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Development of an Integrated Cognitive Behavioral Therapy for Anxiety and Opioid Use Disorder: Study Protocol and Methods

R. Kathryn McHugh[a,b], **Victoria R. Votaw**[a], **David H. Barlow**[c], **Garrett M. Fitzmaurice**[d,e], **Shelly F. Greenfield**[a,b], and **Roger D. Weiss**[a,b]

[a]Division of Alcohol and Drug Abuse, McLean Hospital, 115 Mill Street, Belmont, MA 02478, USA

[b]Department of Psychiatry, Harvard Medical School, 25 Shattuck Street, Boston, MA 02115, USA

[c]Center for Anxiety and Related Disorders, Department of Psychology, Boston University, 648 Beacon Street, Boston, MA 02116, USA

[d]Laboratory for Psychiatric Biostatistics, McLean Hospital, 115 Mill Street, Belmont, MA 02478, USA

[e]Department of Biostatistics, Harvard School of Public Health, 677 Huntington Avenue, Boston, MA 02115, USA

Abstract

Opioid use disorder is a highly disabling psychiatric disorder, and is associated with both significant functional disruption and risk for negative health outcomes such as infectious disease and fatal overdose. Even among those who receive evidence-based pharmacotherapy for opioid use disorder, many drop out of treatment or relapse, highlighting the importance of novel treatment strategies for this population. Over 60% of those with opioid use disorder also meet diagnostic criteria for an anxiety disorder; however, efficacious treatments for this common co-occurrence have not be established. This manuscript describes the rationale and methods for a behavioral treatment development study designed to develop and test an integrated cognitive-behavioral therapy for those with co-occurring opioid use disorder and anxiety disorders. The aims of the study are (1) to develop and pilot test a new manualized cognitive behavioral therapy for co-occurring opioid use disorder and anxiety disorders, (2) to test the efficacy of this treatment relative to an active comparison treatment that targets opioid use disorder alone, and (3) to investigate the role of stress reactivity in both prognosis and recovery from opioid use disorder and anxiety disorders. Our overarching aim is to investigate whether this new treatment improves both anxiety and opioid use disorder outcomes relative to standard treatment. Identifying optimal treatment strategies for this population are needed to improve outcomes among those with this highly disabling and life-threatening disorder.

Corresponding Author: R. Kathryn McHugh, Ph.D., Assistant Professor, Department of Psychiatry, Harvard Medical School, Associate Psychologist, Division of Alcohol and Drug Abuse, McLean Hospital, 115 Mill Street, Belmont, MA 02478, 617-855-3169 (phone), 617-855-2699 (fax), kmchugh@mclean.harvard.edu.

Keywords

opioid use disorder; anxiety disorders; cognitive-behavioral therapy; stress reactivity; co-occurring disorders

1. Introduction

The prevalence of opioid use disorder has escalated substantially in the past 15 years, largely driven by increases in the nonmedical use of opioid analgesic medications [1]. An estimated 2.6 million individuals in the United States met criteria for an opioid use disorder in 2015, a rate nearly 1.5 times greater than in 2005 [2]. This disorder is associated with substantial morbidity and mortality; opioid overdose deaths have tripled in the past 15 years and now represent more than 60% of all drug overdose deaths [3]. Accordingly, effectively treating opioid use disorder is an urgent public health concern.

More than 60% of those with opioid dependence meet criteria for a lifetime anxiety disorder [4], and anxiety symptoms are associated with poorer quality of life [5], treatment dropout [6], and abuse of other substances (e.g., benzodiazepines) in this population [7]. Opioid use and anxiety interact, creating a significant challenge for treating these disorders when they co-occur. For example, opioids are often used to relieve symptoms of anxiety [8], and opioid use can create or worsen anxiety symptoms, particularly during withdrawal [9].

Additionally, these disorders share several risk factors that drive disorder maintenance and relapse risk. Both opioid use disorder and anxiety disorders are associated with low tolerance of distressing internal states [10–12] and elevated emotional and physiological response to stressors [13, 14]. High levels of distress intolerance and stress reactivity have been associated with poorer treatment outcomes in these populations [15–19]. Adequately addressing these interacting and overlapping symptoms by treating these disorders concurrently has promise to improve outcomes among those with co-occurring opioid use disorder and anxiety disorders.

We designed a study to develop and pilot test a treatment that targets opioid use disorder and anxiety disorders concurrently. The overarching aim of this study is to develop a novel integrated cognitive-behavioral treatment (I-CBT) for co-occurring opioid use disorder and anxiety disorders. Cognitive-behavioral therapy is an efficacious and effective treatment for both substance use disorders [20, 21] and the range of anxiety disorders [22–24]. Behavioral therapies that simultaneously target co-occurring psychiatric and substance use disorders have demonstrated efficacy for reducing symptoms of both disorders (e.g., depression, posttraumatic stress disorder, bipolar disorder) [25–27]. These approaches utilize treatment elements that target the interaction of symptoms and shared factors in the recovery process for both disorders [28]. Integrated behavioral treatments have shown promise for co-occurring posttraumatic stress disorder and substance use disorders [26, 29]; however, studies of other anxiety disorders remain largely unaddressed. In addition, no studies to date have focused specifically on treating co-occurring psychiatric disorders among those with opioid use disorder, despite the very high prevalence of co-occurring disorders in this population and their negative impact on severity and treatment outcome.

This paper describes the study design and procedures for a behavioral treatment development trial examining the feasibility, acceptability, and efficacy of I-CBT for co-occurring opioid use disorder and anxiety disorders.

2. Study Design and Aims

This project is funded by the National Institute on Drug Abuse (DA035297). The trial is registered on clinicaltrials.gov (NCT02252068) and all procedures described below were approved by the Partners Healthcare Institutional Review Board.

2.1. Design Overview

This study is a Stage 1 behavioral treatment development trial. The Stage Model of Behavioral Therapies Research delineates a series of steps in treatment development ranging from initial feasibility testing through dissemination to clinical providers and systems [30]. Within this framework, the goal of a Stage 1 trial is to develop the treatment content and to conduct initial testing of feasibility, acceptability, and efficacy in the target clinical population. This trial consists of two phases: Stage 1A (manual development and open pilot trial) and Stage 1B (pilot randomized controlled trial). The results will then be used to determine whether to proceed to further testing in a large randomized trial [30]. At the time of this writing, we have completed Stage 1A and recruitment for Stage 1B of the trial is ongoing, with anticipated completion of the study in 2018.

