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A Randomized, Controlled Trial of the Efficacy of an Interoceptive Exposure-Based CBT for Treatment-Refractory Outpatients with Opioid Dependence

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Abstract

Many patients diagnosed with opioid dependence do not adequately respond to pharmacologic, psychosocial, or combination treatment, highlighting the importance of novel treatment strategies for this population. The current study examined the efficacy of a novel behavioral treatment focusing on internal cues for drug use (Cognitive Behavioral Therapy for Interoceptive Cues; CBT-IC) relative to an active comparison condition, Individual Drug Counseling (IDC), when added to methadone maintenance treatment (MMT) among those who had not responded to MMT. Participants (N=78) were randomly assigned to receive 15 sessions of CBT-IC or IDC as an adjunct to ongoing MMT and counseling. Oral toxicology screens were the primary outcome. Results indicated no treatment differences between CBT-IC and IDC and a small, significant reduction of self-reported drug use, but no change on toxicology screens. Tests of potential moderators, including sex, anxiety sensitivity, and coping motives for drug use, did not yield significant interactions. Among opioid-dependent out-patients who have not responded to MMT and counseling, the addition of IDC or CBT-IC did not result in additive outcome benefits. These results highlight the need for more potent treatment strategies for opioid dependence, particularly among those who do not fully respond to frontline treatment.

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anxiety sensitivity; cognitive behavioral therapy; coping motives; interoceptive exposure; opioid dependence; treatment outcome

Opioid agonist therapies and a number of psychosocial treatment approaches (e.g., cognitive-behavioral therapy) demonstrate efficacy in reducing illicit drug use among opioid-dependent patients (for review, see Dutra et al. 2008; Veilleux et al. 2010). However, many patients receiving treatment for opioid dependence continue to engage in regular use of other illicit substances (van den Brink & Haasen 2006). Among patients enrolled in methadone maintenance treatment programs, 50% report use of other drugs and alcohol (Brands et al. 2004; Nurco et al. 1988; San et al. 1990; Stizer et al. 1992; Woody et al. 1990), and many also meet criteria for alcohol, cannabis, stimulant, or sedative dependence (Strain 2002). Moreover, relapse rates following treatment for opioid dependence are high, with estimates suggesting that less than 25% of opioid-dependent individuals remain abstinent after ending methadone maintenance treatment (Dekimpe et al. 1998). The chronic relapsing nature of opioid dependence has been shown to drastically increase premature mortality (Hser et al. 2001; Jimenez-Trevino et al. 2011), highlighting the need for improved treatment strategies for this population.

Although cognitive-behavioral interventions such as contingency management, relapse prevention, and other focused interventions offer reliable benefit across drug use disorders, these benefits tend to be lower among those with drug dependence characterized by polysubstance use (Dutra et al. 2008). Also, the addition of psychosocial interventions (e.g., enhanced drug counseling, short-term interpersonal therapy, as well as cognitive-behavioral interventions) to agonist maintenance treatments, which generally already include a limited psychosocial counseling component, often does not yield additive benefits (see Amato et al. 2011). For example, a recent Cochrane review indicated that, as a whole, the addition of psychosocial interventions had no effect on treatment retention, rates of abstinence, treatment compliance, or psychiatric symptoms when added to agonist therapy in this manner (Amato et al. 2011). However, psychosocial treatments added to methadone maintenance are extremely heterogeneous with few large-scale randomized controlled trials, indicating that such studies are needed before definitive conclusions can be drawn (Veilleux et al. 2010).

Research on the chronic nature of drug dependence has stressed the importance of environmental contextual cues in drug craving (Rohsenow & Monti 1999). Some treatments, based on exposure to external drug use cues, have demonstrated promising results; however, findings have been somewhat inconsistent, with external cue exposure treatments often failing to show any benefit for reducing drug use behavior (for a review, see Conklin & Tiffany 2002). A possible explanation for this may be the limited ability of external cue procedures carried out in the context of a treatment center to generalize to natural settings (O'Brien et al. 1990; Conklin & Tiffany 2002).

Moreover, research has shown that drug craving may be associated with interoceptive as well as external cues (Marlatt & Gordon 1980; O'Connell & Martin 1987; Siegel 2005;

Wikler 1965). In particular, both induced and naturally occurring negative mood states have been associated with increased drug craving (Childress et al. 1994; Robbins et al. 2000; Sherman et al. 1989) and use (Ouimette et al. 2010). Therefore, a treatment that addresses tolerance of internal cues for drug use may provide a promising approach for helping patients to respond appropriately to craving cues in a way that generalizes beyond the clinic setting (Otto, Powers & Fischmann 2005).

