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Symptoms of Anhedonia, not Depression, Predict the Outcome of Treatment of Cocaine Dependence

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Abstract

The purpose of this paper is to reanalyze data from two studies to determine if anhedonia specifically, rather than depression overall, predicts treatment outcome for patients with cocaine use disorders. Measures of baseline anhedonia symptoms were created using anhedonia items from the Beck Depression Inventory (BDI) to re-examine National Institute on Drug Abuse Cocaine Collaborative Treatment study data (Crits-Christoph et al., 1999) and the contingency management group from the McKay et al. (2010) trial. Baseline anhedonia was used to predict cocaine abstinence rates across the treatment period in both studies. Anhedonia was a significant predictor of cocaine abstinence, even when overall depression scores excluding anhedonia were included in the models. The development of treatments to target individuals with cocaine use disorder who have symptoms of anhedonia has the potential to improve overall outcomes for those with this disorder.

Keywords

cocaine dependence; depression; anhedonia; abstinence

1. Introduction

Despite the promise of evidence-based psychosocial treatments for cocaine use disorders, many patients do not stop using cocaine. A variety of baseline patient factors have been found to be associated with relatively poor treatment outcomes for patients with cocaine use disorder who have received an evidence-based treatment. In particular, co-occurring depression has been found to be associated with outcome and retention in multiple studies (Carroll et al., 1993; Hser et al, 1999; McKay et al., 2002; McKay et al., 2013; Poling et al., 2007; Stulz, Thase, Gallop, & Crits-Christoph, 2011).

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There are several reasons to hypothesize that the specific symptom of anhedonia might be a better predictor of outcome than the broader construct of clinical depression, of which anhedonia is one component, in the treatment of cocaine use disorder. Early on, Gawin and Ellinwood (1988) described that the withdrawal stage of cocaine addiction (and other stimulant addictions) being characterized by anhedonia that can lead to relapse. This clinical symptomatic consequence of cocaine use is can be linked to the neurobiology of such drug use. Studies have found that chronic overstimulation of central nervous system reward circuitry by cocaine (a powerful dopaminergic agent) results in protracted apathy, such that ordinary rewards yield little interest/pleasure (i.e., anhedonia) (Kalivas, 2007; Koob, 2006). The deficits in reward processing and the resultant state of clinical anhedonia from cocaine use may trigger patients to relapse or continue using cocaine in order to experience interest/pleasure. Consistent with this, several studies have reported symptoms of anhedonia among cocaine users who achieve abstinence (Gawin and Kleber, 1986; Kalechstein, Newton, and Leavengood, 2002).

In addition to the symptomatic state of anhedonia induced by cocaine use that might subsequently led to relapse, it is possible that the anhedonia seen in some cocaine use precede the onset of cocaine use. Genetic factors (e.g., Sadler et al.,2014) and/or early environmental influences (e.g., Kippen et al., 2008) might increase the risk for development of a persistent and relapsing course of cocaine use as a way of self-medicating the anhedonia. In the general population, lifetime anhedonia, independent of depressed mood, has been associated with both lifetime amphetamine and lifetime cocaine use (Leventhal et al., 2010).

The role of anhedonia in the treatment of substance use disorders is not specific to cocaine use, but has also been investigated in the context of the treatment of nicotine, alcohol, amphetamine, and opioid use disorders (Garfield, Lubman, & Yücel, 2013). This review article concluded that anhedonia has been shown to correlate with aspects of abstinence (such as duration of abstinence, craving and withdrawal symptoms) in studies of alcohol, nicotine and opioid-dependent populations. However, less research has focused on anhedonia as a predictor of the outcome of treatment of cocaine use disorder

One notable recent study (Wardle et al., 2017) investigated whether anhedonia was associated with poorer outcomes of contingency management (CM) treatment for cocaine use disorder, and whether the addition of levodopa, a dopaminergic drug, would improve the effectiveness of CM especially among cocaine users with high levels of anhedonia. In this study, anhedonia was evaluated at baseline using both a self-report scale and a behavioral measure. Results indicated that, using standard general linear models, neither the self-report nor the behavioral measures of anhedonia were associated with treatment outcome. However, a Bayesian analysis indicated a high probability that self-reported high level of anhedonia was associated with poor treatment outcomes. Levodopa was not found to significantly improve outcomes, nor was the effect of levodopa moderated by baseline anhedonia. The potential predictive role of general symptoms of depression was not evaluated in this study.