2.2. Specific Aims

The specific aims and hypotheses for this trial are as follows:

1. To develop an integrated cognitive-behavioral treatment for opioid use disorder and anxiety disorders (I-CBT) and conduct an open pilot trial testing its feasibility and acceptability.
2. To test the efficacy of I-CBT for the improvement of opioid use and anxiety outcomes relative to an active comparison treatment targeting opioid use disorder alone (Individual Drug Counseling; IDC). We hypothesize that at the completion of treatment, participants who received I-CBT will report (a) fewer opioid-positive weeks, and (b) greater reductions in interviewer-rated anxiety symptom severity, relative to those who received IDC.
3. To examine the association between stress reactivity and treatment outcome in participants with co-occurring opioid use disorder and an anxiety disorder. We hypothesize that (a) higher levels of stress reactivity at baseline will be associated with more opioid-positive weeks and more severe anxiety symptoms following treatment, and that (b) the I-CBT group will exhibit greater reductions in stress reactivity from baseline to post-treatment relative to the IDC group.

2.3. Stage 1A

We conducted an iterative process of manual development, consisting of content development and feedback from both expert clinical researchers and the target clinical population. Content development focused on 1) an integration of theoretical and empirical

perspectives on the unique and shared maintaining factors in opioid use disorder and anxiety disorders [6, 11, 31, 32], and 2) principles from efficacious behavioral therapies for substance use disorders [33, 34] and anxiety disorders [35, 36]. Investigators and consultants with expertise in behavioral therapy development in the areas of substance use disorders, anxiety disorders, and co-occurring substance use and other psychiatric disorders reviewed drafts of the manual and provided feedback on content and ease of use.

This content expert review was complemented by feedback from treatment-seeking adults with opioid use disorder and clinically-significant anxiety. Participants were recruited for a focus group, in which they answered questions about proposed treatment topics, their interest in an anxiety-specific treatment, and their perspectives on the adequacy of current treatment-as-usual for these co-occurring conditions. Specifically, participants were asked a series of open-ended questions about their experiences with substance use and anxiety (e.g., How does substance use contribute to your anxiety?), treatment experiences (e.g., What has been your experience with addressing anxiety in addiction treatment?), and beliefs about key session topics (e.g., If you were designing a treatment for people with anxiety and substance abuse, what do you think would be important to focus on?).

Version 1 of the manual was then administered to 5 participants in an open pilot trial. The study principal investigator (RKM) conducted all treatment sessions in this phase to facilitate ongoing modification of the manual. Following completion of this small open trial, revisions of the manual were completed and submitted to all investigators for review. Based on this feedback, a second version of the manual was then completed for use in the Stage 1B randomized trial.

2.4. Stage 1B

Stage 1B consists of a pilot randomized controlled trial of I-CBT compared to IDC (see description of treatment conditions below). Figure 1 presents the design overview for this trial. Following a baseline assessment, participants are randomized to receive 12 weeks of individual therapy, consisting of either I-CBT or IDC. Major study assessments are conducted at baseline (pre-randomization), end of treatment (after the final treatment session), and 1- and 3-months post-treatment. In a behavioral treatment study, neither the treating clinician nor the participants can be blind to study condition. Primary outcome assessments are conducted by an independent evaluator blind to study condition.

Participants are randomized to one of the therapy conditions following completion of the baseline assessment. Randomization is stratified by two key factors that may predict outcomes: (1) history of any heroin use (a significant poor prognostic indicator in this population) [37, 38], and (2) type of medication prescribed to treat the opioid use disorder (agonist/partial agonist vs. antagonist). Random permuted blocks are used to balance strata across the two treatment conditions.

2.5. Participant Selection, Recruitment, and Retention

Recruitment for the pilot trial is ongoing (target N=54). Eligibility criteria include: (1) Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) [39] diagnosis of opioid use disorder, (2) DSM-5 diagnosis of any anxiety disorder, (3) a score of 14 or

higher on the Hamilton Anxiety Rating Scale (indicative of clinically-significant anxiety) [40], (4) current receipt of pharmacotherapy for opioid use disorder (e.g., buprenorphine/naloxone, methadone, naltrexone), (5) ability to read and provide informed consent, (6) intent to remain in the area for the duration of the study, and (7) age 18 years or older. Exclusion criteria include: (1) current substance use or psychiatric condition requiring a level of care higher than outpatient treatment, (2) current receipt of cognitive-behavioral therapy, (3) recent initiation of a psychiatric medication for anxiety (<4 weeks on a stable dose), (4) prescription of a benzodiazepine for as-needed use, and (5) presence of a psychiatric or medical condition that would interfere with participation or require additional care (e.g., psychosis, acute suicidality).

Participants are recruited primarily through the Alcohol and Drug Abuse Treatment Program at McLean Hospital. This program provides the full continuum of care for opioid use disorder, ranging from inpatient detoxification through outpatient relapse prevention and medication management services. Recruitment also consists of presentations at other local substance use disorder treatment facilities, letters to clinicians soliciting referrals, online advertisements (e.g., clinicaltrials.gov, clinicaltrials.partners.org), and printed advertisements (e.g., flyers). Interested participants meet with a member of the study staff for an initial brief eligibility screening. Those who meet criteria based on this initial screen and are interested are scheduled for an informed consent meeting with a member of the study staff.

Retention is a significant challenge in longitudinal research in this population. Accordingly, several steps are taken to maximize retention. First, study clinicians emphasize the importance of session attendance equally in both conditions, and research staff place reminder calls (or text messages, if preferred by the participant) prior to all treatment sessions and assessment appointments. Research staff maintain bi-weekly contact with participants between the follow-up research appointments. Finally, multiple methods of contact are collected from all participants (e.g., phone, email), including contact information for at least one person who should be able to reach them if research staff are unable to do so.

3. Study Treatments

3.1. Integrated Cognitive-Behavioral Therapy

Integrated Cognitive-Behavioral Therapy (I-CBT) for the treatment of anxiety and opioid use disorder targets overlapping symptoms and purported vulnerability processes that influence the maintenance of these disorders and impede recovery, such as poor inhibitory control and a reliance on avoidance and escape behaviors to alleviate distress. The treatment emphasizes the interaction of disorder symptoms and the need to target both concurrently, conceptualizing these illnesses as a single disorder [34]. Negative reinforcement is a significant focus of treatment; the reliance on behaviors that afford strong, proximal relief of distressing states (e.g., acute and protracted withdrawal, anxiety, anedonia) is targeted through a combination of introducing new skills and rehearsal of these skills in the context of distress. Sessions introduce specific skills to replace maladaptive and risky behaviors (e.g., opioid use, behavioral avoidance), and include active rehearsal of those skills alone and in combination with fear exposure. A brief description of the session topics is presented in Table 1.

The format of treatment consists of one-hour, once-weekly sessions over twelve weeks, and is intended to supplement medication-assisted treatment for opioid use disorder. The first session includes an introduction to treatment, identification of goals, and psychoeducation. The subsequent sessions can be administered in any order at the clinician's discretion; however, the maximum number of sessions (12) will be the same for all participants. Although the use of flexible ordering of sessions introduces some variability to the treatment delivered, it will allow for personalization of treatment while ensuring that the content as a whole is the same across all participants in this condition. Five sessions address specific skills topics, such as developing a coping plan, identifying and responding to triggers, and identifying and modifying maladaptive cognitions. Five sessions are dedicated to fear exposure and skills practice. These sessions allow for flexibility in determining the appropriate exposure or skills practice to implement and include further skills practice and exposure for homework. The final session focuses on reviewing the treatment content, discussing the participant's progress, and developing a written continuing care or relapse prevention plan.

