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The Alpha-1 Adrenergic Antagonist Doxazosin for Treatment of Cocaine Dependence: A Pilot Study

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Abstract

Background—Medications decreasing central noradrenergic activity have been associated with attenuation of cocaine effects.

Aims—This pilot study examined the efficacy of doxazosin versus placebo for reducing cocaine use in treatment-seeking cocaine dependent persons.

Methods—We screened 108 cocaine dependent subjects and assigned 35 participants to receive either doxazosin (8mg/day) or placebo for 13 weeks. Participants were titrated on the study medication according to two different schedules. During the initial phase of the study, patients were titrated onto the study medication over an 8-week period (DOX-slow). After reviewing data from our human laboratory study, a second phase was initiated, wherein titration was accelerated to a 4-week period (DOX-fast). All participants received weekly cognitive behavioral therapy. Urine toxicology was performed thrice weekly.

Results—Baseline subject characteristics were comparable. Thirty subjects entered the study: 8 subjects in DOX-slow, 9 subjects in DOX-fast, and 13 subjects in placebo. Total number of cocaine-negative urines was significantly increased in the DOX-fast group; and percentage of total cocaine-negative urines by group were 10% for DOX-slow group, 35% for DOX-fast group, and 14% for placebo (chi-square=36.3, df=2, $p<0.0001$). The percentage of participants achieving two or more consecutive weeks of abstinence by group was 0% for DOX-slow group, 44% for DOX-fast group, and 7% for placebo (chi-square=7.35, df=2, $p<0.023$).

Conclusions—This pilot study suggests the potential efficacy of doxazosin when rapidly titrated in reducing cocaine use.

Keywords

Adrenergic; doxazosin; cocaine; dependence; treatment

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1. INTRODUCTION

Cocaine use disorders are a significant cause of morbidity and mortality throughout the world. Estimates from the 2010 National Survey on Drug Use and Health (NSDUH) indicate that 1.5 million Americans aged 12 years or older are current (i.e., “past month”) users of cocaine, and 1.0 million Americans meet criteria for past year abuse or dependence (Substance Abuse and Mental Health Services Administration (SAMHSA), 2011a). Further, according to the annual report of the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), an estimated 4 million Europeans aged 15 to 64 years have used cocaine in the past year (EMCDDA, 2010). Cocaine use is associated with numerous acute and chronic medical and psychiatric complications (Devlin and Henry, 2008). Additionally, cocaine use is associated with increased utilization of emergency department (ED) services, as reports from the Drug Abuse Warning Network (DAWN) indicate that cocaine was involved in over 420,000 ED visits, or almost half (43.4%) of visits involving illicit drugs in 2009 (SAMHSA, 2011b).

Cocaine binds and blocks the activity of the dopamine transporter (DAT), norepinephrine transporter (NET), and serotonin transporter (SERT), causing reuptake inhibition and subsequent increase in synaptic levels of these catecholamines (Rothman and Baumann, 2003). The rewarding effects of cocaine are attributed primarily to the resulting activation of dopaminergic neurons, initiated through its activity at the mesolimbic DAT (Koob, 2000). However, it is important to note that DAT knockout mice continue to self-administer cocaine, suggesting that blockage of DAT alone cannot account for the rewarding/reinforcing effects of cocaine and that other neurotransmitter systems must play a contributing role (Carboni et al., 2001).

Both preclinical and clinical trials indicate that activity within the noradrenergic system contributes significantly to the biochemical effects of cocaine. Functionally, the noradrenergic system is coupled to that of dopamine (DA), and it has been demonstrated that stimulation of alpha-1 receptors (1) on DA neurons in the ventral tegmental area (VTA) and (2) in prefrontal cortex (PFC) results in increased firing of VTA dopaminergic neurons (Paladini and Williams, 2004; Blanc et al., 1994). Conversely, antagonism in the noradrenergic system results in decreased activity in the dopaminergic system, evidenced by the effect of prazosin, an alpha-1 adrenergic antagonist, which demonstrated the ability to decrease burst activity of VTA dopaminergic neurons (Grenhoff et al., 1993).

