Study: Dismantling the Components and Dosing of CBT for Co-Occurring Disorders

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Dismantling the Components and Dosing of CBT for Co-Occurring Disorders

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Revision History

Version Date	Summary of Changes	Consent Change? Y/N	Consent Version Date
4-3-2014	Initial partial application (1202S49427)	**N**	**NA**
12/20/2017	Updated protocol to reflect all IRB-approved changes to date.	**Y**	**9/25/17**
2/6/18	Updated appointment time(s) to reflect changes to Lodging Plus programming. Addition of Agreement to be Contact Form at screening appointment.	Y	2/6/18
8/24/18	Addition of Close-Call Interview to all follow-up assessments.	N	NA
4/419	Replacing existing recruitment method with IRB recruitment protocol STUDY000005170.	Y	4/19
10/14/19	Removal of eight-month follow-up study appointment for all participants recruited following approval of MOD00013885	Y	10/19

TABLE OF CONTENTS

ABSTRACT

This study continues our recently completed "parent" R01 grant (AA015069). The parent R01 tested a CBT program for alcohol use disorder (AUD) patients with co-occurring anxiety disorders. The program devoted 3 sessions to each of two putative therapeutic mechanisms: 1) anxiety reduction; and, 2) “de-coupling" the cognitive and behavioral bonds linking anxiety to alcohol use (anxiety reduction alcohol outcome expectancies [AR-AOEs], drinking to cope, and conditioned associations). The RCT showed that when added to AUD treatment as usual (TAU), the CBT resulted in significantly better 4-month alcohol outcomes (e.g., 41% relapse) than did TAU plus a stress/anxiety management control group (e.g., 54% relapse) or a non-randomized cohort undergoing TAU alone (e.g., 61% relapse). However, these effects were only small to medium and fell short by about 50% of fully mitigating the deleterious effect on alcohol outcomes conferred by co-occurring anxiety disorders (e.g., Driessen et al., 2001; Kushner et al., 2005).

Using a dismantling design to test these possibilities, we propose to recruit 350 patients to obtain a final sample of 300 cases with baseline and follow-up data who are randomized to one of three study groups: 1) six sessions of CBT for anxiety reduction (CBT-AR); 2) six sessions of CBT for anxiety-alcohol de-coupling (CBT-DC); or, 3) the original CBT from the parent R01 with three sessions devoted to anxiety reduction and to anxiety-alcohol de-coupling each (CBT-O). To enhance feasibility of the renewal work and ensure its continuity/interpretability with the parent R01, the population and procedures of the proposed work are matched to those used in the parent R01. In brief, alcohol dependent individuals with a co-occurring anxiety disorder will be enrolled within one week of beginning the 28-day residential AUD treatment program, “Lodging Plus.” Patients will undergo five significant assessments: 1) Baseline Assessment (after being deemed eligible but prior to randomization); 2) Post-Treatment Assessment (immediately following the conclusion of the six-session treatment and prior to being discharged from Lodging Plus); 3) One-Month Assessment (about 30 days following completion of the study treatment); 4) Four-Month Assessment (about 120 days following completion of the study treatment); and, 5) Eight-Month Assessment (240 days following completion of the study treatment). Primary alcohol outcomes measures will include categorical variables (any alcohol use) and percent or count variables (e.g., days drinking, drinks per drinking occasion). We will also measure alcohol dependence and hazardous drinking statuses at

follow-ups as well as obtain information about other anxiety or alcohol treatments obtained following the study treatment.

PROJECT DESIGN

Design Overview

We propose to recruit 350 patients to obtain a final sample of 300 cases with baseline and follow-up data who are randomized to one of three study groups: 1) six sessions of CBT for anxiety reduction (CBT-AR); 2) six sessions of CBT for anxiety-alcohol de-coupling (CBT-DC); or, 3) the original CBT from the parent R01 with three sessions devoted to anxiety reduction and to anxiety-alcohol de-coupling each (CBT-O). To enhance feasibility of the renewal work and ensure its continuity/interpretability with the parent R01, the population and procedures of the proposed work are matched to those used in the parent R01. In brief, alcohol dependent individuals with a co-occurring anxiety disorder will be enrolled within one week of beginning the 28-day residential alcohol use disorder (AUD) treatment program, "Lodging Plus." Patients will undergo five significant assessments: 1) Baseline Assessment (after being deemed eligible but prior to randomization); 2)) Post-Treatment Assessment (immediately following the conclusion of the six-session treatment and prior to being discharged from Lodging Plus); 3) One-Month Follow-Up Assessment (30 days following completion of the study treatment); 4) Four-Month Follow-Up Assessment (120 days following completion of the study treatment); and, 5)) Eight-Month Follow-Up Assessment (240 days following completion of the study treatment). Primary alcohol outcomes measures will include categorical variables (any alcohol use) and percent or count variables (e.g., days drinking, drinks per drinking occasion). We will also measure alcohol dependence and hazardous drinking statuses at follow-ups. Predictions are based on the parent R01 findings suggesting (but not demonstrating) a dose-dependent positive relationship for de-coupling therapy elements but not anxiety reduction therapy elements in terms of alcohol outcomes; i.e., CBT-DC > CBT-O > CBT-AR on alcohol outcomes. As a means of confirming that the therapeutic mechanisms targeted were responsible for the group differences obtained, process measures of the therapeutic mechanisms are included at all assessments both to verify their dose-dependent activation in groups and to track temporal patterns of change on the mechanisms relative to the outcomes over follow-ups.

Study Aims:

Primary Aim: To test the dismantled CBT effects by comparing the CBT-DC group to the CBT-AR group on alcohol outcomes. We predict that the CBT-DC group will have superior alcohol outcomes compared to the CBT-AR group. This result would confirm that the de-coupling therapy elements are more active in improving alcohol use disorder (AUD) outcomes than are the anxiety reduction therapy elements.

Secondary Aim: To test dose vs. synergy effects of de-coupling therapy by comparing the CBT-DC group to the CBT-O group on alcohol outcomes. We predict that the CBT-DC group will have superior alcohol outcomes compared to the CBT-O group. This result would show the dose-response effects of de-coupling therapy on alcohol outcomes (6 vs. 3 DC sessions) and confirm that the de-coupling therapy effect on alcohol outcomes is not dependent upon its combination (synergy) with anxiety reduction elements. Alternatively, if CBT-O is superior to CBT-DC, then the critical role of synergy would be demonstrated.

Tertiary Aim: To test the dose effects of anxiety reduction therapy by comparing the CBT-AR group to the CBT-O group on alcohol outcomes. We predict that the CBT-O group will have superior alcohol outcomes compared to the CBT-AR group. Assuming synergy was ruled out in the Secondary Aim, this result would further confirm the hypothesized dose-response effects of de-coupling therapy on alcohol outcomes (3 vs. zero DC sessions). Alternatively, if the CBT-AR group is superior to the CBT-O group, then a critical role for the higher dose of anxiety reduction therapy would be demonstrated.

Recruitment Goal and Strategy:

Strategy: We will recruit individuals entering residential treatment for an alcohol use disorder at the Fairview Hospital Chemical Dependency program (Lodging Plus) for adults in Minneapolis. Participants will be recruited from the Consortium of Addiction Research (CAR) combined screening process, approved as IRB protocol #STUDY00005170. Complete details of the screening process can be found in the protocol for that study. Those who are eligible based on the CAR screening protocol will be invited to participate via the "1404S49427 Invite" and given a copy of the consent form. At the Baseline appointment they will have time to read the consent form and have their questions answered. In addition, they will watch a brief video of the study PI describing key elements of the study. If the staff person conducting the screening appointment is convinced the individual understands the consent form based on their answers to questions highlighting the key elements of participation, the individual will be offered the opportunity to sign the consent form. After signing the Consent Form, the baseline appointment will be completed and the appointments for the CBT therapy will be arranged.

Goals: The Lodging Plus program enrolls about 5 to 10 patients per week and our past experience using this recruitment strategy and inclusion/exclusion criteria allows us to recruit about 2 participants per week. This should allow us to achieve the recruitment goal of 350 individuals in a little over 44 months; however, since recruitment can be uneven at times (e.g., slower around major holidays), we have budgeted 48 months to meet the recruitment goal in this 60 month study. Based on our past experience conducting research in this population, this recruitment goal is feasible using the strategy described.

Participant Population:

Participants will meet DSM IV diagnostic criteria for Panic Disorder (PD), Generalized Anxiety Disorder (GAD), and/or Social Anxiety Disorder (SAD) within the past 30 days; receive current inpatient treatment at Lodging Plus primarily for alcohol (vs. other drug) dependence; and have used in the 30 days preceding the study. They will be recruited through the Fairview Hospital Chemical Dependency program (Lodging Plus) for adults in Minneapolis. Study staff will determine competence to consent and obtain written informed consent from all participants before protocol-specified procedures.

Schema or Brief Procedural Steps:

We propose to recruit 350 patients to obtain a final sample of 300 cases with baseline and follow-up data who are randomized to one of three study groups: 1) six sessions of CBT for anxiety reduction (CBT-AR); 2) six sessions of CBT for anxiety-alcohol de-coupling (CBT-DC); or, 3) the original CBT from the parent R01 with three sessions devoted to anxiety reduction and to anxiety-alcohol de-coupling each (CBT-O). To enhance feasibility of the renewal work and ensure its continuity/interpretability

with the parent R01, the population and procedures of the proposed work are matched to those used in the parent R01. In brief, alcohol dependent individuals with a co-occurring anxiety disorder (SAD, GAD or PD/Ag) will be enrolled within one week of beginning the 28-day residential AUD treatment program, "Lodging Plus." Patients will undergo five significant assessments: 1) baseline (after being deemed eligible but prior to randomization); 2) post-treatment (immediately following the conclusion of the six-session treatment and prior to being discharged from Lodging Plus); 3) one-month (30 days following completion of the study treatment); 4) four-months (120 days following completion of the study treatment); and, 5) Eight-months (240 days following completion of the study treatment). Primary alcohol outcomes measures will include categorical variables (any alcohol use) and percent or count variables (e.g., days drinking, drinks per drinking occasion). We will also measure alcohol dependence and hazardous drinking statuses at follow-ups as well as obtain parallel measures for drug use. Predictions are based on the parent R01 findings suggesting (but not demonstrating) a dose-dependent positive relationship for de-coupling therapy elements but not anxiety reduction therapy elements in terms of alcohol outcomes; i.e., CBT-DC > CBT-O > CBT-AR on alcohol outcomes. As a means of confirming that the therapeutic mechanisms targeted were responsible for the group differences obtained, process measures of the therapeutic mechanisms are included at all assessments both to verify their dose-dependent activation in groups and to track temporal patterns of change on the mechanisms relative to the outcomes over follow-ups

Project Timeline (Table 1):

Months	Activities
1 to 3	1) hire staff; 2) purchase equipment/supplies; 3) create study documents and database; 4) therapist and interviewer training.
4 to 12	1) recruit 65 participants; 2) begin follow-up data collection; 3) begin data entry; 4) quarterly DSMB reports.
13 to 24	1) recruit 95 participants; 2) follow-ups continues; 3) continue data entry; 4) quarterly DSMB reports
25 to 36	1) recruit 95 participants; 2) follow-ups continues; 3) continue data entry; 4) quarterly DSMB reports
37 to 48	1) recruit 95 participants; 2) follow-ups continues; 3) continue data entry; 4) quarterly DSMB reports
49 to 54	1) recruitment complete follow-up data collection only; 2) clean data; 3) break blind; 4) begin data analysis
55 to 60	1) complete data analysis; 2) manuscript preparation and submission

