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Review of Biological Mechanisms and Pharmacological Treatments of Comorbid PTSD and Substance Use Disorder

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Abstract

Posttraumatic stress disorder (PTSD) and alcohol/substance use disorder (A/SUD) are frequently comorbid. Comorbidity is associated with poorer psychological, functional, and treatment outcomes than either disorder alone. This review outlines biological mechanisms that are potentially involved in the development and maintenance of comorbid PTSD and A/SUD including neurotransmitter and hypothalamic-pituitary-adrenal dysregulation, structural differences in the brain, and shared genetic risk factors. The literature regarding pharmacological treatments that have been investigated for comorbid PTSD and A/SUD is also reviewed. Empirical data for each proposed mechanism and pharmacological approach is reviewed with the goal of making recommendations for future research.

1. Introduction

Comorbidity of posttraumatic stress disorder (PTSD) and alcohol/substance use disorder (A/SUD) is extremely high (Kessler et al., 1995; Kessler et al., 2005; Mills et al., 2006; Petrakis et al., 2002). Prevalence of alcohol use disorder (AUD) among those with PTSD is as high as 28% for women and 52% for men, and as high as 85% in treatment seeking samples (Baker et al., 2009; Kessler et al., 1995). Rates of PTSD among patients with AUD are 30–59% (e.g., Jacobsen et al., 2001; Stewart et al., 2000). In a sample of over 10,000 men and women, 34% of respondents with PTSD had at least one substance use disorder (SUD; Mills et al., 2006).

The presence of substance-related comorbidity in PTSD is associated with poor outcomes across a variety of domains, including psychological, functional, and treatment outcomes. Specifically, comorbidity is associated with greater psychological distress, diminished social functioning, poorer treatment adherence and response, more frequent inpatient hospitalizations, more physical health problems, and increased AUD-related problems (e.g.,

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more admissions to the hospital, shorter periods of abstinence following substance-focused treatment, greater current severity of addiction) than having either disorder alone (Brown et al., 1995; Driessen et al., 2008; Norman et al., 2007; Ouimette et al., 1998; Tarrier and Gregg, 2004; Tate et al., 2007).

The high rates of comorbidity and the range of associated problems point to the importance of understanding the mechanisms that underlie comorbid PTSD and A/SUD. Environmental and psychosocial mechanisms have received considerable attention (Coffey et al., 2008; Hien et al., 2005). The self-medication hypothesis posits that individuals use substances to manage symptoms and distress associated with PTSD. The high-risk hypothesis theorizes that exposure to potentially traumatic events and substance abuse are part of a broader tendency toward high risk behaviors (e.g., Brady et al., 1998; Chilcoat and Breslau, 1998). The susceptibility hypothesis postulates that individuals who use alcohol and substances are more susceptible to PTSD development following traumatic event exposure due to poor coping and other addiction related problems (e.g., Bonin et al., 2000; Sharkansky et al., 1999; Stewart et al., 2000), and the common factors hypothesis suggests that PTSD and A/SUD may share common precursors such as prior exposure to traumatic events (e.g., Breslau et al., 1997; Cottler et al., 2001; Fassino et al., 2004). Each of these hypotheses has received empirical support (Coffey et al., 2008; Hien et al., 2005), suggesting a complex interplay of factors contributing to PTSD and A/SUD comorbidity.

Adding further complexity to this relationship is literature suggesting that biological mechanisms link PTSD and A/SUD development and maintenance. These proposed mechanisms include factors shared by both disorders such as dysregulations in certain neurotransmitters, brain structures, and in the hypothalamic–pituitary–adrenal (HPA) axis as well as shared genetic vulnerabilities. Biological mechanisms have been studied less than psychological and environmental ones. The first goal of the present study was to provide an overview of theories and data regarding biological mechanisms that may contribute to PTSD and A/SUD comorbidity. The second goal was to review the small body of literature regarding pharmacological treatments for comorbid PTSD and A/SUD. These reviews inform recommendations for future research on mechanisms and treatment.

2. Method

A search of peer reviewed journals was conducted using PsycINFO and Medline databases. Each search contained three terms (Table 1). The first word(s) was a PTSD term. The second word(s) was a substance use term. For the mechanisms section, the third word(s) was chosen from a list of search criteria terms regarding theories and mechanisms that attempt to explain the relationship between co-occurring PTSD and A/SUD. For pharmacological treatments, the third word was chosen from a list of search criteria regarding pharmacology for comorbid PTSD and A/SUD. All possible combinations of PTSD, substance use, and mechanism or treatment terms were searched. Additional articles were found by examining reference lists and related articles in studies located during the literature search. Thirty-seven articles regarding biological mechanisms were found. Twelve were excluded because both disorders were not examined or the subject matter was not relevant, eight were review articles, and seventeen were empirical evaluations relevant to this review (Table 2). Two randomized controlled trials (RCT's) and five open label or retrospective studies were found that had the goal of evaluating a pharmacological agent for comorbid PTSD and A/SUD. Given that only two RCTs were identified, all seven studies were reviewed (Table 3).

3. Results

3.1 Neurotransmitters

Previous studies examining PTSD or A/SUD independently have highlighted the roles of three neurotransmitters—dopamine, norepinephrine, and serotonin. Studies examining these neurotransmitters in PTSD and A/SUD comorbidity included examinations of genes that dictate the level of their presence and brain structures in which these neurotransmitters are highly concentrated. These investigations have mainly focus on the intersection of stress in the neurobiological mechanisms associated with both PTSD and A/SUD has been highlighted (Brady and Sinha, 2005).