Cocaine’s activity at NET, which serves to increase synaptic levels of norepinephrine (NE) in both PFC and on DA neurons through the process of feedback in the above described circuit, further enhances the activation of the dopaminergic system (Sofuoglu and Sewell, 2008). This effect has been mimicked with systemic administration of reboxetine, a specific inhibitor of NET, which demonstrated the ability to increase burst firing of VTA dopaminergic neurons (Linner et al., 2001). Antagonism of the noradrenergic system has been shown to limit the behavioral effects of psychostimulants, such as d-amphetamine (D-AMPH) or cocaine. Prazosin injected into mPFC completely blocks locomotor hyperactivity induced by intra-accumbens injections of D-AMPH (Blanc et al., 1994). Darracq et al. (1998) demonstrated through microdialysis studies in rats the locomotor activating effects of D-AMPH are caused by stimulation of cortical alpha-1 adrenergic receptors. Prazosin, when administered either locally or systemically, has demonstrated the ability to inhibit D-AMPH induced dopamine release and locomotor activity in mice (Blanc et al., 1994; Darracq et al., 1998; Drouin et al., 2002; Wellman et al., 2002). Additionally, knockout mice lacking alpha-1B NE receptors demonstrate significantly decreased locomotor activity and behavioral sensitization in response to D-AMPH, morphine, and cocaine (Drouin et al., 2002).

Pharmacologic antagonism of the noradrenergic system and its subsequent impact on cocaine use has been the subject of preclinical study by our group. Prazosin attenuates cocaine-induced reinstatement of extinguished drug-seeking behavior in rats (Zhang and Kosten, 2005). Further, prazosin, when co-administered with cocaine pre-treatment, attenuated subsequent self-administration of cocaine under a fixed ratio (FR) schedule and blocked the effect entirely under a progressive ratio (PR) schedule (Zhang and Kosten, 2007). These results further suggest the contribution of the noradrenergic system to the neurochemical and behavioral effects as well as the implications of decreasing alpha noradrenergic stimulation for treatment of cocaine dependence.

This pilot study evaluated the safety and efficacy of doxazosin, a long acting and selective alpha-1 adrenergic antagonist, in reducing cocaine use among cocaine-dependent individuals. We selected doxazosin because of its extended half-life ($t_{1/2}$ up to 22 hours), which is not influenced by age, renal function, or dose, and which is also significantly longer than that of prazosin ($t_{1/2} = 2\text{--}3$ hours; Jaillon, 1980; Rubin et. al., 1981). We hypothesized that doxazosin treatment, in comparison to placebo, would decrease cocaine use behavior as measured by cocaine urine toxicology.

2. METHODS

2.1 Participants

One hundred eight individuals seeking treatment for cocaine dependence were recruited from the greater Houston area and attended clinic at the Outpatient Clinical Trials Research group at the Michael E. DeBakey Veterans Affairs Medical Center (MEDVAMC). At the time of screening, subjects underwent a full physical examination, psychiatric evaluation, and assessment of laboratory values. Subsequently, each participant met the following inclusion criteria: (a) male or female, (b) aged 18–64 years, (c) any race or ethnic origin, (d) current use of cocaine with self-reported use of cocaine at least once weekly for at least one month preceding study entry, toxicology confirmation of cocaine-positive urine, and a score of three (3) or greater on the Severity of Dependence Scale (SDS; Kaye and Darke 2002; Gossop et al., 1995, 1997), (e) diagnosis of cocaine dependence, as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR; American Psychiatric Association, 2000). Exclusion criteria included current diagnosis of alcohol or other drug abuse or dependence (other than nicotine); significant medical conditions (i.e., major cardiovascular, renal, endocrine, or hepatic disorders), such as abnormal liver function (with laboratory findings of SGOT or SGPT greater than three times normal), hypotension or hypertension, a current cardiac condition, or seizure disorder; lifetime diagnosis of schizophrenia, bipolar disorder, or other psychotic disorders; active suicidality or homicidality; current prescription for psychotropic medication; and pregnancy or breastfeeding.

