger. Clonazepam may be an alternative benzodiazepine that avoids some of the pitfalls of alprazolam treatment. Kofoed et al. (21) recommend clonazepam because of its efficacy, and because slow absorption and elimination reduce euphoric responses and hence abuse potential. Interestingly, a recent study by Tietz et al. (172) in rats reports that tolerance develops more slowly to clonazepam as compared with alprazolam. This effect, if also seen in humans, could support decreased abuse liability for this medication.

The issue of benzodiazepine treatment is more extensively reviewed elsewhere in this volume, but it is clear that these agents are a double-edged sword in the treatment of PTSD, especially in the presence of a substance abuse history.

CONCLUSION

Just as the concept of self-medication provides no simple one-to-one correspondence between diagnosis/treatment agent, no one-to-one correspondence can be expected between a PTSD and substance abuse diagnosis and any one method of psychological or pharmacological treatment. Some initial progress has been made in treatment matching to identify patient subgroups best treated with specific approaches, but randomized controlled drug trials and treatment-matching studies of both psychotherapy and pharmacotherapy are needed. The concept of self-medication, if used judiciously, can be useful in understanding the relationships between substance abuse and PTSD symptoms, the biological systems affected, and the drugs patients choose to abuse, and can generate useful hypotheses in the design of needed studies.

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