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Treatment of Co-occurring Anxiety Disorders and Substance Use Disorders

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Abstract

Anxiety disorders co-occur with substance use disorders at a high rate in both the general population and in treatment-seeking samples. The co-occurrence of these disorders is associated with greater symptom severity, higher levels of disability, and poorer course of illness relative to either disorder alone. However, relatively little research focus has been afforded to the treatment of co-occurring anxiety and substance use disorders. This notable gap in the research literature may not only leave anxiety untreated or under-treated, but may also increase the risk for relapse and poor substance use outcomes. The aim of this manuscript is to provide a review of the current state of the literature on the treatment of co-occurring anxiety and substance use disorders. This review includes brief overview of the epidemiology of this co-occurrence, challenges in assessing anxiety in the context of a substance use disorder, evidence for treatment approaches, and new advancements and future directions in this understudied area. The importance of future research to identify optimal behavioral and pharmacologic treatments for co-occurring anxiety and substance use disorders is highlighted.

Keywords

anxiety disorders; substance use disorders; treatment; dual diagnosis; comorbidity

Introduction

Anxiety disorders and substance use disorders are among the most prevalent psychiatric illnesses.[1–3] These disorders frequently co-occur, with rates of co-occurrence even higher than would be expected by chance.[1,4] The co-occurrence of anxiety disorders (ADs) and substance use disorders (SUDs) is associated with greater symptom severity, greater functional impairment[5–8] and poorer course of illness than for either disorder alone.[6,9,10] Despite the substantial public health impact of this co-occurrence, little is known about the optimal treatment approaches for this population. The aim of this review is to provide an overview of the literature on the treatment of co-occurring ADs and SUDs, and to highlight recent developments and future directions in enhancing treatment approaches.

A literature review was conducted by first searching the *PubMed* and the Cochrane library databases using combinations of the following search terms: *anxiety disorder*, *substance-*

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related disorder, *substance use disorder*, *substance abuse*, *substance dependence*, *treatment*, *pharmacotherapy*, *medication*, *psychotherapy*, *behavior therapy* and separate search terms for each of the anxiety and substance use disorders. In addition, the reference sections of relevant articles were reviewed to identify any manuscripts missed in the initial search.

For the purpose of this review, definitions of ADs and SUDs will consist primarily of those provided in the 4th edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-IV*),[11] unless otherwise specified. In the most recent revision of the *DSM* (*DSM-5*), posttraumatic stress disorder (PTSD) and obsessive-compulsive disorder (OCD) are no longer categorized as anxiety disorders, and substance abuse and dependence have been collapsed (and slightly modified) into a single diagnosis.[12] However, because these criteria have been recently published, the studies reviewed in this manuscript have not yet adopted this new classification system. Where possible, findings specific to PTSD and OCD are highlighted separately.

Prevalence and Diagnosis

Large-scale general population surveys in the United States estimate that ADs comprise the most common class of psychiatric disorders, with past year and lifetime prevalence of these disorders approximately 18% and 29%, respectively.[2,13] Even when excluding diagnoses of PTSD and OCD, the prevalence of ADs remains high, with an estimated past year prevalence of 11% and lifetime prevalence of 16%.[1,4] The prevalence of SUDs is approximately 9% for the past year[1,14] and over 10% and 30% lifetime for drug and alcohol use disorders, respectively.[4,15] Although there is some variability internationally, these estimates are comparable to those in populations outside of the United States; ADs are the most prevalent psychiatric disorders in most countries.[3]

The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC)—a large nationally representative study conducted among adults in the US—found that among individuals with ADs (not including PTSD or OCD), almost 15% had a past-year SUD.[1] Among individuals with an SUD, almost 18% had a past-year AD, including 33–43% of those in treatment.[1] Estimates from the NESARC also suggest that over 46% of those with a drug or alcohol use disorder have met full diagnostic criteria for PTSD during their lifetime.[16] There is some variability in rates of co-occurrence based on drug of abuse, with higher rates of co-occurring ADs among those with drug as opposed to alcohol use disorders, and higher rates of ADs among those with substance dependence relative to substance abuse.[1] Among illicit drugs of abuse, particularly high prevalence of ADs is observed for opioid, sedative, and tranquilizer dependence, with lifetime comorbidity rates around 60% (not including PTSD or OCD).[4]

The diagnosis of this co-occurrence is challenging due to its multiple potential causal pathways. Specifically, the co-occurrence of these disorders could represent (a) AD symptoms caused by the effects of substance intoxication or withdrawal (i.e., substance-induced ADs); (b) one disorder occurring as a direct or indirect “consequence” of the other (e.g., substance use initiated to manage anxiety, an AD triggered by the stress associated

with an SUD); or (c) two independent disorders that co-occur either by chance or due to common risk factors.[17,18]

The diagnosis of an AD in the context of an SUD is complicated by the anxiolytic and anxiogenic effects of many substances of abuse. Thus, anxiety can be either masked or exacerbated by the effects of substance intoxication, withdrawal, and chronic administration. Accordingly, diagnostic classification systems such as the *DSM* distinguish between independent ADs and substance-induced ADs, with the latter occurring when the AD symptoms onset during or after periods of substance intoxication or withdrawal, and have not persisted for a significant period of time after discontinuation of the substance.[12]

Substance-induced ADs have been studied less widely than substance-induced mood disorders, and thus the prevalence of these disorders is unclear. Anxiety symptoms are prevalent in those with SUDs, and often these symptoms will decrease substantially early in treatment. For example, some,[19] but not all studies[20] have found that anxiety symptoms decrease significantly following detoxification from alcohol. Data from the NESARC found that the prevalence of substance-induced ADs was low, with less than 1% of ADs among those with SUDs characterized as substance-induced.[1] Although other studies have reported slightly higher estimates, in general these findings suggest that only a small proportion of ADs are substance-induced, and that a greater proportion of mood disorders are substance-induced.[21–23] Studies in mood disorders that utilize semi-structured interviews yield higher estimates of substance-induced disorders than fully-structured interviews administered by lay interviewers; thus, it is possible that large epidemiologic studies underestimate the prevalence of substance-induced ADs.[17] Nonetheless, it appears that the minority of ADs among those with SUDs are directly attributable to the effects of a substance.

