Journal of Substance Abuse Treatment xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Journal of Substance Abuse Treatment

Anhedonia Is Associated with Poorer Outcomes in Contingency Management for Cocaine Use Disorder

Margaret C. Wardle, Ph.D. [a,*], Jessica N. Vincent, B.S. [a], Robert Suchting, Ph.D. [a], Charles E. Green, Ph.D. [a], Scott D. Lane, Ph.D. [a,b], Joy M. Schmitz, Ph.D. [a,b]

[a] Center for Neurobehavioral Research on Addiction, University of Texas Medical Center at Houston, 1941 East Rd., Houston, TX, 77054, USA
[b] Graduate School of Biomedical Sciences, University of Texas Medical Center at Houston, 1941 East Rd., Houston, TX, 77054, USA

ARTICLE INFO

Article history:
Received 29 January 2016
Received in revised form 22 August 2016
Accepted 31 August 2016
Available online xxxx

Keywords:
Contingency management
Incentives
Cocaine use disorder
Anhedonia
Levodopa
Bayesian statistics

ABSTRACT

This study explored anhedonia (lack of interest or pleasure in *non-drug* rewards) as a potentially modifiable individual difference associated with the effectiveness of Contingency Management (CM). It also tested the hypothesis that a dopaminergic drug, levodopa (L-DOPA), would improve the effectiveness of CM, particularly in individuals high in anhedonia. The study was a single-site, randomized, double-blind, parallel group, 12-week trial comparing L-DOPA with placebo, with both medication groups receiving voucher-based CM targeting cocaine-negative urines. Participants were N = 85 treatment-seeking adults with CUD. Anhedonia was measured at baseline using a validated self-report measure and a progressive ratio behavioral measure. Treatment Effectiveness Score (TES) was defined as the total number of cocaine-negative urines submitted. Analyses based on Frequentist general linear models were not significant, but Bayesian analyses indicated a high probability (92.6%) that self-reported anhedonia was associated with poor treatment outcomes (lower TES). L-DOPA did not significantly improve outcomes, nor was the effect of L-DOPA moderated by anhedonia. While the study failed to replicate positive findings from previous studies of L-DOPA in combination with CM, it does provide preliminary evidence that anhedonia may be a modifiable individual difference associated with poorer CM outcomes.

1. Introduction

Cocaine is the third most abused drug in the U.S. (SAMHSA, 2013b), and the drug most often involved in ER visits (SAMHSA, 2013a). Around one-fourth of cocaine users have cocaine use disorder (CUD) and these cases disproportionately account for the health costs associated with cocaine (Degenhardt et al., 2014; SAMHSA, 2013b). Thus, the development of effective interventions for CUD is a public health priority. One of the more effective behavioral interventions for CUD is contingency management (CM; Dutra et al., 2008; Farronato, Dursteler-Macfarland, Wiesbeck, & Petitjean, 2013), a reward-based approach in which individuals receive monetary incentives for objectively verified abstinence (Higgins, Heil, Rogers, & Chivers, 2008; Petry, 2000). CM has frequently been used to help individuals with CUD achieve initial abstinence, often prior to initiation of medication or other therapies (Carroll et al., 2016; Petry, Barry, Alessi, Rounsaville, & Carroll, 2012; Poling et al., 2006; Schmitz, Lindsay, Stotts, Green, & Moeller, 2010; Schmitz et al., 2008, 2014; Schottenfeld et al., 2005). However, studies using CM have found initial attainment of abstinence in anywhere from 20% to 60% of individuals with CUD (Dutra et al., 2008). Indeed, even very high-value, intensive CM results in initial abstinence in only about 40% of individuals with CUD (Schmitz et al., 2014). Thus, even this comparatively strong CUD intervention is variably effective.

Unmeasured individual differences may impact the effectiveness of all CUD treatments, including CM. There are many possible reasons someone may continue to use cocaine or relapse to cocaine, each with potentially different underlying risk factors and mechanisms. Indeed, such unmeasured diagnostic heterogeneity has been identified as a primary problem in the development of all psychiatric treatments (Hyman, 2007; Wong, Yocca, Smith, & Lee, 2010). Thus, one way to quickly increase CUD treatment effectiveness may be to identify individual differences that: 1. are associated with differential treatment effectiveness, and 2. have known mechanisms that are amenable to intervention, so that treatment outcomes can be rapidly improved.

