Pharmacological treatment of comorbid PTSD and substance use disorder: Recent progress

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HIGHLIGHTS

* Evidence supports a strong link between PTSD and substance use disorder (SUD).
* Pharmacotherapies are effective for the treatment of PTSD and SUD alone.
* However, there are no proven medications that will treat both conditions.
* Norepinephrine and glutamate/GABA are treatment targets for comorbid PTSD and SUD.
* Medications acting on these targets need to be tested in controlled clinical trials.

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ABSTRACT

Previous research has identified a strong association between posttraumatic stress disorder (PTSD) and substance use disorder (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 and 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.

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1. Introduction

Previous research supports a strong association between post-traumatic stress disorder (PTSD) and substance use disorder (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, 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 epidemiological 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% respectively had comorbid PTSD (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% in the control group (Gilen, 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 a 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 comorbid substance abuse, nearly 3 times the rate in the general VA patient population (Kerfoot, Petrakis, & Rosenheck, 2011). Co-morbid PTSD and substance abuse were 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% of drug use disorder. In contrast, among veterans of the wars in Iraq and Afghanistan receiving an inpatient treatment these rates were considerably higher at 39% and 20% respectively (Fontana & Rosenheck, 2008). Rates of co-morbid alcohol and drug use disorder 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 (Arnst, 2011; Charmandari et al., 2005). Norepinephrine also plays a key role in stress-induced reinstatement of drug use (Erba, 2010) and encoding of emotional memories in the amygdala and prefrontal cortex (Kristal & Neumeister, 2009). Patients with PTSD have elevated norepinephrine levels in the cerebrospinal fluid, indicating increased norepinephrine activity (Geraci et al., 2008). Medications targeting norepinephrine may have efficacy for treating both SUD and PTSD (Norman et al., 2011; 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 is 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. The presence of either depressive or PTSD symptoms has been shown to increase the expected reward from alcohol (Murphy et al., 2012) and rewarding effects of stimulant drugs (Sofuoglu, Brown, Babb, & Hatsuiki, 2001; Sofuoglu, Dudish-Poulsen, Brown, & Hatsuiki, 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 reported 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. Benzodiazepine is commonly used as an adjunctive treatment of PTSD to alleviate sleep disturbance, irritability, and other hyperarousal symptoms (Hawkins, Matve, 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, & Keijzers, 2002). Atypical antipsychotics (olanzapine, risperidone, quetiapine, ziprasidone, and aripiprazole) are also commonly used as adjunctive treatments 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), 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 the highest affinity for the μ-opioid 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 the 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 an active medication (naltrexone, disulfiram or the combination) than those assigned with 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 a 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; and 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 α1-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 β-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; Hurlemann et al., 2010), although some results have not been positive (Hoge et al., 2012).

Alpha2-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 α2-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, Lonqvist, 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 extracellular glutamate levels in the 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, & O’Dalaug, 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 (Berkm 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). Memantine has shown efficacy in randomized clinical trials for AD and appears to be moderately effective for the treatment of anxiety disorders (Schwartz, Siddique, Raza, & Costello, 2010) and comorbid AD and bipolar disorder (Tolliver, DeSantis, Brown, Prisciandaro, & Brady, 2012). Memantine has not been tested for the treatment of comorbid PTSD and SUD.

Topiramate, an antiseizure medication, is an agonist on the GABA receptor, blocks AMPA/kainute-subtype of glutamate receptor, and inhibits carbonic anhydrase (Gibbs, Sombati, DeDoreno, & Coulter, 2000; Herrera, 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 supports 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).

Table 1
Potential medications for the treatment of comorbid PTSD and SUD.