Each participant gave written informed consent, as approved by the Baylor College of Medicine and Michael E. DeBakey Institutional Review Boards (IRB).

2.2 Design and Procedures

The study was a 17-week, double-blind, placebo-controlled trial in which cocaine dependent individuals were randomly assigned to receive doxazosin (8mg/day) or placebo. Initially, we began this pilot clinical trial by using the dose titration recommended by the Physicians' Desk Reference (PDR), which suggests starting doxazosin at 1mg/day and increasing by 1mg each week to a maximum daily dose of 8mg (PDR, 2012). After analyzing data from our human laboratory study, it became evident that doxazosin could be safely increased at a more rapid rate (Newton et. al., 2012). As a result, the dose escalation schedule was changed so that induction onto the medication would occur at a rate of increase of 2mg/week,

allowing the optimum dose of 8mg/day to be reached after four weeks. Participants reaching the target dose after an 8-week titration period are labeled as the DOX-slow group, while those reaching the target dose after a 4-week period are labeled as the DOX-fast group. Participants were stabilized on doxazosin or placebo over weeks 4–13 (for DOX-fast group) or 8–13 (for DOX-slow group) and then tapered off doxazosin or placebo over study weeks 14–17.

All participants were asked to attend clinic visits for dosing and completion of research tasks on Monday, Wednesday, and Friday of each week of the study. Research staff administered the study medication or placebo on these days (MWF), and participants were given take-home doses of the medication or placebo to self-administer on Tuesday, Thursday, and weekends. Additionally, all participants were required to participate in one hour of weekly, individual, manual-guided cognitive behavioral therapy (Carroll et. al., 1998) to facilitate treatment retention and medication adherence as well as delivering enhanced treatment to all participants, regardless of medication arm.

2.3 Assessments

Participants were assessed during screening, at baseline, weekly during treatment, and at the end of study (week 17). At intake, each participant was interviewed using the Mini International Neuropsychiatric Interview (MINI; Sheehan et. al., 1998) and completed the Addiction Severity Index (ASI-Lite; McLellan et. al., 1985). During both intake and at baseline, participants completed the (a) SDS, (b) Cocaine Selective Severity Assessment (CSSA; Kampman et. al., 1998; Mulvaney et. al., 1999), (c) cocaine craving visual analog scale (Kampman et. al., 1998; Mulvaney et. al., 1999), (d) Beck Depression Inventory (BDI), and (e) Hamilton Anxiety Scale (HAM-A).

The *a priori* primary outcome was reduction in percentage of cocaine positive urines as measured by thrice-weekly cocaine urine toxicology results. Samples were obtained Mondays, Wednesdays, and Fridays and tested for the presence of the cocaine metabolite, benzoylecgonine, as well as other drugs (e.g., opiates, benzodiazepines, barbiturates). Following collection, urine samples were immediately tested on site using an Acon DOA-754 5-Panel One Step Drug Screen Test card (coc/amp/thc/opi/benz). Secondary outcome measures included percentage of participants achieving two weeks of abstinence, retention (weeks in treatment), and adverse effects from medication.

2.4 Data Analyses

Subject demographics and baseline characteristics of participants assigned to the three conditions were compared using chi-square and general linear model (one-way) analysis of variance (ANOVA) for ASI-Lite parameters. Urine toxicologic screening results for cocaine-positive urines collected over the total course of the trial were analyzed using chi-square and repeated measure ANOVA statistical tests with the Least Squares Difference for post hoc two group comparisons. The percentage of cocaine-positive urines per two week period served as the analyzed variable. Urine toxicology was analyzed with consideration of the impact of missing urine results, which were counted as cocaine positive. Comparisons between groups were performed using chi-square statistical analysis. Treatment retention was examined across all treatment groups by performing one-way ANOVA that compared the total number of weeks each participant stayed in study.