Determining whether independent ADs and SUDs are the result of one disorder causing the other or are the result of common risk is even more complex. One approach to investigating this question has been to determine the temporal precedence of disorders based on either retrospective recall of age of onset, or to prospectively examine disorder incidence. Retrospective recall studies have consistently found that the majority of co-occurring disorder cases (some studies estimating >80%) reflect an earlier age of onset for the AD.[24–26] The exception to these findings is PTSD, where the relative age of disorder onset has been more mixed. Some studies suggest that substance use and SUD symptoms have an earlier onset than PTSD symptoms[27,28] and other suggest the reverse association.[29] As such studies relied on group averages (e.g., differences in the average age of onset for PTSD vs. SUDs), it is likely that this discrepancy reflects a heterogeneity across individuals with respect to the relative age of onset of these disorders.

Consistent with these retrospective recall studies, prospective studies have found greater support for risk for development of an SUD among those with ADs than vice versa. In a 10-year follow-up of the National Comorbidity Survey, individuals with an AD were significantly more likely than those without to later develop an SUD, and to initiate illicit drug use.[30] Similarly, in the Epidemiologic Catchment Area study, ADs were associated with risk of developing an SUD in the next year.[31] Another large study (N = 899) found that PTSD diagnosis was associated with risk for the onset of drug use disorders over a 10 year

follow-up.[32] The presence of an SUD has been associated with risk for incidence of ADs in some large population studies,[33] but not others (e.g., NESARC).[34,35] Thus, there is greater evidence for ADs preceding SUDs than SUDs preceding ADs. This course of illness may be more variable when considering PTSD specifically.

However, temporal precedence is an inexact strategy for determining the independence of disorders because relative time of onset alone is insufficient to determine causality. ADs—in general—onset at an earlier age than SUDs.[2] Thus, evidence that ADs often precede SUDs does not necessarily indicate that SUDs are caused by these disorders, but rather may reflect a later developmental vulnerability period. Even if ADs often precede SUDs, their co-occurrence may still be attributable to shared or independent vulnerability. A prospective follow-up from the NESARC found that when not controlling for baseline co-occurring disorders (i.e., psychiatric disorders present prior to the year preceding data collection), there was strong and significant incident risk of SUDs among those with ADs, and vice versa.[34] However, when controlling for baseline psychiatric factors, all but one of these associations (panic disorder and incident drug use disorders) were no longer significant. Similarly, a study of young adults in New Zealand found that the presence of ADs was associated with 1.3–3.9 times higher odds for later development of SUDs; however, when controlling for other risk factors, such as history of childhood adversity, peer factors, other substance dependence, and depression, this association was no longer significant.[36] These findings suggest that the association between these disorders may be accounted for by common vulnerability factors, at least in part.

These studies suggest that there may be multiple casual pathways for the development of co-occurring ADs and SUDs. Although substance-induced ADs may comprise only a small proportion of AD cases, diagnosing ADs in the context of an SUD requires careful consideration of the potential for substance-induced disorders. Thus, for ADs for which there was not a distinctly apparent earlier age of onset or a persistence of symptoms during extended periods of abstinence (typically defined as at least 1 month), establishing a diagnosis may require observation of anxiety symptoms in early stages of treatment. In such cases, focusing treatment on the SUD is indicated. Although it remains unclear the degree to which common vulnerability or risk directly related to the other disorder explains the co-occurrence of ADs and SUDs, research suggests that ADs often onset earlier and that common vulnerability appears to be a contributor to this co-occurrence. Some clinical trials in PTSD have found that treatment response may differ depending on disorder course (see below), highlighting the importance of understanding the differences among subgroups of this population characterized by differing course of illness.

Treatment Outcomes

Studies that have investigated treatment outcomes for co-occurring ADs and SUDs include naturalistic studies, secondary analyses of clinical trials of treatment for either ADs or SUDs, and studies of concurrent or integrated treatments for both disorder types. This literature is challenging to interpret because of the substantial heterogeneity of studies with respect to study design, diagnostic assessment, type of treatment, and clinical population.

Unsurprisingly, results of this area of research have been mixed with respect to the impact of this co-occurrence on clinical outcomes.

Treatments Targeting the Substance Use Disorder

Naturalistic Studies

A number of naturalistic studies have compared SUD treatment outcomes between those with and without co-occurring ADs. These studies provide important information about the outcomes of the subset of this population that seeks treatment in an SUD treatment setting. However, naturalistic studies are often limited by a lack of treatment standardization, the absence of control groups, poor follow-up rates, and inconsistent procedures for diagnostic assessments. Most of these studies do not assess ADs or anxiety symptoms over time, and thus data primarily are focused on substance use outcomes.