The purpose of the current study is to re-examine results from two prior studies (McKay et al., 2010; Stulz et al., 2011, using data from the NIDA Collaborative Cocaine Treatment Study) that reported that depression was associated with relatively poorer outcomes in the treatment of cocaine dependence in order to test the hypothesis that anhedonia, rather than depression per se, predicts outcome. The McKay et al. (2010) study included CM as a treatment and thus provided an opportunity to further evaluate the role of anhedonia as predictor of the outcome of CM, controlling for general depressive symptoms, and therefore build upon the findings of Wardle et al. (2017). The NIDA Collaborative Cocaine Treatment Study evaluated the outcomes of individual drug counseling, group drug counseling, cognitive therapy, and brief dynamic therapy and therefore provided an opportunity to extend and clarify the generalizability of the findings of Wardle et al. (2017). Our primary hypothesis was that anhedonia would be associated with non-abstinence from cocaine.

2. Material and methods

2.1 Study 1: Randomized Trial of Continuing Care Enhancements for Cocaine-Dependent Patients Following Initial Engagement

This study by McKay et al. (2010) was a randomized clinical trial for patients with DSM-IV diagnosed cocaine dependence. The study examined the comparative effects of cognitive-behavioral relapse prevention (RP), contingency management (CM), and a combined treatment incorporating both of these modalities (CM + RP). The methods, interventions, and results have been described in the original study (McKay et al., 2010) and are summarized here.

For the current analyses, the initial patient sample consisted of 79 adults with a current diagnosis of cocaine dependence at study intake who were participating in ongoing community-based intensive outpatient program (IOPs) and were assigned to continuing care with either CM or CM+RP (patients who received RP alone showed no average improvement and received on average only 3 sessions and thus were excluded from the current analyses).

The CM intervention was based on treatment protocols developed by Silverman et al. (1996) and Higgins et al. (1993). Participants in the RP condition were offered weekly, individual sessions of CBT-RP therapy for up to 20 weeks.

The time line follow-back (TLFB; Sobell, Maisto, Sobell, & Cooper, 1979) approach was used to gather self-reports of cocaine use prior to and during the treatment period in the McKay et al. (2010) study. At baseline of the continuing care study treatment period, the TLFB was used to assess cocaine use during the previous 6 months. At 3 and 6 months post-baseline, the TLFB was administered and asked about cocaine use in the previous 3 months. The distribution of the TLFB cocaine use data was highly zero-inflated. At the month 3 assessment, 65.7% of patients reported no cocaine use in the past 3 months. At the month 6 assessment, 70.1% report no cocaine use in the past 3 months. The non-zero scores at month 3 showed a flat distribution ranging from 1 to 69 days; the non-zero scores at 6 months also showed a flat distribution ranging from 1 to 87 days. Because of the high rates of zero use, flat-distribution of the non-zero scores, and the inadequate sample size to employ zero-

inflated statistical models, we created a dichotomous measure of abstinence from any cocaine use for the 0 to 3 month time period and the 3 to 6 month time period. Urine samples tested for the cocaine metabolite benzoylecgonine were also collected at 3 and 6 months post-baseline to validate the self-reports and serve as an outcome.