3. RESULTS

3.1 Baseline Characteristics

Baseline subject characteristics were comparable across groups, except in regards to race, since participants were predominantly African-American (see Table 1). Thirty-five subjects were randomized into the study, with thirty subjects returning and receiving at least one dose of medication (see Figure 1). By the conclusion of the study, there were eight subjects in the DOX-slow group, nine subjects in the DOX-fast group, and thirteen subjects in the placebo group.

3.2 Retention

The retention in the study across groups was 6/8 (75%) from the DOX-slow group, 6/9 (67%) from the DOX-fast group, and 5/13 (38%) from the placebo group completing the trial. However, the mean weeks in treatment (DOX-slow = 10.8; DOX-fast = 9.8; placebo = 6.8) did not significantly differ across groups ($F=1.7$; $df=2, 29$; $p = 0.207$).

3.3 Cocaine Use

The percentage of cocaine-positive urines per two-week period was significantly reduced in the DOX-fast group (shown in Figure 1). The repeated measures ANOVA showed a statistically significant difference between the three groups in terms of cocaine positive urines by two-week interval ($F = 2.328$, $df=2, 12$, $p = 0.009$). Post hoc comparisons between groups showed statistically significant differences in cocaine positive urines (by 2-week interval) between the DOX-fast group and both DOX-slow group ($p = 0.0024$) and placebo ($p = 0.001$), respectively. Because greater than 50% of subjects in the placebo group dropped out from the study by week four, no additional two-way comparisons were calculated, as only the retention for the DOX-slow and DOX-fast groups were comparable.

The total number of cocaine-negative urines was significantly increased in the DOX-fast group to 92 (35%) versus 27 (10%) in the DOX-slow group and 37 (14%) in the placebo group (chi-square = 36.3, $df=2$, $p < 0.0001$). There was no statistically significant difference in the number of missing urine specimens across groups. In the DOX-slow group, the number of missing urines was 44 (17%); in the DOX-fast group, there were 48 (18%); and in the placebo group, 37 (14%) (chi-square = 1.21, $df=2$, $p = 0.545$). The percentage of participants achieving two or more consecutive weeks of abstinence by group was 0/8 (0%) for the DOX-slow group, 4/9 (44%) for the DOX-fast group, and 1/13 (7%) for placebo (chi-square = 7.35, $df=2$, $p = 0.025$). Two or more weeks of abstinence was defined as six or more consecutive cocaine-negative urines, without any missing urine specimens in that period.

3.4 Adverse Events

Over the course of the study, a total of 58 distinct adverse events (AE) were reported, with 26 (45%) reported in the DOX-slow group, and 9 (16%) reported in the DOX-fast group, and with 23 (40%) reported in the placebo group. Among the AEs reported, headache was the most frequently reported AE (total 7/58, 12%), with 2/26 (7.7%) in the DOX-slow group, 2/9 (22.2%) in the DOX-fast group, and 3/23 (13%) in the placebo group. Other AEs included dry mouth (DOX-slow = 3/26 (11.5%); DOX-fast = 1/9 (11.1%); placebo = 2/23 (8.7%)); tiredness (DOX-slow = 1/26 (3.8%); DOX-fast = 2/9 (22.2%); placebo = 1/23 (4.3%)); and nausea/vomiting (DOX-slow = 1/26 (3.8%); DOX-fast = 0/9 (0%); placebo = 1/23 (4.3%)). There were no reported serious adverse events (SAEs) and no participants were discontinued from the study due to adverse events.

