2015

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Addiction Biology

SSA SOCIETY FOR THE STUDY OF ADDICTION

CLINICAL STUDY

doi:10.1111/adb.12275

Role of the α_1 blocker doxazosin in alcoholism: a proof-of-concept randomized controlled trial

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ABSTRACT

Evidence suggests that the norepinephrine system represents an important treatment target for alcohol dependence (AD) and the α_1-blocker prazosin may reduce alcohol drinking in rodents and alcoholic patients. The α_1-blocker doxazosin demonstrates a more favorable pharmacokinetic profile than prazosin, but has never been studied for AD. A double-blind placebo-controlled randomized clinical trial was conducted in AD individuals seeking outpatient treatment. Doxazosin or matched placebo was titrated to 16 mg/day (or maximum tolerable dose). Drinks per week (DPW) and heavy drinking days (HDD) per week were the primary outcomes. Family history density of alcoholism (FHDA), severity of AD and gender were *a priori* moderators. Forty-one AD individuals were randomized, 30 (doxazosin = 15) completed the treatment phase and 28 (doxazosin = 14) also completed the follow-up. There were no significant differences between groups on DPW and HDD per week. With FHDA as a moderator, there were significant FHDA × medication interactions for both DPW ($p_{corrected} = 0.001$, $d = 1.18$) and HDD ($p_{corrected} = 0.00009$, $d = 1.30$). *Post hoc* analyses revealed that doxazosin significantly reduced alcohol drinking in AD patients with *high* FHDA and by contrast *increased* drinking in those with *low* FHDA. Doxazosin may be effective selectively in AD patients with *high* FHDA. This study provides preliminary evidence for personalized medicine using α_1-blockade to treat AD. However, confirmatory studies are required.

Keywords Alcoholism, clinical trial, craving, doxazosin, family history density of alcoholism, α_1-blockade.

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INTRODUCTION

Alcohol dependence (AD) afflicts about 10 percent of the US population causing serious morbidity and mortality. Only a few medications are approved for AD, however, their therapeutic effects are modest or limited to certain subgroups (for review, *see* Leggio *et al.* 2009). Thus, developing new medications for AD remains a priority.

Evidence suggests an important role of the norepinephrine system in AD (for review, see Koob 2008), pointing to the norepinephrine system as a potentially important pharmacological target. Norepinephrine innervates key limbic areas for arousal, reinforcement and stress—processes involved in developing and maintaining AD (Koob 2008). Elevated epinephrine (Ehrenreich *et al.* 1997) and norepinephrine (Patkar *et al.* 2004) plasma levels have been found in abstinent alcoholic patients. Hyperexcitability, a key feature in the predisposition and development of AD, is associated with increased adrenergic activation (Koob 2008). Enhanced acoustic startle response is a proxy for hyperexcitability and brain noradrenergic-α_1 mechanisms mediate enhanced acoustic startle response (Stevens, McCarley & Greene 1994), which is characteristic in alcohol-preferring (P line) animals (Chester, Blose & Froehlich 2004) and AD patients (Krystal *et al.* 1997). In animals, norepinephrine depletion attenuates ethanol self-administration (Amit *et al.* 1977) and alcohol withdrawal symptoms (Trzaskowska *et al.* 1986); α_1-receptor antagonism reduces the locomotor hyperactivity produced by alcohol withdrawal (Trzaskowska *et al.* 1986).

In summary, animal and human studies demonstrate that α_1-blockade may represent a therapeutic approach for AD. Recently, promising results have been obtained with the noradrenergic α_1-blocker prazosin, approved by the Food and Drug Administration (FDA) for hypertension and benign prostatic hyperplasia. Prazosin reduced alcohol self-administration and was more potent in ethanol-dependent rats than in non-dependent, suggesting that prazosin blocks dependence-induced increases in responding to alcohol (Walker *et al.* 2008). Subsequently, both acute and chronic prazosin treatment demonstrated decreased ethanol consumption in alcohol P rats (Rasmussen *et al.* 2009). Prazosin also blocked yohimbine- and footshock-induced reinstatement of alcohol seeking (Le *et al.* 2011).