For a measure of anhedonia, we used the 3-item anhedonia scale (Joiner, Brown, & Metalsky, 2003) derived from the Beck Depression Inventory-I (BDI-I; Beck, Steer, & Garbin, 1988) that included item #4 (loss of enjoyment/satisfaction), item #12 (loss of interest in people), and item #21 (no interest in sex). Items on the BDI-I ask about symptoms in the past week, with subjects asked to rate each item on a scale from 0 to 3. The Cronbach's alpha for the 3-item anhedonia measure in this sample was .62. While marginal, this level of internal consistency is not unexpected given a 3 item scale and was slightly higher than that reported in previous research (e.g., .57 in Joiner et al. 2003). Leventhal et al. (2006) report a correlation of −.33 ($p < .0001$) between the BDI andedonia scale and trait anhedonia as measured by the Snaith-Hamilton Pleasure Scale (Snaith et al., 1995).

We also created a BDI-I total score that excluded the three anhedonia items so that we could investigate whether anhedonia or the other symptoms of depression predicted outcome better. This alpha coefficient for this revised BDI-I total score was = .84. The correlation between the BDI anhedonia scale and the revised BDI total score was .62.

2.2 Study 2: National Institute of Drug Abuse Cocaine Collaborative Treatment Study (CCTS)

The National Institute on Drug Abuse (NIDA) CCTS was a multi-site, randomized clinical trial for patients with DSM-IV diagnosed cocaine dependence. The methods, interventions, and results have previously been described in detail (Crits-Christoph et al., 1999) and are briefly summarized here. Both Study 1 and Study 2 received Institutional Review Board approval and all patients signed written informed consent prior to participation.

The participant sample consisted of 487 individuals, recruited from five sites, who had a principal diagnosis of DSM-IV cocaine dependence and had used cocaine at some point in the past 30 days. Participants were randomly assigned to one of four interventions, each of which included a 6-month active treatment phase. All participants received group drug counseling (GDC). Participants in the other three groups, in addition to GDC, received either (1) individual drug counseling (IDC, Mercer & Woody, 1992), (2) cognitive therapy (CT) (Beck, Wright, Newman, & Liese, 1993), or brief supportive expressive (SE) psychodynamic therapy (Luborsky (1984), with specific modifications for treating cocaine dependence.

The primary outcome measure for the current analyses was the during-treatment monthly composite measure of cocaine used in the original Crits-Christoph et al. (1999) report. This composite was constructed using information from three sources: (1) cocaine use during the past 30 days extracted from an interview measure of drug use, the Addiction Severity Index (ASI) (McLellan et al., 1992), conducted monthly by trained, independent interviewers who were unaware of treatment assignment, (2) a self-report cocaine inventory, administered every week during the 6-month treatment period, which asked about cocaine use during the

past week (Gawin et al., 1989), and (3) weekly observed urine samples, which were sent to a central laboratory and assayed for cocaine and other drugs. As with the McKay et al. (2010) study data, a high rate of non-use was evident during each month. Thus, scores from the cocaine use question from the ASI and the weekly cocaine inventory scores were first transformed into binary use/no use scores. The composite cocaine use outcome measure was then constructed by pooling information from the three measures to code each month of treatment as abstinent versus any cocaine use. Any indication of cocaine use across the three measures during a given month would be used to score the month as "not abstinent" even if scores from the other measures were missing. This procedure therefore minimized the amount of missing data. A summary measure of the number of months (out of 6) of non-abstinence was created from these monthly composite cocaine use scores.

For the NIDA CCTS data, we again constructed the BDI anhedonia scale based on item items 4, 12, and 21. The internal consistency (Cronbach's alpha) of this 3-item scale at baseline was .62 for the NIDA CCTS participant sample. The Cronbach's alpha for the total of the other 18 items was .88. The correlation between the BDI anhedonia scale and the revised BDI total score was .65.