Cognitive Behavioral Therapy for Internal Cues (CBT-IC) is a novel cognitive-behavioral treatment for drug dependence focusing on interoceptive cues (Pollack et al. 2002). CBT-IC is a 15-session intervention (12 weekly sessions plus three booster sessions) emphasizing stepwise exposure, with rehearsal of adaptive behavioral responses to emotional and somatic cues associated with drug craving. In an initial examination of CBT-IC for illicit drug use among patients receiving methadone maintenance treatment, Pollack and colleagues (2002) found that this treatment approach was associated with greater reductions in illicit drug use among women, but not men, compared to a matching number of sessions of intensified treatment with their current outpatient drug counselor. This sex difference may be accounted for by differences in the relationship between affect and drug use in men and women. Research suggests that women may react with stronger craving to negative mood induction (Monti et al. 1995; Perkins et al. 2013; Rubonis et al. 1994), and women presenting for treatment of opioid dependence often report poorer health status, poorer health-related quality of life, and higher rates of co-occurring mental health disorders (Domingo-Salvany et al. 2010; Shand et al. 2011; Williamson et al. 2009). In addition, evidence suggests that women score higher on measures of anxiety sensitivity, indicating that they may be differentially sensitive to biological provocation of anxious states (Zvolensky, Eifert & Lejuez 2001). Women also endorse using licit and illicit drugs to regulate negative mood at a higher rate than men (Hearon et al. 2011; McHugh et al. 2013a; Stewart et al. 1997; Zywiak et al. 1996). Taken together, these results indicate that women may face more psychosocial stressors in daily life, have greater sensitivity to both physical and emotion distress, and be more likely to engage in drug use as a means of coping with these difficulties.

Since the publication of our pilot study (Pollack et al. 2002), the focus on interoceptive cue exposure for drug use disorders has received encouragement from additional pilot studies, including those examining cue exposure for opioid dependence (Tull et al. 2007) and distress tolerance treatments for substance use disorders (Bornovalova et al. 2012) and nicotine dependence (Brown et al. 2008). These studies provide additional evidence that modifying responses to internal cues (emotional or withdrawal related) is a promising avenue for expanding upon cognitive-behavioral interventions for drug use disorders.

To follow up on these promising findings, and to specifically examine potential differential response to CBT-IC among women and men, we conducted a randomized trial of the efficacy of CBT-IC relative to an active comparison treatment, Individual Drug Counseling (IDC; Mercer & Woody 1999). In addition, we focused our study exclusively on individuals who were failing to respond to current counseling and agonist (methadone maintenance) therapy, providing an estimate of the efficacy of a novel treatment strategy relative to an intensification of available counseling approaches. IDC focuses on identifying and avoiding cues for drug use, while making use of available 12-step treatment resources. In contrast,

CBT-IC focuses on enhancing resilience to internal cues using exposure to interoceptive cues for drug use with rehearsal of adaptive responses, provided against a backdrop of other cognitive and coping interventions (Otto, O'Cleirigh & Pollack 2007).

Our study plan included examination of possible moderators of outcome, such as drug use motives and anxiety sensitivity. As specified by Kraemer et al. (2002), these variables meet criteria to be evaluated as moderators by being present before treatment, presumably uncorrelated with the treatments under study, and hypothesized to interact with the treatments under study. We hypothesized that CBT-IC would significantly reduce drug use as assessed by both self-report and biological measures in women but not men. We further hypothesized that those using drugs to cope, and those with elevated fears of somatic sensations of arousal (i.e., those with higher anxiety sensitivity), would respond better to CBT-IC (Otto et al. 2005).