3.1.1 Dopamine—Dopamine is a rewarding or reinforcement neurotransmitter involved in the mesolimbic circuit, which extends from the ventral tegmental area to the nucleus accumbens (Noble, 2000). In the PTSD literature, dopamine has been implicated in two different mechanisms. First, following a stressful event, norepinephrine is released, which in turn stimulates the release of dopamine and serotonin. Serotonin then reduces norepinephrine levels, leaving increased amounts of dopamine in the system. Secondly, norepinephrine transporters reduce dopamine uptake in the frontal cortex where dopamine receptor levels are already in low quantity (Krystal and Neumeister, 2009). With regard to substance abuse, this circuit affects incentive salience (i.e., how rewarding a particular drug is found to be) across a variety of substances (Brady and Sinha, 2005; Gilpin and Koob, 2008).

3.1.2 Norepinephrine—In chronic stress, such as in PTSD, norepinephrine turnover increases in the hippocampus and amygdala (Brady and Sinha, 2005; Jacobsen et al., 2001; Krystal and Neumeister, 2009). In the substance use literature, stress experienced in the context of withdrawal is thought to release norepinephrine (Koob, 2009). Norepinephrine increases during withdrawal from alcohol and nicotine in the hypothalamus and amygdala, and as such, may impact motivation through negative reinforcement (Jacobsen et al., 2001; Koob, 2009).

3.1.3 Serotonin—Stress leads to an increase in the amount of serotonin released and synthesized in the amygdala, ventral striatum, and prefrontal cortex (Krystal and Neumeister, 2009). The two medications currently approved by the FDA for PTSD (i.e., sertraline and paroxetine) block reuptake of serotonin, but specific knowledge of the mechanisms by which serotonin is involved in PTSD is not known (Krystal and Neumeister, 2009). Serotonin has been implicated in many processes associated with PTSD such as impulsivity, depression, arousal, and anxiety (Xie et al., 2009). Preclinical studies have shown a connection between serotonin depletion and alcohol drinking behavior (Gilpin and Koob, 2008; Johnson, 2008).

3.1.4 Summary of Findings—Dopamine, norepinephrine, and serotonin have been independently implicated in mechanisms associated with PTSD and A/SUD such as reward, impulsivity, arousal, and anxiety. However, there remains no clear understanding regarding the link between particular neurotransmitters and the development and maintenance of comorbid PTSD and A/SUD.

3.1.5 Future Directions for Neurotransmitter Research—Previous studies have generally been secondary analyses of samples that happened to have a subset of individuals with both PTSD and A/SUD. Studies designed to compare individuals with PTSD only, A/SUD only, comorbid individuals, and healthy controls would allow for better understanding of any differences in dopamine, norepinephrine, and serotonin levels among these groups.

Once more is known about differences in neurotransmitter levels, spectroscopy and fMRI can be used to correlate reward, impulsivity, arousal, and anxiety to specific neurotransmitter levels in those with and without comorbidity.

3.2 Brain Structures of PTSD and A/SUD

Through the use of neuroimaging, two brain structures have been implicated separately in both PTSD and alcohol use: the hippocampus and the amygdala. The identification of short-term memory deficits in PTSD (Bremner et al., 1993) led to a more focused examination of the hippocampus. Hull (2002) reviewed a series of MRI studies investigating neurobiological changes in PTSD subjects and found that decreased hippocampal volume was the most replicated finding. A criticism of these studies is the use of different exclusionary criteria related to participants' alcohol use (Woodward et al., 2006). Alcohol use has also been related to decreased hippocampal volume. Given this, it is important to control for alcohol use in PTSD studies of hippocampal volume. Hull (2002) reported that decreases in hippocampal volume did not appear to be related to alcohol use in the samples reviewed. However, he recommended further research investigating commonalities and differences related to PTSD and A/SUD as most studies have not controlled for alcohol use.

Early efforts have been made in the line of research recommended by Hull (2002); however, findings have been somewhat contradictory. For instance, researchers have investigated the degree to which the combination of PTSD and AUD decreases hippocampal volume above and beyond the presence of either disorder alone. Hedges and colleagues (2003) conducted a pilot study comparing hippocampal volume among four conditions: PTSD only, AUD only, PTSD and AUD, and a PTSD- and AUD-negative control group. The presence of PTSD, regardless of AUD status, dictated reduced hippocampal volume, suggesting hippocampal volume reductions in PTSD could not be attributed solely to alcohol use. Conversely, Schuff et al. (2008) examined the same four conditions using a different sample and found no hippocampal volumetric differences among any of the four groups. The investigators did identify lower N-acetylaspartate (NAA) levels in the right anterior cingulate cortex and hippocampus of participants with PTSD only, but not in the group with PTSD and comorbid AUD. In an effort to examine the impact of chronic AUD in participants with PTSD, Woodward et al. (2006) compared participants with PTSD and lifetime AUD to participants with PTSD without lifetime AUD. Participants with histories of comorbid PTSD and AUD showed significantly greater reductions in hippocampal volume than did participants with PTSD without AUD suggesting that the combination may affect hippocampal volume beyond the individual impact.

Numerous imaging studies have investigated the amygdala's role in PTSD or A/SUD (Anand and Shekhar, 2003); however, only one study has examined the amygdala with respect to comorbid PTSD and A/SUD. Semple et al. (2000) used a resting scan paradigm with positron emission tomography to examine regional cerebral blood flow (rCBF) at a resting state in patients with comorbid PTSD and AUD related to cocaine and alcohol compared to a control group of participants without either disorder. Comorbid patients had significantly higher rCBF in the right amygdala and the left parahippocampal gyrus, suggesting a reciprocal relationship with amygdala and frontal cortex attention systems, both of which are involved with addiction and PTSD.

3.2.1 Summary of Findings—Imaging studies of comorbid PTSD and A/SUD have examined two structures hypothesized to be related to both disorders: the hippocampus and the amygdala. The evidence regarding the hippocampus has been conflicting; however, the most replicated finding is that PTSD and A/SUD have a detrimental impact on hippocampal

volume. In regard to the amygdala, results suggest higher rCBF during resting states in comorbid subjects than in subjects without PTSD and A/SUD.

