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Review Article

Treatment of Co-Morbid Alcohol Use Disorder and PTSD in Veterans

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Abstract

Combat instigated PTSD is one of the more complicated psychological conditions that occurs in the modern world. To add to the complications of treatment, PTSD is often accompanied by other injuries (such as traumatic brain injury) and psychological comorbidities including anxiety and substance use disorders of which the most frequent is alcoholism. While PTSD is normally associated with veterans (combat or non-combat), many of the studies and treatments designs are based on civilian or non-combat instigated PTSD. The lack of information on PTSD in veterans may weaken society's ability to treat one of the most affected populations and to honor the covenant made with members of the military by that society. Currently treatment for PTSD is still associated with a high incidence of non response and relapse. The purpose of the present paper is three-fold: to evaluate current guidelines for treating PTSD with an emphasis on data from combat veterans; to evaluate treatment of alcohol use disorder in veterans; and finally, to evaluate treatment of co-morbid PTSD with alcohol use disorder in the veteran population.

Objectives: To evaluate current treatment of military or veteran personnel with PTSD and comorbid alcohol use disorder (AUD).

Methods: We compared guideline-based treatment of PTSD with pharmacotherapy effectiveness studies in veteran populations. We evaluated treatment of PTSD with comorbid AUD from veteran populations. Finally, we evaluated available pharmacotherapy against current guidelines and theories of non-medication based treatment for veterans with PTSD. To accomplish this we conducted Pub Med searches focusing primarily on literature from 2000 onwards in clini¬cal populations and available in English as free full text. This was supplemented by other papers using earlier clinical samples as well as preclinical studies when warranted.

Conclusions: While comorbid PTSD and AUD has proven to be a frequent occurrence in veterans, few of the current guidelines were designed from data generated in this at-risk population. Results from the literature suggest that pharma¬cotherapeutic treatments including modulation of cortisol might be beneficial in PTSD patients. By evaluating studies that occurred in veteran populations and taking into account new information in the changes in brain functions in PTSD and AUD, we suggest that more evidence-based decisions can be made for treatments. Thus, the data have suggested that use of Selective Serotonin Reuptake Inhibitors (SSRIs) may warrant a reevaluation in the veteran population. The improved understanding of the brain processing changes that result from PTSD, AUD and their combination can allow clinicians to tailor pharmacotherapy to prevent the masking of the beneficial effects of trauma-focused psychotherapy and the natural extinction of fear responses that occur post-military service. Similarly, a greater understanding of changes in neurotransmitter activity in veterans with PTSD, AUD or both may yield more precise use of medications that target specific aspects of brain chemistry in a hypothesis driven manner. Furthermore, continuing to evaluate the new practice of allowing treatment of both PTSD and AUD with trauma-focused psychotherapy immediately upon diagnosis should increase patient compliance and length of abstinence. By taking advantage of the new developments in our understand¬ing of both the functions of the brain as well as the population specific data for treatment, we can continue to take the necessary steps to allow this population to lead a normal life after their service to our country.

Keywords: Addiction; Alcohol use disorder; Comorbidity; Military veterans; Pharmacotherapy; Psychopathology; PTSD

Introduction

Up to 25% of combat veterans develop Post-Traumatic Stress Disorder(PTSD) [1]. Alcohol Use Disorder(AUD) is the most common comorbid disorder in men with PTSD [2]. Thus, there is a compelling need to look closely at the treatment of this group of patients. Although comorbid PTSD and AUD has proven to be a frequently occurring condition in veterans, few of the cur¬rent guidelines are designed from data generated in this at-risk population. This is, in part due to the fact that the population also presents with additional complications such as Traumatic Brain Injury (TBI) and additional psychiatric co-morbidities (including major depressive disorder and anxiety disorders). This has resulted in most studies of PTSD being conducted on non-veteran popula¬tions.

PTSD and AUD are known to have a compounding effect for an unfavorable treatment outcome in veterans [3-5]. In addition, these co-morbidities add a layer of complexity to the patient's treatment due to their combined effects on the brain chemistry of fear and memory [6]. In addition, as indicated above, the treatment guidelines for PTSD are not based on data from a veteran popula¬tion. This is a potentially important gap, since veterans may, for a variety of reasons, manifest different variants of PTSD than non-veterans, leading to different patterns of treatment effectiveness than for civilians [7].

Approach to the Literature

The focus for this review was on investigations published from 2000 onwards using articles published in English and available as free full text. Searches in Pub Med were conducted for research on PTSD treatment in veteran populations. This was followed by searches of treatment for PTSD plus AUD in veteran populations. Results seen in veterans were compared to those in non-veterans populations and used to assess current PTSD treatment guidelines. Additional searches included preclinical and clinical studies on extinction of fear responding and pharmacological and non-pharmacological methods of treating PTSD or its animal models.

Disease Prevalence and Need for Treatment

AUD prevalence in veterans

AUDs have been well documented in both general military populations and in veterans with diagnosed PTSD. In military vet¬erans, measured AUD prevalence is 15% for the previous year and 42% over the patient's life-time [8,9]. Data from 2009 show that of the 5.5 million veterans who received health services from the Veterans Administration (VA), 7.8% received a diagnosis of either an alcohol or drug disorder. In contrast, among veterans with a diagnosis of PTSD 22.8% had a diagnosis of comorbid substance abuse, nearly 3 times the rate in the general VA patient population [10]. This pattern highlights the need to understand AUD in order to treat a veteran sub-population effectively. AUD is associated with drug use disorders and, significantly, with suicide as well as a substantially elevated burden of psychiatric comorbidities, includ¬ing PTSD, general anxiety disorder and depression [10].

As with PTSD, the odds of developing AUD increase after deployment [11]. Also like PTSD, development of AUD strongly associates with the cumulative burden of trauma over the course of a lifetime. However, PTSD seems to occur in veterans whether or not they were in combat [12]. This is accounted for, in part, by comorbid trauma-related psychopathology in which previous traumatic brain injury and stressful situations may reduce a person's ability to cope with negative experiences [13,14]. As a legal psychotropic agent, alcohol is often used as a coping method for stressful situations and negative experiences [15-17], increasing the odds of developing AUD during or after combat exposure or military service [10].

PTSD prevalence in veterans

The number of combat veterans with PTSD can differ across reports, based on different definitions of the diagnosis, population sampling, and geography. Combat exposure, in particular, is a large factor that effects the development of PTSD. Between 10 and 13% of Gulf War [18] and Iraq or Afghanistan veteran [19] with combat exposure currently have PTSD. After deployment and combat exposure in Iraq and Afghanistan, surveys of the National Guard showed rates of PTSD at 25% [20], and similar surveys of the army and marines showed PTSD rates between 11-20% [21].

In 2016, Tsai [22] re-examined the prevalence of PTSD in veterans using various instruments. The authors showed that different scoring criteria resulted in from 62% to 84% of veterans scoring positive for PTSD via rating instrument versus 40% via by direct diagnosis. The authors suggested that the rating instruments might be valuable as a pre-screening tool, but that their results should be followed up by expert evaluation.

The effects of PTSD have often been considered to be short-term, but the detrimental effects of the condition can extend over the course of a patient's lifetime, ultimately leading to depression, anxiety, and substance use disorders [21]. Eleven percent of Vietnam veterans still reported impaired function due to PTSD symptoms, 40 years after returning from war [23]. These results are conso¬nant with those of civilian PTSD studies where, in spite of treat¬ment with pharmacological and psychological therapies,

74% of patients have symptoms lasting over 6 months, and up to 30% of patients continued to have active PTSD symptoms after 10 years of treatment [24].

Veterans with both PTSD and AUD

Analysis of veterans who have sought treatment for PTSD through VA programs, supports the finding of an increased risk of Substance Use Disorders (SUD) co-existing with PTSD. Follow-up on data collected during 2004-2006 on veterans with war zone exposure from Operation Iraqi Freedom/Operation Enduring Free¬dom (analyzed as one set of events), the first Persian Gulf War and Vietnam show diagnosis of alcohol abuse and dependence of 20%, 25%, and 29% in outpatients and 39%, 44% and 41% in in¬patients. Diagnoses of drug abuse/dependence of 6%, 13%, 13% in outpatients 20%, 34% and 25% in inpatients and were reported. While the most recently exposed veterans have lower rates of drug abuse, the comorbidity between PTSD and substance use disorders remains a hazard for our veterans. These results also demonstrate that there was a consistent rate of diagnosis of PTSD and diagnosis of alcohol or drug abuse / dependence across the wars, but that the percentages of these symptoms did not change with the passage of time [25]. This confirms earlier findings that over half of the veter¬ans from Vietnam with PTSD continued to show abuse of alcohol in 1996, 21 years after the war was officially over [26]. As re¬cent reviews have noted [6,7], each of these disorders has distinct effects on brain activity, requiring that both disorders be treated concomitantly [6]. AUD is the most common comorbid disorder with PTSD [2], with the severity of the PTSD increasing the odds of developing AUD [27].