METHODS

Participants

Participants meeting *Diagnostic and Statistical Manual for Mental Disorders*, 4th ed. (*DSM-IV*; American Psychiatric Association 1995) criteria for opioid dependence were recruited from two urban methadone maintenance treatment facilities between June 2005 and July 2011. Those who had failed to respond to the standard course of treatment provided by these facilities, treatment as usual (TAU; methadone maintenance plus group counseling provided by clinic substance abuse counselors on a weekly basis), were offered the opportunity to participate in a study that included the addition of one of two psychosocial treatments to TAU. Attendance at group treatment provided by the facilities was mandatory; therefore, all participants maintained the minimum required attendance in TAU throughout the study. Failure to respond to TAU was defined by: (1) the failure to achieve "take-home" status (a supply of methadone to be self-administered for one-week periods) for methadone dosing (participants had to have been at the clinic for at least four months before they were eligible to participate); (2) positive test results on at least two toxicology screens for illicit drugs during the two months prior to recruitment (screens were to be conducted by the treatment facility approximately twice per month); and (3) never having achieved two consecutive toxicology screens free of illicit substances since entering the current treatment episode.

Participants were recruited through posted study flyers or were referred to study staff by their substance abuse counselor. Additional eligibility criteria included current use of illicit substances (verified by oral toxicology screen), stable dose of methadone for at least two weeks prior to enrollment, and the presence of a current chronic stressor or affective disorder. Stressors included non- or limited-employment (defined as less than 20 hours per week of employment). Exclusion criteria included significant unstable medical illness, uncontrolled bipolar disorder, psychotic disorder, use of medication affecting methadone metabolism, and inability to complete informed consent procedures.

A total of 133 individuals provided informed consent (see CONSORT diagram, Figure 1). Of this total, 78 individuals remained interested and eligible for the study after completing screening assessments and were randomized to CBT-IC (n = 41) or to IDC (n = 37). These

treatment conditions were provided in addition to any services patients were receiving as adjuncts to methadone maintenance; participants were compensated for completion of assessments and toxicology swabs associated with the study. All study procedures were approved by the Institutional Review Boards at Boston University and Massachusetts General Hospital.

Procedures

Participants were assessed for current Axis I disorders, including substance use, mood, and anxiety disorders, at a screening visit using the Structured Clinical Interview for *DSM-IV* (SCID; First et al. 1996). Those entering the protocol then completed a baseline assessment and were randomized to a treatment condition (CBT-IC vs. IDC). Treatment in both conditions included 12 weekly meetings with a study therapist followed by three booster sessions staggered across the next two months. Assessments occurred throughout the baseline, treatment, and booster phases and included both objective and clinician-rated instruments. Independent evaluators blind to study condition conducted all assessments.

Measures

The primary outcome measure was the percentage of oral toxicology swabs that were positive for any illicit substance. Participants completed these swabs at each assessment point as well as at each study therapy session. Interviewer-administered and self-report measures were used to complement these biological measures. Toxicology swabs were supervised by study staff and used oral specimen collection (Intercept®) to screen for opiates, methadone, cocaine, benzodiazepines, amphetamines, THC, and barbiturates.

Addiction Severity Index—The Addiction Severity Index (ASI; McLellan et al. 1980) is a clinician-administered interview designed to evaluate treatment outcome in substance-abusing populations across a number of domains, including health, employment, social functioning, and drug use behavior (McLellan et al. 1980). The ASI has demonstrated high inter-rater reliability (r =.89) and test-retest reliability (r =.92). This instrument was administered at baseline, mid-treatment, end of treatment, and each follow-up assessment and the Drug Use Composite score was used as an index of current substance use severity.

Drug Use Motives Questionnaire—The Drug Use Motives Questionnaire (DUMQ; Mueser et al. 1995) was used to assess reasons for use. It was adapted from the Drinking Motives Questionnaire (Cooper et al. 1992), which is a 15-item self-report measure assessing reasons for drinking across three dimensions: social, coping, and pleasure enhancement. The drug use adaptation of this measure has been used to assess reasons for drug use among patients with psychosis (Baker et al. 2005) and depression (Kay-Lambkin et al. 2011).

Anxiety Sensitivity Index—Anxiety sensitivity was measured using the Anxiety Sensitivity Index (Peterson & Reiss 1992), a 16-item questionnaire designed to assess one's tendency to respond fearfully to anxiety-related symptoms. Data on the reliability and validity of the Anxiety Sensitivity Index scales have been favorable (Reiss et al. 1986). The Anxiety Sensitivity Index has been used as a measure of distress intolerance (McHugh &

Otto 2011), and is linked to coping motives for drug use (e.g., Hearon et al. 2011; Johnson et al. 2010; Stewart et al. 1997), as well as other, maladaptive avoidance reactions among substance-abusing populations (Lejuez et al. 2008).