Several naturalistic studies have suggested that the presence of ADs is associated with worse treatment outcomes for those with alcohol dependence. A study of 100 patients with alcohol dependence admitted to an inpatient SUD treatment facility found that those with ADs were approximately half as likely to be abstinent at a 6-month follow-up than those without.[37] However, only 68% of the sample completed follow-up. Similarly, in a study of 53 patients with alcohol dependence receiving treatment in a 21-day residential program for SUDs, those with an AD had a more rapid relapse to drinking, and relapse to bring drinking, but similar time to the first 3 consecutive days of drinking.[38] In this study, approximately half of those with an AD at baseline no longer met criteria for the AD at 4-month follow-up. However, only 65% of those initially enrolled were retained at follow-up. A study of 98 patients presenting for outpatient treatment for alcohol use disorders found that those with and without co-occurring ADs (panic disorder, agoraphobia, social phobia, and generalized anxiety disorder) improved to a similar degree with respect to drinks per drinking day and disability, but that those with ADs displayed greater severity at baseline on these measures and continued to exhibit greater severity at a 3-month follow-up (response rate of 72%).[5]

Contrary to these results, several studies have not found different outcomes between those with and without ADs. In a 15-month follow-up of patients presenting for the treatment of alcohol dependence there was no association between ADs (PTSD and OCD were not assessed) and level of alcohol consumption; however, a diagnosis of panic disorder was associated with increased alcohol consumption at follow-up in men (75% of 351 participants were retained).[39] Follow-up 28 months later found no association between ADs and likelihood of abstinence (83% of the 351 participants were retained).[40] Of note, only a small number of participants (16%) remained abstinent, limiting the ability to detect group differences. Similarly, in a study of patients diagnosed with alcohol dependence who presented for detoxification and remained abstinent for at least 4 weeks, participants with social phobia or agoraphobia did not differ from those without ADs with respect to time to relapse of likelihood of abstinence when followed up by phone between 3–42 months after discharge.[41] The follow-up rates were 78.6% and 68.2% in the anxiety and no-anxiety groups, respectively (this difference was just short of statistical significance).

Relatively few naturalistic studies have examined the impact of ADs on treatment outcome in drug use disorders, and these studies have focused on diagnoses of PTSD. In a study of 255 patients receiving opioid substitution treatment at Veterans Health Administration (VA) health care clinics, those with and without PTSD had similar substance use outcomes at 1 year follow-up; however, those with PTSD used more services, including higher medication doses and more psychotherapy sessions, and remained in treatment longer.[42] PTSD symptoms did not significantly improve over time. Consistent with this finding, a prospective study of over 600 patients with opioid dependence found that although PTSD did not appear to interfere with successful treatment of the SUD, PTSD symptoms remained significant and were associated with substantial disability two years following treatment initiation.[43]

A study of participants in methadone maintenance treatment found that a diagnosis of PTSD was associated with more opioid and cocaine use 3 months after beginning treatment. In another study of 322 patients with mixed alcohol and drug use disorders receiving treatment in residential substance use treatment programs, the presence of a PTSD diagnosis was not associated with substance use outcome at 6- or 12-month follow-up.[44] However, trauma occurring during the study period was associated with higher odds of substance use in the previous 30 days at follow-up.[44]

Clinical Trials—Clinical trials of treatments for SUDs often exclude[45] or fail to assess for the presence of ADs (or assess only certain disorders, such as PTSD). Thus, these studies are less common, and are potentially limited by sample selection procedures that may yield co-occurring disorders only of lower severity. For example, it is not uncommon for SUD clinical trials to exclude concurrent antidepressant treatment, thus potentially excluding many potential participants with ADs.

Several randomized clinical trials have examined whether AD diagnoses at baseline were associated with SUD outcome, but the results of these studies also have been mixed. For example, in a secondary analysis of two randomized clinical trials of CBT for alcohol use disorders in women, lifetime ADs (including PTSD) were associated with more drinking days at 6 month follow-up, and current ADs were associated with more drinking days both during treatment and at 6 month follow-up.[46]

With respect to PTSD, a recent study of buprenorphine-naloxone for prescription opioid dependence found that PTSD was not associated with worse outcomes.[47] Similarly, in a randomized trial of 12 weeks of disulfiram, naltrexone, and their combination for alcohol dependence, those with co-occurring PTSD (N = 93) did not have worse alcohol outcomes relative to those without.[48] Those receiving active medication had more consecutive abstinence days and fewer heavy drinking days. There was some reduction in PTSD symptoms, with greater reductions for some outcomes in the disulfiram group.

Summary of Studies Targeting SUDs—These results from naturalistic and clinical trials present a complex picture of the impact of the co-occurrence of these disorders on treatment outcome. The impact of ADs on SUD outcomes is mixed, with some studies suggesting similar outcomes for those with and without ADs, and others suggesting worse

outcomes among those with ADs. These mixed findings with respect to substance use outcomes may be attributable in part to variability in the severity of ADs, and the possibility that these samples included some substance-induced ADs. However, in general these studies suggest that an AD does not necessarily negatively impact SUD outcomes for those in SUD treatment. Importantly, these studies provide initial support for the efficacy of pharmacotherapy for SUDs among those with ADs. There seem to be no clear negative effects of pharmacotherapy on anxiety outcomes, at least among those with PTSD.

Of the few studies that have also examined AD and functional outcomes, results suggest that SUD treatment alone does not generally improve ADs and that populations with co-occurring ADs and SUDs display worse functional outcomes. Thus, although ADs may or may not have a negative impact on SUD treatment, SUD treatment does not appear to offer substantial benefit for anxiety. It is of note that although anxiety *disorders* do not appear to consistently benefit from SUD treatment, significant reduction in anxiety *symptoms* is often reported following detoxification or in early stages of abstinence,[19,49] which may reflect improvement in anxiety symptoms attributable to substance intoxication, withdrawal, or a reduction in stress.