Consistent with similar treatments [33, 34], the structure of each session consists of a "check-in," in which the participant is asked self-report past-week substance use and anxiety, a review of homework (e.g., worksheets) from the previous session, and then the session content. At the end of the session, homework is assigned and discussed. Homework assignments consist of self-monitoring of symptoms, a reading on that session's skill topic, and skill practice and/or exposure.

3.2. Individual Drug Counseling

Individual Drug Counseling (IDC) [41] is an evidence-based behavioral treatment for substance use disorders. Although initially designed for cocaine dependence, the treatment has been modified successfully for other substance use disorders. Clinical trials have supported the efficacy of IDC for the treatment of cocaine dependence [42], co-occurring substance dependence and personality disorders [43], and subgroups of opioid-dependent patients [44]. The IDC manual initially developed for the National Institute on Drug Abuse Collaborative Cocaine Treatment Study [41] was adapted to focus on opioids for the current study.

The treatment manual focuses on addressing substance use and functional consequences (e.g., unemployment, unhealthy relationships) and establishing adaptive behaviors for ongoing recovery. Although the manual allows for flexibility in content depending on the individ ual patient's needs, key elements include: ongoing monitoring of substance use, identification and modification of high-risk situations for use, encouragement of 12-step attendance and participation, and re-engagement in major life domains (e.g., social, leisure, employment) while drug-free. Participants in IDC are encouraged to attend 12-step meetings between sessions and establish other functional goals, such as introducing structure or increasing participation in activities.

3.3. Fidelity Monitoring

All study clinicians have prior experience with cognitive-behavioral therapy and a minimum of a Master's degree in a mental health discipline. Study clinicians are trained by the PI, and administer treatments with equal frequency (i.e., all study clinicians will administer both treatments to counterbalance therapist effects across the two conditions). Training consists of both initial didactic training and ongoing, weekly supervision and feedback with the PI. Treatment fidelity for clinicians is monitored along several dimensions: (1) adherence to the key treatment procedures as delineated in the manual for each session (integrity), (2) presence of any treatment elements that are not included in the treatment manual or inconsistent with the treatment approach (differentiation), and (3) therapist skill in the delivery of the treatment (competence). These three dimensions (integrity, differentiation, and competence) are rated in two ways. First, all treatment sessions are audiotaped to monitor fidelity. Tapes will be rated by an independent rater who is blind to study condition. The Adherence/Competence Scale for IDC [45] will be used for rating IDC sessions; a comparable adherence scale was developed for I-CBT in Stage 1A. Second, study therapists are asked to self-rate adherence and differentiation at the end of each session.

Patient understanding and application of the treatment is another key component of treatment adherence [46]. Literature examining the impact of clinician fidelity on clinical outcomes has been mixed, which may be attributable to a failure to consider not only the delivery of treatment but also the receipt of treatment [47]. Thus, in addition to measurement of therapist adherence, differentiation, and competence, we collect several measures of patient receipt of the treatment. First, session attendance is measured in terms of both presence and duration of session (i.e., attended full session, 15–40 minute session, <15 minute session). Second, at each weekly treatment visit both the study therapist and the participant independently rate homework adherence using a validated scale [48]. Completion of homework is a robust predictor of outcome in CBT for substance use disorders [49, 50]. Finally, therapists rate the degree to which participants received the intervention as intended (e.g., demonstrated understanding of the material, participated in session exercises) at the end of each session. The inclusion of therapist-rated, patient-rated, and independent rater-rated treatment fidelity will provide a rich picture of the degree to which the treatment was both delivered and received as intended.

4. Assessments

The selection of measures for this study was informed by the recommendations of the National Institute on Drug Abuse expert panel on measurement in substance use disorder treatment research [51, 52] and by the PhenX Toolkit (www.phenxtoolkit.org). Measures include those for screening and eligibility, primary and secondary clinical outcomes, and feasibility, acceptability and satisfaction.

Given the challenges in accurate diagnosis of anxiety disorders in the context of a substance use disorder [31], all diagnostic interviews are conducted by the PI who has extensive experience in diagnostic assessment. All other measures--including the primary outcome measures--are collected/administered by an independent evaluator who is blind to study condition.

4.1. Diagnostic Assessment

Diagnoses are collected both for the determination of eligibility at baseline and as a secondary outcome at the post-treatment and the 3-month post-treatment follow-up assessments. The presence of DSM-5 disorders is assessed using the Anxiety Disorders Interview Schedule for DSM-5 (ADIS) [53]. The ADIS provides both determination of the presence of diagnoses, and also a dimensional rating of disorder severity, which allows for a more sensitive measure of change in disorder status over time. Although reliability data are not yet available for the DSM-5 version of the ADIS, data from previous iterations (i.e., DSM-IV) found excellent reliability for this measure [54]. To minimize assessment burden, only past-year diagnoses are assessed at baseline, and current diagnoses at the follow-up assessments.

4.2. Primary Outcomes

For this co-occurring disorders study, we have identified two primary outcomes. First, number of weeks of urine-confirmed self-report of opioid use in the previous month at the end of treatment will be used as the primary opioid use outcome. A study week will be coded as opioid-positive if: (a) the participant self-reports opioid use at any time during that week, but provides a urine drug screen negative for opioids, (b) the participant denies opioid use, but provides an opioid-positive urine drug screen, or (c) the participant both provides an opioid-positive urine drug screen and reports opioid use at any time during that week. For those currently prescribed methadone or buprenorphine, a positive screen for these substances is not coded as an opioid-positive week. Self-report of opioid use is collected using the Timeline Follow Back Method [55] to facilitate participant recall. Participants are encouraged to report accurately and are informed that substance use will not result in their expulsion from the study. Urine-confirmed self-report has been recommended for the measurement of substance use in illicit drug use research to mitigate the limitations of self-report (e.g., dishonest report) with the limitations of urine drug tests (e.g., limited time window for the detection of certain drug metabolites) [51]. The primary anxiety outcome is assessed using a semi-structured interviewer-administered scale, the Hamilton Anxiety Rating Scale [56]. We utilize the structured version of this measure, which has been shown to enhance reliability relative to the original scale [57]. The primary outcome will be anxiety as rated by this scale at the completion of treatment.

4.3. Secondary Outcomes

In addition to primary anxiety symptom and opioid use measures, several secondary outcomes are of interest. For each of these outcomes, data are collected at baseline (prior to randomization) and at the end of treatment, and we will test changes in these variables. In particular, functioning/quality of life has been highlighted as an important outcome to consider in substance use disorder treatment research [52]. Drug craving has also been highlighted as an important secondary outcome [52], and has been linked prospectively to opioid use [58].

