

# PTSD and comorbid AUD: a review of pharmacological and alternative treatment options

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**Background:** Although posttraumatic stress disorder (PTSD) and alcohol use disorders (AUD) frequently co-occur there are no specific treatments for individuals diagnosed with these comorbid conditions. The main objectives of this paper are to review the literature on pharmacological options for PTSD and comorbid AUD, and to summarize promising behavioral and alternative interventions for those with these dual diagnoses.

**Methods:** We conducted a comprehensive search on PsycINFO and MEDLINE/PubMed databases using Medical Subject Headings terms in various combinations to identify articles that used pharmacotherapy for individuals with dual diagnoses of PTSD and AUD. Similar strategies were used to identify articles on behavioral and alternative treatments for AUD and PTSD. We identified and reviewed six studies that tested pharmacological treatments for patients with PTSD and comorbid AUD.

**Results:** The literature on treatment with US Food and Drug Administration approved medications for patients with dual diagnosis of PTSD and AUD is very limited and inconclusive. Promising evidence indicates that topiramate and prazosin may be effective in reducing PTSD and AUD symptoms in individuals with comorbidity. Seeking safety has had mixed efficacy in clinical trials. The efficacy of other behavioral and alternative treatments (mindfulness-based, yoga, and acupuncture) is more difficult to evaluate since the evidence comes from small, single studies without comparison groups.

**Conclusion:** There is a clear need for more systematic and rigorous study of pharmacological, behavioral, and alternative treatments for patients with dual diagnoses of PTSD and AUD.

**Keywords:** dual diagnosis, PTSD, AUD, pharmacotherapy

## Introduction

Posttraumatic stress disorder (PTSD) is a serious psychiatric disorder that can occur after the experience of a traumatic event. The symptoms can include: intrusive thoughts associated with the traumatic event, persistent avoidance of stimuli related to the event, negative changes in cognition and mood, and alterations in arousal and reactivity.<sup>1</sup> One of the clinical issues that complicate the treatment of PTSD is the common co-occurrence of alcohol use disorders (AUD),<sup>2</sup> with rates ranging from 30% to 59%.<sup>3-6</sup> This co-occurrence leads to a worse prognosis in both disorders. While it is unclear what the exact relationship between these disorders is, there is a well-documented link between stress and the development and maintenance of both PTSD and AUD.<sup>7-9</sup> As a result of the recent military conflicts and awareness of the increased rates of PTSD and AUD among returning military personnel, there is an urgent need to find effective

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treatments for those diagnosed with both PTSD and AUD. Although there are several evidence-based treatments for PTSD and AUD when they occur alone, these treatments have often not been rigorously tested in individuals who have both disorders.

The main objective of this paper is to review the most recent literature on pharmacological treatments for individuals diagnosed with PTSD and AUD. For comparative purposes we also briefly review behavioral and alternative treatments. The paper begins with a brief overview of the prevalence rates of PTSD and AUD when they occur alone and when they occur together. This is followed by a review of studies that have examined the efficacy of the US Food and Drug Administration (FDA) approved medications as well as other common pharmacological treatments for PTSD and AUD, when they are diagnosed individually. Next, we review the efficacy of medications used in individuals diagnosed with comorbid PTSD and AUD. We conclude the paper by discussing behavioral approaches and alternative treatment options for individuals diagnosed with PTSD and/or AUD.

## Epidemiology of PTSD

According to the National Comorbidity Survey, PTSD occurs with high frequency in the general population with lifetime prevalence rate of around 7.8% in men and women aged 18 years or older.<sup>10</sup> According to a more recent survey conducted by the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC),<sup>2</sup> the lifetime prevalence rate of PTSD is around 4.8% in men and women aged 18 years or older. The rates among military personnel are much higher than those in the general population. Among male and female soldiers aged 18 years or older returning from Iraq and Afghanistan, rates range from 9% shortly after returning from deployment to 31% a year after deployment.<sup>11</sup> A review of 29 studies that evaluated rates of PTSD in those who served in Iraq and Afghanistan found prevalence rates of adult men and women previously deployed ranging from 5% to 20% for those who do not seek treatment, and around 50% for those who do seek treatment.<sup>12</sup> Vietnam veterans also report high lifetime rates of PTSD ranging from 10% to 31%.<sup>13,14</sup> PTSD is the third most prevalent psychiatric diagnosis among veterans using the Veterans Affairs (VA) hospitals.<sup>15</sup>

