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Carvedilol does not reduce cocaine use in methadone-maintained cocaine users☆

Mehmet Sofuoglu *, James Poling, Theresa Babuscio, Kishorchandra Gonsai, Kevin Severino, Charla Nich, Kathleen M. Carroll

VA Connecticut Healthcare System, West Haven, CT, United States
Yale University, School of Medicine, Department of Psychiatry, New Haven, CT, United States

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ABSTRACT

Introduction: The goal of this study was too test the efficacy of carvedilol (CAR), an adrenergic blocker, for reducing cocaine use in individuals with cocaine use disorder (CUD). We conducted a 17-week, double-blind, randomized controlled trial with 3 treatment arms: 25 mg CAR, 50 mg CAR, and placebo.
Methods: One hundred and six treatment-seeking opioid and cocaine-dependent participants, who were also maintained on methadone during study participation, were randomized to placebo (n = 34), 25 mg/day CAR (n = 37) or 50 mg/day CAR (n = 35). The main outcome measures were cocaine and opioid use as assessed by urine drug screening and self-reported drug use.
Results: No significant group differences were found for treatment retention with 56% of the placebo, 76% of the 25 mg and 66% of the 50 mg CAR groups ($p > 0.05$) completing treatment. The percentage (SD) of cocaine positive urines during the trial showed an overall treatment effect: 59.2 (38.9) for the placebo, 50.8 (33.8) for the 25 mg and 75.1 (33.2) for the 50 mg CAR group. In post hoc comparisons, neither the 25 nor 50 mg CAR condition differed significantly from the placebo; however, the 25 mg CAR group had a significantly lower proportion of cocaine-positive urines than the 50 mg group. No significant group differences were found for the percentage of self-reported days of cocaine abstinence during the trial: 72.9 (25.3) for placebo, 72.9 (29) for CAR 25 mg, and 59.3 (31.7) for CAR 50 mg. Significant groups differences in the proportion of opioid positive urines submitted were not observed ($p > 0.05$). Baseline cocaine withdrawal severity did not predict treatment response ($p > 0.05$).
Conclusions: These findings did not support the efficacy of CAR for the treatment of cocaine use in cocaine and opioid dependent participants maintained on methadone. Further, CAR doses >25 mg should not be used to avoid possible increases in cocaine and opioid use.

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1. Introduction

Cocaine use disorder (CUD) continues to be an important public health problem in the US with significant costs to the individual and society (SAMHSA, 2014). There are no proven pharmacotherapies for CUD despite intense research over the past two decades (Forray & Sofuoglu, 2014). Because cocaine reinforcement is attributed to a drug-induced increase in dopamine (DA) release in reward circuitry, DA has been an important target for the development of pharmacological treatments for CUD (Verrico, Haile, Newton, Kosten, & De La Garza, 2013). However, the noradrenergic system, which uses norepinephrine (NE) as its main chemical messenger, has also been considered a pharmacotherapy target (Szabadi, 2013). Cocaine stimulates both the central and peripheral NE system by blocking the NE transporter (Elliott & Beveridge, 2005) and may therefore modulate a wide range of brain functions including arousal, attention, mood, learning, memory, response inhibition, reward and the stress response (Chamberlain & Robbins, 2013). In preclinical models of cocaine dependence, NE is found to be critically involved in mediating cocaine's behavioral effects including sensitization, drug discrimination, and reinstatement of drug seeking (Schmidt & Weinshenker, 2014; Weinshenker & Schroeder, 2007). These findings laid the groundwork for human studies on the potential efficacy of pharmacotherapies that target NE for CUD (Sofuoglu & Sewell, 2009).