1.0 INTRODUCTION AND OVERVIEW

While it has long been observed that negative affectivity is strongly related to excessive alcohol use (Babor, 1996), it was not until the emergence of modern diagnostic criteria that the size of this association could be quantified using some standard metric. In clinical samples, about 50% of AUD treatment patients can be diagnosed with a co-occurring anxiety disorder (Kushner et al., 2005; Kushner et al., 1990). Numerous community-based epidemiological samples show that alcohol dependence is two to four times more common among individuals with anxiety disorders (Grant et al., 2004; Kessler et al., 1997; Regier et al., 1990). Because anxiety disorders and AUDs are among the most common psychiatric conditions (about 15% and 12% of adults, respectively), the increased risk

for AUDs associated with co-occurring anxiety disorders includes a very large absolute number of individuals. The purpose of this study is to establish a brief CBT intervention that can largely, if not fully eliminate the deleterious effect of common co-occurring anxiety disorders on AUD treatment outcomes

2.0 RESEARCH OBJECTIVES

As noted earlier, this is a continuation study from the parent project showing that a cognitive-behavioral therapy (CBT) we designed to augment standard alcohol use disorder (AUD) treatment for patients with co-occurring anxiety disorder can improve the short-term (i.e., 4 month) alcohol outcomes of these patients compared to those receiving standard AUD treatment with a robust control group (relaxation training) in a randomized controlled trial. The CBT treatment in the parent study divided its focus equally between the goals of anxiety reduction (3 sessions) and decoupling anxiety and alcohol use/urges (3 sessions). However, because both the relaxation control group and the CBT group experienced roughly the same (not significantly different) degrees of anxiety reduction, we deduced that the added clinical benefit came from the decoupling focus of the CBT therapy, which was not present in the control group. This conclusion, along with the modest effect sizes obtained, motivated us to determine two additional pieces of information: 1) could increasing the de-coupling emphasis of the CBT beyond three sessions (i.e., increased dose) provide additional therapeutic benefits; and, 2) is the therapeutic value of the de-coupling elements only realized when combined with a purely anxiety reduction focus. The present study was design to answer these questions by dismantling the two both therapy foci into separate therapy groups (allowing for increased dose of each and an unambiguous evaluation of each foci on its own) and comparing these to the original CBT therapy that combined the therapy foci.

2.1 Primary Aim: To test the dismantled CBT effects by comparing the CBT-Decoupling (DC) group to the CBT-Anxiety Reduction (AR) group on alcohol outcomes. We predict that the CBT-DC group will have superior alcohol outcomes compared to the CBT-AR group. This result would confirm that the de-coupling therapy elements are more active in improving AUD outcomes than are the anxiety reduction therapy elements.

2.2 Secondary Aim: To test dose vs. synergy effects of de-coupling therapy by comparing the CBT-DC group to the CBT-Original (O) group on alcohol outcomes. We predict that the CBT-DC group will have superior alcohol outcomes compared to the CBT-O group. This result would show the dose-response effects of de-coupling therapy on alcohol outcomes (6 vs. 3 DC sessions) and confirm that the de-coupling therapy effect on alcohol outcomes is not dependent upon its combination (synergy) with anxiety reduction elements. Alternatively, if CBT-O is superior to CBT-DC, then the critical role of synergy would be demonstrated.

2.3 Tertiary Aim: To test the dose effects of anxiety reduction therapy by comparing the CBT-AR group to the CBT-O group on alcohol outcomes. We predict that the CBT-O group will have superior alcohol outcomes compared to the CBT-AR group. Assuming synergy was ruled out in the Secondary Aim, this result would further confirm the hypothesized dose-response effects of de-coupling therapy on alcohol outcomes (3 vs. zero DC sessions). Alternatively, if the CBT-AR group is superior to the

CBT-O group, then a critical role for the higher dose of anxiety reduction therapy would be demonstrated.

2.4 Mechanism Manipulation Checks: **Compare groups on pre- to post-treatment change in mechanism process measures.** Determining that the interventions affected the targeted mechanism in the dose-dependent manner intended (e.g., reduction in AR-AOEs is greatest in the CBT-DC group) will allow group differences obtained to be attributed to the action of the targeted mechanisms.

2.5 Time-Dependent Effects: **Explore time-dependent effects between mechanism process measures and alcohol outcomes from BL through 1-mo, 4-mo, and 8-mo FU assessments.** These results will allow for causal inferences between mechanisms and outcomes by demonstrating temporal priority in change.

3. BACKGROUND AND SIGNIFICANCE

3.1. Anxiety disorders frequently co-occur with AUD. While it has long been observed that negative affectivity is strongly related to excessive alcohol use (Babor, 1996), it was not until the emergence of modern diagnostic criteria that the size of this association could be quantified using some standard metric. In clinical samples, about 50% of AUD treatment patients can be diagnosed with a co-occurring anxiety disorder (Kushner et al., 2005; Kushner et al., 1990). Numerous community-based epidemiological samples show that alcohol dependence is two to four times more common among individuals with anxiety disorders (Grant et al., 2004; Kessler et al., 1997; Regier et al., 1990). Because anxiety disorders and AUDs are among the most common psychiatric conditions (about 15% and 12% of adults, respectively), the increased risk for AUDs associated with co-occurring anxiety disorders includes a very large absolute number of individuals.

3.2. Co-occurring anxiety disorders approximately doubles the likelihood of relapse in the months following AUD treatment. Psychopathology in general marks a poor prognosis in substance abuse treatment (Rounsaville et al., 1987) and anxiety disorders mark an approximate doubling of risk for drinking relapse (Driessen et al., 2001; Kushner et al., 2005). For example, Kushner et al. (2005) found that while approximately 21% of the cases with no co-occurring anxiety disorder had relapsed within four months of AUD treatment (i.e., 79% had not relapsed), over 50% with a co-occurring anxiety disorder had relapsed in this same time period. Similarly, Driessen and colleagues (2001) found that a little less than 40% with no co-occurring anxiety disorder had relapsed within six months of AUD treatment compared to over 70% in a group with co-occurring anxiety or depressive disorder. **These and related findings recently led NIAAA to solicit more applications for new research on the treatment of individuals with alcohol dependence and co-occurring anxiety (or depression) disorders (PAS-10-251).**

3.3. Standard psychiatric/psychological treatments for co-occurring anxiety disorders do less to improve AUD outcomes than expected. An intuitively appealing approach for mitigating the increased relapse risk of those with a co-occurring anxiety disorder is simply to treat the anxiety disorder with any of a number of empirically validated psychological/psychiatric treatments.

Eliminating the anxiety disorder – so goes this line of thought – should eliminate its adverse effects on alcohol outcomes. Somewhat surprisingly, however, empirical tests of this idea have not been strongly supportive. Book and colleagues (2008, 2013), for example, found that while social anxiety disorder was well-treated by an SSRI in a group of hazardous drinkers who reported self-medication with alcohol, actual levels of pathological alcohol use remained virtually unchanged following treatment. Similarly, most studies find that adding a standard psychological (e.g., CBT) or pharmacological (e.g., SSRI) anxiety treatment to standard AUD treatment improves anxiety outcomes without improving alcohol outcomes (Bowen et al., 2000; Randall et al., 2001; Schadé et al., 2005). Pursuing this idea further, Hobbs et al. (2011) conducted a meta-analysis of all randomized controlled trials in which a standard CBT or pharmacological treatment for a co-occurring anxiety or depression disorder was given along with standard AUD treatment (study N=15). While there was a medium effect relative to control/placebo for anxiety outcomes (d = .52), there was only a small effect for alcohol outcomes (d = .22). While better internalizing disorder outcomes (i.e., above the median effect; d = .32) were associated with better alcohol outcomes, alcohol and anxiety outcomes were measured at the same time point; i.e., worse alcohol outcomes could have promoted worse anxiety outcomes rather than vice versa.

3.4. Interim summary. There is no affirmative evidence that treating a co-occurring anxiety disorder alone eliminates pathological alcohol use and there is some affirmative evidence that it does not. Treating co-occurring anxiety disorder in parallel with a standard AUD treatment typically provides moderate anxiety relief, but does little to improve AUD treatment outcomes; i.e., effects are sufficiently small to require pooling across multiple studies to identify small effects as significant.

3.5. Concepts aimed at promoting breakthroughs in the treatment of co-occurring disorders.

3.5.1.. Distinguishing initiating from maintaining mechanisms: Mechanisms that initiate a co-occurring disorder may be distinct from those that maintain the disorder once initiated. By analogy, consider that while smoking may cause cancer, quitting smoking is unlikely to cure cancer. From this standpoint, an AUD that initially developed secondary to drinking to cope with an anxiety disorder (e.g., Menary et al., 2011) would not necessarily resolve when the anxiety disorder is treated (e.g., Book et al., 2008, 2013). Similarly, an anxiety disorder that initially developed secondary to physiological and environmental disruptions from pathological alcohol use (e.g., Schuckit & Hesselbrock, 1994) would not necessarily resolve when the AUD is treated (e.g., Kushner et al., 2005). This implies that differences in the order of co-occurring disorder onset, while possibly indicating distinct initiating mechanisms, would not necessarily indicate distinct maintaining mechanisms. Consistent with this inference, there is little prognostic information gained from knowing the order of onset of a co-occurring anxiety or depression disorder in patients (e.g., Carroll et al., 1993; Kushner et al., 2013-a; Rounsaville et al., 1987).

3.5.2. Specifying the mechanisms that promote relapse following treatment: General processes such as "self-medication" and "substance-induced anxiety" do not translate directly into a rich array of mechanism-specific treatment targets. By identifying specific mechanisms that promote relapse following treatment, a roadmap for testable clinical hypotheses emerges that goes beyond the simple provision of independent treatments for co-occurring disorders. For example, the otherwise perplexing failure of standard anxiety therapies to robustly improve AUD treatment

outcomes in patients with co-occurring anxiety disorders could reflect a lack of attention to the dynamic interactions between anxiety symptoms and alcohol use/motivation that persist following standard treatments, such as: a) conditioned associations between anxiety and craving/use; b) the expectation that alcohol resolves anxiety; c) the absence of alternative means of coping with anxiety. Not only could such mechanisms persist following standard treatments, they might promote relapse even when inputs are below clinical thresholds of intensity because the linking mechanisms are already well established. Again, by analogy, a small amount of smoking relative to that which initially caused a cancer could conceivably precipitate a relapse of the cancer after the disease has been arrested.

3.5.3. Recognizing the commonalities in the association of anxiety disorder subtypes with AUD: Based on the neo- Kraepelinian foundation of the DSM III (APA, 1980) and its subsequent revisions, the predominant research paradigm have been to study the association of AUD with each anxiety disorder subtype (e.g., social phobia, panic disorder, generalized anxiety disorder, PTSD) separately in independent and minimally interacting "research silos" (e.g. Driessen et al., 2001; Kushner et al., 2009; Smith & Tran, 2007; Thomas et al., 2008). However, data has been steadily accumulating, indicating that there is a uni-dimensional structure of internalizing psychopathology both in general (e.g., Kendler et al., 2003; Krueger, 1999) and in reference to AUD risk. For example, Kushner et al. (2012a) showed that it is the shared variance among seven common internalizing disorders that relates to AUD risk rather than the variance that is unique to a single internalizing syndrome. Further, Menary et al. (2011) demonstrated that drinking to cope served as a trans-diagnostic mechanism linking a variety of anxiety disorders to both cross-sectional and prospective AUD risk. These findings, along with recent advancements in unified treatment approaches for internalizing disorders (e.g., Barlow et al., 2004; Ellard et al., 2010; Mansell et al., 2008, 2009), converge to suggest that anxiety disorders co-occurring with AUD can be conceptualized and treated trans-diagnostically. This is important because of the high prevalence and inter-correlations among the anxiety disorder subtypes (e.g., Andrews et al., 2002; Boyd et al., 1984; Brown et al., 2001; Kushner et al., 2005; Kushner et al., 2008; Magee et al., 1996). Based on this, the standard paradigm in which multiple independent research teams develop, test, and deploy a separate model and treatment program for every internalizing disorder subtype that co-occurs with AUD is highly inefficient of time, resources and progress and is, moreover, unnecessary.

