# CONCURRENT TREATMENTS OF SUBSTANCE USE DISORDERS WITH ANXIETY OR TRAUMA: A COMPREHENSIVE META-ANALYSIS

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ABSTRACT

Among those seeking treatment for a substance use disorder (SUD), the prevalence of a concurrent anxiety disorder or posttraumatic stress disorder (PTSD) is surprisingly high, with some estimates placing the comorbidity rate at 33% to 43%. There is evidence that this comorbidity is associated with greater symptom severity, impairment, and substance use relapse than when the disorders present independently. One of the greatest challenges that clinicians face when presented with a patient with an anxiety disorder/PTSD and SUD is deciding how to approach treatment. Though the prevailing approach has been to treat the disorders sequentially, with the SUD receiving initial attention, there is a movement towards developing integrated or concurrent treatment models. The current meta-analytic study examined integrated or concurrent psychotherapies or pharmacotherapies for SUDs and anxiety disorders or PTSD. A meta-analysis on this topic is particularly important given the generally mixed findings of existing randomized controlled trials in this area of research. Our main question of interest was how integrated/concurrent treatments compared to single-target treatments. In addition, we explored whether there were outcome differences between psychotherapy and pharmacotherapy, between anxiety disorders and PTSD, and differences based on treatment setting (e.g., substance use treatment center versus other settings).

Our findings suggested that integrated or concurrent treatments were superior in reducing anxiety or PTSD symptoms, compared to treatments that only targeted substance use or anxiety/PTSD. The effect, however, was small. There was no evidence that integrated or concurrent treatments improved substance use outcomes in comparison

to stand alone substance use treatment. We also found evidence that treatment studies conducted at substance use inpatient or outpatient programs produced smaller anxiety/PTSD effects. A trend was found suggesting combined psychotherapy-pharmacotherapy interventions may be more effective than psychotherapy alone. No difference was found between treatments targeting PTSD versus anxiety disorders. Implications of our findings are discussed.

This project is dedicated to my parents.

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# CHAPTER 1

# INTRODUCTION

Data from the National Epidemiologic Survey on Alcohol and Related Conditions showed that, among respondents with a 12-month substance use disorder (SUD), nearly 18% also met criteria for at least one independent, non-substance induced anxiety disorder in the same 12-month period (Grant et al., 2004). Among those with at least one current anxiety disorder, about 15% had an SUD in the past 12 months. The numbers are even more striking when we look at those with a SUD who sought treatment. Of those with an alcohol use disorder (AUD) seeking treatment, 33% had a comorbid anxiety disorder, and 43% of those with drug use disorder seeking treatment had a current, independent anxiety disorder (Grant et al., 2004). Data from the National Comorbidity Survey-Replication (NCS-R) are consistent with this picture, showing that lifetime diagnoses of social anxiety disorder (SAD), generalized anxiety disorder (GAD), panic disorder (PD), and agoraphobia were positively associated with all SUDs (Marmorstein, 2012). Odds ratios ranged from 2.67 (GAD and alcohol abuse) to 5.54 (SAD and drug dependence; Marmorstein, 2012).

Research has shown that an anxiety disorder or posttraumatic stress disorder (PTSD) and SUD comorbidity is associated with greater symptom severity, impairment, and relapse than when the disorders present independently (e.g., Bruce et al., 2005; Driessen et al., 2001; Ouimette, Ahrens, Mops, & Finney, 1997). For instance, among a veteran sample, PTSD-SUD patients reported greater alcohol consumption and more

substance use-related problems at intake than SUD patients without comorbidity; PTSD-SUD patients also reported more psychological symptoms than SUD patients with and without other comorbid diagnoses (Ouimette et al., 1997). Comorbidity is also associated with poorer recovery. One 12-year prospective study found that the co-occurrence of a SUD decreased the likelihood of GAD recovery by nearly fivefold and increased the likelihood of GAD recurrence by more than threefold (Bruce et al., 2005). In another study, anxiety comorbidity was associated with a greater rate of alcohol use relapse following completion of an alcohol treatment program—69% reported lapse or relapse compared to 40% of alcoholics without a comorbid diagnosis (Driessen et al., 2001). Compared to SUD only patients and those with other Axis I SUD-comorbidities, concurrent PTSD-SUD has been associated with more substance-use problems, more psychological distress, and less social support at 1-year post-treatment (Ouimette et al., 1997). Compared to SUD-only patients, PTSD-SUD comorbidity was associated with lower employment rates and greater rates of relapse (Ouimette et al., 1997).

**Explanations for the Etiology and Maintenance of SUD Comorbidity**

Researchers have proposed theories that may explain the high rates of co-occurrence of substance use and other Axis I disorders (Allan, 1995; Chilcoat & Breslau, 1998; George, Nutt, Dwyer, & Linnoila, 1990; Hall & Queener, 2007; Khantzian, 1985; Kushner, Abrams, & Borchardt, 2000; Reiss, 1991; Stewart & Kushner, 2001; Stewart & Pihl, 1994). These theories fall into one of three categories: 1) causal models that posit that an anxiety disorder or PTSD promotes the development of an SUD, 2) causal models that posit that an SUD promotes the development of an anxiety disorder or PTSD, or 3)

"third variable" models which posit that a common underlying vulnerability leads to the development of both disorders (Stewart & Conrod, 2008).

One causal model that has received considerable attention is the self-medication hypothesis (e.g., Chilcoat & Breslau, 1998; Khantzian, 1985). According to the self-medication hypothesis, some individuals use drugs or alcohol to cope with psychological distress, leading to the development of a comorbid SUD. In support of this theory is evidence showing that the onset of anxiety or PTSD symptoms typically precedes the onset of problematic substance use. According to data gathered in the National Comorbidity Survey, 79.3 percent of those with anxiety disorder-SUD comorbidity reported that their anxiety difficulties preceded their substance use (Kessler et al., 1996). NCS-R data showed that Americans reported a median age of onset of 11 years for anxiety disorders, compared to 20 years for SUDs (Kessler et al., 2005). One prospective study also showed that individuals with PTSD but no SUD at study baseline were four times more likely than those without PTSD to develop substance abuse or dependence by 5-year follow-up (Chilcoat & Breslau, 1998). A limitation of the self-medication hypothesis is that it fails to take into consideration the neurobiological changes that occur in the individual as a result of chronic substance use. Consequently, the self-medication hypothesis may explain the etiology of SUD for some individuals, but it does not address the maintenance of problematic substance use even when psychological symptoms are reduced.

Another possible causal explanation is that substance use can promote the development of an anxiety disorder or PTSD, sometimes referred to as the susceptibility

hypothesis (Chilcoat & Breslau, 1998). Generally, these theories posit that repeated substance use reduces the threshold for the development of psychological symptoms. It is sometimes described as a "kindling process" in which repeated substance withdrawal leads to a hyper-responsive central nervous system that may be susceptible to heightened panic and anxiety even in periods of sobriety, leading to more substance use to cope with symptoms (e.g., Allan, 1995; George et al., 1990; Kushner, Sher, & Beitman, 1990). Alternatively, chronic substance use may lead to interpersonal and life problems, resulting in anxiety (Cox, Norton, Dorward, & Fergusson, 1989). Chronic substance use may also hinder the development of effective and healthy coping strategies in response to stress, leading to an increased risk for the development of an anxiety disorder (Chilcoat & Breslau, 1998). There is some evidence supporting the idea that substance use can lead to anxiety. For example, among rape victims surveyed in the National Women's Study, a longitudinal telephone survey of American women, lifetime drug abuse did not increase risk of a new assault but did predict the development of PTSD (Acierno, Resnick, Kilpatrick, Saunders, & Best, 2000).

Specific to PTSD is the high risk hypothesis, which posits that substance use, particularly heavy and chronic substance use, may increase exposure to risky situations (e.g., situations involving violence or which increase the probability of an accident) and therefore increase the chance of exposure to trauma (Chilcoat & Breslau, 1998). In support of this hypothesis is evidence from the National Women's Study that drug use increased the risk of physical assault (Acierno et al., 2000).

A third, model posits that a third variable exists that increases the risk of developing anxiety/PTSD and SUDs. For example, results from one twin study suggest that a common genetic basis contributes to the relationship between anxiety and alcohol consumption (Tambs, Harris, & Magnus, 1997). Another potential third variable is anxiety sensitivity, a tendency to fear bodily sensations associated with the experience of anxiety, as these sensations are interpreted to be signs of an impending negative outcome (Reiss, Peterson, Gursky, & McNally, 1986). Anxiety sensitivity is widely studied as a cognitive risk factor for the development of anxiety disorders, but researchers have also examined its relationship to substance use (see review by Stewart & Kushner, 2001). One hypothesis is that anxiety sensitivity functions as a moderator; that is, those with high anxiety sensitivity are more motivated to avoid anxiety sensations, and using substances is one such avoidance strategy (Reiss, 1991). Alternatively, those high in anxiety sensitivity may experience a more robust anxiolytic effect from substance use (Stewart & Pihl, 1994).

A major limitation of the existing literature is that the majority of the theoretical work has focused on comorbid AUDs, and it is unclear whether these models may apply to other substance use disorders. In addition, the models are probably not mutually exclusive or may simply apply to different subsets of the population of individuals with anxiety disorder/PTSD-SUD comorbidity. Undoubtedly, theorists on this topic would agree that this comorbid relationship is very complex, making successful treatment particularly challenging.

**Issues Regarding Treatment**

The 2002 National Survey on Drug Use and Health, a national household survey of substance use and mental health, found that only 12% of Americans with co-occurring mental health and substance use difficulties received treatment for both (J. Epstein, Barker, Vorburger, & Murtha, 2004). However, this rate could not be attributed to lower prevalence of treatment-seeking among substance users, as rates of mental health treatment-seeking were similar among adults with a psychiatric disorder and substance use (46%) and adults with a psychiatric disorder without substance use (49%). Furthermore, those with a comorbid disorder were more likely to seek specialty substance use treatment than adults who only had an SUD. In a small survey of patients with PTSD, those with a comorbid SUD saw the two disorders as functionally related and reported interest in receiving concurrent treatment (P. J. Brown, Stout, & Gannon-Rowley, 1998). Thus, the low rates of concurrent treatment may reflect a lack of availability of such treatments, rather than a lack of interest.

One of the greatest challenges that clinicians face when presented with a patient with an anxiety disorder/PTSD and SUD is deciding how to approach the order of treatment of the two sets of concerns. There are three main categories of treatment service models: sequential, parallel, and integrated (Kavanagh & Connolly, 2009). Historically, many treatment centers have applied the sequential model for comorbid cases, in which a patient undergoes treatment focused on one disorder before being referred to another treatment center to address the comorbid disorder (Donald, Dower, & Kavanagh, 2005). Kavanagh and Connolly (2009) make the case that the sequential

model is most effective in cases in which there is a clear primary-secondary diagnostic picture and in which treatment of the primary disorder may significantly reduce the need for additional treatment of the secondary disorder. Typically in comorbid SUD and anxiety disorder/PTSD, the substance use is treated first. Back, Waldrop, and Brady (2009) surveyed clinicians about their attitudes about PTSD/SUD treatment and found that a primary concern among clinicians was that exposing patients to traumatic memories before treating the patients' SUD would exacerbate their substance use or result in a relapse.

A limitation of this approach is that it could fail to adequately address the complexity of a patient's difficulties, particularly the inter-relationship between psychological symptoms and substance use. Another approach is the parallel treatment model, in which a patient receives separate treatment from two different treatment teams, one for each disorder or symptom complex. Without careful coordination between treatment teams, however, the parallel treatment approach could suffer from the same limitation of treating each disorder as discrete and separate. At worst, the two treatments could conflict, particularly if the two treatment teams are operating under different policies, protocols, and theoretical approaches (Donald et al., 2005).

A third model is the integrated approach, in which a patient receives treatment addressing both disorders by the same treatment provider/team. Integrated treatment does not necessarily mean simultaneous treatment of both disorders; rather, it entails tailoring of treatment content to attend to the patient's needs, which typically change over the course of treatment (Kavanagh & Connolly, 2009). However, integrated treatments may

be difficult to adapt in most treatment facilities, as they do require treatment teams to have the knowledge and skill to assess and treat the comorbid disorders (Randall, Book, Carrigan, & Thomas, 2008).

Little research has been conducted that has systematically compared the different treatment service models. In their review of randomized clinical trials (RCTs) of integrated treatments targeting mental health and substance use disorders, Donald and colleagues (2005) identified only one study that compared a parallel treatment model to an integrated model, results of which suggested little difference in mental health and substance use outcomes but greater treatment participation among patients in the integrated treatment group (Hellerstein, Rosenthal, & Miner, 1995). Donald and colleagues speculate that treatment retention could lead to better long-term outcomes for the integrated treatment group, although they caution that more research is needed.

With all approaches, the general consensus among providers is that acute substance use should be addressed before other treatment is introduced (Goldstein, Diamantouros, Schaffer, & Naranjo, 2006). However, there is no consensus on the ideal amount of time after withdrawal before anxiety or PTSD treatment should commence.

**Psychotherapies**

**Panic Disorder (PD).** There have been a handful of treatment studies conducted targeting PD and AUD. A pilot study comparing a primarily cognitive therapy to a primarily behavioral therapy for PD and alcohol dependence found that patients in both groups had similarly improved anxiety and alcohol outcomes at the end of treatment, including a reduction in the number of panic attacks (Toneatto, 2005). Bowen, D'Arcy,

Keegan, and Senthilselvan (2000) randomly assigned 231 patients admitted to a residential alcohol treatment program to receive treatment as usual (TAU), or TAU augmented by 12 hours of group CBT for anxiety. Both groups showed PD symptom and alcohol use improvement, but they did not differ from one another, contrary to study hypotheses. In a pilot trial conducted in a residential alcohol program, Kushner and colleagues (2006) compared 31 patients enrolled in an integrated CBT treatment developed for comorbid anxiety and alcohol use disorders to 17 patients who received TAU. There was some evidence for the benefit of the added, integrated anxiety intervention, as the group who received CBT for anxiety had a lower proportion of PD diagnoses at follow up (16% compared to 41%), as well as a lower proportion of alcohol dependence diagnoses (10% compared to 35%).

**Generalized Anxiety Disorder (GAD).** To our knowledge, there have been no published studies of psychotherapies for comorbid GAD and SUD.

**Social Anxiety Disorder (SAD).** The core feature of SAD is a fear of being judged in social situations, which can pose a particular barrier for socially anxious individuals in their willingness to engage in substance abuse treatment. In a study of patients in intensive outpatient substance use programs, social anxiety interfered with patients' ability to talk to a therapist, share in group therapy, attend 12-step meetings, and ask for a sponsor (Book, Thomas, Dempsey, Randall, & Randall, 2009). This barrier highlights the need for treatments that address both SAD and SUDs.