Treatments Targeting the Anxiety Disorder

The vast majority of clinical trials of treatment for ADs exclude SUDs (or at least substance dependence). Thus, there is limited literature available on the efficacy of AD treatments in this population. Moreover, studies of treatments for ADs in individuals with co-occurring ADs and SUDs primarily have been conducted in patients with alcohol use disorders. Unlike in studies of SUDs, these have predominantly involved clinical trials (rather than naturalistic studies).

Medication Trials—Very few clinical trials have examined the safety or efficacy of pharmacotherapy for ADs among those with co-occurring SUDs. The literature in this area has predominantly focused on selective serotonin reuptake inhibitors (SSRIs). In addition to representing the front-line treatment for ADs, SSRIs have received attention in this population because of some evidence for modest benefits for alcohol outcomes in certain subgroups with alcohol dependence.[50,51]

A small placebo-controlled pilot trial of paroxetine for social anxiety and alcohol dependence ($N = 15$) found significant improvement in social anxiety and improvement in some, but not all, alcohol outcomes (clinical global index, but not quantity or frequency of drinking).[52] In a subsequent small ($N = 42$) randomized trial of paroxetine or placebo for co-occurring social anxiety and alcohol abuse or dependence (participants were seeking treatment for social anxiety disorder and reported drinking alcohol to mitigate anxiety), there was a significantly greater reduction in social anxiety symptoms in the paroxetine group relative to the placebo group; however, there were no effects on drinking outcomes in either group.[53] Results suggested that those receiving paroxetine reduced their self-reported use of alcohol to engage in social situations; however, this group did not exhibit significant reductions in drinking.

Another study of SSRIs randomized 94 patients with alcohol dependence and PTSD to receive sertraline or placebo.[54] Although on average sertraline did not result in improvements in either alcohol use or PTSD symptoms, results indicated that treatment effects may have varied in different subgroups. Specifically, those with higher severity of alcohol dependence and late-onset PTSD had better alcohol outcomes with sertraline, with the opposite effect among those with lower severity alcohol dependence and early-onset PTSD. There was a trend toward better clinician-rated PTSD outcomes in the sertraline group; however, these results did not reach statistical significance.

Buspirone has also received some attention in this population given its efficacy for some ADs and low abuse liability. In a small study of 51 patients with generalized anxiety disorder (*DSM-III*) and alcohol dependence, patients were randomized to receive buspirone or placebo for anxiety following alcohol detoxification. Buspirone was associated with significantly greater reduction in anxiety symptoms, greater odds of being a treatment responder (defined as a combination of reduction in anxiety and no relapse to alcohol), and greater self-reported improvements in anxiety and drinking.[55] Contrary to this finding, a randomized study of buspirone ($N = 67$) for recently detoxified alcohol dependent patients who met *DSM-III-R* criteria for generalized anxiety disorder found that both groups exhibited some improvement in alcohol and anxiety outcomes, but buspirone did not outperform placebo.[56] Similarly, a small randomized trial of buspirone for 36 participants with opioid dependence receiving methadone maintenance treatment found no significant improvements in anxiety or substance use outcomes (although there was a subtle trend for a longer time to first illict drug use in the buspirone group).[57]

Few studies have examined other antidepressant medications with efficacy for the treatment of ADs, such as the serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs). A series of case studies of the use of imipramine for the treatment of “phobic anxiety” (roughly equivalent to a *DSM-IV* diagnosis of panic disorder) and SUDs found short-term benefits for both anxiety and substance use outcomes, and those who continued imipramine treatment over the long-term were less likely to relapse to substance use.[58] However, subsequent studies of imipramine for cocaine and opioid dependence failed to find significant benefits for the SUD, and given the greater tolerability of SSRIs and SNRIs these are typically recommended as the first-line treatment.[59,60]

Although benzodiazepines have the benefit of a more rapid anxiolytic effect than antidepressant medications, their use has been controversial in the treatment of ADs and SUDs, in large part due to concerns about abuse liability.[61,62] Unsurprisingly given these concerns, little empirical literature directly addresses the efficacy or safety of benzodiazepines in the treatment of co-occurring ADs and SUDs. Studies have suggested that those with a personal and family history of SUDs may be more susceptible to the addictive effects of benzodiazepines and thus at greater risk of abusing these medications.[63,64] Moreover, benzodiazepine misuse is common among those with SUDs, particularly among those with more severe SUDs, multiple SUDs, and greater psychiatric severity.[65,66]

However, some studies have challenged the belief that these medications cannot be administered safely among those with co-occurring ADs and SUDs. A case series of the use of benzodiazepines in patients with co-occurring ADs and SUDs suggested that when patients were carefully selected and closely monitored, they were able to maintain abstinence.[67] In secondary analyses of the Harvard/Brown Anxiety Disorders Research Program study, a longitudinal naturalistic study of individuals with ADs, researchers have examined differences in benzodiazepine use among those with and without alcohol use disorder histories. Following the first 12 months of follow-up, there were not consistent significant differences in dose or frequency of benzodiazepine use among those with and without an alcohol use disorder.[68] A 12-year follow-up from this study did not find significant risk of the onset of or relapse to an alcohol use disorder among those prescribed benzodiazepines for an AD.[69]