2.3 Statistical Analyses

For the McKay et al. (2010) data, we used logistic regression with the baseline anhedonia symptom scale predicting abstinence vs. non-abstinence in the prior 3 months as measured at the 3 month and separately at the 6 month assessment. Treatment group and baseline cocaine use (days used in the 6 months) were included as covariates. An identical analysis was also conducted with the urine results (positive vs. negative for cocaine) as the binary outcome. The analyses were repeated incorporating the revised BDI score as an additional predictor.

For the NIDA CCTS data, we conducted a general linear model analysis with the baseline anhedonia symptom scale predicting the number of months of abstinence between months 1 and 6. This outcome was chosen because of the theoretical interest in the link between cocaine and abstinence/relapse. Preliminary analyses of this outcome using the Box-Cox power transformation (Box and Cox, 1964) revealed that a square root transformation was needed to achieve normality. After applying the square root transformation, model-based residuals provided a Shapiro-Wilk statistic of .93, which is higher than the value of .90 proposed by Royston (1992) to indicate near normality.

The analysis of the NIDA CCTS data was conducted controlling for treatment group and covariates pre-specified in the original design of the CCTS study, namely site, baseline cocaine use (in past 30 days), and the internalizing-externalizing coping style measured by the Socialization scale of the California Psychological Inventory (Megargee, 1972). Another covariate used in previous reports, psychiatric severity, was not used in the current analyses because it contained a measure of depression, which was separately evaluated as a predictor here. The analyses were conducted with and without the revised BDI total score in the models.

3. Results

Overall, 70.9% (56/79) of those in the McKay et al. (2010) study and 75.5% (366/485) of the patients in the NIDA CCTS reported at least one symptom of anhedonia at baseline.

In the McKay et al. (2010) dataset, we found that the baseline BDI anhedonia symptom scale was a significant predictor of non-abstinence from month 0 to 3 and month 3 to 6 (Table 1). These relations remained significant even after including the revised BDI total score (with anhedonia items removed) in the models. This indicated that all of the successful prediction of outcome was carried by the anhedonia scale. Of those that were not abstinent at 3 months, 87.5% (2½4) had symptoms of anhedonia at baseline (i.e., non-zero score on the BDI anhedonia scale) and 12.5% (3/24) had no symptoms of anhedonia at baseline. The comparable numbers at month 6 were 95% (19/20) and 5% (½0).

Results for the spot urine sample provided at the 3 and 6 month visits were similar, with the BDI anhedonia symptom scale significantly predicting non-abstinence at each assessment (month 3: Odds Ratio = 4.1, 95% CI: 1.3, 13.5; $p = .019$; month 6: Odds Ratio = 5.7, 95% CI: 1.6, 20.4; $p = .007$) significantly predicting non-abstinence. In models predicting the urine result that included the anhedonia scale and the revised BDI scale (without the anhedonia items), the Odds ratios for anhedonia symptoms remained significant when this overlap between the anhedonia scales and depressive symptoms was controlled (month 3: Odds Ratio = 5.4, 95% CI = 1.3, 22.6, $p = .02$; month 6: Odds Ratio = 5.6, 95% CI: 1.3, 24.9; $p = .023$), while the revised BDI total was again not significant (month 3: Odds Ratio = .5, $p = .47$; month 6: Odds Ratio = 1.0, $p = .97$).

In the NIDA CCTS dataset, the BDI anhedonia symptom measure was highly predictive of the number of months of abstinence (Table 2). The effect was consistent across treatment groups (i.e., no interaction with treatment group, $p = .96$). The anhedonia effect remained significant when the revised BDI total score was included in the model. In this model, the BDI revised total score did not significantly predict the number of confirmed months of abstinence between months 1 and 6. As in the McKay et al. (2010) data, all of the successful prediction of outcome was carried by the BDI anhedonia scale.