Quality of life is measured using the 26-item self-report World Health Organization Quality of Life measure [59]. Functional impairment, assessed across life domains (e.g., medical, employment, social/family) will be assessed by the Addiction Severity Index [60], a

structured, interviewer-administered measure of substance use and functioning. Opioid craving will be assessed using the Opioid Craving Scale, adapted from the Cocaine Craving Scale [61]. This scale has demonstrated strong associations with proximal (i.e., next-week) opioid use, and thus may be a potential instrumental outcome in this population [58].

Use of multiple substances is common among those with opioid use disorder. Thus, other substance use in the past month are also examined as a secondary outcome, and are measured using urine-confirmed self-report.

4.4. Participant Satisfaction and Acceptability

Several measures of treatment satisfaction and acceptability are collected. Session attendance is used as a behavioral measure of feasibility/acceptability. In addition, satisfaction is measured directly using self-report measures. These measures are administered by the independent evaluator.

Participant satisfaction is assessed at weeks 6 and 12 using the Client Satisfaction Questionnaire [62]. In addition, a modification of the Credibility and Expectancy Scale [63] is administered to assess whether participants believe that the treatment will be helpful for their symptoms of opioid use disorder and anxiety. This measure is administered at weeks 3 and 7 during treatment.

4.5. Key Covariates

Several domains that may reflect key covariates that are potentially associated with outcome are measured. These include pain severity, types of opioid used (e.g., heroin vs. prescription opioids), presence of concomitant treatment, and demographic variables (e.g., age, education). Examination of both the main and interaction effects of gender is a planned component of the main analysis. Accordingly, efforts to recruit roughly equivalent proportions of men and women throughout the study will be a significant focus of the recruitment strategy. The treatment conditions will be compared with respect to other covariates thought to be strongly related to outcomes.

4.6. Stress Reactivity

Reactivity to stress and negative affective states is a central maintaining mechanism in both anxiety disorders and substance use disorders [18, 19, 59, 64]. The third aim of the study is to examine the role of stress reactivity as both a predictor of outcome and a symptom that may respond differentially to a treatment targeting anxiety relative to a treatment targeting opioid use disorder only.

Stress reactivity is tested using a script-driven imagery protocol developed by Sinha and colleagues [65–67]. Detailed descriptions of the script-driven imagery protocol are available elsewhere [68]. Briefly, this approach is based on theories of emotional imagery [69], and entails the use of individualized stressors to engage a stress response. Specifically, participants are asked to identify a recent stressful situation, which they then describe in detail, including the environmental context, physiological sensations, action tendencies, thoughts, and behaviors. These interviews are then used to develop a brief script describing

the event. An audio recording of this script is then created by a member of the study staff and played to participants on headphones while physiological data are collected. Prior to listening to the audio recording participants receive a brief training in the use of imagery and are instructed to try to fully engage this process while listening to the recording.

For this study, two stressful scripts and two neutral scripts are created for each participant for use at pre- and post-treatment. Both scripts are collected at baseline and their order is randomly determined. The neutral/relaxing scripts serve as a within-subjects control condition for the measurement of outcomes. Outcome measures for the stress reactivity assessment include opioid craving, negative affect, and physiological reactivity (skin conductance). Skin conductance level is collected using the Biopac MP150 system with the EDA100c amplifier.

5. Data Management and Analysis Plan

5.1. Data Collection, Monitoring, and Quality Assurance

Study data are collected using Research Electronic Data Capture (REDCap), a secure, password-protected, HIPAA-compliant, web-based electronic data capture system. We selected this method of data collection to optimize data quality (e.g., reductions in ambiguous responses) and reduce the amount of missing data (e.g., participants unintentionally skipping a question). Participants have the option to complete paper self-report questionnaires if they prefer, or in the case of technology issues. In these cases, self-report data are verified and entered into REDCap by study research staff who are blind to the study condition. Likewise, data from interview-administered measures and urine drug screens are first recorded on paper forms and then entered into REDCap by an independent evaluator.

The following data monitoring procedures are implemented to promote data quality: (1) double data entry for all data completed via paper forms, (2) systematically recording study notes-to-file in the case of any event that threatens data integrity, and (3) routine internal audits. Internal audits assess data quality and participant safety (including confidentiality) by confirming that: (1) informed consent was properly obtained; (2) all data collection forms were completed accurately, or appropriate documentation of missing data was recorded by study staff; (3) all adverse events, unanticipated problems, and protocol deviations were accurately recorded and reported in accordance with IRB guidelines; (4) all participants met study inclusion/exclusion criteria; and (5) proper study close-out procedures were followed (i.e., completing study closeout checklists detailing the continuing care plan and the nature of study discontinuation).

5.2. Data Analysis Plan

Data analysis for Stage 1A focused on descriptive and qualitative methods to inform refinement of the treatment manual and to establish initial evidence of feasibility and safety. Similarly, descriptive methods will be used to characterize feasibility in Stage 1B using treatment completion and satisfaction measures as markers of acceptability.

Data analysis for the main outcomes in Stage 1B will involve the following steps. First, all data will be evaluated for evidence of skewness and univariate outliers. Sociodemographic and clinical characteristics will be compared between the two randomized groups to identify any significant differences. Any variables significantly different between groups that are known to be strongly predictive of outcome will be added to all analyses as covariates. Age and gender have been identified as key covariates for consideration in all analyses.

We will use an intent-to-treat approach to analyzing study data. Linear mixed-effects models will be conducted for the two primary outcome variables: number of opioid-positive weeks in the prior 4 weeks, and total score on the Hamilton Anxiety Rating Scale. Independent variables will include the effects of treatment, time, and the treatment by time interaction. Random intercepts and slopes for the time variables will be included to account for repeated measures within participants.

Stress reactivity analyses will include both: (1) analysis of whether stress reactivity at baseline predicted treatment outcome at post-treatment (week 12), and (2) whether stress reactivity decreased over time. The first analysis will entail use of linear regressions examining the two primary treatment outcomes with indices of stress reactivity at baseline as the independent variables, controlling for treatment condition. The second analysis will regard indices of stress reactivity as the outcome and utilize a linear mixed-effects model controlling for repeated measures. The main effects of treatment condition and time and their interaction will be included as independent variables in this analysis.

Several planned secondary analyses will complement these analyses. These analyses will similarly utilize intent-to-treat approaches and linear mixed effects models for outcomes of interest (e.g., quality of life, weeks of other substance use). Exploratory completer analyses will be conducted to determine whether treatment effects differ based on the dose of treatment received.

5.3. Missing Data and Power Considerations

Although extensive efforts are made to minimize missing data, some amount of missing data is inevitable in a longitudinal study of a population that is both clinically severe and often has unstable housing. The data analytic approach described above allows for the consideration of partial data when data points are missing or when participants are lost to follow-up.

