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Concurrent Treatment of Substance Use and PTSD

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Abstract Substance use disorders (SUD) and posttraumatic stress disorder (PTSD) are chronic, debilitating conditions that frequently co-occur. Individuals with co-occurring SUD and PTSD suffer a more complicated course of treatment and less favorable treatment outcomes compared to individuals with either disorder alone. The development of effective psychosocial and pharmacological interventions for co-occurring SUD and PTSD is an active and critically important area of investigation. Several integrated psychosocial treatments for co-occurring SUD and PTSD have demonstrated promising outcomes. While recent studies examining medications to treat co-occurring SUD and PTSD have yielded encouraging findings, there remain substantial gaps in the evidence base regarding the treatment of co-occurring SUD and PTSD. This review will summarize the findings from clinical trials targeting a reduction in SUD and PTSD symptoms simultaneously. These results may improve our knowledge base and subsequently enhance our ability to develop effective interventions for this complex comorbid condition.

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Introduction

Overview

Extensive literature documents a strong association between substance use disorders (SUD) and posttraumatic stress disorder (PTSD) [1–3]. Epidemiological data indicate that approximately 30 % of the general US population will experience SUD and 8 % will experience PTSD during their lifetime [4]. PTSD co-occurs with SUD among roughly 40 % of civilians and veterans [2, 5, 6]. Individuals with co-occurring SUD and PTSD incur heightened risk for other psychiatric problems (e.g., depression, anxiety), suicidality, neuropsychological impairment, increased morbidity and mortality, unemployment, and social impairment [2, 5, 7, 8]. This complex comorbidity also places a tremendous economic burden on the healthcare system, as it results in poorer treatment outcomes, longer duration of substance use, and more treatment episodes [9–12].

While several theories have been proposed to explain the common co-occurrence of SUD and PTSD, the self-medication theory has received the most empirical support to date [13]. This theory posits that individuals with PTSD incur a heightened risk for substance use and developing substance use disorders due to their propensity to drink alcohol or use drugs to mitigate the distressing symptoms and sequelae of PTSD. Support for this theory has been garnered by studies demonstrating that PTSD typically emerges before co-occurring substance use disorders [14, 15] as well as evidence indicating that PTSD symptom management is a primary

rationale for substance use among individuals with co-occurring SUD and PTSD [16, 17].

Despite the significant impairment, distress, and clinical complications associated with co-occurring SUD and PTSD, effective treatments for this comorbid condition are still in the nascent stage. Ongoing controversies that have informed treatment development efforts for co-occurring SUD and PTSD question the safety of (1) integrated psychosocial modalities which treat SUD and PTSD concurrently, (2) the use of exposure-based psychosocial modalities in particular, and (3) application of pharmacotherapies in comorbid populations. Early approaches to the treatment of co-occurring SUD and PTSD followed the "sequential model", which requires patients to establish and maintain abstinence from substance use before initiating trauma-focused treatment. Adherence to the sequential model historically stemmed from concerns that trauma-focused treatments would lead to a worsening of SUD in those with PTSD. Indeed, providers treating individuals with co-occurring PTSD and SUD face a formidable challenge. Data indicate that providers often view co-occurring SUD and PTSD have difficulty prioritizing and integrating treatment approaches to successfully meet patients' needs [18]. Providers also commonly express concern that integrated treatment may exacerbate symptoms.

Over time, the literature indicating the safety, acceptability, and efficacy of integrated psychosocial interventions for co-occurring SUD and PTSD has grown [19–21]. Data also indicates that many patients prefer to engage in integrated, rather than sequential, models of treatment [22, 23]. As a result, several integrated psychosocial treatments have been developed to treat SUD and PTSD concurrently [24•, 25]. Investigators are also actively pursuing the development of pharmacological treatments [26, 27] and the use of combined psychosocial and pharmacological treatment approaches [28, 29] to treat co-occurring SUD and PTSD.

This review will provide a description of psychosocial, pharmacological, and combined interventions that have been examined to treat co-occurring SUD and PTSD. We will review evidence-based psychosocial treatments including those grounded in exposure approaches, integrated treatment modalities which do not utilize exposure approaches, and pharmacological interventions that have been tested to treat SUD and PTSD concurrently.