The prevalence of AUD rises dramatically in the veteran population with PTSD. Department of Veterans Affairs (VA) data from 2009 show that of the 5.5 million veterans who received health services from the VA 8% had a diagnosis of a substance use disorder, but in the veterans with PTSD the number rose to 23% [8]. The comorbidity has been measured to be as high as one-third of individuals with life-time PTSD developing symptoms of alcohol disorders [28,29]. Also, fewer than 20% of veterans utilize VA healthcare services as their primary source of health-care [30]. Unfortunately, heavy use of alcohol is also as-sociated with more severe PTSD symptoms as well as an extended duration of the condition [4,5].

The patterns noted above also hold for civilian populations. Driessen and colleagues [3] examined the prevalence of posttrau¬matic stress disorder (PTSD) in a general population of individuals who sought treatment for Substance Use Disorder (SUD) in 14 German addiction treatment centers. The authors also examined the association between comorbid PTSD and the characteristics of the addiction. In this population of people seeking treatment for an addiction, 31% had PTSD and 41% of the people depen¬dent on both alcohol and other drugs had PTSD. The authors con¬cluded that PTSD is an independent risk factor for an unfavorable outcome in patients with SUD. The extent to which these results generalize to a population of veterans is unclear and determining if this is the case is one purpose of the present review. If it is the case that the results of Driessen and colleagues [3] do generalize, then it is imperative to look at possible commonalities in the ef¬fects of PTSD and AUD on brain function and how treatment of both disorders can best use this understanding. In addition, in patients with PTSD and comorbid substance abuse, the treatment of PTSD improves symptoms of substance abuse. But unfortunately, treatment directed toward sub¬stance abuse does not appear to ameliorate PTSD symptoms [31].

PTSD

PTSD Overview

It has been suggested that symptoms of PTSD are directly related to a deficit in the extinction of traumatic memories and in-creased generalization of that fearful state [32]. The development of PTSD is normally attributed to alterations of the stress response systems of which the Hypothalamic-Pituitary-Adrenal (HPA) axis is a part [33,5]. In veterans with PTSD, changes in tissue volume are seen in areas of the brain that are related to memory and emo¬tional integration such as the hippocampus [26,34] and amygdale [35]. There are also changes in the negative feedback processes that regulate the amygdala, such as reduction in activity from the Medial Prefrontal Cortex (mPFC), that regulate executive func¬tions-decision making [36,37].

PTSD is induced when fear memories combine with current perceived stress / danger in both veterans and civilian populations. Stress exposure can enhance the effect of learned fear memories. This allows the instigating situation to be less intense than the original, but still results in a strong, quickly formed fear response [38-40] Because of this, a history of stress exposure well before the PTSD-inducing experiences can predispose people to anxiety disorders, phobias, and PTSD [41,42].

Emotionally powerful memories are more likely to be re¬tained by a person since these systems have evolved to help main¬tain organism and species survival. This is due to effects of stress hormones on memory consolidation [43]. Stress hormones originate from the sympathetic nervous system (i.e., epinephrine and norepineph¬rine) and the hypothalamic pituitary adrenal (HPA) axis (i.e., glu¬cocorticoids) [44-47].

Normally, fear memories are consolidated and stored after a traumatic or highly stressful experience. One of the current theories is that patients with PTSD have “over-consolidated” that memory

and highly resistant to normal extinction processes [40,48,32]. Also, the memory has been encoded vigorously enough to be easily recalled in situations that bear only a small resemblance to the original event.

Preclinical Studies

A large amount of our understanding of PTSD developed via studies conducted on rodents. These designs have been based on the Pavlovian fear conditioning procedure in which animals exposed to an unconditioned stimulus (US, usually a mild foot shock) paired with a neutral conditioned stimulus (CS, such as a light or a sound) will develop a fear response to the CS. Because the neurological effect of rodent fear conditioning is well studied and reproducible, it is a popular model for a variety of conditions such as anxiety and fear related disorders [49,50], as well as the effects of particular drugs on learning mechanisms and stress responses [6].

In pre-clinical fear conditioning models, the fear conditioning itself does not generate PTSD. However, animals that given additional uncontrollable stress exposure, such as water deprivation or immobilization, expressed the heightened fear response and increased anxiety that is observed in humans with PTSD [38,51]. This generation of a PTSD-like state is normally attributed to either strengthened encoding [52] or consolidation of the fear memory [53]. Several variations of fear conditioning that contained ines¬capable, random, shock delivery, also generated the symptoms of PTSD [54,55]. Prior exposure to multiple shocks enhances speed of acquisition of subsequent fear conditioning that resists later extinction therapy [40].

Neurological Changes in PTSD

Among the best documented brain changes in veterans with PTSD are reduced volume in the amygdale [35] and the hippocampus [26]. As noted above, there is an abnormal reduction in the activity of the mPFC that is directly related to the heightened amygdala activity exhibited by both veterans and civilians with PTSD [36,37]. Changes in the neuroendocrinology of patients with PTSD are also well documented. Levels of each of the stress hormones appear effected long-term for veterans and civilians. For example, despite increased levels of hypothalamic Corticotrophin-Releasing Hormone (CRH) in the cerebrospinal fluid [56,26], pi¬tuitary adrenocorticotrophic hormone secretion and serum cortisol levels are reduced (when they would be expected to rise) [5]. In addition, civilian studies have shown that lower hair cortisol levels were associated with a greater length of time since trauma expo¬sure and with higher PTSD intrusion symptoms [57,58].

The sympathetic nervous system shows similar persistent ac¬tivation in these populations [59]. Norepinephrine concentrations are increased in the cerebrospinal fluid and serum [60,61]. Also, chronic PTSD patients exhibit greater 24-hour urinary epineph¬rine/norepinephrine excretion and higher nor epinephrine reactiv¬ity to psychological stress than controls than general population [62-65] The veteran population has confirmed evidence of abnor¬mal noradrenergic function in PTSD [64,66-69] and is expected to show similar laboratory values.

Amygdala and Ventromedial Prefrontal Cortex (vmPFC).

The amygdala processes reinforcement in aversive situa¬tions and stress-induced enhancement of fear [51]. The amygdala also plays a key role in the display of anxiety in responsiveness to stress [70], and in the stress-related enhancement of long-term fear memory.51 This brain region receives sensory input from multi¬ple brain regions and sends projections to several limbic system (Papez circuit) areas that mediate fear responses, such as the hip¬pocampus [71,72].

In ongoing PTSD, the amygdala is responsible for the gen¬eration of anxiety, and increased fear responsiveness; the hypo¬thalamus provides the autonomic responses; and the Ventrome¬dial Prefrontal Cortex (vmPFC) proves the negative feedback that should regulate the activity of the amygdale [1,73]. The vmPFC is generally underactive in PTSD, resulting in the continual over-expression of the fear response [51]. This response may be due either to the amygdala's overactivity or the underactivity of the vmPFC [1].

During fear training in stressed mice, serotonin activity in the dorsal raphe and the amygdala will produce stress enhance¬ment of fear memory. This is consonant with the role of acute in-creases in 5HT in inducing anxiety. Also, previous stress exposure increases amygdala sensitivity to serotonin by increasing the density of 5-HT2C receptors, allowing greater stress enhancement of fear memory without higher concentrations of serotonin [51]. It has been well documented, that impairment of the amygdala, as the primary neural region for fear conditioning, through lesion, pharmacological and neurophysiological studies will prevent the formation of fear memory [74-76,77].

Confirmed by data of the structural changes in stressed ani¬mals [78], neuroimaging studies have shown reduced amygdala volume in veterans with PTSD [35]. This is contrary to the increased neural activity of the amygdala in PTSD. It is speculat¬ed that the amygdala is undergoing remodeling in the dendritic morphology and the spine density of neurons in the basolateral amygdala that may contribute to the inhibitions of the extinction

mechanism that are seen in PTSD [79].