3.6. The bi-directional positive-feed back ("vicious cycle") model of co-occurring disorders. Our research group has attempted to establish an innovative model of co-occurring disorders that addresses the issues raised above and that is capable of leading to the type of clinical "breakthroughs" sought in PAS-10-251. Kushner et al. (2000a) described a theoretical model in which anxiety and alcohol use can come to exacerbate the other (regardless of their initial temporal relationship) in a "vicious cycle" of positive feedback until both disorders are ultimately fully developed and semi- or fully autonomous of the other. The model also specifies "linking" mechanisms understood to convey these bi-directional effects including the effects of alcohol outcome expectancies (e.g., Kushner et al., 1994, 1999), conditioned associations (e.g., Cooney et al., 1997; Litt et al., 1990), and coping skills (e.g., Larimer et al., 1999) on drinking-related craving and behavior. More recently we have incorporated into the model, alcohol-induced allostasis of neurobiological systems underlying the expression of anxiety and substance dependence (e.g., Koob

& Le Moal, 2008) as contributing to the initiation and maintenance of this vicious cycle and concluded that these neurobiological systems are especially vulnerable to derangement among those with anxiety disorder (Kushner et al., 2011, 2012b). Notably, the model casts these processes as initiation (vs. maintenance) mechanisms linking co-occurring disorders, not because they cease to operate once both disorders are fully developed (we believe they do not), but because their operation is not necessary for the persistence of the fully-developed disorders.
However, once one or both disorders are remitted these mechanisms would again be expected to take on causal significance by potentially reactivating the vicious cycle in response to relatively low (e.g., sub-clinical) levels of anxiety/stress or alcohol use as discussed above. This suggests that in addition to conventional treatments for co-occurring disorders, severing ("de-coupling") the processes linking stress and anxiety to alcohol use/craving would be critical to preventing relapse.

3.7. Development and proof-of-concept of a CBT treatment based on the vicious cycle model. Over 10 years ago, NIAAA supported the PI with R21 funding (AA012426; 2001-2004) to design and pilot test a CBT program based on the vicious cycle model in AUD treatment patients with a co-occurring panic disorder. We employed an "additive" treatment development approach that combined three one-hour sessions of therapy components aimed at reducing panic anxiety with an equivalent dose of therapy components aimed at modifying alcohol expectancies, motivations, coping skills and conditioned responses linking anxiety to cognitive and behavioral aspects of alcohol use. Using a quasi-experimental design, we demonstrated that standard AUD treatment resulted in significantly better alcohol and panic outcomes at four-months following treatment when augmented by the pilot CBT program (Kushner et al., 2006). However, several potentially important limitations in that work included: 1) non-panic related anxiety cases (e.g., social or generalized anxiety) could not be included; 2) a quasi-experimental design; 3) no active control group.

3.8. Validity testing of an expanded CBT treatment based on the vicious cycle model: "The parent R01." Based on the encouraging R21 results, NIAAA provided additional support (AA0105069; i.e., the "parent" R01; 2005-2010 and 2010-2012) for us to conduct an effectiveness trial of an expanded version of the CBT using: 1) a fully experimental vs. quasi-experimental approach; 2) an active anxiety/stress-reduction control treatment vs. TAU only; and, 3) a trans-diagnostic anxiety disorder sample vs. panic disorder only. Findings from the parent R01 are reviewed in the Progress Report section just below but are summarized here: 1) the CBT produced better alcohol outcomes than did the control treatment; 2) both the CBT and the control treatment produced better anxiety outcomes than TAU only; 3) the CBT but not control treatment produced alcohol outcomes superior to TAU. (Note however that the TAU only cohort was not randomized in the parent R01 so findings based on this group must be interpreted with caution.) We deduced from this overall pattern of findings that the therapy components focused on alcohol-anxiety de-coupling but not the therapy components focused on anxiety reduction, accounted for the superior AUD treatment outcomes in the CBT group.

3.9. Progress toward a clinical "breakthrough." The parent R01 validated a brief exportable CBT treatment protocol for a broad range of co-occurring anxiety disorders in AUD treatment patients. The treatment was extrapolated from an innovative model of co-occurring disorders and refined by the PI and his colleagues over a 20-year period of research devoted to this topic. While encouraging,

the findings fall short of "breakthrough" status defined as either: a) producing "large" clinical effects; or, b) completely (or largely) mitigating the increased relapse risk associated with co-occurring anxiety disorder. Regarding the former, the parent R01 established effects that ranged from small to moderate only (see below). Regarding the latter, while the CBT-treated patients relapsed at a rate of about 40% in the parent R01, Kushner et al. (2005) found a 21% relapse at the same time-point among patients without a co-occurring anxiety disorder undergoing the same AUD treatment program. Using these benchmarks, we judge that the parent R01 progressed approximately 50% of the way toward the goal of a clinical "breakthrough" in the treatment of AUD with co-occurring anxiety disorder. It is the broad aim of the proposed renewal work to build upon the knowledge gained in the parent R01 to enhance the therapeutic effect of the CBT program bringing it meaningfully closer to the status of "breakthrough" as defined above**.**

3.10. A "dismantling" approach to identify the active ingredients of the validated CBT while also examining dose and synergy effects. While the failure of anxiety reduction to contribute to improved alcohol outcomes in the parent R01 might seem counter-intuitive, this finding is consistent with studies showing that anxiety treatment alone, or in conjunction with AUD treatment, does not substantially improve alcohol outcomes (Book et al., 2008, 2013; Bowen et al., 2000; Randall et al., 2001; Schadé et al., 2005). These findings can also be reconciled within the vicious cycle model view and empirical findings showing that even sub-clinical stress and anxiety responses can re-engage a previously well-established vicious cycle (e.g., Kushner et al., 2000a; Sinha, 2012). This suggests that the CBT could be improved by re-balancing the distribution of resources away from anxiety reduction and toward anxiety-alcohol de-coupling. However, alternative interpretations of the parent R01 findings suggest that the anxiety reduction elements of the CBT should not be eliminated and perhaps should even be enhanced. First, anxiety reduction might have significantly impacted alcohol outcomes had it been of a greater magnitude. This possibility is consistent with the positive correlation between degree of anxiety reduction and alcohol outcomes reported by Hobbs et al. (2011) in their meta-analysis. Related to this, the degree of anxiety reduction obtained in the parent R01 at about .5 SD over TAU was about half the effect size obtained in RCTs of standard CBT anxiety treatments (Deacon & Abramowitz, 2004). Second, anxiety reduction and anxiety-alcohol de-coupling therapy elements might need to be delivered in combination (as was done in the parent R01) for either to have a positive impact on alcohol outcomes. If this were true, increasing either the de-coupling or anxiety reduction elements of the CBT at the expense of the other could actually decrease the effectiveness of the treatment. The preceding analysis highlights the tension between the need to improve the sub-optimal performance of the

CBT validated in the parent R01 and the modifications that might either improve or worsen the CBT's performance depending upon which of several plausible interpretations of the parent R01 data is correct. Fortunately, resolution of the conflicting interpretations of the parent R01 data that would directly guide enhancements of the CBT treatment's effectiveness could be achieved by contrasting the clinical impact of strategically modified versions of the CBT. To accomplish this, we would compare groups of AUD treatment patients with co-occurring anxiety disorder randomized to receive either: 1) six sessions of CBT for anxiety reduction (CBT-AR); 2) six sessions of CBT for anxiety-alcohol de-coupling (CBT-DC); or, 3) the original CBT with its three sessions each for anxiety reduction

and anxiety-alcohol de-coupling (CBT-O). The resulting knowledge would serve to refine our theoretical model and treatment approach enabling us to move appreciably closer to the type of clinical "breakthrough."

4.0 PRELIMARY STUDIES

4.1. Parent R01 Funding Dates

The original funding period for the parent R01 (AA015069) was 09/2005 to 08/2010.

4.2. Parent R01: Specific Aims

4.1. Primary AIM 1 (completed in Year 1): Expand the focus of the CBT protocol developed for co-occurring panic disorder/agoraphobia (PD/Ag) in the preceding R21 to also include AUD treatment patients with co-occurring generalized anxiety disorder (GAD) or social anxiety disorder (SAD).

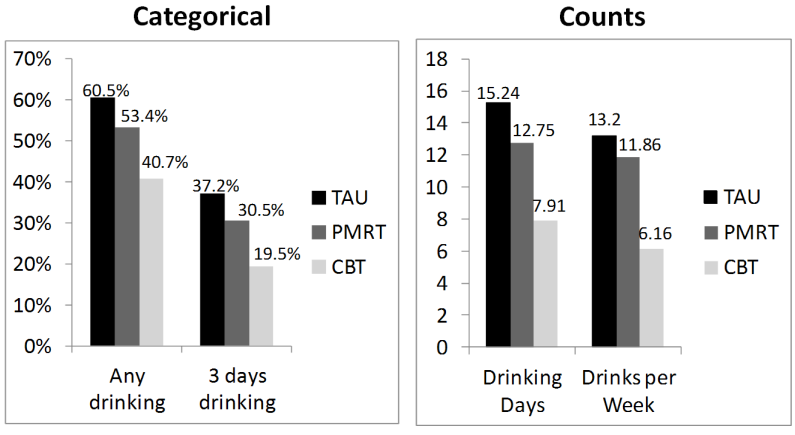
4.2. Primary AIM 2 (completed in Year 5): Conduct a RCT testing the expanded CBT against Progressive-Muscle Relaxation Training (PMRT) in terms of alcohol and anxiety outcomes at 4-mo FU.

4.3. Ad hoc AIM 3 (completed in no cost-extension years 1-2): Obtain non-randomized outcome data in patients with co-occurring anxiety disorders undergoing the AUD TAU to contextualize the size of anxiety and alcohol effects obtained in the RCT. Write reports and publish findings. Begin competitive renewal application.

4.3. Parent R01: Studies and Results

4.3.1. Recruitment. Over the four-year recruitment period for the RCT (Aim 2), we enrolled and randomized 344 cases. This works out to 86 randomized cases per year. In the final year of recruitment for the randomized study, we recruited 88 cases. In the no-cost extension period, we recruited 115 AUD TAU only cases. Based on this, we estimate we can typically recruit about 2 cases per week in the proposed work.

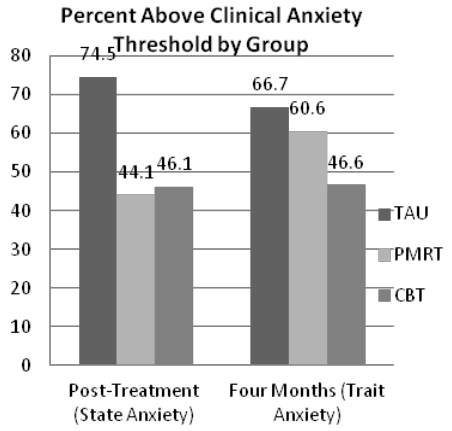
4.3.2. Retention**.** Over the life of the study, our retention rate was 78.5% (i.e., attrition was 21.5%) at the four-month follow-up. Our retention procedures improved significantly as indicated by an 87% retention rate in the final year (i.e., attrition about 13%). Based on this, we estimate a 75% retention rate in the proposed work.



4.3.2. Findings. As can be seen in the graphs, the alcohol outcomes obtained in the CBT group were superior to the other groups in all cases. The effects between the randomized groups (CBT vs. PMRT) were small for categorical outcomes (any drinking: $X^2 = 4.05$, $p = .04$, $d = .26$; and any three consecutive days drinking: $X^2 = 3.71$, $p = .05$, $d = .25$) and medium for count outcomes (drinks per month: $X^2 = 25.63$, $p < .001$, $d = .68$; drinking days per month ($X^2 = 10.23$, $p = .001$, $d = .42$; and number of binge days per month: $X^2 = 13.46$, $p < .001$, $d = .48$ [the latter is not shown in the graph]). These results support the key study hypothesis from Aim 2 of

the parent R01; i.e., that CBT would produce superior alcohol outcomes relative to a randomized active treatment control. They further demonstrate that the active treatment control, PMRT, did not significantly improve alcohol outcomes relative to TAU controls; however, since the TAU group was not randomized, caution must be taken when interpreting the latter findings. Although patient's "principal" anxiety disorder did not moderate these study results, level of BL anxiety was the only significant moderator; i.e., lower BL anxiety was associated with reduced CBT effects.

