Published in final edited form as:

J Subst Abuse Treat. 2017 February ; 73: 63–69. doi:10.1016/j.jsat.2016.11.005.

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

Mehmet Sofuoglu¹, James Poling¹, Theresa Babuscio, Kishorchandra Gonsai¹, Kevin Severino¹, Charla Nich, and Kathleen M Carroll¹

¹VA Connecticut Healthcare System, West Haven, CT and Yale University, School of Medicine, Department of Psychiatry, New Haven, CT

Abstract

Introduction—The goal of this study was to 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 25mg 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 group 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 greater than 25 mg should not be used to avoid possible increases in cocaine and opioid use.

Keywords

Cocaine use disorder; carvedilol; clinical trial; adrenergic blocker

¹Mehmet Sofuoglu, Yale University, Department of Psychiatry, VA Connecticut Healthcare System, 950 Campbell Ave., Bldg. 36/116A4, West Haven, CT 06516, Phone: (203) 937-4809, Fax: (203) 937-3478, Mehmet.Sofuoglu@yale.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

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 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 0–62 (Hamilton, 1960). In addition, the Structured Clinical Interview for DSM–IV (First et al., 1996) was administered at intake to determine any DSM–IV Axis I psychiatric diagnoses including depression and substance use disorders.

2.4. Data Analysis

Data analyses were conducted on the full randomized (intent-to-treat) sample. Comparability of groups on baseline characteristics was evaluated using chi-square tests for categorical measures and ANOVA for continuous measures. Study retention across the three groups was evaluated using a Kaplan-Meier survival analysis. The primary cocaine use outcomes measured once during treatment (proportion of cocaine positive urines during the trial and the self-reported percentage of days without cocaine use during study participation) were evaluated with ANOVA. In addition, we examined whether CAR 25 or CAR 50 mg was associated with a reduction in the probability of obtaining a cocaine positive urine result over the course of the study using a hierarchical linear model (HLM) (Hedeker, Giobbons, du Toit, & Cheng, 2008). HLM manages repeated measures analyses in datasets with some missing data, as it allows for intraparticipant serial correlation and unequal variance and covariance structures across time (Hedeker et al., 2008). Additional HLM analyses were conducted to examine changes in cocaine and opioid withdrawal severity by treatment condition. Parallel analyses were conducted for opioid use outcomes. Secondary outcome measures including scores on the CSSA, OWS, CES-D and HAM-D were also analyzed using the HLM approach.

3. Results

3.1 Baseline Characteristics, Treatment Adherence and Safety

The baseline participant characteristics are presented in Table 1. Treatment groups did not differ in any of the baseline measures ($p > 0.05$). Of the 106 participants randomized to treatment condition, 70 (66 %) completed the study (Fig 1). No significant group differences were found for study completion, days retained in the study, or days of missed medication (Table 2).

The 24 participants with early termination discontinued treatment for a variety of non-medication related reasons including missed clinic visits or non-compliance ($n=17$) or transfer to another program ($n=7$). The adverse events identified in each treatment group are shown in Table 3. In 2 participants, the study medication was discontinued due to a skin rash that was attributed to the study medication (25 mg CAR ($n=1$) and 50 mg CAR ($n=1$)).

3.2 Cocaine Use During Treatment

The ANOVA analyses indicated overall treatment group differences for the proportion of urine samples that were positive for cocaine, with *post hoc* analyses indicating significant differences between the 25 mg and 50 mg CAR groups. No significant group differences were found for self-reported cocaine use during treatment nor were there differences in the end of treatment cocaine use as measured by urine toxicology or self-report (Table 2). Similarly, the generalized estimating equation (GEE) analysis of the urine toxicology and the HLM analysis of self-report data for cocaine use did not indicate a significant treatment effect or treatment by time interaction (urine Week Wald 4.34, $df=1$ $p=.04$, Treatment by Week Wald = 2.24 $df=2$ $p=.37$; SR group by time $F=0.97$, $p=.38$). Inclusion of the baseline CSSA scores in the model did not change the results of this analysis (group by time $F=1.03$, $p=.36$).

