Published in final edited form as:

Addict Behav. 2014 February ; 39(2): . doi:10.1016/j.addbeh.2013.08.014.

Pharmacological Treatment of Comorbid PTSD and Substance Use Disorder: Recent Progress

Mehmet Sofuoglu, M.D., Ph.D., Robert Rosenheck, M.D., and Ismene Petrakis, M.D.

VA Connecticut Healthcare System, West Haven, CT and Yale University, School of Medicine, Department of Psychiatry, New Haven, CT

Abstract

Previous research has identified a strong association between posttraumatic stress disorder (PTSD) and substance use disorders (SUD), necessitating the development of treatments that address both conditions. Some pharmacotherapies are effective for the treatment of PTSD and SUD alone, however; no medications have been proven to be effective for the combination of these conditions. We review the recent advances in pharmacological treatment of comorbid PTSD and SUD. A randomized clinical trial of sertraline, a serotonin reuptake inhibitor (SSRI), did not show overall efficacy for comorbid PTSD and alcohol dependence (AD), although it may have efficacy among light drinkers. Another clinical trial demonstrated the efficacy of both disulfiram and naltrexone for the treatment of AD in individuals with PTSD. A more recent clinical trial suggested that norepinephrine uptake inhibitors may also have efficacy for the treatment of comorbid PTSD and AD. In animal and preliminary human studies, brain norepinephrine or glutamate/GABA have emerged as potential treatment targets for comorbid PTSD and SUD. Noradrenergic medications that are promising for comorbid PTSD and SUD include prazosin, guanfacine, and atomoxetine. Promising glutamate /GABA medications include topiramate, memantine, acamprosate, N-acetylcysteine (NAC), and ketamine. The safety and efficacy of these medications for the treatment of PTSD and SUD need to be tested in controlled clinical trials.

Keywords

PTSD; alcohol dependence; substance use disorder; comorbidity; pharmacotherapy

1. Introduction

Previous research support a strong association between posttraumatic stress disorder (PTSD) and substance use disorders (SUD). In both clinical samples and the general population, a high comorbidity between PTSD and SUD has been observed (Jacobsen, Southwick, & Kosten, 2001). Parallel to these findings, many preclinical and clinical studies support the role of exposure to trauma or stress in initiation and maintenance of SUD (Keyes,

[§]Mehmet Sofuoglu, Yale University, Department of Psychiatry, VA Connecticut Healthcare System, 950 Campbell Ave., Bldg. 36/116A4, West Haven, CT 06516, Phone: (203) 937-4809, Fax: (203) 937-3478, Mehmet.Sofuoglu@yale.edu.

Contributions: All authors participated in developing the overall content. All authors contributed and have approved the final manuscript.

Conflict of interest: MS serves as an expert witness on behalf of Pfizer in lawsuits related to varenicline. Other authors declare that they have no conflicts of interest.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Hatzenbuehler, & Hasin, 2011; Logrip, Zorrilla, & Koob, 2012). In addition, preclinical and clinical studies have provided neurobiological mechanisms linking PTSD and SUD, that may serve as potential treatment targets for this co-morbidity (Norman et al., 2012). This is an important and timely topic, for both military personnel and new veterans. As one might expect the recent conflicts in Iraq and Afghanistan have led to the large numbers of veterans diagnosed with PTSD after exposure to combat. Perhaps even more remarkable is that the number of veterans diagnosed with PTSD from the Vietnam Era who are seeking PTSD treatment from the VA has continued to grow at over 7% per year, even though the war ended over 30 years ago (Hermes, Rosenheck, Desai, & Fontana, 2012).

The goal of this paper is to provide an overview of the recent advances in pharmacological treatment of comorbid PTSD and SUD. We first provide a brief overview of epidemiologic studies examining the comorbidity between PTSD and SUD followed by an overview of possible biological mechanisms linking these disorders. We then review some recent studies focusing on pharmacological treatment of patients with PTSD and SUD, with a particular focus on comorbid PTSD and alcohol dependence (AD). Behavioral treatments of comorbid PTSD and SUD are not covered in this review (for recent reviews on this topic, see Kelly, Daley, & Douaihy, 2012; Keyes et al., 2011; McCarthy & Petrakis, 2010, as well as the 2010 VA/DOD Clinical Practice Guideline for management of PTSD).

2. PTSD and SUD Comorbidity

Strong associations between PTSD and SUD have been described in both civilians and combat veterans. In a population sample, Breslau has shown that adults with a history of PTSD, compared to those without trauma history, were 4.3 times more likely to have SUD (Breslau, Davis, & Schultz, 2003). In the general population, in persons with PTSD, estimates of prevalence of SUD ranged from 21.6% to 43.0%, compared with 8.1% to 24.7% among people with no diagnosis of PTSD (Jacobsen et al., 2001). Similar findings have also been observed in clinical samples. In a study from multiple treatment centers from Germany, among patients seeking treatment for alcohol and drug dependence, 34 and 30% had comorbid PTSD, respectively (Driessen et al., 2008). In another study from Netherlands, in individuals with SUD the rates of PTSD and trauma were 36.6 and 97 %, compared to 10.2 and 86.3 % rates in the control group (Gielen, Havermans, Tekelenburg, & Jansen, 2012). It is important to note that the associations observed in these studies were based on cross-sectional data and have not considered the common risk factors for both disorders. To address these limitations, Reed et al. conducted a longitudinal study in which 988 young adults were assessed for the emergence of SUD over one year period (Reed, Anthony, & Breslau, 2007). In that study, prior PTSD, compared with the no-trauma history, was associated with 4.9 time increased risk of emergence of SUD after controlling for common risk factors including childhood conduct problems, risk taking, and family socioeconomic status. This study supports the role of PTSD as a risk factor for development of SUD.

