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SUBSTANCE USE AND RELATED DISORDERS (F LEVIN AND E DAKWAR, SECTION EDITORS)

At the Crossroads: The Intersection of Substance Use Disorders, Anxiety Disorders, and Posttraumatic Stress Disorder

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Abstract The co-occurrence of substance use disorders with anxiety disorders and/or posttraumatic stress disorder has been widely documented and when compared to each disorder alone, consistently linked to increased risk for a host of negative outcomes including greater impairment, poorer treatment response, and higher rates of symptom relapse. This article focuses on recent advances in the understanding and effective treatment of this common and highly complex comorbidity. Prevalence and epidemiological data are introduced, followed by a review of contemporary models of etiology and associative pathways. Conceptualizations of effective treatment approaches are discussed alongside evidence from the past decade of clinical research trials. Highlighted are ongoing questions regarding the benefit of sequential, parallel, and integrated approaches and the necessity of further investigation into the mechanisms underlying treatment efficacy. Lastly, recent contributions from neuroscience research are offered as a promising bridge for the development and testing of novel, interdisciplinary treatment approaches.

Keywords Anxiety disorders · Posttraumatic stress disorder · Substance use disorder · Comorbidity · Integrated treatment

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Introduction

High rates of substance use disorders (SUDs) comorbid with anxiety and/or posttraumatic stress disorders (AD/PTSD) have been documented internationally [1–5]. These comorbidities are clinically important as they portend challenges that lie ahead for patients and clinicians alike. Individuals with co-occurring SUD and AD/PTSD exhibit more severe symptomatology, greater health problems, greater functional impairments, and fare more poorly in treatment, contributing to a heightened vulnerability to relapse after discharge [6]. Several theoretical models have been proposed that implicate common affective, cognitive, and neurobiological systems in a model of shared vulnerability. Moreover, highlights from the research and clinical arenas point to the complexities inherent in differentially diagnosing and treating individuals with these comorbidities, as temporality or primacy of one disorder over another may not be readily discernible. Further, evidence suggests that once developed, these disorders mutually reinforce and maintain each other, negatively impacting course of treatment and outcome. Thus, differential diagnosis and systematic treatment planning are fraught with challenging clinical decisions about when and how to treat these co-occurring conditions. While empirically-supported integrated treatment approaches have been developed that target co-occurring SUD and PTSD successfully, there are fewer treatments that concurrently address SUD and ADs: a significant unmet need in the latter comorbid population. This article provides a review of the recent literature exploring the prevalence and clinical impact of co-occurring SUDs+AD/PTSD, potential theoretical models for understanding the relationships between these two groups of disorders, existing treatment approaches for these co-occurring disorders, and innovations in treatment development rooted in translational neuroscience. We conclude with a summary of findings and limitations as well as general recommendations for future directions in research and clinical practice.

Prevalence of Co-Occurring SUD+AD/PTSD

Two large-scale United States epidemiological studies have examined SUD+AD and SUD+PTSD: the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) and the National Comorbidity Survey-Replication (NCS-R). NESARC data revealed that 17.7 % of respondents with any past-year SUD had a past-year AD, compared to 11.1 % of the general population, with prevalence rates ranging from 11.8 to 43.0 % among those with alcohol abuse or drug dependence, respectively [1]. The highest prevalence rates of ADs observed among SUD respondents were specific phobia (10.5 %), social phobia (4.7 %), generalized anxiety disorder (GAD; 4.2 %), and panic disorder without (2.7 %) or with agoraphobia (1.5 %). Findings from the NCS-R study corroborated these results, with significant associations among SUDs and ADs [2]. Among individuals with any past-year AD, 14.7 % also had an SUD [2]. Individuals with panic disorder with agoraphobia had the highest prevalence of SUDs (24.2 %), followed by GAD (19.1 %), panic disorder without agoraphobia (17.3 %), social phobia (16.1 %), and specific phobia (13.8 %) [2].