3.3 Opioid Use During Treatment

There were no significant treatment group differences in the percentage of self-reported days of opioid use or the percentage of opioid positive urines submitted during treatment (Table 2). However, the repeated measures analyses showed significant differences in the frequency of opioid use by treatment group (Group by Week $F=9.09$, $p=.003$), indicating that both placebo and CAR 25 show greater reductions than CAR 50 in the prevalence of positive opioid urine over time (Group by Week, Wald chi-square= 8.40, $p=.02$). There was no main effect of Time for either the opioid use self-report or the opioid urine result, indicating the absence of a significant change in opioid use over time during the trial.

3.4 Withdrawal Severity and Other Outcomes

Cocaine withdrawal severity, assessed by composite scores on the CSSA, decreased significantly over the course of treatment, without any significant group differences (Time $F=7.32$, $p=.00$, treatment by time $F=1.27$, $p=.28$). Opioid withdrawal severity also decreased overall during treatment (Time $F=27.97$, $df=1, 868$, $p=.000$), and treatment differences were found, with CAR 50 showing the least change over time (Treatment by time $F=4.96$, $df=1, 868$, $p=.007$).

During treatment, there was a significant overall reduction in the CES-D scores ($F=4.27$, $p=.04$) and HAM-D scores ($F=37.08$, $p<.000$)¹. There was also a significant difference in the rates of change in scores by treatment condition for the HAM-D (treatment by time $F=3.43$, $p=.03$). No treatment differences were seen in the rates of change in secondary analyses.

4. Discussion

In this sample of opioid and cocaine dependent participants, daily treatment with either 25 mg or 50 mg CAR was not more effective than placebo in reducing cocaine use over the course of an 11-week trial. Similar findings were observed for opioid use: while there were differences in the rate of change by treatment group, overall opioid use did not change over time. In addition, baseline cocaine withdrawal severity did not predict response to CAR treatment. Collectively, these findings do not support the use of CAR for reducing cocaine use in individuals dependent on both cocaine and opioids.

Participants assigned to the 50 mg CAR treatment had a greater percentage of positive cocaine urine samples than those who were assigned to 25 mg CAR. However, neither the 25 nor 50 mg CAR groups were significantly different from the placebo group on measures of cocaine use. Similarly, the 50 mg CAR group had greater opioid use than either the 25 mg CAR or placebo groups. Although the underlying mechanism of these differences between the 25 and 50 mg CAR is not clear, one possible explanation is that the affinity of CAR at beta and alpha1-adrenergic receptors is dose-dependent (Tham, Guy, McDermott, Shanks, & Riddell, 1995). At low doses, CAR primarily blocks beta-adrenergic receptors similar to the pure beta-adrenergic blocker propranolol. At higher doses, CAR blocks both alpha1 and beta-adrenergic blocker, similar to a combination of propranolol and prazosin, an alpha1-adrenergic blocker (Tham et al., 1995). In a previous human laboratory study, a single dose

of 50 mg CAR, but not 25 mg CAR, effectively attenuated the blood pressure and heart rate increases induced by cocaine, consistent with a blockage of both alpha1 and beta-adrenergic receptors (Sofuoglu et al., 2000). In contrast, 25 mg CAR, but not a 50 mg dose, reduced cocaine self-administration behavior (Sofuoglu et al., 2000). Given these dose-dependent changes in CAR's pharmacological effect, we selected both the 25 mg and 50 mg CAR doses for our study. Collectively, our findings suggest that in any future studies of CAR in cocaine or opioid users, CAR doses greater than 25 mg should not be used to avoid possible increases in cocaine and opioid use.

In a previous clinical trial, Kampman et al. reported that among cocaine users, higher withdrawal severity was predictive of better treatment response to propranolol (Kampman, Alterman, et al., 2001). This finding is consistent with the proposed increase in NE activity during cocaine withdrawal. In this study, all treatment groups showed similar reductions in cocaine withdrawal severity during treatment participation. However, the severity of cocaine withdrawal before treatment initiation was not predictive of better response to CAR treatment. It is important to note that the participants in the Kampman study were primarily cocaine addicted individuals and thus differed from the opioid and cocaine dependent participants in our study.