In the absence of well-controlled trials, the safety of benzodiazepines in this population as well as its efficacy for both anxiety symptoms and substance use symptoms remains largely unknown. Thus, alternative treatment options with better evidence for safety and efficacy in this population (including behavior therapies) are typically recommended as the first-line treatment approach, with benzodiazepines considered cautiously only after these options have been exhausted.[61,62,67]

Behavior Therapy Trials—Several trials have examined the efficacy of behavior therapies (predominantly CBT) for ADs in this population. In randomized controlled trials and meta-analytic reviews, CBT has consistently been shown to be equal, if not superior, to medication (particularly over the long-term) for the treatment of ADs, and thus represents a treatment of choice for anxiety.[70–72]

A naturalistic study of outpatient group CBT for panic disorder with and without agoraphobia ($N = 83$) found that patients with co-occurring SUDs had worse anxiety outcomes and a higher rate of treatment dropout than those without.[73] Contrary to these findings, a large naturalistic study of patients presenting to an AD specialty clinic with a diagnosis of panic disorder, social anxiety disorder or generalized anxiety disorder ($N = 200$) found that those with an SUD had similar anxiety outcomes following CBT.[74] However, individuals could only receive treatment at this clinic if SUDs were secondary to the AD. In a chart review of 536 individuals with and without alcohol use disorders receiving treatment for PTSD (Cognitive Processing Therapy) in a VA hospital, neither retention nor PTSD outcomes differed among those with a current alcohol use disorder, a past alcohol use disorder, and no alcohol use disorder.[75]

Ciraulo and colleagues[76] conducted a randomized controlled trial with participants diagnosed with co-occurring ADs (*DSM-IV*) and alcohol use disorders. Participants ($N = 82$) were randomized to receive combinations of venlafaxine or pill placebo, and CBT (the Unified Protocol for the Transdiagnostic Treatment of Emotional Disorders)[77] or a credible psychotherapy comparison (progressive muscle relaxation). Although small sample sizes in each of these groups limit the interpretation of these findings, results suggested that the combination of CBT and placebo yielded the strongest alcohol outcomes (reduction in heavy drinking days); this condition was the only active treatment that exhibited significantly

greater reductions than the comparison condition (placebo and progressive muscle relaxation). Neither venlafaxine condition outperformed placebo with respect to alcohol outcomes. Anxiety significantly decreased in all groups with the exception of the venlafaxine-CBT group.

Summary of Studies Targeting ADs—Studies of treatments of ADs are also mixed with respect to whether SUDs contribute to worse AD symptom outcomes. However, AD treatments do not appear to reliably achieve benefits for SUDs. Thus, similar to studies of treatment for SUDs, the presence of a co-occurring disorder may or may not contribute to worse outcomes for the treated disorder, but will likely result in worse post-treatment functioning overall.

There is a significant need for more research on the efficacy and safety of AD medications in individuals with co-occurring ADs and SUDs. In particular, the range of concerns about the interaction of these medications with drugs of abuse (e.g., cross-tolerance of benzodiazepines and alcohol, lowering of seizure threshold with TCAs, impact of medications on the metabolism of SUD medications) as well as concerns about abuse liability must be considered in treating this population. Behavior therapies (e.g., cognitive behavioral therapy) provide a valuable alternative to pharmacotherapy that avoids such concerns; however, the limited availability of providers trained in evidence-based behavior therapies can be a significant barrier to treatment receipt.

Concurrent and Integrated Treatments

Concurrent Treatments—Several recent trials have combined treatment for ADs and SUDs. A study of the addition of 6, 2-hour sessions of CBT for panic disorder among 146 inpatients with alcohol dependence found no significant differences in improvements for both alcohol (relapse and number of drinks) and anxiety and depression outcomes in both groups, with both those in SUD treatment as usual and those receiving adjunctive CBT improving with respect to alcohol and anxiety outcomes.[78]

In a comparison of 32-weeks of alcohol treatment alone versus alcohol treatment plus CBT (and optional SSRI) in 96 alcohol dependent patients with co-occurring panic disorder, agoraphobia, or social phobia, groups exhibited similar alcohol outcomes (relapse to drinking, proportion abstinent), and significant reduction in anxiety.[79] However, participants who received the anxiety treatment exhibited significantly better anxiety outcomes. In a secondary analysis of participants who received the anxiety treatment, the authors found that the severity of alcohol dependence was not associated with anxiety outcome.[80]

Foa and colleagues[81] randomized 165 individuals with *DSM-IV* PTSD and alcohol dependence to receive combinations of evidence-based psychotherapy for PTSD (Prolonged Exposure), pharmacotherapy for alcohol dependence (naltrexone), and psychotherapy (supportive counseling) and pill placebo. Although all groups experienced significant reductions in the number of drinking days, participants receiving naltrexone had better alcohol outcomes relative to those receiving pill placebo. Prolonged Exposure did not worsen alcohol outcomes, but also did not yield significantly superior PTSD symptom reductions to supportive counseling.