Cortical regions, particularly the various sections of the mPFC, act as modulators of the fear responses of the amygdale [73] and contribute to the response inhibition that occurs during extinction [80,81]. Abnormal reductions are shown in the medial prefrontal cortex activity of both veteran and general population patients with PTSD [36,37]. The mPFC normally inhibits the amygdala. With mPFC activity reduced impairments in the extinc¬tion of fear should occur, resulting in prolonged conditioned re¬sponding over time [82]. The symptoms of PTSD may be a result of the hyper-responding of the amygdala to fear stimuli, without the extinction mechanisms of the cortical regions that results in the miscalibrated circuit between the mPFC, the amygdala, and the HPA axis [83]. It is hypothesized that the suppression of the medial prefrontal cortex, resulting in increased generalization and a reduced extinction ability are the foundation of the behaviors associated with PTSD. This suggests that the enhanced acquisition and consolidation of fear memories due to the heightened activity of the amygdala are secondary effects in the development of PTSD [32]. As stated before, because of the connections between the mPFC and the amygdala, the hyper-aroused state may be from either the suppression of the medial prefrontal cortex, or the over activity of the amygdale [1].

The connections between the mPFC and the amygdala have mostly been described in primates but have recently also been observed in humans. The connectivity has been observed using newer techniques such as the Functional Magnetic Resonance Imaging (FMRI) combination with diffusion tensor imaging [84]. In healthy patients, increasing levels of anxiety corresponded to increased activity of the pathways between the vmPFC to the amygdala, resulting in the conclusion that persons with higher levels of anxiety would have well developed white matter tracts between amygdala and PFC [85].

Hippocampus

Both veteran and general population patients with PTSD show decreased hippocampal volumes [26,34]. The reduced hippocampal volume in PTSD can impair the normal HPA response as well as memory processes [86]. The hippocampal reduction is thought to be due to neurotoxicity via increased levels of cortisol during the time of the initial trauma or increased sensitivity [5] of the hippocampus's high concentration of glucocorticoid recep-tors [87]. Resolution of PTSD symptoms and treatment with paroxetine are associated with an increase in hippocampal volume [88]. The hippocampus is an important region for memory forma¬tion, modulation and learning, including fear conditioning [89]. It is also important for the termination of the stress response [87]. While the amygdala is more responsible for emotional memories, the hippocampus is more important for contextual learning and trace fear conditioning [71,90,91]. If the amygdala is damaged or suppressed a patient will remember the US (e.g. mild shock, or unpleasant sound) paired with a neutral conditioned stimulus but not remember the fear [92]. However, if the hippocampus is damaged or suppressed, a patient will recall the fear but not what happened, the unconditioned stimulus [93]. The hippocampus is also involved as a suppressive factor to the stress response of the HPA [89]. Lesions of the hippocampus increase CRH in the brain [87]. This increase in CRH is seen in veteran PTSD populations [56,26] and is a mechanism that is known to increase the effect of the amygdala on memory consolidation, adding an additional pathway of the hippocampal dysfunction to the symptoms of PTSD [1,94].

Hypothalamic-Pituitary-Adrenal Axis (HPA)

The HPA axis is activated by stress, involving activation from the amygdala, resulting in an increase of the release of cortisol (corticesterone in rodents) and other glucocorticoids from the adrenal gland [5]. The increase in cortisol garners the fight or flight response, and eventually inhibits the HPA axis in the self-regulating termination of the stress response [95]. However chronic or extreme stress can cause HPA axis dysregula¬tion. This type of dysregulation is seen in PTSD with low cortisol levels and an enhanced cortisol suppression response in dexam¬ethasone challenge testing [95]. In addition to glucocorticoids, the HPA releases epinephrine/norepinephrine but with a faster peak onset [96].

As mentioned above, HPA axis stress activation results in the release of glucocorticoids. These, in addition to a variety of responses in the body to adapt to confrontation and challenge [96], also act as negative feedback to the acute stress response of the sympathetic nervous system [97] and have an effect on stress relat¬ed memory. Glucocorticoid effects on memory appear to be time dependent. During stress exposure glucocorticoids act in the baso¬lateral amygdala. They appear to allow epinephrine and nor epi¬nephrine to enhance memory of the stress inducing situation [98] After an hour or more, the function of the glucocorticoids changes to suppress new information while shutting down the acute stress responses [99].

The information encountered during the stressor is given pri¬ority in two ways. First, the information encountered during the event is promoted for consolidation and later retrieval. Second, by reducing competing information from the stressor, the formation of memories is enhanced [59]. If the levels of cortisol are already altered before the stressor, the result may be "over-consolidation" and impaired memory retrieval [59]. This explains the studies identifying low cortisol in the face of trauma as a predisposing factor for the development of PTSD [100]. The primary hypothesis is

that the reduced cortisol signaling would impede the cortisol levels necessary to extinguish the HPA axis generated stress response that would result in the mounting fear response characteristic of PTSD. This appears plausible based on corticosterone treatment after stress being able to rescue PTSD like behavioral effects in animal models [101].

Patients with PTSD have increased levels of CRH in the cerebrospinal fluid. This is often released from the hypothalamus during the stress response [102]. However, unlike the normal stress, processing in the presence of CRH, patients with PTSD retain reduced levels of serum cortisol and adrenocorticotropic hormone from the pituitary [5]. The reduction of cortisol levels in patients has been correlated with a greater length of time since the trauma, and higher PTSD intrusion symptoms [58]. In addition as mentioned above, the response suppression to both CRH and cortisol are strongly enhanced in patients with PTSD during a dexamethasone suppression test. Patients also exhibit an elevated sensitivity to glucocorticoids in lymphocytes [53]. The elevated levels of CRH may bias the sensitivity to the negative feedback of cortisol at the pituitary [5]. Also due to the effect of CRH on the basolateral complex of the amygdala, the elevated levels of CRH enhance the influence of the amygdala on mem¬ory consolidation, which may be one pathway to the development of the condition [94].

Sympathetic Nervous System

In response to stress, the sympathetic nervous system rapidly releases epinephrine and norepinephrine. Through second messen¬gers in the basolateral amygdala, the Noradrenergic/Norepineph¬rine (NE) system is a largely implicated in memory consolidation during stress [103]. Epinephrine and norepinephrine are influential in the consolidation and retention of memories during emotional events [59]. Noradrenergic signaling is also critical for the later reconsolidation of fear learning [104]. Abnormal noradrenergic function in PTSD has been found in both general and veteran pa¬tients [5]. As mentioned earlier, veteran and general population PTSD patients show heightened levels of norepinephrine in the cerebrospinal fluid and in serum than civilian controls [60,105]. This is similar to what has been observed for civilians with greater 24-hour urinary excretion of epinephrine/norepinephrine metabo¬lites [5].

In PTSD, abnormal noradrenergic function is theorized to contribute to the deficits in fear acquisition and extinction, and to symptoms of hyper-arousal [106]. Patients with PTSD also exhibit an enhanced norepinephrine response to stress relative to controls [65]. This has led to the theory that the sympathetic nervous sys¬tem is consistently overactive in patients with PTSD [59], which correlates well with the extended low cortisol levels in PTSD pa¬tients. Like CRH, norepinephrine trig¬gers consolidation of fear memory [107]. Noradrenergic blockade by propranolol injection into the lateral nucleus of the amygdala in rats, blocks reconsolidation of fear memory [104,108]. This manipulation was also shown to work with systemic dosing in humans by blocking reconsolidation of cue and context fear conditioning if given within a matter of hours after the trauma [104,108].There are several drug treatment methods that rely on immediate treatment after trauma to block the development of PTSD. Treatment strategies include administering β-adrenergic receptor antagonists following retrieval of fear memories to block the reconsolidation of the fear memory, as secondary prevention with administration directly after the traumatic event. While β-antagonists appear to have potential, α2-agonists such as clonidine, also show promise. In contrast, the β-agonist isoproterenol and the α2-antagonist yohimbine show the reverse effect, enhancing reconsolidation of the fear memory and blocking extinction [104,108,109-111].

Alcohol Use Disorder (AUD) AUD

AUD Overview

AUD has been characterized as a chronic relapsing brain disorder as with many other SUDs [112]. A pattern of both posi¬tive and negative affective states is associated with substance use – early stages and the rising of the brain levels of the drug tend to be associated in at-risk persons with pleasure. In contrast, in later stages of the disorder and falling brain drug levels tend to be associated with negative effect. Elsewhere, we have discussed these ideas in greater detail as reflecting want and need for the drug [113,114]. These changes are thought to be due to adaptations in the brain that constitute the addictive process [115-117].

