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Pharmacogenetics of *Dopamine β-Hydroxylase* in Cocaine Dependence Therapy with Doxazosin

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Abstract

Background—The α_1 adrenergic antagonist, doxazosin, has improved cocaine use disorder (CUD) presumably by blocking norepinephrine (NE) stimulation and reward from cocaine-induced NE increases. If the NE levels for release were lower, then doxazosin might more readily block this NE stimulation and be more effective. The NE available for release can be lower through a genetic polymorphism in dopamine β-hydroxylase (*DBH*) (C-1021T, rs1611115), which reduces DβH's conversion of dopamine to NE. We hypothesize that doxazosin would be more effective in CUD patients who have these genetically lower DβH levels.

Methods—This 12-week, double-blind, randomized, placebo-controlled trial included 76 CUD patients: 49 with higher DβH levels from the *DBH* CC genotype, and 27 with lower DβH levels from T-allele carriers (CT or TT). Patients were randomized to doxazosin (8 mg/day, N=47) or placebo (N=29), and followed with thrice weekly urine toxicology and once weekly cognitive behavioral psychotherapy.

Results—Cocaine use was reduced at a higher rate among patients in the doxazosin than in the placebo arm. We found significantly lower cocaine use rates among patients carrying the T-allele (CT/TT) than the CC genotype. The percentage of cocaine positive urines was reduced by 41% from baseline in the CT/TT group with low DβH and NE levels, as compared to no net reduction in the CC genotype group with normal DβH and NE levels.

Conclusions—The *DBH* polymorphism appears play an important role in CUD patients' response to doxazosin treatment, supporting a pharmacogenetic association and potential application for personalized medicine.

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The authors declare no conflict of interest.

Authors Contribution

Xuefeng Zhang, David Nielsen, Daryl Shorter, Coreen Domingo, and Thomas Kosten were responsible for the study concept and design. David Nielsen contributed to genotyping. David Nielsen and Ellen Nielsen contributed to the data analysis. Daryl Shorter and Coreen Domingo contributed to the acquisition of clinical data. Xuefeng Zhang drafted the manuscript. David Nielsen, Coreen Domingo and Thomas Kosten provided critical revision of the manuscript. All authors critically reviewed content and approved final version for publication.

Introduction

Cocaine use disorder (CUD) remains a globally significant medical and public health concern with approximately 3.8% of the world's population classified with active abuse or dependence (UN World Drug Report, 2016). During 2014 the US had an estimated 1.5 million cocaine users aged 12 or older; about 0.6% of the population(Center for Behavioral Health Statistics and Quality (CBHSQ), 2015). Moreover, cocaine use accounted for one in three drug-related emergency department visits in 2011 per the latest report from the Drug Abuse Warning Network (CBHSQ, 2013). To date, there are no FDA-approved medications for CUD. Because of its strong genetic basis, research on genetic variation may be key to understanding CUD, thereby providing a potential means of preventing and treating this disease based on an individual's unique genetic fingerprint.

The catecholaminergic pathways are the primary brain systems to examine for genetic biomarkers because cocaine increases the levels of the catecholamine neurotransmitters by binding to their transporters and blocking their reuptake from the synapses in the CNS (Baik, 2013; Covey et al., 2014). While the dopamine-induced rewarding and reinforcing pathways in the mesolimbic system are associated with chronic effects such as cravings, tolerance and withdrawal after repeated use of cocaine (Mark et al., 2011; Volkow et al., 2011), norepinephrine (NE) is also critical to these cocaine-induced pharmacological and behavioral effects (Zhang et al., 2005; Havranek et al., 2015; Shorter et al., 2013; Shorter et al., 2016). Dopamine (DA) is converted to NE by the rate-limiting enzyme, dopamine β-hydroxylase (DBH) (Rush and Geffen, 1980). The *DBH* gene has a functional polymorphism (C-1021T, rs1611115) in the promoter region that accounts for up to 52% of overall variation in DβH enzyme levels. This variant in *DBH* regulation may alter the levels of DβH by as much as 100-fold (Cubells and Zabetian, 2004). The T-allele leads to low DβH enzyme levels (Cubells and Zabetian, 2004; Zabetian et al., 2001) and results in reduced amounts of DA being converted to NE. These low levels of NE can substantially affect NE-mediated adrenergic effects, such as cocaine-induced reward, craving, and withdrawal (Cubells and Zabetian, 2004; Kim et al., 2002). Patients having low DβH levels from this *DBH* gene polymorphism may be particularly sensitive to the blockade of post-synaptic α-adrenergic receptors because of their pre-existing low DβH enzyme levels and subsequent low baseline NE levels, as well as potentially highly sensitive NE receptors (Weinshenker et al., 2002). This downstream effect of abnormally sensitive NE receptors from low NE levels would compensate for such genetically low NE levels. According to ligand-receptor binding studies of adrenergic receptors, the maximum binding capacity of ligands may be modulated by multiple factors, but most importantly by ligand availability. The levels of NE are low with low DBH levels, and NE receptor numbers and sensitivities can be increased by low levels of NE ligands analogous to other signaling pathways involving G-protein-coupled receptors, just as they are up-regulated by antagonists or down-regulated by excessive agonist stimulation (Cotecchia, 2010; Nalepa, et al., 2013; Piascik et al., 2001).