Three studies have examined a psychotherapy for SAD and comorbid AUD. One case report showed that the integration of motivational enhancement therapy for alcohol

use problems with individual CBT for SAD appeared to help the patient, who no longer met criteria for either disorder at 6-month follow-up (Buckner, Ledley, Heimberg, & Schmidt, 2008). In an uncontrolled pilot trial, Courbasson and Nishikawa (2010) tested a cognitive behavioral group therapy for SAD (Heimberg & Becker, 2002) that was modified to include content explicitly addressing the link between anxiety and substance use. Results showed significant reduction in anxiety symptoms and negative affect. The authors did not report measuring substance use outcomes, and although they recruited patients with SAD and any SUD comorbidity, they only measured alcohol expectancies; unrealistic alcohol expectancies were unchanged following treatment.

Randall, Thomas, and Thevos (2001) conducted a trial in which socially anxious individuals seeking alcohol use treatment were randomized to receive CBT for alcohol use and social anxiety or CBT for alcohol use only. In the dual-focus treatment group, both disorders were treated individually by the same provider for 12 weeks, although the treatments were presented as distinct; therefore, the researchers considered this a modified parallel treatment approach administered by the same provider and not a true integrated therapy. Intent-to-treat analyses showed that both groups improved on social anxiety outcomes and did not differ from one another. Although both groups also showed improved outcomes on alcohol use from baseline, the dual-focus treatment group showed poorer outcomes on three of the four alcohol use indices (percent days abstinent, percent days heavy drinking, total number of drinks consumed, but not drinks per drinking day). The authors offered several possible explanations for these unexpected alcohol use findings (Randall et al., 2008; Randall, Thomas, et al., 2001). They speculated that the

social anxiety treatment may have resulted in patients avoiding fewer social situations, and they were therefore exposed to more drinking situations. Alternatively, the exposures to social situations may have led to more drinking to cope with the increased anxiety. However, they did not explicitly monitor alcohol use during exposures nor did they explicitly encourage their patients to practice abstinence while engaging in exposures (Randall et al., 2008). This demonstrates a limitation of a non-integrated treatment approach, which fails to address the dynamic relationship between the comorbid disorders.

**Posttraumatic Stress Disorder (PTSD).** The PTSD-SUD treatment literature is relatively robust compared to the anxiety-SUD research. There are a number of integrated treatments for PTSD and SUD that have been developed and are undergoing study. A comprehensive review of all such studies is beyond the scope of this paper (see review by Riggs & Foa, 2008), and as such we will focus our review on studies with more rigorous research designs.

Seeking Safety is a manualized psychotherapy designed to treat patients with comorbid PTSD and SUD (Najavits, 2002). The therapy is aimed at helping patients attain safety, increase self-care, develop better coping strategies, and foster better relationships. Seeking Safety is influenced by cognitive-behavioral, interpersonal, and values-based approaches, and can be administered in an individual or group format. Notably, Seeking Safety purposely omits exposure to traumatic memories as part of therapy, as the focus is to teach patients to better cope with PTSD symptoms and establish safety and control over their current lives.

Large-scale trials of Seeking Safety have produced mixed results. In a study of 107 women from urban, low-income backgrounds, participants receiving the Seeking Safety protocol showed greater improvements in substance use and PTSD at 9-month follow-up than participants in community care, although they did no better than participants receiving a relapse prevention intervention that focused on addiction (Hien, Cohen, Miele, Litt, & Capstick, 2004). In another multisite, controlled trial of homeless female veterans, those enrolled in Seeking Safety showed greater reductions in PTSD and general psychiatric symptoms, as well as better outcomes in employment and social support than homeless female veterans not enrolled in Seeking Safety (Desai, Harpaz-Rotem, Najavits, & Rosenheck, 2008). However, they were also more likely to report having used drugs at follow-up, a result the study authors could not explain. The authors did note that there were differences in two of the measured baseline characteristics between the treatment and control groups: the control group was younger and more likely to be employed. It is possible that these differences—or some other, unmeasured characteristics—were related to why the groups showed different drug use outcomes at follow-up.

In a randomized, controlled pilot study of incarcerated women, TAU augmented by Seeking Safety was compared to TAU alone (Zlotnick, Johnson, & Najavits, 2009). TAU consisted of 30 hours per week of prison-based individual and group substance abuse treatment. Unlike results of previous Seeking Safety studies, no differences were found between TAU+Seeking Safety and TAU alone on PTSD and SUD outcomes, with both groups showing significant improvement. Seeking Safety did show added benefit on

measures of general psychopathology. A large, multisite, RCT of 353 women also found no difference between Seeking Safety and an active health education comparison group, although both groups showed clinically significant reductions in PTSD symptoms (Hien et al., 2009). Neither condition resulted in significant change in substance use. In contrast, an RCT of male veterans showed that the addition of Seeking Safety to substance use TAU resulted in better drug use outcomes, but there was no difference in alcohol use or PTSD symptoms (Boden et al., 2011).

Some evidence suggests that augmenting substance use programs with trauma-focused interventions may be beneficial. van Dam, Ehring, Vedel, and Emmelkamp (2013) conducted an RCT in which a trauma-focused writing therapy was added to an intensive cognitive behavioral substance use treatment. The augmented therapy resulted in greater PTSD remission rates, while showing similar SUD improvement to substance use treatment alone. Mills and colleagues (2012) reported similar results in their RCT, in which patients receiving exposure-based treatment for PTSD in addition to substance use treatment showed greater reduction in PTSD symptom severity than patients who did not receive the augmented therapy. However, substance use did not differ between groups. This pattern of findings was also found in another RCT of an integrated CBT for PTSD-SUD (McGovern, Lambert-Harris, Alterman, Xie, & Meier, 2011). Sannibale and colleagues (2013) also found that an integrated CBT for PTSD-AUD produced greater improvement in PTSD symptoms than a CBT for AUD treatment combined with supportive counseling. However, the AUD+supportive counseling group exhibited greater improvements in alcohol use outcomes.

## Pharmacotherapies

Goldstein, Diamantorous, Schaffer, and Naranjo (2006) describe three general stages of treatment in pharmacotherapies for AUDs, which could be applied to SUDs more widely. They state that these principles apply to the treatment of patients with or without psychiatric comorbidities. Treatment begins with detoxification, which is followed by pharmacological management of acute withdrawal symptoms. Then, through a combination of medications and psychotherapy, patients work towards abstinence or harm reduction. Ideal medications for treating comorbid SUDs-psychiatric disorders: 1) relieve psychiatric symptoms, 2) decrease substance use by relieving withdrawal symptoms or reducing cravings, 3) aid in relapse prevention, 4) have low abuse potential, 5) have infrequent dose administration, 6) are well tolerated, and 7) do not enhance the effects of the patient's substance of choice (Kissin, 1975; Kosten & Kosten, 2004).

**Panic Disorder (PD).** There have been no large-scale studies of pharmacological treatments for comorbid panic-SUD. Brady, Sonne, and Lydiard (1994) reported on two cases in which valproate, an anti-convulsant and mood stabilizer, was used to treat patients with comorbid PD and AUD with apparent success in reducing panic attacks and alcohol use. More research is needed.

**Generalized Anxiety Disorder (GAD).** Benzodiazepines, which are gamma-aminobutyric acid agonists, have been shown to reduce symptoms of anxiety and alcohol withdrawal. However, their use for treating comorbid anxiety disorder/SUD populations has been avoided due to their potential for abuse and dependence (E. J. Marshall, 2008). Buspirone, a partial serotonin agonist anxiolytic, is the most studied medication for

GAD-AUD comorbidity. Alcoholism and anxiety disorders have both been associated with abnormalities in serotonin neurotransmission (Kranzler et al., 1994), and serotonin agonists like buspirone are therefore hypothesized to be effective in treating these disorders when comorbid. Furthermore, buspirone has been shown to have little or no potential for abuse (Griffith, Jasinski, Casten, & McKinney, 1986) and minimal interaction effects with alcohol (Mattila, Aranko, & Seppala, 1982).

Results of studies of the efficacy of buspirone in treating GAD-AUD have been mixed. In one double-blind, controlled trial, alcoholics treated with buspirone showed greater reduction in craving for alcohol, although there was no difference between the buspirone-treated group and the placebo group in the amount of alcohol consumed (Bruno, 1989). Although the study did not look specifically at GAD-AUD comorbidity, buspirone was associated with a greater decrease in anxiety symptoms (Bruno, 1989). Tollefson, Montague-Clouse, and Tollefson (1992) did look at patients with concurrent GAD-AUD and found buspirone to be superior to placebo for reducing anxiety and alcohol craving, and it resulted in greater global improvement. Kranzler and colleagues (1994) reported an interaction of anxiety severity and treatment group; among individuals with high levels of baseline anxiety, buspirone showed a significant anxiolytic effect. The buspirone group also had significantly less treatment attrition (84% completed versus 53% of placebo-treated participants) and reported significantly fewer drinking days at the 6-month follow-up. In contrast, a study of male veterans with GAD-AUD failed to show a significant difference between buspirone and placebo groups in alcohol or anxiety outcomes (Malcolm et al., 1992). One double-blind, placebo-controlled pilot trial

investigated the effectiveness of buspirone for treating anxiety in a methadone-maintenance sample, the majority of whom had GAD (McRae, Sonne, Brady, Durkalski, & Palesch, 2004). Buspirone was not found to reduce anxiety, but the authors noted that a *post hoc* power analysis suggested that the sample size was too small to detect an effect.

**Social Anxiety Disorder (SAD).** Paroxetine, a selective serotonin reuptake inhibitor (SSRI), has been shown to be effective in the treatment of SAD (Stein et al., 1998) and is approved by the U.S. Food and Drug Administration for the treatment of SAD. There is evidence that paroxetine is similarly effective in treating SAD when an AUD is present. In an 8-week, randomized, placebo-controlled pilot trial, patients with SAD and an AUD (primarily alcohol dependence) treated with paroxetine showed greater improvement in SAD symptoms compared to those treated with placebo (Randall, Johnson, et al., 2001). However, the groups showed no difference in quantity and frequency of alcohol use, although clinician ratings of alcohol use indicated improvement. A larger follow-up, randomized, double-blind study extended the study treatment period to 16 weeks and found that paroxetine resulted in improvements in SAD similar in magnitude to medication trials of socially anxious patients without an AUD (Book, Thomas, Randall, & Randall, 2008), but again there was no effect on frequency and quantity of alcohol consumed (Thomas, Randall, Book, & Randall, 2008). Patients treated with paroxetine, however, reported that they relied less on alcohol to cope with social situations at post-treatment (Thomas et al., 2008). A subsequent study found that augmenting paroxetine with a brief alcohol intervention did not decrease alcohol use, underscoring the difficulty of treating this comorbid presentation (Book et al., 2013).

**Posttraumatic Stress Disorder (PTSD).** Sertraline, an SSRI, has been found to be effective in the treatment of PTSD (e.g., Brady et al., 2000) and has shown to modestly reduce alcohol use among alcoholics (e.g., Pettinati et al., 2001). Unsurprisingly, sertraline has been a target of investigation for the treatment of PTSD-AUD comorbidity, although the results have been mixed. A preliminary, open treatment study showed PTSD symptom reduction and more days of abstinence and fewer drinks per day at post-treatment (Brady, Sonne, & Roberts, 1995). However, in a subsequent, large, placebo-controlled study, sertraline was not significantly different from placebo in reducing alcohol consumption, although both groups showed significant alcohol use reduction (Brady et al., 2005). There was, however, a trend for greater PTSD symptom reduction in the sertraline group. Looking more closely at subgroups, the data revealed that patients with less severe alcohol dependence and early-onset PTSD showed greater reduction in alcohol use with sertraline, whereas those with more severe alcohol dependence and later-onset PTSD demonstrated greater alcohol reduction with placebo. The authors speculate that for those with less severe alcohol use and early-onset PTSD, PTSD is the primary diagnosis; their responsiveness to sertraline might be evidence in support of the self-medication hypothesis, such that reduction in PTSD symptomology also results in a reduction in the use of alcohol to cope. However, they note that the subgroups were identified by *post hoc* cluster analysis and that the subgroups were unequal in size, and they caution against over-interpretation of these results.

One study examined the effectiveness of combined medication treatments for PTSD and alcohol dependence among a predominantly veteran sample (Petrakis et al.,

2012). They compared paroxetine to desipramine, a tricyclic antidepressant, in combination with naltrexone, an opioid antagonist typically used to treat alcoholism. Patients were assigned to one of four groups for the 12-week trial: 1) paroxetine with naltrexone, 2) paroxetine with placebo, 3) desipramine with naltrexone, or 4) desipramine with placebo. Desipramine was found to be comparable to paroxetine in reducing PTSD symptoms and superior in reducing heavy drinking days and drinks per drinking day. No main effect of naltrexone was found, and the combination of naltrexone with paroxetine or desipramine did not appear to be more effective than paroxetine or desipramine alone.

In a recent single-blind, randomized trial, Foa and colleagues (2013) paired naltrexone with exposure therapy to treat patients with comorbid PTSD-AUD. Patients were randomly assigned to 1) prolonged exposure with naltrexone, 2) prolonged exposure with pill placebo, 3) supportive counseling with naltrexone, and 4) supportive counseling with pill placebo. Patients in all four groups showed improved drinking and PTSD outcomes, but patients who received naltrexone had a lower percentage of days drinking than those who received placebo. Contrary to hypotheses, patients who received prolonged exposure did not show greater PTSD symptom improvement than those receiving supportive therapy.

Monnelly, Ciraula, Knapp, LoCastro, and Sepulveda (2004) examined quetiapine, an atypical antipsychotic, as a treatment for alcohol dependence in a retrospective chart review study of male veterans enrolled in a substance abuse treatment unit. The study did not focus on PTSD comorbidity, but the researchers reported that 90 percent of patients had a diagnosis of PTSD. Compared to patients with alcohol dependence not receiving

quetiapine, those treated with the medication had fewer hospitalizations and greater number of days abstinent over the course of a year.

**Transdiagnostic Studies**

Ciraulo and colleagues (2013) recently examined the efficacy of a combined medication and CBT treatment for patients with comorbid anxiety disorders and AUD. Patients with PD, SAD, or GAD and an AUD who were seeking treatment at an outpatient anxiety clinic were randomly assigned to receive: 1) venlafaxine, a serotonin-norepinephrine reuptake inhibitor, and progressive muscle relaxation (PMR), 2) venlafaxine and CBT, 3) placebo and CBT, or 4) placebo and PMR. Contrary to hypotheses, the combined venlafaxine-CBT group did not produce outcomes superior to the placebo-PMR group. The placebo-CBT group was the only one to show greater alcohol use reductions than placebo-PMR; at post-treatment, the proportion of individuals showing more than a 50% reduction in drinking compared to baseline was significantly higher with placebo-CBT (90%) than placebo-PMR (53%). No group differences were found in anxiety outcomes, and interestingly, the venlafaxine-CBT group was the only one that did not show evidence of decreased anxiety. The authors stated that venlafaxine did not enhance the effects of CBT but offered no explanation as to why the placebo-CBT group showed decreased anxiety whereas the venlafaxine-CBT group did not. It is possible that venlafaxine attenuated the effects of CBT. Helping patients learn to cope with heightened anxiety is central to CBT approaches for treating anxiety disorders (e.g., Foa, 2011; Heimberg, 2002), including the Unified Protocol for the Transdiagnostic Treatment of Emotional Disorders used in this study (Barlow, Allen, & Choate, 2004).

