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Pilot Investigation of the Effect of Carvedilol on Stress-Precipitated Smoking-Lapse Behavior

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Abstract

Introduction: Separate α 1- and β -adrenergic antagonists have shown efficacy in reducing nicotine-motivated behaviors in rodents and humans, supporting a role for the noradrenergic system in mediating the reinforcing properties of drugs of abuse. However, the effect of the combined α 1- and β -adrenergic antagonist, carvedilol, on stress-related smoking is unknown.

Method: Using a well-established human laboratory model of stress-precipitated smoking-lapse behavior, we examined whether carvedilol (0 or 50 mg/day; between subject, n=17 per group), administered to steady-state, would attenuate the ability to resist smoking following stress imagery (vs. neutral imagery) and reduce subsequent smoking self-administration in nicotine-deprived smokers (n=34 total). Tobacco craving, withdrawal and physiologic reactivity were also assessed.

Results: Latency to start smoking and number of cigarettes smoked during the self-administration period did not differ by medication condition. Counter to our hypothesis, tobacco craving demonstrated a medication $\times$ time effect, with greater craving in the carvedilol condition. Systolic blood pressure and heart rate demonstrated lower values in the carvedilol vs. placebo group, consistent with known effects of carvedilol.

Conclusion: While carvedilol attenuated physiological reactivity consistent with its clinical indication, beneficial effects on smoking outcomes were absent in this preliminary investigation and may suggest possible worsening. Future work may benefit from discerning the single versus combined effects of α 1- and β -adrenergic antagonism on smoking outcomes.

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DECLARATION OF CONFLICTING INTERESTS

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Keywords

smoking; smoking cessation; noradrenergic; stress; carvedilol

INTRODUCTION

Stress plays a critical role in the initiation, maintenance of, and relapse to smoking (McKee et al., 2011; Sinha, 2008). The noradrenergic system is widely implicated in the stress response, and has been found to mediate the reinforcing properties of drugs of abuse (Koob, 2008; Weinshenker and Schroeder, 2007). The noradrenergic brain stress system can be divided into 3 receptor subtypes; α 1-, α 2-, and β -adrenergic receptors. Preclinical and clinical work have demonstrated that medications from each receptor class are efficacious in attenuating drug-seeking and self-administration behavior, including stress-related nicotine-motivated behavior. Given the modest efficacy of Food and Drug Administration (FDA)-approved medications for long-term smoking cessation (Fiore et al., 2008), targeting the noradrenergic system for stress-precipitated smoking behavior may be a viable and clinically relevant next step for the treatment of tobacco dependence.

Focusing on α 1- and β -adrenergic receptors, preclinical work has demonstrated that prazosin, an α 1-adrenergic antagonist, decreased elevations in brain reward thresholds associated with nicotine withdrawal (Bruijnzeel et al., 2010), reduced nicotine self-administration (Forget et al., 2010; Villégier et al., 2007), blocked the acquisition of a nicotine conditioned place preference (CPP) (Forget et al., 2009), attenuated nicotine prime- and nicotine cue-induced reinstatement of nicotine-seeking (Forget et al., 2010), and decreased nicotine-evoked dopamine release in the nucleus accumbens (Forget et al., 2010; Villégier et al., 2007). Propranolol, a non-selective β -adrenergic antagonist, has been found to decrease somatic signs (e.g., number of shakes, eye blinks) associated with nicotine withdrawal (Bruijnzeel et al., 2010), and block nicotine CPP, decrease operant responding for nicotine, and block nicotine prime-induced reinstatement of a nicotine CPP via disruption of memory reconsolidation (Xue et al., 2017). However, other preclinical findings using both prazosin and propranolol to examine nicotine-motivated behaviors have been inconsistent (Yamada and Bruijnzeel, 2011; Bruijnzeel et al., 2012; Bruijnzeel et al., 2010).