In one of our previous studies investigating the use of disulfiram on CUD, we found that patients with the *DBH* gene (C-1021T, rs1611115), which leads to higher or normal levels of NE in contrast to the variant leading to 10-fold lower DBH levels, had a reduction in overall

cocaine use. We therefore focused on advancing this finding by using a medication that specifically targeted one of the many types of NE receptors rather than the non-specific reduction in NE caused by disulfiram. A simple pharmacogenetic extension of the findings with disulfiram was not obvious. Instead, as suggested above, those participants with lower NE levels might be more responsive to reduction in a specific type of adrenergic activity such as post-synaptic α1-adrenergic blockade rather than broad pre-synaptic reduction in NE neurotransmission, which would reduce activity in all types of adrenergic receptors. The *DBH* T-allele carrier patients then may have a pharmacogenetic effect from direct inhibition of these α1-adrenergic receptors by selective blockers such as doxazosin. In this study, examining this hypothesis, we propose that the efficacy of doxazosin for treatment of CUD is related to a specific polymorphism of the *DBH* gene (C-1021T) leading to low DβH enzyme levels and relatively low NE levels and potentially more sensitive α_1 adrenergic receptors.

Preliminary studies have shown promise for treating CUD with doxazosin, a specific α_1-adrenergic antagonist and an FDA-approved medication for hypertension and benign prostate hypertrophy (Haile et al., 2012; Newton et al., 2012; Shorter et al., 2013). A moderate, but rapidly up-titrated dose of doxazosin reduced cocaine use in CUD patients presumably by modulating NE-mediated adrenergic effects and/or altering the balance of dopamine and NE (Shorter et al., 2013). The potential efficacy of doxazosin-induced reduction of cocaine use warranted further investigation of its mechanism, and prompted a double-blinded, randomized, placebo-controlled clinical trial to study how the *DBH* polymorphism might affect the treatment outcome of doxazosin in CUD patients.

Material and Methods

Participants

Seventy-six patients diagnosed with cocaine dependence (DSM-IV criteria, equivalent to CUD in DSM-5) were enrolled in this 12-week pharmacogenetic study (double-blinded, randomized, and placebo-controlled). CUD, instead of cocaine dependence, has been used throughout this paper for scientific consistency based on DSM-5 diagnostic criteria. All participants met DSM-IV criteria for cocaine dependence following screening by a psychiatrist or clinical psychologist. Subject exclusions were a current diagnosis of other drug or alcohol dependence (other than tobacco), current major and/or unstable medical conditions that required medication management, a history of major psychiatric disorders (psychosis, schizophrenia, bipolar), current suicidality, and inability to provide written informed consent. Participants were advised not to drink alcohol or use alcohol-containing products during the study. Breath analysis for alcohol was performed if alcohol use was suspected. Women of childbearing age were included in this study; however, a negative urine pregnancy test and adequate contraception were required throughout the study. Prior to entering the study, all participants signed an informed consent document approved by the institutional review boards of Baylor College of Medicine.

Study Design and Medications

All participants were randomly assigned to placebo (n=29; 16 CC vs. 13 CT/TT) or doxazosin (n=47; 33 CC vs. 14 CT/TT) group. A single dose of doxazosin (8 mg/day) was used in the active medication arm based on the results of our previous study (Shorter et al., 2013), with titration up to 8mg occurring over a 2-week period. All participants who met the entry criteria underwent a standard physical examination, psychiatric evaluation, and laboratory assessment. Patients attended thrice-weekly clinic visits with urine toxicology screening at each visit for 12 weeks. Urines were tested for six categories of drugs: cocaine, amphetamine, methamphetamine, tetrahydrocannabinol, opiates, and benzodiazepines, using a one-step drug screen card (Acon DOA-754 5-Panel Card).