Animal Model

Exposure to alcohol-associated environments or triggers can cause relapse in abstinent alcoholics [118,119]. This mechanism is often modeled in rats strains bred for high alcohol intake us¬ing a training period of alcohol self-administration, followed by extinction training. Various models [120] have been used to test reinstatement and extinction patterns and to study the addiction process [121,122].

Neurological Changes in AUD

Effect of Acute Alcohol Abuse and the Self Treatment of PTSD Symptoms.

One of the factors that may lead to comorbid AUD for patients with PTSD is the attempt to self-medicate PTSD symptoms with alcohol. The acute effect of alcohol on the anterior cingulate cortex may, in part, be responsible for the perpetuation of the alcohol use in these patients. Images or triggers of alcohol activate

several regions of the "emotional" brain including the anterior cingulate cortex and the mPFC [123,124]. The taste of alcohol in heavy drinkers also activates the mPFC [125]. PTSD patients have a hypo-activity in the anterior cingulate cortex [126] and in the mPFC [36,37], with a correspondingly hyperactive amygdala. This change in pattern of brain activity appears to leave leaving PTSD patients with a higher susceptibility for continued AUD.

Effect of Chronic Alcohol Abuse

After alcohol use becomes chronic, individuals exhibit corti¬cal shrinkage [127] and white matter changes [128,129] that are most pronounced in the PFC and orbitofrontal regions of the brain. The abnormal prefrontal activity suppresses executive function and has been associated with the decreased ability to monitor and resolve conflict [130]. Chronic AUD also leads to a reduced activity of the rostral anterior cingulate cortex that has been linked to inappropriate evaluation of negative emotions displayed by other people [131]. Animal and human neuroimaging studies have also shown changes in several neural circuits within the limbic system due to AUD that provide glutamine and dopamine input to other emotion-associated brain structures [125]. These include the ventral striatum - involved in cue-induced drug seeking [132], striatal-palladic-thalamic loop–associated with automaticity of behavior [133], and prefrontal cortices that are directly involved in atten¬tional selection / executive control [134].

The connection between the posterior cingulate cortex, cuneus, and mPFC is referred to as the default mode network [135]. During rest, this network is highly connected, but is decoupled during task performance, which is thought to increase processing efficiency [136]. The connectivity of this network is reduced in alcoholics, but appears to undergo a functional restoration after prolonged periods of alcohol abstinence [137]. The white matter connecting subcortical and cortical portions of the limbic system is also altered in AUD [138,139]. Together, the changes lead to a reduced ability to override learned behavior such as inhibiting strongly incorporated habits and reactive behaviors such as drink¬ing. It appears that the neural changes prevent the patient from overcoming old habits, because of the inability to deactivate the posterior cingulate cortex. These individuals also show a reduced ability to learn some new behaviors [140].

In normal individuals, the posterior cingulate cortex and midbrain are inactive during repetitive or automatic tasks, and ac¬tive during tasks that required flexibility or modification of previ¬ous routines. In alcoholics, the brain activity patterns are reversed [140]. Because the midbrain regions are involved in rewards [133,141], sensorimotor integration [142], and motor based learn¬ing [143], the reduced down regulation of midbrain activity during repetitive tasks is consistent with the reduced ability to learn new repetitive behaviors [125].

AUD also alters executive control and repetition learning through decreased input from the posterior and middle cingulate cortices. The middle cingulate cortex is associated with response selection and decision-making [144]. The middle cingulate is more active during difficult tasks in chronic alcoholics. This is thought to be because of the deterioration in the activation of the posterior portion of the system [125]. There is also an increased connectivity between the striatal regions and the middle cingulate cortex.

Increased activity of the mid plus dorsal anterior cingulate cortices at rest is considered a risk factor for the development of PTSD [126]. Furthermore, smaller brain volumes in the mesocortical limbic system have been linked to relapse in patients with AUDs. As already noted, the limbic system is involved in impulse control, emotional regulation, and craving as a part of providing the links between the current situation and memory and the energy / motivation to carry out behaviors than enhance organismic and species survival [145]. Unfortunately the reduced activity of the mPFC in PTSD may enhance alcoholic relapse. AUD suppresses the cognitive control mechanisms typically invoked to process high conflict and error learning paradigms [146]. This would be expected to complicate the already altered decision making pro¬cesses and baseline anxiety levels of a patient with PTSD.

Effect on reward pathways

There is consensus that dopaminergic transmission in the midbrain and ventral striatum occurs in response to the drug trigger in a person with AUD [1,13,114]. This follows from the concept of "incentive salience" or the role of dopamine in determining which stimuli in the environment are significant to the organism [113,114,147]. Drug exposure elicits a "want" response in the individual [140, 148-150]. The dopaminergic connection between the Ventral Tegmental Area (VTA) and the limbic system, including the nucleus accumbens, and the frontal and prefrontal cortices, is known as the "pleasure pathway" of the brain [113,151]. In AUD, images of alcoholic drinks activate brain regions of the brain associated with "want" (including the anterior cingulate cortex, mPFC, insula and ventral striatum) [123,124,152,153]. Overall, data suggest an important role for limbic system dopamine and the rostral anterior cingulate cortex as well as dopamine receptor concentrations and reactivity in the reward and trigger- processing of drug addiction [140].

Treatment

Review of Ethanol Use Disorder Treatments

The treatment of AUDs, after the acute intoxication is past, is focused on reducing the cravings for the drug. Current theo-

ries indicate that returning the activity of limbic system pathways to-wards normal will reduce drug cravings [113,114]. Three targets that have shown response in reducing alcohol cravings are opi¬ate receptors and voltage gated sodium and calcium channels. By blocking opioid receptors, further development of the addictive process may be halted and the patient's neural firing in the VTA pathways can begin to be normalized [114]. Patient adherence to opioid antagonist therapy (naltrexone or nalmefene) can be an issue since opioid antagonists block en¬dogenous opioids and can induce a hyperalgesic conditions in which normal sensory stimuli can become uncomfortable [154]. Naltrexone (a competitive antagonist at mu and kappa opioid receptors) was one of several agents shown to reduce alcohol cravings and normalize some of biological markers in the treatment of AUDs [114]. There also has been evidence of reduced ethanol cravings from medications that block voltage-gated sodium and calcium channels, including lamotragine, gabapentin and topiramate [155,114]. The major drugs with addictive potential also act on the extended amygdala and the HPA axis, leading to changes in limbic system CRH [44]. Patients with PTSD already have elevations in CRH [56,156] and increased amygdala activity. Thus, such medications might have multiple benefits for patients with PTSD. It is possible that more links between the treatment of PTSD and substance use disorders will be found as the understanding of the brain stress systems develops.

Non pharmacological Treatment of PTSD

Non-drug treatment overview

Currently, the first-line treatment for PTSD is behavioral therapy in one of several forms. Pharmacological treatment is seen as second-line. The US Department of Defense and VA prac¬tice protocols [157], as well as all other major clinical guidelines [158,159] including those of Austria [157] and Australia [160] cite psychotherapy as the predominant treatment approach for PTSD. In particular, Eye Movement Desensitization Reprocess¬ing (EMDR), Cognitive Processing Therapy (CPT), and Prolonged Exposure Therapy (PET) are the most used forms of therapy for these patients [157,158,160,161]. As of 2015, 98% of VA centers in the US offered both CPT and PETs [162-164]. EMDR is not as easily available, but as evi¬dence in veteran populations increase, it is expected to be utilized more widely because of results in civilian studies [162].

Trauma- vs Non-trauma-focused therapy

The behavioral therapies for PTSD are classified into two main types, trauma-focused and non-trauma-focused. Non-trau¬ma focused therapies include supportive therapy, psychodynamic therapy, hypnotherapy and stress management [165]. These thera¬pies focus on current situations, stress and recent reactions as well as personal interactions and future goals [162]. Supportive therapy often relies on active listening and emotional support and encour¬agement. Psychodynamic therapy places more of an emphasis of analyzing unconscious mental processing or confronting and dis¬cussing the underlying sources of a patients actions. Hypnothera¬py, also deals with the subconscious, focuses on inducing a relaxed state in the patient that would be more open to attitude changes. With the exception of stress management therapy, non-trauma based therapies have not shown to reduce the symptoms of PTSD in either civilians or veterans to a significant extent [160,161,166]. Stress management (also called stress inoculation training), is often recommended as an adjunct to trauma-based therapies. This ther¬apy teaches the patient anxiety management skills. This includes, but is not limited to, breathing exercises and methods of positive thinking to help control negative thought patterns [162,167].