## Epidemiology of AUD

Two large epidemiological studies examined the prevalence rates of AUD in the general population. The first, the National Longitudinal Alcohol Epidemiological Survey, conducted between 1991 and 1992, reported 12-month prevalence rates

of 7.4%.<sup>16</sup> The second, the NESARC, conducted between 2001 and 2002, reported 12-month prevalence rates of 8.5% and a lifetime prevalence rate of 30.3%.<sup>17</sup> The differences in rates have been attributed to methodological issues rather than actual increases in the prevalence of AUD among the general population.<sup>18</sup> Research studies comparing military and civilian populations found that the incidence of heavy drinking was greater among military personnel.<sup>19</sup> A large scale study that followed trends in the use of alcohol across all branches of active duty military personnel from 1980 to 2005 found that heavy alcohol use ( $\geq 5$  drinks per drinking occasion, at least once per week, during the past 30 days) increased for all branches.<sup>20</sup> The most significant increases were among males and females aged 18 years or older in the army (17.2% in 1980 to 24% in 2005). In another study that examined mental health problems in both active and reserve soldiers returning from Iraq, 12% to 15% of men and women with a mean age of 30.4 years acknowledged having problematic alcohol use within 3 to 6 months after returning from combat.<sup>21</sup>

## Epidemiology of comorbid PTSD and AUD

Significant comorbidity between PTSD and AUD has been reported among the general population.<sup>22-24</sup> The rates of comorbid PTSD and AUD in clinical samples are also high.<sup>3,25-29</sup> Among adults (mean age 37.5 years) with AUD, 30% to 59% meet current criteria for PTSD.<sup>3-6</sup> Similarly, the lifetime rates of AUD in those with PTSD can range from 28% in women to 52% in men and can be as high as 85% in treatment seeking samples.<sup>10,30</sup>

Among young male and female veterans returning from the recent conflicts, the rates of alcohol misuse range from 11.8% to 25%,<sup>21</sup> and these rates are higher postdeployment than predeployment.<sup>31</sup> Among those exposed to combat, 53% reported binge drinking.<sup>32</sup> Rates of PTSD and AUD have increased in recent years,<sup>33</sup> particularly from 1990 to 2006.<sup>34</sup> It should be noted that this increase has been partly attributed to more detailed mental health evaluations after deployment, expanded reach efforts to underserved veterans, and the reintegration of Vietnam veterans into VA services.<sup>33,34</sup>

## Pharmacological treatments for PTSD

The US FDA and the European Medicines Agency<sup>35</sup> have approved two selective serotonin reuptake inhibitors (SSRIs), sertraline and paroxetine, for the treatment of PTSD. In 2010, the US Department of Veterans Affairs/Department

of Defense (VA/DoD) Clinical Practice Guideline (CPG) for Management of PTSD established sertraline, paroxetine, and the selective serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine as the first line pharmacological treatments for PTSD.<sup>36</sup> These recommendations were established based on results from numerous randomized controlled trials (RCT) using SSRI/SNRIs, including sertraline,<sup>37,38</sup> paroxetine,<sup>39</sup> and venlafaxine.<sup>40</sup> Although the evidence supports the use of SSRI/SNRIs for symptom reduction in PTSD, the overall effect sizes are modest.<sup>41,42</sup> Other SSRIs such as fluoxetine,<sup>43,44</sup> citalopram,<sup>45</sup> and fluvoxamine<sup>46</sup> have been used to treat PTSD with various levels of rigor or efficacy.