Limited clinical work has examined the role of α - or β -adrenergic antagonists for smoking cessation. Our group has demonstrated that doxazosin, an α 1-adrenergic antagonist, decreased tobacco craving, increased the latency to initiate smoking following stress, and reduced subsequent smoking self-administration (Verplaetse et al., 2017). We also demonstrated that guanfacine, an α 2a-adrenergic agonist, is effective in attenuating stress-related increases in tobacco craving and smoking, and in increasing the ability to resist smoking (McKee et al., 2015). Further, in a translational study, propranolol decreased nicotine preference and nicotine craving in human smokers (Xue et al., 2017), suggesting translational efficacy of noradrenergic agents for smoking cessation.

Despite preclinical and human laboratory studies demonstrating that separate α 1- and β -adrenergic antagonists are effective in reducing nicotine-motivated behaviors, the effect of a combined α 1- and β -adrenergic antagonist on smoking behavior in humans is unknown.

Carvedilol, an α 1- and β -adrenergic antagonist, has been found to reduce physiologic reactivity and aversive effects of nicotine in abstinent smokers (Sofuoglu et al., 2006) and labetalol, an α 1- and β -adrenergic antagonist with differing affinities for α 1- and β -adrenergic receptors and more limited central nervous system access than carvedilol, attenuated nicotine-induced increases in heart rate and enhanced the attenuation of tobacco withdrawal symptoms by intravenous (IV) nicotine in nicotine-deprived smokers (Sofuoglu et al., 2003). No studies have yet examined the effects of a combined α 1- and β -adrenergic antagonist on stress-precipitated ad-libitum smoking behavior and tobacco craving.

Using a well-established human laboratory model of stress-precipitated smoking-lapse behavior, we examined whether carvedilol (0 or 50 mg/day) would attenuate the ability of stress to prompt smoking-lapse and reduce subsequent ad-libitum smoking self-administration in nicotine-deprived daily smokers ($n=34$). In this preliminary investigation, it was hypothesized that carvedilol (50 mg/day; vs. placebo) would increase the ability to resist smoking (i.e., increase the latency to initiate ad-libitum smoking) and decrease the number of cigarettes smoked during the ad-libitum smoking self-administration period following overnight nicotine deprivation and personalized stress imagery (vs. neutral imagery). Based on our own prior studies with noradrenergic agents and preclinical findings, we also hypothesized that carvedilol would reduce tobacco craving and physiologic reactivity in response to stress.

METHODS AND MATERIALS

Design.

A between-subject, double-blind, placebo-controlled design was used to compare carvedilol (50 mg/day) to placebo (0 mg/day). Following titration to steady-state medication levels, participants ($n=17$ per medication group; $n=34$ total) completed two laboratory sessions designed to model smoking-lapse behavior (stress vs. neutral imagery, order counterbalanced). Sample size was based on other preliminary human laboratory medication screening investigations from our laboratory (McKee et al., 2015; Verplaetse et al., 2016; Verplaetse et al., 2017).

Participants.

Eligible participants were 18–60 years of age, smoked ≥ 10 cigarettes/day for the past year, had urine cotinine levels of ≥ 150 ng/ml, and were normotensive (sitting blood pressure (BP) $>90/60$ and $<160/100$ mmHg). Participants were excluded if they met criteria for current (past 6-month) DSM-IV Axis-I psychiatric disorders (excluding nicotine dependence; assessed by the Structured Clinical Interview for DSM-IV Axis I disorders (First et al., 1996)), were using illicit drugs (assessed by urine toxicology), had engaged in smoking-cessation treatment in the past 6 months, or had medical conditions or used concurrent medicine that would contraindicate carvedilol use or smoking behavior assessed by physical exam (including electrocardiogram and basic blood chemistries). The study was approved by the Yale Human Investigations Committee. All participants provided written informed consent. Participants were recruited from the community for a smoking laboratory study.

Carvedilol Treatment.