We assessed cocaine craving weekly throughout this trial using the Cocaine Selective Severity Assessment Visual Analog Scale (Kampman et al., 1998; Mulvaney et al., 1999). The scale ranges from 0 (no desire at all) to 7 (unable to resist) and assesses the frequency in the previous 24 hours from 0 (never) to 7 (all the time), assessing for 18 signs and symptoms of CUD with good reliability and validity. In addition, all participants received up to 30-minutes of once-weekly individual cognitive behavioral psychotherapy (CBT) emphasizing treatment retention and medication adherence. Regular clinic visits for dosing and completion of research tasks occurred on Monday, Wednesday, and Friday of each study week. Research staff administered the medication or placebo on these 3 days with self-administration on Tuesday, Thursday, and weekends. Weekly pill counts assessed self-medication compliance.

Genotyping

DNA was isolated from blood as described previously (Kosten et al., 2013). The *DBH* C-1021T variant was genotyped by a 5'-fluorogenic exonuclease assay using the TaqMan method and the ABI PRISM 7900 sequence detection system (ABI, Foster City, CA). The TaqMan® primer-probe sets for the *DBH* C-1021T variant was used (Kosten et al., 2013). The TaqMan assays were performed in duplicate and showed a concordance of 100%. The *DBH* genotype did not show significant evidence for deviation from Hardy-Weinberg Equilibrium ($\chi^2 = 0.686$, $p = 0.4074$).

Data Analysis

The demographics and characteristics of the participants enrolled in the four treatment groups were compared using chi-square and general linear model (one-way) analysis of variance (ANOVA). The proportion of cocaine$^+$ urine toxicology screens was calculated using the following formula: the number of cocaine$^+$ urines / the number of total urines over each 2-week block over the duration of the 12-week trial (a maximum of 6 samples per 2 weeks over six 2-week blocks during the 12-week trial). A repeated measures analysis of variance (ANOVA) for cocaine positive urines of week 3 through 12 was used while a baseline percentage of positive urines (weeks 1–2) for each treatment group served as a covariant (R version 2.9.1, R Development Core Team, 2009). We compared treatment (doxazosin vs. placebo), *DBH* genotypes (CC vs. CT/TT), and time-period (each 2-week period), and analyzed the interactions among these three factors. To present the data, we calculated the percentage of CUD$^+$ urines after subtraction of the baseline percentage of

positive urines during weeks 1–2 (the medication titration period). The real-time numbers of participants at the different time points are shown in Figures 1 and 2.

Urine toxicology was analyzed with consideration of the impact of missing urine results and missing urines were not counted as positive for cocaine. The “missing at random” urine toxicology samples resulted from having less than 6 samples as the denominator for some 2-week blocks that were used for analysis. We calculated the proportion of cocaine-free urines based on the number of available urines for those 2-week blocks that contained missing at random urines, as long as that block included at least 2 out of 6 urine samples. Missing urine results were not counted as cocaine positive. If a subject left the study before week 12, then that subject contributed no data to those 2-week blocks after dropout, since he/she contributed no urines to assess. Those weeks after dropout also were not considered as cocaine positive.

Population structure was determined by genotyping ten ancestry informative markers (AIMs) and comparing our study group against CEPH-HGDP samples (1,035 subjects from 51 populations), as previously described (Kosten et al., 2013; Nielsen et al., 2012). This approach can obtain 94.6% of the maximum informativity value (Lao et al., 2006). Sex was confirmed by genotyping SRY (Kosten et al., 2013). Population structure was run as a covariate in the statistical model. The effect size was calculated as a partial eta-squared statistic using condition or genotype group variance over residual variance. The three general cut-offs for effect size are the following: a large effect is 0.14, a medium effect is 0.06, and a small effect is 0.01 (Cohen, 1988).

Results

Baseline Characteristics by Treatment and *DBH* genetics

As shown in Table 1, the only significant difference among the four treatment by genetics groups was for the percentage of African Americans, who were over-represented in the CC genetic group (88% CC versus 53% CT/TT). We genetically adjusted all of our analyses for this difference, as described in the Methods section under population structure. All the other measures including substance use severity were equivalent. The days of cocaine use in the past month and the lifetime years of cocaine showed no difference among the groups. The Cocaine Selective Severity Assessment (CSSA) at screening showed no differences. Alcohol use also showed no differences during the month before study entry or for lifetime alcohol years.