For this Stage 1 trial, the aim is to obtain an estimate of the reliability of the treatment effect to inform power calculations for a Stage 2 trial. Thus, our focus is on refining the treatment manual, obtaining data on feasibility and acceptability, and obtaining an initial estimate of the magnitude of the treatment effect and its reliability. Nonetheless, correlations between repeated measures for the two main outcomes (opioid use and anxiety symptoms) estimated from unpublished pilot data suggest that the proposed sample size of 54 participants will provide power of at least .80 to detect a between group difference in the magnitude of a large effect size (d = .70–.75). Characterization of effect sizes and their reliability will complement significance testing in this pilot study.

6. Discussion

The majority of adults with opioid use disorder also meet criteria for an anxiety disorder [4], and the co-occurrence of these disorders is associated with greater severity and poorer outcomes. Although opioid use is often anxiolytic in the short-term, chronic opioid use and opioid withdrawal worsen anxiety, resulting in a cycle of chronic anxiety and opioid use that is extremely difficult to interrupt.

Although significant progress has been made developing [70–73] and expanding access [74–76] to medication-assisted treatments for opioid use disorder, approximately 30–50% of patients discontinue treatment prematurely [70, 77–80] and 40–80% continue to use opioids during treatment [81]. Adequate treatment of co-occurring disorders is a promising avenue for enhancing outcomes in this population.

This Stage 1 behavioral treatment development trial aims to develop and test a new approach to addressing co-occurring opioid use and anxiety disorders through targeting interacting and overlapping symptoms, with the ultimate aim of improving outcomes for this highly disabling disorder. This trial will be a first step toward understanding optimal treatment for this population. A number of key questions for future studies will include, for example, whether those with subsyndromal anxiety, or with anxiety related to protracted withdrawal may also benefit from treatment targeted to these symptoms, and whether the effects of an anxiety-focused treatment generalize to substance use disorders for substances other than opioids. The next step after this Stage 1 trial--if hypotheses are supported--will be to conduct a Stage 2 trial consisting of a larger randomized controlled trial of the treatment to investigate efficacy as well as to test potential mediators and moderators of treatment effects [30].

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References

1. Substance Abuse and Mental Health Services Administration. Results from the 2012 National Survey on Drug Use and Health: Detailed tables. Substance Abuse and Mental Healt Services Administration; Rockville, MD: 2013.
2. SAMHSA. Key substance use and mental health indicators in the United States: Results from the 2015. National Survey on Drug Use and Health; 2016.
3. Rudd RA, Aleshire N, Zibbell JE, Matthew Gladden R. Increases in Drug and Opioid Overdose Deaths—United States, 2000–2014. Am J Transplant. 2016; 16(4):1323–1327.
4. Conway KP, Compton W, Stinson FS, Grant BF. Lifetime Comorbidity of DSM-IV Mood and Anxiety Disorders and Specific Drug Use Disorders: Results From the National Epidemiologic Survey on Alcohol and Related Conditions. J Clin Psychiatry. 2006; 67(2):247–258. [PubMed: 16566620]
5. Carpentier PJ, Krabbe PFM, van Gogh MT, Knapen LJM, Buitelaar JK, de Jong CAJ. Psychiatric comorbidity reduces quality of life in chronic methadone maintained patients. Am J Addict. 2009; 18(6):470–480. [PubMed: 19874168]

6. Lejuez CW, Zvolensky MJ, Daughters SB, Bornovalova MA, Paulson A, Tull MT, Ettinger K, Otto MW. Anxiety sensitivity: a unique predictor of dropout among inner-city heroin and crack/cocaine users in residential substance use treatment. Behav Res Ther. 2008; 46(7):811–818. [PubMed: 18466878]
7. Lavie E, Fatséas M, Denis C, Auriacombe M. Benzodiazepine use among opiate-dependent subjects in buprenorphine maintenance treatment: Correlates of use abuse and dependence. Drug Alcohol Depend. 2009; 99(1):338–344. [PubMed: 18824311]
8. Rigg KK, Ibañez GE. Motivations for Non-Medical Prescription Drug Use: A Mixed Methods Analysis. J Subst Abuse Treat. 2010; 39(3):236–247. [PubMed: 20667680]
9. Farrell M. Opiate withdrawal. Addiction. 1994; 89(11):1471–1475. [PubMed: 7841858]
10. Laposa JM, Collimore KC, Hawley LL, Rector NA. Distress tolerance in OCD, anxiety disorders and its relationship with anxiety sensitivity and intolerance of uncertainty. J Anxiety Disord. 2015; 33:8–14. [PubMed: 25956557]
11. McHugh RK, Otto MW. Profiles of distress intolerance in a substance-dependent sample. The Am J Drug Alcohol Abuse. 2012; 38(2):161–165. [PubMed: 22185368]
12. Michel NM, Rowa K, Young L, McCabe RE. Emotional distress tolerance across anxiety disorders. J Anxiety Disord. 2016; 40:94–103. [PubMed: 27161839]
13. Back SE, Gros DF, Price M, LaRowe S, Flanagan J, Brady KT, Davis C, Jaconis M, McCauley JL. Laboratory-induced stress and craving among individuals with prescription opioid dependence. Drug Alcohol Depend. 2015; 155:60–67. [PubMed: 26342626]
14. McLaughlin KA, Kubzansky LD, Dunn EC, Waldinger R, Vaillant G, Koenen KC. Childhood social environment, emotional reactivity to stress and mood and anxiety disorders across the life course. Depress Anxiety. 2010; 27(12):1087–1094. [PubMed: 21132844]
15. Abelson JL, Curtis GC. Hypothalamic-pituitary-adrenal axis activity in panic disorder: prediction of long-term outcome by pretreatment cortisol levels. Am J Psychiatry. 1996; 153(1):69–73. [PubMed: 8540595]
16. Daughters SB, Lejuez CW, Bornovalova MA, Kahler CW, Strong DR, Brown RA. Distress tolerance as a predictor of early treatment dropout in a residential substance abuse treatment facility. J Abnorm Psychol. 2005; 114(4):729–734. [PubMed: 16351393]
17. Daughters SB, Lejuez CW, Kahler CW, Strong DR, Brown RA. Psychological distress tolerance and duration of most recent abstinence attempt among residential treatment-seeking substance abusers. Psychol Addict Behav. 2005; 19(2):208–211. [PubMed: 16011392]
18. Sinha R, Fox HC, Hong KI, Hansen J, Tuit K, Kreek MJ. Effects of adrenal sensitivity, stress-cue-induced craving and anxiety on subsequent alcohol relapse and treatment outcomes. Arch Gen Psychiatry. 2011; 68(9):942–952. [PubMed: 21536969]
19. Sinha R, Garcia M, Paliwal P, Kreek MJ, Rounsaville BJ. Stress-induced cocaine craving and hypothalamic-pituitary-adrenal responses are predictive of cocaine relapse outcomes. Arch Gen Psychiatry. 2006; 63(3):324–331. [PubMed: 16520439]
20. Carroll KM, Easton CJ, Nich C, Hunkele KA, Neavins TM, Sinha R, Ford HL, Vitolo SA, Doebrick CA, Rounsaville BJ. The use of contingency management and motivational/skills-building therapy to treat young adults with marijuana dependence. J Consult Clin Psychol. 2006; 74(5):955–966. [PubMed: 17032099]
21. Carroll ME, Lynch WJ, Roth ME, Morgan AD, Cosgrove KP. Sex and estrogen influence drug abuse. Trends Pharmacol Sci. 2004; 25(5):273–279. [PubMed: 15120494]
22. Barlow DH, Gorman JM, Shear MK, Woods SW. Cognitive-behavioral therapy, imipraminem or their combination for panic disorder: A randomized controlled trial. JAMA. 2000; 283(19):2529–2536. [PubMed: 10815116]
23. Farchione TJ, Fairholme CP, Ellard KK, Boisseau CL, Thompson-Hollands J, Carl JR, Gallagher MW, Barlow DH. Unified protocol for transdiagnostic treatment of emotional disorders: a randomized controlled trial. Behav Ther. 2012; 43(3):666–678. [PubMed: 22697453]
24. Stangier U, Schramm E, Heidenreich T, Berger M, Clark DM. Cognitive therapy vs interpersonal psychotherapy in social anxiety disorder: a randomized controlled trial. Arch Gen Psychiatry. 2011; 68(7):692–700. [PubMed: 21727253]