Lifetime prevalence estimates for PTSD in SUD samples vary from 11 to 41 % [7] depending upon study sample and patient population. The second wave of NESARC findings indicates a lifetime PTSD prevalence of 6.4 %; these individuals had a higher prevalence of SUDs compared to those with trauma history and no PTSD (46.4 %, 43.3 %, and 37.0 %, respectively) [1]. NCS-R data revealed that PTSD was significantly associated with alcohol use disorders (AUDs), but not SUDs [2]. In contrast, one recent prospective study found individuals with PTSD were four times more likely to have SUDs relative to healthy individuals with trauma history, but AUD was not associated with prior PTSD [8].

Sex differences have been identified among individuals with co-occurring AD/PTSD and SUDs. Women are more likely to be diagnosed with PTSD [9] and all ADs except social anxiety disorder (lifetime prevalence=33.3 %) than men (22.0 %) [10]. However, women with ADs or PTSD were less likely to meet diagnostic criteria for SUDs than men (4.9-15.0 % vs. 9.3-33.2 %) [9]. These findings did not differ across racial or ethnic groups. Among individuals seeking treatment for SUDs, prevalence rates range from 24.0 to 80.3 % for ADs and 30 to over 60 % for PTSD [7, 11].

In sum, epidemiological and clinical data indicate higher rates of ADs and PTSD among individuals with SUDs/AUDs compared to those without SUDs/AUDs. Moreover, findings reveal gender differences in the associations between these two disorders, with men more likely than women to have co-occurring SUD and AD/PTSD. To date, studies do not reveal any racial/ethnic differences in rates of AD/PTSD+SUD comorbidity.

Pathways

Several etiological pathways have been proposed to account for the high rates of co-occurring SUD and AD/PTSD. Predominant models include: 1) the self-medication hypothesis, where AD/PTSD increases risk for later development of SUDs; 2) the substance induced hypothesis, where SUDs increase risk for the development of AD/PTSD, and 3) the shared vulnerability model, where a third common factor contributes to the development of both SUD and AD/PTSD [6, 12]. What follows is a brief review of the self-medication hypothesis, which is contrasted with the substance-induced model. Shared cognitive and neurobiological vulnerabilities implicated in the co-occurrence of SUD+AD/PTSD are then reviewed.

Self-Medication and Substance-Induced Hypotheses

The *self-medication hypothesis* proposes that individuals with AD/PTSD use substances to alleviate painful emotional states [6]. Symptom relief reinforces drug use, leading to a reliance on substance use to manage enduring negative affective states, and heightening the risk for the development of SUDs [13, 14]. A substantial proportion of individuals with ADs endorse symptom relief as a goal of their substance use, and this subpopulation was four times more likely to develop a new AUD or SUD three years later [15•].

Despite evidence for the self-medication hypothesis, several challenges remain. First, not all substances lead to reductions in physiological arousal or negative affect [6, 13]. For example, while cannabis may reduce physiological arousal, there is less support for alcohol's objective tension reduction properties among particular comorbid populations. Among those with social anxiety disorder, several laboratory studies have found no direct impact of alcohol on reducing physiological measures of arousal during anxiety-inducing tasks [13]. Instead, it was those who *expected* alcohol to decrease their anxiety that consumed more alcohol and reported experiencing alcohol's anxiety reduction effects [13], highlighting possible dissociations between the objective and subjective benefits of alcohol use. Second, there is also strong support for the *substance-induced hypothesis*, which shows that substance use may actually cause or exacerbate symptoms of AD/PTSD directly through its impact on the central nervous system (via reduced or increased activity of certain neurotransmitters and neurobiological systems) or indirectly through negative psychosocial consequences, which contribute to increased levels of stress and anxiety [6].

Shared Vulnerability Models

Several cognitive mechanisms have been identified as shared vulnerability factors that underlie the strong association between SUDs and AD/PTSD [13, 16]. *Attentional bias* has