4. DISCUSSION

We found that doxazosin, when rapidly titrated, significantly reduced cocaine use and increased the percentage of participants achieving two or more consecutive weeks of abstinence. While we hypothesized that doxazosin would demonstrate an ability to reduce cocaine use, given the ability of the medication to offset the noradrenergic effects of cocaine, we did not expect the effect of slow titration of doxazosin to be similar to that of placebo. Our results suggest the medication effect is due, in part, to the rapid titration of doxazosin to the optimal dose (8mg), rather than to a longer period of time receiving the optimal dose (4 weeks versus 8 weeks).

The clinical practice of using rapid titration (i.e., “loading”) of medications to more quickly control symptoms, as it relates to psychiatric disorders such as bipolar disorder or schizophrenia, has been a subject of frequent study (Hirschfeld et. al., 2003). The rationale is to achieve higher serum levels of the medication within a shorter period of time, thus bringing about a robust treatment effect more quickly. This strategy has shown mixed results, however, since rapid titration can also be associated with early and/or higher incidence of adverse effects. It is important to note, then, that doxazosin was well tolerated, demonstrating a favorable safety profile that was comparable to placebo, even when rapidly titrated.

Our findings are consistent with previous clinical trials of noradrenergic medications for treatment of cocaine dependence. Disulfiram, a copper chelator, inhibits the activity of various enzymes, including aldehyde dehydrogenase and dopamine-beta-hydroxylase (DBH; Gaval-Cruz and Weinshenker, 2009; Barth and Malcolm, 2010). Inhibitory activity at the DBH enzyme, which converts dopamine to norepinephrine, leads to an increase in neuronal and synaptic dopamine and a decrease in brain norepinephrine levels (Bourdlat-Parks et. al., 2005). In human clinical trials, disulfiram has demonstrated an ability to modulate the reinforcing properties of cocaine and reduce cocaine use (Carroll et. al., 1998; McCance-Katz et. al., 1998; Petrakis et. al., 2000). Recently, Oliveto et al. found that disulfiram 250mg/day significantly decreased the number of cocaine-positive urines in methadone-maintained, cocaine dependent persons (Oliveto et. al., 2011). Reduction in noradrenergic activity is thought to underlie the attenuation of cocaine use observed in these disulfiram studies (Schroeder et. al., 2010).

Carvedilol, a mixed alpha-1 and beta-adrenergic receptor blocker, demonstrated an ability to decrease cocaine self-administration among crack cocaine smoking humans when administered at low doses (25mg), although it did not attenuate subjective effects (Sofuoglu et. al., 2000). Doxazosin, in contrast to the mixed alpha-1 and beta-adrenergic activity of carvedilol, is specific for the alpha-1 NE system, allowing for direct action at this receptor. Additionally, as mentioned previously, the co-administration of cocaine and prazosin results in attenuation of cocaine-induced reinstatement, as seen in animal models previously studied by our group (Zhang and Kosten, 2005, 2007). It is likely that the shared ability of these medications to antagonize the alpha-1 adrenergic receptor confers the observed therapeutic effects.

There are several limitations of this study. First, the original design of the study was such that participants were initially randomized into one of two conditions (placebo versus slow titration). After the observation that rapid titration of the study medication was safe, a change to the protocol was made and the third condition (DOX-fast) was created. This did not allow for early participants of the study to be randomized to the rapid titration condition. Second, the placebo group had fewer treatment completers, which limited the ANOVA comparison to placebo. Additionally, the lower retention in the placebo group might reduce

our ability to draw conclusions as to the underlying cause for missing data (i.e., relapse versus retention effect). However, the simple comparisons on percentage of cocaine-free urines and abstinence rates both confirmed that the doxazosin had a better outcome than placebo. Third, the small sample size resulted in a limitation to simple data analysis and makes it difficult to generalize these results to larger populations. In conclusion, the present study demonstrates the safety and efficacy of doxazosin as pharmacotherapy for treatment of cocaine dependence. Additional studies are needed, and currently, a larger, randomized, placebo-controlled trial of rapidly titrated doxazosin for treatment of cocaine dependence is underway.