Trauma-based therapies

These include CPT a specific form of Cognitive Behavior Therapy (CBT), Prolonged Exposure Therapy (PET), and Eye Movement Desensitization Reprocessing (EMDR). Each will be discussed in turn.

Cognitive processing therapy

CPT induces the patient to reprocess the traumatic event(s) through writing, and subsequently speaking about the details of the event. The therapist also questions the patient about the event. Thus, this method is analogous to the reprogramming of memory during a reprocessing window that has been effective in preclin¬ical and clinical studies in addicted populations [168]. CPT has shown positive outcomes in veterans [158,169-171]. CPT includes aspects of the more general CBT [158,169-174]. In CBT, the patient works to identify problem behaviors and develops coping strategies and emotional regulation to reduce the problematic behavior [175,176]. Formal CBT has also shown to be effective in veterans [158,169-171,177,178]. Unlike CPT, CBT does not focus on exposure or re-experiencing the traumatic event.

Prolonged Exposure Therapy

PET, (also termed flooding) is similar to the above in that the patient repeatedly recounts, men¬tally re-experiences, and is encouraged to process the trauma from different perspectives using cues from the therapist. The patient also repeatedly engages with their fear triggers [179].

Eye Movement Desensitization Reprocessing (EMDR)

EMDR is an extension of PET in which the patient is exposed to the traumatic memories coincident with a small distrac¬tion. In

the original version of EMDR, the distraction consisted of hand movements of the therapist to direct movements of the pa¬tient's eyes. More recent versions of EMDR include other types of distractions such as hand-tapping or audio cues [162,180]. Results with EMDR have been obtained from a few studies showing large symptom reduction in veterans [181], including results maintained at 9-month follow-up and 78% of completers no longer meeting criteria for PTSD [182,183-185]. Much of the evidence supporting EMDR is still from studies in civilians [186].

Therapeutic Commonalities

Each of the PTSD treatments discussed above focuses on the idea that learning to reprocess the old emotional memory will allow the patient to develop less dramatically fearful responses to triggers of that memory and help the patient to extinguish their original responses to the memory through re-experiencing the trauma in a safe setting. Trauma based treatments focus on extinction of the original emotional, fearful response. This neurological response will be discussed in greater detail later, as it is also a target for adjunctive pharmacotherapy.

This is expected to be more difficult in the veteran PTSD population than in the general population, in part because a veteran is highly unlikely to have had only one traumatic experience [187-190]. Single versus multiple traumatic exposures may help explain the finding that outcomes for PTSD treatment in civilians tend to be more positive than in the veteran population [191].Veterans and refugees are exposed to chronic and complex trauma, unlike the majority of the general population who are treated for PTSD. This may help explain the higher effectiveness of trauma-based versus non- trauma based therapies in veterans versus the general population [192].

Since the traumatic memories are brought to consciousness in the patient many times during the therapy, such sessions are emotionally demanding and unpleasant, and are intentionally de¬signed to increase the patient's level of anxiety [160]. Also, each session requires from 30-90 minutes and 12 sessions are typically expected for these types of therapy to have an effect [162,193]. The number of required sessions is still a matter of debate, with numbers ranging from 9 to 12 [160, 165, 191]. As mentioned earlier, reducing the required time in sessions is considered an impor¬tant step in increasing patient compliance and reducing drop-out rate in treatment. Options have included a more intense 2-week process [191], decreasing the trauma sessions to 30 min, and adding medications.

Behavioral therapy in veterans

As mentioned above, most studies on PTSD treatment are done in the general population, and this may have led to some disparities in the literature due to differences in gender, types of trauma, and length of time before the initial trauma was treated. Steenkamp and associates [160] conducted a meta-analysis on the current data available from randomized, intent to treat, trials for psychotherapy for military-related PTSD. While only 36 of the available 891 publications qualified for the study, the authors' main conclusion was that trauma-focused therapy, specifically CPT and PET both yielded clinically meaningful improvements, even with high dropout rates. The authors indicated two study weaknesses: up to three quarters of the patients in behavior therapy studies were also on uncategorized psychotropic medications and many studies have been quoted as using "treatment-as-usual" as a control group without further information.158 This meta-analysis defined clinically meaningful symptom improvement as a 10 -12 point re¬duction in PTSD symptoms, as reported by either the patient or the interviewer with either the PTSD Checklist or the Clinician Administered PTSD Scales. However, mean post treatment scores for both types of treatment remained at or above the diagnostic cutoff for PTSD. Thus, 60-72% of the enrolled patients retained their PTSD status at the end of the studies. It should be noted that the two trauma-focused psychotherapy approaches still performed better than non-trauma-based protocols. Overall, CPT has shown large effect sizes when compared with both non-treatment and treatment as usual patients [160]. There is an ongoing multisite trial directly comparing cognitive processing therapy and prolonged exposure in 900 male and female veterans that should yield helpful results [194].

Extinction Training

Extinction is normally associated with the removal or degradation of a consolidated memory response. The response can be a positive response to the stimulus such as reducing craving by taking a drug; it can also be a negative response such as a fear response to a stimulus. Extinction is considered an active learning process where the brain incorporates new information to memories and experiences from the past that have been learned. It thus represents an active inhibition of previously learned emotional and physical responses. Although both AUD and PTSD have shown promise in terms of responses to extinction training in laboratory settings, the treatment of PTSD patients has shown greater prog¬ress in applications in non-laboratory settings. While areas of in¬terest include SUD, anxiety disorders and PTSD [195] the majority of extant extinction research focused on the extinction of aversive memories [196,114]. The goal of extinction therapy in PTSD treatment is to allow the patient to have a new neutral response to a stimulus previously associated with intense fear. In SUD (including AUD) treatment, extinction training focuses on reducing the cravings instigated by objects or situations that the patient associates with alcohol or drinking. The extinction training

for both PTSD and AUD is intended to reduce the consolidated responses of fear or alcohol craving to the stimuli that would normally instigate the condition dependent response in the patient.

Drawbacks of Extinction

One of the primary concerns about extinction therapy is the change from a treatment setting to normal life [195,197]. The treatment is time consuming, and not normally considered pleasant for the patient, and a portion of patients will not respond to treat¬ment, relapse or drop out of treatment [198,199]. Because of this and the possibility of improving the efficiency of the extinction process, pharmaceutical augmentation continues to be an area of strong interest [200].

Extinction in PTSD

Extinction methods have shown to be effective in PTSD therapy and show increasing potential with adjunct pharmaceutical treatment; the extinction mechanism is part of each style of trauma-focused psychotherapy. PTSD is thought to be a result of fear memories that are resistant to extinction. The current theory is that individuals with PTSD have a fear inducing memory that is resistant to extinction or modification via new experiences, due in part to the state of hyper-arousal that a mortally dangerous situ¬ation can cause. It has also been theorized that substance craving triggers are also resistant to extinction because their effect on do¬paminergic pathways is more intense than that of natural reward [196].

As stated above, exposure procedures are a first-line treatment for PTSD [201,202]. Continued exposure of the patients to the fear triggers in a safe environment has shown relative efficacy in the extinction of the fear response in PTSD [186] and anxiety [202,203]. Unlike extinction techniques in substance use disorders which focus on the stimulus-reward pathway, extinction tech¬niques in PTSD also involve fear acquisition. Because of the emo¬tional component in neurological processing of the fear response, extinction therapy for PTSD is thought to focus in the amygdala, the HPA axis and the PFC. This gives additional targets for phar¬maceutical modification [204,205] with promising clinical trials [206]. Adjunctive pharmaceutical treatment is being perused to increase the likelihood that the memories of safety will dominate over the original emotional response of fear [197].