been implicated in the onset and maintenance of both SUDs and AD/PTSD [17]. Individuals with SUD and AD/PTSD have a tendency to preferentially attend to threat-, or substance-related cues in the environment [18, 19], which may contribute to increased anxiety and drug craving [20]. A recent study revealed that cocaine dependent individuals with PTSD displayed a greater attentional bias toward cocaine cues after exposure to a trauma-related script, highlighting the role of cognitive processes in the link between these two disorders [21]. *Anxiety sensitivity*—the fear of anxiety-related symptoms (e.g., increased heart rate, sweating, muscle tension) secondary to beliefs that these sensations may be physically harmful or lead to negative social consequences—has also been implicated [22]. Cross-sectional and prospective studies indicate that anxiety sensitivity is strongly associated with both AD/PTSD symptom severity and alcohol/drug consumption and can predict the development of new ADs and SUDs years later [23–26]. *Outcome expectancies*—positive or negative beliefs about the consequences of substance use—have also been examined as factors in the relationships between SUD and AD/PTSD [27]. Expectancies are presumed to influence levels of craving, substance-seeking behaviors, and frequency and quantity of substance use. Studies consistently find these positive associations among individuals with SUDs alone and co-occurring SUD and AD/PTSD [27, 28].

Overall, these cognitive processes may be moderated by sex, social context, and other cognitive variables such as drinking refusal, self-efficacy, and coping skills [29]. Given some of these studies were cross-sectional and used homogenous samples (e.g., predominantly white college students or treatment-seeking populations) with single substance use, these findings may not generalize to a more racially or ethnically diverse sample with co-occurring SUDs.

Evidence from basic science point to several neurobiological abnormalities that are common to both sets of disorders. Studies have found disruptions in several neurotransmitter levels including dopamine, norepinephrine, and serotonin in the development of SUDs or AD/PTSD [30•]. These neurotransmitters play a role in both regulating the stress response system as well as influencing the incentive salience of drugs of abuse [30•]. Likewise, the hypothalamic-pituitary-adrenal (HPA) axis, a part of the neuroendocrine system responsible for the management of stress, has also been implicated in both the development of SUD and AD/PTSD [30•, 31]. Overall, evidence supports multiple causal pathways in the development of SUD+AD/PTSD comorbidities, which may vary as a function of the specific types of SUDs and ADs involved and the onset and course of these disorders. Nevertheless, once both sets of disorders have developed there is a bidirectional process whereby alcohol/drug use's short-term effects on anxiety/PTSD symptoms and the exacerbation of symptoms that are caused by chronic alcohol/drug intoxication or withdrawal effects are mutually reinforced [6].

Approaches to Treatment

The most significant overarching clinical decision in treatment planning involves when (sequential, simultaneous) and how (psychosocial, pharmacotherapy, or integrated approaches) to treat these co-occurring psychiatric conditions. The three general modes of combined intervention— sequential, parallel, and integrated approaches—differ with regards to timing (one prior to the other disorder in sequential versus simultaneously in parallel and integrated strategies) and level of integration (each disorder considered separately or functionally intertwined as is seen in integrated treatments). Despite mounting empirical evidence in support of integrated behavioral approaches, individuals with SUD who have co-occurring AD/PTSD typically receive SUD treatment only [32]. In PTSD, the assumption has been that PTSD treatment may lead to stress-induced relapse [33]. However, current research has shown that the tolerability and efficacy of addressing PTSD among SUD patients are high [34, 35]. Substance use does not increase and most frequently decreases significantly with the addition of evidence-based trauma-focused interventions in PTSD patients already engaged in SUD treatment [36, 37•, 38, Lopez-Castro et al., Pathways to change: Use trajectories following trauma-informed treatment of women with co-occurring posttraumatic stress disorder and substance use disorders, unpublished manuscript]. Meta-analyses of findings from 15 years of clinical trials addressing SUD and PTSD [7, 39, 40] support integrated behavioral interventions targeting both disorders in rapid sequence or simultaneously, and are preferred by clients [41, 42]. Moreover, reductions in PTSD symptoms impact substance disorder improvement [36, 43, 44], suggesting that integrated treatments optimize patient outcomes.

Behavioral Therapy

Integrated behavioral treatment models for SUD+PTSD may be present- or past-focused [40]. Present-focused models attend to the impact of traumatic stress on current functioning and its relationship to substance and alcohol use. Treatment consists of psychoeducation, emotion regulation strategies, and cognitive-behavioral techniques for confronting urges, with promising evidence supporting several manual-based interventions [40]. However, multiple studies failed to find a significant advantage of present-focused interventions over active control treatment or relapse prevention therapy [45, 46], suggesting the need for further treatment development and research.