Study Therapists and Treatment Conditions

A total of 13 masters- or doctoral-level clinicians provided treatment in this trial. Study therapists provided interventions in both conditions. Sessions were audiotaped and the fidelity of interventions was assessed by a doctoral-level rater. Therapists were provided with weekly supervision by the first author (MWO).

CBT-IC has been described in detail in previous publications (Pollack et al. 2002; Otto et al. 2007). CBT-IC was conducted in 12 weekly, one-hour sessions followed by three booster sessions scheduled at two weeks, one month, and two months following completion of the protocol. Treatment focused on using exposure to emotional and somatic cues to help patients accept and tolerate these negative emotional states and craving sensations, and replace drug-use responses to these emotions and sensations with alternative, adaptive behaviors. This core treatment focus was embedded within four main components: (1) psychoeducation; (2) exposure to interoceptive cues for drug use with rehearsal of adaptive responses; (3) cognitive restructuring; and (4) somatic coping skills. Psychoeducation included a review of the patients' behavioral patterns associated with craving and drug use as well as a rationale for incorporating an alternative response to these cues. Exposure to interoceptive cues involved repeated exposure to mostly emotional cues that the patient identified as increasing his/her drug craving, and focused on reducing conditioned drug craving or drug use by having patients sit with the emotional state followed by practice of a pre-identified alternative response. Cognitive restructuring was used as both an independent strategy and in conjunction with exposure procedures to help modify maladaptive cognitions regarding drug use. Somatic coping skills included muscle relaxation procedures and breathing retraining to aid patients in reducing the intensity of physical sensations associated with withdrawal.

IDC was adapted from the manual used in the National Institute on Drug Abuse Cocaine Collaborative Study authored by Mercer and Woody (1999), which has been adapted for use with other illicit drugs, including opioids (e.g., Weiss et al. 2011). This manual was chosen as an active comparison condition, given its efficacy in the Cocaine Collaborative Study when compared to group counseling alone, psychodynamic psychotherapy, and cognitive therapy for cocaine dependence (Crits-Christoph et al. 1999). The focus of IDC is helping patients to achieve and maintain abstinence through restructuring of behavioral patterns such that drug triggers are identified and avoided. This approach views addiction as a disease that damages multiple areas of an individual's functioning and is consistent with the 12-step philosophy, including attendance at self-help groups such as Narcotics Anonymous. The timing and frequency of sessions were matched to CBT-IC.

Data Analysis

Both self-report and objective measures of drug use were utilized; the primary outcome was the proportion of positive toxicology screens for each participant collected over three time

periods: baseline, treatment, and eight weeks of follow-up. Given that this sample was characterized by the use of multiple substances of abuse and that the treatment was not targeted to any individual substance, we examined whether toxicology screens were positive for any illicit or non-prescribed drug. The drug use composite score of the ASI was examined as a secondary outcome. Separate repeated measures ANOVAs were used to examine the main and interaction effects of time, condition, and sex on these outcomes. When examining toxicology outcomes, proportion of screens positive for illicit substances during the screening, treatment, and final follow-up periods were entered into the model with total number of swabs included as a covariate. For the ASI, drug use composite scores at baseline, termination, and final follow-up were included in the model. Post-hoc comparisons utilized Bonferroni correction to address inflation of alpha.

Linear regression analyses were used to test our hypotheses that coping motives and anxiety sensitivity would moderate the association between treatment condition and drug outcomes. DUMQ coping motives subscale score at baseline, treatment condition, and the coping motive by treatment interaction term (reflecting moderation, if significant) were entered into the model. Baseline ASI drug composite score was entered as a covariate. Finally, given that CBT-IC is targeted at increasing tolerance to interoceptive cues, we used a linear regression analysis to examine changes in anxiety sensitivity over the course of treatment, examining possible differing effects between treatment condition and sex.

Basic assumptions for all analyses were examined, with only one exception noted. Toxicology screen data were skewed in distribution: however, our sample size was sufficient so that effects of skewness should be trivial (see Games 1984), and these data were not transformed prior to analyses.