Another trial compared paroxetine or desipramine plus naltrexone or placebo for co-occurring *DSM-IV* alcohol dependence and PTSD in a sample of 88 male veterans.[82] Clinician-rated PTSD symptoms significantly improved, with no differences between paroxetine and desipramine. However, those receiving despiramine remained in treatment longer and had fewer heavy drinking days. Although naltrexone reduced alcohol craving, it did not improve alcohol use outcomes. A secondary analysis of a randomized trial of naltrexone or placebo for military veterans with alcohol dependence found that the addition of SSRIs among those who developed worsening anxiety or depressive symptoms during the trial did not negatively impact the efficacy of naltrexone for alcohol outcomes.[83]

Among those with PTSD in a 5-year follow-up study of VA patients who received inpatient SUD treatment, treatment engagement (receipt of treatment for PTSD and 12-step meeting attendance) was associated with remission (defined as abstinence from all drugs, no problems associated with use, and minimal alcohol use) from SUDs 5 years later.[84]

Integrated Treatments—Several integrated behavioral treatments have been tested in this population. Kushner and colleagues[85,86] developed an integrated CBT protocol for co-occurring alcohol dependence and panic disorder, which was recently expanded to include social anxiety and generalized anxiety disorder.[87] This treatment integrates elements from evidence-based CBT protocols for ADs and research on the interaction between anxiety and alcohol use. In a small quasi-experimental study of this treatment in panic disorder compared with treatment-as-usual, the integrated treatment group reported better anxiety outcomes.[85] Moreover, participants with greater expectancies that alcohol would relieve anxiety also had superior alcohol use outcomes (relapse and meeting criteria for an alcohol use disorder). In a large randomized controlled trial (N = 344) comparing treatment-as-usual plus the integrated CBT or an active anxiety comparison treatment, both groups exhibited substantial reduction in anxiety, but the integrated treatment was associated with better alcohol outcomes (relapse, binge drinking, and drinking days per month).[87] Anxiety outcomes improved in both conditions, with some evidence for better outcomes in the CBT condition at 4-month follow-up.

The majority of research on integrated treatments in this population has focused on the treatment of co-occurring SUDs and PTSD. Seeking Safety[88]—a treatment approach focused on psychoeducation and building skills for self care and coping—has been the most widely studied treatment in this population. Open and wait-list controlled trials have yielded mixed results, with several studies finding significant (albeit often modest) improvements in PTSD symptoms only,[89] some finding improvements in SUD symptoms only,[90] and some finding improvements in both outcomes.[88] Randomized controlled trials including an active comparison treatment or a strong treatment-as-usual comparison have typically not found Seeking Safety to be superior to psychoeducation comparison treatments[91] or CBT for SUDs.[92] Importantly, these studies consistently suggest that this is a well-tolerated treatment, with no evidence of a worsening of PTSD symptoms.

More recently, integrated treatments informed by existing evidence-based treatments for PTSD have been applied in this population. Integrated CBT (ICBT)[93] utilizes components of CBT for both SUDs and PTSD, including psychoeducation, breathing retraining, and

cognitive restructuring (exposure therapy is not included). This approach has demonstrated initial success in reducing both PTSD and SUD symptom severity and a strong retention rate in both a small open trial[93] and in a small (*N* = 59) randomized trial compared to individual drug counseling.[94] Of note, ICBT appears to yield better (clinically-significant) PTSD outcomes, but similar SUD outcomes compared to individual drug counseling.[94]

Several studies have applied an integration of Prolonged Exposure—an evidence-based behavior therapy for PTSD—with CBT for SUDs. The COPE (Concurrent Treatment of PTSD and Substance Use Disorders Using Prolonged Exposure) treatment has demonstrated substantial and significant improvement in PTSD outcomes as well as significant reductions in substance use, and has been well tolerated (as assessed by lack of an increased risk for relapse).[95] In a larger trial (*N* = 103) comparing COPE to treatment-as-usual, COPE resulted in superior PTSD and SUD outcomes.[96] Drop-out rates have been high in these studies (e.g., over 40% in the largest trial to date did not complete an exposure session);[96] however, it is of note that treatment drop-out in this population in general is high, and 25–35% drop-out rates are not uncommon.[7, 92, 94]

Summary of Concurrent and Integrated Treatment Approaches—Studies examining the concurrent administration of SUD and AD treatments have demonstrated that these treatments can be safely and effectively combined, without evidence for worsening of symptoms of either disorder. However, in several of these studies at least one of these treatments failed to outperform placebo, and thus additional research in this area is needed to understand the optimal combinations of treatment to maximize outcomes for both disorders.

Integrated treatment approaches also have shown promise for this population. Notably, despite some mixed results, findings have consistently suggested that treating ADs is not associated with a reliable *worsening* of SUD symptoms, despite early concerns about the safety of addressing anxiety (particularly trauma) in this population (see discussion below on the safety of using exposure therapy). In general, exposure-based treatments appear to demonstrate the largest reductions in AD symptoms; however, retention may be a particular challenge in these treatments.

Although this has been a relatively understudied area, treatment development is expanding, with a number of ongoing clinical trials testing integrated treatments for co-occurring ADs and SUDs. For example, integrated cognitive-behavioral therapies for co-occurring social anxiety disorder and alcohol[97] and marijuana use disorders[98] are currently being tested. Given the success of integrated behavioral treatments for co-occurring SUDs and other psychiatric disorders, such as bipolar disorder,[99,100] the evaluation of these models in ADs is important to the identification of treatments that maximize benefits for both disorders.

Treatment Challenges and Considerations

As increased recognition of the importance of improving treatment approaches for co-occurring ADs and SUDs has resulted in an increase in research and clinical attention for this population, a number of unique challenges have emerged. Below is a brief discussion of

some of the major treatment challenges that will need to be considered as this area of research and clinical practice advances.