Retention by Treatment Conditions and Genetics

Our treatment groups did not differ in study retention and had an acceptable rate of retention for our analyses out to week 12. Thus, weeks of treatment retention (Mean ± SE) were 9.7 ± 0.7 (placebo) and 10.4 ± 0.5 (doxazosin). Similarly, the four treatment by genotype groups did not differ in study retention and had an acceptable rate of retention for our analyses out to week 12. As such, weeks of treatment retention were 8.9 ± 1.2 (CT/TT group) vs 10.4 ± 0.7 (CC group) in the placebo group, and 9.2 ±1.1 (CT/TT group) vs 10.8 ± 0.5 (CC group) in the doxazosin group.

Treatment with Doxazosin Reduced Cocaine Use in CUD Patients

The treatment outcome (doxazosin versus placebo) in CUD patients regardless of their *DBH* genotypes is shown in Table 2. The percentage of urine$^+$ samples after baseline subtraction (week 1–2) is summarized in Figure 1. We found that the rate of cocaine$^+$ urines decreased in the doxazosin-treated patients compared to the placebo group (medication effect, F=9.40, df=1, 2392; p=0.002, η^2=0.004) (time by medication, F=8.96, df=1, 2392; p=0.003, η^2=0.004). Doxazosin treatment reduced the urine cocaine$^+$ rate by 15% as compared to its baseline level, and by 25% as compared with the placebo group. These results are consistent with our previous study (Shorter et al., 2013) and confirmed that doxazosin can significantly reduce cocaine use in CUD patients.

In addition, we examined the association of missing urine data with treatment type and genotype for any potential bias in the analyses. Since treatment retention did not differ among the four groups, we found no difference in the percentage of missing urine data after dropout, and overall this percentage missing of 17% was acceptable. Most importantly, the number of “missing at random” urines among the four groups formed by doxazosin versus placebo crossed with the two genotype groups (CC versus CT/TT) was quite small and did not differ among the groups: 7% (79/1075) doxazosin/CC, 7% (29/387) doxazosin/T-allele carrier, 10% (50/497) placebo/CC, and 9% (32/347) placebo/T-allele carrier. Thus, we did not introduce any bias to the analyses by counting missing urines as cocaine positive nor by having a disproportionate loss of our urine outcome measures among any one of the four groups.

Doxazosin Showed Greater Efficacy in the CT/TT genotype carriers with CUD

The differences in urine toxicology results among the four groups formed by *DBH* genotype groups crossed with treatment groups is summarized in Table 3. The percentage of cocaine$^+$ urines after baseline subtraction (week 1–2) is shown in Figure 2. Doxazosin was found to reduce the positive urine cocaine rate with greater efficacy in the CT/TT group (medication effect, F=7.38, df=1, 518; p=0.007, η^2=0.014; time by medication, F=5.92, df=1, 518; p=0.015, η^2=0.011) than the CC group (time by medication, p>0.05). The percentage of cocaine positive urines was reduced by 40.7% from baseline in the CT/TT group, while the CC group showed no net reduction from baseline to end of study treatment period at week 12. Due to limited statistical power from the relatively small sample size in the four cells formed from a genotype by treatment categorization, we were only able to show a 3-way interaction on urine toxicology outcome (genotype × treatment × time) using one-tailed significance (p = 0.05).

Adverse Events

Adverse effects were closely monitored during each clinic visit through the study, especially blood pressure (both pre- and post-medication). As consistent with the previous studies (Newton et al., 2012; Shorter et al., 2013), the dose of doxazosin (8mg/day) employed in this trial showed no effects on participants’ blood pressure before or after medication. Only one distinct adverse event was reported during the study. The participant developed unspecified rashes/hives while on doxazosin during the first week of the study. The study medication was then discontinued immediately, and medical intervention was initiated. After a thorough

diagnostic workup, the skin rash was attributed to metronidazole treatment that fully resolved after its discontinuation. The participant was provided with alternative treatment for CUD and discontinued from the study. No serious adverse events occurred, and no other participants were discontinued from the study due to adverse events.