RESULTS

Baseline Characteristics

The sample included 78 adults (35 women) with a mean age of 42.3 years ($SD = 9.9$). Patients self-reported race and ethnicity. The majority of the sample was non-Hispanic (90%), with 68% reporting race as Caucasian, and the remaining 32% reporting race as Black/African American. The sample endorsed high levels of comorbidity, with 91% meeting criteria for at least one Axis I mood or anxiety disorder, and 85.9% meeting criteria for a secondary substance use disorder in addition to opioid dependence. Table 1 provides a breakdown of demographics, drug use history, and psychiatric diagnoses by both sex and treatment condition. These characteristics did not differ by study condition.

Patient Attrition

Eighteen of the sample of 78 (23%) were defined as non-completers based on a failure to complete at least 12 of 15 sessions. Completers and non-completers were not significantly different with respect to sex, race, ethnicity, or total years, but non-completers were significantly younger than completers (mean difference = −6.0 years, $t(76) = -2.33$, $p < .05$; see McHugh et al. 2013b for further details).

Non-completers did not differ by treatment, with 22% in the CBT-IC condition and 24% in the IDC condition failing to complete treatment (Fisher exact test $p = 1.00$).

Treatment Integrity

Therapy sessions were rated by a doctoral-level clinician. For evaluation of CBT-IC, ratings were made using a CBT-IC Adherence Rating Guide designed specifically for this study. This measure consists of five overall structure ratings based on general components of each session. Ratings of adherence to IDC were made using the Adherence/Competence Scale for Individual Drug Counseling (IDC) for Cocaine Dependence (Mercer et al. 1995), assessing five main domains of IDC (including monitoring drug use behaviors, encouraging abstinence, encouraging 12-step participation, relapse prevention, educating the client, and miscellaneous), and summarized for this study as an overall IDC counselor performance score. Finally, tapes from IDC sessions were rated for the presence of proscribed interventions from the CBT-IC condition (e.g., use of a CBT-IC model for treatment or specific cognitive-restructuring, problem-solving, or interoceptive exposure interventions). Sessions to be rated were selected at random from the available sessions for each of the study therapists. For CBT-IC, 24 sessions were evaluated and provided an overall average adherence score of 25.7 from a possible score of 34, indicating that, on average, 76% of session content goals were addressed in CBT sessions. For the IDC sessions, 17 sessions were evaluated and provided a mean quality score of 5.0 from a possible score of 7 (reflecting an overall rating of “good quality”). Importantly, no proscribed interventions (CBT-IC interventions) occurred during the 17 evaluated sessions of IDC.

Treatment Outcome

The treatment groups did not differ on the proportion of positive toxicology screens at baseline (81.3% in CBT-IC and 79.1% in IDC; $t(76) = .34$, $p = .74$), nor did they differ in the baseline ASI Drug Use Composite scores (CBT-IC, $M = .23$, $SD = .09$; IDC, $M = .21$, $SD = .12$ $t(75) = .85$, $p = .40$).

Examining our primary outcome measure, proportion of positive toxicology swabs, a repeated-measures ANOVA revealed no significant main effects of time ($F(2, 116) = 1.19$, $p = .31$, partial $\eta^2 = .02$), condition ($F(1, 58) = .41$, $p = .53$, partial $\eta^2 = .007$) or sex ($F(1, 58) = .07$, $p = .80$, partial $\eta^2 = .001$), nor significant interactions of sex by time ($F(2, 116) = .90$, $p = .41$, partial $\eta^2 = .02$), condition by time ($F(2, 116) = .07$, $p = .93$, partial $\eta^2 = .001$), or their three-way interaction ($F(2, 116) = .34$, $p = .72$, partial $\eta^2 = .006$). We also examined the potential for sleeper effects, given evidence in the literature for delayed efficacy for CBT interventions (Carroll et al. 1994; Carroll et al. 2006; Rawson et al. 2002). An exploratory review of pairwise comparisons across time revealed that patients had a significant decrease in proportion of positive toxicology swabs between the treatment period and followup period ($p = .04$). This occurred after a non-insignificant increase in positive toxicology swabs between the baseline and treatment periods ($p = .94$), indicating that patients slightly increased use during treatment followed by a significant reduction from this highest point of use during follow-up (see Figure 2).