3.2.2 Future Directions for Brain Structures Research—Unfortunately, most of the current brain imaging studies have controlled for either A/SUD or PTSD in subjects, choosing to isolate one disorder over the other. Studies examining comorbidity in regard to hippocampal volume have found contradictory results, possibly due to varying lengths of time since onset of A/SUD, and variability in substances examined. This suggests the need for examinations by substance (e.g., alcohol or cocaine) and that differential effects based on time since A/SUD onset and use severity need to be explored. Functional MRI studies can bring insight to which regions of the brain are activated in comorbid subjects in relation to PTSD or A/SUD-related cues. Studies that include groups of participants that are (1) comorbid, (2) PTSD only, (3) A/SUD only, and (4) normal controls will be most useful in clarifying the role of each disorder and any incremental effect of comorbidity. While the high financial expense of imaging studies presents an obstacle in this line of research, the high rates of comorbidity necessitate further imaging studies investigating the degree to which comorbid PTSD and A/SUD affect brain structure over and above the presence of one disorder.

3.3 Hypothalamic–pituitary–adrenal (HPA) Axis

One promising area of neurobiological overlap between PTSD and A/SUD is the HPA Axis, the body's major neuroendocrine stress response system (Coffey et al., 2008; Rasmusson et al., 2003). Abnormalities in this neuroendocrine system have been found in both PTSD and A/SUD (Jacobsen et al., 2001; Lovallo, 2006; Rasmusson et al., 2003) the overlap in HPA involvement may constitute a neurobiological mechanism underlying the comorbidity of these disorders (Jacobsen et al., 2001). Support for these theories is based on findings regarding the role of stress and corticotropin-releasing hormone (CRH), a hormone secreted when a stressor activates the HPA axis. Stress increases drug intake during initial acquisition of self-administration in untrained rats (Piazza et al., 1990), provokes relapse in previously trained rats (Erb et al., 1996; Shaham and Stewart, 1995), increases reported cravings in humans (Sinha et al., 1999), and is a reported reason for relapse in humans (Brewer et al., 1998). Preclinical literature suggests administering CRH increases some effects of drugs in rats (e.g., increased long-lasting locomotor response to d-amphetamine; Cador et al., 1993) and leads to the reinstatement of drug seeking behavior following extinction (Shaham et al., 1997).

Blocking CRH appears to have opposite effects (Sarnyai et al., 1992; Shaham et al., 1997). Elevated levels of CRH have been found in humans going through withdrawal (Adinoff et al., 1996) and in adults with PTSD (Baker et al., 1999; Bremner et al., 1997). CRH may play a role in the development of PTSD as elevated CRH levels in pre-clinical studies have been shown to strengthen fear-related behaviors similar to those seen in PTSD such as heightened startle response (Jacobsen et al., 2001; Swerdlow et al., 1989). Jacobsen and colleagues (2001) proposed elevated CRH levels in PTSD may mediate and increase hyperarousal symptoms and increase risk of developing A/SUD. In other words, individuals with PTSD may experience elevated CRH in the brain which may increase the euphoric feelings caused by many drugs and/or worsen withdrawal symptoms. Additionally, CRH elevations seen during withdrawal may increase hyperarousal symptoms, which in turn may increase other PTSD symptoms triggering relapse (i.e., self-medication).

Koob (1999; Jacobsen et al., 2001) proposed that CRH may interact with the noradrenergic system creating a “feed-forward system.” The repeated stress exposure seen in PTSD may result in a gradual increase of the stress response under this system. Experiencing stress may

lead to the release of CRH in the locus coeruleus, activating this brain nucleus and causing the release of norepinephrine in the cortex. This release of norepinephrine then results in the release of CRH in the hypothalamus and amygdala. Koob (1999) suggested the interaction between CRH and the noradrenergic system may mediate hyperarousal symptoms in PTSD. Individuals with PTSD may be drawn to substance use in an attempt to attenuate this feed-forward cycle to reduce the activity of the locus coeruleus (Kosten and Krystal, 1988).

While no studies have set out to specifically investigate the role of stress and CRH as a possible mechanistic link between PTSD and A/SUD, findings from more general studies of HPA Axis functioning may provide preliminary information. For instance, if neuroendocrine abnormalities are seen in both PTSD and A/SUD (Jacobsen et al., 2001), it follows that individuals with both disorders may exhibit greater neuroendocrine dysregulation (Brady et al., 2006b) and/or that a stronger relationship between stress response and alcohol/drug use may be seen in both disorders compared to either disorder alone (Brady et al., 2006a). Findings from four studies failed to support greater dysregulation (Brady et al., 2006b; Lovallo et al., 2000; Santa Ana et al., 2006); or a stronger relationship between stress response and alcohol/drug use (Brady et al., 2006a). Importantly, the aforementioned studies sought to investigate HPA Axis functioning in relation to levels of cortisol and adrenocorticotrophic hormone (ACTH) rather than to examine the role of stress and CRH as a possible mechanism linking PTSD and A/SUD. While these studies provide a useful starting point, they do not directly examine CRH, the hormone believed to play a central role in the possible mechanistic link between comorbid PTSD and A/SUD.

3.3.1 Summary of Findings—Studies examining PTSD or A/SUD independently have identified abnormalities in the body's major neuroendocrine stress response system, the HPA Axis. Increased stress and levels of CRH have been linked to drug taking behavior (e.g., use, relapse, craving, withdrawal). Elevated levels of CRH increase fear related behaviors in animal models and have been implicated in theories explaining PTSD symptoms. These findings have led to theories suggesting this overlap in CRH dysregulation between the two disorders may partially explain the onset of co-occurring PTSD and A/SUD. There are no studies yet that examine the HPA Axis in comorbid PTSD and A/SUD.