Actual reduction in anxiety through medication, and/or patients' attribution that anxiety was reduced by medication, may have rendered the exposures that are a part of CBT less "potent" or resulted in patients being less invested in practicing CBT skills (for further discussion of concurrent pharmacological treatments with CBT for anxiety, see Heimberg, 2002; Pontoski & Heimberg, 2010).

Kushner and colleagues (2013) tested their integrated treatment for anxiety-AUD comorbidity in a residential alcohol treatment program. The authors describe their integrated therapy as a hybrid CBT treatment—based on CBT treatments for anxiety, it also included parallel content aimed at disrupting psychological processes linking anxiety feelings to alcohol use (Kushner et al., 2013). Three hundred forty-four patients with PD, SAD, or GAD receiving alcohol TAU were randomized to also receive CBT or PMR. Both groups showed a significant decrease in anxiety, but those receiving CBT showed better alcohol use outcomes. Although this treatment seems promising, more research is needed.

In their 32-week trial, Schadé and colleagues (2005) randomly assigned patients with either agoraphobia or SAD and alcohol dependence to a relapse prevention program, with or without additional anxiety treatment. Anxiety treatment consisted of CBT, with the option to receive an SSRI. As expected, additional anxiety therapy reduced anxiety symptoms. No group differences were found on alcohol use relapse rates.

**Previous Systematic Reviews**

There have been a handful of systematic reviews on the subject of integrated and parallel interventions for mental disorders and substance use disorders. They are reviewed below.

Hobbs, Kushner, Lee, Reardon, and Maurer (2011) included 15 RCTs in their analysis of supplemental treatments for depressive or anxiety disorders in adult patients treated for alcohol dependence. Six of the 15 studies tested treatments of co-occurring anxiety disorders, including GAD, PD, and SAD. Of the six, two were studies of CBT, and four were studies of pharmacotherapies. Anxiety treatment studies produced a medium pooled effect size (Cohen's $d = 0.52$) for anxiety symptom outcomes and a small effect size ($d = 0.27$) for alcohol use outcomes.

Baker and colleagues (2012) focused only on RCTs of psychological interventions that targeted co-occurring alcohol misuse and mood or anxiety disorders. Their systematic review included eight studies in total, three of which were focused on anxiety disorders (SAD, PD/agoraphobia). Anxiety disorder-AUD studies showed standardized mean differences in the expected direction, with a decrease in days of heavy alcohol use and increase in the number of days abstinent, as well as a decrease in anxiety scores. The authors did not calculate pooled effect sizes, arguing that this procedure would be inappropriate given the heterogeneity of clinical characteristics of participants, treatments, and measures.

Torchalla, Nosen, Rostam, and Allen (2012) conducted a meta-analysis of studies of integrated psychological treatments for individuals with SUDs and previous trauma

experiences. They included 17 studies in their analyses but identified only one as an RCT; they chose not to consider a number of the other seven controlled trials as RCTs due to insufficient descriptions of randomization procedures in the source articles. Integrated treatments were shown to reduce PTSD symptoms and alcohol use in within-group comparisons but failed to show any difference from nonintegrated treatments. The authors noted that the failure to detect between-group differences may have been due to the small number of studies examined that had stringent control groups and because of the generally small sample sizes across studies.

*Current Study*

Since the preparation and publication of even the most recent meta-analysis (Torchalla et al., 2012), a number of RCTs have been published in this area (e.g., Foa et al., 2013; Kushner et al., 2013; McGovern et al., 2011; Mills et al., 2012). This creates an opportunity to expand upon previous meta-analyses, which included few RCTs and did not include PTSD and anxiety disorders in the same meta-analytic study. There is certainly a lot of overlap between these diagnostic categories, recognized previously when PTSD was classified as an anxiety disorder. Furthermore, only Hobbs and colleagues (2011) included pharmacotherapies in their study. The current study examined integrated or parallel psychotherapies or pharmacotherapies for SUDs and anxiety disorders or PTSD. A meta-analysis on this topic is particularly important given the generally mixed findings (reviewed above) of existing RCTs.

In addition to only including RCTs, we placed other restrictions on the inclusion criteria that were not employed in the previous systematic reviews. For one, we required

that studies use a diagnostic interview to establish one of the diagnoses and required that patients meet criteria for an anxiety disorder/PTSD and a SUD (or be enrolled in a substance use program). The use of a diagnostic interview is important to improve diagnostic accuracy. As Myrick and Brady (2003) point out, the distinction between anxiety symptoms and substance-induced symptoms can be hard to make, especially during times of intoxication or withdrawal. Secondly, we looked specifically at experimental treatments that included components that targeted both anxiety disorders/PTSD and substance use disorders. This is because our main question of interest is how integrated/concurrent treatments compared to single-target treatments, a question that differed slightly from the ones posed in Hobbs et al. (2011) and Baker et al. (2012), who included studies with a different types of comparison groups (e.g., placebo, or two different integrated treatments groups compared to one another without a third, single-target control). Lastly, we explored whether there were outcome differences between psychotherapy and pharmacotherapy, between anxiety disorders and PTSD, and differences based on treatment setting (e.g., substance use treatment center versus other settings).

# CHAPTER 2

# METHOD

## Study Eligibility Criteria

**(a) Distinguishing features**. Eligible studies involved the use of interventions to reduce anxiety or PTSD symptoms and substance use. Interventions included psychotherapy, pharmacotherapy, or psychotherapy combined with pharmacotherapy, and were compared to interventions that targeted only anxiety/PTSD or only substance use.

**(b) Research respondents**. Eligible studies involved adults (age 18 or older) as treatment and comparison participants. Studies were included if participants had a current *Diagnostic and Statistical Manual of Mental Disorders* (DSM; edition III, III-R, or IV; American Psychiatric Association [APA], 1980, 1987, 1994) diagnosis of 1) an anxiety disorder (PD with or without agoraphobia, GAD, or SAD) or PTSD and a current diagnosis of an SUD (substance dependence or substance abuse). At least one of the diagnoses must have been made through a structured or semi-structured interview. We made an exception for some studies in which participants were recruited from substance use programs; in such cases, patients were assumed to meet criteria for an SUD.

Studies that enrolled a portion of participants without a comorbid diagnosis were included (e.g., some participants were diagnosed with a SUD but exhibited subthreshold anxiety symptoms, or some participants were diagnosed with an anxiety disorder but exhibited subthreshold SUD symptoms). Research shows that even individuals with subthreshold symptoms of mental disorder or substance use difficulties demonstrate

significant impairment, greater comorbidity, suicidal ideation (e.g., R. D. Marshall et al., 2001) and higher likelihood of developing the full disorder compared to individuals with no symptoms (e.g., McBride & Adamson, 2010).

**(c) Key variables**. Studies reported at least one quantitative outcome measure of anxiety or PTSD symptoms and at least one quantitative outcome measure of frequency or amount of substance use. Only studies from which an effect size could be computed were eligible for inclusion.

(**d) Research methods**. Studies used randomized controlled trial design. The control condition for present purposes could be "treatment as usual" or any other intervention that targeted only the anxiety disorder/PTSD or substance use disorder, but not both. Placebo or delayed treatment controls were not considered.

**(e) Cultural and linguistic range.** Studies were reported in English.

**(f) Time frame**. Eligibility was not restricted by publication date.

**(g) Publication types**. Published and unpublished studies were eligible, including those appearing in peer-reviewed journals, non-peer-reviewed journals, dissertations, government reports, technical reports, etc. Re-analyses, secondary analyses, and subsample analyses of the original data were excluded.

Studies had to provide sufficient information to allow the calculation or estimation of effect sizes, such as the mean, standard deviation, *t* or *F* values, change scores, frequencies, and/or probability levels. If this information was not given, we attempted to contact the authors. Failing in that endeavor, those studies were excluded.

**Search Strategy**

An extensive literature search was conducted through PsycINFO and MEDLINE; the search was not restricted by publication date. We searched for the following terms in any field, using a combination of three sets of general identifier types: (1) anxiety disorder or PTSD (e.g., *anxiety, panic, agoraphobia, trauma, PTSD, posttraumatic stress disorder);* (2) drug or alcohol use (*e.g., addiction, substance use, substance abuse, substance dependence, alcohol, alcohol abuse, alcohol dependence, stimulant, amphetamine, cocaine, opioid, opiate, heroin, marijuana, cannabis)*; and (3) treatment (e.g., *treatment, therapy, intervention, medication, drugs)*. The search of electronic databases yielded more than 25,000 citations; we thus narrowed the search by limiting results to articles labeled "treatment outcome/clinical trial," which resulted in almost 400 articles. In addition to the search in electronic databases, we examined the reference lists of all the articles we included based on our searches, as well as the reference lists of literature reviews and chapters. To reduce the file-drawer effect and to inquire about any articles "in press," we contacted researchers who were authors of at least 3 reports relevant to the meta-analysis topic and asked if they knew of additional studies or unpublished data. Researchers who cited relevant unpublished studies were also contacted and requested to provide unpublished manuscripts. The most recent full search was completed in May 2014.

Figure 1 provides a detailed description of the study selection process. In total, 13 studies were included in the current meta-analysis, and all were published, peer-reviewed journal articles.

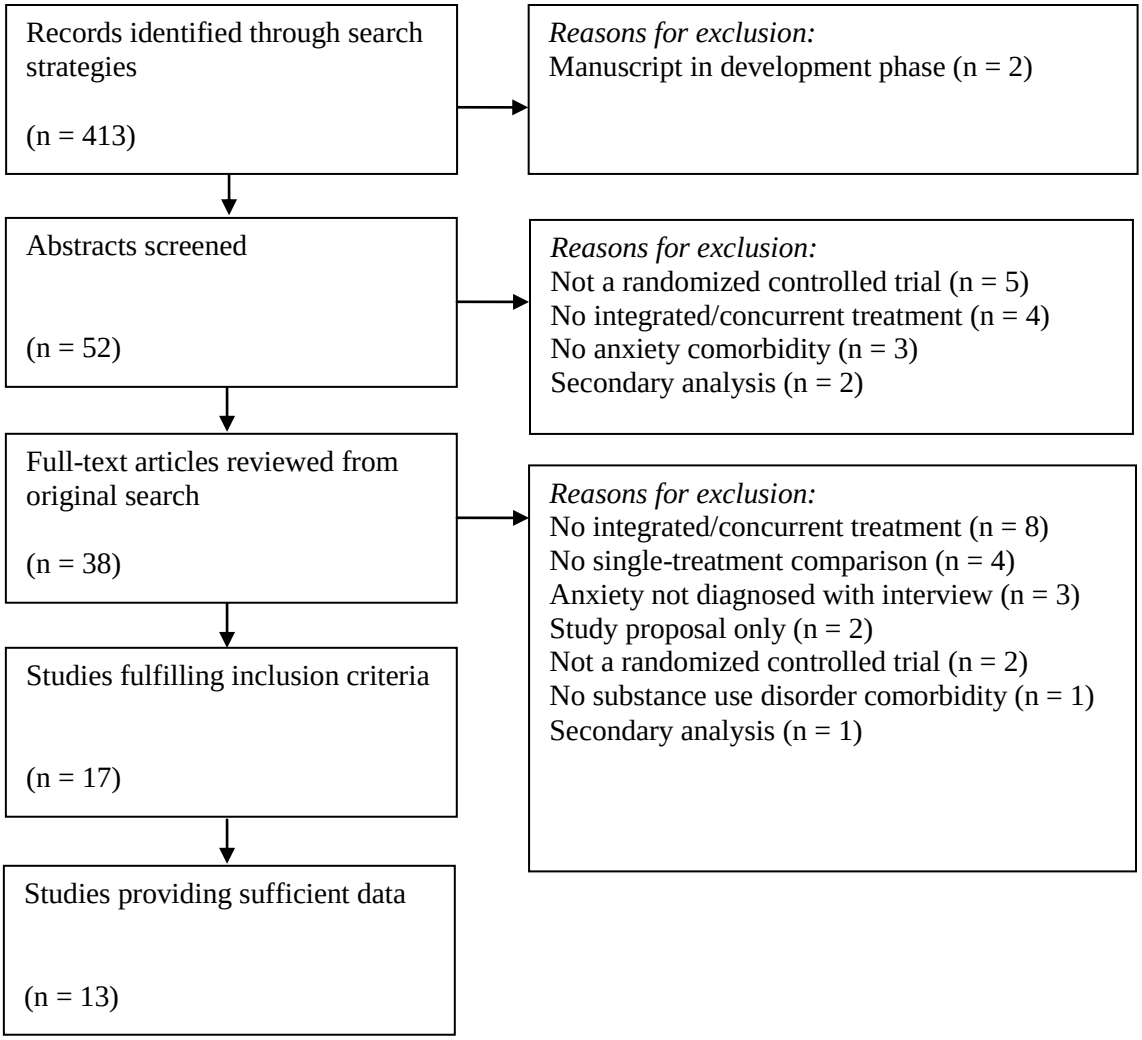


Figure 1. *Flow chart of study selection.*

**Coding of Variables**

Studies were coded for methodological, clinical, and other variables (see Appendix for the coding manual). Variables included participant demographic information such as mean age, gender distribution, and ethnicity/race. Clinical characteristics included participant diagnoses, diagnostic interview used in the study, and the version of the DSM on which diagnoses were based. We also coded the type of clinic in which the study took place (e.g., university, Veterans' Affairs hospital, private community), location where the study took place, and type of publication in which the study appeared (e.g., peer-reviewed journal in clinical psychology or cognitive behavioral therapy, peer-reviewed journal in psychiatry, other peer-reviewed journal, book chapter, dissertation, etc.). We also coded methodological variables including type of control condition, specific drug used (e.g., paroxetine), drug class (e.g., SSRIs, benzodiazepines, anticonvulsants, other), drug dosage, type of psychotherapy, length of total treatment, and number of sessions. A number of these variables were coded and the data used in the analyses. Other variables, such as treatment weeks, study medication used, and age of participants, were coded for the purpose of characterizing the studies included in our meta-analysis and/or the participants enrolled in the studies.