Department of Veterans Affairs (VA) data from 2009 show that of the 5.5 million veterans who received health services from 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 co-morbid substance abuse, nearly 3 times the rate in the general VA patient population (Kerfoot, Petrakis, & Rosenheck, 2011). Co-morbid PTSD and substance abuse was especially prevalent among younger veterans reaching 31.3% among those aged 35–54 dropping to 25.2% among those aged 55–65 and less than 10% among those over 65. However, a study of outpatients receiving specialized treatment for PTSD showed that among the youngest generation of combat veterans from Iraq and Afghanistan, 20% had a diagnosis of co-morbid alcohol use disorder and 6% drug use disorder. In contrast, among veterans of the wars in Iraq and Afghanistan receiving inpatient treatment these rates were

considerably higher at 39% and 20% respectively (Fontana & Rosenheck, 2008). Rates of SUD were even higher among Vietnam veterans treated in these specialized PTSD programs reaching 29% and 13%, respectively among outpatients, and 41% and 25% among inpatients.

3. Biological Mechanisms

The influence of stress system on drug-seeking and relapse is thought to be the key in uncovering the biological mechanisms linking PTSD and SUD (Logrip et al., 2012). A large body of evidence supports the role of stress in initiation and maintenance of drug use behavior. In animal studies, induction of physical or psychological experimental stress facilitates initiation of drug self-administration (Koob, 2008; Sinha, 2008) and facilitates relapse to drug use. Similarly, in humans, stress induction increases craving and drug use behavior (Brady & Sinha, 2005; Buchmann et al., 2010).

In preclinical studies examining the influence of stress on vulnerability to drug seeking behavior, both corticotropin releasing hormone (CRH) and norepinephrine emerged as important mediators (Charmandari, Tsigos, & Chrousos, 2005). CRH initiates the neuroendocrine response to stress and elevated CRH levels were found in the cerebrospinal fluid of PTSD patients (Bremner et al., 1997). Many studies have shown that CRH administration enhances the pharmacological effects of stimulant drugs and facilitates stress-induced drug-seeking behavior in rodents (Shaham et al., 1997).

The neurotransmitter norepinephrine modulates many brain functions including attention, arousal, and stress response (Arnsten, 2011; Charmandari et al., 2005). Norepinephrine also plays a key role in stress-induced reinstatement of drug use (Erb, 2010) and encoding of emotional memories in the amygdala and prefrontal cortex (Krystal & Neumeister, 2009). Patients with PTSD have elevated norepinephrine levels in the cerebrospinal fluid, indicating increased norepinephrine activity (Geraciotti et al., 2008). Medications targeting norepinephrine may have efficacy for treating both SUD and PTSD (Norman et al., 2012; Sofuoglu & Sewell, 2009).

In addition to CRH and norepinephrine, other neurotransmitters, especially glutamate and GABA play key roles in neurobiology of PTSD and SUD. Glutamate signaling through the NMDA- and AMPA-type receptors are central in memory process through initiation of long term potentiation (LTP), a prominent mechanism underlying learning and memory (Myers, Carlezon, & Davis, 2011). GABA is the main inhibitory neurotransmitter in the brain. Both glutamate and GABA are important potential treatment targets for comorbid PTSD and SUD.

Cumulating evidence suggests that an important mechanism that maintains drug use behavior may be the relief of negative affect. Presence of either depressive or PTSD symptoms have been shown to increase the expected reward from alcohol (Murphy et al., 2012) and rewarding effects of stimulant drugs (Sofuoglu, Brown, Babb, & Hatsukami, 2001; Sofuoglu, Dudish-Poulsen, Brown, & Hatsukami, 2003). For many substances of abuse including alcohol, opioids, sedatives, stimulants, and nicotine (Hughes, Higgins, & Bickel, 1994), abstinence from use is characterized by negative affective symptoms including dysphoric or depressed mood, anxiety, frustration, anger, and irritability. Thus, alleviation of the negative affect may be a motivation for addicted individuals with PTSD to continue using substances (Logrip et al., 2012). The core symptoms of PTSD including persistent re-experiencing of the traumatic event, persistent avoidance of stimuli associated with the trauma, and persistent symptoms of increased arousal may all further enhance the negative affective symptoms when the person abstains from drug use.

Human laboratory studies provided further support for mechanisms linking the comorbidity between PTSD and SUD. Individuals with comorbid PTSD and SUD report increased craving for alcohol and cocaine following exposure to personalized trauma cues, in the absence of cues related to drugs and alcohol (Coffey et al., 2002). These results support the importance of trauma-related memories in ongoing drug use.

4. Pharmacotherapies

Pharmacotherapies for PTSD have targeted reduction of PTSD symptom severity. Selective serotonin reuptake inhibitors (SSRIs) are effective in reducing symptoms of PTSD (Ravindran & Stein, 2009). However, limitations exist: their effects are modest, they have mostly been tested in civilian populations, and some evidence suggests they may be less effective in men than in women. Benzodiazepines are commonly used as adjunctive treatment of PTSD to alleviate sleep disturbance, irritability, and other hyperarousal symptoms (Hawkins, Malte, Imel, Saxon, & Kivlahan, 2012). Benzodiazepines, however, did not show efficacy in controlled studies as adjunctive medications for individuals with PTSD (Braun, Greenberg, Dasberg, & Lerer, 1990; Gelpin, Bonne, Peri, Brandes, & Shalev, 1996). Further, the abuse liability of benzodiazepines as well as the negative influence of benzodiazepines on exposure treatment for PTSD further underscores the potentially harmful effects of benzodiazepines in patients with PTSD (van Minnen, Arntz, & Keijsers, 2002). Atypical antipsychotics (olanzapine, risperidone, quetiapine, ziprasidone, and aripiprazole) are also commonly used as adjunctive treatment to reduce symptoms of PTSD such as hyperarousal symptoms (Ravindran & Stein, 2009). A meta-analysis of seven studies (Pae et al., 2008) found that antipsychotics reduce the severity of re-experiencing/intrusion subscale of the Clinician Administered PTSD Scale (CAPS) (Blake et al., 1995), but a recent multisite, double-blind placebo controlled study did not find risperidone effective in reducing symptoms of PTSD in military-related PTSD patients (Krystal et al., 2011). Clearly more effective medication treatments are needed for the treatment of PTSD.