3.3.2 Future Directions for HPA Research—Studies examining neuroendocrine abnormalities including CRH levels in those with comorbid PTSD and A/SUD are needed. Investigations designed to examine the possible increase in craving and or substance use in the presence of heightened hyperarousal may provide early empirical evidence for the theories described above. Investigations of neuroendocrine response to stress may provide a useful starting point. For instance, examining CRH levels while in withdrawal from substances in dually diagnosed individuals compared to individuals with A/SUD only would allow for observation of possible differences in neuroendocrine functioning. Similarly, investigations involving stress tasks, such as public speaking, physical challenges, and/or cold pressor tasks, comparing healthy controls, comorbid, PTSD only, A/SUD only participants would allow for examination of the hypothesized increase in neuroendocrine dysregulation in dually diagnosed individuals.

3.4 Genetics of PTSD and A/SUD

While genetic influences in both PTSD (Broekman et al., 2007) and A/SUD (Ray and Hutchison, 2009) have received attention, there is a paucity of research examining the genetic influences of PTSD and A/SUD comorbidity.

The majority of studies examining genetics of comorbid PTSD and A/SUD are twin studies, all of which were generated from the Vietnam Era Twin Registry (VETR). Xian et al. (2000)

reported that 35% of the variance of PTSD was accounted for by additive genetic factors, with 15% related solely to A/SUD and 20% related solely to PTSD. In a later twin study, McLeod et al. (2001) looked at the impact of genetics on combat exposure, PTSD, and AUD and found common genetic influences with combat and alcohol use as well as combat and avoidance/arousal and reexperiencing. These findings suggest certain genes believed to make individuals vulnerable to PTSD symptoms following combat exposure may also contribute to vulnerability to alcohol use. Koenen et al. (2003) reported that combat exposure was significantly associated with increased risks for both alcohol and cannabis dependence above and beyond PTSD diagnosis. Combat-related PTSD was a significant predictor of nicotine dependence. In direct contrast, Scherrer et al. (2008) found that the genetic variance between PTSD, combat exposure, AUD and nicotine dependence is explained best by PTSD, and not combat exposure. Wolf et al. (2010) examined the relationship between internalizing (i.e., related to anxiety) and externalizing (i.e., related to A/SUD) factors. Externalizing factors were significantly more heritable (69%), but internalizing factors showed a moderate genetic component (41%). When both factors were combined, 67% of the variance in comorbid PTSD and A/SUD disorders was explained.

One twin study examined shared genetic influences in PTSD and A/SUD in females. Sartor et al. (2010) reported that 71% of the variance in PTSD and 72% of the variance in AUD was accounted for by additive genetic factors. The genetic correlation between PTSD and AUD was 0.54. These findings replicate the evidence of genetic overlap between PTSD and AUD seen in other studies. However, the PTSD heritability estimate for this female sample is twice as high as other studies. Sartor and colleagues propose that higher PTSD heritability in their female sample may be due to sex differences, varying types of trauma, or may reflect a lower reported rate of PTSD in the sample.

A limited number of studies have examined single genetic variants in PTSD and A/SUD, focusing specifically on DRD2, 5-HTTLPR, and ADCYAP1R1. Comings et al. (1991) examined the relationship between a variant in the dopamine receptor gene (DRD2) and comorbid PTSD and A/SUD, and reported that the presence of TaqI A1 allele was not associated with PTSD and AUD. This study was limited by a small sample size for the PTSD group ($n = 35$). Young et al. (2002) also examined the DRD2 gene, this time specifically examining PTSD and AUD with veterans. Participants who had PTSD and the A1 allele of TaqI of DRD2 consumed more than twice the amount of alcohol daily and consumed alcohol at twice the hourly rate as subjects with PTSD only. This suggests that PTSD patients with the A1 allele may find alcohol more reinforcing, leading to rapid and excessive amounts of alcohol use for self-medication of their PTSD symptoms.

Kaufman et al. (2007) examined the role of 5-HTTLPR in adults with a history of childhood maltreatment and current alcohol use. 5-HTTLPR is responsible for encoding the serotonin transporter protein that regulates serotonin function in the brain. History of childhood maltreatment and 5-HTTLPR predicted alcohol use. Xie et al. (2009) examined interactive effects of 5-HTTLPR with PTSD, and found that 5-HTTLPR interacted significantly with childhood adversity to predict PTSD in adulthood. This sample originated from a study examining the genetics related to A/SUD, but did not include discussion regarding PTSD and A/SUD comorbidity.

The genetic variant ADCYAP1R1, which regulates the CRF hormone, was found to significantly correlate with PTSD in two different female samples ($p < .001$; Ressler et al., 2011). The authors reported no association between the genetic variant and A/SUD in either sample. Further, the method of measuring A/SUD status was not described.

3.4.1 Summary of Findings—Genetic studies investigating comorbid PTSD and A/SUD are still in their infancy. Only twin studies and single variant gene studies have examined the genetic factors common to both PTSD and A/SUD. Results suggest common genetic risk factors for dually-diagnosed populations; however, the following limitations should be considered: single variant gene studies may have been underpowered and all but one of the twin studies was from a single twin registry (VETR).

3.4.2 Future Directions for Genetics Research—There has been little focus on the intersection of PTSD or A/SUD. Studies examining the overlap in disorders are needed, especially with regard to gene by environment (GxE) interaction. For example, in a sample generated from a study on the the genetics of substance abuse, Xie et al. (2009) assessed the interaction between 5-HTTLPR and childhood adversity on PTSD. GxE studies are especially relevant for PTSD and A/SUD, as both disorders are conceptualized as involving certain environmental risk factors. Research is also needed to tease apart different types of PTSD (combat, domestic violence), and different substance types (alcohol, illicit drugs) to examine if differences are explained by genotype. Xie and colleagues' (2009) work also supports the feasibility of investigating the comorbidity of PTSD and A/SUD with 5-HTTLPR and other single nucleotide polymorphisms. Additionally, while genome wide association studies are still in their infancy, their use is becoming more prevalent. Using this methodology might allow for discovery of novel genes implicated in both disorders. The gender differences reported by Sartor et al. (2010) and Ressler et al. (2011) (i.e., higher proportions of heritability and genetic correlations with PTSD in female samples) highlight the need to examine the extent to which genetics contribute to gender differences in comorbid PTSD and A/SUD.