Anhedonia is one individual difference that appears likely to impact CM outcomes. Anhedonia, defined here as lack of interest or pleasure in *non-drug* rewards, is common in CUD and other addictions (Franken, Rassin, & Muris, 2007; Garfield, Lubman, & Yücel, 2013; Leventhal et al., 2008, 2010). Anhedonia is distinct from negative mood (e.g. sadness, anxiety) and from clinical depression. Along with negative mood, it is one possible symptom of depression, but it is not necessary for a depression diagnosis (American Psychiatric Association, 2000). In fact, anhedonia has been hypothesized to constitute a distinct endophenotype related to, but not synonymous with, depression (Pizzagalli, 2014).

* Corresponding author at: Center for Neurobehavioral Research on Addiction, University of Texas Medical Center at Houston, 1941 East Rd., Houston, TX, 77054, USA.
E-mail address: Margaret.C.Wardle@uth.tmc.edu (M.C. Wardle).

http://dx.doi.org/10.1016/j.jsat.2016.08.020
0740-5472/

Consistent with this, anhedonia is present at clinical levels in individuals without a depression diagnosis, including individuals with addictions (Franken et al., 2007). Anhedonia also appears particularly problematic in addiction treatment. For example, anhedonia predicts post-treatment relapse to smoking even after controlling for negative mood symptoms (Leventhal, Piper, Japuntich, Baker, & Cook, 2014). Similarly, in a prospective study of CUD, low positive moods predicted relapse to cocaine following treatment, while negative moods did not, suggesting anhedonia is a risk factor for a difficult clinical course in CUD (Hall, Havassy, & Wasserman, 1991). Anhedonia has high face validity as a moderator of CM treatment in particular, as lack of interest in non-drug rewards would naturally tend to work against the reward-based mechanism of CM; however, to our knowledge, this hypothesis has not previously been tested. Of note, studies examining the impact of depression on CM outcomes have produced mixed results (no association, worse outcomes, better outcomes), possibly due to the failure to distinguish anhedonia from negative mood symptoms of depression (Garcia-Fernandez, Secades-Villa, Garcia-Rodriguez, Pena-Suarez, & Sanchez-Hervas, 2013; Garcia-Fernandez et al., 2011; Gonzalez, Feingold, Oliveto, Gonsai, & Kosten, 2003; Milby et al., 2015). Thus, one objective of this study is to specifically test the relationship of anhedonia with CM outcomes.

Anhedonia is associated with relatively well-understood deficits in underlying neural circuitry, which may be addressable using pharmacological interventions. Recent reviews suggest that the clinical phenomenon of anhedonia may be caused by deficits in either the ability to *experience* pleasure, thought to be mediated by opioid "hotspots" in NAcc and ventral pallidum (VP), or the *motivation* to pursue pleasure, thought to be mediated by dopaminergic (DA) activity in the ventral tegmental area (VTA) and NAcc (Argyropoulos & Nutt, 2013; Treadway & Zald, 2011). Given its known neural pathology, CUD might impair either of these processes (Volkow, 2010). However, attention has largely focused on prominent DAergic impairments in CUD, including deficient striatal dopamine functioning and lowered neural responsiveness to non-drug rewards in DAergic brain regions (Goldstein, Alia-Klein, et al., 2007; Goldstein, Tomasi, et al., 2007; Goldstein et al., 2008; Martinez et al., 2004, 2009; Tomasi et al., 2010; Volkow et al., 2010). Importantly, deficient striatal DA functioning predicts failure to attain abstinence in CM (Martinez et al., 2011). Further, medications that enhance DA, such as levodopa (L-DOPA) increase CM success rates (Schmitz et al., 2008). Previous studies in non-CUD populations show that DA enhancing medications increase responsiveness to reward (Leyton et al., 2007; Wardle & de Wit, 2012; Wardle, Treadway, Mayo, Zald, & de Wit, 2011), suggesting that these medications may enhance CM by increasing responses to the incentives provided in CM. Putting this evidence together, we hypothesize that variations in anhedonia may help explain differences in CM outcomes, and that DAergic drugs may improve CM outcomes by improving anhedonia (Martinez et al., 2011).