Overall, CAR treatment was well-tolerated with similar drop-out rates among the 3 treatment groups. The 50 mg CAR group seemed to have a lower average number of days in treatment and treatment retention than the 25 mg CAR or placebo groups. However, these differences did not reach statistical significance. Similarly, the type and frequency of adverse events were similar across the 3 treatment groups.

As mentioned before, case reports suggest potential effectiveness of CAR for the treatment of cocaine-induced cardiac toxicity and ischemia (Littmann et al., 2013; Ocal et al., 2015; Self et al., 2011). It has been suggested that CAR may have an advantage over pure beta-adrenergic blockers like propranolol for attenuating the cardiovascular stimulation induced by cocaine use (Damodaran, 2010). However, no clinical trials have tested if CAR will reduce the cardiovascular complications associated with cocaine use.

The main limitation of this study is the small sample size, with a total of 106 participants randomized. In addition, the study participants were cocaine and opioid dependent and were stabilized on methadone. Individuals addicted to more than one drug are less likely to respond to treatment than those addicted to one substance (Dutra et al., 2008). For example, cocaine users had better treatment response to disulfiram than opioid maintained cocaine users (Oliveto et al., 2011). Disulfiram also acts on NE, reducing the NE/DA ratio in the synapse by inhibiting dopamine beta-hydroxylase (Sofuoglu & Sewell, 2009). Thus, our study findings may not generalize to cocaine users who are not maintained on methadone. One particular strength of the study was that the study medications were administered under supervision of study staff for 6 days a week thereby markedly decreasing the probability that our negative findings were due to inconsistent exposure to the study medication.

In conclusion, 11 weeks of treatment with either 25 or 50 mg CAR did not reduce cocaine use more than placebo in methadone-maintained cocaine users. These results do not support

the use of CAR for the treatment of CUD in this population at this dose range. Further, CAR doses of 50 mg or higher should not be used to avoid possible increases in cocaine and opioid use.

Acknowledgments

Supported by the VA New England Mental Illness, Research, Education and Clinical Center (MIRECC) and NIDA Grants R01 DA019885 and KO2 DA021304.