3.5 Pharmacotherapy for the Treatment of Comorbid PTSD and A/SUD

Five open label or retrospective studies and two randomized controlled trials (RCTs), with the goal of testing one or more pharmacological agents to treat comorbid PTSD and A/SUD, were identified (Table 3).

3.5.1 Pharmacotherapy in PTSD—The goal of pharmacological agents in the treatment of PTSD is generally symptom reduction. There is evidence supporting the use of selective serotonin reuptake inhibitors (SSRIs) for reducing symptoms of PTSD across multiple RCTs; however, overall effect sizes are small (Ravindran and Stein, 2009; Stein et al., 2006). While some studies of anticonvulsants have demonstrated positive improvements in PTSD symptoms, overall results for anticonvulsants have been mixed (Ravindran and Stein, 2009). A meta-analysis of seven double blind placebo controlled trials for PTSD indicated reduction in PTSD symptoms using atypical antipsychotics (Pae et al., 2008). Atypical antipsychotics are most often used as adjunctive medications to target specific symptoms such as those associated with dopaminergic dysfunction (e.g., hyperarousal; Ravindran and Stein, 2009). Of the alpha adrenergic antagonists, prazosin shows improvement not only in recurring distressing dreams and sleep but also in overall PTSD symptoms in a double blind RCT (Raskind et al., 2003). While benzodiazepines are frequently prescribed, RCTs have not found that they are effective for PTSD symptom reduction (e.g., Dunner, 2001; Ravindran and Stein, 2009).

3.5.2 Pharmacotherapy in A/SUD—For A/SUD, psychopharmacological applications generally take one of five approaches: targeting comorbid Axis I symptoms that may increase likelihood of use or relapse (e.g., SSRIs), craving reduction (e.g., naltrexone), substitution therapy designed to prevent withdrawal and functional impairment (e.g., methadone maintenance), aversive therapy believed to counteract the reinforcing effects of the substance (e.g., disulfiram), and/or targeting withdrawal symptoms (Bukstein et al.,

2006). A meta-analysis concluded there is no evidence for treatment of alcohol dependence with antidepressants in individuals who are not depressed (Torrens et al., 2005). There is evidence for the use of the competitive opioid antagonist naltrexone (Bouza et al., 2005; Srisurapanont and Jarusuraisin, 2005). Use of acamprosate, which is thought to work by blocking glutamatergic receptors while activating GABA type A receptors, has mixed results (Anton et al., 2006; Kranzler and Gage, 2008; Mason et al., 2006). Of the other agents tried, the anticonvulsant topiramate showed effectiveness in treating AUD in two double blind controlled trials (Johnson et al., 2003; Johnson et al., 2007). Disulfiram, an alcohol sensitizing agent that leads individuals to feel physically ill after alcohol consumption by blocking the conversion of alcohol to non-toxic byproducts via inhibition of aldehyde dehydrogenase was evaluated in double blind RCTs with negative results (Kranzler et al., 2009). There is evidence supporting methadone and buprenorphine, full and partial opioid agonists respectively, for the treatment of other substances.

3.5.3 SSRIs—Serotonin has been implicated in symptoms and disorders associated with both PTSD and A/SUD including depressed mood, irritability, and arousal (Gilpin and Koob, 2008; Xie et al., 2009). While the exact role of serotonin in PTSD is not fully understood, SSRIs have been used to treat PTSD effectively. For PTSD with concurrent A/SUD, an open label preliminary study of sertraline with nine participants showed PTSD symptom and alcohol intake reduction (Brady et al., 1995). In one of only two RCTs of pharmacological treatment for comorbid PTSD and A/SUD, Brady and colleagues (2005) randomly assigned 94 individuals with PTSD and alcohol dependence to sertraline or placebo using a double blind design. While the majority of participants showed reductions in both PTSD symptoms and alcohol use (21% were PTSD only responders, 14% were alcohol only responders, 46% were responders in both PTSD and AUD, and 18% were non-responders), outcomes did not differ significantly by group assignment. For example, 51% of the sertraline group and 48% of the placebo group were global responders. Earlier onset PTSD and less severe alcohol dependence were associated with having fewer drinks per drinking day at the end of treatment in the sertraline group while later onset PTSD and more severe alcohol dependence were associated with fewer drinks per drinking day in the placebo group, suggesting characteristics of trauma history and AUD may require consideration in treatment selection. Given that use of SSRIs in the absence of a depressive disorder lacks empirical support as a treatment for AUD (Torrens et al., 2005), it is possible that alcohol use is declining in response to decreased PTSD symptoms. A recent study examining psychotherapy outcomes for comorbid PTSD and A/SUD found that decreased PTSD symptoms led to decreased alcohol use while decreased alcohol use did not lead to improvement in PTSD symptoms (Hien et al., 2009).

3.5.4 Atypical Antipsychotics—Atypical antipsychotics have antagonistic effects at serotonin 5 HT₂ and dopamine D₂ receptors. Dopaminergic dysfunction has been implicated in PTSD and A/SUD. In particular, dopaminergic dysfunction has been associated with hyperarousal symptoms such as irritability, hypervigilance, and exaggerated startle (Weiss, 2007). A retrospective study of 50 veterans with AUD, 90% of whom had PTSD, showed that the mean number of days abstinent was significantly greater, and the number of hospitalizations was significantly lower, for the group that had received quetiapine than for the group that had not (Monnelly et al., 2004). Additionally, the mean number of days to relapse approached significance as being greater for the quetiapine group.

3.5.5 Anticonvulsants—Anticonvulsants have been used to treat PTSD due to the theory that kindling is occurring during reexperiencing symptoms, and anticonvulsants have anti-kindling effects. In addition, anticonvulsants showed reduction in SUD symptoms in two RCTs (Johnson et al., 2003; Johnson et al., 2007). An open label pilot study of the

anticonvulsant topiramate with 43 male combat veterans in intensive PTSD treatment (29 completers) showed mean PTSD symptom reduction of 19 points on the Clinician Administered PTSD Scale (CAPS) and decline in high risk drinking patterns, but neither reached statistical significance (Alderman et al, 2009). Significantly fewer participants did report nightmares and anxiety prior to falling asleep.