Discussion

The *DBH* gene polymorphism (C-1021T) has been reported to moderate treatment outcome with several medications in patients with various medical and psychiatric conditions including CUD (Fang et al., 2015; Kosten et al., 2013; Liu et al., 2014; Schottenfeld et al., 2014). Here, we report greater efficacy of doxazosin (8 mg/day) in reducing cocaine use in individuals with the *DBH* C-1021T CT or TT genotype (low DβH and NE levels) than those with the CC genotype. Our study demonstrates a key role of the *DBH* (C-1021T) polymorphism in CUD pharmacotherapy, and provides new insights into tailored and individualized pharmacotherapy for CUD patients based on their *DBH* genotype.

Both doxazosin and disulfiram act through reductions in NE activity (directly vs indirectly) in CUD. However, disulfiram, which inhibits DβH enzyme activity and subsequent NE production, exhibited a better treatment outcome in those patients with a CC genotype, who have higher levels of DβH and NE (Kosten et al., 2013). In contrast, doxazosin blocks the α_1-receptor-medicated adrenergic effects of NE, and this receptor specificity may lead to pharmacological effects through a different mechanism than a simple reduction in NE globally and a resultant reduction in the stimulation of all types of adrenergic receptors. Furthermore, disulfiram has many other actions besides reducing NE levels including changes in serotonin and inhibition of over 100 copper dependent enzymes (Gessner and Gessner. 1992). Doxazosin is likely to be inhibiting a greater density of adrenergic receptors and/or more highly sensitive receptors in those individuals who have genetically low DβH and NE activities compared to those with the normal *DBH* genotype, as we suggested in the Introduction. In further support of this hypothesis, rodent studies have indicated that modulation of dopamine and NE receptors may occur with these genetic variants in *DBH*. DBH-deficient rodents have increased dopamine D2 receptors (DRD2) with high affinity in the striatum (Skinbjerg et al., 2010) and increased expression of α_1-adrenergic receptors in the hippocampus. At the same time, these DβH-deficient rodents have a modest decrease in α_2-adrenergic receptor expression in the septum, the hippocampus, and the amygdala (Sanders et al., 2006). Therefore, the functional consequences of this *DBH* gene polymorphism on brain circuitry merit investigation in humans with CUD and support our hypothesized mechanism for the pharmacogenetic specificity of doxazosin for the individuals with genetically lower DβH levels. Mechanisms that are more complicated also may be involved in the *DBH* gene polymorphism moderation of doxazosin-induced reduction of cocaine use (Haile et al., 2012; Shorter et al., 2013). For example, a recent study indicated profound effects of *DBH* variants on DβH expression in two sympathetically innervated organs, the lungs and liver, although not specifically in the brain (Barrie et al., 2014). This difference among organ systems is relevant to CUD pathology because smoking and snorting cocaine, two common routes of cocaine administration among CUD patients, stimulate both the peripheral and central nervous system during cocaine-induced reward and associated craving. The lung differences in DβH expression may contribute some portion of

our demonstrated pharmacogenetic effect on treatment with doxazosin in CUD, a multi-system disorder.

Recent studies have linked baseline blood pressure and treatment outcome using α_1-antagonist agents such as doxazosin. Higher blood pressure has been correlated with a better treatment outcome using prazosin in posttraumatic stress disorder (PTSD) (Raskind et al., 2016). Haass-Koffler et al. have reported that higher pretreatment blood pressure is associated with greater alcohol drinking reduction after treatment with doxazosin (Haass-Koffler et al., 2017). Those findings support the role of the norepinephrine/adrenergic receptor pathway in the pathogenesis of anxiety and associated symptoms, which are shared among PTSD, AUD and CUD. Since the pathogeneses of these disorders are quite different, further studies are warranted to investigate if higher baseline blood pressure may be a predictor for doxazosin-induced reduction of cocaine use. Sympathetic instability is seen in patients with DβH deficiency. Our study was not able to show baseline blood pressure variations by the *DBH* gene polymorphism, or whether higher pretreatment blood pressure may be an indicator of better treatment outcome for doxazosin in CUD. This may reflect the highly unstable blood pressures of patients who repeatedly use cocaine including at the time of outpatient assessments.