4.1 Randomized clinical trials for comorbid SUD and PTSD

Only three randomized clinical trials have examined the efficacy of pharmacotherapies for comorbid SUD and PTSD.

Brady et al. (2005) randomized 94 individuals with comorbid PTSD and AD to 150 mg/day of sertraline, a selective serotonin reuptake inhibitor, or placebo for 12 weeks. Overall, sertraline was not better than placebo for reducing alcohol use or PTSD severity. Interestingly, individuals with less severe AD and early-onset PTSD had greater reduction in alcohol use with sertraline treatment. These findings need be replicated in future clinical trials (Brady et al., 2005).

Petrakis et al. (2006) examined the safety and efficacy of the two Food And Drug Administration (FDA)-approved medications (at the time) of disulfiram and naltrexone in alcohol dependent veterans with comorbid psychiatric disorders including PTSD. Disulfiram inhibits the alcohol dehydrogenase enzyme, which converts acetaldehyde to acetate, resulting in the disulfiram-alcohol reaction which is characterized by flushing, weakness, nausea, tachycardia, hypotension, and in severe cases death (Chick, 1999). Naltrexone is an opioid antagonist with highest affinity for the μ -opiate receptor type. A total of 254 veterans with a major Axis I psychiatric disorder and comorbid AD were treated for 12 weeks at three outpatient VA clinics. Randomization included (1) open randomization to disulfiram or no disulfiram; and (2) double-blind randomization to naltrexone or placebo in a two-by-two design. This resulted in four treatment groups: (1) naltrexone alone; (2) placebo alone; (3) disulfiram and naltrexone; or (4) disulfiram and placebo. Out of 254 randomized, a significant number, 93 patients or 36.6% met DSM-IV criteria for PTSD. Results suggested

that those with PTSD had better alcohol outcomes when treated with active medication (naltrexone, disulfiram or the combination) than they if assigned placebo; further overall symptoms of PTSD improved suggesting that disulfiram and naltrexone are effective and safe for individuals with PTSD and comorbid AD (Petrakis et al., 2006).

A more recent study, compared paroxetine, an SSRI, to desipramine, a norepinephrine reuptake inhibitor, and also evaluated the adjunctive efficacy of naltrexone, relative to placebo in 88 predominantly male veterans with current diagnosis of AD and PTSD (Petrakis et al., 2012). Individuals were randomly assigned under double-blind conditions to one of four groups: paroxetine plus naltrexone; paroxetine plus placebo; desipramine plus naltrexone; desipramine plus placebo. While paroxetine was as effective as desipramine for the treatment of PTSD symptoms, desipramine was superior to paroxetine with respect to study retention and alcohol use outcomes. Naltrexone reduced alcohol craving relative to placebo, but it conferred no advantage on drinking use outcomes. Although the serotonin uptake inhibitors are the only FDA-approved medications for the treatment of PTSD, the current study suggests that norepinephrine reuptake inhibitors may present clinical advantages when treating male veterans with PTSD and AD with PTSD (Petrakis et al., 2012).

4.2 Other promising pharmacotherapies for SUD and PTSD

4.2.1 Noradrenergic Medications—The α_1 -adrenergic agonist prazosin reduces cocaine, alcohol, nicotine, and heroin self administration in rodents (Forget et al., 2010; Greenwell, Walker, Cottone, Zorrilla, & Koob, 2009; Le et al., 2011). In three controlled trials, prazosin, compared to placebo, improved sleep as well as other symptoms of PTSD (Raskind et al., 2007; Taylor et al., 2006; Taylor et al., 2008). In these clinical studies, prazosin treatment increased the total sleep time and shifted dream content from trauma-related nightmares to more “normal”, less distressing content. Prazosin also improved emotional responses to trauma cues in individuals with PTSD (Taylor et al., 2006). A clinical trial is underway to test the efficacy of prazosin in patients with PTSD and SUD (NCT00744055; clinicaltrials.gov).

The beta-adrenergic antagonist, propranolol, attenuates stress induced cocaine and cue-induced nicotine self-administration (Chiamulera, Tedesco, Zangrandi, Giuliano, & Fumagalli, 2010). In human studies, propranolol showed some promise for treatment of cocaine addiction, especially in those with high withdrawal severity (Kampman et al., 2006). Propranolol has shown promise as a preventative agent for PTSD (Brunet et al., 2011; Hurlmann et al., 2010), although some results have not been positive (Hoge et al., 2012).

α_2 -adrenergic agonists block the stress-and cue induced self-administration of cocaine and alcohol (Le et al., 2011; Smith & Aston-Jones, 2011). In preliminary human studies, guanfacine, an α_2 -adrenergic agonist showed promise for cue-induced craving in cocaine users (Fox et al., 2012). In a small randomized study, guanfacine did not show efficacy for the treatment of PTSD (Neylan et al., 2006).

Given the promising findings with desipramine (Petrakis et al., 2012), other norepinephrine transporter inhibitors with greater selectivity and better side-effect profile may be considered. One such medication is atomoxetine, which is marketed for the treatment of ADHD. In a human laboratory study, atomoxetine showed promise for amphetamine addiction (Sofuoglu, Poling, Hill, & Kosten, 2009), but it has not been examined for the treatment of PTSD.

4.2.2 Glutamate and GABA Medications—Memantine, a non-competitive NMDA antagonist has also shown efficacy in reducing cue-induced craving for alcohol in AD

patients (Krupitsky et al., 2007). In a small open label study, memantine reduced the severity of PTSD symptoms in combat veterans (Battista, Hierholzer, Khouzam, Barlow, & O'Toole, 2007). In a double-blind randomized comparison of memantine and escitalopram, a selective serotonin reuptake inhibitor, for the treatment of major depression comorbid with AD, both treatments were equally effective (Muhonen, Lonnqvist, Juva, & Alho, 2008). Efficacy of memantine for comorbid PTSD and AD has not been tested.