Although other antidepressants have been used for the treatment of PTSD, such as mirtazapine and nefazodone, tricyclic antidepressants (eg, imipramine and amitriptyline), and monoamine oxidase inhibitors (eg, phenelzine), there is limited evidence for their efficacy in treating PTSD symptoms.<sup>47-50</sup> In addition, their use has been associated with greater side effects. Tricyclic antidepressants and monoamine oxidase inhibitors have been discontinued due to their low therapeutic benefit and numerous side effects related to toxicity; mirtazapine has been associated with weight gain problems (particularly among patients at risk for metabolic syndromes or suffering from diabetes), and nefazodone has been found to be hepatotoxic.<sup>51</sup>

Other medications frequently prescribed for PTSD are anticonvulsants, atypical antipsychotics, and benzodiazepines. There are studies that show positive results with the anticonvulsants such as topiramate, with moderate effect sizes, although these results are mostly based on open label and small studies, so definitive studies are still needed.<sup>52,53</sup> The results from studies using other anticonvulsants, such as divalproex, are even less promising.<sup>51</sup> While initial evidence for the use of antipsychotics such as risperidone as adjunct medications targeting specific symptoms of PTSD (eg, hyperarousal) was positive,<sup>54,55</sup> a recent multisite RCT and the largest to date conducted across 23 VA outpatient medical centers throughout a 6 month period revealed that treatment with risperidone for 6 months compared to placebo did not reduce antidepressant-resistant symptoms of chronic, service-related PTSD.<sup>56</sup> Importantly, because of the publication of this multicenter trial, the VA/DoD CPG now recommends against the use of risperidone for the treatment of PTSD.<sup>36</sup> Also, the CPG now states that due to the lack of scientific evidence, the use of other antipsychotic medications is discouraged for the treatment of PTSD. The evidence for the use of benzodiazepines, such as alprazolam<sup>57</sup> or clonazepam,<sup>58</sup> is very limited and negative.<sup>41,59</sup> In these studies the sample

sizes were small ( $N < 13$  subjects), alprazolam was not more effective than placebo,<sup>57</sup> and neither alprazolam nor clonazepam had a significant effect on PTSD symptoms when administered early in the treatment.<sup>58</sup> Given the abuse liability of benzodiazepines, and the limited evidence of efficacy, their use is not well supported. Overall, the most promising of these groups of medications is the anticonvulsant group, although further research is needed in this area.

One promising medication is the alpha-1 adrenergic receptor antagonist prazosin, which has shown considerable promise in reducing nighttime symptoms, such as nightmares and sleep disturbances,<sup>60</sup> but also in reducing other PTSD symptoms.<sup>61</sup> A large, multisite, randomized, placebo-controlled study in 326 veterans is now underway,<sup>62</sup> and results are pending.

## Pharmacological treatments for AUD

Four medications are currently approved by the FDA to treat AUD: disulfiram, naltrexone, an intramuscular (IM) form of naltrexone, and acamprostate. Disulfiram was the first medication approved by the FDA in 1951 and has been used clinically for over 50 years. Disulfiram was designed to prevent relapse by inducing an aversive reaction when alcohol is ingested. Published research on the efficacy of disulfiram has produced mixed results mainly due to significant methodological limitations, such as the lack of randomization and the lack of blinding conditions among others.<sup>63</sup> The largest study to date, conducted at the VA in the 1980s, showed that disulfiram did not significantly improve alcohol use outcomes.<sup>64</sup> Disulfiram's use in this study was severely limited by poor compliance.<sup>64</sup> It is important to note that the efficacy of disulfiram increases when its intake is supervised or when compliance is addressed as part of treatment. The opioid antagonist naltrexone was the second medication approved by the FDA in 1994. For the past two decades, its efficacy has been evaluated in a number of clinical trials and laboratory studies.<sup>65-70</sup> The main consensus is that naltrexone works by inhibiting relapse to heavy drinking. A number of meta-analyses that have evaluated the efficacy of naltrexone support its efficacy in reducing drinking with a somewhat modest effect.<sup>71,72</sup> These findings have been supported by the largest multisite trial to date, COMBINE (combined pharmacotherapies and behavioral interventions for alcohol dependence).<sup>73</sup> An IM version of naltrexone (Vivitrol) was approved by the FDA in 2006. Studies to date suggest it is well tolerated and effective in reducing drinking.<sup>74-77</sup> The main limitations of IM naltrexone are the very high cost and