Exposure-Based Treatments for Co-occurring SUD and PTSD

Prolonged Exposure (PE) is a highly efficacious, evidence-based, cognitive-behavioral therapy for PTSD [30]. Although some studies have included individuals with SUD in clinical trials examining the efficacy of PE to treat PTSD, findings regarding the effect of PE on substance use have not typically been reported [31–33]. One study by Schnurr and colleagues reported on the impact of PE on SUD symptoms as a secondary outcome in a study examining the use of PE in comparison to present centered therapy in a sample of female veterans [34]. Despite reductions in PTSD symptoms, there were no significant changes in substance use outcomes at either post-treatment or the six month follow-up. Similarly, Pacella and colleagues reported no significant reductions in substance use in a sample of HIV patients receiving PE [35].

There has been a recent increase in studies examining the efficacy of integrated treatments that combine PE with cognitive-behavioral SUD approaches. Concurrent Treatment of PTSD and Substance Use Disorders using Prolonged Exposure (COPE) [36] is one such modality that synthesizes empirically-validated cognitive-behavioral treatment for SUD with PE. Back and colleagues first reported in detail on the acceptability and feasibility of using COPE through a case study on an Iraq Veteran with PTSD and co-occurring alcohol use disorder [37]. Mills and colleagues conducted a randomized clinical trial of COPE among Australian civilians and found COPE to be superior in reducing PTSD and substance use symptoms compared to treatment-as-usual [24•]. Recently, Back and colleagues completed a randomized clinical trial evaluating the efficacy of COPE among Veterans. Participants were randomized to receive COPE or cognitive-behavioral relapse prevention [38]. Preliminary results indicate significant reductions in SUD and PTSD symptoms, and indicate that reductions in PTSD symptoms during treatment account for more than half of the variance in substance use reduction [39•]. Replication will be needed to provide additional support for the efficacy for this novel and promising approach, especially as it relates to dissemination and implementation in across treatment settings.

Existing literature suggests that treating co-occurring SUD and PTSD using exposure-based approaches such as PE is safe, acceptable, and effective. Nevertheless, there remain substantial gaps in the literature and further investigations examining the use of exposure-based integrated treatments alone and in combination with pharmacotherapies are needed to more fully discern the efficacy of these approaches and considerations for modifying treatments for subpopulations with specific treatment needs.

Non-exposure-Based Treatments for SUD and PTSD

The majority of studies to date have investigated non-exposure-based psychosocial interventions for the treatment of co-occurring SUD and PTSD. Although exposure-based treatments are highly effective in reducing PTSD, there is reluctance among some clinicians and researchers to employ exposure-based methods to treat PTSD among patients presenting with a comorbid SUD. Similar to the previously noted reservations regarding integrated modalities for co-occurring SUD and PTSD, this reluctance is due mainly to anecdotal

concerns that substance use during treatment would impede therapeutic efforts, and that exposure-based trauma work would result in increased substance use and/or relapse [40, 41]. Over the past decade, however, a growing body of empirical research has demonstrated that like exposure-based treatments, non-exposure-based treatments are also safe and effective to use among patients with co-occurring SUD and PTSD.

As indicated by the title, non-exposure-based treatments exclude exposure to the trauma memory (i.e., no imaginal exposure) or exposure to stimuli that are safe, but avoided because they are reminders of the trauma (i.e., no in vivo exposure). Rather, non-exposure-based treatments focus on topics such as psychoeducation, the relationship between substance use and PTSD symptoms, enhancing coping skills, managing negative emotions, and exploring the impact of trauma symptoms.

The most widely used and investigated non-exposure-based treatment to date is *Seeking Safety* (SS), a 24-session manualized therapy that focuses on establishing and maintaining safety [25, 42, 43•]. Topics include, for example, detaching from emotional pain, asking for help, compassion, honesty, integrating the split self, community resources, setting boundaries in relationships, coping with triggers, self-nurturing, and recovery thinking. Hien and colleagues compared SS to relapse prevention in a community sample of women ($N = 107$) with SUD and PTSD or sub-threshold PTSD [25]. Patients were randomly assigned and then completed individual sessions twice weekly for 12 weeks. No significant differences in SUD or PTSD symptoms were observed between the SS and relapse prevention group. In addition, PTSD symptom severity as measured by the Clinician Administered PTSD Scale (CAPS) at post-treatment remained in the moderately severe range (total score range 48–60). In a larger multisite community study, Hien and colleagues compared SS to a women's health education (WHE) control group among 353 women [43•]. Patients were randomized to 12 twice-weekly sessions of SS or WHE delivered in a group format. The results showed that PTSD symptoms significantly reduced in both groups with no between-groups difference. Neither treatment group had a significant impact upon abstinence rates.