N-acetylcysteine (NAC), a medication used for the treatment of acetaminophen overdose, is thought to act by normalizing reduced extracellular glutamate levels in nucleus accumbens by stimulating the cystine–glutamate antiporter (Baker et al., 2003). NAC has shown some positive results in small clinical trials for cocaine and nicotine addiction and gambling (Grant, Kim, & Odlaug, 2007; Knackstedt et al., 2009; Mardikian, LaRowe, Hedden, Kalivas, & Malcolm, 2007). In an open label clinical trial, NAC also showed efficacy as an adjunct treatment for bipolar depression (Berk et al., 2011). Larger studies are underway to test its efficacy in these disorders. An ongoing study is testing the efficacy of NAC for the treatment of PTSD (NCT01664260; clinicaltrials.gov).

Ketamine is an NMDA receptor antagonist. It has well-documented psychotomimetic effects at low doses and dissociative anesthetic effects at high doses. Ketamine is shown to have rapid antidepressant effects in depressed individuals (Berman et al., 2000). Interestingly, among OIF/OEF soldiers with burns and who received ketamine during their operations were less likely to have PTSD compared to those who did not receive ketamine (McGhee, Maani, Garza, Gaylord, & Black, 2008). Further studies in this area are underway. Ketamine is currently being tested in randomized clinical trial for the rapid treatment of PTSD (NCT00749203; clinicaltrials.gov) as well as for the treatment of comorbid AD and major depression (NCT01551329; clinicaltrials.gov).

Acamprosate, an NMDA and GABA receptor modulator, is approved for the treatment of AD. However, acamprosate has shown mixed findings in randomized clinical trials for AD and appears to be moderately effective in preventing relapse (Gual & Leher, 2001; Rosner et al., 2010). Preliminary evidence suggest that acamprosate may be effective for the treatment of anxiety disorders (Schwartz, Siddiqui, Raza, & Costello, 2010) and comorbid AD and bipolar disorder (Tolliver, DeSantis, Brown, Prisciandaro, & Brady, 2012). Acamprosate has not been tested for the treatment of comorbid PTSD and SUD.

Topiramate, an antiseizure medication, is an agonist on the GABA_A receptor and blocks AMPA/kainite-subtype of glutamate receptor, and inhibits carbonic anhydrase (Gibbs, Sombati, DeLorenzo, & Coulter, 2000; Herrero, Del Olmo, Gonzalez-Escalada, & Solis, 2002; Shank, Gardocki, Streeter, & Maryanoff, 2000). Topiramate has shown efficacy for the treatment of AD in a multisite clinical trial (Johnson et al., 2007). An 8- week open label study demonstrated topiramate's safety and potential efficacy for comorbid PTSD and AD in 43 male combat veterans (Alderman, McCarthy, Condon, Marwood, & Fuller, 2009). Topiramate's efficacy for PTSD and AD needs to be tested in randomized clinical trials.

5. Conclusions

To summarize, cumulating evidence support a strong link between PTSD and SUD, necessitating the development of treatment agents and strategies that can address both conditions. Although effective pharmacotherapies are available for the treatment of PTSD and SUD alone, currently there are no proven medications for the treatment of both conditions.

Table 1 summarizes several randomized clinical trials that have been conducted for the pharmacotherapy of PTSD and SUD including the quality of evidence (US Preventive

Services Task Force, 1989). Sertraline did not show overall efficacy for comorbid PTSD and AD (Brady et al., 2005), although it may have efficacy among light drinkers. Another clinical trial demonstrated the efficacy of both disulfiram and naltrexone for the treatment of AD in individuals with PTSD (Petrakis et al., 2006). A more recent clinical trial suggested that norepinephrine uptake inhibitors may have efficacy for the treatment of comorbid PTSD and AD (Petrakis et al., 2012). It is notable that there are no published randomized clinical trials testing the efficacy of promising medications for comorbid PTSD and other drugs of abuse.

As summarized above, animal and preliminary human studies suggested that norepinephrine, glutamate, or GABA are potential treatment targets for pharmacologic intervention in comorbid PTSD and SUD. Promising noradrenergic medications include prazosin (Raskind et al., 2007; Taylor et al., 2008), guanfacine (Fox et al., 2012), and atomoxetine (Sofuoglu, Poling, Hill, & Kosten, 2009). Promising glutamate/GABA medications include topiramate (Alderman et al., 2009), memantine (Battista et al., 2007), acamprosate (Tolliver et al., 2012), NAC (Mardikian, LaRowe, Hedden, Kalivas, & Malcolm, 2007), and ketamine (McGhee et al., 2008). The safety and efficacy of these medications for the treatment of PTSD and SUD need to be tested in controlled clinical trials.

Future studies also need to address how these medication treatments can be optimally combined with behavioral treatments. A good example of such an approach is an ongoing study conducted by Foa et al. which combined naltrexone with exposure treatment for individuals with PTSD and AD (Foa & Williams, 2010). The treatment arms include naltrexone alone, exposure treatment alone, combination of naltrexone and exposure treatment, and pill placebo. Such studies will provide better guidance for the clinical management of patients with PTSD and SUD.

Acknowledgments

Role of funding sources: This research was supported by the Veterans Administration Mental Illness Research, Education and Clinical Center (MIRECC) and National Institute on Drug Abuse (NIDA) grants K02-DA021304 (MS).