Coding was conducted by the primary investigator (PI) and by a research assistant. In the first phase of training, the PI and research assistant coded a selection of articles related to the general topic of the meta-analysis, but which were not included in the meta-analysis (i.e., studies of RCTs of depression and AUD). Inter-rater agreement was informally assessed after this phase, disagreements discussed and adjustments to the

coding manual were made as needed. In the next phase, a selection of three representative articles was chosen from the pool of articles eligible for inclusion in the meta-analysis. In this pilot phase, these articles were coded independently by the PI and the research assistant. Reliability was assessed, disagreements were discussed, and further adjustments to the coding manual were made as needed. Disagreements were discussed with another expert to aid resolution. Finally, coding was conducted independently for the entire sample of articles. Kappas ranged from .22 to 1.00, with 56% of variables having excellent inter-rater reliability (i.e., κ greater than .75) and 35% falling in the fair to good range (i.e., κ between .40 and .75). Three of the four items that had poor reliability (κ = .30 - .39) involved the coding of dropout from treatment, which was influenced by the heterogeneous definitions of "treatment completer" among the studies. The data regarding dropout, reported below, was recoded by the primary researcher and specifies how completion was defined by the researchers. Reliability was also low (κ = .22) for the item regarding treatment setting, partly because this information was not always explicitly reported in our sample of studies, thus requiring more subjective judgment in coding this item. (See Results below for more information on how we ultimately coded this item for the purpose of subgroup analysis.)

The primary investigator coded and processed data for effect size calculations. The coding was then checked by a doctoral-level clinical psychologist, who also double-checked the calculations of data that were entered into the meta-analysis statistical software.

**Diagnostic Interviews and Outcome Measures**

Below are descriptions of commonly-used diagnostic interviews and measures used in anxiety, PTSD, or SUD research, and which were used in the studies included in this meta-analysis.

**Diagnostic interviews.**

*Clinician-Administered PTSD Scale* (CAPS). The CAPS (Blake et al., 1995) is considered the gold-standard measure in PTSD assessment, used in more than 200 published studies (Weathers, Keane, & Davidson, 2001). The 30-item clinician-administered structured interview was originally developed to correspond to DSM-III-R (APA, 1987) criteria, but it was later revised to correspond to DSM-IV (APA, 1994) Criteria A through F. The CAPS can be used as a diagnostic tool for current, past or lifetime PTSD, as well as a measure of PTSD symptom severity. For individual symptoms, frequency and intensity are rated on separate five-point (0-4) scales and can be summed to create a 0-8 severity score. A total score for the 17 core symptom items can also be derived as an indicator of symptom severity, with a 15-point change in this score interpreted as clinically significant (Weathers et al., 2001). Weathers and colleagues (2001) reviewed several psychometric studies and concluded that the CAPS consistently showed excellent inter-rater reliability (coefficients consistently at the .90 level and above), high diagnostic agreement, high levels of internal consistency (alphas typically in the .80 -.90 range), and good convergent validity (correlations typically .70 and above) across clinical research settings and trauma populations.

*Composite International Diagnostic Interview* (CIDI). The CIDI (World Health Organization, 1990) is a fully structured diagnostic interview of psychiatric disorders

based on the criteria of the International Classification of Diseases (ICD) and of the DSM and designed so that it may be administered by trained lay persons. It was first published in 1990 and has been subsequently updated to reflect the changes in the ICD and DSM. According to review of reliability and validity studies (Wittchen, 1994), the CIDI demonstrated adequate test-retest reliability of DSM-III-R diagnoses (κ = .52 - .84), high inter-rater reliability (the vast majority of κs in the .80-.99 range), and good convergent validity (κ = .73 - .83). For DSM-IV diagnoses, concordance between the CIDI and the Structured Clinical Interview for DSM (SCID) was acceptable for diagnosis of any anxiety disorder in the past 12 months (area under the curve = .88, κ = .72; Haro et al., 2006) .

*Diagnostic Interview Schedule* (DIS). The DIS is a fully structured diagnostic interview, first developed to reflect the diagnostic criteria of the DSM-III (APA, 1980), but which has been updated in accordance with subsequent versions of the DSM. The most recent version, based on DSM-IV (APA, 1994), was tested among individuals with SUDs (Horton, Compton, & Cottler, 1998) and found to have good to excellent test-retest reliability for the diagnoses of SUDs (κ = .53 - .87) and acceptable values for most anxiety disorders and PTSD (κ = .41 - .52), though poor reliability for GAD (κ = .35) and specific phobia (κ = .25).

*Post Traumatic Stress Disorder Symptom Scale* (PSS). The PSS (Foa, Riggs, Dancu, & Rothbaum, 1993) is a 17-item assessment instrument that is available in a clinician-administered semi-structured interview version (PSS-I) and as a self-report measure (PSS-SR). The PSS was originally developed to correspond to DSM-III-R

(APA, 1987) criteria, but more recent versions have been adapted to DSM-IV (APA, 1994) symptom criteria for PTSD. It assesses the three clusters of PTSD symptoms: re-experiencing (five items), avoidance (7 items), and arousal (five items). For the PSS-I, the interviewer rates severity within the past 2 weeks on each item, using a 4-point scale (0 = *not at all/0 times a week;* 3 = *very much/5 or more times a week*). A score for overall severity can range from 0 to 51, with higher scores indicating more severe PTSD symptomatology. The scoring for both versions is identical.

Researchers recently examined the reliability and validity of the most recent version of the PSS-I using a sample of participants with PTSD and alcohol dependence (Powers, Gillihan, Rosenfield, Jerud, & Foa, 2012). The total symptom severity coefficient was excellent ($\alpha = .90$), demonstrating high internal consistency. The total score was shown to have good test-retest reliability ($r = .80$). Inter-rater reliability was also high for diagnosis ($\kappa = .79$, 86% agreement on diagnosis) and overall severity (ICC = .73). The PSS-I also showed convergent validity with other measures of PTSD and related psychopathology ($r = .63$ - $.78$), and there was also substantial agreement with another structured clinical interview ($\kappa = .75$).

*The Structured Clinical Interview for the DSM* (SCID). The SCID is a widely used, semi-structured interview first developed by Spitzer, Williams, Gibbon, and First (1990) to establish diagnoses according to DSM-III (APA, 1980) criteria. Subsequent revisions to the SCID were made to correspond to DSM-III-R criteria (APA, 1987), and then to DSM-IV (APA, 1994) criteria (First, Spitzer, Gibbon, & Williams, 2002). For Axis I disorders, the SCID for DSM-III-R (APA, 1987) has shown acceptable inter-rater

reliability (κ = .43 - .86; Williams et al., 1992), as has the most recent revision (κ = .61 - .83; Lobbestael, Leurgans, & Arntz, 2011). Kranzler and colleagues (1996) found evidence for good to excellent concurrent and discriminant validity for substance use disorders diagnoses using the DSM-III-R version of the SCID.

**Clinician-rated and self-report measures.**

*Hamilton Rating Scale for Anxiety* (HAM-A). The HAM-A (Hamilton, 1959) is one of the first scales developed to measure anxiety symptom severity and remains widely-used in clinical and research settings. Clinicians give ratings for 14 items, each scored on a scale of 0 (not present) to 4 (severe). The total HAM-A score has demonstrated good inter-rater reliability (ICC = .74) and concurrent validity (r = .63 - .75; Maier, Buller, Philipp, & Heuser, 1988).

*Impact of Events Scale – Revised* (IES-R). The IES-R (Weiss & Marmar, 1997) assesses self-reported PTSD symptomatology experienced in the past 7 days. It consists of 22 items, and participants rate each item on a five-point scale from 0 (not at all) to 4 (extremely). The scale showed acceptable psychometric properties in a study conducted with substance dependent individuals with a history or trauma, more than half of whom met criteria for a PTSD diagnosis (Rash, Coffey, Baschnagel, Drobes, & Saladin, 2008). Internal consistency was high (α = .95), and the IES-R total score showed good convergent validity with other measures of PTSD and psychopathology (*r* = .41 - .70). Although it is not designed to be a diagnostic tool, the IES-R showed good sensitivity (.92), though lower specificity (.57). In addition, it correctly identified 77% of patients

diagnosed with PTSD when using a cutoff score of 22-24, thus supporting its use as a screening tool (Rash et al., 2008).

*Posttraumatic Diagnostic Scale* (PDS). The PDS (Foa, Cashman, Jaycox, & Perry, 1997) is a self-report measure designed to serve as a PTSD diagnostic screener, in addition to an assessment of PTSD symptom severity, corresponding to DSM-IV (APA, 1994) diagnostic criteria. The scale is divided into four sections. The first section is a checklist of 12 categories of traumatic events (i.e., accident or fire, natural disaster, nonsexual assault with known assailant, nonsexual assault with unknown assailant, sexual assault with known assailant, sexual assault with unknown assailant, combat or war zone, sexual abuse, imprisonment, torture, life-threatening illness, and other). Respondents indicate which of the 12 categories of traumatic events they have witnessed or experienced, and in the next section, are asked to indicate and describe the event that has disturbed them most in the past month. Respondents are asked to refer to this event in completing the third section, comprised of 17 items assessing the frequency of re-experiencing (5 items), avoidance (7 items), and arousal (5 items) symptoms. Items are rated on a 4-point Likert-type scale (*0 = not at all or only one time; 3 = five times or more a week/almost always*). Lastly, respondents complete a 9-item section assessing impairment in different life domains in the past month, using a yes-no format. A sum of the 17 items from the symptom section yields a symptom severity score that ranges from 0 to 51. Foa and colleagues (1997) demonstrated that the PDS symptom severity subscales and total score have good internal consistency ($\alpha = .78 - .92$) and good test-retest reliability over 2 to 3 weeks ($r = .77 - .85$). The PDS total symptom score also

showed acceptable convergent validity with other symptom measures ($r$ =.66 - .80). As a diagnostic tool, the PTDS was also found to have good test-retest reliability ($\kappa$ = .74) and 87% agreement in diagnoses across two time points. When compared with diagnoses obtained from the SCID, a $\kappa$ of .65 was found, with 82% agreement between the two measures. The sensitivity of the PDS was .89, and specificity was .75. A more recent study of patients with PTSD and alcohol dependence showed similar values for internal consistency, test-retest reliability, and convergent validity (Powers et al., 2012).

*Social Phobia Inventory* (SPIN). The SPIN is a 17-item self-report measure designed to assess fear, avoidance, and physiological symptoms associated with social anxiety (Connor et al., 2000). Each item is rated on a 0 (not at all) to 4 (extremely) scale; the full scale score ranges from 0 to 68, with higher scores indicating greater distress. Among those diagnosed with SAD, the SPIN has demonstrated acceptable psychometric properties in the original validation study and in a subsequent replication study; the total score has shown good internal consistency ($\alpha$ = .87 - .92), test-retest reliability (Spearman's $\rho$ =.78; $r$ = .86), convergent validity ($r$ = .57 - .92), discriminant validity ($r$ = .01 - .34), and sensitivity to change following treatment (Antony, Coons, McCabe, Ashbaugh, & Swinson, 2006; Connor et al., 2000).

*State-Trait Anxiety Inventory* (STAI). The STAI (Spielberger, Gorush, Lushene, Vagg, & Jacobs, 1983) is a commonly used self-report measure of anxiety, comprised of 40 items divided into two 20-item subscales. The STAI-State (STAI-S) subscale assesses how the person feels at the moment, and the STAI-Trait (STAI-T) subscale assesses how a person generally feels. According to a reliability generalization study (a meta-analytic

approach), the STAI-T has strong internal consistency (mean coefficient = .89) and test-retest reliability (mean coefficient = .88); the STAI-S was found to have similarly strong internal consistency (mean coefficient = .91) and good test-retest reliability (mean coefficient = .70; Barnes et al., 2002). Both scales have been shown to have high discriminant and convergent validity with other measures of anxiety and related constructs (Spielberger et al., 1983).

*Timeline Follow-Back* (TLFB). The TLFB (Sobell, Maisto, Sobell, & Cooper, 1979) is a widely-used interview method for retrospectively measuring the frequency and amount of substance use. In the TLFB, the respondent looks at a calendar and marks down memorable "anchor" dates (e.g., holidays, the respondent's birthday) to aid in recall of the amount of alcohol or substance used each day over a specified period of interest. Originally designed to measure alcohol consumption, the TLFB has been adopted by clinicians and researchers working with patients using other substances. Results from multiple studies suggest that the TLFB is reliable and valid for use among users of opiates, cocaine, and cannabis (Fals-Stewart, O'Farrell, Freitas, McFarlin, & Rutigliano, 2000; Hjorthøj, Hjorthøj, & Nordentoft, 2012; Robinson, Sobell, Sobell, & Leo, 2012), in addition to alcohol (e.g., Sobell, Sobell, Leo, & Cancilla, 1988).

*Trauma Symptom Checklist 40* (TSC-40). The TSC-40 (Elliott & Briere, 1992) measures symptoms in the past 2 months that are associated with the effects of sexual abuse. The 40-item checklist uses a 4-point frequency rating scale (0 = *never*, 3 = *often*), yielding possible scores of 0 to 120. The scale yields six subscales scores (Dissociation, Anxiety, Depression, Sexual Abuse Trauma Index, Sexual Problems, and Sleep

Disturbances) and a total scale score. Among a sample of inpatient women receiving psychiatric treatment, the TSC-40 correctly identified 84% of the patients with a history of sexual abuse, and the subscales demonstrated good convergent validity with other measures ($r$ = .56 - .78; Zlotnick et al., 1996).

*Days of Use and/or Abstinence*. When reported, we coded the number of days of substance or alcohol use and/or number of days of abstinence for the duration of treatment.

**Statistical Analyses**

The Comprehensive Meta-Analysis software 2.2 was employed to calculate effect sizes and pooled estimates of effect across studies.

We examined outcomes for 1) anxiety disorders, 2) PTSD, and 3) substance use. Our measurement of substance use outcomes was modeled after previously published meta-analyses involving treatment outcome for SUDs (Baker et al., 2012; Dutra et al., 2008; Hobbs et al., 2011). They were:

1. Mean days of substance use for the entirety of the treatment, or
2. Percentage of days use/abstinent from substance use for the entirety of the treatment.

Ideally, we would have also measured substance use intensity (e.g., days of heavy substance use), but such data were not widely or uniformly reported. Measures of days of use and abstinence are the most commonly-reported information across the studies.

In addition to examining overall effect sizes of treatment on anxiety, PTSD, and substance use outcomes, we also compared effect sizes within the pool of studies. We conducted these subgroup analyses using Welch's independent sample *t*-tests:

1. Anxiety/PTSD outcomes for psychotherapy compared to medication.
2. Anxiety/PTSD outcomes for anxiety disorder compared to PTSD.
3. Anxiety/PTSD outcomes in substance use treatment centers compared to treatment settings not specializing in substance use.

Subgroup analyses were exploratory in nature. We had planned to conduct subgroup analyses for substance use outcomes as well, but we did not have enough data to do so.