Also pertaining to Aim 2, is the hypothesis that the CBT would produce superior anxiety outcomes relative to the randomized PMRT control treatment. These results are shown in the graph below. (Note that State Anxiety ratings best captured the brief time-frame between the conclusion of treatment and the post-treatment assessment, while Trait Anxiety ratings best captured the 120-day period between the conclusion of treatment and the four-month assessment.) As can be seen on the left side of the graph, both the CBT and
PMRT groups were significantly less likely to exceed the clinical threshold score (i.e., $\geq$ 44) relative to the TAU group (X^2 = 11.24, p < .001, d = .56; and X^2 = 13.36, p < .001. d = .58, respectively). The right side of the graph shows that at the four-month assessment, both the CBT and TAU groups had changed little since the post-treatment assessments in terms of the percent that were above the clinical threshold; i.e., CBT still



demonstrated a significant advantage over TAU in terms of clinical anxiety status (X^2 = 6.34, p = .01, d = .40). By contrast, the PMRT group was substantially worse in terms of the anxiety threshold at the 4-month assessment relative to the post-treatment assessment. This change is reflected in the significant CBT vs. PMRT group difference at the latter (but not the former) assessment point (X^2 = 4.19, p = .04, d = .29). Again, however, it is important to note that the TAU group was not randomized so comparisons involving this group are qualified.

4.3.4. Publications. Primary data from the parent R01 were recently published (Kushner et al., 2013-a, 2013-b) in the Journal *of Consulting and Clinical Psychology* (JCCP) and *Psychological Medicine* (PM). Note however, that numerous other publications have been supported by the parent R01 as listed in subsection 4.6 below.

4.4. Parent R01: Significance

The practical significance of the parent R01 findings is in showing that augmenting AUD TAU with a six-session CBT reduces four-month relapse rates in those with co-occurring anxiety disorders by about one-quarter to one-third (i.e., TAU = 60%; PMRT = 53%; CBT = 41%). Although this eliminates only about half of the estimated increase in relapse risk attributable directly to the presence of a co-occurring anxiety disorder (e.g., Kushner et al., 2005), the large number of AUD treatment patients affected by co-occurring anxiety disorders (up to 50% of all cases) amplifies the potential benefit to the public health of these results. The aspects of the parent R01 findings with the greatest potential for theoretical significance are those pointing to the active ingredients by which the CBT improved AUD outcomes. The CBT and PMRT both produced a significant reduction in the percent of patients experiencing clinical-level anxiety at the post-treatment assessment, while only

the CBT demonstrated significantly better alcohol outcomes relative to TAU at the four-month assessment. These findings reinforce past studies showing that anxiety disorder treatment does not produce detectable improvements in alcohol outcomes (above). More importantly, these findings imply that the de-coupling therapy elements were the active ingredients that improved alcohol outcomes in the CBT group. This conclusion has the theoretical potential of informing modification to the CBT that would substantially improve its clinical effectiveness.

4.5. Parent R01: Plans

The parent R01, while having successfully achieved its specific aims and confirmed its primary hypothesis, fell short of producing a clinical "breakthrough" defined as a treatment with large clinical effects that eliminates most or all of the deleterious effect of co-occurring anxiety disorders on AUD treatment outcomes. Fortunately, the results of the parent R01 point the way to modifications to the CBT that could further amplify its therapeutic effects. Our plan is to employ a "dismantling" research approach in a renewal of the parent R01 to implement and test these ideas. We believe this will allow us to achieve our ultimate goal of establishing a brief CBT intervention that can fully (or largely) mitigate the deleterious effect of common co-occurring anxiety disorders on AUD treatment outcomes.

4.6. Parent R01: Publications

The following list contains publications that either present the results of the parent R01 or were otherwise supported by the parent R01 and related to its specific aims.

1. **Kushner, M.G**., Donahue, C., Sletten, S., Thuras, P., Abrams, K., Peterson, J., Frye, B. (2006). Cognitive behavioral treatment of comorbid anxiety disorder in alcoholism treatment patients: Presentation of a prototype program and future directions, *Journal of Mental Health, 15*, 697-708.

2. Donahue, C., **Kushner, M.G**. (2007). Stress, anxiety, and addiction: Intervention strategies. In M. Al'Absi (Ed.), Stress and Addiction (pp. 301-314). Academic Press, London

3. **Kushner, M.G**., Donahue, C., Frye, B. Book, S.W., Randall, C.L (2007). Which to treat first: Comorbid anxiety or alcohol disorder, *Current Psychiatry, 6(8),* 55-64.

4. **Kushner, M.G**., Krueger, R., Frye, B., Peterson, J. (2008). Epidemiological perspectives on co-occurring anxiety disorder and substance use disorder. In Anxiety and Substance Use Disorders Co-morbidity, S. Stewart and P. Conrod (Eds.). Springer Publishing

5. Donahue, C.B., **Kushner, M.G.**, Thuras, P.D., Murphy, T.G., Van Demark, J.B., Adson D.E. (2009). Effect of quetiapine vs. placebo on response to two virtual public speaking exposures in individuals with social phobia, *Journal of Anxiety Disorders,* 23(3), 362-368. PMID: 19157776

6. **Kushner, M.G**., Sletten, S., Donahue, C., Thuras, P., Maurer, E., Schneider, A., Frye, B., Van Demark, J. (2009). Cognitive-behavioral therapy for panic disorder in patients being treated for alcohol dependence: Moderating effects of alcohol outcome expectancies. *Addictive Behaviors, 34*, 554-560. PMCID: PMC2810649

7. **Kushner**, **M.G**., Maurer, E., Menary, K., Thuras, P. (2011). Vulnerability to the rapid ("telescoped") development of alcohol dependence in individuals with anxiety disorder, Journal of Studies on Alcohol and Drugs, 72(6), 1019-27. PMID: 22051216. PMCID: PMC3211955

8. Hobbs , J.D.J., **Kushner, M.G**., Lee , S., Reardon, S.M., Maurer, E. (2011) Meta-analysis of supplemental treatment for depressive and anxiety disorders in patients being treated for alcohol dependence, *American Journal on Addictions, 20*, 319-329. PMCID: PMC3124006

9. Menary, K., **Kushner, M.G**., Maurer, E., Thuras, P. (2011). The prevalence and clinical implications of self-medication among individuals with anxiety disorder. *Journal of Anxiety Disorders, 25*, 335-339. PMCID: PMC3053060

10. **Kushner, M.G.**, Menary, K.R., Maurer, E.W., Thuras, P. (2012). Greater elevation in risk for nicotine dependence per pack of cigarettes smoked among those with an anxiety disorder, *Journal of Studies on Alcohol and Drugs. 73(6),* 920-924. PMID: 23036209

11. **Kushner, M.G**., Wall, M.M., Krueger, R.F., Sher, K.J., Maurer, E. Thuras, P., Lee, S. (2012). Alcohol dependence is related to overall internalizing psychopathology load rather than to particular internalizing disorders: Evidence from a national sample, *Alcoholism: Clinical and Experimental Research, 36(2),* 325-31. PMID: 21895708. PMCID: 3235250

12. **Kushner, M.G**., Maurer, E., Thuras, P., Donahue, C., Frye, B., Menary, K.R., Hobbs, J.D.J, Haeny, A., Van Demark, J. (2013-a). Hybrid cognitive-behavioral therapy versus relaxation training for co-occurring anxiety and alcohol disorder: A randomized clinical trial. *Journal of Consulting and Clinical Psychology, 81(3*), 429-442.

13. **Kushner, M.G**., Krueger, R.F., Wall, M.M., Maurer, E.W., Menk, J.S., Menary, K.R., (2013-b) Modeling and treating internalizing psychopathology in a clinical trial: A latent variable structure equation modeling approach, *Psychological Medicine*, online pending print publication, DOI: http://dx.doi.org/10.1017/S0033291712002772

14. Book, S.W., Thomas, S.E., Smith, J.P., Randall, P.K., **Kushner, M.G**., Bernstein, G.A., Specker, S.M., Miller, P.M., Randall, C.L. (2013). Treating individuals with social anxiety disorder and at-risk drinking: Phasing in a brief alcohol intervention following paraxotine. *Journal of Anxiety Disorders*, *27(2),* 252-258. doi: 10.1016/j.janxdis.2013.02.008.

15. **Kushner, M.G.** (accepted). 75 years of comorbidity research in the journal of studies on alcohol and drugs, *Journal of Studies on Alcohol and Drugs*. Invited for the Journal's 75th anniversary edition.

5.0 RESEARCH DESIGN

5.1 . Overview.

This is a between-group randomized clinical trial with 350 patients to randomized to one of three study groups: 1) six sessions of CBT for anxiety reduction (CBT-AR); 2) six sessions of CBT for anxiety-alcohol de-coupling (CBT-DC); or, 3) the original CBT from the parent R01 with three sessions devoted to anxiety reduction and three sessions devoted to anxiety-alcohol de-coupling (CBT-O). Alcohol dependent individuals with co-occurring SAD, GAD or PD/Ag will be enrolled within one week of beginning the 28-day residential AUD treatment program, Fairview "Lodging Plus" in Minneapolis. All study treatments will take place while patients are still in the Lodging Plus program; i.e., one hour sessions during patient free-time (i.e., no conflicting programming) for six consecutive business days. Patients will undergo four significant assessments: 1) baseline (after being deemed eligible but prior to randomization); 2) post-treatment (immediately following conclusion of the six-session treatment and prior to being discharged from Lodging Plus; 3) one-month (30 days following completion of the

study treatment); and, 4) four-months (120 days following completion of the study treatment); 5)) Eight-Month Follow-Up Assessment (240 days following completion of the study treatment). Primary relapse measures will include categorical (any alcohol use, hazardous drinking, alcohol dependence) and continuous/counts (e.g., days drinking, drinks per drinking occasion, binge days) variables. Following approval of MOD00013885 we will not complete the eight-month follow-up assessment on recruited participants. Because the primary outcomes for this study will be collected at the four-month follow-up appointment, this modification will allow us to continue recruitment through February 2020, with recruited participants able to complete the four-month follow-up prior to the end of the funding period for this project in June 2020.

5.2. Overview of Study Visits (Table 2)

The following table provides a general overview of the study visits:

	Baseline	CBT (6 sessions daily sessions)	Post-Treatment	1 month follow-up	4 month follow-up	8 month follow-up
Consent	X					
Interviews	X			X	X	X
Questionnaires	X		X	X	X	X
Talk therapy		X				
Duration	1-2 hours	1-1.5 hours Ea session	2-2.5 hours	2-2.5 hours	2-2.5 hours	2-2.5 hours
Protocol Days	1	2-7	8	40	130	250
Payment	$25	$5 per completed session	$25	$50	$100	$100

6.0 STUDY PROCEDURES

6.1. Recruitment Strategy. Strategy: We will recruit individuals entering residential treatment for an alcohol use disorder at the Fairview Hospital Chemical Dependency program (Lodging Plus) for adults in Minneapolis. Participants will be recruited from the Consortium of Addiction Research (CAR) combined screening process, approved as IRB protocol #STUDY00005170. Complete details of the screening process can be found in the protocol for that study. Those who are eligible based on the CAR screening protocol will be invited to participate via the "1404S49427 Invite" and given a copy of the consent form. At the Baseline appointment they will have time to read the consent form and have their questions answered. In addition, they will watch a brief video of the study PI describing key elements of the study. If the staff person conducting the screening appointment is convinced the individual understands the consent form based on their answers to questions highlighting the key elements of participation, the individual will be offered the opportunity to sign the consent form. After signing the Consent Form, the baseline appointment will be completed and the appointments for the CBT therapy will be arranged.