References

- Alderman CP, McCarthy LC, Condon JT, Marwood AC, Fuller JR. Topiramate in combat-related posttraumatic stress disorder. *Ann Pharmacother.* 2009; 43(4):635–641. [PubMed: 19336652]
- Arnsten AF. Catecholamine influences on dorsolateral prefrontal cortical networks. *Biol Psychiatry.* 2011; 69(12):e89–99. [PubMed: 21489408]
- Baker DA, McFarland K, Lake RW, Shen H, Toda S, Kalivas PW. N-acetyl cysteine-induced blockade of cocaine-induced reinstatement. *Annals of the New York Academy of Sciences.* 2003; 1003:349–351. [PubMed: 14684458]
- Battista MA, Hierholzer R, Khouzam HR, Barlow A, O'Toole S. Pilot trial of memantine in the treatment of posttraumatic stress disorder. *Psychiatry.* 2007; 70(2):167–174. [PubMed: 17661541]
- Berk M, Dean O, Cotton SM, Gama CS, Kapczinski F, Fernandes BS, Malhi GS. The efficacy of N-acetylcysteine as an adjunctive treatment in bipolar depression: An open label trial. *Journal of Affective Disorders.* 2011; 135(1–3):389–394. [PubMed: 21719110]
- Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, Krystal JH. Antidepressant effects of ketamine in depressed patients. *Biol Psychiatry.* 2000; 47(4):351–354. [PubMed: 10686270]
- Blake DD, Weathers FW, Nagy LM, Kaloupek DG, Gusman FD, Charney DS, Keane TM. The development of a Clinician-Administered PTSD Scale. *Journal of traumatic stress.* 1995; 8(1):75–90. [PubMed: 7712061]

- Brady KT, Sinha R. Co-occurring mental and substance use disorders: the neurobiological effects of chronic stress. *Am J Psychiatry*. 2005; 162(8):1483–1493. [PubMed: 16055769]
- Brady KT, Sonne S, Anton RF, Randall CL, Back SE, Simpson K. Sertraline in the treatment of co-occurring alcohol dependence and posttraumatic stress disorder. *Alcohol Clin Exp Res*. 2005; 29(3): 395–401. [PubMed: 15770115]
- Braun P, Greenberg D, Dasberg H, Lerer B. Core symptoms of posttraumatic stress disorder unimproved by alprazolam treatment. *The Journal of clinical psychiatry*. 1990; 51(6):236–238. [PubMed: 2189869]
- Bremner JD, Licinio J, Darnell A, Krystal JH, Owens MJ, Southwick SM, Charney DS. Elevated CSF corticotropin-releasing factor concentrations in posttraumatic stress disorder. *Am J Psychiatry*. 1997; 154(5):624–629. [PubMed: 9137116]
- Breslau N, Davis GC, Schultz LR. Posttraumatic stress disorder and the incidence of nicotine, alcohol, and other drug disorders in persons who have experienced trauma. *Arch Gen Psychiatry*. 2003; 60(3):289–294. [PubMed: 12622662]
- Brunet A, Poundja J, Tremblay J, Bui E, Thomas E, Orr SP, Pitman RK. Trauma reactivation under the influence of propranolol decreases posttraumatic stress symptoms and disorder: 3 open-label trials. *Journal of clinical psychopharmacology*. 2011; 31(4):547–550. [PubMed: 21720237]
- Buchmann AF, Laucht M, Schmid B, Wiedemann K, Mann K, Zimmermann US. Cigarette craving increases after a psychosocial stress test and is related to cortisol stress response but not to dependence scores in daily smokers. *J Psychopharmacol*. 2010; 24(2):247–255. [PubMed: 18957475]
- Charmandari E, Tsigos C, Chrousos G. Endocrinology of the stress response. *Annual review of physiology*. 2005; 67:259–284.
- Chiamulera C, Tedesco V, Zangrandi L, Giuliano C, Fumagalli G. Propranolol transiently inhibits reinstatement of nicotine-seeking behaviour in rats. *J Psychopharmacol*. 2010; 24(3):389–395. [PubMed: 18832430]
- Chick J. Safety issues concerning the use of disulfiram in treating alcohol dependence. *Drug Saf*. 1999; 20(5):427–435. [PubMed: 10348093]
- Coffey SF, Saladin ME, Drobos DJ, Brady KT, Dansky BS, Kilpatrick DG. Trauma and substance cue reactivity in individuals with comorbid posttraumatic stress disorder and cocaine or alcohol dependence. *Drug Alcohol Depend*. 2002; 65(2):115–127. [PubMed: 11772473]
- Driessen M, Schulte S, Luedecke C, Schaefer I, Sutmann F, Ohlmeier M, Havemann-Reinicke U. Trauma and PTSD in patients with alcohol, drug, or dual dependence: a multi-center study. *Alcoholism, clinical and experimental research*. 2008; 32(3):481–488.
- Erb S. Evaluation of the relationship between anxiety during withdrawal and stress-induced reinstatement of cocaine seeking. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*. 2010; 34(5):798–807. [PubMed: 19969038]
- Foa EB, Williams MT. Methodology of a randomized double-blind clinical trial for comorbid posttraumatic stress disorder and alcohol dependence. *Ment Health Subst Use*. 2010; 3(2):131–147. [PubMed: 22942892]
- Fontana A, Rosenheck R. Treatment-seeking veterans of Iraq and Afghanistan: comparison with veterans of previous wars. *J Nerv Ment Dis*. 2008; 196(7):513–521. [PubMed: 18626291]
- Forget B, Wertheim C, Mascia P, Pushparaj A, Goldberg SR, Le Foll B. Noradrenergic alpha1 receptors as a novel target for the treatment of nicotine addiction. *Neuropsychopharmacology*. 2010; 35(8):1751–1760. [PubMed: 20357760]
- Fox HC, Seo D, Tuit K, Hansen J, Kimmerling A, Morgan PT, Sinha R. Guanfacine effects on stress, drug craving and prefrontal activation in cocaine dependent individuals: preliminary findings. *J Psychopharmacol*. 2012; 26(7):958–972. [PubMed: 22234929]
- Gelpin E, Bonne O, Peri T, Brandes D, Shalev AY. Treatment of recent trauma survivors with benzodiazepines: a prospective study. *The Journal of clinical psychiatry*. 1996; 57(9):390–394. [PubMed: 9746445]
- Geraciotti TD Jr, Baker DG, Kasckow JW, Strawn JR, Jeffrey Mulchahey J, Dashevsky BA, Ekhtator NN. Effects of trauma-related audiovisual stimulation on cerebrospinal fluid norepinephrine and