Neurochemical Changes In PTSD and Pharmacotheapy

Serotonin

Affective disorders, including PTSD, are linked to dys¬regulation of serotonergic systems. Serotonin is one of the car¬dinal mediators involved in the amygdala's ability to consolidate fear memories and regulate anxiety and emotions such as anger [207]. Studies of civilians with PTSD show patterns of decreased amygdala Serotonin Transporter Protein (SERT) binding [208]. Above, we noted a loss of amygdala volume. Together such chang¬es may contribute to the loss of extinction and to a hyper-excitable state. The result is less control over anger and other emotions. The amygdala's enhanced consolidation of fear memory in people with PTSD is mediated by serotonin, primarily through serotonin-2 re¬ceptors. As indicated above, the enhanced consolidation is selec¬tively enabled by a prior history of inescapable stress exposure [51]. Both animal and human studies of control subjects show an increase in fear memory acquisition and expression after Selective Serotonin Reuptake Inhibitor (SSRI) treatment [209-211]. The re¬duced expression of the SERT leads to serotonin remaining in the synaptic cleft for a longer period and greater stimulation of sero¬tonin receptors and a net increase in serotonin activity. Excess sero¬tonin activity is linked to altered threat processing, with increased amygdala reactivity to phasic aversive stimuli [212]. Essentially, excess serotonin during the time of fear conditioning increased the fear response generated by the experimental protocol. Administra¬tion of a serotonin 2A receptor agonist (that mimics endogenous serotonin) after fear conditioning increases the expression of the fear, and concordant with the expected pattern; administration of a serotonin 2A receptor antagonist blocks acquisition of the fear memory [213]. These results support a therapeutic opportunity to modulate fear processing using serotonin-2 receptor antagonists. In basolateral amygdala neurons there is a high concentration of serotonin-2 receptors; these are thought to help to regulate anxiety [214]. Similar to the serotonin 2A receptor responses to agonists and antagonists, increased expression of the receptors (through gene modification therapy in animals) increases sensitivity to sero¬tonin induced anxiety levels [215], and pharmacologic blockade of the serotonin-2C receptor prevents stress induced anxiety [216].

The amygdala, hippocampus, and frontal cortex receive serotonergic input via projections form the dorsal and median raphe nucleus [217-219]. During rodent aversive learning, serotonin is released in the dorsal raphe nucleus projection regions [220-222], where it remains elevated in the downstream target of the baso¬lateral amygdala for an hour or more after training is complete [223,224]. Rodent studies have shown that repeated stress expo¬sure increases the intensity of fear learning [38] that is induced due to the serotonergic processes involved in the consolidation of fear training. Fear learning requires serotonin activity in the

dorsal raphe nucleus during fear conditioning as well as serotonin activ¬ity at the serotonin-2 receptor of the basolateral amygdala after the fear conditioning is complete [217,225-228]. Stress enhances the expression of serotonin-2 receptors in the amygdala, but does not alter the serotonin levels present during fear conditioning. This allows serotonin stimulation in the dornal raphe nuclei that is not present in unstressed animals and may alter processing of fear con¬ditioning in a stressed animal. Also, inhibition of the serotonergic dorsal raphe during fear conditioning prevents the stress induced enhancement of the fear training [51]. Consistent with these re-sults, administration of a serotonin-2C antagonist agomelatine seems to reduce the consolidation or reconsolidation of traumatic memories; this agent has had beneficial effects in PTSD [229].

Role of Serotonin in Extinction Therapy

Fear-learning and extinction are fundamentally controlled via the amygdala, interacting with the hippocampus and the mPFC [80,230,231]. Serotonin is expected to play a pivotal part in fear acquisition, expression and extinction, since (as noted above) acute administration of a serotonin-2A receptor agonist can change the development and processing of fear. If the serotonin 2A agonist is administered after fear conditioning, it increases the expression of the conditioned fear [232]. If the serotonin 2A antagonist is admin¬istered before fear conditioning, the fear development is blocked [213]. If the serotonin 2A agonist is administered before extinction, extinction is enhanced [232]. However, chronic SSRI use impairs fear learning, and interferes with the extinction of fear memories [233]. It is well documented that SSRIs increased cued fear acqui¬sition and expression in rodents and human patients [209-211].

It is thought that the serotonin decreases the activity of the amygdala during the extinction process and during initial fear con¬ditioning by down-regulating the NR2B subunit of the N-Methyl-D-Aspartate (NMDA) receptors in the lateral and basal nuclei of the amygdala through a change in glutamate transmission. Fear learning during both initial fear conditioning and extinction de¬pends on the activation of these receptors [233,234]. SSRI's are a first line pharmacological treatment for PTSD. Thus, the effects of such medications on extinction treatments is of direct clinical importance, since it may explain the lack of clinical effectiveness in SSRI treatment with psychological fear extinguishing [233].

Glucocorticoids

As mentioned above, the HPA releases cortisol (a glucocorticoid) as a response to stress. Patients and rodent models of PTSD show that dysregula¬tion of cortisol during or after chronic or extreme stress is linked to symptoms of PTSD, with reduction of symptoms of veterans with PTSD reduced by treating with a combination of hydrocortisone and traumatic memory reactivation therapy [235]. Glucocorticoid modulation enhances extinction, since extinction therapy using a combination of such medications with behavioral therapy has been shown effective in non-PTSD disorders [236,237]. Glucocor¬ticoid modulation in the forms of hydrocortisone combined with prolonged exposure therapy has resulted in greater patient reten¬tion during fear extinction therapy sessions [238]. In preclinical studies, glucocorticoids are also linked to modulation of memory consolidation [106, 237,239].

Opioids

Opioids are involved in the regulation of conditioned fear extinction. Opioid signaling in the ventro-laterial periaqueductal gray matter is thought to be responsible for the activation of the mPFC and the baso-lateral nucleus of the amygdale [240,241]. Opioid antagonists increase conditioned fear [32]. In rodent studies, opioid antagonists either prevent fear extinction or enhance fear acquisition [242-244]. In rodent studies, mu opioid receptor antagonism increases contextual fear conditioning [245,246] and prevents the extinction of previous trained fear responses [247]. This represents a problem for individuals suffering from both PTSD and AUD. This is because mu opioid receptor antagonists (naltrexone and nalmefene) are considered first-line for the treatment of AUD and opioid use disorders.

Kappa opioid receptor antagonism decreases conditioned fear, in both the baso-lateral and the central nuclei of the amygda¬la. If the antagonism is only in the central nuclei, there is a gener¬alized anxiolytic effect. Fear conditioning increases the density of kappa opioid receptors in the baso-lateral amygdala while reduc-ing them in the corpus striatum (of the basal ganglia) [245,246]. In humans, lower kappa opioid receptor expression is associated with greater symptoms following trauma [248]. Opioid agonists, such as morphine have been shown to block conditioned fear ac-quisition in both rodent and human testing in normal fear train-ing and post-stress fear training [249,250]. This model is being investigated for secondary preventative treatment after trauma to prevent PTSD [32]. In rodents, nociceptin/orphanin FQ receptors (also known as the kappa-type 3 opioid receptor), activation ap¬pears to block contextual and cued fear consolidation in controls and model-PTSD subjects.

Post retrieval Extinction

The normal pattern of extinction training appears more ef¬fective if the patient or subject receives a memory cue before the extinction therapy (post-retrieval extinction) [195]. This appears to be because activation of the PFC allows more effective extinction of the fear mechanism than during the normal extinc-

tion training when the PFC is not activated [251]. In rodents the memory cue is a reminder foot shock paired with the conditioned stimulus 10 minutes before the extinction training takes place. This is thought to reactivate the original memory and to expose the subject to the extinction training during the reconsolidation window. This window is speculated to close within 6 hours of the memory retrieval, but during that period the original memory is thought to be altered (instead of layering on new conflicting memories) [251-253]. The reconsolidation system seems to be a method for the brain to update an old memory or response to be consistent with current contexts [254,255]. This effect on fear extinction was reduced when rodents were housed in groups as opposed to the dramatic effects when the animals were housed separately [195]. This may be due to increased stress on the animals effecting the extinction learning of fear responses [256-258] In humans, the effect of post-retrieval extinction therapy has been classified as moderate in preventing the return of fear [195]. Mirroring the effectiveness in animal models, convincing suppression of heroin use for 180 days in humans has been shown [259,195]. The effect of post-retrieval extinction vs. standard extinction therapy for fear is also time dependent. Studies that tested return of fear after a long delay after training (6-30 days) showed large and significant effects. Studies that tested the return of fear after a shorter delay (1-3 days) only showed small and non-significant effects. This pattern was not seen in extinction of appetitive studies. This is an area that requires more research [195].