the potential for severe, although uncommon, reactions at the site of injection. Acamprosate received FDA approval in 2004 primarily on the basis of three large European trials, but published studies in the US have reported mixed results.<sup>78–80</sup> In the large COMBINE trial, there was no advantage of acamprosate over placebo.<sup>73</sup> Meta-analyses that examined the efficacy of acamprosate alone, or that compared acamprosate to naltrexone, showed that both drugs were effective but the effects were modest.<sup>81,82</sup> Findings from more recent meta-analyses were consistent but suggest that acamprosate may be better for maintaining abstinence while naltrexone may be better for preventing relapse.<sup>83,84</sup> Similar results were reported in a meta-analysis that compared the efficacy of acamprosate, naltrexone, and disulfiram.<sup>85</sup>

While there are many other medications currently under development for the treatment of AUD, the anticonvulsant topiramate is the most promising. Considerable evidence supports the efficacy of topiramate, when compared to placebo, as a treatment option for individuals diagnosed with AUD. Support comes from open label, chart review, and case studies that show topiramate significantly reduces drinking in those with AUD.<sup>86–88</sup> The best evidence, however, comes from two large RCTs, including one multisite study supporting its efficacy with an effect size larger than that of naltrexone.<sup>89,90</sup> Topiramate seems to be effective in decreasing heavy drinking. Interestingly, a number of smaller studies have compared topiramate to the FDA approved medications for AUD. One open label study for relapse prevention found that topiramate was superior to disulfiram.<sup>91</sup> Another open label study found a significant reduction in drinking for all subjects and no difference between topiramate and oral naltrexone.<sup>92</sup> The only RCT comparing topiramate, naltrexone, and placebo found no difference between topiramate and naltrexone on time to relapse, cumulative days of abstinence, or number of weeks of heavy drinking.<sup>93</sup> Interestingly, a review of VA National Patient Care Database from 2009 to 2012 to identify the use of FDA approved or off label prescriptions for veterans with AUD revealed that topiramate was prescribed more often than acamprosate, IM naltrexone, and disulfiram combined.<sup>94</sup> Despite topiramate's promise, its clinical use is somewhat limited by its side effect profile, which includes cognitive deficits and requires a long (multiweek) titration to the desired dose. The side effects result in high dropout rates as reported in the two RCTs.<sup>89,91</sup>

Zonisamide, an anticonvulsant with properties similar to topiramate but with the advantage of a more tolerable side effect profile, is another promising medication. The evidence for its efficacy comes from laboratory<sup>95</sup> and open label studies<sup>96</sup>

as well as two small clinical trials.<sup>97,98</sup> The first 12-week RCT compared zonisamide to placebo and found that zonisamide significantly reduced drinking outcomes.<sup>97</sup> The second RCT compared zonisamide to the benzodiazepine diazepam for alcohol withdrawal symptoms and found no statistically significant difference between the two medications.<sup>98</sup>

## Methods

We conducted a comprehensive search on PsycINFO and MEDLINE/PubMed databases using the following Medical Subject Headings terms in various combinations: “alcohol”, “alcohol use disorders”, “alcohol dependence”, “substance use disorders”, “PTSD”, “medication treatment”, “pharmacotherapy”, “comorbid”, and “dual diagnosis”. We did not limit the search to a specific time period. The study was included in the review if: (1) it evaluated the efficacy of a pharmacotherapy, and (2) if the sample consisted of individuals diagnosed with AUD and PTSD. We did not include studies that used other psychosocial interventions since that was not the focus of this paper. We excluded studies with substance use disorders (cocaine, marijuana, opiates) without AUD to focus on a more homogeneous sample and to simplify the interpretation of the results. We also eliminated studies that included individuals with AUD and other substances if the authors did not provide results on the subgroup of individuals with AUD. Our search on “substance use disorders”, “PTSD”, and “pharmacotherapy” resulted in 258 articles. The search using “alcohol”, “PTSD”, and “pharmacotherapy” identified 235 articles. When “alcohol dependence”, “PTSD”, and “pharmacotherapy” were combined we identified 97 articles. Only six studies met the criteria for inclusion. These studies are listed in Table 1. Similar strategies were used to identify articles on behavioral and alternative treatments for AUD and PTSD. Since the literature on behavioral treatments has been carefully and rigorously evaluated by others, and was used for comparative purposes in this review, we limited the discussion to the summary of the current state of findings in this literature. Because only few studies evaluated alternative treatments in comorbid AUD and PTSD, we expanded the search to include studies that evaluated these treatments in AUD and PTSD alone.