**Individual study effect sizes.** The standardized mean difference is an effect size statistic used to compare research findings that compare two groups (e.g., treatment versus control) on a dependent, continuous variable (e.g., anxiety or PTSD symptoms, alcohol use) that is operationalized differently across study samples; it is commonly used in treatment outcome meta-analyses (Lipsey & Wilson, 2001). The standardized mean difference effect size statistic for each research study, in two-group designs, was calculated as follows:

$$Cohen's\ d = ES_i = \frac{\bar{X}_{G1} - \bar{X}_{G2}}{s_p}$$

where $\bar{X}_{G1}$ is the mean for Group 1, and $\bar{X}_{G2}$ is the mean for Group 2. The pooled standard deviation, $s_p$ is defined as:

$$s_p = \sqrt{\frac{(n_{G1} - 1)s_{G1}^2 + (n_{G2} - 1)s_{G2}^2}{(n_{G1} - 1) + (n_{G2} - 1)}}$$

where $s_{G1}$ is the standardized deviation for Group 1 and $s_{G2}$ is the standard deviation for Group 2. Hedges (1981) points out that that this effect size statistic is slightly biased upward when used for small sample sizes, particularly with samples less than 20. For this reason, we used the correction that Hedges provides to calculate an unbiased effect size statistic, which is calculated as follows:

$$Hedge's\ g = ES_i' = \left[1 - \frac{3}{4N - 9}\right] ES_i$$

where *N* is the total sample size ($n_{G1} + n_{G2}$).

To convert various statistics to Cohen's *d*, we employed the following formulas:

$$For\ t\text{:}\quad d = \frac{2t}{\sqrt{df}}$$

$$For\ F(df = 1)\text{:}\quad d = \frac{2\sqrt{F}}{\sqrt{df_d}}$$

$$For\ r\text{:}\quad d = \frac{2r}{\sqrt{1 - r^2}}$$

To maintain statistical independence, each study only contributed one effect size for a given construct. When a study included more than one measure for a single construct, we calculated a combined mean and variance using the following formulas:

$$\bar{X}_{combined\ measures} = \frac{1}{m}\sum_{i=1}^{m} X_i$$

$$V_{combined\ measures} = \left(\frac{1}{m}\right)^2 \left(\sum_{i=1}^{m} V_i + \sum_{i \neq j} (r_{ij}\sqrt{V_i}\sqrt{V_j})\right)$$

where *m* is the number of measures. In our calculations, we estimated *r*, the correlation between measures, to equal 1 as correlations between measures were not reported in any of the studies for which we needed to combine measures.

When a study included more than one integrated/concurrent treatment condition or comparison condition, we combined groups to form a single integrated/concurrent treatment condition or single-target intervention, respectively. We calculated a weighted mean (by sample size) across groups and a combined standard deviation using the following formulas:

$$\bar{X}_{combined\ groups} = \frac{n_{11}\bar{X}_{11}+n_{12}\bar{X}_{12}}{n_{11}+n_{12}}$$

$$S_{combined\ groups} = \frac{(n_{11}-1)S_{11}^2 + (n_{12}-1)S_{12}^2 + \frac{n_{11}n_{12}}{n_{11}+n_{12}}(\bar{X}_{11}-\bar{X}_{12})^2}{n_{11}+n_{12}-1}$$

where $n_{11}$, $s_{11}$, and $\bar{X}_{11}$ refer to the values of first group, and $n_{12}$, $s_{12}$, and $\bar{X}_{12}$ refer to the values of the second group.

Effect sizes for anxiety and PTSD outcomes were calculated. Effect sizes for substance or alcohol use—which may be operationalized as average number of days of use or percentage of days abstinent—were also calculated.

**Mean effect size.** The formulas for calculating combined mean effect sizes are based on a random effects model. In a random effects model, variation among individual study effect sizes is assumed to be affected by sampling error (within-study variance) *and* random differences among studies (between-study variance). This is in contrast to a fixed effect model, in which it is assumed that variance among studies is accounted for solely by sampling error and that the true population effect is the same for all studies included in

the meta-analysis (i.e., the samples are drawn from a single population of interest). The mean effect size thus represents an estimate of the true population effect. In a random effects model, there is no assumption of a single true population effect size; rather, it is assumed that there is a possibility that there is a distribution of true effect sizes reflecting multiple populations. The mean effect size in a random effects model is thought to represent the mean of the population of true effects. It is generally difficult to make the case that the assumptions of a fixed effect model apply for a meta-analysis of clinical outcome studies conducted by different researchers. Differences in recruitment methods and participant characteristics mean that the populations from which the study samples are drawn may in fact be different. For example, a trauma intervention administered to survivors of sexual assault may have a true effect that is different from the true effect of the same intervention applied to combat veterans. Given the range of disorders and interventions that we included in our meta-analysis, a random effects model seems the most reasonable.

**Assigning weights to the studies**. The likelihood that a study's observed effect size closely represents the true population effect is influenced by the study's sample size; a study with 10 participants will produce a less accurate true effect size estimate than a study with 100 participants. Thus to calculate an aggregated mean effect size in a meta-analysis, a common approach is to weight each effect size by the study's sample size. Hedges (1982) makes the case that the optimal weights are derived from the error variance of the effect size. Because larger error variances represent less precise effect size values, we used the inverse of the error variance as the actual weight. Thus, studies with a

more precise estimate of the population effect size (a low variance) were assigned more weight, whereas studies with a less precise estimate of the population effect size (a high variance) were assigned less weight. The general formula for calculating inverse variance weights for each study was as follows:

$$w_i = \frac{1}{V_i + T^2}$$

where $V_i$ is the within-study variance unique to each study, and $T^2$ is the estimate of the between-study variance common to all studies. $V_i$ was calculated as follows:

$$V_i = \sqrt{\frac{n_{G1} + n_{G2}}{n_{G1} n_{G2}} + \frac{(ES_i')^2}{2(n_{G1} + n_{G2})}}$$

As Borenstein, Hedges, Higgins, and Rothstein (2010) explain, there are three steps to calculating $T^2$. First, we compute the amount of observed study-to-study variation. Second, we estimate how much the observed effects would be expected to vary from each other if the true effect was identical across studies. Lastly, we calculate the excess variance, which is presumed to reflect true heterogeneity in effect size. The weighted method of moments (Dersimonian & Laird, 1986) is one approach to calculating $T^2$, and it is the method utilized by Comprehensive Meta Analysis Software. The formula is as follows:

$$T^2 = \frac{Q - df}{C}$$

where the statistic $Q$ is total variance, $Q - df$ represents the excess variation between studies, and $C$ is a scaling factor that converts the estimate to the same metric used to report within-study variance. The formulas for these statistics are:

$$Q = \sum_{i=1}^{k} w_i (ES'_i - \overline{ES})^2$$

$$df = k - 1$$

$$C = \sum w_i - \frac{\sum w_i^2}{\sum w_i}$$

Where $\overline{ES}$ is the weighted mean effect size (see below) and $k$ is the number of studies.

**Computing the mean effect**. The general formula for the weighted mean effect size is:

$$\overline{ES} = \frac{\sum(w_i \, ES_i)}{\sum w_i}$$

where $ES_i$ are the values of the individual effect sizes, $w_i$ is the inverse variance weight. In other words, each effect size is multiplied by its respective weight, and summed and divided by the sum of the weights.

**Computing the meta-analysis study variance and standard error**. The variance of the mean effect, $V_{\overline{ES}}$, is calculated by taking the inverse of the sum of the weights:

$$V_{\overline{ES}} = \frac{1}{\sum w_i}$$

The standard error of the mean effect is the square root of the meta-analysis variance:

$$SE_{\overline{ES}} = \sqrt{V_{\overline{ES}}}$$

**Confidence Errors and Statistical Significance of the Mean Effect Size**

The 95% lower and upper limits for the mean effect were estimated as follows:

$$\mathrm{LL}_M = \overline{ES} - 1.96 \times SE_{\overline{ES}}$$

$$\mathrm{UL}_M = \overline{ES} + 1.96 \times SE_{\overline{ES}}$$

And a *p*-value for a two-tailed test was obtained using the following formulas:

$$Z = \frac{\overline{ES}}{SE_{\overline{ES}}}$$

$$p = 2[1 - (\Phi(|Z|))]$$

where Φ is the standard normal cumulative distribution function.

**Addressing Potential Sampling Bias**

It is a well-known and well-documented concern in the scientific community that there is a bias towards publishing studies with positive, significant results. This publication bias can threaten the validity of meta-analyses and literature reviews if not addressed in some way. One way to minimize the "file drawer" problem is to conduct as comprehensive a search as possible of unpublished studies. There are also statistical methods to address publication bias, which we employed in our study.

A note about a method we did not use: the fail-safe N. The fail-safe N method was one of the first statistical methods described to address publication bias (Rosenthal, 1979). It estimates the number of additional studies showing an effect size of zero (i.e., a null result) that it would take to reduce the cumulative effect to nonsignificance. There are several criticisms of this method (Sutton, 2009). The fail-safe N does not take into account the sample size or heterogeneity of studies, and it gives no estimate of the magnitude of the potential sampling bias (Lipsey & Wilson, 2001; Sutton, 2009). In addition, the choice of a hypothetical effect size of zero is arbitrary, as unpublished

studies could potentially show a negative effect, thereby reducing the number of studies needed to reduce the effect size to nonsignificance (Sutton, 2009).

Orwin (1983) proposed an alternative method for estimating the number of unpublished studies needed to bring the overall effect to a level other than zero that is determined by the researcher, typically $d = 0.2$, which Cohen (1992) suggests is a small effect size. Orwin's fail-safe N is based on effect size rather than *p*-value. It is calculated as follows:

$$N_{fs} = \frac{N(\overline{ES} - d_c)}{d_c}$$

where $N$ is the number of studies in the meta-analysis and $d_c$ is the criterion value selected.

A nonparametric approach to adjusting for publication method is the trim and fill method (Duval & Tweedie, 2000a, 2000b). It produces an estimate of the effect size after adjusting for bias. The trim and fill method uses the funnel plot of the data—a scatter plot of a measure of study size (e.g., standard error) against a measure of effect sizes. If no publication bias is present, the plot is expected to be symmetrical (i.e., that effect sizes in a random effects model are evenly distributed around the mean of the population of effect sizes) and with greater variability in smaller studies, thus producing a funnel shape. Through an iterative process, the trim and fill method removes the most extreme small studies with large effect sizes from the funnel plot, and imputes studies thought to be missing from the meta-analysis (i.e., studies demonstrating small effects). A new effect size is computed at each iteration, until the funnel plot is symmetrical around the new effect size.

We calculated the Orwin's fail-safe N and utilized the trim and fill method in the current meta-analysis.

# CHAPTER 3

# RESULTS

## Study and Sample Characteristics

Effect sizes were calculated for a total of 13 studies. From those 13, effect sizes for PTSD/anxiety outcomes were calculated for 12 studies, as sufficient data could not be obtained for the thirteenth. Substance use outcome was operationalized as days of substance use over the course of the entire treatment. Effect sizes for SUD outcomes were calculated for eight studies. However, given the heterogeneous approach to assessing substance use outcomes across studies (particularly regarding the timeframe of interest), we calculated the pooled effect size for substance use outcomes based only on the four studies that used duration of treatment as the assessment time frame. We also omitted studies that took place in inpatient treatment centers from this calculation, as substance use had to be assessed after discharge from the center and not immediately after post-study treatment. A Welch's independent *t*-test showed no significant difference between the pooled effect sizes of the four used to calculate and the pooled effect size of the four not used ($t = 0.35$, $df = 3$, $p > .05$).

Across all 13 studies, 742 participants entered integrated/concurrent treatment conditions, and 758 entered single-target treatment comparison conditions. The mean age of the participants across all studies was 40.4 years (range of means = 33.7 to 54.0, $SD = 5.4$). On average, samples were 42.7% female and 67.6% were of European descent. In two studies, significant baseline differences between participants in the experimental and comparison conditions were reported. In the study by Kranzler and colleagues (1994),

patients in the comparison group reported consuming more drinks per day than those in the experimental group at pre-treatment. Zlotnick and colleagues (2009) reported that participants in the experimental group were older. In both studies, the researchers reported that these differences were controlled for in their analyses.

Table 1 presents a detailed overview of methodological features of the studies. In two studies (Foa et al., 2013; Petrakis et al., 2012), treatment conditions were combined to calculate effect sizes, and for the study by Foa et al. (2013), data from the placebo-attention control condition were not included in our analyses. The majority of the studies examined alcohol as the targeted substance. Nine studies examined PTSD. All but two studies (Kranzler et al., 1994; Randall, Thomas, et al., 2001) utilized DSM-IV (APA, 1994) diagnostic criteria.

Regarding the characteristics of the interventions, all but one study featured a psychotherapy intervention (with or without concurrent pharmacotherapy); the mean length of the experimental treatment was 10.1 weeks (range = 1 to 24 weeks, *SD* = 6.2), and the average number of sessions was 12.5 (range = 1 to 24 sessions, *SD* = 5.8). Session length ranged from 45 to 90 minutes, with a median of 82.5 minutes.

For the four studies that featured a pharmacotherapy, the mean length of the treatment was 14.0 weeks (range = 8 to 24 weeks, *SD* = 6.9). The medications featured in our collection of studies include: 1) buspirone, a partial serotonin agonist use in the treatment of anxiety disorders; 2) desipramine, a tricyclic antidepressant; 3) naltrexone, an opioid agonist used in the treatment of alcohol dependence and opioid dependence; and 4) paroxetine, an SRRI used in the treatment of anxiety disorders and PTSD.

Table 1.

*Study Descriptions*

| Study | Diagnoses | Diagnostic Interview Used for Anxiety/PTSD, SUD diagnosis | Type of Substance Use Program (if applicable) | Integrated/ Concurrent Treatment(s) | No. of Treatment Weeks | Medication Target Daily Dosage (Mean Dosage), in mg | Comparison Treatment(s) |
|---|---|---|---|---|---|---|---|
| Boden et al., 2011 | PTSD[1], Any SUD | CAPS | Outpatient | Seeking Safety and TAU for SU | 12 | N/A | TAU for SU |
| Foa et al., 2013 | PTSD, Alcohol Dependence | PSS-I | N/A | Prolonged Exposure and naltrexone | 24 | 100 (93.3) | Exposure for PTSD and placebo; Naltrexone and supportive therapy |
| Hien et al., 2009 | PTSD[1] Any SUD | CAPS, CIDI | Outpatient | Seeking Safety and TAU for SU | 6 | N/A | Attention control and TAU for SU |
| Kranzler et al., 1994 | GAD[1], Alcohol Dependence | DIS, SCID | N/A | CBT for alcohol and buspirone | 12 | 60 (52.5) | CBT for alcohol and placebo |
| Kushner et al., 2013 | Panic Disorder, SAD, GAD, Alcohol Dependence | SCID, SCID | Inpatient | CBT for anxiety and alcohol, and TAU for alcohol | | N/A | Progressive Muscle Relaxation and TAU for alcohol |

Table 1.