References

- Carroll KM. Integrating psychotherapy and pharmacotherapy to improve drug abuse outcomes. *Addict Behav.* 1997; 22:233–245. [PubMed: 9113217]
- Carroll, KM. A Cognitive-Behavioral Approach: Treating Cocaine Addiction. National Institute on Drug Abuse, National Institute on Drug Abuse; 1998. NIH Publication 98-4308
- Chamberlain SR, Robbins TW. Noradrenergic modulation of cognition: therapeutic implications. *J Psychopharmacol.* 2013; 27(8):694–718. [PubMed: 23518815]
- Damodaran S. Cocaine and beta-blockers: the paradigm. *Eur J Intern Med.* 2010; 21(2):84–86. [PubMed: 20206876]
- Dutra L, Stathopoulou G, Basden SL, Leyro TM, Powers MB, Otto MW. A meta-analytic review of psychosocial interventions for substance use disorders. *Am J Psychiatry.* 2008; 165(2):179–187. [PubMed: 18198270]
- Elliott JM, Beveridge TJ. Psychostimulants and monoamine transporters: upsetting the balance. *Curr Opin Pharmacol.* 2005; 5(1):94–100. [PubMed: 15661632]
- First MB, Spitzer RL, Gibbon M, Williams JB. Structured clinical interview for DSM-IV Axis I disorders patient edition. 1996
- Forray A, Sofuoglu M. Future pharmacological treatments for substance use disorders. *Br J Clin Pharmacol.* 2014; 77(2):382–400. [PubMed: 23039267]
- Frishman WH. Carvedilol. *N Engl J Med.* 1998; 339(24):1759–1765. [PubMed: 9845712]
- Hamilton M. A rating scale for depression. *Journal of Neurology, Neurosurgery, and Psychiatry.* 1960; 23:56–62.
- Hedeker, D.; Giobbons, R.; du Toit, M.; Cheng, Y. SuperMix: Mixed effects models. Lincolnwood, IL: Scientific Software International, Inc; 2008.
- Kampman KM, Alterman AI, Volpicelli JR, Maany I, Muller ES, Luce DD, O'Brien CP. Cocaine withdrawal symptoms and initial urine toxicology results predict treatment attrition in outpatient cocaine dependence treatment. *Psychol Addict Behav.* 2001; 15(1):52–59. [PubMed: 11255939]
- Kampman KM, Dackis C, Lynch KG, Pettinati H, Tirado C, Gariti P, O'Brien CP. A double-blind, placebo-controlled trial of amantadine, propranolol, and their combination for the treatment of cocaine dependence in patients with severe cocaine withdrawal symptoms. *Drug Alcohol Depend.* 2006; 10:10.
- Kampman KM, Volpicelli JR, McGinnis DE, Alterman AI, Weinrieb RM, D'Angelo L, Epperson LE. Reliability and validity of the cocaine selective severity assessment [In Process Citation]. *Addict Behav.* 1998; 23(4):449–461. [PubMed: 9698974]
- Kampman KM, Volpicelli JR, Mulvaney F, Alterman AI, Cornish J, Gariti P, O'Brien C. Effectiveness of propranolol for cocaine dependence treatment may depend on cocaine withdrawal symptom severity. *Drug Alcohol Depend.* 2001; 63(1):69–78. [PubMed: 11297832]
- Kosten TR, Rounsaville BJ, Kleber HD. Comparison of clinician ratings to self reports of withdrawal during clonidine detoxification of opiate addicts. *Am J Drug Alcohol Abuse.* 1985; 11(1–10)
- Littmann L, Narveson SY, Fesel NM, Marconi SL. Beta blocker treatment of heart failure patients with ongoing cocaine use. *Int J Cardiol.* 2013; 168(3):2919–2920. [PubMed: 23664043]
- Ocal L, Cakir H, Tellice M, Izci S, Alizade E, Esen AM. Successful treatment of cocaine-induced cardiotoxicity with carvedilol therapy. *Herz.* 2015; 40(1):159–161. [PubMed: 24173375]

- Oliveto A, Poling J, Mancino MJ, Feldman Z, Cubells JF, Pruzinsky R, Kosten TR. Randomized, double blind, placebo-controlled trial of disulfiram for the treatment of cocaine dependence in methadone-stabilized patients. *Drug Alcohol Depend.* 2011; 113(2–3):184–191. doi: S0376-8716(10)00268-1 [pii] 10.1016/j.drugalcdep.2010.07.022. [PubMed: 20828943]
- Radloff LS. The CES-D Scale: A self-report depression scale for research in the general population. *Applied Psychological Measurements.* 1977; 1:385–401.
- SAMHSA. Substance Abuse and Mental Health Services Administration. Results from the 2013 National Survey on Drug Use and Health: national findings; 2014
- Schmidt KT, Weinshenker D. Adrenaline rush: the role of adrenergic receptors in stimulant-induced behaviors. *Mol Pharmacol.* 2014; 85(4):640–650. [PubMed: 24499709]
- Self T, Rogers ML, Mancell J, Soberman JE. Carvedilol therapy after cocaine-induced myocardial infarction in patients with asthma. *Am J Med Sci.* 2011; 342(1):56–61. [PubMed: 21293248]
- Shorter D, Lindsay JA, Kosten TR. The alpha-1 adrenergic antagonist doxazosin for treatment of cocaine dependence: A pilot study. *Drug Alcohol Depend.* 2013; 131(1–2):66–70. [PubMed: 23306096]
- Sobell LC, Sobell MB, Leo GI, Cancilla A. Reliability of a timeline method: assessing normal drinkers' reports of recent drinking and a comparative evaluation across several populations. *British journal of addiction.* 1988; 83(4):393–402. [PubMed: 3395719]
- Sofuoglu M, Brown S, Babb DA, Pentel PR, Hatsukami DK. Carvedilol affects the physiological and behavioral response to smoked cocaine in humans. *Drug Alcohol Depend.* 2000; 60(1):69–76. [PubMed: 10821991]
- Sofuoglu M, Sewell RA. Norepinephrine and stimulant addiction. *Addict Biol.* 2009; 14(2):119–129. [PubMed: 18811678]
- Szabadi E. Functional neuroanatomy of the central noradrenergic system. *J Psychopharmacol.* 2013; 27(8):659–693. [PubMed: 23761387]
- Tham TC, Guy S, McDermott BJ, Shanks RG, Riddell JG. The dose dependency of the alpha- and beta-adrenoceptor antagonist activity of carvedilol in man. *British Journal of Clinical Pharmacology.* 1995; 40(1):19–23. [PubMed: 8527263]
- Verrico CD, Haile CN, Newton TF, Kosten TR, De La Garza R. Pharmacotherapeutics for substance-use disorders: a focus on dopaminergic medications. *Expert Opin Investig Drugs.* 2013; 22(12):1549–1568.
- Wei LJ, Lachin JM. Properties of the urn randomization in clinical trials. *Control Clin Trials.* 1988; 9(4):345–364. [PubMed: 3203525]
- Weinshenker D, Schroeder JP. There and back again: a tale of norepinephrine and drug addiction. *Neuropsychopharmacology.* 2007; 32(7):1433–1451. doi: 1301263. [PubMed: 17164822]

