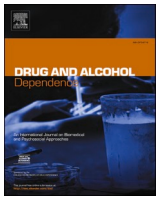
Drug and Alcohol Dependence 253 (2023) 110990

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep



Review

# Integrated behavioral treatments for comorbid anxiety and substance use disorders: A model for understanding integrated treatment approaches and meta-analysis to evaluate their efficacy

Kate Wolitzky-Taylor *

*University of California, Los Angeles, United States*

ARTICLE INFO

*Keywords:*
Meta-analysis
Integrated behavioral treatment
Comorbidity
Anxiety disorders
Substance use disorders

ABSTRACT

*Introduction:* Substance use disorders (SUD) and anxiety disorders are highly comorbid, and this comorbidity is associated with poor clinical outcomes. Emerging research in the last decade has shifted from addressing these problems separately to the development and evaluation of behavioral treatments that integrate care for anxiety disorders (or elevated symptoms of anxiety) and SUD.

*Methods:* An extensive literature search revealed a sufficient number of studies (K=11) to conduct a meta-analysis comparing the efficacy of integrated SUD/anxiety disorder behavioral treatment to SUD treatment alone on substance use and anxiety symptom outcomes. Randomized clinical trials including those with SUD and either anxiety disorders or elevations in constructs implicated in the maintenance of anxiety disorder/SUD comorbidity were included. This study meta-analyzes the effects of these studies.

*Results:* Integrated treatments outperformed SUD treatments alone on both substance use and anxiety outcomes, with small to moderate effects favoring integrated treatments. There was no significant heterogeneity across studies in the primary analyses, such that moderator analyses to identify variables that yielded differential patterns of effect sizes were not conducted.

*Discussion:* Integrated treatments for SUD/anxiety disorders demonstrate an incremental but significant and clinically meaningful improvement over SUD treatment alone for SUD/anxiety disorder comorbidity. Implications for future research and clinical practice paradigm shifting are discussed.

## 1. Introduction

The high comorbidity of anxiety disorders and substance use disorders (SUD) is well-established (Compton et al., 2007; Conway et al., 2006; Grant et al., 2004; Lai et al., 2015). This comorbidity is associated with greater symptom severity, impairment, and health care utilization compared to having only one of these disorders (Burns et al., 2005; Glasner-Edwards, Rawson 2010; Ouimette et al., 2000; Schmitz and Kruse, 2002). It is also associated with poorer treatment outcomes, poorer engagement in SUD treatment, greater likelihood of relapse, and poorer functioning after treatment (Book et al., 2009; Kushner et al., 2005; Schellekens et al., 2015; Smith and Book, 2010). This comorbidity is observed across the anxiety disorders and across a variety of substances of dependence (Compton et al., 2007; Grant et al., 2004). Therefore, identifying effective solutions for the treatment of comorbid anxiety and substance use disorders is critical to improving public health.

Several prior review articles and books have already provided a comprehensive overview of the nature of anxiety disorder and SUD comorbidity and most of these reviews make the case for the need for integrated treatment approaches (e.g., Wolitzky-Taylor et al., 2011; McHugh, 2015; Stewart and Conrod, 2008). This article provides only a brief overview of these topics, and instead emphasizes: (1) an operational definition of an integrated treatment for comorbid anxiety disorders and SUD, with a framework for understanding the diverse ways in which treatment for these problems can be creatively woven together; and (2) presents the first meta-analysis of integrated treatments for anxiety (conceptualized both categorically and dimensionally) and substance use disorders.

* Correspondence to: UCLA Department of Psychiatry and Biobehavioral Sciences, Semel Institute for Neuroscience and Human Behavior, 760 Westwood Plaza, Los Angeles, CA 90095, United States.
*E-mail address:* kbtaylor@mednet.ucla.edu.

https://doi.org/10.1016/j.drugalcdep.2023.110990
Received 11 July 2023; Received in revised form 9 October 2023; Accepted 10 October 2023
Available online 12 October 2023

### 1.1. Theories to explain anxiety and substance use disorder comorbidity

There have been several theories to explain the high comorbidity between anxiety disorders and SUD. Most theories converge on the idea that some individuals with anxiety disorders will begin to use substances to alleviate, or cope with anxiety. This negative reinforcement leads to a pattern of maladaptive substance use, and eventually a SUD. These classic tension-reduction (Conger, 1956; Greeley and Oei, 1999), self-medication (Khantzian, 1985; Robinson et al., 2011) and stress-dampening (Sher and Levenson, 1982) theories account for approximately 75% of cases, in which the anxiety disorder precedes the onset of the SUD (Kushner et al., 2008). From a cognitive and behavioral perspective, alcohol and drugs in these cases are considered safety aides that are used to mitigate anxiety in the short-term yet maintain anxiety in the long-term by preventing threat disconfirming evidence. That is, individuals may misattribute their "safety" (i.e., "I went to the party and was able to talk to people and they liked me"; "I was able to relax enough to talk only because I drank") to the fact that they used their safety behavior (i.e., drinking alcohol), rather than to the fact that they would have been able to talk to people with positive outcomes at the party even without alcohol, and despite feeling anxious during the conversation. The other ~25% of cases, in which the SUD precedes the onset of the anxiety disorder, are explained by the substance-induced anxiety enhancement theory (Kushner et al., 2008, 1990; Zvolensky et al., 2003), which posits that multiple withdrawal or intoxication experiences engender anxiety, which eventually leads to an onset of an anxiety disorder over time.

The mutual maintenance model of anxiety disorder and SUD comorbidity (Stewart and Conrod, 2008) emerged later, and is now a well-established model of understanding anxiety disorder and SUD comorbidity. This model recognizes that while there may be multiple pathways to the onset of the comorbidity, once an individual has both problems, they serve to mutually maintain and exacerbate one another. Taking the example of the individual with social anxiety and alcohol use disorder above, the negative reinforcement from the alcohol at the social gathering may lead to repeated use of alcohol in social situations, and eventually, increased severity and range of alcohol use disorder symptoms, until there is an alcohol use disorder onset. Multiple withdrawal experiences may increase anxiety. In addition, the consequences of having an alcohol use disorder may lead to additional anxiety. For example, an individual may black out during intoxication and then learn of something they did that was embarrassing at a gathering, leading to post-event rumination. Therefore, integrated solutions that simultaneously address both problems are needed. A more detailed case example can be found in Ries et al. (2011).

### 1.2. Limitations of the current clinical paradigms to effectively treat comorbid anxiety and substance use disorders

Despite the theory-driven support for integrating anxiety disorder and SUD treatment to mitigate the mutual maintenance of anxiety and SUD symptoms, the current clinical landscape remains limited in providing such treatment. There are several reasons for this. First, for many decades, the zeitgeist was to treat these problems separately, typically addressing the SUD first (Gallanter and Nace, 1988). This conventional wisdom at the time was presumably due to the mistaken beliefs that the anxiety disorder could not be effectively treated until the SUD was addressed first, or that treating the anxiety disorder may exacerbate the SUD. However, treating SUD without addressing the underlying anxiety disorder (or symptoms) contributing to the maintenance and exacerbation of the substance use is likely to lead to relapse, and thus may account for the poor outcomes observed among those with this comorbidity. Moreover, this approach typically results in the need for multiple referrals and sequential treatments that often result in the mental health condition (in this case, anxiety disorders) going untreated (Havassy et al., 2009).

There has been a relative acknowledgment of the limitations of the prior conventional wisdom, and an increased awareness of the need for integrated treatment in the past decade (Barry, Huskamp 2011; Burnam and Watkins, 2006; SAMHSA, 2022). The emergence of "dual diagnosis" programs is one such example of a systemic consequence of this newer messaging. However, these programs remain limited and systems of care for mental health and SUD continue to remained siloed. Epidemiological studies estimate that ~8% of those with co-occurring mental and substance use disorders receive treatment for both problems (Office of Applied Studies, 2007; Watkins et al., 2001). Indeed, most SUD specialty clinics do not diagnose or treat underlying anxiety disorders that may be contributing to substance use (McGovern et al., 2006; SAMHSA, 2020), and most mental health clinics continue to refer out for SUD care, noting they are inadequately equipped to manage this subspecialty. This siloing of care begins as early as in psychology and psychiatry training programs and is then reinforced by systems of care that hire those clinicians following their training into subspecialty clinics to provide care for SUD *or* mental health.

Second, until recently, research has remained limited in the area of integrated treatments for anxiety disorders and SUD. Early work attempting to treat comorbid anxiety disorders used parallel or sequential treatments was relatively unsuccessful and largely found that CBT for the SUD + CBT for the anxiety disorder did no better than CBT for the SUD alone (Bowen et al., 2000), and sometimes worse (Randall et al., 2001). Some have suggested that participating in two simultaneous CBT protocols may be too demanding (Kushner et al., 2006), given the higher attrition rates in the parallel CBT group. Over the past decade, there has been an emerging and growing body of empirical research evaluating the efficacy of integrated treatment for comorbid anxiety disorders and SUD. Prior articles have qualitatively reviewed this growing body of research (e.g., Hesse, 2009; McHugh, 2015; Wolitzky-Taylor et al., 2011), but until recently, there were insufficient numbers of empirical studies to warrant a meta-analysis on this topic. Indeed, a prior review and meta-analysis of treatment for SUD and co-occurring disorders was unable to meta-analyze studies comparing treatments for comorbid anxiety and SUD to SUD treatments alone due to the insufficient number of studies in this category and could only meta-analyze clinical trials comparing treatment for comorbid depression and SUD to SUD treatment alone (Hesse, 2009). The time is now ripe for an objective evaluation of the efficacy of integrated behavioral interventions for comorbid anxiety disorders and SUD. In order to ask meaningful questions about these interventions that will inform clinical training and practice, it is important to operationalize the definition of an integrated treatment for comorbid anxiety disorders and SUD, and to outline the types of integrated treatments that are emerging for anxiety disorders and SUD. Below is a descriptive model for understanding the nature of integrated treatments for this comorbidity, followed by the research questions that this meta-analysis aims to answer.

### 1.3. What is an integrated treatment for comorbid anxiety disorders and SUD?

As the field begins to put forth the recommendation for integrated treatments, a model for understanding and conceptualizing the diverse ways in which this can be achieved is needed, both for continued research advancement and to guide clinical recommendations in real-world settings. Otherwise, outside of a relatively small group of researchers conducting this work, the "integrated treatment" buzzword reaching clinical and organizational settings has the potential to become vague and ill-defined. Below, a 3-level integration model is presented and described. See Fig. 1 for a summary of the model. Note that the levels of integration do not at all imply superiority of one level of integration over another; rather, they indicate the degree to which the treatments are fully integrated. Whether one level is superior to another in terms of clinical outcomes is an empirical question that this meta-analysis sets out to address. From an implementation perspective,

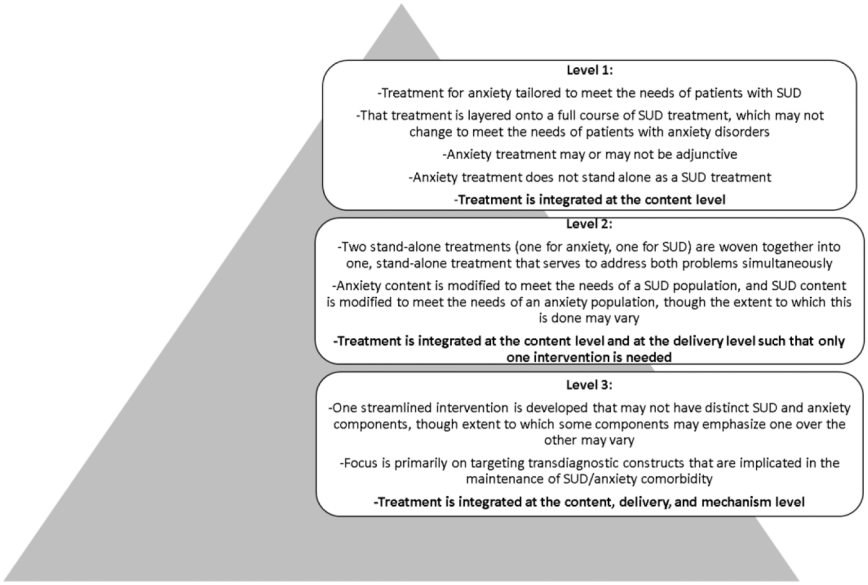



**Fig. 1.** A model for diverse ways to integrate SUD and anxiety disorder behavioral treatment.

there are a number of organizational factors that should be evaluated to determine which level of integration will be the most likely to be adopted and sustainable in a given clinical setting.