## Results

The literature search on published studies evaluating treatments for individuals with comorbid PTSD and AUD identified three open label or retrospective studies and three randomized, double-blind treatment trials that tested one or more pharmacological agents (for summary of studies and main findings see Table 1).<sup>99–104</sup>

**Table 1** Summary of characteristics for treatment studies designed for individuals with posttraumatic stress disorder and comorbid alcohol use disorders

Study	Demographics	Age ( $\bar{x}$ , SD) for treatment group	Treatment setting	Study type	Main dependent variables Cohen's d	Results
<b>FDA meds for PTSD</b>						
Sertraline <sup>99</sup>	9 Non Vets (3 M/6 F)	Sertraline: 34.6 (3.5) No control	Outpatients	Open label	Days abstinent: $d=-1.73$ MPSS: $d=2.69$	Sertraline decreased days of abstinence and PTSD symptoms
Sertraline <sup>100</sup>	94 Non Vets (51 M/43 F)	Sertraline: 36.7 (8.4) Pla: 36.6 (8.6)	Outpatients	Double-blind, RCT	Heavy drinking days: $d=0.63$ Number of drinks per day: $d=0.25$ CAPS: cluster analysis	Sertraline benefited only patients with early onset PTSD and late onset AUD compared to placebo
Paroxetine versus desipramine (in combination with naltrexone or placebo) <sup>101</sup>	88 (81 Vets) (80 M/8 F)	Par + Nal: 45.14 (6.71) Par + Pla: 49.15 (8.95) Des + Nal: 47.05 (9.96) Des + Pla: 47.04 (9.71)	Outpatients	Double-blind, RCT	Heavy drinking days: $d=0.43$ Drinks per drinking day: $d=0.47$ CAPS: no significant group differences	Desipramine significantly reduced all drinking outcomes. Naltrexone had no additive effect. Desipramine and paroxetine were equally effective in reducing PTSD symptoms
<b>Other meds for PTSD</b>						
Quetiapine <sup>102</sup>	50 Vets (50 M/0 F)	Quetiapine: 50.5* Control: 46.4	Outpatients	Retrospective, control group not receiving quetiapine	Number of hospitalizations: $d=0.99$ Total days abstinent: $d=0.71$ Time to relapse: $d=0.54$	Those on quetiapine had a greater number of abstinent days and lower number of hospitalizations when compared to the control group. Changes in PTSD symptoms were not reported
<b>FDA meds for AUD</b>						
Naltrexone, disulfiram, or naltrexone + disulfiram <sup>103</sup>	254 Vets (247 M/7 F)	Nal: 47.7 (7.4) Dis: 45.8 (9.0) Dis + Nal: 48.2 (9.3) Pla: 46.2 (7.2)	Outpatients	Secondary analysis of a double-blind, RCT	Maximum consecutive days of abstinence <sup>d</sup> Nal: $d=0.67$ Dis: $d=0.96$ Dis + Nal: $d=0.60$ CAPS <sup>d</sup> Nal: $d=-0.04$ Dis: $d=0.15$ Dis + Nal: $d=-0.01$	Any medication alone or in combination resulted in better alcohol use outcomes. PTSD symptoms decreased significantly in abstainers. Disulfiram was more effective than naltrexone in reducing total PTSD and hyperarousal symptoms. For re-experiencing, disulfiram and naltrexone alone were better than the combination
<b>Other meds for AUD</b>						
Topiramate <sup>104</sup>	29 Vets (29 M/0 F)	Topiramate: 58.1 (8.8) No control	Inpatients and outpatients	Open label	AUDIT: $d=0.23$ CAPS: $d=0.84$ Mississippi PTSD: $d=0.58$	Subjects in the risky and high risk category reported less drinking after 8 weeks of treatment with topiramate. Topiramate significantly improved PTSD symptoms (eg, nightmares)

**Notes:** \*No standard deviations were provided. <sup>d</sup>No means and standard deviations were available to calculate effect sizes; <sup>e</sup>data was analyzed comparing paroxetine to placebo and separately naltrexone to placebo; <sup>f</sup>effect sizes were calculated comparing each medication condition to placebo.