Another recent study examined the use of cognitive processing therapy (CPT) for PTSD among Veterans receiving at least one session of CPT in a VA medical center PTSD outpatient clinic [44]. Using a chart review method, this study found a high prevalence (49.3 %) of alcohol use disorder among veterans with PTSD who received CPT. While veterans with co-occurring alcohol use disorder presented with higher PTSD, results indicated no difference in the number of sessions completed or reductions in PTSD or depression symptoms between those with PTSD only and those with co-occurring PTSD and alcohol use disorder.

Preliminary findings in support of Couple Treatment for Alcohol Use Disorder and Posttraumatic Stress Disorder (CTAP) are also promising [45]. CTAP is a 15-session manualized intervention which integrates Behavioral Couples Therapy for alcohol use disorder [46] with cognitive-behavioral conjoint therapy for PTSD [47]. In a recent open-label trial of CTAP among veterans with co-occurring alcohol use disorder and PTSD, participants demonstrated significant reductions in self-, clinician-, and partner-rated PTSD symptoms, depression symptoms, and percentage of heavy drinking days. A larger randomized controlled trial of CTAP is currently underway.

Additional non-exposure-based treatments for co-occurring SUD and PTSD include *Trauma Exposure and Empowerment Model* (*TREM*) [48], *Transcend* [49], *Addictions and Trauma Recovery Integrated Model* (*ATRIUM*) [50], *CBT for PTSD* [51], *Substance Dependency Posttraumatic Stress Disorder Therapy* [52], and *Trauma Affect Regulation*: *Guidelines for Education and Therapy* (*TARGET*) [53]. While early, mostly uncontrolled trials of these interventions showed promising outcomes, however limited empirical support for these treatments exists. *TREM* was originally developed for women with trauma exposure and comorbid severe mental disorders, including addiction [48]. Amaro and colleagues compared TREM (25 sessions) added to a comprehensive treatment package to treatment-as-usual among women ($N = 342$) with trauma history and SUD [54]. Women in TREM, as compared to treatment-as-usual, evidenced significantly greater reductions in PTSD symptoms and SUD at the 12-month follow-up. However, because TREM was added to a more comprehensive package it is difficult to interpret the results.

Transcend is a 12-session, manualized group treatment initially developed to be part of partial hospitalization programs among veterans. It emphasizes the development of coping skills during the first half of treatment then includes trauma processing during the second half of treatment [49]. During treatment, clinicians encourage 12-step attendance, teach relapse prevention skills, and encourage peer support. In an open study among male Vietnam veterans ($N = 46$) enrolled in a partial hospitalization program, Transcend resulted in significant reductions in PTSD symptoms at post-treatment. Transcend participants also experienced reductions in alcohol and drug use severity. Although the initial findings were promising, they were uncontrolled and, to our knowledge, were not followed up with a randomized controlled trial.

For a more extensive review of non-exposure-based treatments for co-occurring SUD and PTSD, please refer to Torchalla et al. [55] and van Dam et al. [56]. In addition, Roberts and colleagues recently completed a Cochrane report of 14 randomized clinical trials (1506 participants total) for the treatment of co-occurring SUD and PTSD [57]. They found little evidence to support the use of non-exposure-

based group or individual interventions among patients with co-occurring SUD and PTSD. Roberts and colleagues noted that the review is limited by low quality studies and high attrition rates. More rigorously designed trials are clearly needed.

Pharmacologic Interventions

The use of medication to treat SUD and PTSD has largely focused on the treatment of either disorder alone [58]. Recent findings regarding several medications to treat SUD alone, and alcohol use disorders in particular, are encouraging [59–61]. However, one important remaining limitation is that the only FDA-approved medications to treat alcohol use disorders target relapse prevention only. Similar limitations exist with regard to the pharmacologic treatment of PTSD. While many medications have been investigated to treat PTSD [62], only selective serotonin reuptake inhibitors (SSRI) have received FDA approval. Across clinical trials, approximately 20–30 % of patients achieve PTSD remission with SSRI treatment [63–66].

In addition to these limitations, there remains a scarcity of outcome data from randomized clinical trials regarding effective medications to treat co-occurring SUD and PTSD. One explanation is that individuals with SUD are often excluded from participation in psychopharmacology trials, both out of concern for patient safety and to maintain sample homogeneity. When a medication has shown efficacy in either or both of these disorders separately and common mechanisms of action have been identified, they are then considered for exploration among those with co-occurring SUD and PTSD.