Several human studies have examined the potential utility of medications that target the NE system, most notably adrenergic blockers. In two clinical trials, the beta-adrenergic blocker propranolol has showed promise as a treatment of CUD (Kampman et al., 2006; Kampman, Volpicelli, et al., 2001). In an 8-week clinical trial with 108 cocaine dependent individuals, propranolol was more effective than placebo in

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* Corresponding author at: Yale University, Department of Psychiatry; VA Connecticut Healthcare System, 950 Campbell Ave., Bldg. 36/116A4, West Haven, CT 06516, United States.
E-mail address: Mehmet.Sofuoglu@yale.edu (M. Sofuoglu).

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reducing cocaine use in those with high withdrawal severity. The authors suggested that the utility of propranolol for cocaine dependence could be due to reduction of NE activity during early cocaine abstinence (Kampman, Volpicelli, et al., 2001). More recently, in a pilot clinical trial with 22 cocaine users, doxazosin, an alpha1-adrenergic blocker similar to prazosin, reduced cocaine use (Shorter, Lindsay, & Kosten, 2013). Taken together, these studies with adrenergic blockers indicate their potential utility in the treatment of CUD.

The goal of this double-blind, placebo-controlled study was to test the efficacy of carvedilol (CAR) for reducing cocaine use. CAR is an alpha1- and beta-adrenergic receptor blocker used primarily for the treatment of congestive heart failure and hypertension (Frishman, 1998). CAR may also have utility for the treatment of cocaine addiction as indicated by a human laboratory study in which CAR attenuated both cocaine-induced blood pressure and heart rate increases, as well as cocaine self-administration behavior (Sofuoglu, Brown, Babb, Pentel, & Hatsukami, 2000). In addition, CAR has been administered to cocaine users for the treatment of cardiac disorders including myocardial infarction, heart failure and cocaine-induced cardiac toxicity (Littmann, Narveson, Fesel, & Marconi, 2013; Ocal et al., 2015; Self, Rogers, Mancell, & Soberman, 2011). However, no previous studies have examined the safety and efficacy of CAR for the treatment of CUD. In this study, we tested the hypothesis that CAR at 25 or 50 mg/day will be more effective than placebo in reducing cocaine use as measured by urine toxicology screens. Furthermore, based upon the propranolol findings of Kampman (Kampman, Volpicelli, et al., 2001), we also hypothesized that CAR's efficacy in reducing cocaine use will be more effective in those with higher withdrawal severity.

2. Materials and methods

2.1. Participants

One hundred and six (79 male and 27 female) treatment-seeking opioid and cocaine users were recruited from the greater New Haven area between September 2007 and December 2012 (see Consort Diagram). To be considered for inclusion, participants were required to meet the DSM-IV criteria for current opioid and cocaine dependence, as determined by a study physician and confirmed with the Structured Clinical Interview for DSM-IV (SCID) (First, Spitzer, Gibbon, & Williams, 1996). Additional eligibility criteria included a positive urine screen that confirmed recent cocaine and opioid use during the month prior to study entry. Women were asked to provide a urine pregnancy test at entry and to use adequate birth control during study participation. Monthly urine pregnancy tests were performed as an additional safety measure. A medical evaluation that included blood work, electrocardiogram (ECG), urine analysis, urine toxicology, medical history and a psychiatric evaluation was performed to exclude prospective participants with a current diagnosis of alcohol, benzodiazepine and other drug abuse or dependence (other than opioids, cocaine, and nicotine); serious medical (e.g., major cardiovascular, renal, endocrine, hepatic or neurological illnesses) or psychiatric disorders (e.g., history of schizophrenia, or bipolar disorder); and current use of over-the-counter or prescription psychoactive drugs (antidepressant, anxiolytics, antipsychotics, mood stabilizers, psychostimulants). Finally, participants were also required to be able to read and understand the consent form.

This study was approved by the West Haven VA Human Studies Subcommittee and the Yale University Human Investigations Committee and was registered at clinicaltrials.gov (NCT 00566969). Participants received compensation for their transportation expenses and for attending clinic visits.