When the same model was examined looking at ASI drug composite scores at baseline, termination, and final follow-up, results revealed a significant main effect of time ($F(2, 84) = 67.59$, $p < .01$, partial $\eta^2 = .15$); however, no significant effects emerged for condition ($F(1, 42) = .02$, $p = .89$, partial $\eta^2 = .00$), sex ($F(1, 42) = .75$, $p = .39$, partial $\eta^2 = .02$), sex by time ($F(2, 84) = .04$, $p = .96$, partial $\eta^2 = .001$), condition by time ($F(2, 84) = .44$, $p = .65$, partial $\eta^2 = .01$), nor their three-way inter-action ($F(2, 84) = .41$, $p = .67$, partial $\eta^2 = .01$). Pairwise comparisons revealed a significant reduction in ASI scores between baseline and treatment termination ($p < .01$) that was maintained at final follow-up.

Moderators of Treatment Outcome

Multiple regression analyses were used to examine the predictive influence of anxiety sensitivity on our selected outcome variables. In the first model, the Anxiety Sensitivity Index score ($\beta = .30$; $t = 2.25$; $p = .03$) and the covariate (ASI drug use severity at baseline: $\beta = .33$: $t = 2.41$; $p = .02$) significantly predicted ASI drug use severity at termination, but the interaction term (reflecting moderation) did not predict significantly. An identical model was examined predicting ASI at follow-up; in this model, only ASI at baseline emerged as a significant individual predictor ($\beta = .38$; $t = 2.34$; $p = .03$). In a similar regression analysis examining toxicology screen results, Anxiety Sensitivity Index score approached significance as a predictor ($\beta = -.29$; $t = -2.01$; $p = .051$), with non-significant results for the covariate, baseline ASI drug composite ($\beta = -.12$; $t = -.82$; $p = .42$).

In the regression examining moderational effects of coping motives on toxicology outcomes, there was no evidence for a moderational effect of either variables and only the covariate (baseline ASI drug use severity) was significantly associated with toxicology outcomes.

Changes in Anxiety Sensitivity Across Treatment

To examine whether our treatment changed anxiety sensitivity scores across treatment, change scores from baseline to termination for the Anxiety Sensitivity Index was calculated. Multiple regression was used to predict changes in this moderator with treatment condition, sex, and their interaction included as predictors. Results indicate no significant effects for treatment condition ($\beta = -.10$; $t = -.22$; $p = .83$), sex ($\beta = -.09$; $t = -.57$; $p = .57$), or their interaction ($\beta = .19$; $t = .39$; $p = .70$) in predicting changes in anxiety sensitivity.

DISCUSSION

In a previous study, CBT-IC offered significant benefit over ongoing counseling treatment only for women (Pollack et al. 2002). This finding fits well with the available literature on differences between the sexes in both drug use motives and sensitivity to internal cues (for review, see Otto et al. 2005). However, in the current study we found no evidence for the superiority of CBT-IC over the active comparison condition, IDC, for either women or men. The failure to detect differences between treatments was not due to both intervention groups doing well; although there were subtle signs of benefit for specific contrasts at followup for the objective measure, and self-report of decreased use, the primary analysis of change in objective data on illicit drug use over time failed to support the efficacy of the interventions.

This mirrors recent findings in prescription opioid dependence that found no benefit of adding counseling (IDC) to buprenophine-naloxone maintenance (Weiss et al. 2011).

There are several potential explanations for the failure of this trial to replicate findings from our pilot study. One difference between the pilot study and the current trial concerns the comparison condition. Instead of relying on counseling treatment provided by current therapists in the clinic as done in the pilot study, treatment in the comparison condition in the current trial was provided by study therapists in addition to the ongoing counseling provided as part of the methadone maintenance treatment program. Thus, in the current study, we were attempting to detect outcome benefits relative to another active treatment strategy among patients who had not initially responded to treatment.

Indeed, all patients enrolled in the trial had been unable to achieve an illicit drug-free state despite at least four months of combined counseling and agonist therapy. Most of these patients (52%) had been using more than one illicit drug for over 10 years, and all patients had been enrolled in the clinic for at least three months. Hence, the failure of benefit of CBT-IC in this study reflects a lack of efficacy in a sample that has not responded to a frontline treatment for chronic opioid dependence (methadone maintenance therapy plus counseling).