Highlights

- The goal of this study was to test the efficacy of carvedilol (CAR), an adrenergic blocker, for reducing cocaine use in individuals with cocaine use disorder (CUD).
- One hundred and six treatment-seeking opioid and cocaine-dependent participants were randomized to placebo (n=34), 25 mg/day CAR (n=37) or 50 mg/day CAR (n=35).
- Eleven weeks of treatment with either 25 or 50 mg CAR did not reduce cocaine use more than placebo in methadone-maintained cocaine users.
- These results do not support the potential use of CAR for the treatment of CUD in patients maintained on methadone.

CONSORT Diagram

Figure 1.
Flow of participants through the phases of the trial.

Figure 2. Weekly percentage of participants retained in the study for the 3 treatment groups across the 11-week maintenance phase of the trial: placebo (n=34), carvedilol at 25 mg/day, and carvedilol at 50 mg/day.

Figure 3.

HLM estimates of the weekly changes in the CSSA scores for the 3 treatment groups across the 11-week maintenance phase of the trial: placebo (n=34), carvedilol at 25 mg/day, and carvedilol at 50 mg/day.

Figure 4.

Weekly number of urine toxicology screens positive for the 3 treatment groups across the 11-week maintenance phase of the trial: placebo (n=34), carvedilol at 25 mg/day, and carvedilol at 50 mg/day. Participants were asked to submit 3 urine samples in each week of study participation.

Table 1
Baseline demographic, psychiatric and drug use characteristics by treatment condition

	Placebo (n=34)		CAR 25 (n=37)		CAR 50 (n=35)		Total (n=106)		F, χ^2	df	p
	N	%	N	%	N	%	N	%			
Sex (Female)	15	44.1	14	37.8	11	31.4	40	37.7	1.18	2	.55
Race											
White	21	61.8	24	64.9	25	71.4	70	66	8.20	4	.09
Black	12	35.3	10	27	4	11.4	26	24.5			
Other	1	2.9	3	8.1	6	17.1	10	9.4			
Education											
Some college or more	13	38.2	21	56.8	14	40.0	48	45.3	3.35	4	.50
High school graduate/GED	17	50	14	37.8	17	48.6	48	45.3			
Less than high school	4	11.8	2	5.4	4	11.4	10	9.4			
Marital Status											
Married	8	23.5	5	13.5	6	17.1	19	17.9	1.23	2	.54
Not married	26	76.5	32	86.5	29	82.9	87	82.1			
Lifetime major depression	6	18.8	7	19.4	7	21.2	20	19.8	0.37	4	
	mean	sd	mean	sd	mean	sd	mean	sd	F, χ^2	df	p
Age	37.6	9.1	37.7	10.9	39.1	10.9	38.1	10.3	0.23	2,98	.79
Days paid in the last 28 days	7.1	8.7	9.3	10.1	11.2	11	9.2	10	1.36	2,98	.26
Lifetime years heroin use	11.7	11.3	13.1	11.7	12.6	12.8	12.5	11.8	0.12	2,98	.89
Lifetime years cocaine use	15.7	10.9	16.6	11.7	17.1	9.6	16.5	10.6	0.13	2,98	.88
Lifetime years alcohol use	16.9	11.6	17.9	12.3	18.5	13.6	17.8	12.4	0.14	2,98	.87
Days of heroin use, past 28 days	14.5	11.8	8.9	9.7	12.5	11.4	11.9	11.1	2.32	2,98	.10
Days of cocaine use, past 28 days	12.8	12.8	13.1	8.8	13.4	8.1	13.1	8.9	0.04	2,98	.96
Days of alcohol use, past 28 days	0.75	1.5	0.94	2.1	1.3	3.8	1	2.6	0.37	2,98	.69
CSSA score at baseline	36.8	21.5	31.3	21.3	34.1	18.3	34	20.3	0.60	2,99	.55
FTND score at baseline	5.1	2.2	5.3	2.7	4.9	2.4	5.1	2.4	0.13	2,79	.88
HAM-D score at baseline	8	5.1	5.1	5.1	5.5	5.7	6.1	5.4	2.80	2,98	.07