<table>
<thead>
<tr>
<th>Medication (target)</th>
<th>Patient population</th>
<th>Type of the study</th>
<th>Quality of evidencea</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sertraline (5-HT)</td>
<td>Community sample of AD and PTSD (n = 94)</td>
<td>RCT, sertraline = PLA for AD or PTSD</td>
<td>Level I: RCT</td>
<td>Brady et al. (2005)</td>
</tr>
<tr>
<td>Naltrexone vs. disulfiram vs. naltrexone + disulfiram (opioid and ADH)</td>
<td>Veterans with AD and PTSD (n = 254)</td>
<td>RCT, naltrexone, disulfiram or combination of two &gt; PLA for AD</td>
<td>Level I: RCT</td>
<td>Petrakis et al. (2006)</td>
</tr>
<tr>
<td>Paroxetine + naltrexone vs. paroxetine vs. desipramine vs. naltrexone + disulfiram (5-HT, opioid, NE)</td>
<td>Veterans with AD and PTSD (n = 88)</td>
<td>RCT, paroxetine = desipramine for PTSD, naltrexone &gt; paroxetine for AD, naltrexone &gt; PLA for alcohol craving</td>
<td>Level I: RCT</td>
<td>Petrakis et al. (2012)</td>
</tr>
<tr>
<td>Topiramate (glutamate/GABA)</td>
<td>Veterans with AD and PTSD (n = 43)</td>
<td>Open label, topiramate &gt; PLA for AD and PTSD</td>
<td>Level II-III: Open label</td>
<td>Alderman et al. (2009)</td>
</tr>
<tr>
<td>Not tested for PTSD/SUD</td>
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</tr>
<tr>
<td>Prazosin (NE)</td>
<td>Veterans with PTSD (n = 53)</td>
<td>RCT, prazosin &gt; PLA for PTSD</td>
<td>Level I: RCT</td>
<td>Raskind et al. (2007); Taylor et al. (2008)</td>
</tr>
<tr>
<td>Propranolol (NE)</td>
<td>Community sample with acute trauma (n = 41)</td>
<td>RCT, propranolol = PLA</td>
<td>Level I: RCT</td>
<td>Hoge et al. (2012)</td>
</tr>
<tr>
<td>Guanfacine (NE)</td>
<td>Veterans with PTSD (n = 63)</td>
<td>RCT, guanfacine = PLA</td>
<td>Level I: RCT</td>
<td>Neylan et al. (2006)</td>
</tr>
<tr>
<td>Mirtazapine (glutamate)</td>
<td>Veterans with PTSD (n = 4)</td>
<td>Open label, mirtazapine reduced PTSD symptoms</td>
<td>Level III: Case series</td>
<td>Battista et al. (2007)</td>
</tr>
<tr>
<td>N-acetylcysteine (glutamate)</td>
<td>Community sample with cocaine dependence (n = 23)</td>
<td>Open label, N-acetylcysteine &gt; PLA</td>
<td>Level III: Open label</td>
<td>Mardikian et al. (2007)</td>
</tr>
<tr>
<td>Ketamine (glutamate)</td>
<td>OIF/OIF soldiers with burn (n = 147)</td>
<td>Retrospective, ketamine prevented PTSD</td>
<td>Level III: Descriptive study</td>
<td>McGhee et al. (2008)</td>
</tr>
<tr>
<td>Acamprosate (glutamate/GABA)</td>
<td>Community samples of AD, multiple studies (n = 6915)</td>
<td>RCT, acamprosate &gt; PLA for AD in some studies</td>
<td>Level I: Multiple RCT</td>
<td>Rosner et al. (2010)</td>
</tr>
</tbody>
</table>

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, and GABA are potential treatment targets for the pharmacological 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 et al., 2009). Promising glutamate/GABA medications include topiramate (Alderman et al., 2009), mecamantine (Battista et al., 2007), acamprosate (Tolliver et al., 2012), NAC (Mardikian et al., 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 (Foа & Williams, 2010). The treatment arms include naltrexone alone, exposure treatment alone, combination of naltrexone and exposure treatment, and a placebo pill. Such studies will provide better guidance for the clinical management of patients with PTSD and SUD.

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Contributors
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.

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