#### *1.3.1. Level 1 integration: anxiety (or SUD) treatment tailored for comorbidity as an adjunct to the other treatment*

Level 1 integration involves integration at the content level. In this approach, treatment for one problem (e.g., anxiety) is added to an existing treatment for the other problem (e.g., substance use), and the added treatment is specifically tailored for the comorbid population, with linkages to the original treatment to which it is being added. The result is typically an adjunctive, tailored treatment for one problem that is incorporated into the care for patients being treated for the other problem. The adjunctive treatment dose may be smaller than the treatment for the other problem. That is, the adjunctive or additive component of the intervention is adapted specifically for patients with comorbid anxiety and substance use disorders.

For example, in the Coordinated Anxiety Learning and Management for Addiction Recovery Centers (CALM ARC) study (Wolitzky-Taylor et al., 2018), a cognitive behavioral therapy (CBT) protocol for anxiety disorders was adapted to meet the needs of patients with comorbid anxiety and substance use disorders. Implementation-related adaptations such as using a group format and making treatment brief were made to increase likelihood of adoption and sustainability in community practice. In addition, content adaptations included but were not limited to psychoeducation focusing on the mutual maintenance of anxiety and substance use, developing and utilizing video examples of skill delivery with mock patients who had comorbid anxiety and substance use disorders, and framing exposure in an adaptive way for this population and not at odds with their ongoing SUD treatment; that is, making the distinction between approaching objectively safe situations that are fear provoking (e.g., expressing disagreement with a friend) even if those situations provoke the internal trigger of anxiety v. avoiding external cues for substance use (e.g., going to a bar). Patients with comorbid anxiety disorders and SUD who were already receiving a SUD treatment at an Intensive Outpatient Program in an SUD specialty care clinic received the CALM ARC program as an adjunctive intervention.

Another example of this level of integration is an integrated treatment for panic disorder and alcohol use disorder (AUD) (Kushner et al., 2006), which was later expanded to include other anxiety disorders (Kushner et al., 2009, 2013). As with the above treatment, this intervention focused on the interaction between panic disorder symptoms and alcohol use, with the panic disorder treatment components conceptualized as an add-on for individuals already undergoing AUD treatment.

#### *1.3.2. Level 2 integration: stand-alone treatment for comorbidity with components directly targeting both problems*

Level 2 integration includes interventions integrated at the content and delivery level, such that only one intervention is needed for both the anxiety disorder and SUD. Thus, Level 2 integration involves a stand-alone treatment for comorbid anxiety disorders and SUD that includes components of both SUD treatment and anxiety disorder treatment, and typically weaves content together with an overarching mutual maintenance (Stewart and Conrod, 2008) or similar model framing the intervention. That is, patients are taught to understand how their anxiety disorder and SUD are functionally related and linkages between substance use and anxiety (e.g., as a safety behavior or maladaptive coping strategy) are made whenever possible. There is variability in how this is achieved. In most cases, a set of two distinct protocols (e.g., one for SUD, one for anxiety disorders) are woven together into one protocol, tailored for patients with this comorbidity, and delivered in equal doses simultaneously. Note that this differs from prior work in which patients received two parallel treatments simultaneously, in which they would meet with therapists separately for anxiety treatment sessions and SUD treatment sessions, which were not integrated (Randall et al., 2001).

For example, one study developed and evaluated the effectiveness of an intervention for comorbid social anxiety and alcohol use disorder that included social anxiety treatment components (e.g., cognitive restructuring, exposure) and alcohol use disorder components (e.g., relapse prevention and coping skills, identifying and managing triggers, scheduling adaptive activities, 12-step facilitation) in equal measure (Wolitzky-Taylor et al., 2022), with the mutual maintenance of AUD and social anxiety disorder as the overarching framework. The social anxiety components were tailored for those with alcohol use disorder. The therapeutic approach utilized the group therapy modality and 12-step groups as a platform for social anxiety exposures that also enhanced engagement in addiction treatment, and the alcohol use disorder components were tailored for those with social anxiety. For example, alcohol use disorder treatment content was tailored to address issues such as social support, assertive communication, honesty, seeking employment, and 12-step facilitation in the context of someone with social anxiety. Stapinski et al. (2021) also developed and evaluated an integrated treatment for comorbid social anxiety and alcohol use disorder that

utilized many of the same principles and strategies.

In another example of a level 2 integrated treatment for cannabis use disorder and anxiety disorders, (Buckner et al., 2019), an integrated treatment combined evidence-based treatment approaches for treating cannabis use disorder (drawn from both CBT and Motivational Enhancement Therapy [MET]) with a transdiagnostic anxiety disorder treatment drawn from cognitive and behavioral therapies in each session (Schmidt et al., 2012). The resulting integrated treatment emphasized the reciprocal relation between cannabis use and anxiety and targeted cannabis use as a safety behavior.

#### 1.3.3. Level 3 integration: stand-alone treatment that targets processes implicated in both problems

Level 3 integration includes interventions integrated at the content, delivery, and mechanism level, such that one streamlined set of treatment components directly targets trait-like but malleable processes that have been shown to link anxiety (symptoms or disorders; dimensional elevations or categorical diagnoses) with SUD. There has been an emerging body of research supporting the idea that the high comorbidity between anxiety disorders and substance use disorders can be largely explained by several underlying transdiagnostic constructs that typically represent maladaptive reactivity to negative affect (see Wolitzky-Taylor et al., 2022a for a discussion and model). These constructs, such as anxiety sensitivity, negative urgency, distress intolerance, and several facets of emotion dysregulation are elevated in both anxiety disorders and substance use disorders (e.g., Bernstein et al., 2009; Buckner et al., 2011a,b; Chawla and Ostafin, 2007; Cougle et al., 2012; Hearon et al., 2011; McHugh and Otto, 2012; Wolitzky-Taylor et al., 2016), and have been found to statistically mediate the associations between anxiety symptoms and substance use severity (Buckner et al., 2007; Wolitzky-Taylor et al., 2015). Moreover, these transdiagnostic processes have been shown to decline during treatment for both anxiety disorders (e.g., Smits et al., 2006), SUD (e.g., Bornovalova et al., 2012; Glasner et al., 2017), and the treatment of their comorbidity (e.g., Wolitzky--Taylor et al., 2022), and mediate treatment outcomes (e.g., Wolitzky--Taylor et al., 2018). The logical clinical implication of this work is that interventions that directly target these transdiagnostic mechanisms thought to account for this high comorbidity may be effective and parsimonious ways in which to address this critical problem. Level 3 integration goes beyond a stand-alone treatment for comorbid anxiety disorders and SUD that combines components of CBT for anxiety disorders and SUD. Instead, these interventions target the underlying processes that have been shown to link these problems. This transdiagnostic approach is gaining traction, with a number of studies in recent years that have taken this approach (Olthuis et al., 2015; Raines et al., 2020; Wolitzky-Taylor et al., 2022). While some level 3 integrated treatments include only minimal discussion of SUD (e.g., Worden et al., 2017), others weave more explicit SUD-related content into the intervention (e.g., Bradizza et al., 2016).

Although there are few randomized clinical trials with clinical SUD and anxiety disorder populations currently in this level of integration (with prior work more commonly using high risk/hazardous use samples; Watt et al., 2006; Lammers et al., 2017; Shuai et al., 2022), this is a rapidly growing area as the field moves away from diagnostic categories and towards a dimensional framework for understanding psychopathology (Cuthbert, 2014), and may provide a more parsimonious approach to treating comorbid anxiety symptoms and SUD by directly targeting malleable processes known to link the two problems. Thus, a model for the operationalization of integrated treatments at the cutting-edge of the field would be remiss to exclude these interventions (classified as level 3 in this model) simply due to the nature of dimensional (as opposed to categorical) approaches to the treatment. Rather, there are many strengths to this approach making it worth including in this framework. For example, these approaches do not rely on a full diagnostic assessment of anxiety disorders to identify patients who should receive the intervention. Identification of individuals through brief screening questionnaires who may benefit from these transdiagnostic, mechanism-targeted approaches may be more scalable in SUD clinical settings, where diagnostic assessments for anxiety disorders are rarely conducted. Moreover, using treatment strategies that target these dimensional processes known to link anxiety symptoms and substance use eliminates the complexities and potential barriers of finding creative ways to combine seemingly disparate behavioral treatment components for anxiety disorders and SUD.

### 1.4. The present study

The present study goes beyond the significant contributions of the many comprehensive reviews of anxiety disorder/SUD comorbidity and its treatment. The primary aim of this study is to conduct the first meta-analysis comparing integrated treatments for comorbid anxiety disorders and SUD to treatments for SUD alone, in order to evaluate the incremental benefit of incorporating treatment for comorbid anxiety disorders (or symptoms) into SUD care. Given that no studies have directly compared fully integrated approaches to non-integrated/parallel approaches to treating this comorbidity (which is logical given the poor outcomes that were observed with this early work), there are no studies to yield a comparison of integrated v non-integrated treatments. Moreover, the scope of this meta-analysis is limited to non-medication interventions.

It was hypothesized that integrated treatments would outperform SUD treatment alone on anxiety and substance use outcomes. A priori plans included examining each level of integration (described above) in separate analyses, and then combined, in order to evaluate the relative effect sizes for each level of integration. However, this aim was known to be limited by the number of existing studies in the field that fell into each category and thus the categories for analyses were ultimately based on sufficient numbers of studies (i.e., $K > 3$) to warrant meta-analytic comparison. A secondary aim of the study was to evaluate potential moderators of the effects whenever significant heterogeneity across studies was observed, including (1) anxiety population (e.g., multiple anxiety disorders v. social anxiety disorder v. panic disorder v. elevations in anxiety/SUD-related constructs); (2) substance type; (3) level of integration; and (4) sex. Given the novelty of this investigation, we had no hypotheses regarding the moderator analyses. To prevent redundancy and focus on providing new, empirical information, this study does not set out to conduct a systematic review.

## 2. Methods

### 2.1. Study selection criteria

Several criteria were required for studies to be included in the meta-analysis. First, studies were required to be published in peer reviewed journals (any date of publication) in the English language. The studies needed to enroll adult participants (18+ years old) on the basis of having a SUD (i.e., any drug use disorder or alcohol use disorder) *and* either a DSM-5 anxiety disorder or elevations in one or more constructs known to be elevated in anxiety disorders and implicated in anxiety disorder/SUD comorbidity. These constructs (see *Literature Search and Study Selection* below for search terms) included negative affect, anxiety sensitivity, negative urgency, distress tolerance, emotion regulation, emotion dysregulation, reactivity to negative affect, maladaptive responding to negative affect. Studies were included if they reported outcomes from a randomized clinical trial comparing a behavioral (non-medication) intervention that aimed to treat comorbid anxiety (symptoms or disorders) and SUD to a behavioral (non-medication) intervention that treated SUD alone.

With regard to the integrated intervention, for the study to be included, the integrated SUD/anxiety behavioral treatment could be integrated at any level (see Fig. 1.) Specifically, the treatment could be either: (1) focused on anxiety disorders as an integrated adjunct to SUD

treatment (level 1), *or* (2) an integrated anxiety disorder/SUD protocol that stood alone as an intervention (level 2), *or* (3) a treatment that targeted one or more constructs elevated in anxiety disorders and implicated in anxiety disorder/SUD comorbidity (level 3), *or* (4) a treatment that combined SUD treatment with a treatment that targeted one or more constructs elevated in anxiety disorders and implicated in anxiety disorder/SUD comorbidity (level 3). Additionally, studies needed to include a comparison condition consisting of SUD treatment alone (either manualized or non-manualized community-based SUD care), include at least one SUD-relevant outcome measure, and provide sufficient data in the article to generate effect size estimates (or authors sent appropriate data via email upon request in order to calculate effect sizes).[1]

#### 2.1.1. Inclusion clarifications

Anxiety conditions for the analyses involving categorical diagnoses included any DSM-5 anxiety disorder (one or more). Including DSM-IV anxiety disorders (which would have broadened the search to include studies of behavioral treatment for PTSD/SUD) was considered. However, the literature focusing on treatment for PTSD/SUD comorbidity specifically is quite large compared to all of the other anxiety disorders collectively. Given the current directions in conceptualizing PTSD as having distinct, and potentially more complex clinical presentations than the other anxiety disorders, coupled with the numerous studies evaluating treatment for PTSD/SUD (see Hien et al., 2023, for a comprehensive review) compared to the other anxiety disorders, including PTSD is likely to unduly influence the overall effect sizes obtained across the other studies; thus, a separate meta-analysis focusing on these studies is warranted. Moreover, many of the PTSD/SUD treatment studies include a variety of special populations (e.g., incarcerated, Veterans, women only, adolescents) that would suggest a different set of putative moderators and may detract from the scope of the current analysis.