Lodging Plus evaluates approximately 1000 chemically dependent patients per year, approximately 70% of whom are seeking treatment for alcohol dependence. Based on our experience in the parent R01 (see above), we should be able to recruit about two patients per week and a total of about 90-100 patients per year. Based on this, the target sample of 350 will be recruited in slightly less than 4 years. Our attrition rate over the entire life of the study was about 20% but was approximately 15% in the final year. (Note improvements in recruitment and retention over the course of the parent R01 reflects refined and improved methods based on our accumulating experience.) Based on the attrition estimate of 15%, we would have approximately 300 cases with four-month follow-up data, which will well power the study (see power estimates below).

6.2. Participant Selection

6.2.1 General description of participants anticipated. Male and female ages 18-65 will be recruited from among those individuals seeking treatment for an alcohol use disorder at the Fairview Hospital Chemical Dependency program (Lodging Plus) for adults in Minneapolis. Based on our earlier studies conducted in this same population and program, we anticipate that the mean age of participants will be approximately 39 years old. The sample will be 40% female with 83% self-described as Caucasian, 10% African American, 5% American Indian, 1% Hispanic, and 1% Asian. We are seeking to recruit 350 individuals over a 48 month period.

6.2.2. Lodging Plus alcohol use disorder (AUD) treatment as usual (TAU). As noted, all patients will be selected from incoming patients at the Lodging Plus TAU. Individuals from whom we will attempt to recruit will undergo the Lodging Plus TAU whether or not they participate in the research. The AUD TAU program is based on the "Minnesota Model" in which the primary goal is lifetime abstinence from alcohol with therapies based on principles of the 12-step philosophy, including frequent meetings with other recovering people, repair of family relationships, healthy changes in daily behaviors and attention to spiritual growth. Treatment programming primarily takes place in 1 hour group sessions with programming from 8:30 a.m. to 4:30 p.m., with two, one-hour breaks during the day, Monday through Friday. (All study activities involving patients take place during patient free-time when there is no conflicting programming).

6.3. Screening

6.3.1. Participant Screening:

We will recruit individuals entering residential treatment for an alcohol use disorder at the Fairview Hospital Chemical Dependency program (Lodging Plus) for adults in Minneapolis. Participants will be recruited from the Consortium of Addiction Research (CAR) combined screening process, approved as IRB protocol #STUDY00005170. Complete details of the screening process can be found in the protocol for that study.

6.3.2 Consent (10 minutes): Those who are eligible based on the CAR screening protocol are next given the consent form and baseline appointment invitation via a sealed note slipped under the door of their semi-private bedroom on Lodging Plus or handed to them if they answer their door when the staff member knocks. The note will be marked "Confidential" and will be stapled shut with only their first name, last initial, and room number visible. They will be directed to read the Consent Form and at the Baseline appointment the staff member will answer their questions and clarify through a set of pre-determined questions whether the individual understood the key tasks, risks and benefits of participating described in the consent form. In addition, they will watch a brief video of the study PI

describing key elements of the study. If the individual understands these details and chooses to sign the consent form, they next undergo the baseline assessment described in section 6.4.2. These activities take place during the patients free time in the Lodging Plus program (i.e., no conflicting programming) in the Ambulatory Research Center on the 2nd floor of the Fairview West building (a location on a different floor in the same building as the Lodging Plus program that is private relative other LP patients or staff members).

6.3.3. Inclusion criteria include**:**

a) DSM IV diagnosis of PD, GAD, and/or SAD within the past 30 days;
b) inpatient treatment at Lodging Plus primarily for alcohol (vs. other drug) dependence
c) alcohol use in the 30 days preceding the study
d) ability to provide informed consent
e) minimum of a sixth grade reading level (deemed necessary to complete study materials);
f) Willingness to provide contact information to confirm study follow-up appointments
g) Lives within proximity to the Twin Cities (e.g., within about an hour's drive) for the purpose attending follow-up visits
h) between the ages of 18 and 65

6.3.4. Exclusion criteria include**:**

a) lifetime history of psychosis or mania by history
b) cognitive or physical impairment that precludes study participation
c) currently and seriously suicidal (i.e., plan and intent)
d) primary PTSD as determined by the qualifying assessment or borderline personality disorder as determined by the screening form
e) In Lodging Plus because they were court ordered to receive chemical dependency treatment.

Note that all inclusion and exclusion criteria is assessed as part of the Consortium of Addiction Research combined screening process approved as IRB protocol #STUDY000005170.

6.4. Assessments: (about 2 hours for each assessment including Baseline, Post-Treatment, 1-mo, 4-mo and 8-mo follow-up assessments; see Table above). A general description of the task of each assessment is given here with a fuller

6.4.1 Interviews/Diagnoses

a). Structured Clinical Interview for DSM IV (SCID). (45 minutes) Selected modules from the SCID to determine diagnostic status with reference to anxiety disorders, depression and alcohol/drug use disorders. The SCID is essentially a checklist of psychiatric diagnostic criteria (i.e., symptoms and problems) that are rated by the interviewer as "present," "absent" or "sub-clinical" or "in-determinant." This is administered at the follow-up appointments of the study.

b) Timeline Follow-Back (TLFB). (15 minutes)The TLFB interview will be used in all primary assessment to identify daily drinking patterns of patients in the four months before treatment and in the intervals between study assessments. Using a calendar, the respondent provides retrospective estimates of daily drinking over a specified amount of time.

6.4.2 Questionnaire Packets (1 to 1.5 hours) (Each questionnaire takes about 5 minutes to complete and typically includes 20 multiple choice questions or less) (References and rationale for questionnaires are provided below).

a) Anxiety.
- State-Trait Anxiety Inventory (STAI)
- Penn State Worry Questionnaire (PSWQ)
- Beck Depression Inventory (BDI)
- Panic Disorder Severity Scale (PDSS)
- Social Phobia Scale (SPS)
- Inventory of Depression and Anxiety Symptoms (IDAS)
- Perceived Stress Scale (PSS)

b) Alcohol.
- Alcohol Expectancy Questionnaire (AEQ)
- Inventory of Drinking Situation (IDS)
- Situational Confidence Questionnaire (SCQ)
- Obsessive-Compulsive Drinking Scale (OCDS)
- Addiction Severity Index (ASI)
- Reasons for Drinking Questionnaire (RFDQ).
  - Drinking to Cope Questionnaire (DCQ)
  - Negative Emotions and Use Questionnaire (NEUQ)

c) Other
- Demographics
- Treatment Services Summary (TSS)
- Suicidality Questionnaire (SQ)
- Personality Inventory for DSM-5 Brief Form (PID-5)

6.5. The CBT Therapy (six daily one-hour sessions)

6.5.1. Background of the CBT and modifications pertinent the proposed work. The CBT treatment used in the parent R01 (see Kushner et al., 2013) included three 1-hour anxiety reduction sessions (AR content set) and three 1-hour alcohol-anxiety de-coupling sessions (DC content set). Parallel clinical domains are addressed in both the AR and DC content sets focused on: 1) cognitive restructuring; 2) coping skills training; and, 3) practice with exposure/habitation. The material for the AR content set was synthesized from a survey of published work related to the bio-psycho-social model of anxiety (e.g., Barlow, 2001; Barlow et al., 1989), cognitive restructuring of anxiety related cognitions (e.g., Beck, 1976; Beck et al., 2005; Ellis & Harper, 1975), breathing retraining for coping with anxiety (e.g., Han et al., 1996), and exposure for habituating conditioned anxiety responses (e.g., Foa & Kozak, 1986). The material for the DC content set was synthesized from published work related to the vicious cycle model of alcohol and anxiety (e.g., Kushner et al., 2000a), cognitive restructuring of alcohol-related beliefs and expectancies (e.g., Beck et al. 1993, Kushner et al., 2000b), alternatives to drinking for coping with anxiety (e.g., Larimer et al., 1999), and exposure for habituating conditioned associations between anxiety and alcohol cues (e.g., Cooney et al., 1997; Litt et al., 1990; Sinha, 2009). The therapy doses chosen in the parent R01 (3 sessions for anxiety reduction and 3 for alcohol-anxiety de-coupling for 6 total sessions) represented a balancing of

competing interests in delivering therapeutic levels of the interventions for both theoretically central mechanisms (anxiety reduction and anxiety-alcohol de-coupling) while: 1) not interfering with the full day of standard AUD programming; 2) beginning at least one week after detoxification to accommodate recruitment time and to ensure therapy is delivered post-acute detoxification; and, 3) concluding treatment prior to discharge from the 28-day residential AUD program to avoid conflicts with re-location, return to place of employment, transportation etc. These parameters will apply to the renewal project conducted in the same institutional setting was the parent R01. The CBT-O group in the renewal work will be the same CBT protocol used in the parent R01; i.e., the three-session AR content set plus the three-session DC content set for a total of six sessions. The two dismantled CBT therapy conditions will include one of the three-session content sets (AR or DC) plus one additional session devoted to each of the three clinical domains (cognitive restructuring, coping skills, and exposure/habituation) within that set for a total of six sessions for all therapy groups.

6.5.2. Elements common to all three CBT therapy group conditions:

a) Psycho-Education in which the participant is introduced to the basics of the CBT model of therapy. This portion of the treatment is largely didactic and includes powerpoint slides that are narrated by the therapist.

b) Cognitive Coping Skills in which the participant is taught how to distinguish between thoughts, feelings and situations that are associated with negative affect (i.e., stress, anxiety and depression) and how each of these components interact with the others. Participants are then taught and practice a standard CBT skill referred to as "cognitive-restructuring" in which thoughts and beliefs that aggravate negative affect through their inaccuracy, incompleteness, or exaggeration are systematically examined and modified to better align with probabilistic reality and logical inference. This process has been shown in 100s of separate studies to improve anxiety and depression symptoms in psychiatric patients.

c) Behavioral Coping Skills in which the participant is taught behavioral strategies to reduce negative affect and tension. These include slow-paced diaphragmatic breathing and "behavioral activation." Behavioral activation is an intervention in which goals identified as important by the participant in several domains of life (e.g., social, health, occupational, educational) are identified and a specific realistic plan of activities aimed at moving toward those goals is developed. Past studies in psychiatric patients have shown that engaging in behavioral activation relieves negative affect and improves life satisfaction.

d) Coping Skills Practice with Guided Imagery exposure in which participants will have the opportunity to apply cognitive and behavioral coping skills while imagining being in a common situation in which they have experienced moderate negative affect associated with their anxiety disorder. The actual content of the guided imagery exercise is provided by the participant with explicit instructions and therapist guidance aimed at avoiding content related to extreme distress such as that associated with trauma. Using guided imagery "exposure" in this way is a standard component of CBT used when real life (in-vivo) exposures are too intense or are not feasible; as will generally be the case while residing at Fairview hospital during the course of the CBT It is generally found that imagery based exposures of this sort are less intense than actually being in the situation imagined. Also, it is a central tenet of CBT that therapeutic skills that are practiced while being in stressful situations (or imagining them in this case) are more clinically effective; i.e., are more likely to be deployed at all or to be deployed effectively when real-life stressors occur. The PI is a licensed

psychologist and practicing CBT therapist who has routinely used this and other CBT techniques described for over 20 years.

e) Post therapy session knowledge quizzes will be given after each session to document that the participant understood the major points covered in that session. These quizzes are designed to be easy to answer correctly if the patient was actively participating in the session. The therapist will provide immediate feedback on the quiz and will emphasize why another answer is considered correct if any questions are answered incorrectly.

f) Between session practice and monitoring will be assigned following each of the six CBT therapy sessions that will focus on practicing the skill taught in the session and keeping a simple record of their anxiety level and urge to use alcohol between the sessions as well as whether they were able to effectively use the therapy skill to reduce the negative affect/urge.