**Abbreviations:** AD, alcohol dependence; AUDIT, alcohol use disorder; AUDIT, alcohol use disorders identification test; CAPS, clinician-administered posttraumatic stress disorder scale; Des, desipramine; Dis, disulfiram; FDA, US Food and Drug Administration; M/F, male/female; meds, medications; MPSS, modified posttraumatic stress disorder symptom scale; Nal, naltrexone; Par, paroxetine; Pla, placebo; PTSD, posttraumatic stress disorder; RCT, randomized clinical trial; SD, standard deviation; Vets, veterans;  $\bar{x}$ , mean.

## Medication used to treat PTSD symptoms

The efficacy of sertraline (mainly targeting depressive symptoms) for the treatment of co-occurring PTSD and AUD was first tested in one very small open label trial conducted with nine participants.<sup>99</sup> In this study, PTSD symptoms, depression symptoms, and average number of drinks significantly decreased during the follow-up period. In a larger (N=94), 12-week, double-blind, placebo controlled RCT, the overall results were disappointing, and only individuals characterized with early onset PTSD and late onset AUD benefited from sertraline treatment when compared to placebo.<sup>100</sup>

More recently, another randomized, double-blind treatment study was designed to compare the efficacy of the FDA approved SSRI paroxetine to the norepinephrine uptake inhibitor desipramine, in combination with either naltrexone or placebo in veterans with comorbid PTSD and AUD.<sup>101</sup> The objective was to test whether the addition of naltrexone (an opiate receptor antagonist designed to decrease heavy drinking of alcohol) to antidepressants (with established efficacy in decreasing depressive symptoms in PTSD) would be effective in reducing both PTSD and AUD symptoms in those with dual diagnosis. The main outcomes included measures of drinking, craving, and PTSD symptoms. Desipramine treatment resulted in a significantly greater reduction in drinking when compared to paroxetine. The addition of naltrexone had no additive effect on reducing drinking but was superior to placebo in reducing alcohol craving. PTSD symptoms significantly declined with treatment and desipramine and paroxetine were equally effective for PTSD symptoms.

A retrospective study assessed the efficacy of the atypical antipsychotic quetiapine in veterans with AUD, 90% of whom also had a diagnosis of PTSD.<sup>102</sup> The objective was to evaluate the efficacy of quetiapine on alcohol use outcome. The main outcome measures included alcohol abstinence, number of hospitalizations for detoxification, and days to first relapse over a 1-year period. Thirty male veterans treated with quetiapine (25 to 200 mg nightly) for sleeping problems (symptoms associated with diagnoses of both PTSD and AUD) were compared to 20 veterans in the control group who were not treated with quetiapine. Veterans treated with quetiapine had a greater number of abstinence days, and a lower number of hospitalizations when compared to the control group. Changes in PTSD symptoms were not reported in this study.

## Medications used to treat AUD symptoms

In a large (N=254), randomized, double-blind clinical trial of veterans with AUD and other Axis I disorders, four treatment groups were compared: naltrexone, disulfiram, naltrexone + disulfiram, and placebo.<sup>103</sup> The objective was to test if reduction in drinking by an FDA established medication for AUD (naltrexone and disulfiram), or their combination, would result in reduction in alcohol use outcomes among those with comorbidity. Results showed that for all patients, treatment with any medication (naltrexone or disulfiram alone or in combination) resulted in better alcohol use outcomes than placebo, but there was no advantage to the combination. In the subgroup of patients with PTSD (N=87), the findings were similar and more robust in terms of alcohol use outcomes. PTSD symptoms decreased significantly only in those who abstained from alcohol. Disulfiram was more effective than naltrexone in reducing total PTSD and hyperarousal symptoms. For re-experiencing, disulfiram and naltrexone alone were better than the combination. As mentioned above, another study which evaluated the efficacy of naltrexone augmentation to antidepressant medication found no real advantage to naltrexone in drinking use outcomes.<sup>103</sup>