To provide a more descriptive view of the effect, we examined a binary outcome of 3 or more months of confirmed abstinence (score of 0) versus fewer than 3 months of confirmed abstinence (score of 1). This criterion provided a reasonable distribution for a binary abstinence variable, with 53.5% of the sample achieving this abstinence outcome. Of those who failed to achieve 3 or more months of abstinence, 79.9% (175/219) had symptoms of anhedonia at baseline (i.e., non-zero score on BDI anhedonia scale), versus 20.1% (44/219) of those without anhedonia.

4. Discussion

Our principal finding was that severity of self-reported anhedonia symptoms at baseline was significantly related to achieving cocaine abstinence. This finding was consistently observed across treatment groups in both the NIDA CCTS study and the McKay et al. (2010) study.

The strength and consistency of the effect across studies is noteworthy given the measure of anhedonia was not ideal (3 item scale).

A second major finding was that self-reported anhedonia symptoms was a strong predictor of poor treatment response, independent of participants' overall levels of depression. The anhedonia effect remained significant in predicting treatment outcome when the BDI total score (excluding the items related to anhedonia) was included in the analytical model. By itself in these models, the revised BDI total score did not predict outcome, demonstrating that the severity of non-anhedonia related depressive symptoms is not the important variable in relation to cocaine treatment outcomes.

The current findings replicate and extend the recent results reported in Wardle et al. (2017). As was found in Wardle et al. (2017), at least in the Bayesian analysis in that report, we found that anhedonia was associated with relatively poorer outcomes for CM treatment. Based on the possibility that a lack of interest in non-drug rewards would tend to work against the reward-based mechanism of CM, Wardle et al. (2017) hypothesized an associated between anhedonia and CM treatment outcomes for patients with anhedonia. The current study clarifies that indeed anhedonia symptoms and not general depressive symptoms is the basis of this association. The current results from the NIDA CCTS dataset, however, extend the findings of Wardle et al. (2017) by indicating that the association between baseline anhedonia symptoms and outcome of those with cocaine use disorder is not specific to CM. Across the broad range of treatment modalities in the NIDA CCTS study (GDC, individual drug counseling, cognitive therapy, supportive-expressive therapy), anhedonia symptoms at baseline were associated with fewer months of abstinence during treatment.

The neurobiology of anhedonia has received considerable attention, with research indicating that anhedonia is characterized not only by deficits in hedonic capacity but also with disruptions in reward valuation, decision-making, anticipation, and motivation (Der-Avakian & Markou, 2012). Mu opioid and endocannabinoid receptors in the nucleus accumbens and ventral pallidum have been found to mediate hedonic perception of rewards (Berridge & Kringelbach, 2008), and disruption of these reward centers is thought to be involved in the lack of pleasure experienced in those with anhedonia. The lack of motivation evident in the clinical presentation of anhedonia has been linked with deficits in dopaminergic activity in the ventral tegmental area and nucleus accumbens (Treadway & Zald, 2011). Although cocaine use has been primarily linked to alternations in dopaminergic activity, interactions between dopamine and opioid systems may also be involved (Volkow, 2010; Volkow et al., 2010). Thus, cocaine use make affect both of the neurobiological systems involved in anhedonia.

The clinical implications of the current findings, together with the results of Wardle et al. (2017), are important to consider. Wardle et al. (2017) found no evidence that enhancing dopamine through administration of levodopa moderates the relation of anhedonia to outcome of CM treatment for cocaine use disorder, despite previous evidence indicated that levodopa improves the outcome of CM treatment in general (Schmitz et al., 2008), and suggested other treatment approaches, such as stimulant drugs and behavioral therapies should be considered to target those cocaine users with anhedonia.