2.2. Procedure

This study was a double-blind, outpatient clinical trial in which 106 participants were randomized to one of three treatment groups: placebo, 25 mg/day CAR or 50 mg/day CAR. Participants attended clinic six days per week (Monday-Saturday) to receive methadone and the study medication under direct supervision. On Saturdays, participants received take home bottles of methadone and the study medication to self administer on Sundays. In addition to receiving medication, all participants received individual, manual-guided Cognitive Behavior Therapy (Carroll, 1998) as the 'behavioral platform' (Carroll, 1997).

Participants completed weekly assessments and submitted thrice weekly urine samples. The study had 3 phases: methadone induction (2 weeks), treatment (11 weeks) and detoxification (4 weeks). For methadone induction, participants were started on 30 mg of methadone and the dose was then increased to a stable dose over a 2-week period with a maximum dose of 140 mg/day. During this phase, all participants also received a placebo pill, as CAR treatment did not begin until treatment phase. In the treatment phase, CAR was initiated at 25 mg/day, and for the high dose condition, the CAR dose was increased gradually over 2 weeks up to 50 mg/day. Dose selection was based on our previous human laboratory (Sofuoglu et al., 2000) and open label outpatient studies (Sofuoglu et al., unpublished) that assessed the effects of CAR in cocaine users. Treatment groups remained on their full dosage for 11 weeks. At the end of the study, participants discontinued the active/placebo medication over a 4-week phase and either underwent detoxification from methadone, or were referred to a methadone program. Randomization was done by the data manager using a computerized urn randomization program (Wei & Lachin, 1988), balancing groups on sex, race, frequency of cocaine use within the past month and the severity of cocaine withdrawal measured with the Cocaine Selective Severity Assessment (CSSA). All research staff other than the data manager and the research pharmacist were blind to medication condition.

If a participant missed one dose, they received their usual dose of methadone if they came to the clinic the next day at their scheduled time. Participants missing three consecutive doses of study medication were discharged from the study.

2.3. Outcomes

The primary outcome measures were cocaine use, as determined by urine toxicology results, and self-reported days of drug use as determined by the Timeline Follow Back method (Sobell, Sobell, Leo, & Cancilla, 1988). Urine samples were collected three times a week (Monday, Wednesday, Friday) during study participation to measure opioids, benzoylecgonine (a cocaine metabolite), and other drugs of abuse (e.g., benzodiazepines, marijuana, amphetamines). The cutoff for a positive urine result was >300 ng/ml for cocaine and >200 ng/ml for opioids. This analysis was performed at the clinical laboratory of the VA CT Healthcare System, West Haven Campus.

Cocaine withdrawal severity was assessed at intake and then weekly thereafter using the Cocaine Selective Severity Assessment (CSSA). The CSSA is a clinician-administered instrument that measures early cocaine abstinence symptomatology by rating 18 signs and symptoms associated with early cocaine abstinence based on a scale of 0 (no symptoms) to 7 (maximum score) (Kampman et al., 1998). Opioid withdrawal symptoms were measured with the Opioid Withdrawal Checklist Scale (Kosten, Rounsaville, & Kleber, 1985). This scale consists of 43 items describing possible opioid withdrawal symptoms that are rated on a scale from 1 (not at all) to 4 (very much) as well as symptoms not associated with opioid withdrawal (as controls) that are rated on a scale from 1 (very much) to 4 (not at all). Depressive symptoms were measured at baseline and monthly using the Center for Epidemiological Studies Depression Inventory (CES-D) and the Hamilton Depression Scale (HAM-D). The CES-D is a 20-item self-report measure of depressive symptoms that yields a total score of 0 to 60 with higher scores reflecting increased depressive symptoms (Radloff, 1977). The HAM-D is an interviewer rated scale and covers 21 symptoms with a total score ranging from 0 to 62 (Hamilton, 1960). In addition, the Structured Clinical Interview for DSM–IV (First et al., 1996) was administered at