## Other medications

An open label pilot study tested the efficacy of topiramate as an add on therapy in male combat veterans diagnosed with PTSD, the majority of whom (82.1%) reported drinking.<sup>104</sup> They were treated for 8 weeks and their alcohol consumption was closely monitored to identify whether they were low risk drinkers ( $\leq 28$  standard drinks/week), risky drinkers (29–42 standard drinks/week), or high risk drinkers ( $\geq 43$  standard drinks/week). There was a significant improvement in PTSD symptoms (eg, nightmares) when compared to baseline and participants who were in the risky or high risk category also reported significantly less drinking after 8 weeks of treatment. Another anticonvulsant, zonisamide, that has shown promise in the treatment of AUD, is currently being evaluated as an adjunct treatment to Enhanced Cognitive Processing Therapy in a RCT in veterans with comorbid PTSD and AUD.<sup>105</sup> Prazosin, another medication previously shown to be effective in treating PTSD symptoms (particularly sleep and nightmares), has shown some promise in treating AUD.<sup>106</sup> The efficacy of prazosin to reduce PTSD and AUD symptoms is also currently being tested in an ongoing, multisite, placebo-controlled RCT in veterans with PTSD and AUD.<sup>107</sup> The results from this study are expected in 1 year.

## Behavioral approaches for treating PTSD and AUD

The studies evaluating behavioral treatments for individuals diagnosed with PTSD and AUD have been carefully reviewed elsewhere.<sup>108–113</sup> The best studied intervention is Seeking Safety, a treatment developed specifically to address comorbidity, which was evaluated in five studies, including two RCTs.<sup>114–118</sup> Although the results showed improvement in symptoms, the two RCTs did not find a difference between the active and control groups.<sup>117,118</sup> In the past decade Eye Movement Desensitization and Reprocessing (EMDR) therapy has been evaluated for its efficacy in PTSD.<sup>119</sup> There is evidence that supports its efficacy in reducing distress but EMDR has not been tested in individuals with comorbid AUD and PTSD. A number of single studies have evaluated other behavioral treatments based on cognitive behavioral therapy, exposure therapy, and other interventions.<sup>108</sup> Although all of those studies reported improvement in either PTSD symptoms, drinking, or both, the data needs to be interpreted cautiously because the interventions were examined in single studies and none included a comparison group.

## Alternative approaches for treating PTSD and/or AUD

Mindfulness, acupuncture, and yoga have been studied as alternative approaches for treating individuals with PTSD and/or AUD. Interventions that increase mindfulness, defined as “paying attention in a particular way: on purpose, in the present moment, and nonjudgmentally,”<sup>120</sup> have been associated with improvement in PTSD symptoms and a reduction in drinking. Mindfulness-based interventions reduced PTSD symptoms in women with a history of sexual abuse,<sup>121</sup> and among high school students in Kosovo,<sup>122</sup> reduced PTSD symptoms<sup>123</sup> and drinking in Vietnam veterans<sup>124</sup> and incarcerated individuals,<sup>125</sup> and also decreased drinking among those with substance use disorders.<sup>126–129</sup> The most recent support for this type of intervention comes from a study conducted in veterans with PTSD, some of whom (19.6%) also had substance use disorders.<sup>130</sup> The veterans participated in an 8-week, mindfulness-based stress reduction intervention with a 6-month follow-up. There was a significant reduction in PTSD symptoms at the end of intervention, and this improvement was retained at the 6-month follow-up.