Diagnosing and Assessing Co-occurring Disorders

The diagnosis of ADs in the context of an SUD must take into account the potential for the symptoms to be substance-induced. In the absence of clear presence of the AD prior to the onset of regular substance use, or during a period of extended abstinence, observation and reassessment of symptoms following a period of substance abstinence is indicated. This further highlights the importance of assessing anxiety disorders, and not only anxiety symptoms, which are more variable across contexts and over time. Symptom measures with validated cut-off scores can be useful; however, these measures typically have not been validated in populations with SUDs, and thus the validity of standard cut-off scores in this population is unclear. Thus, symptom measures should be interpreted with caution, and structured or semi-structured diagnostic interviews are ideal when the setting allows for the use of such measures.

In the assessment of ADs and SUDs, the consideration of sub-syndromal symptoms of these disorders is also of potential clinical benefit. Anxiety symptoms may be an impediment to achieving abstinence. Anxiety often precedes (and possibly precipitates) substance use,[101] is a common response to substance-related cues,[102,103] and is often reported as a reason for use (i.e., substance use to relieve anxiety).[104] Thus, attention to anxiety management strategies within the context of SUD treatment may be helpful even to those without a diagnosable independent AD.

Likewise, in assessing potential SUDs among those with ADs, it is important to consider both SUD diagnoses as well as problematic levels of use. Self-medication of anxiety symptoms is associated with incident risk for SUDs.[105] Moreover, the use of substances to manage anxiety may serve as either a problematic safety behavior (e.g., using alcohol to manage anxiety in a social situation) or interfere with the consolidation of extinction learning during exposure-based therapies. Thus, addressing problem-level substance use, or substance use as a strategy for managing affective states may be beneficial even among those who do not meet full diagnostic criteria for an SUD.

Is It “Safe” to Treat Anxiety Disorders in Patients with Substance Use Disorders?

Exposure-based therapies are the front-line behavioral therapy for the treatment of the majority of ADs. Despite their strong efficacy and tolerability in the treatment of ADs,[106,107] it is not uncommon for clinicians to report concern about the safety of exposure, particularly among those with SUDs.[108] In particular, concerns about a potential worsening of symptoms or an increased risk for relapse may lead to either suboptimal delivery of exposure or the decision not to use exposure at all.[109]

Several recent studies have provided empirical support for the safety of using exposure therapy in patients with SUDs. For example, in recent studies utilizing an integration of Prolonged Exposure for PTSD and CBT for substance dependence, this treatment was tolerable and acceptable and did not increase use or risk for relapse.[95,96] Although attrition is high in these exposure-based therapies (less than half of participants in the two COPE

trials received *a priori* adequate doses of treatment), the degree of PTSD improvement in these therapies has exceeded that from other, non-exposure based therapies. Moreover, the majority of participants who dropped out of treatment in these studies did so prior to beginning exposure.

Treatments for both ADs and SUDs involve difficult and triggering topics that are likely to cause distress. Exposure-based therapies aim to intentionally activate emotional reactivity in order to achieve the extinction of fear responses and disorder remission. Although appropriate caution related to the individual's ability to manage stressors is always indicated in such settings, the evidence to date consistently suggests that treating ADs—including with exposure-based therapies—does not appear to confer greater risk for adverse SUD outcomes.

Will Exposure Therapies Work in Individuals with Substance Use Disorders?

Another potential problem with the use of an exposure therapy in SUD populations entails whether extinction learning may be hampered in this population. Extinction learning is the process of decreasing fear responses to stimuli by presenting the stimulus in the absence of a feared consequence.[110] In other words, extinction learning involves creating a new memory associating the feared stimulus with safety. This learning process involves a well-established neurocircuitry including fronto-limbic pathways that may be enhanced or disrupted pharmacologically.[111] However, it is not clear how the acute and sustained effects of substances of abuse may impact this process.

Research in animals has suggested that the presence of substances of abuse can interfere with both fear conditioning and fear extinction. Models of chronic alcohol use in mice suggest that fear extinction is impaired, possibly due to down-regulation of NMDA receptors in the medial prefrontal cortex, a crucial piece of the neural pathways implicated in extinction learning.[112] Additionally, alcohol withdrawal[113] and acute alcohol administration[114] have been shown to impair fear extinction in rats. Although other substances are less well studied, there is also evidence for impaired extinction (particularly between-session consolidation) following chronic nicotine,[115] morphine,[116] and cocaine exposure.[117]

Studies of the effect of substances of abuse in the human brain suggest that these neural circuitries are impacted by a number of these substances. However, the direct examination of the effects of substances on extinction learning has been very limited. A study in opioid-dependent methadone maintenance patients found that fear conditioning was significantly impaired in this group.[118] Fear extinction could not be evaluated because the acquisition of fear was so poor that extinction could not be tested.

Together, this research suggests that acute and chronic substance administration has potentially deleterious effects on the process of fear extinction. Nonetheless, recent studies have supported the efficacy of exposure-based therapies in this population.[96] As such, additional research—particularly in humans—to understand the potential for impairment of extinction learning is needed. In particular, such research may be important for determining

the optimal timing of exposure therapies relative to substance cessation (e.g., following detoxification, after a month of abstinence) to maximize the efficacy of exposure.

Concurrent, Integrated, or Single Disorder Treatment

The literature reviewed above is clearly mixed with respect to outcomes. However, general conclusions appear to support that addressing one of these disorders does not consistently confer benefits for the other. Thus, with the exception of substance-induced ADs, treating both disorders appears to be the best clinical course of action. Although the research in this area is too limited to draw definitive conclusions at this time, it appears that integrated treatments (i.e., those that incorporate treatment for both disorders) may offer a number of benefits over concurrent treatments (i.e., simultaneously providing separate treatments for anxiety and SUDs) with respect to outcome. Moreover, a small study of returning veterans with co-occurring PTSD and SUDs found that 66% preferred an integrated treatment approach.[119] Given the importance of patient preferences to evidence-based care, and evidence for better retention and outcome for those who receive their preferred treatment[120,121] consideration of patient preference is of considerable importance.