- corticotropin-releasing hormone concentrations in post-traumatic stress disorder. *Psychoneuroendocrinology*. 2008; 33(4):416–424. [PubMed: 18295412]
- Gibbs JW 3rd, Sombati S, DeLorenzo RJ, Coulter DA. Cellular actions of topiramate: blockade of kainate-evoked inward currents in cultured hippocampal neurons. *Epilepsia*. 2000; 41(Suppl 1):S10–16. [PubMed: 10768293]
- Gielen N, Havermans RC, Tekelenburg M, Jansen A. Prevalence of post-traumatic stress disorder among patients with substance use disorder: it is higher than clinicians think it is. *Eur J Psychotraumatol*. 2012;3.
- Grant JE, Kim SW, Odlaug BL. N-acetyl cysteine, a glutamate-modulating agent, in the treatment of pathological gambling: a pilot study. *Biological psychiatry*. 2007; 62(6):652–657. [PubMed: 17445781]
- Greenwell TN, Walker BM, Cottone P, Zorrilla EP, Koob GF. The alpha1 adrenergic receptor antagonist prazosin reduces heroin self-administration in rats with extended access to heroin administration. *Pharmacol Biochem Behav*. 2009; 91(3):295–302. [PubMed: 18703080]
- Gual A, Leher P. Acamprosate during and after acute alcohol withdrawal: a double-blind placebo-controlled study in Spain. *Alcohol Alcohol*. 2001; 36(5):413–418. [PubMed: 11524307]
- Hawkins EJ, Malte CA, Imel ZE, Saxon AJ, Kivlahan DR. Prevalence and trends of benzodiazepine use among Veterans Affairs patients with posttraumatic stress disorder, 2003–2010. *Drug and alcohol dependence*. 2012
- Hermes ED, Rosenheck RA, Desai R, Fontana AF. Recent trends in the treatment of posttraumatic stress disorder and other mental disorders in the VHA. *Psychiatr Serv*. 2012; 63(5):471–476. [PubMed: 22422018]
- Herrero AI, Del Olmo N, Gonzalez-Escalada JR, Solis JM. Two new actions of topiramate: inhibition of depolarizing GABA(A)- mediated responses and activation of a potassium conductance. *Neuropharmacology*. 2002; 42(2):210–220. [PubMed: 11804617]
- Hoge EA, Worthington JJ, Nagurney JT, Chang Y, Kay EB, Feterowski CM, Pitman RK. Effect of acute posttrauma propranolol on PTSD outcome and physiological responses during script-driven imagery. *CNS neuroscience & therapeutics*. 2012; 18(1):21–27. [PubMed: 22070357]
- Hughes JR, Higgins ST, Bickel WK. Nicotine withdrawal versus other drug withdrawal syndromes: similarities and dissimilarities. *Addiction*. 1994; 89(11):1461–1470. [PubMed: 7841857]
- Hurlemann R, Walter H, Rehme AK, Kukolja J, Santoro SC, Schmidt C, Onur OA. Human amygdala reactivity is diminished by the beta-noradrenergic antagonist propranolol. *Psychological medicine*. 2010; 40(11):1839–1848. [PubMed: 20102667]
- Jacobsen LK, Southwick SM, Kosten TR. Substance use disorders in patients with posttraumatic stress disorder: a review of the literature. *Am J Psychiatry*. 2001; 158(8):1184–1190. [PubMed: 11481147]
- Johnson BA, Rosenthal N, Capece JA, Wiegand F, Mao L, Beyers K, Swift RM. Topiramate for treating alcohol dependence: a randomized controlled trial. *JAMA*. 2007; 298(14):1641–1651. [PubMed: 17925516]
- Kampman KM, Dackis C, Lynch KG, Pettinati H, Tirado C, Gariti P, O'Brien CP. A double-blind, placebo-controlled trial of amantadine, propranolol, and their combination for the treatment of cocaine dependence in patients with severe cocaine withdrawal symptoms. *Drug and alcohol dependence*. 2006; 85(2):129–137. [PubMed: 16697124]
- Kelly TM, Daley DC, Douaihy AB. Treatment of substance abusing patients with comorbid psychiatric disorders. *Addict Behav*. 2012; 37(1):11–24. [PubMed: 21981788]
- Kerfoot KE, Petrakis IL, Rosenheck RA. Dual Diagnosis in an Aging Population: Prevalence of Psychiatric Disorders, Comorbid Substance Abuse, and Mental Health Service Utilization in the Department of Veterans Affairs. *Journal of Dual Diagnosis*. 2011; 7(1–2):4–13.
- Keyes KM, Hatzenbuehler ML, Hasin DS. Stressful life experiences, alcohol consumption, and alcohol use disorders: the epidemiologic evidence for four main types of stressors. *Psychopharmacology (Berl)*. 2011; 218(1):1–17. [PubMed: 21373787]
- Knackstedt LA, LaRowe S, Mardikian P, Malcolm R, Upadhyaya H, Hedden S, Kalivas PW. The role of cystine-glutamate exchange in nicotine dependence in rats and humans. *Biological psychiatry*. 2009; 65(10):841–845. [PubMed: 19103434]