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References

- American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4. APA; Washington, DC: 2000. text rev
- Barth KS, Malcolm RJ. Disulfiram: an old therapeutic with new applications. *CNS Neurol Disord Drug Targets*. 2010; 9:5–12. [PubMed: 20201810]
- Blanc G, Trovero F, Vezina P, Herve D, Godeheu AM, Glowinski J, Tassin JP. Blockade of prefronto-cortical alpha 1-adrenergic receptors prevents locomotor hyperactivity induced by subcortical D-amphetamine injection. *Eur J Neurosci*. 1994; 6:293–298. [PubMed: 7912614]
- Bourdelat-Parks BN, Anderson GM, Donaldson ZR, Weiss JM, Bonsall RW, Emery MS, Liles LC, Weinshenker D. Effects of dopamine beta-hydroxylase genotype and disulfiram inhibition on catecholamine homeostasis in mice. *Psychopharmacol (Berl)*. 2005; 183:72–80.
- Carboni E, Spieleswoy C, Vacca D, Nosten-Bertrand M, Giros B, DiChiara G. Cocaine and amphetamine increase extracellular dopamine in the nucleus accumbens of mice lacking the dopamine transporter gene. *J Neurosci*. 2001; 21:141–144.
- Carroll KM, Nich C, Ball SA, McCance E, Rounsaville BJ. Treatment of cocaine and alcohol dependence with psychotherapy and disulfiram. *Addiction*. 1998; 93:713–727. [PubMed: 9692270]
- Darracq L, Blanc G, Glowinski J, Tassin JP. Importance of the noradrenaline-dopamine coupling in the locomotor activating effects of d-amphetamine. *J Neurosci*. 1998; 18:2729–2739. [PubMed: 9502830]
- Devlin RJ, Henry JA. Major consequences of illicit drug consumption. *Critical Care*. 2008; 12:202. [PubMed: 18279535]
- Drouin C, Darracq L, Trovero F, Blanc G, Glowinski J, Cotecchia S, Tassin JP. Alpha-1b-adrenergic receptors control locomotor and rewarding effects of psychostimulants and opiates. *J Neurosci*. 2002; 22:2873–2884. [PubMed: 11923452]
- European Monitoring Centre for Drugs and Drug Addiction. Annual Report 2010: The State of the Drugs Problem in Europe. Lisbon: 2010.
- Gaval-Cruz M, Weinshenker D. Mechanisms of disulfiram-induced cocaine abstinence: antabuse and cocaine relapse. *Mol Interv*. 2009; 9:175–187. [PubMed: 19720750]
- Gawin FH, Kleber HD. Cocaine abuse treatment: open pilot trial with desipramine and lithium carbonate. *Arch Gen Psychiatry*. 1984; 41:903–909. [PubMed: 6431939]
- Gossop M, Darke S, Griffiths P, Hando J, Powis B, Hall W, Strang J. The Severity of Dependence Scale (SDS): psychometric properties of the SDS in English and Australian samples of heroin, cocaine and amphetamine users. *Addiction*. 1995; 90:607–614. [PubMed: 7795497]
- Gossop M, Best D, Marsden J, Strang J. Test-retest reliability of the Severity of Dependence Scale. *Addiction*. 1997; 92:353. [PubMed: 9219397]