*continued*

| Study | Diagnoses | Diagnostic Interview Used for Anxiety/PTSD, SUD diagnosis | Type of Substance Use Program (if applicable) | Integrated/ Concurrent Treatment(s) | No. of Treatment Weeks | Medication Target Daily Dosage (Mean Dosage), in mg | Comparison Treatment(s) |
|---|---|---|---|---|---|---|---|
| McGovern et al., 2011 | PTSD, Any SUD | CAPS | Outpatient | CBT for PTSD and SU, and TAU for SU | 12 | N/A | Individual addiction counseling and TAU for SU |
| Mills et al., 2012 | PTSD, Any Substance Dependence | CAPS, CIDI | N/A | COPE for PTSD and SU, and TAU for SU | 13 | N/A | Any TAU for SU in community |
| Petrakis et al., 2012 | PTSD, Alcohol Dependence | SCID, SCID | N/A | Paroxetine and naltrexone; Desipramine and naltrexone | 12 | Paroxetine 40 (39.7), Desipramine 200 (187.2), Naltrexone 50 | Paroxetine and placebo; Desipramine and placebo |
| Randall, Johnson, et al., 2001 | SAD, AUD | SCID, SCID | N/A | Paroxetine and motivational interviewing | 8 | 60 (46.7) | Placebo and motivational interviewing |

Table 1.

*continued*

| Study | Diagnoses | Diagnostic Interview Used for Anxiety/PTSD, SUD diagnosis | Type of Substance Use Program (if applicable) | Integrated/ Concurrent Treatment(s) | No. of Treatment Weeks | Medication Target Daily Dosage (Mean Dosage), in mg | Comparison Treatment(s) |
|---|---|---|---|---|---|---|---|
| Randall, Thomas & Thevos, 2001 | SAD, Alcohol Dependence | DIS, SCID | N/A | CBT for SAD and alcohol | 12 | N/A | CBT for alcohol |
| Sannibale et al., 2013 | PTSD, Alcohol Dependence | CAPS, SCID | N/A | CBT for PTSD and alcohol | 12 | N/A | CBT for alcohol and supportive counseling |
| van Dam et al., 2013 | PTSD[1], Any SUD | SCID, SCID | Inpatient and outpatient | Structured Writing Therapy and TAU for SU | 10 | N/A | TAU for SU |
| Zlotnick et al., 2009 | PTSD[1], Any Substance Dependence | CAPS, SCID | Inpatient (Prison program) | Seeking Safety and TAU for SU | 18 | N/A | TAU for SU |

*Note.* 1 = Included participants who did not meet full criteria for an anxiety or PTSD diagnosis. N/A = not applicable. AUD = alcohol use disorder (abuse or dependence); CAPS = Clinician-Administered PTSD Scale; CBT = cognitive behavioral therapy; CIDI = Composite International Diagnostic Interview; DIS = Diagnostic Interview Schedule; GAD = generalized anxiety disorder; PTSD = posttraumatic stress disorder; PSS-I = Post Traumatic Stress Disorder Symptom Scale – Interview Version; SAD = social anxiety disorder; SCID = Structured Clinical Interview for the DSM; SU = substance use; SUD = substance use disorder; TAU = treatment as usual.

In two studies—both of which involved pharmacotherapy—a period of abstinence was required prior to randomization, one requiring 7 days (Kranzler et al., 1994) and the other requiring 2 days (Petrakis et al., 2012). In another study, researchers did not state that patients were required to be abstinent but noted that the baseline assessment typically occurred after one week of patients' participation in a residential substance use program (Kushner et al., 2013). Two studies—including one that involved pharmacotherapy—required a period of abstinence before the start of treatment (as opposed to randomization); one required 3 days (Foa et al., 2013) and the other 28 days before the start of the experimental component of treatment (van Dam et al., 2013).

**Treatment Retention**

The approaches to reporting treatment retention rates varied somewhat across studies; the definitions of "treatment completion" were heterogeneous, and some studies reported treatment exposure rates without providing clear information regarding completion rates (see Table 2). Most commonly reported was the number of participants classified as "completers" relative to the number of people who were randomized. Based on the available data, approximately 68.6% of the participants randomized to integrated/concurrent treatment conditions completed 75% or more treatment weeks (based on 7 studies), and 65.9% completed at least half the treatment weeks (based on 10 studies). For the single-target comparison condition, the rates were 69.7% (based on 7 studies) and 65.5% (based on 9 studies), respectively.

Table 2.

*Retention Rates*

| Study | Completion rates among those randomized (%) | | Completion rates among those who initiated treatment (%) | | Percentage of randomized exposed to treatment (%) | |
|---|---|---|---|---|---|---|
| | Integrated/ Concurrent | Comparison | Integrated/ Concurrent | Comparison | Integrated/ Concurrent | Comparison |
| Boden et al., 2011 | | | | | 90.7 | 89.1 |
| Foa et al., 2013 | | | | | 65.0 | 65.9 |
| Hien et al., 2009[1] | 58.5 | 54.2 | 73.6 | 64.4 | | |
| Kranzler et al., 1994 | 83.9 | 53.3 | | | | |
| Kushner et al., 2013 | 74.3 | 85.5 | 78.9 | 89.2 | 94.2 | 96.0 |
| McGovern et al., 2011[2] | 50.0 | 47.6 | 64.0 | 90.9 | 78.1 | 52.4 |
| Mills et al., 2012 | | | | | 81.8 | 87.5 |
| Petrakis et al., 2012[3] | 68.2 | 72.7 | | | | |
| Randall, Johnson, et al., 2001 | 83.3 | 88.9 | | | | |
| Randall, Thomas, & Thevos, 2001[3] | 57.1 | 52.3 | | | | |
| Sannibale et al., 2013[4] | 60.6 | 62.1 | 66.7 | 66.7 | 90.9 | 93.1 |
| van Dam et al., 2013[5] | 52.6 | 73.3 | | | | |
| Zlotnick et al., 2009 | | | | | 100 | |

*Note.* Cells with missing values indicate that the data were unavailable for that study. 1 = Completed 6 of 12 of treatment weeks; 2 = Completed 8 of 12 treatment weeks; 3 = Completed 10 of 12 treatment weeks. 4 = Completed 9 of 12 treatment weeks; 5 = Completed 8 of 10 treatment weeks.

**Pooled Effect Sizes**

Anxiety/PTSD and substance use outcome data are summarized in Table 3. Regarding anxiety/PTSD outcomes, three of the studies demonstrated significant ($p <$ .05) effects in favor of the integrated/parallel treatment condition (Foa et al., 2013; McGovern et al., 2011; Mills et al., 2012), none showed a significant negative effect, and nine showed a non-significant effect. The pooled effect size for anxiety/PTSD outcomes across all studies was small but significant ($g = 0.32$), with a 95% confidence interval (CI) of 0.08 to 0.56.

For substance use outcome data, we included in the table the individual study effect sizes for studies that assessed days of substance use and noted what time frame they assessed. Of these studies, one showed a significant negative effect of the integrated/parallel treatment condition on days of use (Randall, Thomas, et al., 2001), in that the parallel treatment group demonstrated worse outcomes. One showed a non-significant and negative result (Hien et al., 2009), and the remainder showed non-significant but positive results. The pooled effect size for the four studies was very small ($g = 0.09$) and nonsignificant, with a 95% CI of -0.36 to 0.55.

**Comparing Anxiety/PTSD Effect Sizes Between Subgroups**

Four studies included treatments that involved medications, with three studies combining medication with psychotherapy in the integrated/concurrent treatment condition. When we compared the four treatments with a medication component ($g =$ 0.53, 95% CI = -0.15 to 1.08) to the eight of psychotherapy alone ($g = 0.22$, 95% CI =

Table 3.

*Individual Study Effect Sizes*

| Study | Sample Size | PTSD or Anxiety Outcome Measures | Effect Size | 95% CI | Substance Use Assessment Period | Effect Size | 95% CI |
|---|---|---|---|---|---|---|---|
| Boden et al., 2011 | 83 | IES-R | .08 | -.35, .50 | Past 30 days | .24 | -.19, .66 |
| Foa et al., 2013 | 122 | PSS-I | **1.04** | .64, 1.44 | Past 6 months | .20[1] | -.17, .58 |
| Hien et al., 2009 | 353 | CAPS, PSS-SR | .06 | -.15, .26 | Past 7 days | -.01 | -.22, .20 |
| Kranzler et al., 1994 | 61 | HAM-A | .44 | -.07, .94 | Past 90 days | .49[1] | -.02, .99 |
| Kushner et al., 2013 | 344 | STAI | -.10 | -.31, .11 | Past 4 months, at 4-month FU | .20 | -.01, .41 |
| McGovern et all, 2011 | 53 | CAPS | **.80** | .24, 1.37 | Past 90 days | .29[1] | -.26, .83 |
| Mills et al., 2012 | 103 | CAPS, STAI | **.72** | .33, 1.12 | -- | -- | -- |
| Petrakis et al., 2012 | 62 | CAPS | -.04 | -.53, .45 | -- | -- | -- |

Table 3.

*continued*

| Study | Sample Size | PTSD or Anxiety Outcome Measures | Effect Size | 95% CI | Substance Use Assessment Period | Effect Size | 95% CI |
|---|---|---|---|---|---|---|---|
| Randall, Johnson, et al., 2001 | 12 | SPIN | .76 | -.34, 1.87 | -- | -- | -- |
| Randall, Thomas & Thevos, 2001 | 93 | -- | -- | -- | Past 90 days | **-.54**[1] | -.94, -.13 |
| Sannibale et al., 2013 | 62 | CAPS, STAI-S, PDS | .24 | -.25, .74 | -- | -- | -- |
| van Dam et al., 2013 | 34 | PDS | .46 | -.22, 1.13 | Past 90 days | .60 | -.07, 1.28 |
| Zlotnick et al., 2009 | 49 | CAPS, TSC-40 | -.19 | -.74, .37 | -- | -- | -- |

*Note.* Cells with missing values indicate that we were unable to calculate one of the effect sizes for that study. Numbers in bold indicate that the effect size was statistically significant at the $p < .05$ level. 1 = Included in calculation of pooled effect size. CAPS = Clinician-Administered PTSD Scale; HAM-A = Hamilton Rating Scale for Anxiety; IES-R = Impact of Events Scale – Revised; PDS = PTSD Diagnostic Scale; PSS-I = Post Traumatic Stress Disorder Symptom Scale – Interview Version; PSS-SR = Post Traumatic Stress Disorder Symptom Scale – Self-Report Version; SPIN = Social Phobia Inventory; STAI = State-Trait Anxiety Inventory; STAI-S = State-Trait Anxiety Inventory – State subscale; TSC-40 = Trauma Symptom Checklist-40

-0.02 to 0.46), no difference was found on anxiety/PTSD symptoms between these subgroups of studies ($t = 2.15$, $df = 3$, $p > .05$). When we looked at the three combined medication-psychotherapy treatments ($g = 0.77$, 95% CI = 0.34 to 1.20), the difference showed a trend towards significance ($t = 4.08$, $df = 2$, $p < .10$).

When looking at treatments targeting PTSD (9 studies; $g = 0.35$, 95% CI = 0.06 to 0.64) and anxiety disorders (3 studies; $g = 0.22$, 95% CI = -0.28 to 0.71), we found no difference ($t = 0.87$, $df = 2$, $p > .05$). We also looked at treatments administered at substance use programs (5 studies) compared to those provided in other settings (4 studies).[1] Treatments administered at inpatient or outpatient substance use programs ($g = 0.15$, 95% CI = -0.10 to 1.17) and treatments provided in other settings ($g = 0.64$, 95% CI = .30 to .98) showed a significant difference ($t = 4.69$, $df = 4$, $p < .05$).

Subgroup comparisons were not conducted for substance use, given the small number of studies in our sample that provided an effect size that we could use.

**Publication Bias**

For the anxiety/PTSD effect size, Orwin's *fail-safe N* calculation showed that 7 to 8 missing studies could reduce the pooled effect size to 0.20. Investigation of the funnel plot indicated that a publication bias may be present. After trimming and filling three studies to enhance symmetry, the random effects model estimated a smaller pooled effect size of $g = .17$, with a 95% CI of -0.08 to 0.42.

[1] Note that in this subgroup analysis we omitted the study by Zlotnick et al. (2009), as that research took place in a women's prison and was deemed to be too dissimilar to the other treatment settings. We also omitted the study by Randall, Johnson, et al. (2001) as it was unclear from the description whether or not they enrolled participants from a substance use program. In addition, the first author's affiliated center is known to offer inpatient and outpatient substance use services.

Because the pooled effect size for substance use was so small, we did not conduct publication bias analyses for that outcome.

# CHAPTER 4

# DISCUSSION

We conducted this meta-analytic study to examine whether integrated or concurrent treatments for comorbid anxiety disorders/PTSD and SUD were effective interventions compared to single-target treatments. This work builds on earlier systematic reviews (Baker et al., 2012; Hobbs et al., 2011; Torchalla et al., 2012) by including more recent studies, resulting in a total of eight studies not included in previous analyses. In addition, we employed more stringent inclusion criteria, such as only including randomized controlled trials, requiring that a diagnostic interview have been used in these studies, and requiring that the experimental treatment must include components that target both anxiety/PTSD and substance use. Furthermore, our main inquiry differed slightly from the previous meta-analyses that included anxiety disorders (Baker et al., 2012; Hobbs et al., 2011) in that we were interested in how integrated/concurrent treatments compared to single-target treatments, and so we excluded studies with comparison groups with presumably less active interventions (e.g., placebo) or no interventions.

Our findings provide some evidence suggesting that integrated or concurrent treatments may be more beneficial in reducing anxiety or PTSD symptoms compared to treatments that only targeted substance use or anxiety/PTSD. Of the three studies that found a significant effect, all showed positive effect sizes in favor of the integrated or concurrent treatment. In addition, we found a positive pooled effect size for anxiety/PTSD outcomes. This is unsurprising, since the large majority of the studies in

our analyses featured comparison conditions in which the intervention targeted substance use, as one would expect some anxiety/PTSD treatment to be better than no anxiety/PTSD treatment. Our finding is consistent with the previous meta-analysis conducted by Hobbs and colleagues (2011), which found that supplemental treatments are effective in reducing anxiety symptoms. It is also consistent with Baker and colleagues' conclusion from their review that interventions targeting anxiety and alcohol misuse generally show positive effects. However, it is inconsistent with the small and non-significant pooled effect size reported by Torchalla and colleagues (2012) in their comparison of integrated and non-integrated treatments for trauma and SUD. It is unclear why our results differed, but this may be related to the fact that Torchalla et al. included uncontrolled studies in their analysis and that the characteristics of the studies varied more broadly (e.g., including a study of adolescents, one of smoking cessation, and one in which a diagnosis of PTSD was not established).