The medication condition was double-blind and placebo-controlled. Carvedilol was titrated to steady-state medication levels over 5 days (12.5 mg/day on Day 1, 25 mg/day on Days 2–3, and 50 mg/day on Days 4–5). Placebos were matched in appearance and were taken on the same schedule as the active medication conditions. Medication compliance, assessed by pill counts and riboflavin markers, was 100%. The last dose was administered on the day of the last laboratory session (Day 7 or 8). Carvedilol dose was selected for this preliminary investigation based on previous studies that 50mg/day carvedilol was effective in reducing cardiovascular reactivity in tobacco smokers and smoked cocaine users (Sofuoglu et al., 2000; Sofuoglu et al., 2006).

Adverse Events.

Adverse events were assessed throughout the titration period and once weekly during treatment (Levine and Schooler, 1986). Participants were queried regarding common adverse events associated with carvedilol (e.g., diarrhea, dizziness, and fatigue; see Table 2) (GlaxoSmithKline, 2015).

Laboratory Assessment of Stress-Precipitated Smoking Lapse

Procedures.: Each subject completed two 6.5-hour laboratory sessions (stress vs. neutral imagery; see Figure 1 for a timeline of laboratory procedures). The first laboratory session was completed on Day 5. The second laboratory session was completed on Day 7 or 8. Participants remained on steady state medication levels between laboratory sessions.

Baseline Assessment Period: Laboratory sessions started at 8:00am. Participants were instructed to smoke a final cigarette at 10:00pm on the previous night. At 8:00am on laboratory session days, abstinence was confirmed with an expired breath carbon monoxide (CO) reading of less than 50% of their baseline CO level at intake (Kahler et al., 2012; Odum et al., 2002). Baseline assessments of breath alcohol, urine drug screen, and urine pregnancy screen were also collected at 8:00am. Next, medication administration occurred to standardize the time between medication administration, peak plasma levels of carvedilol, and the start of the ad-libitum smoking self-administration period. Following medication administration, vital signs (i.e., blood pressure, pulse) and assessments of tobacco craving and withdrawal were obtained. Participants were provided with a standardized lunch at 11:15am to control for time since last food consumption. From 10:00am (i.e., the end of the baseline assessment period) to 12:30pm (i.e., the start of the personalized imagery procedure), participants were able to watch television or read.

Personalized Imagery Procedure: Exposure to stress and neutral imagery used personalized guided-imagery methods (McKee et al., 2015; McKee et al., 2011; Sinha, 2009). In a prior session, stress-imagery scripts were developed by having participants identify and describe in detail highly stressful experiences occurring within the past 6 months. Only situations rated as 8 or higher (1=‘not at all stressful’ and 10=‘the most stress they recently felt in their life’) were accepted as appropriate for script development. A neutral-relaxing script was developed from participants’ descriptions of personal neutral-relaxing situations. Scripts were developed by a PhD-level clinician and audiotaped for presentation during the

laboratory sessions. Each script was approximately 5 min in length. During the laboratory session at 12:55pm, participants listened to scripts (stress or neutral) via headphones.

Delay Period: At 1:10pm, participants were presented with a tray containing 8 cigarettes of their preferred brand, a lighter, and an ashtray. Participants were instructed that they could commence smoking at any point over the next 50 min. However, for each 5 min block of time they delayed or ‘resisted’ smoking, they would earn \$1 for a maximum of \$10. The time when participants announced they wanted to smoke (range 0–50 min) was recorded.

Smoking Self-Administration Period: The ad-libitum smoking period duration was 60 min in length and started once the participants decided to end the delay period (or delayed for the full 50 min). Participants were instructed to ‘smoke as little or as much as you wish’. Following the smoking self-administration period on the second laboratory session day, participants were asked whether they believed they had received placebo or carvedilol. Participants were discharged at 3:15pm.