Also, despite the finding that anxiety sensitivity was a significant predictor of drug use across the treatment period, we did not find the expected interactions between this sensitivity to internal cues and our treatment designed to address these sensitivities. This outcome reflects a failure to change one of the specific instrumental outcomes under study. Given ample evidence for the efficacy of interoceptive exposure for reducing anxiety sensitivity and aiding medication discontinuation in other populations (Otto et al. 2010; Smits et al. 2008), there may be factors unique to this population that prevented therapeutic learning from occurring. Our therapist adherence data indicated adequate differentiation of the two treatment conditions and that, in general, component interventions for CBT-IC were provided to patients. Nonetheless, supervision indicated that helping patients attend to therapeutic content, recall therapeutic interventions between sessions, and engage in homework outside of the session was a challenge. In particular, the presence of ongoing illicit drug use in addition to methadone treatment may have interfered with the acquisition and/or consolidation of therapeutic learning hypothesized to be the active mechanism of this type of treatment approach. This is consistent with evidence for fear-conditioning deficits among this population of patients (Basden 2010). If this is the case, the question of whether CBT-IC has greater efficacy when used in individuals who have achieved a period of abstinence and/or who are not currently receiving opioid agonist treatment remains an interesting but untested issue. The application of this treatment to a population that is not characterized by such learning deficits may achieve benefits that were not detected in this chronic, treatment-refractory population.

There are several study limitations. In this study, we used both biological and self-report outcomes to attempt to minimize the limitations of measuring illicit drug use. The discrepant results between self-report and biological measures may be attributable to a reduction in use or a reduction in functional interference related to use, which is captured by the ASI, but not

drug screens. Nonetheless, the absence of an effect in the primary outcome measure (drug screens) suggested that the impact of the treatments on outcomes was minimal. Second, a number of participants (23%) did not receive a full dose of treatment (i.e., non-completers); however, this did not differ by treatment condition. Third, we did not find evidence of a moderational effect of sex that was observed in a pilot trial of this treatment. Although it is possible that a small effect was present but could not be detected with this moderate sample size, the absence of a treatment by sex effect is consistent with the literature on sex differences in treatment outcome for substance use disorders (see Greenfield et al. 2007). Finally, despite efforts to retain participants, a number of participants were lost to follow-up. This is not unexpected in this population, which is characterized by high rates of homelessness and incarceration; however, it is possible that the results would have differed if these participants had completed all follow-up assessments.

In this treatment-refractory, opioid-dependent sample, the addition of a novel cognitive-behavioral treatment (CBT-IC) or Individual Drug Counseling (IDC) did not differ from each other and did not result in reliable benefits over time, with significant changes on self-report but not objective measures of illicit drug use. These results, considered along with evidence for high rates of relapse following discontinuation of opioid agonist therapies (Dekimpe et al. 1998; Weiss et al. 2011), highlight the need for the development of new treatment strategies for addressing ongoing illicit drug use during opioid agonist treatment.