One encouraging area of progress that has informed efforts to develop effective medications for co-occurring SUD and PTSD is research identifying shared neurobiological underpinnings of these disorders [67]. Neurobiological systems that demonstrate salient and overlapping dysregulation in both SUD and PTSD include the hypothalamic-pituitary-adrenal (HPA) axis and noradrenergic system. Individuals with PTSD have high levels of cerebral spinal fluid corticotropin releasing hormone (CRF) and norepinephrine, which has also been shown to mediate the relationship between stress and substance seeking behavior [68, 69]. Interactions between high CRF and norepinephrine levels might explain why many individuals choose to use substances to self-medicate PTSD symptoms [70]. Furthermore, research indicates that dysregulation of corticolimbic brain circuitry is centrally involved in both SUD and PTSD pathophysiology [71, 72]. Individuals with SUD and PTSD consistently demonstrate lower connectivity in corticolimbic brain regions compared with healthy controls [72–77].

Several different medications have been examined to treat co-occurring SUD and PTSD. Early studies examining the use of noradrenergic reuptake inhibitors (NRIs), selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) in patients with co-occurring SUD and PTSD have had mixed or modest effects, particularly with regard to alcohol use outcomes [26, 70]. Although one study demonstrated greater reductions in heavy alcohol use among patients receiving desipramine (an SNRI) plus naltrexone compared to paroxetine (an SSRI) plus naltrexone. The addition of naltrexone to these common antidepressant medications did not confer any additional treatment benefits [26]. A recent study by Hien and colleagues compared Seeking Safety (SS) with either sertraline (titrated to 200 mg daily) or placebo in a sample of women with co-occurring alcohol use disorder and PTSD [29]. Women randomized to receive SS combined with sertraline had a significantly greater reduction in PTSD symptom severity as measured by the CAPS at the end of treatment than those randomized to receive SS combined with placebo (CAPS reductions of 32.8 versus 16.7 points, respectively; $p < 0.002$). These treatment gains were maintained at 12 months follow-up. No statistically significant group differences emerged with regard to alcohol use outcomes. These results suggest that the combination of a non-exposure-based psychosocial intervention with antidepressant medication was beneficial in the treatment of co-occurring SUD and PTSD.

Medications that target SUD and PTSD concurrently are not only beneficial in preventing PTSD symptom exacerbation but can facilitate engagement in psychosocial treatments, particularly exposure therapies. Naltrexone, an opioid antagonist approved for the treatment of alcohol use disorder, has been used as an adjunct to psychosocial interventions, and combined with other pharmacological agents to reduce cravings and alcohol use [26, 28]. Foa and colleagues examined the use of naltrexone as an adjunct to psychosocial treatment among individuals with co-occurring alcohol use disorder and PTSD [28]. Four groups were examined: PE combined with naltrexone, PE combined with matching placebo, supportive counseling in combined with naltrexone, and supportive counseling combined with matching placebo. All groups had large reductions in percent days drinking, but those randomized to receive naltrexone demonstrated larger reductions in alcohol use than those randomized to receive placebo. There were no significant differences in PTSD symptoms between the treatment groups at post-treatment. However, individuals randomized to receive PE combined with naltrexone had lower PTSD severity at six month follow-up than the other groups. This study demonstrates the potential utility of augmenting exposure-based treatments such as PE with medications such as naltrexone.

Prazosin is an alpha$_1$ adrenergic agonist currently FDA-approved for use as a hypertensive agent. Prazosin has been explored in the treatment of SUD and PTSD separately, but only recently in the treatment of co-occurring SUD and PTSD. Prazosin has demonstrated efficacy to reduce PTSD-

related nightmares and daytime hyperarousal symptoms, and to improve sleep among individuals with PTSD [27, 78]. Among individuals with single alcohol use disorder diagnosis, prazosin has been shown to reduce alcohol consumption and reduce craving to alcohol cues [79, 80]. In a small randomized controlled trial comparing prazosin to placebo in individuals with co-occurring alcohol use disorder and PTSD, improvements in drinking outcomes favoring prazosin emerged, but no significant between-groups differences were found with regard to PTSD symptoms [81]. However, another recent clinical trial found no advantage of prazosin (16 mg daily) over placebo in reducing PTSD symptoms, sleep disturbances, or drinking outcomes over 12 weeks. These null findings suggest that alcohol consumption may interfere with prazosin's efficacy in improving PTSD symptoms [82•]. One commonly noted barrier to treatment adherence in the use of prazosin is the short half-life of the medication. Some patients necessitate multiple daily dosing to achieve their desired dose and thus, medication compliance remains a challenge for some patients. Doxazosin is a longer acting alpha$_1$ adrenergic antagonist that can be administered once daily. It is currently being explored among individuals with co-occurring alcohol use disorder and PTSD.