Past-focused models of integrated treatment for SUD+PTSD employ exposure techniques involving imaginal exploration of traumatic memories and in-vivo confrontation of avoided (safe) trauma-reminders. Long since recognized as

an effective treatment for PTSD [47] the efficacy of prolonged exposure therapy [48] for co-occurring SUD+PTSD has only recently been examined in clinical trials. Mills and colleagues [37•] compared a novel combination of PE and relapse prevention called concurrent treatment of PTSD and substance use disorders using prolonged exposure (COPE) to treatment as usual (TAU) in an Australian sample (N=103). Patients in COPE demonstrated significantly greater improvement in PTSD symptoms than the TAU participants, with equal completion rates, and no increased risk of relapse. Another study compared the efficacy of a 12-week intervention of CBT for AUD only [49] with the same intervention integrating an exposure-based therapy for PTSD [38] in an Australian PTSD+AUD sample (N=65). Completion of at least one exposure session of integrated therapy was associated with clinically significant PTSD change, but the CBT for AUD only therapy performed significantly better on a variety of AUD outcomes.

Among ADs, psychological treatments have garnered substantial support from two decades of randomized clinical trials [50, 51]. Nonetheless, treating SUD+AD from an integrated approach poses both theoretical and practical dilemmas. Exposure-based interventions for AD involve the confrontation of avoided objects or situations through gradual, systematic exposure. In contrast, avoidance of high-risk situations and triggers is routinely prescribed across evidence-based SUD therapies, particularly in early recovery. Consequently, effective design of combined treatment for AD and PTSD must skillfully navigate both contexts of recovery.

The recent literature on psychotherapies for co-occurring SUDs and ADs is notable for its numerous reviews on the topic [6, 10, 29, 52–54] and its lack of conclusive findings in favor of combined treatment of SUD+AD. In light of studies that have demonstrated improvements only in the domain of AD [55] in both SUD and AD symptoms [56], and in neither disorder [57, 58], previous reviews have been mixed in recommending combined treatment [10, 29, 54], sometimes concluding that combination treatment adds no benefit compared to SUD treatment alone [52]. A number of methodological factors have contributed to the heterogeneity of findings across randomized trials including relatively small sample sizes [59], use of unpublished treatment manuals [58] inclusion of optional pharmacotherapy [55], and unbalanced intervention time [58].

One recent meta-analysis of AUD+AD treatment (N=15) found small to moderate effect sizes for alcohol (d=.22) and anxiety (d=.32) outcomes [60]. AD treatment was associated with alcohol reduction and relapse severity but not abstinence. In comparison to effect sizes between .5 and 1.5 for psychiatric patients treated for AD without SUD, the pooled effect size of AD treatment (d=.32) suggests the attenuation of traditional AD treatment efficacy when delivered in the context of co-occurring SUD, which may indicate etiological, functional, and contextual differences between stand-alone AD and AD comorbid with SUD. A closer examination of the unique characteristics of AD as it co-occurs with SUD may clarify questions regarding the efficacy of combined treatment.

Lack of integration between the therapies tested in published trials is a significant limitation [29, 61]. For instance, the "combined" treatment in a study of co-occurring social phobia and AUD consisted of 45 minutes of AUD-focused therapy and 45 minutes of separate social phobia treatment [58]. The AUD condition outperformed the dual treatment condition in all drinking outcomes; both groups experienced moderate improvements in anxiety symptoms. Independent, adjunctive treatment for AD has also been tested as a combined treatment. A trial of parallel treatment of social phobia and agoraphobia with co-occurring AUD resulted in less anxiety when compared to treatment as usual for AUD but no significant benefit in drinking outcomes [55].

In contrast to interventions that eschew associations between the two disorders, integrated therapies attend to a theoretical framework highlighting bidirectional processes at work in co-occurring SUD and AD. One published clinical trial has tested such an integrated intervention, hypothesizing an underlying mechanism that linked AD to AUD vis-à-vis alcohol expectancies [62•]. The integrated cognitive behavioral therapy directly targeted associations between alcohol use and anxiety and was compared to progressive muscle relaxation therapy (PMRT) as a means to assess benefits above and beyond anxiety reduction. At follow up, the integrated therapy participants achieved reductions in alcohol outcomes that were significantly better than those who received PMRT. No difference was found in anxiety reduction between treatment conditions (both improved).