Assessments.: Primary measures included the length of the time to initiate smoking (the ability to resist smoking; measured in minutes) and number of cigarettes smoked during the ad-libitum smoking period. Tobacco craving (Questionnaire of Smoking Urges-Brief) (Cox et al., 2001) was assessed on a visual analogue scale (VAS 1–100). Nicotine withdrawal was assessed with the 8-item Minnesota Nicotine Withdrawal Scale (MNWS; score range 0–32) (Hughes and Hatsukami, 1986).

Physiologic Measures: A pulse sensor was attached to the subject’s forefinger to obtain a measure of pulse rate. Blood pressure was measured using a Critikon Dynamap.

Timing of Assessments: Tobacco craving, withdrawal, and physiologic reactivity were assessed at baseline (8:00am), pre-imagery, post-imagery (prior to the presentation of cigarette cues), end of delay, the start of the ad-libitum self-administration period, and +20, +40, and +60 min during the ad-libitum self-administration period.

Statistical Analyses.: Multivariate analysis of variance was used to examine within-subject effects of imagery condition (stress vs. neutral) and time by medication condition (0 vs. 50 mg/day carvedilol) on the primary outcomes (i.e., time to initiate smoking, number of cigarettes smoked during the ad-libitum smoking period). Multivariate analyses of variance were also used to examine within-subject effects of imagery condition and time by medication condition on tobacco craving, withdrawal, and physiologic reactivity. The post-imagery timepoint occurred prior to the start of the smoking-lapse task. According to the predefined analytical plan, age, sex, Fagerström Test for Nicotine Dependence (FTND; (Heatherton et al., 1991)) scores, and Center for Epidemiological Studies-Depression Scale (CES-D; (Radloff, 1977)) scores were evaluated as covariates and were retained if they were significantly associated with each outcome. Baseline cigarettes per day was included as a covariate in all analyses. A manipulation-check of the blind was assessed using chi-square to determine if participants were correctly able to identify their medication condition.

RESULTS

Baseline Demographics.

Carvedilol (50 mg/day) and placebo were well-matched for baseline demographics (see Table 1). All baseline comparisons across medication condition were not significant ($p>0.05$).

Adverse Events.

All adverse events were rated as minimal to mild, and no subject discontinued treatment or required a dose adjustment due to an adverse event (see Table 2). Chi-square comparisons demonstrated a higher incidence of fatigue ($p=0.03$) in the placebo vs. carvedilol medication condition.

Latency to Smoke, Ad-libitum Smoking, and Tobacco Craving.

Mean CO levels at the start of the laboratory sessions (8:00am) were 9.74 (SE=1.12) and 9.50 (SE=0.72) for the stress and neutral/relax imagery conditions, respectively, and values did not differ by medication. Latency to smoke demonstrated a significant main effect of imagery condition ($F(1,31)=9.79$, $p=0.004$; Cohen's $d=1.12$), with lower values in the stress imagery condition (stress mean=12.57, standard error (SE)=4.19, neutral mean=15.63, SE=4.43). Latency to smoke did not demonstrate significant main or interactive effects of medication or medication by imagery (all p 's >0.05 ; see Figure 2). Ad-libitum smoking during the self-administration period demonstrated a trend effect of medication ($F(1,31)=3.03$, $p=0.09$; Cohen's $d=0.63$; see Figure 3), with higher values in the carvedilol group. Ad-libitum smoking did not demonstrate significant main or interactive effects of imagery condition or medication by imagery condition (all p 's >0.05 ; see Figure 3). Tobacco craving demonstrated a significant imagery condition by time interaction ($F(1,30)=4.29$, $p=0.05$; Cohen's $d=0.76$) and a significant time by medication interaction ($F(1,30)=5.61$, $p=0.02$; Cohen's $d=0.86$; see Figure 4), with higher values in the stress imagery condition and in the carvedilol group throughout the laboratory session, respectively. However, there were no significant within timepoint contrasts for either interaction.

Withdrawal.

Nicotine withdrawal did not demonstrate significant main or interactive effects of medication, medication by imagery condition, or medication by imagery condition by time (all p 's >0.05 ; grand mean=5.64, SE=0.75).