25. Lydecker KP, Tate SR, Cummins KM, McQuaid J, Granholm E, Brown SA. Clinical outcomes of an integrated treatment for depression and substance use disorders. Psychol Addict Behav. 2010; 24(3):453–465. [PubMed: 20853931]
26. Mills KL, Teesson M, Back SE, Brady KT, Baker AL, Hopwood S, Sannibale C, Barrett EL, Merz S, Rosenfeld J, Ewer PL. Integrated exposure-based therapy for co-occurring posttraumatic stress disorder and substance dependence: a randomized controlled trial. JAMA. 2012; 308(7):690–699. [PubMed: 22893166]
27. Weiss RD, Griffin ML, Kolodziej ME, Greenfield SF, Najavits LM, Daley DC, Doreau HR, Hennen JA. A randomized trial of integrated group therapy versus group drug counseling for patients with bipolar disorder and substance dependence. Am J Psychiatry. 2007; 164(1):100–107. [PubMed: 17202550]
28. Wasan AD, Butler SF, Budman SH, Fernandez K, Weiss RD, Greenfield SF, Jamison RN. Does report of craving opioid medication predict aberrant drug behavior among chronic pain patients? The Clin J Pain. 2009; 25(3):193–198. [PubMed: 19333168]
29. Hien DA, Wells EA, Jiang H, Suarez-Morales L, Campbell AN, Cohen LR, Miele GM, Killeen T, Brigham GS, Zhang Y. Multisite randomized trial of behavioral interventions for women with co-occurring PTSD and substance use disorders. J Consult Clin Psychol. 2009; 77(4):607. [PubMed: 19634955]
30. Rounsaville BJ, Carroll KM, Onken LS. A stage model of behavioral therapies research: Getting started and moving on from Stage 1. Clinical Psychol. 2001; 8(2):133–142.
31. McHugh RK. Treatment of co-occurring anxiety disorders and substance use disorders. Harv Rev Psychiatry. 2015; 23(2):99–111. [PubMed: 25747923]
32. Tull MT, Schulzinger D, Schmidt NB, Zvolensky MJ, Lejuez CW. Development and initial examination of a brief intervention for heightened anxiety sensitivity among heroin users. Behav Modif. 2007; 31(2):220–242. [PubMed: 17307936]
33. Carroll, KM. A Cognitive-Behavioral Approach: Treating Cocaine Addiction. (NIH Publication Number 98–4308). National Institute on Drug Abuse; Rockville, MD: 1998.
34. Weiss, RD., Connery, HS. Integrated Group Therapy for Bipolar Disorder and Substance Abuse. Guilford; New York: 2011.
35. Barlow, DH., Farchione, TJ., Fairholme, CP., Ellard, KK., Boisseau, CL., Allen, LB., Ehrenreich-May, J. Unified Protocol for Transdiagnostic Treatment of Emotional Disorders: Therapist Guide. Oxford University Press; New York, NY: 2011.
36. Otto, MW., Pollack, MH. Stopping Anxiety Medication. Oxford University Press; New York: 2009.
37. Dreifuss JA, Griffin ML, Frost K, Fitzmaurice GM, Potter JS, Fiellin DA, Selzer J, Hatch-Maillette M, Sonne SC, Weiss RD. Patient characteristics associated with buprenorphine/naloxone treatment outcome for prescription opioid dependence: Results from a multisite study. Drug Alcohol Depend. 2013; 131(1–2):112–118. [PubMed: 23333292]
38. Nielsen S, Hillhouse M, Thomas C, Hasson A, Ling W. A comparison of buprenorphine taper outcomes between prescription opioid and heroin users. J Addict Med. 2013; 7(1):33–38. [PubMed: 23222095]
39. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5. American Psychiatric Association; Arlington, VA: 2013.
40. Lenze EJ, Mulsant BH, Shear MK, Dew MA, Miller MD, Pollock BG, Houck P, Tracey B, Reynolds CF 3rd. Efficacy tolerability of citalopram in the treatment of late-life anxiety disorders: results from an 8-week randomized placebo-controlled trial. Am J Psychiatry. 2005; 162(1):146–150. [PubMed: 15625213]
41. Mercer, DE., Woody, GE. An Individual Counseling Approach to Treat Cocaine Addiction (NIH Publication Number 99-4380). National Institute on Drug Abuse; Bethesda: 1999.
42. Crits-Christoph P, Siqueland L, Blaine J, Frank A, Luborsky L, Onken LS, Muenz LR, Thase ME, Weiss RD, Gastfriend DR, Woody GE, Barber JP, Butler SF, Daley D, Salloum I, Bishop S, Najavits LM, Lis J, Mercer D, Griffin ML, Moras K, Beck AT. Psychosocial treatments for cocaine dependence: National Institute on Drug Abuse Collaborative Cocaine Treatment Study. Arch Gen Psychiatry. 1999; 56(6):493–502. [PubMed: 10359461]