N-acetylcysteine (NAC) is an amino acid derivative supplement used for acetaminophen toxicity and as a mucolytic for chronic pulmonary conditions. NAC restores substance-induced glutamatergic dysregulation and has shown some modest efficacy in reducing cocaine use and craving [83]. In one recent clinical trial, adolescents receiving 1200 mg NAC twice daily were twice as likely to have cannabinoid-free urine drug screens compared to those randomized to receive placebo [84]. Several randomized controlled trials exploring the efficacy of NAC versus placebo in patients with co-occurring SUD and PTSD are currently in progress.

Additional behavioral targets guiding pharmacotherapy development research among individuals with co-occurring SUD and PTSD is emotion dysregulation and fear expression, which are hallmark PTSD symptoms that can be exacerbated by substance use. The neuropeptide oxytocin is a promising candidate to augment psychosocial treatments targeting SUD and PTSD. Higher endogenous oxytocin levels are associated with improved fear extinction [85, 86], which is a central component of exposure-based therapies for PTSD. Recent studies show that oxytocin reduces substance-related withdrawal, craving, and self-administration [87–90]. Oxytocin also has anxiolytic and fear-modulating effects [86, 91, 92]. Furthermore, recent neuroimaging studies show that oxytocin may mitigate the dysregulation of corticolimbic brain circuitry which is centrally involved in SUD and PTSD pathophysiology [93, 94]. Accumulating literature suggests that combining oxytocin with psychosocial treatments may simultaneously address the neurobiological and psychosocial underpinnings of co-occurring SUD and PTSD, resulting in improved treatment outcomes [39•, 89, 95].

Topiramate, a GABA receptor agonist and a glutamate receptor antagonist, has been explored separately in individuals with substance use disorders (alcohol in particular) and PTSD. Only recently has topiramate been examined to target co-occurring alcohol use disorder and PTSD [96–98]. Batki explored the use of topiramate versus placebo in a 12-week randomized control trial in veterans with co-occurring alcohol use disorder and PTSD [99]. Veterans in the topiramate group had fewer standard drinks per week and drinks per drinking day compared to the placebo group, although these reductions were not statistically significant. There was also a greater improvement in PTSD symptom severity in the topiramate versus the placebo group but only at a trend level of statistical significance. Although initial support for use of this medication is promising, the transient learning and memory deficits observed in the veterans taking topiramate may interfere with the efficacy of psychosocial interventions for PTSD [99].

Although the number of ongoing pharmacotherapy trials targeting co-occurring SUD and PTSD continues to increase, existing findings need to be replicated and studies must be conducted among larger samples sizes to validate preliminary safety and efficacy findings. Retention and treatment exposure remain problematic limitations in these studies and longer follow-up periods are indicated as improvement in one disorder may take a longer time to impact the other disorder. Another area to improve upon is the scarcity of studies in civilian populations, where PTSD is often more complex and SUD is often associated with a greater diversity and number of substances used. Finally, studies examining medications to augment evidence-based psychosocial therapies are warranted as combined approaches in other areas of mental health are known to produce enhanced outcomes and are more likely to be used in clinical practice.

Conclusions and Future Directions

Despite the significant distress, impairment, and complicated clinical course facing individuals with co-occurring SUD and PTSD, substantial gaps remain in the literature regarding effective treatment approaches. Recent encouraging advances include the development of integrated psychosocial treatments, and the examination of combined psychosocial and pharmacological approaches to treating the complex presentation of SUD and PTSD. In the future, it is essential to replicate the existing findings.

Another important area for future research is the need to elucidate underlying neurobiological mechanisms of action and moderators of the various integrated and combined interventions. These factors may serve as prognostic and diagnostic indicators of pathophysiology and treatment outcome in co-occurring SUD and PTSD. Structural and functional neuroimaging approaches are one such unique opportunity to

achieve that goal. For example, some literature suggests that some patients may benefit from the use of cognitive training tasks to enhance cognitive control functioning in the prefrontal cortex prior to engaging in psychosocial treatments. Some investigators have proposed that cognitive training might help mitigate prefrontal cortex hypoactivity observed in co-occurring SUD and PTSD by training neurocircuits to perform at a level of cognitive control needed for one to receive the greatest benefit from the treatment [100].

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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