Physiologic Reactivity.

Systolic blood pressure demonstrated a significant imagery condition by time interaction ($F(1, 31)=4.97$, $p=0.03$; Cohen's $d=0.80$), with higher values in the stress imagery condition. However, there were no significant within timepoint contrasts. Systolic blood pressure also demonstrated a significant time by medication interaction ($F(1,31)=9.08$, $p=0.005$; Cohen's $d=1.08$), with lower values in the carvedilol group at the pre-imagery and post-imagery timepoints (see Figure 5a). Diastolic blood pressure demonstrated a significant time by medication interaction ($F(1,31)=4.22$, $p=0.05$; Cohen's $d=0.74$), with lower values overall in

the carvedilol group (see Figure 5b). However, there were no significant within timepoint contrasts. Heart rate demonstrated a significant time by medication interaction ($F(1,31)=4.30$, $p=0.05$; Cohen's $d=0.74$), with lower values in the carvedilol group at the pre-imagery and post-imagery timepoints (see Figure 5c).

Manipulation Check of the Medication Blind.

There was no significant difference in the ability of participants in the placebo or carvedilol groups to correctly identify their medication condition ($p=1.00$). A total of 50% of participants correctly identified their medication condition.

DISCUSSION

To our knowledge, this is the first preliminary investigation to examine the effect of carvedilol (50mg/day) on stress-precipitated smoking-lapse behavior. Using a well-validated human laboratory paradigm (McKee et al., 2012), findings suggest that carvedilol attenuated physiological reactivity, consistent with its clinical indication. However, beneficial effects on smoking outcomes were absent in this preliminary investigation. Counter to our hypothesis, carvedilol was associated with greater tobacco craving during the laboratory procedure. While ad-libitum smoking during the self-administration period demonstrated a trend effect of medication (Cohen's $d=0.63$), the carvedilol group smoked more cigarettes than the placebo-treated group. These findings suggest that a combined $\alpha 1$ - and β -adrenergic target may worsen smoking-motivated behavior.

Consistent with prior findings (Sofuoglu et al., 2006), the present results demonstrated that carvedilol reduced physiologic reactivity and did not affect nicotine withdrawal. Thus, the purely physiologic effect of carvedilol is not translating to a positive impact on behavior. This may be related to its action at the β -adrenergic receptor or the combined effect at $\alpha 1$ - and β -adrenergic receptors. Previous work with carvedilol demonstrated an attenuation of a subjective rating of 'bad effects' in response to nicotine lozenge (Sofuoglu et al., 2006), but this study did not examine cigarette smoking behavior (e.g., time to first smoking, smoking self-administration). Other research examining the $\alpha 1$ -adrenergic antagonist doxazosin is positive, such that doxazosin increased the latency to start smoking following stress, and reduced tobacco craving and number of cigarettes smoked in the same human laboratory paradigm used in the present investigation (Verplaetse et al., 2017). Disentangling $\alpha 1$ - from β -adrenergic effects on smoking-lapse behavior is a critical next step for future research.

Relatedly, it is possible that carvedilol was not effective in attenuating our primary smoking outcomes because it has different binding affinities for $\alpha 1$ - vs. β -adrenergic receptors. Carvedilol has a two- to three-fold higher affinity to $\beta 1$ -adrenergic receptors than to $\alpha 1$ -adrenergic receptors (Bristow, 2000). Prior work with $\alpha 1$ -adrenergic antagonists have shown efficacy in decreasing nicotine-motivated behavior in rodents and smoking-lapse behavior in humans (Bruijnzeel et al., 2010; Forget et al., 2009; Forget et al., 2010; Villégier et al., 2007; Verplaetse et al., 2017). Thus, carvedilol may not reduce smoking-lapse behavior because it binds to $\alpha 1$ -adrenergic receptors to a lesser extent than to β -adrenergic receptors. However, while β -adrenergic blockers have been investigated for smoking behavior to a lesser degree than $\alpha 1$ -adrenergic antagonists, non-selective β -adrenergic antagonists also show some

efficacy in reducing nicotine-associated outcomes (Bruijnzeel et al., 2010; Xue et al., 2017), suggesting that this hypothesis is unlikely.