For the analyses of interventions targeting dimensional constructs associated with comorbid anxiety disorders and SUD, these included studies that targeted populations with elevations in distress intolerance, emotion dysregulation, experiential avoidance, anxiety sensitivity or negative affect. Any SUD was considered inclusionary. Studies with SUD interventions that included a non-behavioral component (e.g., nicotine replacement therapy) were included as long as there was also a behavioral component considered central to the intervention.

As described above, broadening the criteria to include studies in which participant inclusion was based on dimensional indices of anxiety or transdiagnostic constructs implicated in the comorbidity of anxiety and SUD, rather than a categorical anxiety disorder diagnosis was intentional and in line with current directions in understanding and treating this comorbidity. In particular, level 3 integration uses this dimensional framework to provide a parsimonious way to directly target constructs known to mediate the associations between anxiety and SUD. Therefore, the study inclusion criteria allowed for this in order to allow for an analysis of level 3 integrated treatments.

#### 2.1.2. Exclusion clarifications

Studies that did not utilize a randomized clinical trial design were excluded (e.g., open, non-randomized trials, observational studies, quasi-experimental studies). Studies with comparison conditions that did not include an active SUD treatment with at least some evidence-based treatment components were excluded (e.g., waitlist controls, brief educational videos). Studies that included samples at risk for SUD (e.g., hazardous drinking) or were framed as prevention interventions were excluded, typically because the control conditions for these studies resembled no-treatment or placebo control groups (e.g., brief educational videos), which would increase heterogeneity across studies, and yet there were too few in this category to warrant a separate analytic comparison; and because the focus of this meta-analysis is on populations with clinically significant SUD. Therefore, whereas anxiety disorders or the presence of elevations in constructs relevant to anxiety disorders were included, only those with SUD were included. Relatedly, studies that targeted a relevant transdiagnostic construct (e.g., distress intolerance) among those with SUD were excluded if the sample was not selected on the basis of elevations in that construct.

### 2.2. Literature search and study selection

A literature search was conducted in 2023 by author KWT and a research assistant supervised by the author. The research assistant conducted the initial literature search and initially identified potential articles for author KWT to review. Inclusion/exclusion determination was made by author KWT. The literature search was conducted in PubMed, googlescholar, PsycINFO, and Cochrane Library using combinations of the following anxiety-related keywords: *anxiety disorder, generalized anxiety disorder, social anxiety disorder, panic disorder, agoraphobia, specific phobia, distress tolerance, anxiety sensitivity, negative urgency, emotion regulation, emotion dysregulation, reactivity to negative affect, maladaptive responding to negative affect* with the following substance use-related keywords: *substance use disorder, addiction, cocaine, methamphetamine, cannabis, marijuana, heroin, opioids, alcohol, nicotine, hallucinogens* with the word *treatment.* There were no restrictions on date of publication (see *Study Selection Criteria*, above). When review articles were identified in the search, the reference sections were examined to identify any unique articles described the reviews that were not otherwise identified in the search that may meet inclusion criteria.

### 2.3. Study selection

The literature search yielded 83 articles that appeared relevant when initially reviewing titles and abstracts. Upon closer inspection of the abstracts and review of the article content, 72 of them did not meet the criteria to be included in the meta-analysis for one or more reasons (see inclusions/exclusions). Reasons for exclusion across the studies were that they reported on a study protocol with no outcome data, did not include a SUD treatment control group, used a non-randomized design (i.e., open trial design or reported only secondary data analyses such as predictors of outcome or used a quasi-experimental study design), reported on a prevention trial, did not select on the basis of SUD, did not report a SUD outcome variable, selected on the basis of a broad category of co-occurring disorders that included anxiety but the sample was primarily comprised of patients with other disorders such as MDD, evaluated a non-behavioral intervention, or targeted a transdiagnostic construct (e.g., distress tolerance) in a SUD sample but did not limit the sample to those elevated in that construct. The majority of the studies were excluded due to more than one reason. Therefore, it was not possible to describe the number of studies excluded for each individual reason, due to significant overlap. Thus, 11 studies were identified as meeting the criteria for inclusion in the meta-analysis.

### 2.4. Measures and standardization procedures

Table 2 outlines several key factors for each study included in the meta-analysis, including the measures that were used to tap into the constructs of interest, as well as the timepoints included for assessment. Not all studies presented data that could be included in each of the categories described below, but all data relevant for each construct were included. In the case when there was a clear primary measure for a given construct, that was used. When multiple indices of a given construct were reported, each was included and the mean effect size across variables for that construct was included so that studies reporting multiple

[1] Authors for two of the 13 included studies were contacted to provide additional data needed to compute effect sizes; authors for both of these studies provided the data.

measures for the same construct were not weighted more heavily (Rosenthal, 1991). For example, a study that reported drinking frequency/quantity in three different ways (e.g., number of drinking days in the past 30 days, drinks per drinking day in the past 30 days, % abstinence) would have each effect size calculated individually, and then the mean of that effect size was entered into the final analysis.

#### 2.4.1. SUD/AUD severity

SUD (or AUD) severity measures included dimensional measures that tapped into substance-related problems/consequences and diagnostic symptom severity. These measures included the *Marijuana Problems Scale* (*MPS;* Stephens et al., 2000), the *Alcohol Dependence Scale (ADS;* Doyle and Donovan, 2009), the *Short Inventory of Problems (SIP;* Blanchard et al., 2003), the *Severity of Alcohol Dependence Scale (SADS;* Stockwell et al., 1994), the *Cannabis Abuse Screening Test (CAST;* Legleye et al., 2007), and the *European Addiction Severity Index (EuroASI;* Scheurich et al., 2000). Note that the minority of studies included data on these types of dimensional measures; thus, they were collapsed into one "substance use outcome" variable along with the substance use/-frequency/quantity variable described below. When studies reported both a severity outcome measure and use index (described below), one mean effect size was calculated so studies with multiple outcomes within a given category were not weighted more heavily than other studies (Rosenthal, 1991; Borenstein et al., 2021).

#### 2.4.2. Substance use/frequency/quantity

Substance use indices were largely obtained from the administration of the *Timeline Followback (TLFB;* Sobell and Sobell, 1992). There were a few studies that did not explicitly state what instrument was used to collect these data (noted in Table 1). These indices included quantity (i.e., number of times used X substance over the past X days, drinks per drinking day, # times engaged in binge drinking) and frequency (i.e., number of drinking days/drug use days in past X days).

#### 2.4.3. Anxiety symptom severity

Dimensional symptom severity measures of anxiety across the studies were psychometrically sound and included the *Depression Anxiety Stress Scale (DASS;* Lovibond and Lovibond, 1995), the *State Trait Anxiety Inventory (STAI;* Spielberger, 1983), the *Hamilton Anxiety Rating Scale (SIGH-A;* Hamilton 1959), the *Leibowitz Social Anxiety Scale (LSAS;* Liebowitz, 1987a,b), the *Social Interaction Anxiety Scale (SIAS;* Heimberg et al., 1992), the *Social Phobia Scale (SPS;* Heimberg et al., 1992), the *Fear Questionnaire (FQ;* Marks and Matthews, 1979), the *PROMIS – Anxiety Subscale* (Pilkonis et al., 2011), and the *Overall Anxiety Severity and Impairment Scale (OASIS;* Campbell-Sills et al., 2009) (Table 2).

#### 2.4.4. Target construct severity

For level 3 integration studies (i.e., treatments targeting transdiagnostic constructs implicated in both anxiety and substance use), the measures included the *Anxiety Sensitivity Index (ASI;* Peterson and Reiss, 1992), *Distress Tolerance Scale (DTS;* Simons and Gaher, 2005), the *Difficulties with Emotion Regulation Scale (DERS;* Gratz and Roemer, 2004), and the *Smoking Self-Efficacy-Negative Affect Subscale (SSES-NA;* Diclemente et al., 1985). Note that these measures were not included in the analyses with anxiety symptom severity as the outcome variable but were viewed as a separate set of constructs for analysis.

#### 2.4.5. Putative moderator variables

Moderator analyses were planned for analyses in which there was significant heterogeneity observed across effect sizes. These moderators included level of integration (1, 2, or 3, conceptualized above), sex (% male), targeted type of substance (mixed SUD v. cannabis use disorder v. AUD v. nicotine), and target anxiety population (mixed anxiety disorders v. social anxiety disorder v. panic v. elevated transdiagnostic constructs relevant to anxiety disorders and SUD [anxiety sensitivity, negative affect, distress intolerance]).

**Table 1**
Basic study characteristics.

| Study | N | % male | Racial/ Ethnic Breakdown | SUD pop | Anx pop. |
|---|---|---|---|---|---|
| Bradizza et al. (2016) | 70 | 0 | 42.9% African-American, 30% Caucasian, 15.7% Hispanic, 5.7% Native American, 5.7% other | Nicotine use disorder | Elevated NA (≥ M for those who smoke [M=5.6] on NA reduction scale of Brief Smoking Consequences Questionnaire) |
| Buckner et al. (2019) | 37 | 56.2 | 63.7% non-Hispanic White, 23.65% non-Hispanic African-American, 10.9% Hispanic White, 1.8% multiracial | CUD | Mixed anx d/o |
| Kushner et al. (2013) | 344 | 60.5 | 78.5% White, 10.5% African-American, 7% American Indian, 2% other race, 1% Asian, 1.5% Hispanic | AUD | Mixed anx d/o |
| Morley et al. (2016) | 37 | 46 | DNR | AUD | Mixed anx d/o |
| Schade et al. (2005) | 96 | 67.7 | DNR | AUD | Agoraphobia and social phobia |
| Smits et al. (2021) | 150 | 32.7 | 86.7% White, 6% more than one race or other, 4% Black or African American, 2.7% Asian, 1% Native American/ Alaska Native | nicotine | Elevated AS (≥23 on the ASI-3) |
| Stapinski et al. (2021) | 79 | 63.2 | 76.1% Oceania, 3.4% Americas, 3.4% Sub-Saharan Africa, 2.6% Southern and Eastern Europe, 1.7% Southern and Central Asia, 0.9% missing | AUD | Social anxiety d/o |
| Wolitzky-Taylor et al. (2018) | 60 | 57.3 | 72% White, 10.7% Hispanic/ Latino, 9.3% Asian-American, 6.7% multiracial, | Mixed SUD | Mixed anxiety d/o |

(*continued on next page*)

**Table 1** (*continued*)

| Study | N | % male | Racial/ Ethnic Breakdown | SUD pop | Anx pop. |
|---|---|---|---|---|---|
| Wolitzky-Taylor et al. (2022a) | 32 | 47.3 | 1.3% Pacific Islander 41.7% White/Non-Hispanic Latino, 30.6% Hispanic/ Latino non-White, 13.9% multiracial/ other, 5.6% Black/ African-American, 5.6% Asian-American/ Pacific Islander, 2.8% American Indian/ Alaska Native | AUD | Social anxiety d/o |
| Wolitzky-Taylor et al. (2022b) | 36 | 57.7 | 42.3% White, 25% Hispanic/ Latinx, 17.3% Asian, 5.8% Pacific Islander, 5.8% multiracial, 3.8% Black | CUD | Elevated NA and either elevated AS, TS, or DI, each at least 1 SD above the normative mean for each measure |
| Worden et al. (2017) | 25 | 63.4 | 39% Caucasian, Non-Hispanic, 29.3% African-American/ Black, Non-Hispanic, 24.4% Caucasian, Hispanic, 7.3% African-American/ Black, Hispanic | Mixed SUD | Elevated AS above clinical cutoff (ASI score $\geq$ 25) |

Note: CUD=cannabis use disorder; AUD=alcohol use disorder; AS=anxiety sensitivity; ASI=Anxiety Sensitivity Index; NA=negative affect; TS=thought suppression; DI=distress intolerance. N refers to the sample size available for the first assessment following treatment (included in analyses), not the total N at baseline reported, from which the demographic characteristics are based. Due to attrition in all studies, Ns changed over time. DNR=did not report. Corresponding authors for all three studies lacking this information in the article were emailed requesting this information. One replied with data using the Australian Standard of Classification of Cultural and Ethnic groups; the other two who did not reply are noted as "DNR." Also note that for studies that used NIH reporting categories, Hispanic/Latino is a separate ethnic category from race; therefore, some percentages may exceed 100% in order to capture both racial and ethnic diversity within a study.