- Grenhoff J, Nisell M, Ferre S, Aston-Jones G, Svensson TH. Noradrenergic modulation of midbrain dopamine cell firing elicited by stimulation of the locus coeruleus in the rat. *J Neural Transm Gen Sect.* 1993; 93:11–25. [PubMed: 8373553]
- Hirschfeld RM, Baker JD, Wozniak P, Tracy K, Sommerville KW. The safety and early efficacy of oral-loaded divalproex versus standard-titration divalproex, lithium, olanzapine, and placebo in the treatment of acute mania associated with bipolar disorder. *J Clin Psychiatry.* 2003; 64:841–846. [PubMed: 12934987]
- Jaillon P. Clinical pharmacokinetics of prazosin. *Clin Pharmacokinet.* 1980; 5:365–376. [PubMed: 6994981]
- Kampman KM, Volpicelli JR, McGinnis DE, Alterman AI, Weinrieb RM, D'Angelo L, Epperson LE. Reliability and validity of the Cocaine Selective Severity Assessment. *Addict Behav.* 1998; 23:449–461. [PubMed: 9698974]
- Kaye S, Darke S. Determining a diagnostic cut-off on the Severity of Dependence Scale (SDS) for cocaine dependence. *Addiction.* 2002; 97:727–731. [PubMed: 12084142]
- Koob GF. Neurobiology of addiction. Toward the development of new therapies. *Ann NY Acad Sci.* 2000; 909:170–185. [PubMed: 10911930]
- Linner L, Endersz H, Ohman D, Bengtsson F, Schalling M, Svensson TH. Reboxetine modulates the firing pattern of dopamine cells in the ventral tegmental area and selectively increases dopamine availability in the prefrontal cortex. *J Pharmacol Exp Therapeutics.* 2001; 297:540–546.
- McCance-Katz EF, Kosten TR, Jatlow P. Disulfiram effects on acute cocaine administration. *Drug Alcohol Depend.* 1998; 52:27–39. [PubMed: 9788003]
- McLellan AT, Luborsky L, Cacciola J, Griffith J, Evans F, Barr HL, et al. New data from the Addiction Severity Index. Reliability and validity in three centers. *J Nerv Ment Dis.* 1985; 173:412–423. [PubMed: 4009158]
- Mulvaney FD, Alterman AI, Boardman CR, Kampman K. Cocaine abstinence symptomatology and treatment attrition. *J Subst Abuse Treat.* 1999; 16:129–135. [PubMed: 10023610]
- Newton TF, de Garza RL 2nd, Brown G, Kosten TR, Mahoney JJ 3rd, Haile CN. Noradrenergic alpha-1 receptor antagonist treatment attenuates positive subjective effects of cocaine in humans: a randomized trial. *PLoS One.* 2012; 7:e30854. [PubMed: 22319592]
- Oliveto A, Poling J, Mancino MJ, Feldman Z, Cubells JF, Pruzinsky R, Gonsai K, Cargile C, Sofuoglu M, Chopra MP, Gonzalez-Haddad G, Carroll KM, Kosten TR. Randomized, double blind, placebo-controlled trial of disulfiram for the treatment of cocaine dependence in methadone-stabilized patients. *Drug Alcohol Depend.* 2011; 113:184–191. [PubMed: 20828943]
- Paladini CA, Williams JT. Noradrenergic inhibition of midbrain dopamine neurons. *J Neurosci.* 2004; 24:4568–4575. [PubMed: 15140928]
- Petrakis IL, Carroll KM, Nich C, Gordon LT, McCance-Katz EF, Frankforter T, Rounsaville BJ. Disulfiram treatment for cocaine dependence in methadone-maintained opioid addicts. *Addiction.* 2000; 95:219–228. [PubMed: 10723850]
- Physicians' Desk Reference. 66. Thomson PDR; Montvale, NJ: 2012.
- Rothman RB, Baumann MH. Monoamine transporters and psychostimulant drugs. *Eur J Pharmacol.* 2003; 479:23–40. [PubMed: 14612135]
- Rubin PC, Scott PJ, Reid JL. Prazosin disposition in young and elderly subjects. *Br J Clin Pharmacol.* 1981; 12:401–404. [PubMed: 7295470]
- Schroeder JF, Cooper DA, Schank JR, Lyle MA, Gaval-Cruz M, Ogbonmwan YE, Pozdeyev N, Freeman KG, Iuvone PM, Edwards GL, Holmes PV, Weinshenker D. Disulfiram attenuates drug-primed reinstatement of cocaine seeking via inhibition of dopamine beta-hydroxylase. *Neuropsychopharmacology.* 2010; 35:2440–2449. [PubMed: 20736996]
- Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry.* 1998; 59(Suppl):22–23. [PubMed: 9881538]
- 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; 60:69–76. [PubMed: 10821991]