3.5.6 Competitive Opioid-Receptor Antagonists—In a RCT, Petrakis et al. (2006) used naltrexone and disulfiram to treat 254 subjects with an Axis I disorder and alcohol dependence. All subjects were openly randomized to disulfiram and double blindly randomized to naltrexone or placebo leading to four conditions: (1) disulfiram and placebo, (2) naltrexone alone, (3) placebo alone, and (4) disulfiram and naltrexone. Subjects with PTSD ($n = 93$) had fewer heavy drinking days and more consecutive days of abstinence when taking medication (naltrexone, disulfiram, or combination) compared to those taking placebo, with those on disulfiram showing the greatest gains.

3.5.7 Opioid Substitution—Hien and colleagues (2000) showed that among individuals in methadone treatment for multiple substance use disorders, those with PTSD did not drop out at higher rates than those without, but they did not respond as well to treatment – significantly more were using substances at 3-months post-treatment. On the other hand, in a prospective observational study of 255 veterans, opioid substitution (methadone) reduced substance use in patients with PTSD at the same rate as in patients without PTSD (Trafton et al., 2006). Review of the medical records indicated a diagnosis of PTSD in 28% of the patients and outcomes were compared to those on opioid substitution without PTSD. At 12-month follow-up, participants with PTSD showed a significantly greater reduction in alcohol, cocaine, and heroin use than participants without PTSD. Veterans with PTSD attended more treatment sessions and took higher doses of opioid substitution medication. There was little improvement in PTSD symptoms during treatment. Whether patients were receiving PTSD-specific treatments was not reported.

3.5.8 Summary of Findings—Only two RCT's have examined psychopharmacology for comorbid PTSD and A/SUD. In one, no differences were found between an SSRI and a placebo with regard to outcomes for PTSD or A/SUD. In the other, pharmacotherapy for addictions improved A/SUD but not PTSD symptoms. Of note, most studies have used veteran samples.

3.5.9 Future Directions for Psychopharmacological Research—Open label and retrospective studies that show promise (i.e., quetiapine, topiramate) for the treatment of both disorders should be evaluated using larger samples and more rigorous scientific methodology. Because serotonin and dopamine have been implicated in both disorders, further evaluation of agents that act on these neurotransmitter systems are warranted. Since benzodiazepines are not supported as effective agents in treating PTSD and given concerns in prescribing benzodiazepines to individuals with addictions given their potential for dependence, this class of medication is not a promising target for the treatment of comorbid PTSD and A/SUD. The Institute of Medicine (2007) has recommended exposure therapy as a first line treatment for PTSD and recent studies suggest that exposure therapies are acceptable and helpful to individuals with comorbid A/SUD (Back et al., 2006; Riggs and Foa, 2008). As of yet, there are no published studies of psychotherapy with medication for the treatment of PTSD and A/SUD but such studies are an important step. Studies with non-veteran samples, including females and civilians with diverse types of trauma, are needed.

4. Discussion

This review of the biological mechanisms possibly implicated in PTSD and A/SUD comorbidity highlights that while there are several promising theories regarding mechanisms of comorbidity, data to support or refute these theories is sparse. Systems impacted by stress appear to be a common thread among existing theories of biological mechanisms for PTSD and A/SUD comorbidity and may help to build a more integrative model for future research. Negative affectivity also appears to be a common thread involved in mechanisms linking PTSD and A/SUD (Coffey et al., 2008). Many studies of each disorder purposely excluded individuals with the other disorder, making it challenging to draw conclusions regarding possible mechanisms of comorbidity from the existing literature.

Individuals with A/SUD tend to report more severe PTSD symptoms than do individuals with PTSD only (Jacobsen et al., 2001). As such, studies that examine comorbid participants need to thoroughly assess both PTSD and A/SUD to control for differences in analyses, and to ensure that findings are due to comorbidity, rather than to differences in severity or frequency in one disorder over the other. For this reason, assessments should include not only diagnostic instruments, but also measures of symptom severity.

Studies of environmental and psychosocial factors have elucidated that a number of pathways to comorbidity are possible. Similarly, there is likely an interaction of neurobiological changes that occur along with environmental factors in the face of trauma and substance use that interplay in multiple ways resulting in comorbidity. Given the sparse literature, alcohol and other substances were reviewed together in this study. However, various substances (e.g., alcohol, cocaine, opioid) affect the brain differently, and examinations of PTSD comorbid with specific substances will be necessary. Future studies should examine severity and duration of addiction as recent onset use may involve different mechanisms than long-term use.

In regard to pharmacotherapy, some agents may be able to target both disorders. However, the evidence is preliminary and at times contradictory. A recent study of psychotherapy for comorbid PTSD and A/SUD suggested that PTSD severity reductions following psychotherapy were associated with decreased substance use at a later time point, while initial SUD reduction did not affect later PTSD symptoms (Hien et al., 2009). This would suggest that targeting PTSD symptoms may have greater impact on reduction of symptoms of both disorders than would targeting primarily A/SUD symptoms. However, in the only two RCTs conducted with comorbid PTSD and A/SUD populations, sertraline did not outperform placebo in one study, while PTSD patients on AUD medications did better than those that were not on AUD medications in the other study. These results which contradict findings from the psychotherapy literature highlight the importance of understanding these underlying factors to further the study of PTSD and A/SUD treatment.