### 2.5. Treatments included

The SUD comparison conditions for each study are reported in Table 2. These largely utilized CBT for SUD and motivational interviewing (MI)/motivational enhancement therapy (MET). Several studies used manualized treatments with these evidence-based components, whereas some studies described non-manualized, "typical" or "usual" SUD care that included CBT, MI, relapse prevention, family therapy for SUD, addiction counseling, 12-step approaches, and healthy behavior change. One study included nicotine replacement therapy and one study included medication for alcohol use disorder, with these medication components as adjunctive to a primarily behavioral intervention (in line with study inclusion criteria). Similarly, a few studies described medication as part of "usual care" practices, but these medications were available in both conditions in those studies.

With regard to the integrated interventions, these largely used various cognitive and behavioral components of treatment for anxiety disorders (e.g., psychoeducation, *in vivo* and interoceptive exposure, cognitive restructuring, safety behavior fading), typically framed in the context of reducing substance use. Some interventions also included traditional components of CBT for SUD and elements of MI/MET in addition to the anxiety-specific CBT components, and others used exercise (framed as targeting interoceptive fear as seen in interoceptive exposure). See Table 2 for a brief description of the integrated interventions and the SUD interventions included in each study.

### 2.6. Statistical analysis

#### 2.6.1. Study database and final inclusion of studies

The database was created through the Comprehensive Meta-Analysis program (Version 2; Borenstein et al., 2006). Comprehensive Meta-Analysis has been used for the analyses of several published meta-analyses (e.g., Olatunji and Wolitzky-Taylor, 2009; van IJzendoorn et al., 2005; Wolitzky-Taylor et al., 2020). Eleven studies met the criteria to be included in the meta-analysis. All 11 of these studies include substance use/frequency variables, five included dimensional measures of substance use severity/problems, nine studies reported on dimensional measures of anxiety symptom severity, and four reported on a relevant transdiagnostic construct (e.g., anxiety sensitivity, negative affect).

As shown in Table 2, there was significant heterogeneity with regard to assessment period timepoint following treatment, ranging from immediately post-treatment to 6-mo follow-up. Therefore, in order to retain a sufficient number of studies in each comparison, first an analysis for each outcome of interest was conducted collapsing across all timepoints (i.e., post-treatment and follow-up), and then additional analyses of effects at post-treatment were conducted, and then separate analyses were run with any follow-up data available (i.e., $\geq$4 weeks from final session through 6 months). Separate analyses (all comparing integrated anxiety/SUD treatment) were conducted for SUD-relevant measures and anxiety severity measures as outcomes. An analysis of the effect of integrated treatment v. SUD treatment alone on transdiagnostic constructs targeted in level 3 integration studies (e.g., anxiety sensitivity, distress intolerance) was also planned if there were sufficient studies to warrant meta-analytic comparison (i.e., K > 3).

Due to the heterogeneity of statistics reported for each study, either (a) the means, SDs, and sample sizes at the assessment point of interest for each group, (b) the *t*-statistic for the between-group effect and sample sizes; (c) $X^2$ statistic; (d) standard difference in means and sample sizes; or (e) *p*-value of the between-group effect and sample size were entered to obtain effect sizes. When insufficient information was presented in the studies, the corresponding authors of the studies were emailed to request raw data. Raw data was received from the authors of two of the included studies.

#### 2.6.2. Effect size calculation

For each study, we computed effect sizes for each analysis of interest. For example, separate effect sizes were calculated for each group and were then aggregated into an average effect size during the analysis. Only these pooled effect size outcomes were used so that each study only contained one effect size per analysis of each outcome measure. This

**Table 2**
Clinical study characteristics.

| Study | Int Lev | Comparison condition (manualized Y/N) | Integrated treatment condition | Variables (measures) obtain SUD outcome effect size (E.S.) | Variables (measures) to obtain anxiety (or transdx construct) outcome E.S. | Assess. pds after tx | Effect sizes for primary outcomes |
|---|---|---|---|---|---|---|---|
| Bradizza et al. (2016) | 3 | CBT for smoking cessation+ Health and Lifestyle intervention (Y)<br>8, 1-hr individual sessions | CBT (same in both conditions) + ER tx: coping skills to manage NA and DI, imaginal exp to elicit neg emotions assoc with smoking, mindfulness and urge surfing<br>8 sessions, 1-hr individual sessions | # cigarettes smoked per day (TLFB) | NA severity (BSCQ-A; for screening only, no outcomes); transdx construct (SSES-NA) | 2- and 4-mo f/u | SUD outcomes pooled $d$ =0.61 at FU<br>Transdx construct pooled across FUs $d$ =0.84 |
| Buckner et al. (2019) | 2 | MET-CBT<br>(Y)<br>12, 1-hr individual sessions | Integrated Cannabis and Anxiety Reduction treatment: psychoed about cannabis/ anxiety relation and safety behaviors, reduction of avoidance and false safety behaviors while managing cravings and high-risk use situations | # joints smoked (TLFB), cannabis problem severity (MPS) | Anxiety severity (SIGH-A) | Post-tx | SUD outcomes pooled $d$ =0.22 at post; anx severity $d$ =0.23 |
| Kushner et al. (2013) | 1 | Community based AUD tx (includes AA, family therapy, healthy behavior change, etc) (N) 21-day residential program, daily TAU + PMR (Y), 6, 1-hr sessions | TAU in residential tx + Psychoed about panic, panic/ ETOH links and comorbidity, self-monitoring ETOH and anxiety/panic, cognitive restructuring around beliefs about panic and about ETOH effects on panic, in vivo and interoceptive exposure, testing beliefs about need for ETOH to cope with panic, alternative coping<br>6, 1-hr sessions | # binges past 30 days, # days used past 30 days, # times used past 30 days | Anxiety severity (STAI) | 4 mo | SUD outcomes pooled $d$ =0.22 at FU; anx severity $d$ =0.24 at FU |
| Morley et al. (2016) | 2 | Usual care for AUD (MET+ alcohol medication, alcohol support and counseling) (Y) | Cognitive restructuring around ETOH and anxiety-related cognitions, exposure therapy and behavioral experiments targeting anxiety, coping skills and motivational enhancement to reduce ETOH<br>7–10 individual sessions | % days abstinent, drinks per drinking day*, AUD severity (ADS) | Anxiety severity (DASS-Anx) | 12 weeks from BL | SUD outcomes pooled at post $d$ = 1.19; anx severity $d$ = −0.45 at post** |
| Schade et al. (2005) | 1 | Psychosocial relapse prevention with coping skills, social skills, and covert sensitization in inpatient center, 25 hr/wk, 12–16 wks (N) | Same SUD group treatment (6 sessions of it prior to CBT, 6 sessions of CBT during SUD aftercare) + CBT for anxiety: cognitive restructuring around distress-provoking thoughts/situations associated with alcohol consumption, behavioral experiments<br>12, 1-hr individual sessions | % abstinent; % relapse (EuropeASI) | Anxiety severity (FQ) | Post-tx | SUD outcomes pooled $d$ =0.22 at post; anx severity $d$ =0.74 at post |
| Smits et al. (2021) | 3 | Quitline counseling + nicotine replacement therapy + recommendation for exercise for physical health (Y)<br>6 Quitline sessions, | Exercise program framed as interoceptive exposure + identifying quit date, quitline counseling + nicotine replacement therapy<br>15 sessions of interoceptive exposure-framed exercise regimen, 6 Quitline sessions | % abstinent | Anxiety severity (secondary outcome; PROMIS-Anxiety); ***<br>Primary: transdx construct (ASI) | 6 mo | SUD outcome $d$ =0.44 at FU<br>Transdx construct $d$ =0.17 at FU |
| Stapinski et al. (2021) | 2 | MET-CBT (Y)<br>10, 1-hr individual sessions | MI+integrated CBT including development of alternative reinforcers, emotion surfing, developing coping plans for high-risk situations, cognitive therapy round ETOH and social anxiety-related thoughts, social anxiety-focused behavioral experiments, identification of safety behaviors, attention | AUD severity (SADS); drinks per drinking day (TLFB) | Social anxiety severity (SIAS, SPS composite) | 3 and 6 mo | SUD outcomes pooled $d$ =0.18 at post, −0.16 at FU; anx severity $d$ =0.50 at post and $d$ =0.45 at FU |

(*continued on next page*)

**Table 2** (*continued*)

| Study | Int Lev | Comparison condition (manualized Y/N) | Integrated treatment condition | Variables (measures) obtain SUD outcome effect size (E.S.) | Variables (measures) to obtain anxiety (or transdx construct) outcome E.S. | Assess. pds after tx | Effect sizes for primary outcomes |
|---|---|---|---|---|---|---|---|
| | | | training, social support, relapse prevention<br>10, 1-hr individual therapy sessions | | | | |
| Wolitzky-Taylor et al. (2018) | 1 | Matrix Model (CBT + 12-step facilitation) with family education (Y)<br>IOP (9 hrs/wk for ~12 wks) | Same Matrix Model IOP without family education (CALM ARC in its place to control for therapy time): CALM ARC: psychoed about mutual maintenance of substance use and anxiety/ functional relations and about anxiety components, cognitive restructuring, exposure therapy (imaginal, in vivo, and interoceptive)<br>2 hr/wk for 7 weeks, group<br>Orientation session + 6 sessions | Drinking days past 30 days, drug use days past 30 days (TLFB) | Anxiety severity (OASIS) | Post, 6 mo | SUD outcomes pooled $d$ =0.38 at post and.38 at FU; anx severity $d$ =0.40 at post and $d$ =0.56 at FU |
| Wolitzky-Taylor et al. (2022a) | 2 | Matrix Model (CBT + 12-step facilitation) (Y)<br>IOP (9 hrs/wk for 12 wks) | Fully Integrated Treatment for Comorbid Social Anxiety and Alcohol Use Disorder (FIT): Matrix topics tailored for patients with social anxiety, psychoed about social anxiety/ETOH mutual maintenance, cognitive restructuring, exposure to social situations (using group context and AUD recovery contexts when possible)<br>IOP (9 hrs/wk for 12 weeks), group | Drinking days past 30 days, drinks per drinking day (TLFB); AUD severity (SIP) | Social Anxiety Severity (LSAS) | Post, 6 mo | SUD outcomes pooled $d$ =0.76 at post and.65 at FU; anx severity $d$ =0.32 at post and $d$ =0.92 at FU |
| Wolitzky-Taylor et al. (2022b) | 3 | CBT + MI (Y)<br>12 weekly, 1-hr individual sessions | MI, psychoed about how reactivity to NA contributes to cannabis use, mindfulness, problem solving, cognitive reappraisal skills, exposure to distressing stimuli (imaginal, interoceptive, and in vivo) that typically lead to cannabis craving or use, skill practice<br>12 sessions, individual | # days used past 30, total # times used past 30 (TLFB); SUD severity (CAST) | Anxiety severity (DASS-Anx); Transdx construct (ASI, DERS, DTS) | Post, 6 mo | SUD outcomes pooled $d$ =0.40 at post and −0.17 at FU; anx severity $d$ =0.34 at post and $d$ =0.22 at FU; transdx construct pooled (across time and constructs) $d$ =0.50 |
| Worden et al. (2017) | 3 | Addiction TAU (MI, 12-step + CBT) (N)<br>IOP, 9–20 hrs/wk, 3–5 weeks | Interoceptive exposure, psychoed about relationship between substance use and anxiety, cognitive reappraisal about body sensations<br>2xwk, 90-min sessions over 3 weeks=6 sessions, group | % days abstinent (TLFB) | Anxiety (DASS-Anx)<br>Transdx construct (ASI) | Post, 3 mo | SUD outcome $d$ = −0.22 at post and.27 at FU; anx severity $d$ =0.14 at post; and $d$ =0.26 at FU; transdx construct pooled across time $d$ =0.39 |