6.5.2. Elements distinguishing the three randomized CBT therapy group conditions:

a) CBT-Anxiety Reduction Condition: Those assigned to this group will undergo all of the CBT elements outlined above but with all six sessions focused on negative affect without specific reference to alcohol alcohol use.

b) CBT Anxiety-Alcohol Interaction Condition: Those assigned to this group will undergo all of the CBT elements outlined above but with all six sessions focused on the interaction of negative affect with alcohol use/urges.

c) CBT Combination Condition: Those assigned to this group will undergo all of the CBT elements outlined above but with three of the six sessions focused exclusively on reducing negative affect without reference to alcohol use and the other three sessions focused exclusively on the interaction of negative affect with alcohol use/urges.

6.5.3. Therapist training. The study PI is primarily responsible for training and supervision of study therapists. The training sequence established in the parent R01 will also be used in the renewal work including: 1) reading the therapist and patient treatment manuals; 2) observing training tapes that have been prepared for that purpose; 3) observing the trainer administer the treatment; and 4) being observed and critiqued by the trainer while delivering the treatment. Our experience suggests that delivery of the therapy via the structured PowerPoint slideshow (above) ensures a uniform delivery of the basic content of the therapy, even with newly trained therapists. Supervision with the PI takes place on a weekly basis throughout the treatment phase of the project (separately for each therapist) in which the progress of each case is discussed and any treatment issues are resolved.

6.5.4. Therapy compliance and fidelity. The renewal project is fortunate to have added a new Co-I, Dr. Marc Mooney, who has served in the role of therapy compliance and fidelity assessment in substance abuse treatment protocols using psycho-social interventions. All therapy sessions will be recorded and a randomly selected 15% will be reviewed by Dr. Mooney according to a checklist and scales modified after the *Yale Adherence and Competency Scale (YACS) (2nd ed) (*Di Rezze et al., 2012; *Nuro et al., 2005)*. The YACS "is a general system for rating therapist adherence and competence in delivering behavioral treatments for substance use disorders" (p. 1). Fidelity checklists and scales will include prescribed and proscribed content, as well as therapy processes (Waltz et al., 1993). All deviations from the therapy protocol, especially contamination across treatment conditions, will be addressed at weekly supervision sessions with the research therapists. The PI will decide whether any protocol violation identified warrants remedial training for the therapist and the implications for data integrity. All such violations will be logged and incorporated into final data reports (Perepletchikova

et al., 2009). As of September, 2016, Hoa Le, M.A., a former therapist for this study, took over the role of therapy compliance and fidelity checks from Dr. Mooney.

6.6. Treatment Duration

The study treatment lasts for six consecutive business days, which, given weekends and occasional interruptions due to things such as family meetings, illness, and outside appointments leads us to reserve 10 days to complete the six sessions. These sessions all take place while the participant is a residential patient in the Fairview Lodging Plus AUD TAU, which is typically a 28-day treatment program.

6.7. Study Duration

6.7.1. Grant funding period. The grant is being funding for a period of 60 months (5 years). (See Table 2 above)

6.2.2. Projected timeline of grant-related activities. See Table 1 above for the projected timeline of all primary study phases.

6.8. Measures. All assessments (except for the qualifying assessment) are identical. However, the timeframe around which interview questions are posed refers to "since your last assessment.

6.8.1. Screen for current intoxication. If we suspect that a patient is intoxicated, blood alcohol concentration will be measured using the AlcoMate Core Breathalyzer measures BAC% between 0.00% and 0.40% in 0.01% steps. Sensor accuracy of the AlcoMate is +/- 0.005% BAC. This measure will be taken prior to any study related interactions with patients to insure they are not intoxicated at the time. If a patient's BAC is above .04% scheduled tasks for that day will be rescheduled. If the patient is driving their self, alternative arrangements will be made for their transportation home and arrangements will be made with parking services to allow their car to remain on the facilities for up to 24 hours at no cost to the patient.

6.8.2. The Structured Clinical Interview for DSM IV (SCID): The SCID (First et al., 1989) will be used to establish all relevant study diagnoses during the STUDY000005170 screening process and at follow-up appointments. Diagnostic modules include panic disorder (with or without agoraphobia) (PD), social anxiety disorder (SAD), generalized anxiety disorder (GAD), major depressive disorder (MDD), post-traumatic stress disorder (PTSD), alcohol dependence (AD) and drug *dependence (DD*). The SCID will also be slightly modified to establish a "principal" anxiety disorder (PD, SAD, or GAD) for those participants with more than one of the inclusionary anxiety disorders (Andrews et al., 2002). A qualified SCID trainer (includes the PI and Co-I, Skalski) will be responsible for training the *blinded assessor* in the valid use of the SCID using standard training materials (First et al., 1989). All diagnostic decisions will be made using a clinical consensus model with the PI adjudicating any cases in which the team could not reach consensus. All interviews will be videotaped and 15% will be double-scored to index reliability (Co-I, Skalski will oversee this along with therapy fidelity).

6.8.3. The Time Line Follow-Back (TLFB). The TLFB interview (Sobell & Sobell, 1995) will be used to identify daily drinking patterns of patients in the four months before treatment and in the intervals between study assessments. The TLFB has been shown to have adequate psychometric *qualities* in both clinical and non-clinical populations (Sobell & Sobell, 1995). Using a calendar, the respondent provides retrospective estimates of daily drinking over a specified amount of time. All primary and

secondary alcohol outcomes, with the exception of alcohol dependence from the SCID, will be derived from the TLFB assessment including: 1) any use vs. abstinence; 2*) percent or number (depending on the distribution) days drinking per month; 3) number of drinks per drinking day; and*, 4) NIAAA-defined "hazardous drinking" (for men: > 4 drinks in a day or 14 drinks in a week; for women: > 3 drinks in a day or 7 drinks in a week*) status.*

6.8.5. Anxiety questionnaires. Because we recruit patients with a variety of anxiety disorder subtypes characterized by a distinct constellation of anxiety symptoms (i.e., generalized anxiety disorder, social anxiety disorder or panic disorder with or without agoraphobia), it is challenging to find a single index that reasonably characterizes anxiety levels for the entire sample. Based on work in the parent R01, we have identified several solutions to this problem. First, in Kushner et al. (2013-a) we used the State and Trait Anxiety Inventory (STAI) (Spielberger et al., 1999) as a general measure capable of representing anxiety-related dysfunction across the range of specific anxiety disorders included (c.f., Oei, et al., 1990). Second, in Kushner et al. (2013-b) we showed that multiple domains of internalizing psychopathology symptoms – Penn State Worry Questionnaire (Meyer et al., 1990); Beck Depression Inventory (Beck et al., 1961); Panic Disorder Severity Scale (Houck et al., 2002); Social Phobia Scale (SPS) (Brown et al., 1997); Mobility Inventory (Chambless et al., 1985); State and Trait Anxiety version of the State-Trait Anxiety Inventory (STAI) (Spielberger et al., 1999) – can be well represented by two latent factors labeled "fear" and "distress." By establishing that these latent structures were invariant across time and treatment, we demonstrated they could be used to quantify treatment effects. A third approach uses SCID-based anxiety diagnoses: 1) determining at FU the participant no longer meets diagnostic criteria for the qualifying (principal) anxiety disorder diagnosis; or, b) determining at FU the participant no longer meets diagnostic criteria for any if the three inclusionary anxiety disorder diagnosis assessed. Each of these approaches to quantifying change in anxiety by group will be utilized; however, latent fear and distress measures will constitute the primary anxiety process measures (see Data Analysis section below).

6.8.6. Alcohol-anxiety de-coupling questionnaires . The following measures will be used to quantify change in alcohol-anxiety de-coupling: 1 Expectancies - the Alcohol Outcome Expectancy Questionnaire (OEQ) (tension-reduction scale) (Leigh & Stacy, 1993); 2) Coping - the Situational Confidence Questionnaire (SCQ) (unpleasant emotions and social tensions subscales) (Annis, 1988); 3) Conditioned Associations - the Obsessive-Compulsive Drinking Scale (OCDS) (Flannery et al., 1999, 2001).

6.8.7. Determinants of relapse measures**.** The Reasons for Drinking Questionnaire (RFDQ) (Zywiak et al., 1996) will be employed at BL and all FUs to establish scores on participants' reasons for drinking. At BL, the 16-item questionnaire will be referenced to their "typical drinking" in the past 4 months (reasons for drinking). At the FU's, the questionnaire will be referenced to the first use of any alcohol since the previous assessment and also to any other uses of alcohol after at least 14 days of abstinence, as was done in Project MATCH (e.g., Zywiak et al., 2006). Based on factor analytic work produced by Zywiak et al. (2003), the RFDQ will be scored using three subscales including: 1) Negative Affect; 2) Social Pressure; 3) Craving/Cued. Each relapse assessed at follow-up will use the Zywiak et al. (2003) scoring algorithm to obtain both a continuous score on each subscale and a categorical assignment on one scale as the primary determinant of the relapse.

6.8.9. Close-Call Interview. An investigator-developed close-call interview will be administered at all follow-ups to obtain information on "close-call" relapse situations (i.e., situations in which the

participant believes they were at risk of using alcohol ("relapse") but managed to refrain) as well as the therapy "tools" the participant used (if any) to avoid the relapse. This information will be useful to evaluate the effectiveness of the tools we are currently teaching and to help identify areas in which we may need improvement.

6.9. Early Termination and Relapse

Participants will be encouraged to attend study visits regardless of drinking status. Participants who miss a scheduled study appointment will be encouraged to reschedule or, if that is not possible, to attend subsequent study activities. In all cases, participants will be carefully monitored for relapse and clinical deterioration at study appointments and a detailed Safety Monitoring Plan is in place to respond to such situations. Participants who request early termination will not be followed or contacted further regarding the study.

6.10. Risks to Study Participants

6.10.1. Treatment response. It is not known if the treatment protocol proposed here will significantly modify the course of anxiety disorder or alcohol dependence for any given participant, and he/she may continue to experience the adverse consequences of these conditions during or after completion of this treatment study.

6.10.2. CBT**.** The main risk associated with participating in CBT is embarrassment or other discomfort participants may feel in sharing personal information with the therapist. In our experience of delivering the CBT to over 150 patients there were no reported adverse events associated with the therapy. Also, as a standard part of some of the CBT sessions participants will undergo the five-minute negative affect imagery challenge as a means of allowing them to practice newly learned coping skills in a simulated real-life situation. The content of the negative imagery challenge will be based on idiographic information provided by the patient. The challenge is designed to produce brief negative affect by imagining an actual stressful situation that occurred in the patient's recent past related to their anxiety disorder. Typically patients recover their baseline affect within several minutes after completion of the challenge. Participants are instructed and therapists are trained to avoid traumatic or highly distressing content for the imagery exercise. Ratings of discomfort are obtained throughout the exercise and therapists are trained to observe patients reactions indicating high stress responding. The patient is advised that they or the therapist are expected to discontinue the exercise if anxiety is higher than the "moderate" level target or is not tolerable to the patient. Patients may also experience discomfort when being asked to provide personal and potentially sensitive information regarding their experiences with anxiety, worry, and drinking behavior and other psychiatric / substance abuse history in the assessments. Although we do not know the likelihood of this happening, we do know that any discomfort caused by the assessments was not sufficiently great to cause any participants in our earlier study of over 300 Lodging Plus patients to discontinue the study for this stated reason or to decline to answer any of the questions they were asked.

6.10.4. Risks Due to Breach of Confidentiality and Loss of Privacy Breach of confidentiality would be potentially harmful to the psychological well-being of the patient and could have wider implications in the area of employment, insurance or interpersonal relationships. Breach of confidentiality could cause particular harm if it included sensitive or stigmatizing information

regarding medical diagnoses or history of drug use. The risk of loss of privacy in this study is judged to be minimal due to the procedures in place to protect against this.