Pharmacological effects

One of the effective treatments in fear [252] and appetitive memory training in animals is the use of protein-synthesis inhibi-tors or receptor blockers, to interfere with the original memory. For example, the administration of a beta-adrenergic or NMDA receptor antagonist during the reconsolidation window can block the return of the fear or the craving [252]. Thus far, the pharmaco¬logic blockade approach has a moderate effect size in reducing ap¬petitive responses in animals [260] and fear responses in humans [261,195]. Extinction in both PTSD and drug-seeking for ethanol [262], and nicotine (smoking) [262-264] was facilitated with the administration of d-cycloserine (a partial agonist at NMDA receptors, producing some of the effects of glutamate) after extinction training. Propranolol (beta-adrenergic blocker) has been used in post-retrieval sessions to lower sympathetic nervous system reactivity to mental imagery of the trauma a week after treatment [265]. This was replicated in PTSD patients and yielded a reduction of PTSD symptoms over time [266]. These approaches appear promising, as post-retrieval extinction strategies become more common in clinical practice.

Pharmacological Treatment Of Veteran PTSD Patients

Pharmacological treatment of PTSD

Guidelines agree that pharmacotherapy should occur in conjunction with behavior therapy. However, most medication regimens have inadequate evidence for treating PTSD even in the general population [267]. As stated above, most guidelines are established in civilians; also, these studies utilize a greater proportion of females than occurs with veterans. Female veterans need to be treated for PTSD just as much as their male counterparts. However, gender differences in response may dictate additional studies to insure that both male and female veterans receive optimal therapies.

Serotonin Reuptake Inhibitors

Based on the discussion above that serotonergic dysfunction underlie many PTSD symptoms, both first -line treatments for PTSD include Selective Serotonin Reuptake Inhibitors (SSRIs) or Selective Norepinephrine Serotonin Reuptake Inhibitors (SNRI). The most commonly cited SSRIs are fluoxetine, paroxetine or sertraline, or the SNRI venlafaxine XR [159-161,165]. Veteran PTSD has had positive results using paroxetine (SSRI) [268] and flu¬voxamine (SSRI) [269,270] in open trials. Additional medication classes such as Tricyclic Antidepressants (TCA) and Monoamine Oxidase (MAO) inhibitors are normally either not encouraged or not considered until SSRI's or SNRI's have been attempted because of the greater risk for side effects with these agents [160]. In veterans, this approach has been questioned [271]. There is a lower proportion of female veterans with PTSD [9]. Also, most veterans are exposed to a multiple traumatic experiences over an extended time period often in conjunction with traumatic brain injury. Finally, we noted above that SSRI's may interfere with the extinction process, although this remains a topic of some controversy. We note that newer drug treatments for PTSD are often compared against an SSRI because it is often considered a standard of care, or because an SSRI is allowed during evaluations of behavioral therapy.

According to the VA DoD Clinical Practice Guidelines, af¬ter an adequate trial of SSRI/SNRI, agents with different mechanisms of action (such as the G-protein coupled receptor blocker mirtazepine) should be considered [272,165] and this agent has shown with good responses in civilians [273]. Also, mirtazepine has shown high response rates in the treatment of veteran PTSD in two open trials [274,275] and a randomized, open label trail in the military population compared with sertraline (SSRI) [274].

Tricyclic antidepressants

TCAs are effective in treat¬ing major depressive disorder

but considered to be third-line agents because of a host of significant side effects. Two TCAs, imipramine [276,277] and amitriptyline [278], are considered 3rd line treatments [159] with good responses in civilians with PTSD. The effectiveness of TCAs in the treatment of PTSD is thought to be related to their reuptake inhibition of norepinephrine rather than the lesser reuptake inhibition of serotonin. Desipramine (TCA), an additional 3rd line agent in the treatment of civilian PTSD, was more effective than paroxetine (SSRI) in a double blind study in veterans with PTSD plus comorbid AUD [268].

Antipsychotics

The so-called atypical antipsychotics (that either block sero¬tonin-2A plus dopamine receptors or act as partial dopamine and serotonin agonists) olanzapine, risperidone, quetiapine, ziprasidone and aripiprazole have used as monotherapy to reduce PTSD symptoms [279]. In treatment algorithms for PTSD these agents are currently considered to be 3rd line agents. Their effectiveness in PTSD appears to be due to their ability to restore the balance in dopamine modulation of the limbic system (including mPFC and amygdala) [159]. This is the same mechanism and neural substrate upon which these agents act in persons with schizophrenia. In the general population, a meta-analysis of antipsychotics showed a reduction of PTSD re-experiencing and intrusion symptoms [280]. However, the extrapyramidal side effects of weight gain, dyslipidemia and elevated blood glucose that may be present with the atypical antipsychotics suggest that metabolic monitoring should be considered during the course of treatment [160]. Aripiprazole and ziprasidone are considered less likely to be induce extrapy-ramidal side effects. Quetiapine has also been used as a treatment for PTSD associated insomnia [159], and is often preferred by clinicians vs. olanzapine and risperidone [193] due to it's reduced likelihood of causing extrapyramidal or metabolic side effects [160]. Consultation with a specialist is normally advised, especially because this is recommended after several other therapy regimens have failed [193].

In the veteran population, quetiapine was shown by some studies to be effective as monotherapy in comparison to SSRIs [281,282]. As adjunctive therapy to SSRI treatment, risperidone failed to show improvements in PTSD symptoms in a large six-month randomized controlled trial of 250 veterans with SSRI-resistant PTSD symptoms [283]. This result is not consistent with the trends from previous small trials showing the effectiveness of risperidone as adjunctive therapy in veterans [284], and civilians [285-287]. Olanzapine has been shown to be effective as adjunctive therapy in military patients with treatment resistant PTSD [288].

Benzodiazepines

At best, benzodiazepines have only very limited value in the treatment of PTSD and may actually worsen the disorder [159,160,165]. Nevertheless benzodiazepines are still often used as adjunctive therapy, often as treatment to improve sleep quality and reduce nightmares [9]. Benzodiazepine has also been shown to treat irritability and hyper-arousal in veterans [289]. In controlled studies in the general population, benzodiazepine adjunctive therapy did not prove to be effective in the treatment of PTSD [290,291,292] The modest efficacy of the benzodiazepines in the treatment of veterans with PTSD, may be explained by the use of nighttime dosing, that improves symptoms of insomnia.

Adrenergic agents

Prazosin (an alpha-1 adrenergic antagonist) has shown consistent efficacy in improving sleep quality and decreasing nightmares in veterans [293] by blocking the changes in sleep architecture mediated by norepinephrine [159,159]. Also, because prazosin is not itself an addictive agent (versus benzodiazepines), it holds a prominent position in PTSD treatment guidelines for sleep augmentation [159-161,165]. Trials in military populations of various ages have confirmed prazosin's effectiveness as a treatment for sleep disturbances and nightmares [282,294-297]. A larger study was more recently done that confirmed the effective use of prazosin over the course of 15 weeks in a military population, giving credence to safety and the long term effectiveness of prazosin sleep augmentation in both male and female veterans [293]. Although the indication would require further study [159], prazosin has also shown promise as a preventative treatment for the prevention of PTSD and this is expected to be due to it's effect on the extinction mechanism [298].

Opioids

While it has been thought that opiates, such as morphine, may confer protective effects if given immediately afterwards or during trauma, this may not be a practical solution for veteran or combat induced PTSD that is not related to a physical trauma and may need to be repeated many times during a deployment. The use of morphine in military personnel and civilians who sustained physical trauma during combat has been tied to decreased development of PTSD [299] in part due to morphine's ability to block the acquisition of conditioned fears [249,250,32].

Opioid antagonists provide a well-documented component in the treatment of the SUD to opioids and ethanol, but opioids have shown mixed effects in the treatment of PTSD [159]. Some open label data from both civilian [300-302] and veteran [303] populations, indicate that naltrexone also treats flashbacks associated with PTSD. In civilian studies opioid antagonists shown promise in the treatment of depersonalization and derealization

symptoms that can be induced by trauma [304,305]. This contrasts with the actions noted above that blocking opioid receptors may enhance fear memory.

Naloxone and naltrexone can also aggravate symptoms of opiate withdrawal after trauma exposure and may increase the pre¬senting symptoms of PTSD such as stress, and anxiety by blocking the effects of endogenous endorphins and enkephalins [159]. Also, discordant opioid signaling may be an underlying cause of PTSD [306]. Also, as opioids are among the most commonly abused agents in the PTSD population, opiate antagonists as therapy may have an additional risk in this population by inducing opioid withdrawal. Current guidelines do not support the use of opiate antagonists in the treatment of PTSD at this time and a broader understanding of the role of endogenous opioids and the effects of exogenous opioids on brain function is needed before agents acting on this system can be used safely and effectively.