Results from the present investigation are also in contrast to preclinical findings that combining $\alpha 1$ - and β -adrenergic antagonists are effective in reducing drug intake. Low dose prazosin in combination with propranolol was more effective than either drug alone in decreasing alcohol self-administration in non-dependent rodents (Verplaetse and Czachowski, 2015). In alcohol-dependent rodents, the combination of prazosin and propranolol reduced alcohol intake during withdrawal from chronic alcohol consumption and following prolonged abstinence more effectively than either drug alone (Rasmussen et al., 2014). To our knowledge, preclinical work combining $\alpha 1$ - and β -adrenergic antagonists for nicotine-seeking and self-administration has yet to be established. It is possible that combining $\alpha 1$ - and β -adrenergic antagonists may be effective for alcohol use but not for smoking-related behavior in humans.

Carvedilol demonstrated expected effects in reducing physiologic reactivity, consistent with its clinical indication and prior findings in humans (Sofuoglu et al., 2000; Sofuoglu et al., 2006). Carvedilol was well-tolerated in our sample of non-treatment seeking daily smokers. Mean severity ratings for each adverse event commonly associated with carvedilol were reported as minimal to mild, and no subject discontinued medication treatment or required a dose adjustment due to an adverse event. There was only one difference in frequency ratings of adverse events during the titration and treatment period. Rates of fatigue were greater in the placebo vs. carvedilol group (35.5% placebo, 5.9% carvedilol). Despite our null results, findings suggest that carvedilol appears to be safe and well-tolerated in adult daily smokers.

There are some limitations to the present investigation. This study had a modest sample size of 34 daily smokers. While the sample size and n size per medication group is comparable to other similar human laboratory studies (McKee et al., 2015; Verplaetse et al., 2016; Verplaetse et al., 2017), we did not find effects of carvedilol on our primary outcomes. Due to the modest sample size, we consider these outcomes to be preliminary in nature. Second, this sample of nicotine-deprived daily smokers were non-treatment seeking. The results may not generalize to treatment seeking daily smokers or individuals who are not nicotine-deprived. It will be important to examine noradrenergic agents for smoking cessation in those who are treatment seeking, and in both nicotine-deprived and satiated individuals. Third, we only tested a singular dose of carvedilol (50 mg/day) in the present investigation. While other studies using 25 and 50 mg/day carvedilol have demonstrated an attenuation of nicotine-related increases in physiologic reactivity and subjective 'bad effects' of nicotine in abstinent smokers (Sofuoglu et al., 2006), the dose-ranging effects of carvedilol on stress-precipitated smoking-lapse have not yet been examined and should be considered in future work. Fourth, carvedilol was titrated to steady-state medication levels over 5 days (Days 1 – 5) and the final dose was administered on the morning of the last laboratory session (Day 7 or 8). Perhaps, a longer treatment period is needed for carvedilol to exhibit effects on smoking behavior. However, this may be unlikely given that other studies administered carvedilol on the day of experimental laboratory sessions only and demonstrated effects of carvedilol on blood pressure, heart rate, subjective aversive effects of nicotine, and smoked cocaine self-administration (Sofuoglu et al., 2006; Sofuoglu et al., 2000). Finally, because

our smoking self-administration period was limited to 60 minutes in length, it is possible that we captured a limited range of smoking self-administration behavior (e.g., smoked cigarettes). However, in prior investigations, we have found medication differences in amount smoked during the 60-minute ad-libitum period (McKee et al., 2015; Verplaetse et al., 2017). It will be important to replicate our findings in a larger sample to thoroughly examine carvedilol for smoking cessation, especially given the limitations to the present investigation.