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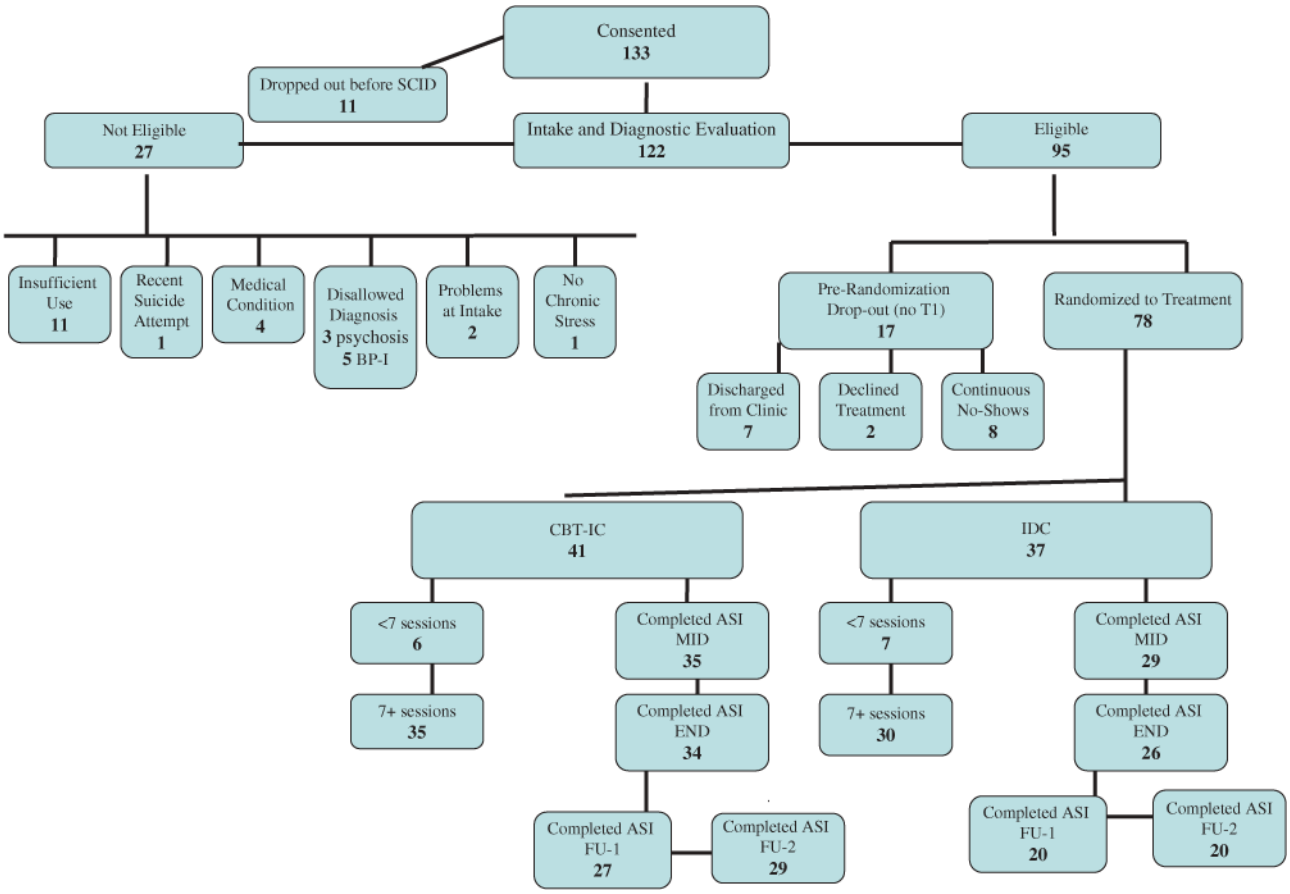

FIGURE 1.
Consort Diagram Illustrating Derivation of Final Sample

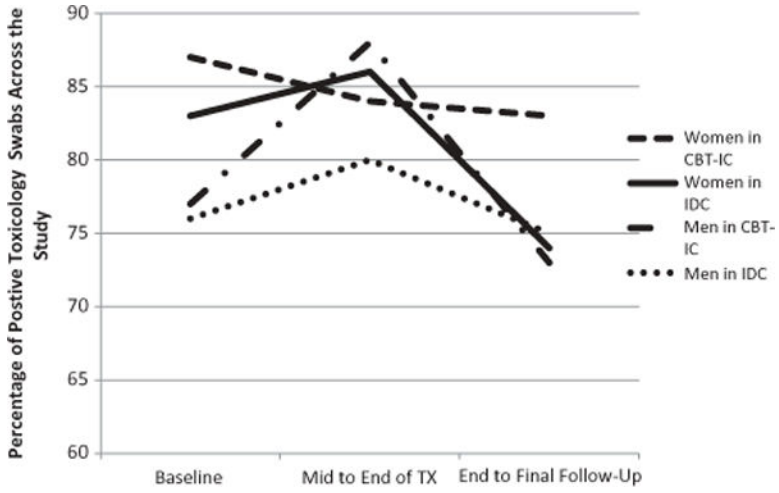

FIGURE 2.

Percentage of Positive Toxicology Screens across the Study by Sex and Treatment Condition

TABLE 1

Baseline Drug Use and Psychiatric Characteristics of the Sample

	Women		Men	
	CBT-IC	**IDC**	**CBT-IC**	**IDC**
Sample size	18	17	23 20	
Age (years)	45 (10)	44 (10)	40 (10)	41 (10)
Duration of heroin addiction (years)	13 (8)	13 (9)	15 (10)	16 (12)
% with at least 1 secondary SA disorder	67%	94%	91%	90%
Additional substance use disorders (%):				
Cocaine Use Disorder	56%	71%	48%	75%
Sedative Use Disorder	11%	24%	26%	25%
Cannabis Use Disorder	33%	18%	26%	35%
Amphetamine Use Disorder	0%	6%	0%	0%
Mood Disorder (%)	72%	59%	48%	60%
Anxiety Disorder (%)	89%	82%	91%	70%

Note: CBT-IC = Cognitive Behavioral Therapy for Internal Cues; IDC = Individual Drug Counseling.