	Placebo (n=34)		CAR 25 (n=37)		CAR 50 (n=35)		Total (n=106)		F, χ^2	df	p
CES-D score at baseline	N	%	N	%	N	%	N	%			
	17.6	8.9	18.4	8.1	16.5	8.6	17.5	8.5	0.42	2,93	.66

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Outcomes of self-reported substance use and urine results

Table 2

	Placebo (N=34)		CAR 25 (N=37)		CAR 50 (N=35)		Total (N=106)		F, χ^2	df	p
	N	%	N	%	N	%	N	%			
Completed the study n (%)	19	55.9	28	75.7	23	65.7	70	66	3.10	2	.21
Days of missed medications	mean	sd	mean	sd	mean	sd	mean	sd	F, χ^2	df	p
	2.6	4.3	4.1	5.8	1.7	2.5	2.8	4.5	2.41	2,91	.10
Percent days abstinent from cocaine self report	72.9	25.3	72.9	29.2	59.3	31.7	68.1	29.4	2.34	2,91	.10
Number of days abstinent from cocaine in the last 2 weeks of the trial. self report	7.8	4.9	8.1	5.0	6.4	4.7	7.5	4.9	0.9	2,90	0.4
Percent cocaine positive urines submitted	59.2	38.9	50.8	33.8	75.1	33.2	61.8	38.5	3.59	2,91	.03
Percent days abstinent from heroin self report	88.2	16.7	88.4	20.0	77.4	32	84.5	24.6	2.19	2,91	.12
Percent heroin positive urines submitted	50.4	35.8	41.3	37.1	39.4	35.1	43.3	36.1	0.79	2,91	.46
Percent any opioid positive urines submitted	52.3	35.6	43	39.1	42.2	35.6	45.5	36.7	0.68	2,91	.51

Table 3

Adverse events by treatment condition

		PLAC	CAR 25	CAR 50	Total	X ²	df	p
Psychiatric								
Disturbed concentration	6	16.7	5	14.7	7	23.3	18	.65
Agitation	11	30.6	13	38.2	7	23.3	31	.44
Tiredness	13	36.1	13	38.2	11	36.7	37	.98
Drowsiness	6	16.7	10	29.4	7	23.3	23	.45
Insomnia	14	38.9	13	38.2	11	36.7	38	.98
Nightmares	5	13.9	5	14.7	7	23.3	17	.54
Depression	10	27.8	11	32.4	11	36.7	32	.74
Anxiety	8	22.2	10	29.4	11	36.7	29	.44
Neurological								
Numbness	3	8.3	7	20.6	7	23.3	17	.21
Cramps	4	11.1	4	11.8	4	13.3	24	.96
Headache	7	19.4	9	26.5	8	26.7	24	.73
Gastrointestinal								
Constipation	13	36.1	11	32.4	13	43.3	37	.66
Decreased appetite	6	16.7	7	20.6	4	13.3	17	.74