- Koob GF. A role for brain stress systems in addiction. *Neuron*. 2008; 59(1):11–34. [PubMed: 18614026]
- Krupitsky EM, Neznanova O, Masalov D, Burakov AM, Didenko T, Romanova T, Krystal JH. Effect of memantine on cue-induced alcohol craving in recovering alcohol-dependent patients. *The American journal of psychiatry*. 2007; 164(3):519–523. [PubMed: 17329479]
- Krystal JH, Neumeister A. Noradrenergic and serotonergic mechanisms in the neurobiology of posttraumatic stress disorder and resilience. *Brain Res*. 2009; 1293:13–23. [PubMed: 19332037]
- Krystal JH, Rosenheck RA, Cramer JA, Vessicchio JC, Jones KM, Vertrees JE, Pmid. Adjunctive risperidone treatment for antidepressant-resistant symptoms of chronic military service-related PTSD: a randomized trial. *JAMA: the journal of the American Medical Association*. 2011; 306(5): 493–502. [PubMed: 21813427]
- Le AD, Funk D, Juzysch W, Coen K, Navarre BM, Cifani C, Shaham Y. Effect of prazosin and guanfacine on stress-induced reinstatement of alcohol and food seeking in rats. *Psychopharmacology (Berl)*. 2011; 218(1):89–99. [PubMed: 21318567]
- Logrip ML, Zorrilla EP, Koob GF. Stress modulation of drug self-administration: implications for addiction comorbidity with post-traumatic stress disorder. *Neuropharmacology*. 2012; 62(2):552–564. [PubMed: 21782834]
- Mardikian PN, LaRowe SD, Hedden S, Kalivas PW, Malcolm RJ. An open-label trial of N-acetylcysteine for the treatment of cocaine dependence: a pilot study. *Progress in neuro-psychopharmacology & biological psychiatry*. 2007; 31(2):389–394. [PubMed: 17113207]
- McCarthy E, Petrakis I. Epidemiology and management of alcohol dependence in individuals with post-traumatic stress disorder. *CNS drugs*. 2010; 24(12):997–1007. [PubMed: 21090836]
- McGhee LL, Maani CV, Garza TH, Gaylord KM, Black IH. The correlation between ketamine and posttraumatic stress disorder in burned service members. *The Journal of trauma*. 2008; 64(2 Suppl):S195–198. Discussion S197–198. [PubMed: 18376165]
- Muhonen LH, Lonnqvist J, Juva K, Alho H. Double-blind, randomized comparison of memantine and escitalopram for the treatment of major depressive disorder comorbid with alcohol dependence. *The Journal of clinical psychiatry*. 2008; 69(3):392–399. [PubMed: 18348597]
- Murphy JG, Yurasek AM, Dennhardt AA, Skidmore JR, McDevitt-Murphy ME, Mackillop J, Martens MP. Symptoms of depression and PTSD are associated with elevated alcohol demand. *Drug and alcohol dependence*. 2012
- Myers KM, Carlezon WA Jr, Davis M. Glutamate receptors in extinction and extinction-based therapies for psychiatric illness. *Neuropsychopharmacology*. 2011; 36(1):274–293. [PubMed: 20631689]
- Neylan TC, Lenoci M, Samuelson KW, Metzler TJ, Henn-Haase C, Hierholzer RW, Marmar CR. No improvement of posttraumatic stress disorder symptoms with guanfacine treatment. *Am J Psychiatry*. 2006; 163(12):2186–2188. [PubMed: 17151174]
- Norman SB, Myers US, Wilkins KC, Goldsmith AA, Hristova V, Huang Z, Robinson SK. Review of biological mechanisms and pharmacological treatments of comorbid PTSD and substance use disorder. *Neuropharmacology*. 2012; 62(2):542–551. [PubMed: 21600225]
- Pae CU, Lim HK, Peindl K, Ajwani N, Serretti A, Patkar AA, Lee C. The atypical antipsychotics olanzapine and risperidone in the treatment of posttraumatic stress disorder: a meta-analysis of randomized, double-blind, placebo-controlled clinical trials. *International clinical psychopharmacology*. 2008; 23(1):1–8. [PubMed: 18090502]
- Petrakis IL, Poling J, Levinson C, Nich C, Carroll K, Ralevski E, Rounsaville B. Naltrexone and disulfiram in patients with alcohol dependence and comorbid post-traumatic stress disorder. *Biol Psychiatry*. 2006; 60(7):777–783. [PubMed: 17008146]
- Petrakis IL, Ralevski E, Desai N, Trevisan L, Gueorguieva R, Rounsaville B, Krystal JH. Noradrenergic vs Serotonergic Antidepressant with or without Naltrexone for Veterans with PTSD and Comorbid Alcohol Dependence. *Neuropsychopharmacology*. 2012; 37(4):996–1004. [PubMed: 22089316]
- Raskind MA, Peskind ER, Hoff DJ, Hart KL, Holmes HA, Warren D, Pmid. A parallel group placebo controlled study of prazosin for trauma nightmares and sleep disturbance in combat veterans with post-traumatic stress disorder. *Biol Psychiatry*. 2007; 61(8):928–934. [PubMed: 17069768]