Hydrocortisone

Current guidelines include hydrocortisone as an experimental treatment option [159]. As we noted above, glucocorticoids may act in PTSD by facilitating the extinction mechanism [307]. Hydrocortisone has been shown to resolve the symptoms of model-PTSD in rodent studies when administered after stress exposure. As discussed earlier, hydrocortisone normalizes the low cortisol associated with PTSD [308]. Previously, hydrocortisone had been investigated primarily as a secondary prevention therapy after trauma to minimize PTSD. As such it was hypothesized to reduce“PTSD” development in rodent models when administered within a short time window after trauma [101,309-311]. More re¬cent humans studies expanded the use of this approach, showing that in veterans with PTSD, hydrocortisone administration com¬bined with behavior therapy induced traumatic memory reactiva¬tion in therapeutic settings and resulted in a reduction of PTSD symptoms. Studies in the general population showed increased patient acceptance of prolonged exposure therapy with concomi¬tant hydrocortisone use [238]. Of course there are substantial risks associated with long-term systemic dosing with glucocorticoids that need to be weighed against the potential benefits in patients. However, such studies suggested that glucocorticoid modulation enhances the extinction mechanism, with promising results in augmenting exposure therapy in other fear-based disorders and phobias [246,312,236-238]. Yehuda, et al. [247] conducted a double blind randomized trial in 24 veterans, comparing prolonged exposure therapy augmented with hydrocortisone versus placebo. In addition, receptor sensitivity to glucocorticoids was assessed via pre- and post-treatment cultured peripheral blood mononuclear cell response in the in vitro lysozyme inhibition test. In this small study, hydrocortisone augmentation was shown to be significantly more effective in reducing PTSD symptoms than placebo. This effect was attributed to the greater patient retention in the hydrocortisone treatment group. An additional feature noted was that complete responders also had the highest pre-treatment sensitivity to glucocorticoids in vitro that diminished over the course of treatment. Thus, patients may well need to be phenotyped for glucocorticoid response prior to initiation of therapy [238].

Others approaches

Additional treatment possibilities for veteran PTSD are now under investigation that are based on a better understanding of fear extinction and retrieval processes. Human studies in civilians show promise in the use of the protein synthesis inhibitor D-cycloserine and the alpha-2 adrenergic antagonist yohimbine, as well as deep brain stimulation to enhance the effects of extinction training [206,235-238,313-318]. The toxicity and side effects of such pharmacological agents and the dangers associated with the implantation of electrodes for chronic brain stimulation render these options not appropriate for treatment but of potential value in elucidating novel mechanisms upon which practical therapies could be based. As indicated above, propranolol (which is thought to block the norepinephrine triggered fear response in the amygdala), is also under study for use in human patients. Like hydrocortisone, D-cycloserine (a modulator of NMDA receptors), memantine (an NMDA antagonist used in Alzheimer’s disease patients) and even ketamine-like drugs (a blocker of NMDA receptors) are thought to enhance extinction and might improve the effects of such training in humans.

Relationship Between non-Drug Therapies For PTSD And AUD

The relationship between behavioral treatments of comorbid PTSD and AUD have not been well explored. This may in part be due to the idea that exposure therapy and cognitive processing therapy could cause relapse in SUD patients [319]. This is because such treatments are designed to increase anxiety and stress in a safe environment. As mentioned earlier, treatment studies for PTSD typically exclude individuals with conditions such as AUD [320]. In the past, trauma-focused treatment was not allowed for a patient with comorbid substance abuse until they had been in remission for at least 6 months to prevent relapse of the substance and because the SUD was thought to directly hinder effectiveness of the treatment of the patient’s PTSD [321-327]. While studies addressing these concerns exist, the data is still sparse [319]. However, recent research evaluating the exposure-based treatment for patients with comorbid PTSD and AUD supports the initiation of trauma-based treatment [328-331]. Unfortunately cognitive treatments have been less well studied at this point.

The veteran population mimics the general population in that not treating PTSD increases the possibility of relapse for SUD [332].Furthermore, alcohol consumption is likely to impair desensitization to stressors and modification of maladaptive mental paradigms [333]. Currently, the focus has shifted to treat both conditions simultaneously [319]. Randomized control studies in the general population showed that patients with comorbid PTSD and AUD receiving exposure therapy for PTSD showed less cue-reactivity (in the form of alcohol craving) in response to trauma or traumatic memories and significantly greater decreases in triggered distress than non-trauma focused therapy [334].

In 2014, Kaysen and colleagues [319] conducted a chart review comparing the effectiveness of CPT(cognitive processing therapy) for over 500 veterans with PTSD and AUD past and present against PTSD without AUD that participated in a VA outpatient treatment program. This study did not show strong differences in drop-out rate in the treatment groups, and showed similar attendance rates among the three groups. As expected, in this study the PTSD patients with comorbid AUD had more severe self-reported PTSD symptoms before treatment was initiated [335-337]. However, treatment effectiveness appeared unaffected by AUD diagnosis. This study helps support the growing concept that CPT, and other trauma focused therapies should be initiated for the treatment of PTSD even if the patient has AUD or another SUD [338].

As non-pharmacological therapies have gained interest, veteran studies are still less abundant and less statistically powerful than those in the general population. However, available results suggest that trauma related psychotherapy is well tolerated in the dual diagnosis population, and improves the symptoms of both PTSD and AUD [325,339,340].

Conclusions and Future Directions

The above discussion has highlighted that some behavioral therapies may work well in persons with PTSD and AUD. Little has yet been done to determine the effects of medications plus behavior therapy in veterans with both PTSD and AUD and these complex studies need to be done. While not a focus of the present paper, the clinical and preclinical literature also suggests that there may be gender differences in response to therapy that must be addressed in future work. New agents continue to be evaluated. For example, clinical trials are being conducted with the agent MDMA (3,4-Methylenedioxymethamphetamine, "ecstasy") [341,342] and of BNC210 (also known as IW-4123, a negative allosteric modulator of the alpha7-nicotinic acetylcholine receptor found to be an effective anti-anxiety agent [343].

Studies are currently being conducted on device-based treatments for the enhancement of extinction learning for anxiety disorders and PTSD [313,317,318]. Some the techniques under investigation include including deep brain stimulation, vagus nerve stimulation, transcranial direct current stimulation and transcranial magnetic stimulation [344,345]. Deep brain stimulation is one of the most extensively studied for the treatment of psychiatric disorder and shows promise for the treatment of PTSD [344,346-349]. Transcranial magnetic stimulation of the mPFC is also under study as a noninvasive alternative [350]. This has shown reduction of PTSD symptoms when combined with exposure therapy, over the course of 2 weeks [351-353]. These techniques are thought to be a promising option for future treatments and offer a potential way to complement behavioral therapy and medications.

Although comorbid PTSD and AUD has proven to be a common and chronic syndrome in veterans, few of the current guidelines are designed from data generated in this at-risk population. In the future, treatments based on an improved knowledge of the role of the stress systems of the brain (including the HPA axis and sympathetic nervous systems) could be expected to take a more central role in the treatment of PTSD patients. Also, it is now being recognized that the nature of PTSD in veterans may be fundamentally different than that in civilians because of the greater likelihood of coexistent traumatic brain injury and of repeated traumatic experiences in this population. By evaluating studies of veterans and taking into account new information in the neurological changes in brain that occur in both PTSD and AUD, more appropriate clinical decisions can be made for behavioral and pharmacological treatments. Furthermore, the appreciation of the potential importance of combination behavioral plus medication therapy is allowing more effective treatments to be explored. Also, it will be important to evaluate the use of current medications including SSRIs and opioid antagonists that may be beneficial in AUD but not in PTSD since the literature demonstrates that these therapies may actually have negative effects on persons with PTSD. By having additional information about the changes in the processing of the brain we can tailor pharmacotherapy to refrain from hindering trauma-focused therapy and the natural extinction of fear responses that can occur over time.

By understanding more about the consequences of neurotransmitter change in both PTSD and AUD more stringent parameters for pharmacotherapy during future studies would yield less variability between studies. Continuing to evaluate the new practice of allowing treatment of both PTSD and AUD with trauma-focused therapy immediately upon diagnosis should increase patient compliance and length of abstinence. By taking advantage of the new developments in our understanding of the functions of the brain as well as the population specific data for treatment, we can continue to take the necessary steps to allow this population to lead a normal life after their service.

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