Note: "Pooled" refers to the computed mean effect size when multiple measures or timepoints (or both) are included in a particular analysis. Effect sizes are pooled for SUD and pooled for anx when multiple DVs, computed by CMA software. Effect sizes of transdiagnostic constructs are pooled across time and constructs, as there was only one analysis of effects on these constructs across post/FU timepoints. Int lev = Integration level; BL=baseline; FU=follow-up; NA = negative affect; TS = thought suppression; DI = distress intolerance; MI = motivational interviewing; MET= motivational enhancement therapy; TLFB = Timeline Followback; CBT = cognitive behavioral therapy; BSCQ-A = Brief Smoking Consequences Questionnaire; SIP = Short Inventory of Problems; CAST=Cannabis Abuse Screening Test; EuropeASI = European Addiction Severity Index; ADS = Alcohol Dependence Scale; SADS = Severity of Alcohol Dependence Scale; MPQ = Marijuana Problems Questionnaire; DASS= Depression Anxiety Stress Scale – Anxiety Subscale; FQ=Fear Questionnaire; OASIS=Overall Anxiety Severity and Impairment Scale; SIAS= Social Interaction Anxiety Scale; SPS=Social Phobia Scale; LSAS=Leibowitz Social Anxiety Scale; ASI=Anxiety sensitivity Index; DERS=Difficulties with Emotion Regulation Scale; DTS=Distress Tolerance Scale; SSEQ-NA=Smoking Self-Efficacy Scale-Negative Affect Subscale. TAU=treatment as usual; MI=motivational interviewing. *indicates that no assessment tool was described for substance use data collection; **cross-sectional Cohen's $d$ effect sizes at post or follow-up do not take into account that there were baseline/pre-treatment differences between conditions on the variable, leading to negative or smaller effect size not accounting for within-group change from pre- to post-treatment (or follow-up). ***did not report sufficiently to include this variable in analyses and did not obtain from authors. DNR=did not report.

procedure decreased the risk that studies with several measures of the same construct would be more influential than those with fewer groups (Rosenthal, 1991; Borenstein et al., 2021). In order to ensure that the comparisons reported were based on a meaningful number of studies and that fail-safe N (FSN) analyses could be conducted, analyses were only conducted when three or more studies could be included. In addition, this commonly practiced, conservative approach (e.g., Bar-Haim et al., 2007) also limits the likelihood of a given effect size being driven by a study that may be an outlier (McKay, 2008). For all comparisons, Cohen's $d$ was selected as the index of effect size, with $d$ values

of 0.2, 0.5, and 0.8 representing small, medium, and large effect sizes, respectively. Average effect sizes for each outcome in each relevant comparison were weighted using the inverse variance estimate in order to minimize the risk that a small, outlying sample would exert a disproportionate influence over the final effect size for a comparison (Rosenthal, 1991).

The use of random-effects models also helped to weight the studies appropriately and were used to increase the generalizability of findings beyond the studies that were able to be included in the meta-analysis. In addition, in order to account for the bias that may be present by including only published studies (i.e., file drawer effect), we conducted an FSN analysis for each comparison. Because meta-analyses are largely limited to published studies, the FSN statistic accounts for the number of nonsignificant findings (that presumably may not have been published) needed to bring a significant effect size to nonsignificance. Thus, a large FSN statistic indicates that the significant effect is not likely to be due to the bias of published studies having larger effects than unpublished studies. Specifically, if the FSN is greater than five times the number of available studies (K) in a given comparison, the effect is robust and not due to publication bias (Rosenthal, 1979). When FSN indicated the effect size was not robust to publication bias, an additional measure was taken to assess publication bias and adjust effect sizes, using the Duval and Tweedie (2000) trim and fill technique.

For each comparison, the weighted mean effect size, the statistical significance (*p*-value) of this effect size, the within-comparison heterogeneity index (*Q*), the *p*-value for the heterogeneity index, and the $I^2$ index as a secondary assessment of heterogeneity were calculated. If the Q-statistic was non-significant and the $I^2$ statistic was less than 50 (equating to < 50%), the outcome was considered non-heterogenous, and moderator analyses were thus not indicated. When the heterogeneity index (Q) was statistically significant or $I^2$ exceeded 50, moderator analyses were conducted. Moderators of interest included sex (i.e., % male), substance type population, anxiety disorder population, and level of integration (1−3). Additional calculations included the (a) standard error, (b) variance (c) 95% confidence intervals for each weighted mean effect size.

## 3. Results

### 3.1. Study characteristics

Eleven studies were included in the meta-analysis, which comprised N = 966 with data available at post-treatment. On average, across the samples the studies were comprised of 52.4% males and 68.4% non-Hispanic white participants (with one study not reporting sex/gender and three studies either not reporting race/ethnicity of the sample or not reporting it in standard categories that could be collapsed with the others) at the baseline assessment. Details regarding each study can be found in Tables 1 and 2. As shown in Table 2, too few studies at each level of integration were available to examine each level in a separate set of analyses.

### 3.2. Substance use and severity outcomes

When collapsing all substance use-relevant outcomes and all timepoints (post-treatment and follow-up) into one analysis (K =11), a small-to-moderate effect size favoring integrated anxiety/SUD treatments (compared to SUD treatments alone) was observed $d = 0.31$, *se* =0.08, var =0.01, 95% CIs: 0.15–0.47, $z = 3.72$, $p < 0.001$. The heterogeneity index was non-significant, $Q\ (10) = 11.77$, $p = .30$ and $I^2 = 15.05$, indicating that there was not significant heterogeneity of effects across studies. Therefore, a moderator analysis was not conducted for this analysis. The FSN statistic was $z = 4.28$, $p < 0.001$, with 42 additional studies needed to bring the effect size to non-significance. Therefore, the effect was not robust to the file-drawer effect. An additional test of bias, the Duval and Tweedie's trim and fill test (Duval and Tweedie, 2000) was conducted which indicated that no studies needed to be removed for re-adjustment of the variance, and the effect size remained as reported above.

#### 3.2.1. Post-treatment effects of integrated treatment v. SUD treatment alone

Additional effect sizes were calculated on sub-sets of this larger sample. First, those studies that reported post-treatment outcomes, and then those studies that reported follow-up outcomes. At post-treatment (K = 8), a small-to-moderate effect size was observed favoring integrated treatment for anxiety/SUD over SUD treatment alone, $d$ =0.35, *se* =0.12, var =0.01, 95% CIs: 0.11–0.58, $z = 2.90$, $p < 0.01$. The heterogeneity index was non-significant, $Q\ (7) = 9.17$, $p = .24$ and the $I^2 = 23.65$, so moderator analyses were not conducted. The FSN statistic was significant, $z = 3.45$, $p < 0.001$, though only 17 studies were needed to bring the finding to non-significance. Therefore, the Duval and Tweedie's trim and fill test was conducted, which indicated that no studies needed to be removed for re-adjustment of the variance and the effect size remained as reported above.

#### 3.2.2. Effects of integrated treatment v. SUD treatment alone at follow-up assessments on SUD outcomes

Among those studies that reported follow-up SUD outcomes (K = 8), a small effect was observed favoring integrated SUD/anxiety treatments over SUD treatment alone, $d$ =0.25, *se* =0.09, var =0.01, 95% CIs: 0.08–0.43, $z = 2.87$, $p < 0.01$. The heterogeneity index was non-significant, $Q\ (8) = 7.68$, $p = .36$, $I^2 = 8.88$; therefore, no moderator analyses were conducted. The FSN statistic was significant, $z = 3.00$, $p < 0.01$, but with 11 studies needed for the effect to become non-significant. Therefore, Duval and Tweedie's trim and fill test was conducted, which indicated that no studies needed to be removed for re-adjustment of the variance, and the effect size remained as reported above.

### 3.3. Anxiety severity outcomes

Across all outcome timepoints (post-treatment and follow-up), K = 9 studies were included and revealed a small-to-moderate effect size favoring integrated treatment over SUD treatment alone, $d = 0.34$, *se* =0.10, var =0.01, 95% CIs: 0.14–0.55, $z = 3.32$, $p = .001$. The heterogeneity was not significant, $Q\ (8) = 11.17$, $p = .19$, $I^2 = 28.35$. Therefore, moderator analyses were not conducted. The FSN statistic was $z = 3.87$, $p < 0.001$, with 27 additional studies needed to bring the finding to non-significance. Thus, the effect size was not robust to publication bias. However, Duval & Tweedie's trim and fill approach did not indicate any studies should be trimmed and thus the effect size remained the same.

When including studies with a post-treatment assessment of anxiety symptom severity (K = 8), a small-to-moderate effect size was observed favoring integrated treatment over SUD treatment alone, $d = 0.34$, *se* =0.12, var =0.02, 95% CIs: 0.10–0.59, $z = 2.78$, $p < 0.001$. The heterogeneity index was non-significant, $Q\ (7) = 9.83$, $p = .20$, $I^2 = 28.81$. Therefore, moderator analyses were not conducted. The FSN statistic was $z = 3.12$, $p < 0.01$, with only 13 additional studies needed to bring alpha to non-significance. Therefore, an additional measure of assessment of publication bias was taken using Duval & Tweedie's trim and fill. In this adjustment, no studies to the left of the mean and three studies to the right of the mean were trimmed, resulting in an adjusted effect size of $d = 0.51$.

At follow-up assessments, K = 6 studies were included that provided data on a dimensional index of anxiety severity. This analysis yielded a small-to-moderate effect size favoring integrated treatment over SUD treatment alone on anxiety severity outcomes, $d = 0.33$, *se* =0.09, var =0.01, 95% CIs: 0.16–0.51, $z = 3.80$, $p < 0.001$. The heterogeneity index was non-significant, $Q\ (5) = 4.02$, $p = .55$, $I^2 = 0.0$. Therefore, moderator analyses were not conducted. The FSN statistic was $z = 3.84$, $p < 0.001$, with 18 studies needed to bring alpha to non-significance, indicating the effect size was not considered robust to the file drawer effect. Therefore,

an additional measure of assessment of publication bias was taken using Duval & Tweedie's trim and fill. In this adjustment, two studies to the left of the mean were trimmed, resulting in an adjusted effect size of $d =$ 0.29.

#### 3.3.1. Secondary analysis comparing integrated anxiety/SUD treatment to SUD treatment alone on transdiagnostic constructs implicated in anxiety disorder/SUD comorbidity

All four of the studies comparing the efficacy of level 3 integrated treatments to SUD treatments alone reported on the outcomes of a transdiagnostic treatment target implicated in the maintenance of anxiety/SUD comorbidity. Consistent with the 3-level integration model, the studies that presented these data as primary outcomes were all categorized in level 3 and all included participants on the basis of having a SUD and elevations in these constructs (as opposed to on the basis of a categorical anxiety disorder diagnosis). The effect size favoring integrated treatments over SUD treatment alone on these transdiagnostic outcomes was moderate, $d$ =0.40, $se$ =0.16, var =0.03, 95% CIs: 0.19–0.72, $z$ = 2.50, $p$ =.01. The heterogeneity index was non-significant, $Q$ (3) = 2.74, $p$ =.43, $I^2$= 0.0. Therefore, moderator analyses were not conducted. The FSN statistic was $z = 2.67, p < 0.001$, with only 4 studies needed to bring alpha to non-significance, indicating the effect size was not considered robust to the file drawer effect. Therefore, an additional measure of assessment of publication bias was taken using Duval & Tweedie's trim and fill. In this adjustment, two studies to the left of the mean were trimmed, resulting in an adjusted effect size of $d =$ 0.21.