- Ravindran LN, Stein MB. Pharmacotherapy of PTSD: premises, principles, and priorities. *Brain research*. 2009; 1293:24–39. [PubMed: 19332035]
- Reed PL, Anthony JC, Breslau N. Incidence of drug problems in young adults exposed to trauma and posttraumatic stress disorder: do early life experiences and predispositions matter? *Arch Gen Psychiatry*. 2007; 64(12):1435–1442. [PubMed: 18056552]
- Rosner S, Hackl-Herrwerth A, Leucht S, Leherer P, Vecchi S, Soyka M. Acamprosate for alcohol dependence. *Cochrane Database Syst Rev*. 2010; (9):CD004332. [PubMed: 20824837]
- Schwartz TL, Siddiqui UA, Raza S, Costello A. Acamprosate calcium as augmentation therapy for anxiety disorders. *Ann Pharmacother*. 2010; 44(12):1930–1932. [PubMed: 21062908]
- Shaham Y, Funk D, Erb S, Brown TJ, Walker CD, Stewart J. Corticotropin-releasing factor, but not corticosterone, is involved in stress-induced relapse to heroin-seeking in rats. *J Neurosci*. 1997; 17(7):2605–2614. [PubMed: 9065520]
- Shank RP, Gardocki JF, Streeter AJ, Maryanoff BE. An overview of the preclinical aspects of topiramate: pharmacology, pharmacokinetics, and mechanism of action. *Epilepsia*. 2000; 41(Suppl 1):S3–9. [PubMed: 10768292]
- Sinha R. Chronic stress, drug use, and vulnerability to addiction. *Annals of the New York Academy of Sciences*. 2008; 1141:105–130. [PubMed: 18991954]
- Smith RJ, Aston-Jones G. $\alpha(2)$ Adrenergic and imidazoline receptor agonists prevent cue-induced cocaine seeking. *Biol Psychiatry*. 2011; 70(8):712–719. [PubMed: 21783176]
- Sofuoglu M, Brown S, Babb DA, Hatsukami DK. Depressive symptoms modulate the subjective and physiological response to cocaine in humans. *Drug and alcohol dependence*. 2001; 63(2):131–137. [PubMed: 11376917]
- Sofuoglu M, Dudish-Poulsen S, Brown SB, Hatsukami DK. Association of cocaine withdrawal symptoms with more severe dependence and enhanced subjective response to cocaine. *Drug and alcohol dependence*. 2003; 69(3):273–282. [PubMed: 12633913]
- Sofuoglu M, Poling J, Hill K, Kosten T. Atomoxetine attenuates dextroamphetamine effects in humans. *The American journal of drug and alcohol abuse*. 2009; 35(6):412–416. [PubMed: 20014909]
- Sofuoglu M, Sewell RA. Norepinephrine and stimulant addiction. *Addiction biology*. 2009; 14(2): 119–129. [PubMed: 18811678]
- Taylor FB, Lowe K, Thompson C, McFall MM, Peskind ER, Kanter ED, Raskind MA. Daytime prazosin reduces psychological distress to trauma specific cues in civilian trauma posttraumatic stress disorder. *Biol Psychiatry*. 2006; 59(7):577–581. [PubMed: 16460691]
- Taylor FB, Martin P, Thompson C, Williams J, Mellman TA, Gross C, Raskind MA. Prazosin effects on objective sleep measures and clinical symptoms in civilian trauma posttraumatic stress disorder: a placebo-controlled study. *Biol Psychiatry*. 2008; 63(6):629–632. [PubMed: 17868655]
- Tolliver BK, DeSantis SM, Brown DG, Prisciandaro JJ, Brady KT. A randomized, double-blind, placebo-controlled clinical trial of acamprosate in alcohol-dependent individuals with bipolar disorder: a preliminary report. *Bipolar Disorders*. 2012; 14(1):54–63. [PubMed: 22329472]
- US Preventive Services Task Force. Guide to clinical preventive services: an assessment of the effectiveness of 169 interventions. Baltimore: Williams & Wilkin; 1989.
- van Minnen A, Arntz A, Keijsers GP. Prolonged exposure in patients with chronic PTSD: predictors of treatment outcome and dropout. *Behav Res Ther*. 2002; 40(4):439–457. [PubMed: 12002900]

Highlights

Evidence supports a strong link between PTSD and substance use disorders (SUD).

Pharmacotherapies are effective for the treatment of PTSD and SUD alone.

However; there are no proven medications that will treat both conditions.

Norepinephrine or glutamate/GABA are treatment targets for comorbid PTSD and SUD.

Medications acting on these targets need to be tested in controlled clinical trials.

Table 1

Potential medications for the treatment of comorbid PTSD and SUD

Medication (Target)	Patient population Sample size of cited studies (n)	Type of the study Results	Quality of evidence *	Reference
Tested for PTSD/SUD				
Sertraline (5-HT)	Community sample of AD and PTSD (n=94)	RCT, Sertraline=PLA for AD or PTSD	Level I:RCT	(Brady et al., 2005)
Naltrexone vs. disulfiram vs. naltrexone+disulfiram (Opioid and ADH)	Veterans with AD and PTSD (n=254)	RCT, Naltrexone, Disulfiram or combination of two >PLA for AD	Level I:RCT	(Petrakis et al., 2006)
Paroxetine+naltrexone vs.paroxetine vs. desipramine vs. desipramine vs. naltrexone (5-HT, opioid, and NE)	Veterans with AD and PTSD (n=88)	RCT, Paroxetine=Desipramine for PTSD, Desipramine>paroxetine for AD, Naltrexone>PLA for alcohol craving	Level I:RCT	(Petrakis et al., 2012)
Topiramate (Glutamate/ GABA)	Veterans with AD and PTSD (n=43)	Open label, Topiramate>PLA for AD and PTSD	Level II-3:Open label	(Alderman, McCarthy, Condon, Marwood, & Fuller, 2009)
Not tested for PTSD/SUD				
Prazosin (NE)	Veterans with PTSD (n=53)	RCT, Prazosin>PLA for PTSD	Level I:RCT	(Raskind et al., 2007; Taylor et al., 2008)
Propranolol (NE)	Community sample with acute trauma (n=41)	RCT, Propranolol=PLA	Level I:RCT	(Hoge et al., 2012)
Guanfacine (NE)	Veterans with PTSD (n=63)	RCT, Guanfacine=PLA	Level I:RCT	(Neylan et al., 2006)
Memantine (Glutamate)	Veterans with PTSD (n=4)	Open label, Memantine reduced PTSD symptoms	Level III-Case series	(Battista, Hierholzer, Khouzam, Barlow, & O'Toole, 2007)
N-acetylcysteine (Glutamate)	Community sample with cocaine dependence (n=23)	Open label, N- acetylcysteine >PLA	Level II-3: Open label	(Mardikian, LaRowe, Hedden, Kalivas, & Malcolm, 2007)
Ketamine (Glutamate)	OIF/OIF soldiers with burn (n=147)	Retrospective, Ketamine prevented PTSD	Level III: Descriptive study	(McGhee, Maani, Garza, Gaylord, & Black, 2008)
Acamprosate (Glutamate/GABA)	Community samples of AD, multiple studies (n=6,915)	RCT, Acamprosate> PLA for AD in some studies	Level I:Multiple RCT	(Rosner et al., 2010).

* Based on the United States Preventative Services Task Force (1989).

Abbreviations: ADH: Aldehyde dehydrogenase; 5-HT: Serotonin; AD: Alcohol dependence; SUD: Substance Use Disorder; PLA: Placebo; RCT: Randomized controlled trial; NE: Norepinephrine; DA: Dopamine