Overall, our preliminary results suggest that the combined $\alpha 1$ - and β -adrenergic antagonist carvedilol may not be effective for stress-precipitated smoking-lapse behavior. Counter to our hypothesis, carvedilol increased tobacco craving during the laboratory session. These findings are inconsistent with prior literature examining noradrenergic treatment targets for smoking cessation, and may suggest that carvedilol worsens smoking-motivated behavior in non-treatment seeking daily smokers. Future work may benefit from examining carvedilol for smoking-lapse in a larger sample and discerning the single versus combined effects of $\alpha 1$ - and β -adrenergic antagonism on smoking outcomes.

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Figure 1.

Timeline of study procedures to evaluate the effect of carvedilol on stress-precipitated smoking-lapse behavior.

Figure 2. Mean ($\pm$ SE) latency to start smoking (min). Latency to smoke did not demonstrate a significant interactive effect of medication by imagery condition (stress vs. neutral; $p=0.89$).

Figure 3.

Mean ($\pm$ SE) cigarettes smoked during the 60-minute ad-libitum smoking self-administration period. Ad-libitum smoking self-administration demonstrated a trend effect of medication ($p=0.09$). Ad-libitum smoking self-administration did not demonstrate a significant interactive effect of medication by imagery condition (stress vs. neutral; $p=0.84$).

Figure 4. Mean ($\pm$ SE) subjective tobacco craving ratings (VAS 1–100) by time by medication condition.

5a. **5b.** **5c.**

Figure 5. Physiologic reactivity by time by medication condition for (a) mean ($\pm$ SE) systolic blood pressure; (b) mean ($\pm$ SE) diastolic blood pressure; (c) mean ($\pm$ SE) heart rate. *Carvedilol 50mg/day significantly different vs. placebo.

Table 1.

Baseline demographics by medication condition.

	Placebo (n=17)	Carvedilol 50 mg/day (n=17)	<i>p</i>
Baseline (mean, SD [*] or n, %)			
Age	32.41, 11.21	32.18, 7.86	0.33
Gender (male)	6, 35.3%	7, 41.2%	0.72
Race (White)	9, 52.9%	10, 58.8%	0.24
Education (high school)	4, 23.5%	4, 23.5%	0.53
Income			0.75
Less than \$19,999	6, 37.5%	10, 62.5%	
\$20,000-\$39,999	7, 43.8%	4, 25.0%	
Over \$40,000	3, 18.8%	2, 12.5%	
Cigarettes per day	14.18, 4.08	18.12, 11.10	0.79
FTND ^a	5.29, 1.76	6.06, 2.84	0.33
CO [*] levels at intake	27.71, 18.44	21.82, 15.31	0.40

^{*}SD=standard deviation; CO=carbon monoxide

^aFagerström Test of Nicotine Dependence (Heatherton et al., 1991), range 1–10 for measure.

Table 2.

Frequency counts of treatment emergent adverse events commonly associated with carvedilol vs. placebo during the titration period and laboratory sessions.

	Placebo (n=17)	Carvedilol 50 mg/day (n=17)
Adverse event (n, %)		
Diarrhea	4, 23.5%	3, 17.6%
Dizziness	1, 5.9%	1, 5.9%
Fatigue *	6, 35.3%	1, 5.9%
Weakness	1, 5.9%	1, 5.9%
Lightheadedness	1, 5.9%	1, 5.9%
Nausea	1, 5.9%	3, 17.6%
Headache	2, 11.8%	4, 23.5%
Weight increase	1, 5.9%	0, 0.0%
Irregular or unusually slow heartbeat	0, 0.0%	1, 5.9%

Note: All events were rated as minimal to mild on a four-point scale (1=minimal, 2=mild, 3=moderate, 4-severe). No subject discontinued treatment or required a dose adjustment due to an adverse event.

* A chi-square comparison across medication conditions revealed a higher incidence of fatigue ($p=0.03$, placebo > carvedilol).