## 4. Discussion

This article presented a conceptual framework by which to understand the diverse ways in which evidence-based behavioral treatments for anxiety disorders can be integrated into treatment for SUD and presented a meta-analysis of 11 studies examining the efficacy of integrated behavioral treatment for comorbid anxiety disorders and SUD compared to SUD treatment alone. The findings from the meta-analysis revealed small to moderate effect sizes favoring integrated treatment over SUD treatment alone on SUD outcomes and anxiety symptom severity outcomes. These findings provide convergent, empirical support for the current directions in both the research and clinical practice paradigm shifts in the treatment of co-occurring disorders, which call for integrated treatment both from clinical/theoretical (Stewart and Conrod, 2008) and policy (SAMHSA, 2022) perspectives.

A small-to-moderate effect size implies an incremental effect over the comparison condition. Importantly, this incremental effect is clinically meaningful for several reasons. First, as shown in Table 1, the majority of the "SUD treatment only" comparison conditions included gold standard, evidence-based SUD treatments, including CBT and MET, making this a highly stringent comparison group. Although the comparison conditions for some studies used non-manualized approaches that likely lacked fidelity monitoring, they were still described as largely using evidence-based principles and components and reflect common practice in SUD treatment. Second, the majority of the studies were actually effectiveness studies rather than efficacy studies, in that they were evaluating clinical outcomes in real-world, community-based samples, often using community-based clinicians to deliver care and including complex patients with other comorbidities; thus, these effect size estimates have direct implications for translation to community-based care and are not inflated by the tight controls on internal validity observed in clinical research laboratory-based studies. Third, the superiority of integrated treatments over SUD treatments was maintained into follow-up periods, indicating that these gains are maintained over time both for substance use and anxiety symptom improvement. These findings are encouraging given that anxiety disorder comorbidity is associated with increased likelihood of substance use relapse following typical SUD treatment alone (Schellekens et al., 2015), and support the use of integrating anxiety disorder treatment into SUD care to prevent relapse (consistent with self-medication and mutual maintenance theories; Stewart and Conrod, 2008; Khantzian, 1985; Robinson et al., 2011). Fourth, even a relatively small to moderate superiority of integrated SUD/anxiety treatments over SUD treatments alone (in terms of statistical magnitude) suggests that there is a clinical benefit to training the clinical workforce to deliver these interventions to improve outcomes. Indeed, modest contributions to variance by independent variables in individual studies may dramatically understate their contributions in the long-term (Abelson, 1985). Interventions that can reduce substance use and anxiety symptoms in a single, integrated intervention to a greater extent than standard, evidence-based practice paradigms, however modestly that incremental improvement over standard practice is, can have a dramatic cumulative public health impact. Moreover, this integration provides a parsimonious, potentially more scalable approach than the less effective parallel or sequential treatment approaches of the past (e.g., Randall et al., 2001).

Moderator analyses were planned for comparisons with a significant heterogeneity index, which would have signaled variation in effect sizes across studies that would warrant identification of individual factors that could predict differential outcomes. However, contrary to expectation, significant heterogeneity was not observed for any of the primary analyses. Although an investigation of the putative moderators would have been interesting, the primary findings indicated that they were unlikely to yield any significant effects. Perhaps more heterogeneity would have been observed had the inclusion criteria been broader (e.g., including high-risk/hazardous use, including studies that targeted a transdiagnostic construct relevant to anxiety that did not select on the basis of that construct being elevated, including medication trials). However, given that this was the first meta-analysis of its kind, the choice was made intentionally to restrict the sample to share in the core features needed to draw clinically meaningful interpretations and recommendations. Future research may explore the effects of a broader range of interventions on a broader range of samples.

In particular, level of integration was planned as a putative moderator, but was not examined due to the lack of heterogeneity across studies as described above. Secondary analyses examining the effects of integrated treatment compared to SUD treatment alone within each level of integration separately were also planned but could not be conducted because there were too few studies at each level to examine each of the three levels separately. However, the consistent lack of heterogeneity across studies suggests that there may not be a clinically meaningful benefit at this point in the field to select one type of integration over another. Therefore, the incremental utility of one approach to integration over another will be a question for future research when more studies have been conducted that would warrant a larger meta-analysis, thereby permitting such level-specific analyses. At this point, these findings suggest there are a variety of options for providing clinically effective integrated treatment for anxiety/SUD. Selection of an intervention strategy then can be based on an evaluation of implementation factors within a setting to optimize the likelihood of adoption and sustainability in a clinical practice.

This study represents the first meta-analysis comparing integrated behavioral treatment for anxiety disorders and SUD, a common comorbidity associated with poor outcomes. Although there were several strengths of the study, it was not without limitations. As with all meta-analyses, the study was inherently limited by the limitations of the studies included (e.g., small sample sizes for many of the studies, non-manualized treatment for some of the SUD control conditions, attrition over follow-up periods as is common with this comorbid population; Krawczyk et al., 2017). Clearly, more research is needed on these interventions with larger sample sizes, and improvements to engagement and retention strategies should be the focus of future research with this population known to have poor engagement in treatment (Book et al., 2009). Still, the studies all converge (with minimal heterogeneity across studies) to support the utility of integrated treatments over SUD

treatment alone for the treatment of comorbid anxiety/SUD. The fact that the heterogeneity index was non-significant for all analyses strengthens the argument that these findings are consistent across numerous studies.

Another limitation was that with a single-author paper, inter-rater reliability checks could not be conducted to ensure that studies were classified into the correct integration levels and metrics of study bias and quality could not be evaluated, as those require multiple raters. However, these limitations are offset by the fact that integration levels were developed by the sole author conducting the meta-analysis; thus, it is unlikely that they were wrongly classified, and even if they were, this would have no bearing on the primary outcomes of the meta-analysis. When more randomized clinical trials emerge in the literature comparing integrated anxiety/SUD treatments to active SUD treatment comparison conditions, there will be sufficient numbers of studies to draw firmer conclusions about the utility and clinical effectiveness of one level over another, which may validate the model or imply the need for revisions to the conceptualization.

Finally, it is worth noting that not all studies included participants who had a diagnosed anxiety disorder, but a few enrolled participants on the basis of dimensional anxiety symptoms, or elevations in constructs relevant to anxiety and SUD (e.g., anxiety sensitivity). Although this may be considered non-traditional or a limitation, this is actually a strength. Although clinical practice paradigms still typically emphasize diagnostic categories, and thus, researchers and clinicians may be looking for meta-analytic results that specifically map onto these categories, most SUD specialty care settings do not actually diagnose emotional disorders such as anxiety. Thus, there is a practical contribution to these findings that they hold even for those without a diagnosed anxiety disorder. That is, the findings from this study demonstrate that integrated interventions, particularly at level 3, can benefit those who may not necessarily have a diagnosed anxiety disorder, thus broadening the potential reach of these interventions. Also, it is worth noting that in these studies, given that these constructs are elevated in anxiety disorders, many participants likely had anxiety disorders but were simply not included on that basis. Moreover, current directions in the understanding and treatment of psychopathology are moving towards dimensional, process-based treatments that target mechanisms implicated in these common comorbidities (see Sauer-Zavala, 2017, for a review).

Taken together, these findings support the call for integrated treatments for comorbid anxiety and SUD in clinical practice. These studies, while sharing a fairly narrow and rigorous set of inclusion/exclusion criteria, also represented a diverse and creative set of studies that addressed this problem in different ways, using different methods of content and systemic integration at different levels, and addressing a heterogeneous set of samples with regard to substance of dependence and anxiety disorder. That these effects were observed across a variety of anxiety disorders, a variety of substances of dependence, and a variety of levels of integration and strategies for weaving evidence-based treatments for anxiety and SUD together, suggests that there are many effective ways to approach the complex problem of anxiety disorder and SUD comorbidity in clinical practice. Perhaps due to the siloing of training experiences early on in clinical programs, one of the biggest limitations now is the lack of a trained workforce to carry out high quality integrated treatment with fidelity. Future work, both in research and clinical care, should aim to disseminate these treatment approaches.

## Author contributions

As sole author, Dr. Wolitzky-Taylor provided all contributions to the design, methods, analysis, and writing of the manuscript.

## Declaration of Competing Interest

There are no conflicts of interest to declare.

## Acknowledgments

Many thanks to Kayla Sharf for her assistance with the literature search and administrative management.

## References

*Included in the meta-analysis.
Abelson, R.P., 1985. A variance explanation paradox: When a little is a lot. Psychol. Bull. *97* (1), 129–133. https://doi.org/10.1037/0033-2909.97.1.129.
Bar-Haim, Y., Lamy, D., Pergamin, L., Bakermans-Kranenburg, M.J., van IJzendoorn, M. H., 2007. Threat-related attentional bias in anxious and nonanxious individuals: A meta-analytic study. Psychol. Bull. *133* (1), 1–24. https://doi.org/10.1037/0033-2909.133.1.1.
Barry, C.L., Huskamp, H.A., 2011. Moving beyond parity — mental health and addiction care under the ACA. N. Engl. J. Med. *365* (11), 973–975. https://doi.org/10.1056/nejmp1108649.
Bernstein, A., Zvolensky, M.J., Vujanovic, A.A., Moos, R., 2009. Integrating anxiety sensitivity, distress tolerance, and discomfort intolerance: A hierarchical model of affect sensitivity and tolerance. Behav. Ther. *40* (3), 291–301. https://doi.org/10.1016/j.beth.2008.08.001.
Blanchard, K.A., Morgenstern, J., Morgan, T.J., Labouvie, E.W., Bux, D.A., 2003. Shortened inventory of problems–Alcohol and Drugs. PsycTESTS Dataset. https://doi.org/10.1037/t17417-000.
Book, S.W., Thomas, S.E., Dempsey, J.P., Randall, P.K., Randall, C.L., 2009. Social anxiety impacts willingness to participate in addiction treatment. Addict. Behav. *34* (5), 474–476. https://doi.org/10.1016/j.addbeh.2008.12.011.
Borenstein, M., Hedges, L.V., Higgins, J.P.T., Rothstein, H.R., 2006. Comprehensive Meta-Analysis(Version 2.2.027) [Computer software]. Englewood, NJ: Biostat.
Borenstein, M., Hedges, L.V., Higgins, J.P., Rothstein, H.R., 2021. Introduction to Meta-analysis. John Wiley & Sons.
Bornovalova, M.A., Gratz, K.L., Daughters, S.B., Hunt, E.D., Lejuez, C.W., 2012. Initial RCT of a distress tolerance treatment for individuals with Substance Use Disorders. Drug Alcohol Depend. *122* (1–2), 70–76. https://doi.org/10.1016/j.drugalcdep.2011.09.012.
Bowen, R.C., D'Arcy, C., Keegan, D., Senthilselvan, A., 2000. A controlled trial of cognitive behavioral treatment of panic in alcoholic inpatients with Comorbid Panic disorder. Addict. Behav. *25* (4), 593–597. https://doi.org/10.1016/s0306-4603(99)00017-9.
(*) Bradizza, C.M., Stasiewicz, P.R., Zhuo, Y., Ruszczyk, M., Maisto, S.A., Lucke, J.F., Brandon, T.H., Eiden, R.D., Slosman, K.S., Giarratano, P., 2016. Smoking cessation for pregnant smokers: Development and pilot test of an emotion regulation treatment supplement to standard smoking cessation for negative affect smokers. Nicotine Tob. Res. *19* (5), 578–584. https://doi.org/10.1093/ntr/ntw398.
Buckner, J.D., Bonn-Miller, M.O., Zvolensky, M.J., Schmidt, N.B., 2007. Marijuana use motives and social anxiety among marijuana-using Young Adults. Addict. Behav. *32* (10), 2238–2252. https://doi.org/10.1016/j.addbeh.2007.04.004.
Buckner, J.D., Heimberg, R.G., Schmidt, N.B., 2011. Social anxiety and marijuana-related problems: The role of Social Avoidance. Addict. Behav. *36* (1–2), 129–132. https://doi.org/10.1016/j.addbeh.2010.08.015.
Buckner, J.D., Zvolensky, M.J., Smits, J.A.J., Norton, P.J., Crosby, R.D., Wonderlich, S. A., Schmidt, N.B., 2011. Anxiety sensitivity and marijuana use: An analysis from ecological momentary assessment. Depress. Anxiety *28* (5), 420–426. https://doi.org/10.1002/da.20816.
(*) Buckner, J.D., Zvolensky, M.J., Ecker, A.H., Schmidt, N.B., Lewis, E.M., Paulus, D.J., Lopez-Gamundi, P., Crapanzano, K.A., Bakhshaie, J., 2019. Integrated Cognitive Behavioral therapy for Comorbid Cannabis use and anxiety disorders: A pilot randomized controlled trial. Behav. Res. Ther. *115*, 38–45. https://doi.org/10.1016/j.brat.2018.10.014.
Burnam, M.A., Watkins, K.E., 2006. Substance abuse with mental disorders: Specialized Public Systems and integrated care. Health Aff. *25* (3), 648–658. https://doi.org/10.1377/hlthaff.25.3.648.
Burns, L., Teesson, M., O'Neill, K., 2005. The impact of comorbid anxiety and depression on alcohol treatment outcomes. Addiction *100* (6), 787–796. https://doi.org/10.1111/j.1360-0443.2005.001069.x.
Campbell-Sills, L., Norman, S.B., Craske, M.G., Sullivan, G., Lang, A.J., Chavira, D.A., Bystritsky, A., Sherbourne, C., Roy-Byrne, P., Stein, M.B., 2009. Validation of a brief measure of anxiety-related severity and impairment: The Overall Anxiety Severity and Impairment Scale (OASIS). J. Affect. Disord. 112 (4), 92–101.
Chawla, N., Ostafin, B., 2007. Experiential avoidance as a functional dimensional approach to psychopathology: An empirical review. J. Clin. Psychol. *63* (9), 871–890. https://doi.org/10.1002/jclp.20400.
Compton, W.M., Thomas, Y.F., Stinson, F.S., Grant, B.F., 2007. Prevalence, correlates, disability, and comorbidity of DSM-IV drug abuse and dependence in the United States. Arch. Gen. Psychiatry *64* (5), 566. https://doi.org/10.1001/archpsyc.64.5.566.
Conger, J.J., 1956. II. reinforcement theory and the dynamics of alcoholism. Q. J. Stud. Alcohol *17* (2), 296–305. https://doi.org/10.15288/qjsa.1956.17.296.
Conway, K.P., Compton, W., Stinson, F.S., Grant, B.F., 2006. Lifetime comorbidity of DSM-IV mood and anxiety disorders and specific drug use disorders. J. Clin. Psychiatry *67* (02), 247–258. https://doi.org/10.4088/jcp.v67n0211.
Cougle, J.R., Timpano, K.R., Goetz, A.R., 2012. Exploring the unique and interactive roles of distress tolerance and negative urgency in obsessions. Personal. Individ. Differ. *52* (4), 515–520. https://doi.org/10.1016/j.paid.2011.11.017.