Neuroimaging, genetic, and other neurobiological studies targeting comorbid individuals are clearly the next step to advance our understanding of mechanisms and treatments for PTSD and A/SUD comorbidity. Such studies will not be without their challenges. Neuroimaging studies are expensive, large-scale twin cohorts are difficult to amass, and accruing adequately powered samples in genetics studies is difficult. In addition, studies of PTSD and/or A/SUD have high dropout rates from research (Dutra et al., 2008; Schottenbauer et al., 2008). However, prospective studies using multiple and comprehensive methods of assessment are needed to further our understanding of the complex interplay of these disorders. Studies examining diverse civilian populations (females, children) are also needed (Ressler et al., 2011, Xie et al., 2009). Such work will allow for developing

pharmacotherapeutic approaches that use agents targeting not only clinical symptoms but also causal mechanisms underlying the comorbidity.

Research Highlights

- Little is known about pharmacotherapy to treat comorbid PTSD and alcohol/substance use disorder (A/SUD)
- High rates of comorbidity poor prognoses make understanding mechanisms of PTSD and A/SUD comorbidity important
- Proposed biological mechanisms are neurotransmitter and HPA dysregulation, structural brain differences, shared genetic risk
- Stress and negative affectivity are common threads involved in mechanisms linking PTSD and A/SUD

Research Highlights

- Frequent comorbidity and poor prognoses make understanding PTSD and SUD important
- Neurotransmitters, HPA, brain structure, genetic risk involved in both disorders
- Stress and negative affectivity link theories of PTSD and A/SUD comorbidity

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Table 1

Search Terms

First	Second	Third
PTSD	Substance Use	Mechanisms
Posttraumatic Stress Disorder	Alcohol	Psychopharmacology
PTSD	Alcohol Use	Medication
	Substance Use	Pharmacotherapy
	Substance Use Disorder	Genes
	Addiction	Neuroimaging
		Brain Imaging
		Neuroendocrine
		HPA Axis

Table 2**Genetic and Neuroimaging Studies of Comorbid PTSD and A/SUD**

Authors	Emphasis	Participants	Findings
Comings et al., 1991	Genetics	314; 24 PTSD and AUD diagnoses	1 The presence of the A1 allele was 45.7% with the comorbid sample. **
Hedges et al., 2003	Imaging	8 (all male); 4 PTSD-substance negative, 4 control	1 PTSD participants who were A/SUD-negative evidenced reduced hippocampal volume as compared to control subjects. *
Hull, 2002	Imaging	-- (Review study)	1 Reduced hippocampal volume was the most replicated finding among PTSD imaging studies.
Kaufman et al., 2007	Genetics	127; 76 maltreated children, 51 matched controls	1 Maltreated children reported alcohol use at follow-up 7x more often than controls. ** 2 Maltreated children drank alcohol 2 years earlier than controls (11.2 vs. 13.5 years). * 3 5-HTTLPR and maltreatment showed an interaction associated with the s allele of 5-HTTLPR that increased risk for alcohol use. **
Koenen et al., 2003	Genetics	1874 monozygotic twin pairs from the VETR; All PTSD, 524 comorbid AUD	1 Combat exposure was associated with an increase risk in alcohol and cannabis use, after controlling for PTSD. * 2 Combat-related PTSD mediated the effects of major depression and tobacco use. *
McLeod et al., 2001	Genetics	4072 male-male twin pairs from VETR	1 The relationship between combat and alcohol use and between PTSD and alcohol use was related to shared genetic factors. * 2 Unique environmental factors explain more of the variance with PTSD, while shared genetic factors explain more of the variance with alcohol use. *
Sartor et al., 2010	Genetics	3768 female twin pairs; 138 PTSD dx, 46 PTSD and AUD dx	1 Rates of comorbid PTSD and AUD were higher in assaultive-related versus not assault-related PTSD (40% vs. 33.1%). ** 2 71% of the variance in PTSD and 72% of the variance in AUD was explained by additive genetic factors, compared to 28% of the variance in trauma exposure explained by genetic factors. 3 Genetic factors that contribute to PTSD/trauma exposure account for 30% of the variance in AUD.
Scherrer et al., 2008	Genetics	5312 male twin pairs from the VETR; 295 PTSD dx, 1728 AUD dx	1 Genetic influences common to PTSD explain 20% of the variance in AUD. ** 2 Non-shared environmental influences related to PTSD only explained 1% of the variance in AUD.
Schuff et al., 2008	Imaging	104 (91 male); 28 PTSD ⁺ /SUD ⁺ , 27 PTSD ⁺ /SUD ⁻ , 23 PTSD ⁻ /SUD ⁺ , 26 PTSD ⁻ /SUD ⁻	1 No significant hippocampal volume differences were found between any of the four comparison groups. 2 PTSD only was associated with lower NAA/Cr in the hippocampus and anterior cingulate cortex. *
Semple et al., 2000	Imaging	13 all male; 7 PTSD and A/SUD	1 PTSD patients who abused both cocaine and alcohol had higher rCBF in the amygdala and parahippocampus and lower rCBF in the frontal cortex compared to controls. **

Authors	Emphasis	Participants	Findings
Wolf et al., 2010	Genetics	3372 male-male twin pairs from VETR; 323 PTSD dx, 1841 AUD dx	<ol style="list-style-type: none"> 1 69% heritability of externalizing factors (related to A/SUD) and 41% heritability of internalizing factors (related to anxiety). 2 Shared genetic heritability across both internalizing and externalizing factors explain 67% of the variance in phenotypes.
Woodward et al., 2006	Imaging	99 (92 male); 51 PTSD dx, 22 AUD dx	<ol style="list-style-type: none"> 1 Participants with comorbid A/SUD and PTSD had larger hippocampal volume than participants with PTSD only (9% vs. 3%).*
Xian et al., 2000	Genetics	3304 male-male twin pairs from VETR; 317 PTSD dx, 1163 AUD dx	<ol style="list-style-type: none"> 1 PTSD risk was due to 15.3% common genetics for AUD and SUD. 2 AUD risk accounted for by 55.7% common genetics between SUD and PTSD. 3 Common genetic accounted for 25.2% of the risk for SUD.
Xie et al., 2009	Genetics	1253 (656 male); 229 PTSD dx	<ol style="list-style-type: none"> 1 5-HTTLPR genotype interacted with adverse childhood events to increase the risk of PTSD by 1.93 times higher than either genotype or childhood events independently.*
Young et al., 2002	Genetics	142 (18 males); 91 PTSD dx, 51 healthy controls	<ol style="list-style-type: none"> 1 The presence of the DRD2 A1 allele was significantly higher in the patients with comorbid PTSD and AUD than any other group (19.8% vs. 6.9%).** 2 Participants with PTSD and the DRD2 A1 allele drank at twice the rate of the patients with PTSD alone.