43. Ball SA, Maccarelli LM, LaPaglia DM, Ostrowski MJ. Randomized trial of dual-focused vs. single- focused individual therapy for personality disorders and substance dependence. J Nerv Ment Dis. 2011; 199(5):319–328. [PubMed: 21543951]
44. Weiss RD, Griffin ML, Potter JS, Dodd DR, Dreifuss JA, Connery HS, Carroll KM. Who benefits from additional drug counseling among prescription opioid-dependent patients receiving buprenorphine-naloxone and standard medical management? Drug Alcohol Depend. 2014; 140:118–122. [PubMed: 24831754]
45. Mercer, DE., Woody, GE. Individual Drug Counseling. University of Pennsylvania, Veterans Affairs Medical Center; 1999. NIH Pub. No 99-4380
46. Lichstein KL, Riedel BW, Grieve R. Fair tests of clinical trials: A treatment implementation model. Adv Behav Res Ther. 1994; 16:1–29.
47. McHugh RK, Murray HW, Barlow DH. Balancing fideilty and adaptation in the dissemination of empirically-supported treatments: The promise of transdiagnostic interventions. Behav Res Ther. 2009; 47:946–953. [PubMed: 19643395]
48. Primakoff L, Epstein N, Covi L. Homework compliance: An uncontrolled variable in cognitive therapy outcome research. Behav Ther. 1986; 17:433–436.
49. Carroll KM, Ball SA, Martino S, Nich C, Babuscio TA, Nuro KF, Gordon MA, Portnoy GA, Rounsaville BJ. Computer-assisted delivery of cognitive-behavioral therapy for addiction: a randomized trial of CBT4CBT. Am J Psychiatry. 2008; 165(7):881–888. [PubMed: 18450927]
50. Decker SE, Kiluk BD, Frankforter T, Babuscio T, Nich C, Carroll KM. Just showing up is not enough: Homework adherence and outcome in cognitive-behavioral therapy for cocaine dependence. J Consult Clin Psychol. 2016; 84(10):907–912. [PubMed: 27454780]
51. Donovan DM, Bigelow GE, Brigham GS, Carroll KM, Cohen AJ, Gardin JG, Hamilton JA, Huestis MA, Hughes JR, Lindblad R, Marlatt GA, Preston KL, Selzer JA, Somoza EC, Wakim PG, Wells EA. Primary outcome indices in illicit drug dependence treatment research: systematic approach to selection and measurement of drug use end-points in clinical trials. Addiction. 2012; 107(4):694–708. [PubMed: 21781202]
52. Tiffany ST, Friedman L, Greenfield SF, Hasin DS, Jackson R. Beyond drug use: a systematic consideration of other outcomes in evaluations of treatments for substance use disorders. Addiction. 2012; 107(4):709–18. [PubMed: 21981638]
53. Brown, TA., Barlow, DH. Anxiety and Related Disorders Interview Schedule for DSM-5. Oxford University Press; New York: 2014.
54. Brown TA, Campbell LA, Lehman CL, Grisham JR, Mancill RB. Current and lifetime comorbidity of the DSM-IV anxiety and mood disorders in a large clinical sample. J Abnorm Psychol. 2001; 110(4):585–599. [PubMed: 11727948]
55. Sobell, LC., Sobell, MB. Alcohol Timeline Followback (TLFB) Users' Manual. Addiction Research Foundation; Toronto: 1996.
56. Hamilton M. The assessment of anxiety states by rating. Brit J Med Psychol. 1959; 32(1):50–55. [PubMed: 13638508]
57. Shear MK, Vander Bilt J, Rucci P, Endicott J, Lydiard B, Otto MW, Pollack MH, Chandler L, Williams J, Ali A, Frank DM. Reliability and validity of a structured interview guide for the Hamilton Anxiety Rating Scale (SIGH-A). Depress Anxiety. 2001; 13(4):166–178. [PubMed: 11413563]
58. McHugh RK, Fitzmaurice GM, Carroll KM, Griffin ML, Hill KP, Wasan AD, Weiss RD. Assessing craving and its relationship to subsequent prescription opioid use among treatment-seeking prescription opioid dependent patients. Drug Alcohol Depend. 2014; 145:121–126. [PubMed: 25454409]
59. The Group WHOQOL. Development of the World Health Organization WHOQOL-BREF quality of life assessment. Psychol Med. 1998; 28(3):551–558. [PubMed: 9626712]
60. McLellan AT, Kushner H, Metzger D, Peters R, Smith I, Grissom G, Pettinati H, Argeriou M. The Fifth Edition of the Addiction Severity Index. J Subst Abuse Treat. 1992; 9(3):199–213. [PubMed: 1334156]