A key consideration in the development of integrated treatments is which specific ADs and SUDs to target. The approach, particularly for behavior therapy development, has been to focus on specific disorders. However, considering the variable combinations of ADs and SUDs, a single disorder approach (e.g., treatment for generalized anxiety disorder and cannabis dependence) would result in at least 49 discrete treatments. This does not include the potential combinations of co-occurrence among ADs, for which the lifetime co-occurrence ranges from 64% for panic disorder (with and without agoraphobia) to 94% for PTSD.[122] Although approaches to date have focused on the most prevalent co-occurring disorder combinations, such as panic disorder and alcohol use disorders[85] and social phobia and cannabis use disorders,[98] these approaches may have less utility relative to those that can be more widely applied.

A treatment initially developed for a combination of panic disorder and alcohol use disorder has been modified and expanded to include other common ADs.[87] This strategy of initial testing with a discrete combination of disorders and later extending to more disorders may provide a balance of specificity and generalizability, but has the limitation of taking many years to complete. Given that behavioral treatments within the SUDs are very similar, as are treatments for ADs, their evaluation for multiple combinations of co-occurring disorders may be of greater benefit in a research setting (e.g., the ability to establish sufficient sample homogeneity and appropriate outcome measures) than a clinical setting. Nonetheless, research will be needed to determine the optimal balance of specificity and breadth of integrated treatment approaches in this population.

The development of integrated treatments may progress more rapidly and more precisely by building on advances in the understanding of common underlying vulnerabilities. For example, the Research Domain Criteria (RDoC) initiative of the National Institute of Mental Health is examining core processes that may play a role in the development and maintenance of disorders across current diagnostic categories.[123] Concurrent efforts to target these processes with treatment may allow for the refinement of treatments for this co-

occurrence by intervening at the level of contributing processes rather than resultant symptoms.

Summary and Conclusions

Anxiety disorders and substance use disorders commonly co-occur and present particular challenges in treatment settings. Although the treatment literature is somewhat limited at this time, several tentative conclusions can be drawn from what is known to date. In general, studies are mixed with respect to whether ADs interfere with SUD treatment and vice versa. A consistent finding in this literature is that treating one disorder does not typically confer improvements in the other and that when only a single disorder is treated, significant distress and disability may remain. Nonetheless, whether co-occurring disorders are associated with worse outcome for the treated disorder (i.e., whether an anxiety disorder is associated with worse SUD outcomes) remains unclear.

The inconsistency across studies may be attributable to a number of factors. Most notably, the methods utilized vary widely and sample sizes typically have been small. In particular, sample selection biases (e.g., whether an individual presents to an SUD or mental health treatment setting, the exclusion of substance dependence in studies of AD treatment) may mitigate the impact of co-occurring disorders on treatment. In addition, it is possible that the heterogeneity of this population contributes to these mixed findings. Individuals with substance-induced ADs and those with varied courses of illness (earlier onset of ADs vs. SUDs) may respond differently to treatment. This is an important consideration for future research.

Concurrent SUD and AD treatment has received relatively little attention, but studies to date have been promising for the safety of combining front-line treatments for these disorders. Although integrated treatment approaches have begun to show promise, most of these treatments are in relatively early stages of investigation. Integrated treatments with an AD treatment approach focused on coping or managing anxiety rather than exposure or cognitive restructuring have shown inconsistent and often modest effects, but may be associated with better treatment retention.

There are several research priorities at this stage. First, treatment outcome research in this population has focused predominantly on alcohol use disorders and PTSD relative to other SUDs and ADs. Increased attention to other disorders with high base rates, such as social anxiety disorder and cannabis use disorders, is promising; however, further expansion in this area is needed. Second, studies of the mechanisms of change in treatment will also be important. For example, if treating a single disorder results in changes in other co-occurring disorders, this could mean treating one disorder successfully helps the others, that the other disorder was caused by the treated disorder, or that treatment may act via an improvement of a shared mechanism between the disorders. Although studies examining the temporal precedence of symptoms can provide some initial indication of mechanisms, this is at best a very rough proxy. For example, the few studies that have considered the interaction of these symptoms have suggested that the improvement of PTSD is associated with positive SUD outcomes, whereas the persistence of PTSD is associated with worse substance use

outcomes.[124,125] Third, determining the treatments that can be utilized for the largest group of patients while maintaining efficacy is needed to ensure maximum public health impact. The strategy of treating only distinct combinations of disorders (e.g., panic disorder and alcohol dependence) may yield promising results in clinical research settings, but will have little public health utility if they cannot be disseminated on a wide scale. Finally, research utilizing the new *DSM-5* classification of SUDs and ADs is needed, and may benefit from consideration of the range of *DSM* syndromes in which anxiety is a core symptom, such as PTSD, OCD, and illness anxiety disorder (a somatic symptom disorder).

Co-occurring anxiety disorders and substance use disorders present a particular public health problem and clinical challenge. Treatments that address both disorders may be necessary to reduce symptoms in both areas and to achieve improvements in functioning. Enhanced understanding of the nature of the development and maintenance of these disorders when they occur together may help to advance the development of novel treatment strategies for this population.

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