Based on this pre-clinical evidence, a 6-week pilot randomized clinical trial (RCT) was performed (Simpson *et al.* 2009); 24 AD individuals were treated with placebo or prazosin 16 mg, divided over three daily doses. During the last 3 weeks of the study, the prazosin group, compared with placebo, had a statistically significant reduction in drinking days per week and a trend in reduction in drinks per week (DPW; Simpson *et al.* 2009). No significant medication effect on craving was found. Although frequent non-serious adverse events (AEs), such as dizziness, lack of energy, drowsiness and one case of syncope, were reported, there were no serious AEs (Simpson *et al.* 2009). In a more recent study with detoxified abstinent AD individuals ($n = 17$), prazosin (16 mg/day), compared with placebo, decreased both stress- and cue-induced alcohol craving measured via guided imagery exposures to stress, alcohol cue and neutral-relaxing/control conditions (Fox *et al.* 2012).

The noradrenergic α_1-blocker doxazosin is also FDA-approved for hypertension and benign prostatic hyperplasia. Doxazosin and prazosin share the same piperazine ring structure and have a non-specific action on all three α_1-subtypes, i.e. α_{1A}, α_{1B} and α_{1D} (Gross, Hanft & Mehdorn 1989). However, doxazosin has a more manageable dosing and safety profile than prazosin. Specifically, doxazosin is long-acting [half-life ($t_{1/2}$) approximately 22 hours)] and dosed only once daily, thus facilitating adherence (Kirby *et al.* 1998). Doxazosin is also less likely to produce hypotension because of the slower onset of action and long $t_{1/2}$. Furthermore, unlike other α_1-blockers (i.e. prazosin), doxazosin can be taken at any time of day, with or without food, properties that further promote patient adherence (Kirby *et al.* 1998). Thus, in clinical practice, doxazosin is often preferred to treat hypertension or benign prostatic hyperplasia over short-acting α_1-blockers, such as prazosin (Akduman & Crawford 2001). Therefore, given its favorable pharmacokinetics, a proof-of-concept RCT was conducted to test the hypothesis that doxazosin may represent a safe and effective medication for the treatment of AD. Specifically, the primary aim of the study was that doxazosin, compared with placebo, may significantly reduce alcohol consumption. Secondary aims were that doxazosin may significantly reduce alcohol craving, anxiety and stress levels. Finally, we hypothesized that family history of alcoholism, severity of AD and gender may moderate doxazosin's response on alcohol consumption.

METHODS AND MATERIALS

Study design

A 10-week between-subject double-blind placebo-controlled RCT with doxazosin was conducted at the Brown University Center for Alcohol and Addiction Studies (ClinicalTrials.gov: NCT01437046). The Brown University Institutional Review Board reviewed and approved the study. Patients were individuals seeking outpatient treatment for AD. For inclusion/exclusion criteria, see Supporting Information Table S1.

Study drug

Doxazosin or matched placebo were prepared as opaque capsules by a compounding pharmacy and inserted into blister packs. Consistent with the recommended titration, doxazosin was titrated up to 16 mg daily (or maximum tolerable dose) during the first 4 weeks (Supporting Information Table S2). A 1-week downward titration for safety reasons was also planned. The choice to test 16 mg daily, the highest dose used in hypertension, was made on the basis of the prazosin alcohol trial (Simpson *et al.* 2009), where: (1) prazosin was used at the highest dose for hypertension (16 mg/day); and (2) participants had a statistically significant reduction in alcohol consumption during the last 3 weeks, when prazosin was administered at the full dose. Study medication adherence was assessed by self-report and pill count. Additionally, capsules contained 25 mg riboflavin as a marker of adherence through urine sample (Del Boca *et al.* 1996).