Though integrated/concurrent treatments appeared to be somewhat beneficial for reducing PTSD and anxiety symptoms, the small pooled effect size we found contrasts with the effect size of PTSD and anxiety treatments in non-SUD samples—meta-analyses have revealed that those RCTs tend to show large effect sizes (e.g., Butler, Chapman, Forman, & Beck, 2006; Hofmann & Smits, 2008; Powers, Halpern, Ferenschak, Gillihan, & Foa, 2010). This supports clinical observations and research showing that substance use comorbidity increases symptom severity and hinders treatment response (Bruce et al., 2005; Driessen et al., 2001; Ouimette et al., 1997). With regard to treatment attrition, rates of completion do not appear to differ greatly from rates reported for PTSD and

anxiety treatments in samples without SUD comorbidity. In a review of different types of PTSD treatments, average completion rates among those who initiated cognitive and/or exposure-based treatments ranged from 73% to 80% (Hembree et al., 2003). A review of studies of anxiety disorders showed a wider range, with completion rates ranging from 43% to 89% (Santana & Fontenelle, 2011). Thus, the acceptability of integrated treatments seems to be close to, if not on par with, single-target interventions in a non-SUD population.

Regarding substance use outcomes, we were only able to calculate a pooled effect size based on four studies, and it suggested that the effect of integrated/concurrent treatments on SUD outcomes was not significant. This was similar to the pooled effect sizes reported in the two previous meta-analyses (Hobbs et al., 2011; Torchalla et al., 2012). The issue of substance use outcomes in integrated/concurrent treatments relates to a concern of many clinicians that treating anxiety disorders or PTSD—particularly with exposure-based approaches—will exacerbate substance use (Back, Waldrop, & Brady, 2005). These concerns are not without merit, of course. With regards to PTSD, multiple studies suggest that exposure to trauma cues can affect substance use cravings. For example, in a laboratory study with a sample of participants with comorbid PTSD-SUD, Coffey and colleagues (2002) showed that imaginal exposure to participants' self-reported worst trauma increased substance use cravings compared to exposure to a neutral cue. In another study, those with PTSD and alcohol dependence exposed to personal trauma cues also exhibited elevated salivary response, a physiological response associated with alcohol craving (Coffey et al., 2010). Furthermore, using the same

paradigm, Saladin and colleagues (2003) found that those with more severe PTSD symptomatology exhibited stronger substance use cravings when exposed to personal trauma cues. In addition to cravings, exposure to anxiety-provoking cues may activate expectancies that substance use will reduce anxiety. For instance, highly socially anxious individuals are more likely to report that they use alcohol to cope with social situations compared to low anxious peers (Buckner & Heimberg, 2010).

In regards to the findings of our current study, individual study effect sizes showed no significant difference between the integrated/concurrent treatment and single-target treatments (primarily substance use treatments) in seven of eight studies. This could be interpreted as somewhat encouraging, in that these treatments did not show evidence of *greater* rates of substance use as a result of anxiety/PTSD treatment. Only one study showed that concurrent treatment was associated with greater substance use (Randall, Thomas, & Thevos, 2001). As we discussed earlier, this may have been because patients in this study were exposed to more drinking situations as a result of successful SAD treatment or because patients were drinking to cope with the increased anxiety. However, the researchers did not explicitly monitor alcohol use during exposures nor did they explicitly encourage their patients to practice abstinence while engaging in exposures. This highlights the need to assess and address increased cravings and desire to use substances throughout the course of integrated/concurrent treatment, as patients are asked to confront stimuli that elevate anxiety and distress.

**Subgroup Analyses**

We explored potential differences between subgroups of studies on anxiety/PTSD symptoms. Although we did not have an *a priori* hypothesis predicting a difference, it was a question not examined in previous meta-analyses. We did not find a difference between treatments targeting PTSD and those targeting anxiety disorders, suggesting that integrated/concurrent treatments are beneficial for both categories of disorders. We did, however, find a trend suggesting that combined medication and psychotherapy interventions may be superior to psychotherapy alone. The question of the superiority of combined treatments for anxiety disorders has received a fair amount of discussion (Foa, Franklin, & Moser, 2002; Heimberg, 2002; Otto, McHugh, & Kantak, 2010; Otto, Smits, & Reese, 2005; Pontoski & Heimberg, 2010). On the face of it, one might assume that combined approaches could produce an additive, and perhaps even synergistic, effect. One of the primary hypotheses about why this would be the case is the idea that medication may reduce anxiety symptoms enough for the patient to tolerate greater exposure to feared situations (Foa et al., 2002). For those with co-occurring SUDs, medications may help reduce substance use cravings and give patients more confidence to move forward with anxiety treatment, with less worry about an episode of relapse. However, as pointed out in reviews of the research in non-SUD samples, the evidence for the superiority of combined treatments for anxiety disorders is mixed, with many studies showing that combined treatments produce a magnitude of effect similar to psychotherapy or medication alone (e.g., Foa et al., 2002; Gould, Buckminster, Pollack, Otto, & Yap, 1997; Gould, Otto, Pollack, & Yap, 1997). In the area of substance use treatment research, there is little research comparing combined to stand-alone treatments.

One large RCT that attempted to address this question showed that combined treatment (represented by three different experimental conditions in the study) was not more efficacious than naltrexone or intensive behavioral intervention alone in reducing drinking outcomes among patients with alcohol dependence (Anton et al., 2006).

Our findings suggest a possibility that combined treatments may be more beneficial for comorbid anxiety/PTSD and SUD patients than psychotherapy alone, but our findings alone are, of course, not conclusive. For one, we only found a trend towards significance, and our sample of studies with combined treatments was small and may have included an outlier (three studies, including one that had the largest ES out of all the studies in our meta-analysis). Furthermore, we only examined immediate post-treatment outcomes, and it is unclear how the treatments compare in the long-term. Patterns of gains shown at post-treatment do not always extend to the months after treatment ends. For example, in one large RCT of treatment for PD, combined treatment showed a larger effect than CBT at post-treatment, but CBT was superior at 6 months after treatment discontinuation (Barlow, Gorman, Shear, & Woods, 2000). Findings from meta-analyses comparing CBT to pharmacotherapy for the treatment of SAD or GAD show that patients who receive CBT continue to show modest gains following treatment, whereas discontinuation of medication leads to no such gains (Gould, Buckminster, et al., 1997; Gould, Otto, et al., 1997). Thus, further research is necessary to examine the efficacy of combined treatments for comorbid anxiety/PTSD-SUD at long-term follow-up, compared to medication or psychotherapy alone.

Lastly, we found that studies conducted in substance use programs produced smaller PTSD/anxiety effects than studies conducted in other settings. One possible explanation is that specialty substance use programs attract patients with greater substance use severity and for whom the SUD is primary. For these patients, learning to manage substance use may be more of a priority.

Speculations about patient characteristics aside, we wanted to explore treatment setting differences because of potential differences in how integrated or concurrent treatments are adapted to fit the setting in which they are administered. A part of responding to the needs of the patient is considering how to adapt integrated approaches to the treatment setting. Although they write specifically about exposure therapy for PTSD in residential treatment, Henslee and Coffey (2010) provide good examples of how exposure-based treatments can be adapted for inpatient settings in general. For example, one of the barriers to PTSD or anxiety treatment may be limited opportunities for *in vivo* exposures in inpatient substance use programs. Among their many recommendations, they suggest accessing images on the internet as a starting point for exposure, and planning for exposures higher on the hierarchy following discharge. We imagine this could also be applied to treatment of PD. Henslee and Coffey also discuss the importance of ensuring that patients have time and privacy to engage in imaginal exposures for PTSD, which may be achieved by allowing patients time alone in their rooms for this exercise, with the use of headphones. For SAD, we can imagine that creativity in coming up with exposure ideas, as well as carefully planning the involvement of staff members and/or other patients, could result in potent exposure experiences. Another adaptation,

which was observed in the inpatient studies in our sample, is to adjust the frequency and length of psychotherapy sessions to fit the duration of residential treatment; this may involve having more than one session a week and/or additional sessions following discharge (Henslee & Coffey, 2010). In outpatient settings, a very important consideration is how to address opportunities to use substances. This is particularly true for some patients for whom improvement in their symptoms could lead to greater opportunities to use (e.g., increased invitations to parties for those with SAD, decreasing the number of places avoided for those with agoraphobia or PTSD). In short, it may not be that one type of treatment setting leads to better outcomes per se; rather, it may be that the treatment that is best adapted to a particular setting will produce the best outcomes.

**Strengths and Limitations**

Inherent to the meta-analytic approach are particular strengths and weaknesses. One of its main strengths is that it serves as a systematic and quantitative approach to reviewing the current state of an area of research. As Lipsey and Wilson (2001) point out, meta-analyses are helpful in bringing the attention to effect sizes over the typical focus on significance values, which can be the case with qualitative reviews. In addition, synthesized effect sizes have greater statistical power than individual studies. However, there are limitations to and common criticisms about meta-analyses, some of which we attempted to mitigate in the current investigation. One of the main concerns is that estimates produced from aggregated data are difficult to interpret if 1) the studies and outcome measures are so different from one another that we are in effect comparing apples and oranges, and/or 2) we include many low quality studies. The issue with the

latter situation is that methodological errors of low quality studies become obscured in the meta-analytic process. To address the both points, we made a concerted effort to be conservative in the kind of studies we included. For instance, we limited our studies to RCTs and to ones in which the comparison condition included a single-target treatment (i.e., treatment for anxiety/PTSD or SUD) rather than placebo or waitlist conditions. This resulted in the exclusion of a number of studies. The disadvantage of this restrictiveness in criteria was, of course, that we were left with a relatively small number of studies. To further limit our analyses, particularly in the case of substance use outcomes, we maintained a fairly strict definition of how substance use outcomes were measured for inclusion in the pooled effect size calculation. As a result of these conservative choices, we limit the generalizability of our findings.

Another primary criticism of meta-analyses is that results are invalid if we are missing data due to publication bias. In this regard, we attempted to reduce the file drawer effect by conducting as thorough a search as we could and by making contact with many researchers to request unpublished manuscripts. As for our assessment of publication bias, the Orwin *fail-safe N* suggests that the inclusion of at least seven yet-unpublished negative studies would be needed to reduce the anxiety/PTSD effect size we found to .20. Although this is possible, it seems unlikely that we were unable to identify as many as seven unpublished RCTs given our concerted efforts to contact leading researchers in this area of study. The trim-and-fill method estimated an adjusted effect that was smaller and nonsignificant. However, the method is susceptible to overestimating publication bias, particularly in the presence of studies with small samples

that show true, large effects (Song, Khan, Dinnes, & Sutton, 2002). In our study, the smallest study contributed the third largest effect size and was one of the three studies trimmed in the publication bias analysis. Thus the trim-and-fill findings should be interpreted with caution. Song and colleagues (2002) argue that "there may be no statistical method that is a superior remedy for assessing publication bias than another, and any method used in meta-analysis for detecting publication bias is by nature indirect and exploratory" (p. 94).

**Future Directions**

The goal of the current study was to summarize and reflect on the state of a very important and emerging area of research. As the study of integrated treatments for comorbid conditions continues, there are a few questions we hope will be examined. For one, there is a need for studies to compare integrated treatments to anxiety/PTSD-only interventions, especially to examine their effectiveness in reducing substance use. This was difficult to glean from current studies, as most compared their treatments to substance use-focused interventions.

Our next recommendation is to increase the duration of the treatments that are being tested. It may be no coincidence that the study that produced the largest effect size in our sample (Foa et al., 2013) also offered the longest period of treatment (6 months). Given the chronicity of SUDs, and the complex relationship between SUDs and PTSD/anxiety, treatment may necessarily extend for a longer period of time than treatment for PTSD or anxiety alone. Our clinical observations suggest that patients with anxiety/PTSD and a long history of comorbid substance dependence require more time to

engage in treatment compared to those without substance dependence comorbidity. Furthermore, it has been argued that the acute treatment approach is at odds with the view of addiction as a chronic condition (Dennis & Scott, 2007). Of course, it is impractical to conduct RCTs that feature years of treatment, but extending the length of treatment beyond two to three months could give us a clearer picture about its effectiveness with this population and could be an important step forward.

Another issue with substance use research is the question of how to measure substance use outcomes and what it means in regards to recovery. Much of the debate is related to the issue of whether recovery should be characterized by abstinence or by harm reduction. It is beyond the scope of this paper to review the specific arguments in this debate, but it seems that a legacy of the abstinence stance in research is to determine successful outcomes by counting the instances of use. This approach gives us limited information about the nature of a patient's use patterns. Researchers should broaden their assessments to include measures of intensity of use (such as days of heavy use) and to examine the impact that use has on other domains of functioning. To be fair, some studies in our sample utilized measures of substance use other than counting days of use, but this practice was not consistent across studies, preventing us from including those measures in our pooled analysis.

Future research should also examine how treatment effects may differ for different subgroups of persons with PTSD/anxiety-SUD comorbidity. For example, it is unclear whether individuals with PTSD-cocaine dependence will respond similarly to integrated treatments compared to those with PTSD-alcohol dependence. At present, we

know less about treatments for SUD comorbidity other than comorbidity with AUDs, evidenced by the fact that half the studies in our meta-analyses looked exclusively at alcohol abuse or alcohol dependence. However, differences exist between SUD subgroups. One example of this was shown in the trauma cue-reactivity study mentioned earlier (Coffey et al., 2002). In that study, researchers found a difference in cue-reactivity between participants with alcohol dependence and those with cocaine dependence. In reviewing the self-reported trauma scripts, the researchers noticed that some scripts contained references to substance use at the time of the trauma. They then compared participants who made reference to drugs or alcohol in their trauma scripts to those who did not and found that alcohol dependent-PTSD participants showed no difference in cravings in either case. However, among cocaine dependent-PTSD participants, those who referenced substance use in their scripts showed greater cue-induced cravings than those with "pure" trauma scripts. The authors cited previous research showing that negative emotion was associated with increased alcohol cravings in alcohol dependent individuals and mixed findings that it increased cocaine cravings in cocaine dependent individuals (e.g., Cannon et al., 1992; Cooney et al., 1997; Rubonis et al., 1994; Sinha et al., 1999); thus, the authors hypothesized that the differential response to "pure" trauma scripts in their sample may suggest that PTSD-related negative emotion plays a more important role in cravings among alcohol dependent individuals (Coffey et al., 2002).