Cuthbert, B.N., 2014. The rdoc framework: Facilitating transition from ICD/DSM to dimensional approaches that integrate neuroscience and psychopathology. World Psychiatry *13* (1), 28–35. https://doi.org/10.1002/wps.20087.
Diclemente, C.C., Prochaska, J.O., Gibertini, M., 1985. Self-efficacy and the stages of self-change of smoking. Cogn. Ther. Res. *9*, 181–200.
Doyle, S.R., Donovan, D.M., 2009. A validation study of the Alcohol Dependence Scale. J. Stud. Alcohol Drugs *70* (5), 689–699. https://doi.org/10.15288/jsad.2009.70.689.
Duval, S., Tweedie, R., 2000. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics *56* (2), 455–463. https://doi.org/10.1111/j.0006-341x.2000.00455.x.
Gallanter, M., Nace, E.P., 1988. Posttraumatic stress disorder and substance abuse clinical issues. Recent Developments in Alcoholism. Springer, New York, NY, pp. 9–26 (essay).
Glasner, S., Mooney, L.J., Ang, A., Garneau, H.C., Hartwell, E., Brecht, M.-L., Rawson, R. A., 2017. Mindfulness-based relapse prevention for stimulant dependent adults: A pilot randomized clinical trial. Mindfulness *8* (1), 126–135. https://doi.org/10.1007/s12671-016-0586-9.
Glasner-Edwards, S., Rawson, R., 2010. Evidence-based practices in addiction treatment: Review and Recommendations for public policy. Health Policy *97* (2–3), 93–104. https://doi.org/10.1016/j.healthpol.2010.05.013.
Grant, B.F., Stinson, F.S., Dawson, D.A., Chou, S.P., Dufour, M.C., Compton, W., Pickering, R.P., Kaplan, K., 2004. Prevalence and co-occurrence of substance use disorders and Independentmood and anxiety disorders. Arch. Gen. Psychiatry *61* (8), 807. https://doi.org/10.1001/archpsyc.61.8.807.
Gratz, K.L., Roemer, L., 2004. Difficulties in emotion regulation scale. PsycTESTS Dataset. https://doi.org/10.1037/t01029-000.
Greeley, J., Oei, T., 1999. Alcohol and tension reduction. In: Leonard, K.E., Blane, H.T. (Eds.), Psychologicaltheories of drinking and alcoholism. The Guilford Press, pp. 14–53 (essay).
Hamilton, M., 1959. Hamilton Anxiety Rating Scale. PsycTESTS Dataset. https://doi.org/10.1037/t02824-000.
Havassy, B.E., Alvidrez, J., Mericle, A.A., 2009. Disparities in use of mental health and Substance Abuse Services by persons with co-occurring disorders. Psychiatr. Serv. *60* (2), 217–223. https://doi.org/10.1176/ps.2009.60.2.217.
Hearon, B.A., Calkins, A.W., Halperin, D.M., Kathryn McHugh, R., Murray, H.W., Otto, M.W., 2011. Anxiety sensitivity and illicit sedative use among opiate-dependent women and men. Am. J. Drug Alcohol Abus. *37* (1), 43–47. https://doi.org/10.3109/00952990.2010.535581.
Heimberg, R.G., Mueller, G.P., Holt, C.S., Hope, D.A., Liebowitz, M.R., 1992. Assessment of anxiety in social interaction and being observed by others: The Social Interaction Anxiety Scale and the social phobia scale. Behav. Ther. *23* (1), 53–73. https://doi.org/10.1016/s0005-7894(05)80308-9.
Hesse, M., 2009. Integrated psychological treatment for substance use and co-morbid anxiety or depression vs. treatment for substance use alone. A systematic review of the published literature. BMC Psychiatry *9* (1). https://doi.org/10.1186/1471-244x-9-6.
Hien, D.A., Morgan-López, A.A., Saavedra, L.M., Ruglass, L.M., Ye, A., López-Castro, T., Back, S.E., 2023. Project Harmony: a meta-analysis with individual patient data on behavioral and pharmacologic trials for comorbid posttraumatic stress and alcohol or other drug use disorders. Am. J. Psychiatry 180 (2), 155–166.
Khantzian, E.J., 1985. The self-medication hypothesis of addictive disorders: Focus on heroin and cocaine dependence. Am. J. Psychiatry *142* (11), 1259–1264. https://doi.org/10.1176/ajp.142.11.1259.
Krawczyk, B., Minku, L.L., Gama, J., Stefanowski, J., Woźniak, M., 2017. Ensemble learning for data stream analysis: A survey. Inf. Fusion *37*, 132–156. https://doi.org/10.1016/j.inffus.2017.02.004.
Kushner, Matt, G., Donahue, C., Sletten, S., Thuras, P., Abrams, K., Peterson, J., Frye, B., 2006. Cognitive behavioral treatment of comorbid anxiety disorder in alcoholism treatment patients: Presentation of a prototype program and Future Directions. J. Ment. Health *15* (6), 697–707. https://doi.org/10.1080/09638230600998946.
Kushner, Matt, G., Sletten, S., Donahue, C., Thuras, P., Maurer, E., Schneider, A., Frye, B., Demark, J.V., 2009. Cognitive-behavioral therapy for panic disorder in patients being treated for alcohol dependence: Moderating effects of alcohol outcome expectancies. Addict. Behav. *34* (6–7), 554–560. https://doi.org/10.1016/j.addbeh.2009.03.011.
Kushner, M.G., Sher, K.J., Beitman, B.D., 1990. The relation between alcohol problems and the anxiety disorders. Am. J. Psychiatry *147* (6), 685–695. https://doi.org/10.1176/ajp.147.6.685.
Kushner, Matt G., Abrams, K., Thuras, P., Hanson, K.L., Brekke, M., Sletten, S., 2005. Follow-up study of anxiety disorder and alcohol dependence in comorbid alcoholism treatment patients. Alcohol. Clin. Exp. Res. *29* (8), 1432–1443. https://doi.org/10.1097/01.alc.0000175072.17623.f8.
Kushner, Matt G., Krueger, R., Frye, B., Peterson, J., 2008. Epidemiological perspectives on co-occurring anxiety disorder and substance use disorder. Anxiety Subst. Use Disord. 3–17. https://doi.org/10.1007/978-0-387-74290-8_1.
**Kushner, Matt, G., Maurer, E.W., Thuras, P., Donahue, C., Frye, B., Menary, K.R., Hobbs, J., Haeny, A.M., Van Demark, J., 2013. Hybrid cognitive behavioral therapy versus relaxation training for co-occurring anxiety and alcohol disorder: A randomized clinical trial. J. Consult. Clin. Psychol. *81* (3), 429–442. https://doi.org/10.1037/a0031301.
Lai, H.M., Cleary, M., Sitharthan, T., Hunt, G.E., 2015. Prevalence of comorbid substance use, anxiety and mood disorders in epidemiological surveys, 1990–2014: A systematic review and meta-analysis. Drug Alcohol Depend. *154*, 1–13. https://doi.org/10.1016/j.drugalcdep.2015.05.031.
Lammers, J., Goossens, F., Conrod, P., Engels, R., Wiers, R.W., Kleinjan, M., 2017. Effectiveness of a selective alcohol prevention program targeting personality risk factors: Results of interaction analyses. Addict. Behav. *71*, 82–88. https://doi.org/10.1016/j.addbeh.2017.02.030.
Legleye, S., Karila, L., Beck, F., Reynaud, M., 2007. Validation of the CAST, a general population Cannabis Abuse Screening Test. J. Subst. Use 12, 233–242.
Liebowitz, M.R., 1987a. Liebowitz Social Anxiety Scale. PsycTESTS Dataset. https://doi.org/10.1037/t07671-000.
Liebowitz, M.R., 1987b. Liebowitz Social Anxiety Scale. PsycTESTS Dataset. https://doi.org/10.1037/t07671-000.
Lovibond, S.H., Lovibond, P.F., 1995. Depression anxiety stress scales. PsycTESTS Dataset. https://doi.org/10.1037/t01004-000.
Marks, I.M., Matthews, A.M., 1979. Marks Fear Questionnaire. PsycTESTS Dataset. https://doi.org/10.1037/t08203-000.
McGovern, M.P., Xie, H., Segal, S.R., Siembab, L., Drake, R.E., 2006. Addiction treatment services and co-occurring disorders: Prevalence estimates, treatment practices, and barriers. J. Subst. Abus. Treat. *31* (3), 267–275. https://doi.org/10.1016/j.jsat.2006.05.003.
McHugh, R.K., 2015. Treatment of co-occurring anxiety disorders and substance use disorders. Harv. Rev. Psychiatry *23* (2), 99–111. https://doi.org/10.1097/hrp.0000000000000058.
McHugh, R.K., Otto, M.W., 2012. Refining the measurement of distress intolerance. Behav. Ther. *43* (3), 641–651. https://doi.org/10.1016/j.beth.2011.12.001.
McKay, P.F., Avery, D.R., Morris, M.A., 2008. Diversity climate scale–4 item version. PsycTESTS Dataset. https://doi.org/10.1037/t35623-000.
(*) Morley, K.C., Baillie, A., Leung, S., Sannibale, C., Teesson, M., Haber, P.S., 2016. Is specialized integrated treatment for comorbid anxiety, depression and alcohol dependence better than treatment as usual in a public hospital setting. Alcohol Alcohol. *51* (4), 402–409. https://doi.org/10.1093/alcalc/agv131.
Olatunji, B.O., Wolitzky-Taylor, K.B., 2009. Anxiety sensitivity and the anxiety disorders: A meta-analytic review and synthesis. Psychol. Bull. *135* (6), 974–999. https://doi.org/10.1037/a0017428.
Olthuis, J.V., Watt, M.C., Mackinnon, S.P., Stewart, S.H., 2015. CBT for high anxiety sensitivity: Alcohol outcomes. Addict. Behav. *46*, 19–24. https://doi.org/10.1016/j.addbeh.2015.02.018.
Ouimette, P.C., Moos, R.H., Finney, J.W., 2000. Two-year Mental Health Service use and course of remission in patients with substance use and posttraumatic stress disorders. J. Stud. Alcohol *61* (2), 247–253. https://doi.org/10.15288/jsa.2000.61.247.
Peterson, R.A., Reiss, S., 1992. Anxiety Sensitivity Index Manual, 2nd ed. International Diagnostic Systems, Worthington, OH.
Pilkonis, P.A., Choi, S.W., Reise, S.P., Stover, A.M., Riley, W.T., Cella, D., PROMIS Cooperative Group, 2011. Item banks for measuring emotional distress from the Patient-Reported Outcomes Measurement Information System (PROMIS®): depression, anxiety, and anger. Assessment 18 (3), 263–283.
Raines, A.M., Allan, N.P., McGrew, S.J., Gooch, C.V., Wyatt, M., Laurel Franklin, C., Schmidt, N.B., 2020. A computerized anxiety sensitivity intervention for opioid use disorders: A pilot investigation among veterans. Addict. Behav. *104*, 106285 https://doi.org/10.1016/j.addbeh.2019.106285.
Randall, C.L., Thomas, S., Thevos, A.K., 2001. Concurrent alcoholism and Social Anxiety Disorder: A first step toward developing effective treatments. Alcohol. Clin. Exp. Res. *25* (2), 210–220. https://doi.org/10.1111/j.1530-0277.2001.tb02201.x.
Ries, R., Wolitzky-Taylor, K.B., Operskalski, J.T., Craske, M.G., Roy-Byrne, P., 2011. Treatment of comorbid substance use and anxiety disorders. J. Addict. Med. *5* (4), 248–253. https://doi.org/10.1097/adm.0b013e318233d64b.
Robinson, J., Bolton, J.M., Cox, B.J., Sareen, J., 2011. Role of self-medication in the development of comorbid anxiety and substance use disorders. Arch. Gen. Psychiatry *68* (8), 800. https://doi.org/10.1001/archgenpsychiatry.2011.75.
Rosenthal, R., 1979. The file drawer problem and tolerance for null results. Psychol. Bull. Vol 86 (3), 638–641. May 1979.
Rosenthal, R., 1991. Meta-Analysis: A review. Psychosom. Med. *53* (3), 247–271. https://doi.org/10.1097/00006842-199105000-00001.
Sauer-Zavala, S., Gutner, C.A., Farchione, T.J., Boettcher, H.T., Bullis, J.R., Barlow, D.H., 2017. Current definitions of "transdiagnostic" in treatment development: A search for consensus. Behav. Ther. *48* (1), 128–138.
(*) Schade, A., Marquenie, L.A., van Balkom, A.J.L.M., Koeter, M.W.J., de Beurs, E., van den Brink, W., van Dyck, R., 2005. The effectiveness of anxiety treatment on alcohol-dependent patients with a comorbid phobic disorder: A randomized controlled trial. Alcohol. Clin. Exp. Res. *29* (5), 794–800. https://doi.org/10.1097/01.alc.0000163511.24583.33.
Schellekens, A.F.A., de Jong, C.A.J., Buitelaar, J.K., Verkes, R.J., 2015a. Co-morbid anxiety disorders predict early relapse after inpatient alcohol treatment. Eur. Psychiatry *30* (1), 128–136. https://doi.org/10.1016/j.eurpsy.2013.08.006.
Scheurich, A., Müller, M.J., Wetzel, H., Anghelescu, I., Klawe, C., Ruppe, A., Lörch, B., Himmerich, H., Heidenreich, M., Schmid, G., Hautzinger, M., Szegedi, A., 2000. Reliability and validity of the German version of the European Addiction Severity index (europasi). J. Stud. Alcohol *61* (6), 916–919. https://doi.org/10.15288/jsa.2000.61.916.
Schmidt, N.B., Buckner, J.D., Pusser, A., Woolaway-Bickel, K., Preston, J.L., Norr, A., 2012. Randomized controlled trial of False Safety Behavior Elimination Therapy: A unified cognitive behavioral treatment for anxiety psychopathology. Behav. Ther. *43* (3), 518–532. https://doi.org/10.1016/j.beth.2012.02.004.
Schmitz, N., Kruse, J., 2002. The relationship between mental disorders and medical service utilization in a representative community sample. Soc. Psychiatry Psychiatr. Epidemiol. *37* (8), 380–386. https://doi.org/10.1007/s00127-002-0567-2.