In terms of behavioral therapies, a number of studies have reported on the efficacy of behavioral activation (BA) as a treatment for individuals with substance use problems (often cocaine) and symptoms of depression (Daughters et al., 2008). Of interest, however, is the fact that BA is based on a theory that conceptualizes depression as a function of reduced rewards, and that the treatment focuses mainly on increasing rewarding activities. Rather than a treatment for global depression, BA therefore can be conceived of as a treatment for low interest/rewards (i.e., anhedonia). Thus, it may be that the success of BA in the treatment of substance abusers with depression is due to the alleviatory effects of BA on anhedonic symptoms, which are relatively common among substance/alcohol abusers, particularly cocaine users. Although not a study of BA per se, Lewis and Petry (2005) used CM to increase activity levels among 159 cocaine-dependent adults. They found that participants who engaged in family activities remained in treatment longer, were abstinent for more weeks, and reported greater reduction in family conflict compared to participants who did not engage in family activities. Such activities are exactly what BA is designed to increase, and therefore this finding is consistent with the results of the current study and the inference that addressing motivational anhedonia through increasing positive activities of those with a cocaine use disorder might yield improved outcomes.

The greatest limitation of the present study is that our analysis draws from two studies that were primarily intended to test the efficacy of different treatments for cocaine addiction. Neither of these original studies was designed to specifically investigate the correlation between anhedonia and cocaine abstinence or compare it with the correlation between non-anhedonic depression and cocaine relapse and we could only construct a brief measure of anhedonia from the BDI. Future research will allow for direct and comprehensive comparisons of the relationships between anhedonia, depression without anhedonia, and cocaine abstinence, while also allowing us to examine the effects of specific anhedonia-targeting treatments and treatment combinations on abstinence outcomes.

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Table 1

Relation of Baseline Anhedonia to Self-Report Abstinence at Month 3 and Month 6 Post-Baseline in the McKay et al. (2010) Study

	Month 3 Abstinence			*Month 6 Abstinence*		
Predictor	***Odds Ratio***	***95% CI***	***p***	***Odds Ratio***	***95% CI***	***p***
Model with anhedonia and covariates						
Baseline BDI anhedonia scale	5.4	1.7, 17.7	.005	8.4	2.1, 33.5	.003
Baseline cocaine use (past 3 months)	1.0	.96, 1.0	.58	1.0	.98, 1.1	.38
Treatment Group	1.0	.3, 2.9	.97	1.6	.5, 5.4	.48
Model with anhedonia, Revised BDI, and covariates						
Baseline BDI anhedonia scale	4.7	1.2, 17.8	.023	8.5	1.7, 42.9	.009
BDI total score (revised)	1.4	.26, 7.9	.67	.97	.16, 6.1	.97
Baseline cocaine use (past 3 months)	1.0	.96, 1.0	.56	1.0	.98, 1.1	.38
Treatment group	1.0	.3, 2.9	.97	1.6	.5, 5.5	.48

Note. N=70 at month 3 and 67 at month 6 of patients with outcome data. Treatment groups consist of contingency management (CM) and CM plus usual services. BDI = Beck Depression Inventory – I.

Table 2

Relation of Baseline Anhedonia to Outcome in the NIDA Cocaine Collaborative Study

Predictor	*F*	*DF*	*p*	Effect Size (*d*)
Model with anhedonia and covariates				
Baseline BDI anhedonia scale	9.4	1, 458	.002	.29
Site	5.4	4, 458	<.001	.43
Treatment Group	3.4	3, 458	.018	.30
Socialization Scale	3.9	1, 458	.05	.18
Baseline cocaine use (past month)	2.0	1, 458	.15	.13
Model with anhedonia, Revised BDI, and covariates				
Baseline BDI anhedonia scale	4.7	1, 457	.03	.20
BDI total score (revised)	.25	1, 457	.62	.06
Site	5.3	4, 457	<.001	.43
Treatment group	3.4	3, 457	.017	.29
Socialization Scale	4.1	1, 457	.04	.20
Baseline cocaine use (past month)	1.9	1, 457	.17	.06

Note. Treatment groups consist of group drug counseling (GDC), individual drug counseling plus GDC, cognitive therapy plus GDC, supportive-expressive dynamic therapy plus GDC. BDI = Beck Depression Inventory – I.