Our study findings are limited by some methodological issues. (1) We had a relatively small sample size with more participants from the African ancestral group with the CC genotype. DβH deficiency was reported initially only in Western Europeans (Robertson et al., 2003) and racial differences in plasma DβH activities have been observed (O'Connor et al., 1983; Zabetian et al., 2001 and 2003; Chen et al., 2010). Although the plasma DβH activities have been higher in Caucasian than African patients, the direction of genotype–plasma DβH activity associations at rs1611115 was identical in both populations according to a recent study (Tang et al., 2007). In our trial, less African Americans were found with the CT/TT genotypes. Therefore, our statistical analyses were adjusted for population structure. (2) Only a few participants were alcohol-using and none had alcohol use disorder (AUD), which may be atypical for community cocaine users who can have substantial alcohol abuse with AUD. These low rates of alcohol use were due to our screening procedures, which eliminated any severe alcohol use or AUD. (3) Incomplete retention of patients led to missing data in the analyses, but retention was equivalent across the four treatment by genetics groups, which minimized potential bias. (4) Our postulated neurobiological links of the *DBH* genetic variant to the pharmacogenetic response with doxazosin treatment also are limited by not considering other *DBH* genetic variants involved in DβH enzyme activity (Mustapic et al., 2014), but this *DBH* variant is both common and functionally significant. (5) We neglected the multiple neurotransmitters (i.e. dopamine, serotonin, γ-aminobutyric acid, norepinephrine, and glutamate) and associated pathways involved in CUD (Schmidt and Pierce, 2010; Shorter et al., 2015; Wolf, 2010). However, our treatment agent doxazosin is relatively specific in comparison to our previous studies using disulfiram with its multiple neurotransmitter actions. Future brain circuitry studies involving this DBH genetic polymorphism may be very helpful in clarifying these neurobiological links and mechanisms that we have hypothesized for the interaction of doxazosin with the functional genetic changes induced by *DBH*.

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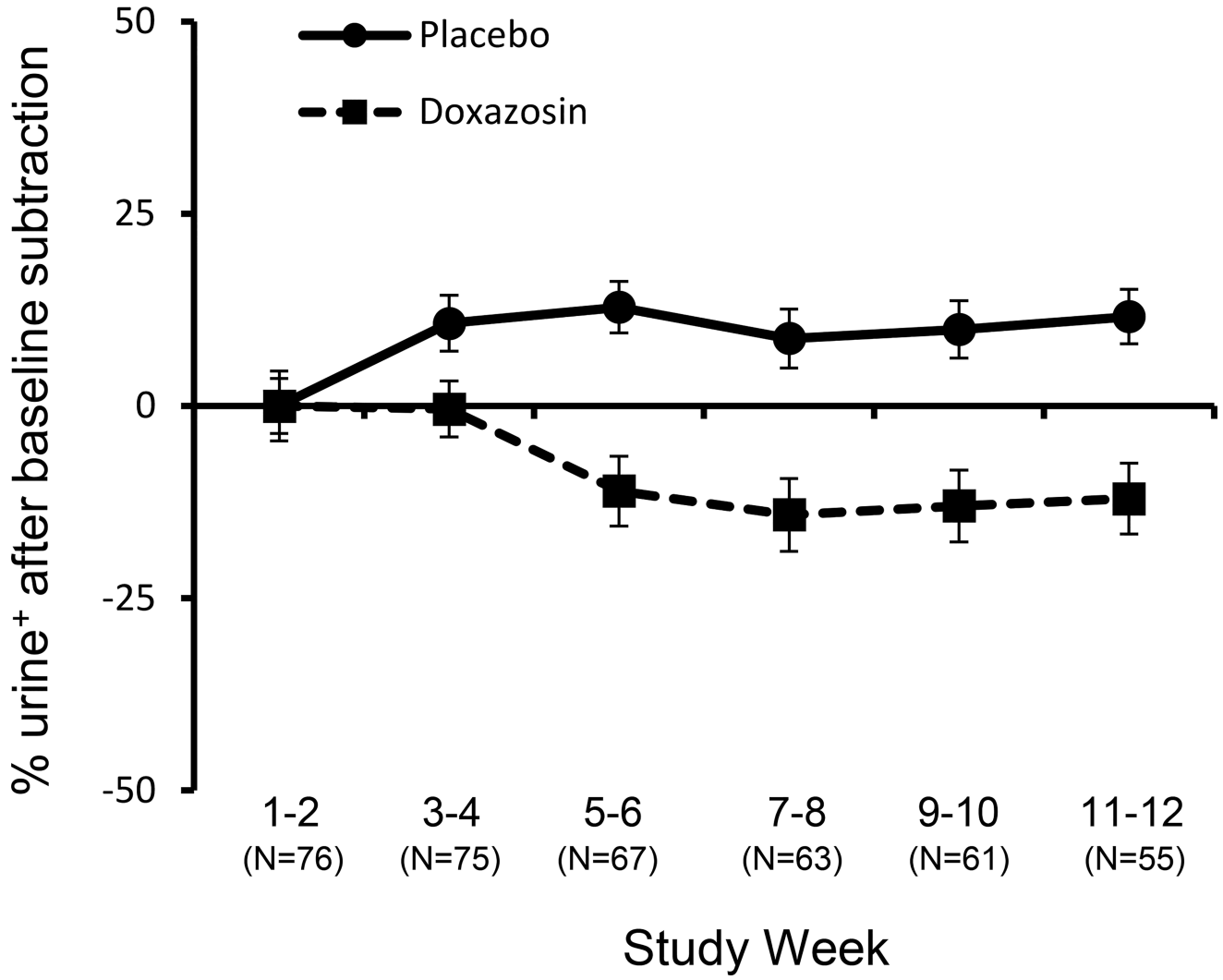