Sher, K.J., Levenson, R.W., 1982. Risk for alcoholism and individual differences in the stress-response-dampening effect of alcohol. J. Abnorm. Psychol. *91* (5), 350–367. https://doi.org/10.1037/0021-843x.91.5.350.

Shuai, R., Bravo, A.J., Anker, J.J., Kushner, M.G., Hogarth, L., 2022. The direct effect of drinking to cope on alcohol problems is not mediated by alcohol consumption: Invariance across gender and countries. Addict. Behav. Rep. *16*, 100469 https://doi.org/10.1016/j.abrep.2022.100469.

Simons, J.S., Gaher, R.M., 2005. Distress tolerance scale. PsycTESTS Dataset. https://doi.org/10.1037/t13498-000.

Smith, J.P., Book, S.W., 2010. Comorbidity of generalized anxiety disorder and alcohol use disorders among individuals seeking outpatient substance abuse treatment. Addict. Behav. *35* (1), 42–45. https://doi.org/10.1016/j.addbeh.2009.07.002.

Smits, J.A., Rosenfield, D., McDonald, R., Telch, M.J., 2006. Cognitive mechanisms of social anxiety reduction: An examination of specificity and temporality. J. Consult. Clin. Psychol. *74* (6), 1203–1212. https://doi.org/10.1037/0022-006x.74.6.1203.

(*) Smits, J.A., Zvolensky, M.J., Rosenfield, D., Brown, R.A., Otto, M.W., Dutcher, C.D., Papini, S., Freeman, S.Z., DiVita, A., Perrone, A., Garey, L., 2021. Community-based smoking cessation treatment for adults with high anxiety sensitivity: A randomized clinical trial. Addiction *116* (11), 3188–3197. https://doi.org/10.1111/add.15586.

Sobell, L.C., Sobell, M.B., 1992. Timeline follow-back. Meas. Alcohol Consum. 41–72. https://doi.org/10.1007/978-1-4612-0357-5_3.

Spielberger, C.D., 1983. State-Trait Anxiety Inventory for adults. PsycTESTS Dataset. https://doi.org/10.1037/t06496-000.

(*) Stapinski, L.A., Sannibale, C., Subotic, M., Rapee, R.M., Teesson, M., Haber, P.S., Baillie, A.J., 2021. Randomised controlled trial of integrated cognitive behavioural treatment and motivational enhancement for comorbid social anxiety and Alcohol Use Disorders. Aust. N. Z. J. Psychiatry *55* (2), 207–220. https://doi.org/10.1177/0004867420952539.

Stephens, R.S., Roffman, R.A., Curtin, L., 2000. Marijuana dependence scale. PsycTESTS Dataset. https://doi.org/10.1037/t03579-000.

Stewart, S.H., Conrod, P.J., 2008. Anxiety disorder and substance use disorder co-morbidity: Common themes and future directions. *Anxiety and substance use disorders: The vicious cycle of comorbidity*, 239-257.

Stockwell, T., Sitharthan, T., McGrath, D., et al., 1994. The measurement of alcohol dependenceand impaired control in community samples. Addiction 89, 167–174.

Substance Abuse and Mental Health Services Administration, 2007. Office of Applied Studies. National Survey ofSubstance Abuse Treatment Services (N_SSAT): 2006. Data on substance Abuse Treatment Facilities, DASIS Series: S39, DHHHS publication no. (SMA) 07-4296, Rockville, MD..

Substance Abuse and Mental Health Services Administration (SAMHSA), 2020. Substance Use Disorder Treatment for Persons with Co-Occurring Disorders: A Treatment Improvement Protocol (TIP Series, No. 42).

Substance Abuse and Mental Health Services Administration (SAMHSA), 2022. The Case for Screening and Treatment of Co-Occurring Disorders.

van IJzendoorn, M.H., Juffer, F., Poelhuis, C.W., 2005. Adoption and cognitive development: A meta-analytic comparison of adopted and nonadopted children's IQ and school performance. Psychol. Bull. *131* (2), 301–316. https://doi.org/10.1037/0033-2909.131.2.301.

Watkins, K.E., Burnam, A., Kung, F.-Y., Paddock, S., 2001. A national survey of care for persons with co-occurring mental and substance use disorders. Psychiatr. Serv. *52* (8), 1062–1068. https://doi.org/10.1176/appi.ps.52.8.1062.

Watt, M., Stewart, S., Birch, C., Bernier, D., 2006. Brief CBT for high anxiety sensitivity decreases drinking problems, relief alcohol outcome expectancies, and conformity drinking motives: Evidence from a randomized controlled trial. J. Ment. Health *15* (6), 683–695. https://doi.org/10.1080/09638230600998938.

Wolitzky-Taylor, K., Operskalski, J.T., Ries, R., Craske, M.G., Roy-Byrne, P., 2011a. Understanding and treating comorbid anxiety disorders in substance users. J. Addict. Med. *5* (4), 233–247. https://doi.org/10.1097/adm.0b013e31823276d7.

Wolitzky-Taylor, K., Zimmermann, M., Arch, J.J., De Guzman, E., Lagomasino, I., 2015. Has evidence-based psychosocial treatment for anxiety disorders permeated usual care in community mental health settings. Behav. Res. Ther. *72*, 9–17. https://doi.org/10.1016/j.brat.2015.06.010.

Wolitzky-Taylor, K., McBeth, J., Guillot, C.R., Stone, M.D., Kirkpatrick, M.G., Zvolensky, M.J., Buckner, J.D., Leventhal, A.M., 2016. Transdiagnostic processes linking anxiety symptoms and substance use problems among adolescents. J. Addict. Dis. *35* (4), 266–277. https://doi.org/10.1080/10550887.2016.1207969.

(*) Wolitzky-Taylor, K., Krull, J., Rawson, R., Roy-Byrne, P., Ries, R., Craske, M.G., 2018. Randomized clinical trial evaluating the preliminary effectiveness of an integrated anxiety disorder treatment in substance use disorder specialty clinics. J. Consult. Clin. Psychol. *86* (1), 81–88. https://doi.org/10.1037/ccp0000276.

Wolitzky-Taylor, K., LeBeau, R., Perez, M., Gong-Guy, E., Fong, T., 2020. Suicide prevention on college campuses: What works and what are the existing gaps? A systematic review and meta-analysis. J. Am. Coll. Health 68, 419–429.

(*) Wolitzky-Taylor, K., Sewart, A., Karno, M., Ries, R., Stimson, J., 2022. Development and initial pilot testing of a fully integrated treatment for comorbid social anxiety disorder and alcohol use disorder in a community-based SUD clinic setting. Behav. Res. Ther. *148*, 103999. https://doi.org/10.1016/j.brat.2021.103999.

(*) Wolitzky-Taylor, K., Glasner, S., Tanner, A., Ghahremani, D.G., London, E.D., 2022. Targeting maladaptive reactivity to negative affect in emerging adults with cannabis use disorder: A preliminary test and proof of concept. Behav. Res. Ther. *150*, 104032. https://doi.org/10.1016/j.brat.2022.104032.

Worden, B.L., Genova, M., Tolin, D.F., 2017. Randomized pilot of an anxiety sensitivity-based intervention for individuals in a substance use day program. J. Psychoact. Drugs *49* (4), 333–343. https://doi.org/10.1080/02791072.2017.1329570.

Zvolensky, M.J., Schmidt, N.B., Stewart, S.H., 2003. Panic disorder and smoking. Clin. Psychol. Sci. Pract. *10* (1), 29–51. https://doi.org/10.1093/clipsy.10.1.29.