- Sofuoglu M, Sewell RA. Norepinephrine and stimulant addiction. *Addict Biol.* 2008; 14:119–129. [PubMed: 18811678]
- Substance Abuse and Mental Health Services Administration. Results from the 2010 National Survey on Drug Use and Health: Summary of National Findings, NSDUH Series H-41, HHS Publication No (SMA). Rockville, MD: 2011a. p. 11-4658.
- Substance Abuse and Mental Health Services Administration. HHS Publication No (SMA). Rockville, MD: 2011b. Drug Abuse Warning Network, 2008: National Estimates of Drug-Related Emergency Department Visits; p. 11-4659.DAWN Series D-35
- Wellman P, Ho D, Cepeda-Benito A, Bellinger L, Nation J. Cocaine-induced hypophagia and hyperlocomotion in rats are attenuated by prazosin. *Eur J Pharmacol.* 2002; 455:117–126. [PubMed: 12445577]
- Zhang XY, Kosten TA. Prazosin, an alpha-1 adrenergic antagonist, reduces cocaine-induced reinstatement of drug-seeking. *Biol Psychiatry.* 2005; 57:1202–1204. [PubMed: 15866561]
- Zhang XY, Kosten TA. Previous exposure to cocaine enhances cocaine self-administration in an alpha-1 adrenergic receptor dependent manner. *Neuropsychopharmacology.* 2007; 32:638–645. [PubMed: 16794571]

Figure 1.

Flow chart of study participants

^aDid not meet inclusion criteria (described in study eligibility)

^bAfter completion of screening, participant did not return for randomization

^cDid not return to receive study medication

Figure 2.

Percentage of cocaine-positive urine toxicology per two-week time block across the 13-week trial for the placebo (green line) versus doxazosin (blue – DOX-Slow; red – DOX-Fast) treatment groups. This graph includes participants only during their enrollment in the study; once the participant discontinued involvement in the trial (i.e., missing three consecutive clinic visits), their urine data was no longer included in this graphical representation.

Table 1

Baseline Demographics

		Dox Slow	Dox Fast	Placebo	Significance
Gender					
	Male	8	7	11	$\chi^2 = 1.893$, $df=2$, $sig = 0.388$
	Female	0	2	2	
Race					
	African American	7	3	10	$\chi^2 = 6.678$, $df=2$, $sig = 0.035^{**}$
	Non-African American	1	6	3	
Age (years)					
	Mean	50.1 $\pm$ 7.4	47.4 $\pm$ 11.0	48.2 $\pm$ 8.6	0.805
Employment					
	Employed over past 3 years	6/8 (75%)	7/9 (78%)	9/13 (69%)	$\chi^2 = 0.326$, $df=2$, $sig = 0.85$
ASI-Lite					
	Alcohol use – Past 30 days (days)	6.63 $\pm$ 3.77	10.11 $\pm$ 9.55	7.85 $\pm$ 9.89	0.697
	Alcohol use – Lifetime (years)	21.75 $\pm$ 16.37	24.22 $\pm$ 17.82	18.92 $\pm$ 12.98	0.730
	Cocaine use – Past 30 days (days)	18.13 $\pm$ 8.90	7.89 $\pm$ 6.92	14.85 $\pm$ 10.25	0.070
	Cocaine use – Lifetime (years)	19.00 $\pm$ 8.16	15.89 $\pm$ 9.60	14.62 $\pm$ 7.89	0.522

*** Statistically significant ($p < 0.05$)