Figure 1.

Percentage of cocaine$^+$ urine toxicology screens for 2-week periods across the 12-week trial for the placebo (solid line) vs doxazosin (8mg/day, dashed line) treatment groups. Percentages of cocaine$^+$ urines after baseline subtraction (week 1–2) are shown as mean ± SE. The percentage urine$^+$ after baseline subtraction was calculated using the formula: % of urine$^+$ after baseline subtraction = % of urine$^+$ at each time points – % of urine$^+$ at the week1–2. The numbers of participants (N) at the indicated time points are shown.

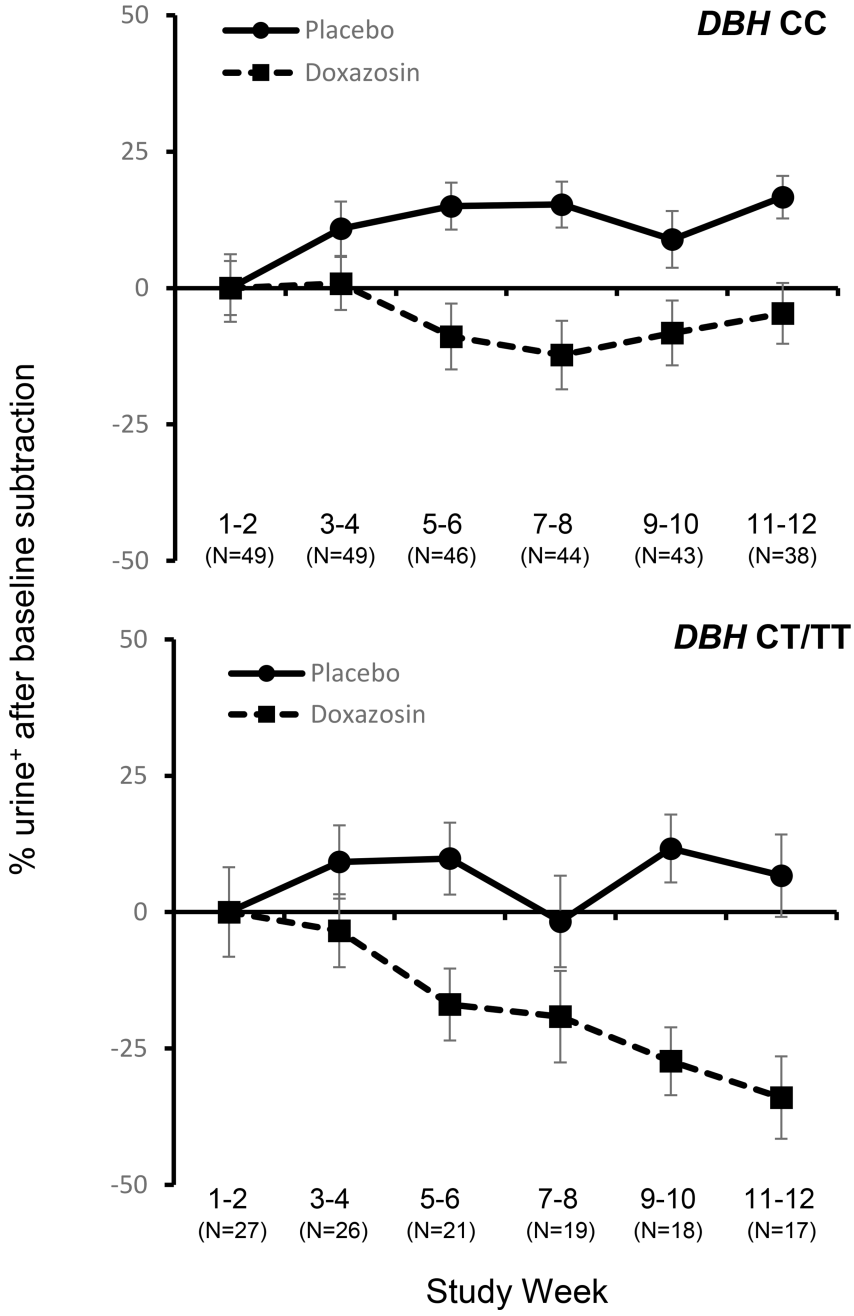

Figure 2.

Percentage of cocaine^{+} urine toxicology screens for 2-week periods across the 12-week trial for the placebo vs. doxazosin (8mg/day) treatment groups by the CC genotype and the CT/TT genotype. Percentages of cocaine^{+} urines after baseline subtraction (week 1–2) are presented as mean ± SE. The percentage urine^{+} after baseline subtraction was calculated using the same formula described in Figure 1. The numbers of participants (N) at the indicated time points are shown.

Table 1

Demographic and Clinical Characteristics by Treatment and *DBH* Genotype

Characteristics (Mean ± SD)	Placebo		Doxazosin		Significance
	CC (N=16)	CT/TT (N=13)	CC (N=33)	CT/TT (N=14)	