Pharmacotherapy

Pharmacotherapy for AD/PTSD is typically aimed at the primary symptoms of these disorders; while pharmacotherapy for SUDs generally targets the reinforcing effects of drugs of abuse, acute withdrawal symptoms, or substance cravings. Evidence generally supports the use of selective serotonin reuptake inhibitors (e.g., sertraline and paroxetine) for PTSD and naltrexone for AUD [7]. One randomized clinical trial has tested the efficacy of sertraline in co-occurring AUD+PTSD, finding it significantly enhanced PTSD outcomes [63]. Paroxetine and desipramine were compared to placebo and in combination with naltrexone for the treatment AUD+PTSD in a male veteran sample (N=165) [64]. The addition of naltrexone provided significant reduction in alcohol cravings but no differential improvement in alcohol use. Further examination of naltrexone in co-occurring AUD+PTSD has revealed promising results, with naltrexone reducing drinking and cravings when given alone or in combination with prolonged exposure therapy [65•]. In line with prior findings

however, naltrexone conferred no advantage in the PTSD domain. When taken collectively, findings suggest the utility of naltrexone in reducing AUD severity within the context of co-occurring PTSD.

Overall, the past decade of findings suggest that the combined treatment of SUD+AD/PTSD is clinically warranted and beneficial. However results of both psychotherapy and medication trials have been limited by the lack of clearly identified and understood mechanisms underlying this comorbidity [52] and the documented heterogeneity of this population. Based on the evidence to date, treatments should include a multimodal, problem-oriented approach focusing attention to individualized needs in the timing and sequencing of treatment services and the application of relevant treatment models.

Future Directions: Translational Neuroscience Approaches to Treatment Development

Classical conditioning provides a basic framework for experimental models relevant to the understanding and treatment of SUD, AD, and PTSD [66, 67]. This type of associative learning occurs in the context of addiction when neutral cues associated with substance use trigger cravings [68], and in ADs when cues associated with trauma in PTSD, phobic objects in phobias, or internal bodily sensations in panic disorder, trigger a variety of threat responses [69]. Extinction entails repeated presentations of the conditioned stimulus in the absence of the unconditioned stimulus, eventually leading to a *new* memory that *inhibits* conditioned responses [70]. Impaired extinction capability may be an underlying mechanism contributing to the comorbidity of AD/PTSD and SUD, and is the putative treatment target of exposure therapies [71]. Brain circuits associated with the two types of disorders overlap in prefrontal regions [72] and several cognitive enhancers at various stages of development have been proposed to facilitate exposure therapy [73, 74, Papini et al., Targeting the Endocannabinoid System in Posttraumatic Stress Disorder: A Critical Review of Preclinical Animal and Human Research, unpublished manuscript]. A relatively novel line of research with implications for both SUDs and AD/PTSD aims to target the emotional or motivational trace of memories directly, rather than create new inhibitory memories [75].

Consolidation is the neurobiological process involved in the formation of new long-term memories; however, the stability of consolidated memories depends on a separate process termed reconsolidation [76]. Memories that are recalled by a cue or context enter a labile state during which they may either be restored in their original configuration, or updated with new information [77]. The latter offers an opportunity for modifying memories that provoke anxiety [78] or drug cravings [79]. Reconsolidation and extinction are distinct processes; whereas extinction requires extended or repeated presentations of conditioned cues resulting in a new inhibitory memory that competes with the original memory, reconsolidation can be targeted by a reactivation of the memory with a single or brief presentation of conditioned cues [80].

Several preclinical studies have targeted memory reconsolidation in the context of SUD and ADs. Pharmacological blockade of reconsolidation has been attempted with the β-adrenergic receptor antagonist propranolol. Propranolol after drug-memory reactivation attenuated recall of the memories one day later in heroin- [81] and cocaine-dependent [82] participants. However, in the cocaine-dependent cohort, this gain was not maintained in a one week follow-up assessment [82], indicating a potential limitation of this method (this was not assessed in the heroin study). In studies with normal human subjects, propranolol impaired reconsolidation of emotional memories [83] and prevented reinstatement of the fear response when administered after memory reactivation [84, 85]. However, propranolol administration shortly after trauma did not prevent the development of PTSD [86], highlighting the challenge of translation from basic science to clinical application.