Another potential approach to identifying meaningful subgroups is to look at substance use change in the period between treatment seeking initiation and actual start of treatment (Stasiewicz, Schlauch, Bradizza, Bole, & Coffey, 2013). Building on

previous research showing that 46% of patients in one study achieved abstinence prior to the first treatment session (E. E. Epstein et al., 2005), Stasiewicz and colleagues (2013) conducted a study in which they assessed substance use among treatment seekers in an outpatient alcohol use treatment center. They found that a proportion of patients, whom they called "rapid changers," exhibited an average of 89% abstinent days between the baseline assessment and the first treatment session. In contrast, the "gradual change" group reported 25% abstinent days in the same period. Interestingly, at the baseline assessment, no differences were found between the groups on severity of alcohol dependence, though the rapid change group scored higher on measures of problem recognition (indicating greater recognition that they have problem with drinking and contemplation about change) and on taking steps towards change. Following a 12-week CBT treatment for alcohol dependence, the "rapid changers" exhibited maintenance of these pretreatment changes and had better treatment outcomes than the "gradual change" individuals, though the latter group showed larger treatment effects. This suggests that treatment helped "rapid changers" to stabilize and maintain meaningful gains made before the start of treatment. With regard to anxiety/PTSD comorbidity, "rapid changers" may be particularly good candidates to begin integrated anxiety/PTSD treatment after entering a substance use treatment program, as this would capitalize on their motivation and demonstrated emergent ability to manage their substance use.

Though we grouped studies of PD, GAD, SAD, and PTSD together for this meta-analysis, we would probably benefit from a better understanding of the treatment effects for the individual disorders. Furthermore, research should also examine potential

subtypes among individuals who share the same diagnoses. One example of this was seen in a treatment study of PTSD-alcohol dependence by Brady and colleagues (2005).[2] In it, a cluster analysis based on treatment response identified different subgroups of patients. One group was characterized by patients who reported PTSD onset at an earlier age—likely before the onset of alcohol dependence—and less severe alcohol dependence at baseline. This group responded the best to medication relative to placebo on drinking outcomes post-treatment. The group with later-onset PTSD and more severe alcohol dependence at baseline showed poorer response to medication. The authors hypothesized that the first group might be described as a primary PTSD group and that alcohol dependence may have developed out of attempts to self-medicate. In any case, this study demonstrates that we need to consider how variables such as age-of-onset, severity, and other factors influence treatment response.

Lastly, one question highly related to the topic of this paper remains unresolved. As mentioned in the introduction, little research has been conducted directly comparing the different models of treatment (i.e., sequential, parallel, and integrated) when comorbidity is present (Donald et al., 2005). Although we have reason to suspect that integrated treatments offer the most treatment flexibility and greatest ability to meet the patient's changing needs over parallel and sequential models, we do not yet have the empirical evidence to support this assertion. It is likely the answer will be much more nuanced, such that the "best" form of treatment will depend on patient factors, consideration of the treatment setting, and pragmatic concerns regarding the cost of

[2] This study was eligible for inclusion in our study, but we were unable to calculate effect sizes due to insufficient data.

treatments and limitations to treatment provider training. In any case, any attempt to better understand how best to treat comorbid conditions will be a much needed step forward.

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## APPENDIX

Coding Manual

General Coding Guidelines:

- If the information is unavailable for a particular variable, enter -99. There should be no empty cells for any of the variables when coding is completed.
- If variable is not applicable to the particular study (e.g., psychotherapy session length for medication trials), enter -88.

Study-Level Variables

*Bibliographic Reference*. Write the name of authors and study year.

1. *Study ID Number*. Assign a unique identification number to each study. If a report presents two independent studies, i.e., two independent outcome studies with different participants, then add a decimal to the study ID number(e.g., study 137.1 and 137.2, if report 137 contains two studies) to distinguish each study within a report and code each independent study separately.

2. *What type of publication is the report*?

| | |
|---|---|
| 1 Journal article | 4 Book chapter |
| 2 Thesis or doctoral dissertation | 5 Conference paper |
| 3 Unpublished manuscript | 6 Other |

3. *What is the publication year?*

Research Design and Sample Descriptors

4. *Anxiety Disorder?* Code the primary disorder(s) of interest that was (were) assessed and targeted for treatment.

| | |
|---|---|
| 1 Generalized Anxiety Disorder | 4 PTSD |
| 2 Panic Disorder with/without Agoraphobia | 5 Multiple anxiety disorders (specify) |
| 3 Social Anxiety Disorder/Social Phobia | |

5. *Did the study include participants with subthreshold symptoms (i.e., some participants did not meet full criteria for the disorder?)*

| |
|---|
| 1 Yes<br><br>2 No |

6. *Version of DSM used for diagnosing anxiety disorder/PTSD?* Note that you may sometimes infer this based on the diagnostic interview that was used (e.g., ADIS-IV is based on DSM-IV criteria).

| | |
|---|---|
| 1 DSM-IV | 3 DSM-III |
| 2 DSM-III-R | |

7. *Which diagnostic interview was used for diagnosing anxiety disorder/PTSD?*

| | |
|---|---|
| 1 SCID | 4 DIS |
| 2 CAPS | 5 Other (Specify) |
| 3 ADIS | |

8. *Substance Use Disorder?* Code the primary SUD of interest that was assessed and targeted for treatment. Also, an article might report that "at-risk" drinkers were recruited for the study, but report that in their sample, 23% met criteria for Alcohol Dependence, and 39% met for Alcohol Abuse. In this situation, this item would be coded as "3" for this article.

| | |
|---|---|
| 1 Alcohol Abuse | 4 Other Substance Abuse (specify substance) |
| 2 Alcohol Dependence | 5 Other Substance Dependence (specify) |
| 3 Alcohol Abuse or Dependence | 6 Any substance or alcohol use disorder |

9. *Did the study include participants with subthreshold substance use difficulties (i.e., some participants did not meet full criteria for the disorder?)* If the authors recruited "heavy drinkers" or "problematic users" (or uses similar language), this indicates subthreshold symptoms. However, for studies where participants were recruited from inpatient or outpatient substance use treatment centers, assume that participants met abuse criteria (at the very least) and would not be considered subthreshold.

| |
|---|
| 1 Yes<br><br>2 No<br><br>3 Did not specify |

10. *Version of DSM used for diagnosing SUD?* Note that you may sometimes infer this based on the diagnostic interview that was used (e.g., ADIS-IV is based on DSM-IV criteria).

| | |
|---|---|
| 1 DSM-IV<br><br>2 DSM-III-R | 3 DSM-III |

11. *Which diagnostic interview was used for diagnosing the SUD?*

| | |
|---|---|
| 1 SCID<br><br>2 CAPS<br><br>3 ADIS | 4 DIS<br><br>5 Other (Specify) |

Treatment and Comparison Conditions

*Please note that for items 12-15, pill placebo is not considered "medication." For example, an active treatment condition which combines psychotherapy with pill placebo should be coded as "Other" and not as "Combination therapy and medication." Also, supportive therapy and progressive muscle relaxation are often meant to serve as "placebo" or "attention control" therapy. Do not code as an active treatment, unless the authors state otherwise.*

12a. *Integrated or concurrent treatment condition - 1.* Select the code that best describes the first active treatment condition mentioned in the text in the Method section. If there is no clear order in the text, code the first treatment listed in the first table with this information. In specifying the treatment, indicate which aspect of the treatment was targeted at the anxiety disorder/PTSD, and which targeted the SUD.

| | |
|---|---|
| 1 Individual/Group therapy (specify) | 4 Other (specify) |

| |
|---|
| 2 Medications (specify)<br><br>3 Combination therapy and medication (specify) |

12b. *If treatment includes pharmacotherapy, specify the type of medication (e.g., SSRI, benzodiazepine, opioid receptor antagonist, etc.)*

13a. *Integrated or concurrent treatment condition - 2.* Select the code that best describes the first active treatment condition mentioned in the text in the Method section. If there is no clear order in the text, code the second treatment listed in the first table with this information. In specifying the treatment, indicate which aspect of the treatment was targeted at the anxiety disorder/PTSD, and which targeted the SUD.

| | |
|---|---|
| 1 Individual/Group therapy (specify)<br><br>2 Medication (specify)<br><br>3 Combination therapy and medication (specify) | 4 Other (specify) |

13b. *If treatment includes pharmacotherapy, specify the type of medication (e.g., SSRI, benzodiazepine, opioid receptor antagonist, etc.)*

14a. *Integrated or concurrent treatment condition - 3.* Select the code that best describes the first active treatment condition mentioned in the text in the Method section. If there is no clear order in the text, code the third treatment listed in the first table with this information. In specifying the treatment, indicate which aspect of the treatment was targeted at the anxiety disorder/PTSD, and which targeted the SUD.

| | |
|---|---|
| 1 Individual/Group therapy (specify)<br><br>2 Medication (specify)<br><br>3 Combination therapy and medication (specify) | 4 Other (specify) |

14b. *If treatment includes pharmacotherapy, specify the type of medication (e.g., SSRI, benzodiazepine, opioid receptor antagonist, etc.)*

15. *Comparison condition.* Select the code that best describes the first comparison condition.

| | |
|---|---|
| 1 Psychotherapy TAU for SU | 5 Medication as usual for |

| | |
|---|---|
| | anxiety/PTSD |
| 2 Psychotherapy TAU for anxiety/PTSD | 6 Pill placebo |
| 3 Psychotherapy attention control | 7 Waitlist |
| 4 Medication as usual for SU | 8 Other (specify) |

| |
|---|
| 16a. **Total** sample size at start of study (i.e., total randomized). |
| 16b. **Total** sample included in the statistical analyses. |

| |
|---|
| 17a. **Treatment group 1** (item 12a) sample size at start of study (i.e., those randomized to an active treatment). |
| 17b. **Treatment group 1** (item 12a) sample included in the statistical analyses. |
| 17c. Percent attrition (e.g., "dropouts" who didn't finish) from **Treatment group 1**. |

| |
|---|
| 18a. **Treatment group 2** (item 13a) sample size at start of study (i.e., those randomized to an active treatment). |
| 18b. **Treatment group 2** (item 13a) sample included in the statistical analyses. |
| 18c. Percent attrition (e.g., "dropouts" who didn't finish) from **Treatment group 2**. |

| |
|---|
| 19a. **Treatment group 3** (item 14a) sample size at start of study (i.e., those randomized to an active treatment). |
| 19b. **Treatment group 3** (item 14a) sample included in the statistical analyses. |
| 19c. Percent attrition (e.g., "dropouts" who didn't finish) from **Treatment group 3**. |

| |
|---|
| 20a. **Comparison group** (item 15) sample size at start of study (i.e., those randomized to control) |
| 20b. **Comparison group** (item 15) included in the statistical analyses. |
| 20c. Percent attrition (e.g., "dropouts" who didn't finish) from **Comparison group**. |

21. *Mean age of total sample*. Specify the approximate or exact mean age at the beginning of the intervention. Code the best information available. If means are reported separately for the different groups, calculate the mean for the total sample from the available information. Round to the nearest tenth (e.g., 36.65 = 36.7).

$$Mean_{Total} = \frac{(Mean_1 \times n_1) + (Mean_2 \times n_2)}{(n_1 \times n_2)}$$

22. *Ethnicity of sample*. If information is available, code the percentage of participants in the study who fall into these categories. Report percentages to the nearest tenth, if possible.

    Note: If the article only reports ethnicity percentages for the treatment and control groups, and not number counts, try to determine the number of people who fall into an ethnic category. Then use that number to calculate a more accurate total percentage. For example, the treatment group is listed as having 69% Caucasian, with a treatment group *n* of 35. 35 multiplied by .69 is 24.15—therefore, we can assume that there were 24 European American/Caucasians in the treatment group.

    However, if the group samples are very large, it might be difficult to determine, for example, whether 69% of 167 is actually 116 people or 115 people. In that case, just average the percentages reported for each group to estimate the percentage for the entire sample.

    If a category is not reported in the data, code as -99 even if you could guess that the rest of the categories should be 0%. For instance, if a sample is reported to be 92% European American, 4% African American, and 4% Other, you might assume the other categories should be 0. However, unless 0% is explicitly reported in the article, code the other boxes as -99. This will eliminate confusion due to the fact that researchers' "Other" category will vary in regard to what ethnicities it includes.

| | |
|---|---|
| 17a. European American/European/White | 17d. Asian American/Asian/Pacific Islander |
| 17b. African American/African/Black | 17e. Native American |
| 17c. Latino/a | 17f. Other |

23. *Gender of the sample.* Code the percentage of participants in the study identified as male or female. Report percentages to the nearest tenth, if possible. (Note: Same instructions for calculating ethnicity percentages apply here.)

| |
|---|
| 23a. Female |
| 23b. Male |

24. *Was the equivalence of the groups tested at pretest? That is, were the participants in the treatment and control groups tested for similarity on demographic, anxiety/PTSD/substance use variables prior to treatment?* You will typically find this information reported at the beginning of the of the Results section.

| |
|---|
| 1 Yes<br>2 No |

25a. *Were statistically significant differences found*?

| |
|---|
| 1 Yes |
| 2 No |

25b. *If yes, please specify what variable(s) was found to be different between the groups.*

26. *If pretest differences were found, were these controlled for in the statistical analyses?* Researchers will report this as "controlling for" or including variables as "covariates."

| |
|---|
| 1 Yes<br>2 No |

Descriptors of the Nature of the Treatment

27. *What were the participants primarily seeking treatment for during the recruitment phase?* For example, participants recruited from substance use treatment centers were presumably looking primarily for substance use treatment. Or researchers may report that their recruitment materials stated that they were looking for individuals seeking anxiety treatment. If it unclear from the article, mark as -99.

| |
|---|
| 1 Substance use treatment |
| 2 Anxiety or PTSD treatment |
| 3 Both |

28. *Was study treatment provided in an inpatient or outpatient substance use treatment program?* Treatment must be provided within the SU program to endorse this item. If participants were recruited from SU programs, but no mention is made of whether treatment therapy/medication was provided within the program and it is unclear where treatment was provided, mark as -99.

| |
|---|
| 1 Substance use, in-patient (residential) program |
| 2 Substance use, out-patient (or day) program |
| 3 Substance use, both inpatient and outpatient programs |
| 4 No |

29a. *Minimum number of **days** of abstinence required before intake interview/enrollment in study.*

29b. *Minimum number of **days** of abstinence required before start of active treatment.*

30a. *Psychotherapy treatment duration in weeks, if applicable.* Approximate (or code exact) duration of active treatment***** in weeks from first treatment event to last treatment event, excluding follow-ups designated as such (divide number of days by 7 and round; multiply number of months by 4.3 and round). **Report the maximum number of treatment weeks, if a range is reported.**

*For example, if the active treatment condition is comprised of therapy targeting anxiety and TAU for alcohol, and the comparison condition is TAU for alcohol, count only the weeks of the therapy targeting anxiety.

30b. *Total number of treatment sessions, if applicable.*

30c. *Length of each session, in minutes.*

31a. *Pharmacotherapy treatment in weeks, if applicable.*

31b. *Maximum daily medication dosage.*

31c. *Mean daily medication dosage, if reported.*

32. *Please write out the study's exclusion criteria.*