% Male	75	83.3	67	74	X^2=6.8, df=3, *P*=0.077
% African American	88.2	50.0	87.5	57	X^2=58.7, df=3, *P*<0.001
Age (years)	47.9 ± 7.8	48.5 ± 8.4	48 ± 9.0	48.1 ± 7.5	F=0.014, *P*=0.998
Education (years)	12.6 ± 1.5	13.1 ± 2.7	12.6 ± 1.1	13.2 ± 2.9	F=0.479, *P*=0.698
Cocaine (last 30 days)	11.8 ± 8.8	15.5 ± 9.7	12.8 ± 8.3	12.4 ± 7.3	F= 0.512, *P*=0.675
Cocaine years	17.1 ±11.5	15.6 ± 9.6	18.5 ±10.2	19.0 ± 8.0	F=0.354, *P*=0.786
Alcohol (last 30 days)	5.5 ± 9.0	7.1 ± 7.6	7.8 ± 8.1	7.9 ± 8.9	F=0.31, *P*=0.818
Alcohol years	14.5 ± 14.9	22.8 ± 14.7	17.9 ± 12.6	17.8 ±12.4	F=0.916, *P*=0.437

Table 2

Percentage of cocaine^{+} urine toxicology (Mean± SE)

Study Week	Placebo	Doxazosin
Week 1–2	75.8 ± 4.7	86.9 ± 3.6
Week 3–4	86.5 ± 3.6	86.5 ± 3.6
Week 5–6	88.6 ± 3.4	75.9 ± 4.6
Week 7–8	84.5 ± 3.9	72.8 ± 4.7
Week 9–10	85.7 ± 3.7	73.9 ± 4.7
Week 11–12	87.4 ± 3.5	74.9 ± 4.6

Table 3

Percentage of cocaine^{+} urine toxicology (Mean ± SE)

Study week	CC		CT/TT	
	Placebo	Doxazosin	Placebo	Doxazosin
Week 1–2	75.0 ± 6.2	86.0 ± 5.0	76.7 ± 8.2	89.3 ± 6.0
Week 3–4	85.9 ± 5.0	86.8 ± 4.9	85.9 ± 6.7	85.9 ± 6.7
Week 5–6	90.0 ± 4.3	77.1 ± 6.0	86.5 ± 6.6	72.4 ± 8.7
Week 7–8	90.3 ± 4.3	73.7 ± 6.3	75.0 ± 8.4	70.2 ± 8.9
Week 9–10	83.9 ± 5.3	77.7 ± 6.0	88.4 ± 6.2	62.0 ± 9.4
Week 11–12	91.7 ± 4.0	81.3 ± 5.6	81.4 ± 7.6	55.3 ± 9.7