6.11. Plan for Clinical Deterioration

6.11.1. Medical deterioration**.** The study physician (Dr. Specker) will be made aware of all adverse medical events related to study participants whether or not they are judged to be study related. The study physician and project coordinator will both carry a pager and will be available to all study subjects for emergencies throughout the trial. If a subject is judged by the physician to be in need of hospitalization for a medical condition, the physician will make the clinical referral immediately, and a serious adverse event report will be made to both the IRB and the sponsor. In all cases, participants will be followed for research purposes, and the data will be included in the intent-to-treat analysis and safety analyses.

6.11.2. Alcohol/drug deterioration. This clinical trial will recruit from inpatients in an alcohol dependence treatment center who will leave the treatment with the expectations of remaining abstinent from alcohol thereafter. However, based upon our past work in this population, about 40 to 60% of participants can be expected to use some alcohol over the course of the follow-up period. Participants will be seen for assessments one month, four months, and eight months following the completion of the inpatient treatment. At these assessments, the staff will closely monitor participant's alcohol consumption as part of the standard assessment battery (i.e., the TLFB interview, BAL breath test if alcohol consumption is suspected). If it is determined that a participant is currently intoxicated above .08 BAC, a car service will be called to transport participants home and hospital security will be informed that the participant's car will remain in the parking structure over night. In the case of severe alcohol deterioration, appropriate referrals to detox and/or additional alcohol dependence treatment will be made by the study physician or PI.

6.11.3. Psychiatric deterioration. We exclude individuals with severe mental illness (i.e., history of psychosis or mania) or anyone who is at imminent risk for suicide. Thus, it is unlikely that participants will experience a significant psychiatric crisis that requires additional mental health care. Suicidality is monitored at each therapy session and assessment, so any changes are monitored throughout the trial. If significant psychiatric deterioration is detected, the participant will be referred for appropriate treatment by the study physician or PI.

6.11.4. Data and Safety Monitoring Board (DSMB). An independent DSMB will monitor this project over its complete life-cycle. All three DSMB members will be faculty and senior clinical researchers/Professors in the Department of Psychiatry at the University of Minnesota who have significant experience with the protection of human subjects in clinical trials. In addition, all three DSMB members are otherwise independent of the project.

6.11.5. DSMB reports**.** The statistician or Project Coordinator will generate quarterly reports for the DSMB that will be reviewed by the PI prior to the DSMB meeting and will include: 1) current recruitment and attrition rates; 2) Serious Adverse Events and Adverse Events; 3) rates of data entry, data queries and data completeness; 4) the inclusion of women, children and members of ethnic minorities. Since any interim effect size might not be sufficient in size for detection, particularly on a quarterly basis given our projected recruitment, neither the PI nor the DSMD will assess efficacy and feasibility data by treatment assignment.

6.11.6. Serious Adverse Events (SAEs). SAEs will be defined as any significant psychiatric or medical problem requiring an overnight hospitalization at an acute care facility. Adverse Events will be defined as any adverse change in health or side effect that occurs while a participant is enrolled in the trial that is serious and unanticipated and probably, possibly, or definitely related to study participation.

6.11.7. Responsible reporter**.** The Principal Investigator, Matt Kushner, Ph.D. (licensed clinical psychologist), along with the study physician (Sheila Specker, M.D.) will be responsible for accurate and timely reporting of prevalent adverse events, unexpected but study-related adverse events, and serious adverse events in the case report form, and appropriately reporting events to the local IRB and to the NIAAA Project Officer (Dr. Deidra Roach), within 48 hours for all SAEs. Other unexpected, study related or possibly-related serious events will be reported to the local IRB and to the NIAAA Project Officer within 48 hours. Additionally, all adverse events occurring during the study follow-up period will be reported to the local IRB and NIAAA Project Officer; reports will be made within 48 hours if they are SAEs. A report of the number and nature of events will be supplied to the NIAAA Project Officer (Dr. Deidra Roach) in the Annual Progress Report/Noncompeting Renewal Application.

6.11.8. Referral to treatment due to clinical deterioration. During the study follow-up phase, patients deemed by the PI, (clinical psychologist, Matt Kushner, Ph.D.), along with the study physician (Sheila Specker, M.D.), to require additional intervention due to significantly increased alcohol consumption or serious psychiatric/medical symptoms will be referred for appropriate treatment.

6.11.9**.** Based on the PI's reports to the DSMB, each of the three DSMB members will make a recommendation to either: 1) continue recruitment; or 2) schedule a formal DSMB meeting immediately. If the latter is recommended by any of the three members, the PC will schedule a DSMB meeting within seven days, keep meeting minutes and present a typed report to the PI with 24 hours of the meeting. At the meeting, the DSMB will vote on whether the trial should: 1) continue recruitment; 2) continue recruitment but make a protocol amendment; 3) temporarily suspend recruitment while making a protocol amendment; or 4) suspend recruitment until further investigation can be completed. If the DSMB makes any decision other than to continue recruitment, the PI will notify the IRB within 72 hours.

6.12. Time

Total amount of time, including completion of self-report forms, should not exceed 50 hours (excluding travel time).

6.13. Location

All study activities will take place at the University of Minnesota Hospital located at 2450 Riverside Ave., Minneapolis MN 55454. All study activities take place in the same building on the second floor in the University of Minnesota's Ambulatory Research Center (ARC). The ARC provides devoted space for clinical research with a full time receptionist, a waiting room and private interview/therapy rooms.

6.14. Treatment and Compensation for Injury

In the event that research activity results in an injury, treatment will be available, including first aid, emergency treatment and follow-up care as needed. Care for such injuries will be billed in the ordinary manner to the patient or his/her insurance company.

6.15. Costs and Reimbursement of Subjects

The only costs to participants is travel to Fairview for the three follow-up assessments at 1-, 4-, and 8-month follow-ups. Participants wil be reimbursed for their time for all study activities. A total of $330 can be earned for each participant that completes each study task. (The exact payment per task is shown in Table 2 above). Payments are made within one business day of the completion of each study task via a Greenphire Clincard. Reinbursements for the the follow-up visits are graduated (increased for later follow-ups) reflecting the greater value of these data to the aims of the study and our expieriance indicating that participants' motivation to attend follow-up assessments decreases with increasing time since the intital treatment. Note participants recruited after approval of MOD00013885 will not complete the eight-month follow-up visit and will therefore be compensated up to $230.

6.16. Confidentiality of Records

Research records are coded by number and the master list matching subject numbers to names is kept by the study statistician and Research Coordinator. All data are stored in a locked cabinet and password protected computer files. The only exception to this is data obtained with the subjects' permission.

6.17. Qualifications of Investigators

6.17.1. Matt Kushner, Ph.D. (Professor of Psychiatry and Study P.I.) Dr. Kushner has been funded by NIAAA to study the problem of anxiety disorders co-occurring with AUDs since 1994. He is a licensed clinical psychologist and a Full Professor in the University of Minnesota's Psychiatry Department. He has conducted multiple clinical trials, the most recent being the parent R01 grant study to the current "renewal/continuation" study. In the parent R01, Dr. Kushner performed all of the duties and activities relevant to the proposed work. He has over 70 peer-reviewed publications and is considered a leading expert in his field, serving as an NIH standing scientific reviewer for the past 4 years, presenting at national and international conferences and consulting to numerous junior investigators.

6.17.2. Shelia Specker, M.D. (Associate Professor of Psychiatry and Study Co-I and Physician). Dr. Specker's research and clinical experience over 20 years in the same institution and clinical department as the PI (Dr. Matt Kushner) leave her well qualified to participate in this project as a co-Investigator. For example, she has been a NIDA funded investigator both as a PI and co-I so gaining experience in the planning and execution of clinical trials in a chemically dependent population. She has also served as a co-I on a recently completed NIAAA clinical trial with the PI of this project. That study examined the effect of SSRI treatment in hazardous drinking individuals with social anxiety disorder. In the course of that five-year study, the Dr. Specker and the PI demonstrated a cordial and effective working relationship in the same area of study as the proposed work. That work resulted in a manuscript that is currently under review. It is also relevant to her role as Co-I in the proposed work is her academic training, residencies and fellowship, were in family medicine, psychiatry, and

addiction psychiatry. Clinically, she has 20 years of experience as attending psychiatrist and faculty member in the Dept of Psychiatry and as the Medical Director of the University of Minnesota Medical Center's combined mental health and substance abuse treatment program. Administratively, she is Program Director for the newly ABAM accredited Residency in Addiction Medicine. As such, she will be able to bring my medical training and significant clinical and research experience to bear on the proposed work as a Co-I. In particular, Dr. Specker will be involved with planning, trouble-shooting, clinical decision-making and data interpretation and manuscript preparation.

6.17.3. Paul Thuras, Ph.D. (Assistant Professor of Psychiatry and Study Co-I and statistician). Dr. Thuras and the PI have collaborated in the role of statistician and research methodologist with Dr. Kushner for nearly 20 years. This association began when he was a statistician housed in the University Of Minnesota's Department of Psychiatry and continued after he moved to lead the statistical core in the Minneapolis Veterans Affairs Medical Center's Psychiatry Department. In the last several of Dr. Kushner's NIAAA-sponsored grants, Dr. Thuras has served as both a Co-I and a statistician. As a Co-I of the proposed work, Dr. Thuras will provide Dr. Kushner with input regarding data-base management, design, randomization, statistical analysis and manuscript preparation for publication. In addition to his work with the PI, Dr. Thuras has served in similar roles in many project including one that is ongoing investigating long term effects of combat exposure (including mild TBI) and deployment on MN National Guard soldiers and an RCT investigating Mindfulness Based Stress Reduction in veterans with PTSD. Dr. Thuras has extensive experience working on clinical trials, especially in the areas of anxiety disorders and substance use disorders. After working with Dr. Kushner successfully for many years, there is a proven track record of his working well and effectively with the PI on projects like the one proposed in here.

6.17.4. John Connett, Ph.D. (Professor of Biostatistics; Study Head Statistician) Dr. Connett's focus of research since joining the Division of Biostatistics as a postdoctoral trainee in 1975 has been clinical trials. He has served as Principal Investigator for Lung Health Studies I, II and III, for two studies of eye disease, for a study of granulocyte transfusions for patients undergoing treatment for leukemia or aplastic anemia, and for a study of retinoic acid therapies for emphysema. All of these have been multicenter NIH-sponsored randomized clinical trials. Dr. Connett has also served on over 20 Data and Safety Monitoring Committees for NIH-sponsored clinical trials, including service as a member of the data monitoring committee for the Sickle Cell Disease Network, funded by the National Heart, Lung and Blood Institute. Dr. Connett was Head of the Division of Biostatistics at U Mn from 2001 to 2010. He now serves as Director of the Biostatistical Design and Analysis function of the U Mn CTSA. Dr. Connett's role in the proposed clinical trial will be to work with Dr. Kushner to finalize the design, outcome measures related to alcohol use, and timeline; to direct the work of Mr. Menk in monitoring, reporting, and data analysis and to participate in authorship of publications and presentations.

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7.0 STATISTICAL CONSIDERATIONS

7.1. Data management

The database will be created and maintained by BDAC staff and will be stored on a security-enabled server (HIPAA-compliant, firewall protected) to be accessed only by designated study personnel. The database for the study will use REDCap (consortium agreement through the University of Minnesota's CTSA) via a web-based interactively edited data entry with secure login through the

University of Minnesota. Data quality control will be monitored regularly within the REDCap data system by Rebecca Freese.

7.2. Data quality/integrity

All data will be inspected for missing and outlier values and response set patterns. Distributions will be graphically represented and inspected visually and quantitatively for departures from normality and other irregularities. All data will be characterized in terms of means, standard deviations,
histograms, and response ranges for continuous variables and frequencies and counts for categorical variables. A random sample of 5% of cases will have all hard copy data compared to entered data for accuracy, including all measures scored by computer algorithms. The need for data re-entry or recoding, data transformations and non-linear or non-parametric analyses will be based on these results.