A number of studies have examined the effectiveness of acupuncture among individuals diagnosed with various anxiety disorders (including PTSD), AUD, and comorbid PTSD and substance use disorders.<sup>131</sup> Systematic reviews

of RCTs that used acupuncture for the treatment of PTSD found encouraging evidence in support of acupuncture as an effective treatment for PTSD.<sup>131–133</sup> In contrast, the review of a RCT that examined the efficacy of acupuncture in AUD found no support for the use of acupuncture as a treatment for AUD.<sup>134</sup>

There is some preliminary evidence to support the use of yoga in the treatment of anxiety disorders, including PTSD.<sup>135–140</sup> For example, a controlled investigation of the 2004 tsunami survivors showed that participation in an 8 hour yogic breathing intervention resulted in a 60% decline in scores on the 17 item Post-Traumatic Stress Disorder Checklist; this reduction was sustained over a 6-month period.<sup>138</sup> Findings from a series of four small studies examining the effect of yoga on PTSD symptoms in Australian Vietnam veterans was promising; a combination of yoga postures and breathing practices were found to significantly reduce symptoms of PTSD.<sup>135,137</sup> Similarly, published studies on the use of yoga in individuals with AUD showed that yoga contributes to sustaining abstinence.<sup>141</sup> However, the findings relating to alternative treatments in PTSD and AUD need to be interpreted with caution because the number of studies is small and RCTs are lacking.

## Discussion

PTSD and AUD frequently co-occur with rates ranging from 28% to as high as 85% among treatment seeking individuals, and up to 53% among veterans exposed to combat. This pattern of comorbidity has been associated with negative consequences on symptom severity, treatment, and general functioning. Despite the high rates of comorbidity there are no FDA approved medications for treatment of comorbid AUD and PTSD.

We focused on six studies that evaluated pharmacotherapies for patients with PTSD and comorbid AUD. All studies reported that the study medication improved drinking outcomes either alone or in comparison to placebo, although in two studies<sup>100,104</sup> the improvement was limited to a subgroup of patients. In contrast, only half of the studies reported that medication was superior to placebo in reducing PTSD symptoms.

Our review raises a number of methodological issues that need to be considered in future research. RCTs are lacking. Most participants in the studies were middle-aged male veteran outpatients. Therefore, comparisons between male and female participants, those in different age groups, veteran versus non veteran, or inpatients versus outpatients

are sorely needed. Additionally, across studies the samples of patients varied widely with respect to the type of trauma and severity of PTSD, drinking criteria, comorbid disorders, and concomitant medication use, and this could have influenced the findings.

The studies evaluating behavioral treatments for individuals diagnosed with PTSD and AUD are plagued by similar methodological problems. The number of studies is small, large RCT studies are few, the findings are inconsistent, and the majority of interventions (excluding Seeking Safety) are limited to single studies without comparison groups. The studies evaluating alternative treatments for PTSD and AUD have to overcome even bigger methodological challenges. Although promising, mindfulness-based interventions, acupuncture, and yoga have not been rigorously tested in individuals with dual diagnosis, the number of studies is very small, no RCTs have been conducted, and very often comparison groups are not included.

Despite the above limitations, evidence supports the efficacy of pharmacological, behavioral, and alternative treatment for those with comorbid AUD and PTSD. The current review represents a foundation for future research in this area. The limited research underscores the need for studies that more systematically and rigorously examines these treatments. More methodologically rigorous studies that include a comparison group, are adequately powered, and that include more diagnostically and demographically homogenous groups are recommended.

## Conclusion and suggestions

Considerable evidence indicates a strong comorbidity of PTSD and AUD, necessitating treatments that are effective in individuals who have comorbid conditions. Research on FDA approved and common treatments for individuals with PTSD or AUD alone indicates that the efficacy of those medications in individuals with comorbidity has been limited and mixed. While these medications should still be considered when treating individuals with comorbid conditions, there is a clinical need to search for other options for treatment of this dual condition. Anticonvulsants such as topiramate and the alpha-1 adrenergic receptor antagonist prazosin are some promising options.

Although pharmacological agents are one the first lines of treatment for PTSD and AUD, behavioral and alternative interventions such as mindfulness-based interventions, acupuncture, yoga, and EMDR have been increasingly tested as possible treatment alternatives. Future studies should

focus not only on more rigorous testing of existing treatment options but also on evaluating treatments that combine pharmacological, behavioral, and alternative interventions to optimize treatment efficacy in individuals with a dual diagnosis of PTSD and AUD.

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