An appealing non-pharmacological approach is the administration of extinction training *during* the window of memory reconsolidation. This typically involves retrieval of the memory with a single presentation of a reminder, followed by a minimum 10 minute delay (after which the memory is theorized to become labile) before onset of extinction training. Schiller and colleagues [87] were the first to succeed with this approach in an aversive conditioning paradigm relevant to both PTSD and ADs, demonstrating that healthy participants who underwent extinction within the window of reconsolidation did not experience spontaneous recovery of their conditioned responses like their normal-extinction counterparts whose responses increased even after successful conditioning, a difference that persisted in a one year follow-up. The retrieval-extinction approach was also found to reduce recovery of fear in similar paradigms [88–90]. Functional magnetic resonance imaging (fMRI) studies suggest that disruption of reconsolidation diminishes fear-circuit connectivity in the amygdala [91] and retrieval-extinction procedures bypass prefrontal cortex activation [92]. However, several experiments failed to replicate results showing an advantage of extinction targeting memory reconsolidation [93, 94]. While these paradigms used neutral stimuli like colored squares, this procedure is also translatable to ADs where the objects of specific phobias, interpersonal cues in social anxiety, bodily sensations in panic disorder, or trauma reminders in PTSD, or drug cues in SUDs evoke conditioned responses that may be targeted vis-à-vis memory reconsolidation. In one recent application, the retrieval-extinction approach attenuated heroin cravings up to 6 months later [95•], but this promising finding requires replication and extension to other substances.

Summary and Conclusions

Overall, the evidence from the last several years suggests the likelihood of multiple etiological and interactional pathways between SUD and AD/PTSD and the necessity of further elaboration of underlying processes. Both the self-medication and substance-induced hypotheses continue to be well-supported in the literature. Emerging data also support shared cognitive (e.g., attentional bias, anxiety sensitivity, and outcome expectancies) and neurobiological vulnerability factors (e.g., disruptions in the HPA axis, reduced hippocampal volume, and hyperactive amygdala) that may be implicated in the co-occurrence of both disorders. In line with recommendations from the National Institutes on Mental Health and in addition to ongoing utilization of the DSM-5 diagnostic criteria, future studies should incorporate the Research Domain Criteria (RDoC) approach by examining mechanisms that cut across SUD and AD/PTSD. Examining sub-groups with similar underlying causal factors will allow for tailored prevention and treatment efforts.

In contrast to the field-wide recognition for superiority of integrated behavioral treatment in co-occurring SUD+PTSD, support for the preferential use of integrated therapies over sequential or parallel intervention strategies of SUD+AD remains in its nascent stages. Questions regarding the temporality of change across these co-occurring disorders are largely unanswered and warrant attention. In addition to testing treatment efficacy, future research should explore the role of treatment-matching: targeted interventions tailored to the client's presentation (e.g., type and severity of comorbid SUD+AD/PTSD, personality traits, and level of social support) and preference.

Novel lines of treatment development research are emerging that utilize various pharmacological enhancers to facilitate exposure therapies and non-pharmacological approaches such as extinction training during the window of memory reconsolidation to modify memories that provoke anxiety and drug craving. Data supporting these approaches are promising.

Because it is likely that co-occurring SUD and AD/PTSD represent a diverse set of combinations and relationships, research on interventions that specifically address the nature of the functional relationship between each disorder is critical. Most studies have focused exclusively on the comorbidity of SUD+PTSD or AUD+AD, thus more investigations on the impact of AD on other substance use trajectories and treatment are needed to discern whether significant substance-specific relationship to AD exists and merit separate research. Given the support for variations in etiology and course of SUD and AD by sex, sex differences in response to the combined treatment of AD+SUD have not been sufficiently explored and remain an area of important investigation.

Compliance with Ethics Guidelines

Conflict of Interest Lesia M. Ruglass, Teresa Lopez-Castro, Soumia Cheref, Santiago Papini, and Denise A. Hien 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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