7.3. Randomization

Although we had considered using an Urn randomization (Stout et al., 1994), we ultimately decided against this since extensive moderator tests in the parent R01 were negative with one exception; i.e., level of baseline trait anxiety. Although only about 11% of cases were below the threshold cut-off for clinically significant trait anxiety, this status interacted with group assignment such that CBT was less effective in this small group. Therefore, we will utilize a permuted-block randomization scheme with stratification on this variable. This should result in the approximate 33 cases below the clinical threshold being distributed evenly across the three groups. (Note we had considered that the anxiety disorder of these low trait anxiety cases could be mis-diagnosed but an inspection of the parent R01 data suggest they are typically cases
whose anxiety response is triggered in very specific circumstances so trait anxiety can be lower.)

7.4. Descriptive analyses

To confirm that the randomization scheme achieved the intended aim of evenly distributing important study characteristics, groups will be statistically compared on baseline demographic and clinical variables. Any significant group differences on these baseline variables would be factored into study analyses (e.g., using covariates).

7.5. Primary Aim: To compare the CBT-DC and CBT-AR groups on alcohol outcomes

We predict that the CBT-DC group will have superior alcohol outcomes compared to the CBT-AR group. The primary intention to treat (ITT*)* population will include all patients randomized. The per-protocol (PP*)* population will include patients who completed at least four of six (66%) of the therapy sessions with CBT-O patients not missing any more than one of the three AR or DC content sessions. Hypotheses based on the vicious cycle model and parent R01 findings suggest that without alcohol-anxiety de-coupling therapy, drinking relapse is more likely to occur and more severe when it does occur. Therefore, we consider as primary outcomes both categorical relapse status (yes vs. no) and continuously measurement of relapse severity (percent/number days drinking and drinks per drinking day). Secondary alcohol outcomes tested include categorical status on: a) alcohol dependence (yes vs. no) and hazardous drinking (yes vs. no). Follow-up assessments occur 1-, 4- and 8-months following the conclusion of the study therapy and are keyed to the time since the last assessment. To align study findings with the parent R01, the primary assessment point will be the 4-month FU. However, hypotheses will also be tested across all time points to establish temporal patterns of group effects. We test the hypotheses using mixed effects models if data residuals are

normally distributed and generalized estimating equations (GEE) if the data are non-normally distributed (Gueorguieva, & Krystal, 2004; Liang & Zeger, 1986). Both are flexible regression methods for incomplete repeated measures data and allow continuous and categorical covariates, fixed and time-dependent covariates, and a specification of unstructured as well as structured covariance matrix. Categorical outcomes will be evaluated using chi-square tests of proportions and logistic regression, with statistical significance criterion also set at $p < 0.05$. Zero-inflated negative binomial analyses will be used to contrast the study groups on count variables if warranted by a high percetage of zero alcohol use days over the follow-up (e.g., Agresti, 2002).

The principal power estimate focuses on categorical analyses since these will provide the most conservative power estimates and because we have somewhat more information available to estimate these outcomes for the Primary Aim study groups. (ES for continuous/count alcohol outcomes all demonstrated larger group effects than the categorical outcomes in the parent R01 [Kushner et al. 2013-a].) The best estimate for the categorical CBT-AR alcohol outcome comes from the PMRT group (also devoted exclusively to anxiety reduction) in the parent R01 (i.e., 53% relapse at four months). The parent R01 does not provide a point estimate for the CBT-DC group relapse rate but our prediction that the CBT-DC group will ameliorate all (or most) of the deleterious effect on recovery conferred by a co-occurring anxiety disorder allows us to place this estimate at 21%; i.e., the relapse rate at four months of an AUD treatment group with no co-occurring anxiety disorder (Kushner et al., 2005; also see Driessen et al., 2001 for similar estimates). These estimated results would represent a large effect size (OR = 4.2), which would require a sample of only 41 per group to identify an effect at an alpha = .05 level with 80% power; however, a larger sample size would be required to identify other predicted effects with the same power. Further, we cannot be certain that our empirically- and theoretically-informed prediction that the CBT-DC will mitigate all/most of the risk for relapse conferred by co-occurring anxiety disorder is correct until the study is conducted. Therefore, we also calculated a minimum detectable ES showing that we could detect an OR as small as 2.3 with 80% power in the planned sample size using a two-tailed test and 0.05 alpha-level. Although we would be at a higher risk of missing effects even smaller than this, such negative findings would not constitute a meaningful Type II error because they would be of increasingly trivial clinical importance (e.g., Ferguson, 2009). **Therefore, the Primary Aim will be put to a meaningful and scientifically valid test under a wide range of clinically meaningful effect sizes**.

7.6. Secondary Aim: To compare the CBT-DC and CBT-O groups on alcohol outcomes

The importance of this comparison includes confirming our hypothesis that 6 DC sessions are superior to 3 DC sessions in terms of alcohol outcomes (DC dose: high vs. low) while also ruling out the alternative hypothesis that, contrary to study predictions, de-coupling therapy elements can only exert a therapeutic effect on alcohol outcomes when combined with anxiety reduction elements ("synergy"). Regarding the affirmative dose prediction, we can estimate the effect of the CBT-O group to be the same as that of the CBT in the parent R01 (i.e., 41% relapse at 4 months), while keeping all other parameters, including the CBT-DC group effect estimate of 21% relapse, the same as outlined for the Primary Aim. These estimated results would represent a medium effect (OR = 2.6), which would require a sample of 94 per group to identify with 80% power an effect with alpha = 0.05. (Again, we anticipate continuous/count tests will have greater power than categorical tests.) If, however, contrary to our study predictions, synergy between the therapy components is necessary,

then we would expect CBT-DC to resemble TAU only in outcome (61% relapse) with the CBT-O result still being the same as in the parent R01 (again, 41% relapse). This would provide roughly the same power to detect the unexpected synergy effect as there will be to detect the predicted dose effect; albeit, with opposite directional effects.

7.7. Tertiary Aim: To compare the CBT-O and CBT-AR groups on alcohol outcomes

The importance of this comparison includes confirming our hypothesis that 3 DC sessions are superior to zero DC sessions (DC dose: low vs. none) in terms of alcohol outcomes, while also exploring the alternative hypothesis that, contrary to study predictions, a high vs. a low dose of anxiety reduction therapy (i.e., 6 vs. 3 sessions) is needed to improve alcohol outcomes. Regarding the former, just as the CBT-DC group has three more DC sessions than the CBT-O group (6 vs. 3), the CBT-O group has three more DC sessions than the CBT-AR group (3 vs. zero). Regarding the affirmative dose prediction, we anticipate that the size of this effect will be the same as the size of the effect for the Secondary Aim: i.e., requiring 94 cases per group to obtain 80% power to detect an affect with alpha set at the .05 level. However, this dose-based prediction, if confirmed, will be somewhat more ambiguous that in the Secondary Aim because it could result either from the greater DC dose (as predicted) or DS-AR synergy. (In the Secondary Aim, by contrast, the group effects for dose and synergy should be in the opposite direction.) Alternatively, if the CBT-AR group is superior to the CBT-O group, this would suggest unambiguously that a higher dose of anxiety reduction is more important to improving alcohol outcomes than is a lower dose, even when combined with a low dose of de-coupling therapy.

7.8. Mechanism manipulation checks

The specific aims of this clinical research are to demonstrate the group differences in clinical outcomes predicted above. However, inferring that these differences were due the mechanisms targeted in the specific groups require demonstrating that the levels of change in the mechanisms as a result of treatment varied according to the group assignments as expected. This will be done using the anxiety reduction and de-coupling process measures described above taken at the pre-treatment baseline compared to the immediate post-treatment assessment. Given our sample size of 100 subjects per group, we will have 80% power to detect group differences of 0.40 SD units using a two-tailed test and a 0.05 alpha level. Since this minimally detectable ES is less than half of the natural variability of the measure and, therefore, on the low end of clinical and theoretical significance (e.g., Ferguson, 2009), our difficulty in detecting even smaller effects is not considered problematic.

8.0 ADMINISTRATIVE CONSIDERATIONS

8.1 Conduct of the Trial

The University Of Minnesota IRB will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The study will only be conducted at sites where IRB/EC or Campus Administrator approval has been obtained. The protocol, informed consent, written information given to the patients, annual progress reports, and any revisions to these documents will be provided to the IRB by the investigator. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

8.2 Data Management

8.2.1. Data management. The database will be created and maintained by BDAC staff and will be stored on a security-enabled server (HIPAA-compliant, firewall protected) to be accessed only by designated study personnel. The database for the study will use REDCap (consortium agreement through the University of Minnesota's CTSA) via a web-based interactively edited data entry with secure login through the University of Minnesota. Data quality control will be monitored regularly within the REDCap data system by Rebecca Freese.

8.2.2. Data quality/integrity. All data will be inspected for missing and outlier values and response set patterns. Distributions will be graphically represented and inspected visually and quantitatively for departures from normality and other irregularities. All data will be characterized in terms of means, standard deviations,
histograms, and response ranges for continuous variables and frequencies and counts for categorical variables. A random sample of 5% of cases will have all hard copy data compared to entered data for accuracy, including all measures scored by computer algorithms. The need for data re-entry or recoding, data transformations and non-linear or non-parametric analyses will be based on these results.

8.3. Data and Safety Monitoring Plan

8.3.1. Data and Safety Monitoring Board (DSMB). A DSMB will monitor this project over its complete life-cycle. The DSMB will include John Grabowski, Ph.D., Eric Dieperink, M.D. and Scott Crow, M.D. All three DSMB members are senior clinical researchers and have significant experience with the protection of human subjects in clinical trials. In addition, all three DSMB members are otherwise independent of the project.

8.3.2 . DSMB reports**.** The statistician or Project Coordinator will generate annual reports for the DSMB that will be reviewed by the PI prior to the DSMB meeting and will include: 1) current recruitment and attrition
rates; 2) Serious Adverse Events and Adverse Events; 3) rates of data entry, data queries and data completeness; 4) the inclusion of women, children and members of ethnic minorities. Since any interim effect size might not be sufficient in size for detection, particularly on a quarterly basis given our projected recruitment, neither the PI nor the DSMD will assess efficacy and feasibility data by treatment assignment.

8.3.3. Serious Adverse Events (SAEs). SAEs will be defined as any significant psychiatric or medical problem requiring an overnight hospitalization at an acute care facility. Adverse Events will be defined as any adverse change in health or side effect that occurs while a participant is enrolled in the trial that is serious and unanticipated and probably, possibly, or definitely related to study participation.

8.3.4. Responsible reporter. The Principal Investigator, Matt Kushner, Ph.D., is responsible for accurate and timely reporting of prevalent adverse events, unexpected but study-related adverse events, and serious adverse events in the case report form, and appropriately reporting events to the DSMB, the IRB and NIAAA. Other unexpected, study related or possibly-related serious events will be reported to the IRB and NIAAA as soon as possible and within required reporting guidelines. A report

of the number and nature of events will be supplied to NIAAA in the Annual Progress Report/Noncompeting Renewal Application.

8.3.5. DSMB actions. Based on the PI's reports to the DSMB, each of the three DSMB members will make a recommendation to either 1) continue recruitment; or 2) schedule a formal DSMB meeting immediately. If the latter is recommended by any of the three members, the PC will schedule a DSMB meeting within seven days, keep meeting minutes and present a typed report to the PI with 24 hours of the meeting. At the meeting, the DSMB will vote on whether the trial should: 1) continue recruitment; 2) continue recruitment but make a protocol amendment; 3) temporarily suspend recruitment while making a protocol amendment; or 4) suspend recruitment until further investigation can be completed. If the DSMB makes any decision other than to continue recruitment, the PI will notify the IRB within 72 hours.

8.3.6. Keeping data confidential. For the life-cycle of the project, standard practices will be used to protect participant confidentiality and personal health information, including removing identifiers from all data collected; using only numbers to identify participant data; and keeping data files, when not in use in a locked filing cabinet in a locked office. No names or other identifiers will be used in computerized data files. When a study participant signs the informed consent and the HIPAA agreement, s/he will receive a Notice of Privacy Practices, outlining the confidentiality procedures that are being used.

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