PTSD = Posttraumatic Stress Disorder, AD = Alcohol Dependence, VETR = Vietnam Era Twin Registry, dx = diagnosis, A/SUD = Alcohol and/or Substance Use Disorder, rCBF = Regional Cerebral Blood Flow, NAA/Cr = N-acetylaspartate/creatine.

*
p < 0.05,

**
p < 0.001

Table 3

Pharmacological Studies of Comorbid PTSD and A/SUD Treatment.

Authors	Design	Participants	Length of Trial	Active Drug	Change in PTSD & A/SUD Symptoms
Alderman et al., 2009	Open label, completers analyzed	43 (29 completers); all male combat veterans in treatment for PTSD diagnosis; 23 (82.1%) reported alcohol use	8 week	Topiramate (200 mg/day) (anticonvulsant)	<ol style="list-style-type: none"> 1 CAPS score reduction (from 86.3 ± 21.1 to 67.1 ± 25.1).[*] 2 Decline in high risk drinking patterns (AUDIT; 31% to 14%, $p = .08$).
Back et al., 2006 ^d and Brady et al., 2005 ^d	Double-blind, placebo controlled study, intent to treat analyses	94 (51 male); civilian trauma; all current PTSD & AUD diagnoses	12 week	Sertraline (150 mg/titrated) (SSRI)	<ol style="list-style-type: none"> 1 21.1% were PTSD only responders ($\geq 30\%$ CAPS reduction), 14.5% were alcohol only responders ($\geq 75\%$ reduction in frequency of drinks and number of drinks per day), 46.1% were responders in both PTSD and AUD, and 18.4% were non-responders. 2 Results did not differ significantly by treatment group. 3 Reduction in PTSD symptoms correlated significantly with fewer percent days drinking, percent heavy drinking days, and average drinks per day (AUDIT; ASI).[*] 4 Significant correlation between treatment completion and PTSD symptom improvement.[*] 5 Improvement in alcohol symptoms alone or combined with PTSD symptoms first for 86% of participants. 6 Sertraline participants with less severe alcohol dependence and early-onset PTSD had significantly fewer drinks per drinking day.^{**} 7 Placebo participants with more severe alcohol dependence and later onset PTSD had significantly greater decreases in drinks per drinking day[*] and average number of drinks consumed per day.[*]
Brady et al., 1995	Open label pilot study, completers analyzed	9 (3 male); 6 completers; all PTSD & AUD diagnoses	12 week	Sertraline (50–200 mg/day)	<ol style="list-style-type: none"> 1 Significant decrease in PTSD symptoms. 2 Significant increase in days abstinent and decrease in number of drinks per days.
Hien et al., 2000	Open enrollment at methadone clinic	96 (47 male); 19.8% of participants had PTSD, 2/3 experienced some form of civilian trauma; reported alcohol and polysubstance use	--	Methadone	<ol style="list-style-type: none"> 1 Dropout rates did not differ between those with and without PTSD. 2 PTSD patients disclosed significantly more ongoing drug use (any substance) at 3 months, measured by positive urine drug screens (M 24.3, SD 20.9) than those without PTSD (M 8.9, SD 11.8).[*]

Authors	Design	Participants	Length of Trial	Active Drug	Change in PTSD & A/SUD Symptoms
Monnelly et al., 2004	Retrospective 30 treated with study med, 20 not	50 male veterans with AUD diagnoses; 90% of whom had PTSD	--	Quetiapine (atypical anti-psychotic); mean 58.8mg	<p>3 PTSD participants had significantly more ongoing cocaine use at 3 months at follow up (M 51.6, SD 37.6).*</p> <p>1 Quetiapine group had more days abstinent (M 280, SD 92.1) to (M 213.9, SD 99.1) *; and more days to relapse (M 217.3, SD 135.5) to (M 149.4, SD 115.4), p< 0.07.</p> <p>2 Mean number of hospitalizations for detox lower for quetiapine group (33% versus 45% in control group)</p>
Petrakis et al., 2006	(1) open randomization to disulfiram or no disulfiram; (2) double-blind randomization to naltrexone or placebo. Intent to treat analyses	93 (91 male); veterans; all current PTSD & AUD diagnoses	12 week	(1) Naltrexone 50 mg/day alone; (2) Placebo alone; (3) Disulfiram 250 mg/day and Naltrexone 50 mg/day; or (4) Disulfiram 250 mg/day and Placebo.	<p>1 Participants on any active medication showed improvements in alcohol symptoms (TLFB).</p> <p>2 PTSD participants on active medication had significantly more consecutive days of abstinence * and a lower percent of heavy drinking days. *</p> <p>3 Participants showed significant decrease in CAPS scores regardless of group assignment. **</p> <p>4 Disulfiram showed greater improvement in PTSD symptoms than naltrexone. *</p>
Trafton et al., 2006	Prospective, Observational	255 (248 male) opioid dependent veterans; 71 had PTSD diagnoses	--	Methadone or Levo-Alpha-Acetyl-Methadol (LAAM)	<p>1 Opioid substitution reduced substance use in patients with PTSD at the same rate as in patients without PTSD.</p>

^a same participants.

PTSD = Posttraumatic Stress Disorder, AUD = Alcohol Dependence, CAPS = Clinician Administered PTSD Scale, AUDIT = Alcohol Use Disorders Identification Test, ASI = Addiction Severity Index, TLFB = Timeline Follow Back,

* p < .05,

** p < .001