This study is the first to test the possible role of anhedonia in CM outcomes, and the role of anhedonia in enhancement of CM with DAergic medication. Our hypotheses were: 1. greater anhedonia at baseline, as measured using both a self-report and a behavioral task, would be associated with poorer outcomes in a treatment involving CM, 2. L-DOPA would improve outcomes in a treatment involving CM, replicating previous findings, and 3. individuals higher in anhedonia would benefit more from L-DOPA enhancement of CM, as this drug would target the deficits in DAergic circuitry and corresponding low reward motivation that interfere with the ability of these individuals to succeed in CM.

2. Methods

2.1. Study design

The study was a single-site, randomized, double-blind, parallel group, 12-week trial comparing levodopa/carbidopa with placebo. Medication was administered along with behavioral therapy with a prominent CM component.

Participants providing written informed consent underwent a one-week screening and pretreatment assessment to determine eligibility, including medical history and physical examination, laboratory tests, thrice-weekly on-site urinalysis, and cardiac evaluation (i.e., 12-lead electrocardiogram). Self-report and behavioral measures of anhedonia were also taken at this time. Eligible participants were then urn randomized to medication group based on severity of cocaine dependence (>15 days cocaine use in past 30 days vs. ≤15 days), baseline level of cognitive functioning as determined by the MicroCog (global cognitive functioning score >80 vs. <80; Aharonovich et al., 2006), attentional bias (baseline cocaine-Stroop >46 ms vs. <46 ms, measure not further reported on here; Liu et al., 2011), and the behavioral measure of anhedonia (baseline performance in progressive ratio task >66%, see Measures; Lane, Cherek, Pietras, & Steinberg, 2005). The behavioral anhedonia measure was selected for use as a stratification variable based on the study's original conceptual model linking this task with motivational anhedonia, and thus the dopaminergic basis of L-DOPA treatment (see Measures).

Following randomization to a medication group, participants entered treatment, which began with a 2-day dose escalation run-up, followed by 12 weeks of behavioral treatment. Behavioral treatment consisted of abstinence-based CM thrice weekly, with cocaine levels in urine samples used to determine rewards (see Treatment). Participants also received one 50-minute manual-driven cognitive behavioral therapy (CBT) session weekly (see Treatment). The 12 treatment weeks were followed by a 2-day dose reduction run-down. Throughout treatment, participants made thrice-weekly clinic visits (Monday, Wednesday, and Friday). At each visit vital signs and adverse events were assessed, study medication was dispensed, and urine samples obtained for on-site testing of cocaine use (see Measures).

2.2. Participants

Participants were treatment-seeking adults (18–60 years old) with cocaine dependence per the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, 4th Ed. (SCID-IV; First, Spitzer, Gibbon, & Williams, 1996). In addition to a diagnosis of cocaine dependence, other required inclusion criteria were: 1. self-reported cocaine use in the past 30 days; 2. at least one cocaine positive urine during the screening/pre-treatment period; 3. no medical contraindications to L-DOPA, including use of medications known to have significant interactions with L-DOPA; 4. no current dependence on any psychoactive substances aside from cocaine, nicotine, and marijuana; 5. no other current neurological or psychiatric disorders that would make participation difficult (e.g. bipolar disorder, psychosis, major depression); 6. no other current or recent (within the last 3 months) treatment for substance use or another psychiatric disorder; 7. no conditions of probation or parole requiring reports of drug use to officers of the court; 8. no impending incarceration; 9. no pregnant or nursing females.

All participants were recruited from the greater Houston and surrounding areas via news media advertisements, public service announcements, community flyers, and various informational outreach projects. The study took place at the outpatient Center for Neurobehavioral Research on Addiction (CNRA), part of the University of Texas Health Science Center Department of Psychiatry and Behavioral Sciences. There were 129 participants screened for eligibility with N = 85 enrolled and randomly allocated to placebo (N = 40) or L-DOPA (N = 45). See study CONSORT diagram (Fig. 1).

2.3. Treatments

2.3.1. Contingency management (CM)

The study used a very similar abstinence-based CM procedure to that which demonstrated efficacy when combined with L-DOPA in a previous study (Schmitz et al., 2010). Participants earned vouchers according to the reward schedule recommended by Budney and Higgins

Please cite this article as: Wardle, M.C., et al., Anhedonia Is Associated with Poorer Outcomes in Contingency Management for Cocaine Use Disorder, *Journal of Substance Abuse Treatment* (2016), http://dx.doi.org/10.1016/j.jsat.2016.08.020