61. Weiss RD, Griffin ML, Mazurick C, Berkman B, Gastfriend DR, Frank A, Barber JP, Blaine J, Salloum I, Moras K. The relationship between cocaine craving, psychosocial treatment, and subsequent cocaine use. Am J Psychiatry. 2003; 160(7):1320–1325. [PubMed: 12832248]
62. Larsen DL, Attkisson CC, Hargreaves WA, Nguyen TD. Assessment of client/patient satisfaction: development of a general scale. Eval Program Plann. 1979; 2(3):197–207. [PubMed: 10245370]
63. Borkovec TD, Nau SD. Credibility of anologue therapy rationales. J Behav Ther Exp Psy. 1972; 3:257–260.
64. Abelson JL, Curtis GC. Hypothalamic-pituitary-adrenal axis activity in panic disorder: prediction of long-term outcome by pretreatment cortisol levels. Am J Psychiatry. 1996; 153(1):69–73. [PubMed: 8540595]
65. Boden MT, Kimerling R, Jacobs-Lentz J, Bowman D, Weaver C, Carney D, Walser R, Trafton JA. Seeking Safety treatment for male veterans with a substance use disorder and post-traumatic stress disorder symptomatology. Addiction. 2012; 107(3):578–586. [PubMed: 21923756]
66. Sinha R, Catapano D, O'Malley S. Stress-induced craving and stress response in cocaine dependent individuals. Psychopharmacology. 1999; 142(4):343–351. [PubMed: 10229058]
67. Sinha R, Fuse T, Aubin LR, O'Malley SS. Psychological stress, drug-related cues and cocaine craving. Psychopharmacology. 2000; 152(2):140–148. [PubMed: 11057517]
68. Sinha R, Talih M, Malison R, Cooney N, Anderson GM, Kreek MJ. Hypothalamic-pituitary-adrenal axis and sympatho-adreno-medullary responses during stress-induced and drug cue-induced cocaine craving states. Psychopharmacology. 2003; 170(1):62–72. [PubMed: 12845411]
69. Lang PJ, Kozak MJ, Miller GA, Levin DN, McLean A Jr. Emotional imagery: conceptual structure and pattern of somato-visceral response. Psychophysiology. 1980; 17(2):179–192. [PubMed: 7375619]
70. Comer SD, Sullivan MA, Elmer Y, Rothenberg JL, Kleber HD, Kampman K, Dackis C, O'Brien CP. Injectable, sustained-release naltrexone for the treatment of opioid dependence: A randomized placebo-controlled trial. Arch Gen Psychiatry. 2006; 63(2):210–218. [PubMed: 16461865]
71. Fiellin DA, Pantalon MV, Chawarski MC, Moore BA, Sullivan LE, O'Connor PG, Schottenfeld RS. Counseling plus Buprenorphine–Naloxone Maintenance Therapy for Opioid Dependence. N Engl J Med. 2006; 355(4):365–374. [PubMed: 16870915]
72. Weiss RD, Potter JS, Fiellin DA, Bryne M, Connery HS, Dickinson W, Gardin J, Griffin ML, Gourevitch MN, Haller DL, Hasson AL, Huang Z, Jacobs P, Kosinski AS, Lindblad R, McCance-Katz EF, Provost SE, Selzer J, Somoza EC, Sonne SC, Ling W. Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: A 2-phase randomized controlled trial. Arch Gen Psychiatry. 2011; 68(12):1238–1246. [PubMed: 22065255]
73. Woody W, Poole SA, Subramaniam GA, Dugosh K, Bogenschutz M, Abbott P, Ashwin P, Publicker M, McCain K, Potter JS, Forman R, Vetter V, McNicholas L, Blaine J, Lynch KG, Fudala P. Extended vs short-term buprenorphine- naloxone for treatment of opioid-addicted youth: A randomized trial. JAMA. 2008; 300(17):2003–2011. [PubMed: 18984887]
74. Fiellin DA, O'Connor PG. New Federal Initiatives To Enhance the Medical Treatment of Opioid Dependence. Ann Intern Med. 2002; 137(8):688–692. [PubMed: 12379070]
75. Jaffe JH, O'Keeffe C. From morphine clinics to buprenorphine: regulating opioid agonist treatment of addiction in the United States. Drug Alcohol Depend. 2003; 70(2):S3–S11. [PubMed: 12738346]
76. SAMHSA. Medication Assisted Treatment for Opioid Use Disorders. Final rule. Fed Regist. 2016; 81(131):44711–44739. [PubMed: 27400463]
77. Hser Y-I, Saxon AJ, Huang D, Hasson A, Thomas C, Hillhouse M, Jacobs P, Teruya C, McLaughlin P, Wiest K, Cohen A, Ling W. Treatment retention among patients randomized to buprenorphine/naloxone compared to methadone in a multi-site trial. Addiction. 2014; 109(1):79–87. [PubMed: 23961726]
78. Kelly SM, O'Grady KE, Mitchell SG, Brown BS, Schwartz RP. Predictors of methadone treatment retention from a multi-site study: A survival analysis. Drug Alcohol Depend. 2011; 117(2–3):170–175. [PubMed: 21310552]

79. Soeffing JM, Martin LD, Fingerhood MI, Jasinski DR, Rastegar DA. Buprenorphine maintenance treatment in a primary care setting: outcomes at 1 year. J Subst Abuse Treat. 2009; 37(4):426–430. [PubMed: 19553061]

80. Soyka M, Zingg C, Koller G, Kuefner H. Retention rate and substance use in methadone and buprenorphine maintenance therapy and predictors of outcome: results from a randomized study. International Journal of Neuropsychopharmacology. 2008; 11(5):641–653. [PubMed: 18205978]

81. Connery HS. Medication-Assisted Treatment of Opioid Use Disorder: Review of the Evidence and Future Directions. Harv Rev Psychiatry. 2015; 23(2):63–75. [PubMed: 25747920]

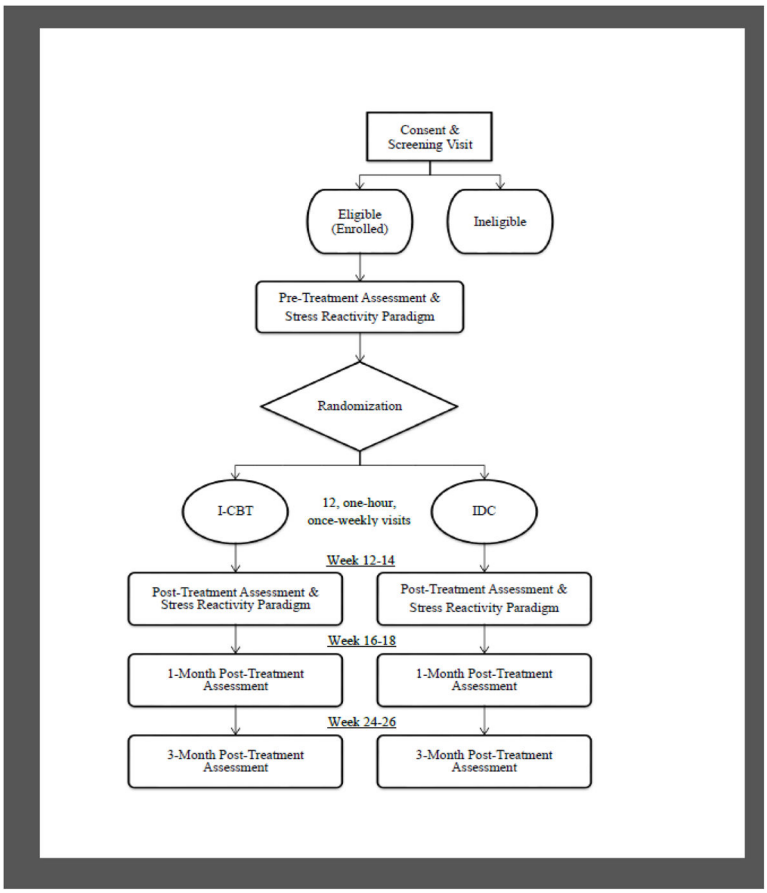

Figure 1.

Table 1

Integrated Cognitive-Behavioral Therapy Session Overview

	Session Topic	**Key Aims**
1	Introduction to Treatment	Introduce the treatment; provide psychoeducation on the interaction and overlap of opioid use and anxiety; establish treatment goals.
2	Identifying and Responding to Triggers	Introduce functional analysis and the role of “quick fix” behaviors to alleviate distress; practice functional analysis.
3	Developing a Coping Plan	Discuss coping skills and develop individualized coping plan; provide psychoeducation on emotion.
4	Stuck Thinking and Thinking Traps	Discuss the role of cognition in opioid use and anxiety, practice cognitive reappraisal or stimulus control for modifying cognition.
5	Interpersonal Skills	Discuss the importance of effective interpersonal communication; rehearse effective communication.
6	Problem Solving	Discuss the interference of opioid use and anxiety with effective problem solving; rehearse effective problem solving.
7–11	Exposure and Skills Practice	Conduct in-session exposure practice; this can incorporate practice of skills from previous sessions.
12	Continuing Care/Relapse Prevention	Review treatment concepts, patient’s progress, and develop a continuing care plan

Note. Sessions 2–11 can be conducted in any order at the discretion of the therapist based on the priorities and needs of the patient.