Medical management

At each medication visit, participants also received a medical management session. Medical management is an intervention with demonstrated efficacy as a behavioral platform for the treatment of AD (Anton *et al.* 2006). The medical management sessions provide personalized education regarding alcohol. It is structured to help the participant develop and implement a plan to stop/reduce drinking, motivate participants for medication adherence and assess AEs and concomitant medication use. The medical management approach was based on the COMBINE study (Anton *et al.* 2006) and revised and

adapted for this study. For example, special emphasis in the assessment of AEs was given to side effects already described for doxazosin; particular attention was given not only to medication adherence *per se* but also to the compliance to the study medication titration during the first 4 weeks of the trial. Special attention was given to those concomitant medications with known possible interaction with doxazosin.

Study procedures

The study consisted of four phases: telephone pre-screening, in-person screening, 10-week treatment and 2-week follow-up. Potential participants, recruited via advertisements in public transportation and mass media, and referrals from other clinics were phone screened. Those meeting initial pre-screening criteria came for an in-person screen in which they provided written informed consent. Screening (week 00 visit) included psychological assessments, medical history, physical, electrocardiogram and blood/urine laboratories (e.g. liver and kidney function tests, complete blood count, urine drug and pregnancy tests). Breath alcohol concentration was measured, vital signs were taken and recent alcohol consumption was collected using the timeline follow-back (TLFB; Sobell *et al.* 1988). At week 01 visit (day 01), eligible participants were randomized to doxazosin or placebo. A brief telephone assessment occurred at days 2–4 to assess possible AEs. Then, participants were assessed in person at weeks 2, 3, 4, 6, 8 and 10 for in-person visits, during which medical assessments, questionnaires, study medication and medical management sessions were provided. A brief telephone assessment occurred at weeks 5, 7 and 9 to address possible AEs. At Week 10, a downward titration dose of doxazosin/placebo was administered. Subsequently, 2 weeks after week 10 (thus, ~ 1 week after the last study medication dose), a brief in-person follow-up visit took place to assess general health status.

Study outcomes and assessments

Drinking outcomes

Primary outcomes were DPW and heavy drinking days (HDD) per week, as assessed by the TLFB.

Craving, anxiety and stress

It has been suggested that the role of prazosin in AD may be mediated by its effects on stress-related anxiety (Walker *et al.* 2008; Rasmussen *et al.* 2009; Simpson *et al.* 2009), therefore secondary outcomes were stress, anxiety and craving. Alcohol craving was assessed by the obsessive compulsive drinking scale (OCDS), including the total, obsessive (ODS) and compulsive (CDS) scores (Anton, Moak & Latham 1995). Anxiety and stress were assessed using the Hamilton anxiety scale (HAMA) (Hamilton 1959), the perceived stress scale (PSS; Cohen, Kamarck & Mermelstein 1983) and the anxiety-tension subscale of the profile of mood states (POMS-TA) (Pollock *et al.* 1979).

Moderators

Analyses of family history of alcoholism, severity of AD and gender as potential moderators of a medication effect were planned *a priori*. Consistent with the literature (Trzaskowska *et al.* 1986; Koob 2008; Walker *et al.* 2008), α_1-blockade represents a mechanism of action more likely to be effective in patients with more biologically based AD and/or higher severity of dependence. For example, prazosin's ability to reduce ethanol self-administration was more potent in ethanol-dependent rats than in non-dependent rats (Walker *et al.* 2008). Consistent with previous reports (Rohsenow *et al.* 2007; Capone *et al.* 2011), we used the family tree questionnaire (Mann *et al.* 1985) to calculate the family history density of alcoholism (FHDA) among first-degree relatives; FHDA was dichotomized at 0.50 (median split) into *low* or *high* FHDA. We used the alcohol dependence scale (ADS) (Skinner & Allen 1982) as a direct measure of severity of dependence; ADS was dichotomized into *low* or *high* ADS based on the median of 10.5. Finally, we assessed gender as it has been associated with severity of AD (Rohsenow *et al.* 2007).

AEs

AE were assessed at each visit using the SAFTEE (Levine & Schooler 1986), revised and adapted for this study. Clinical assessments [e.g. blood pressure (BP)] were used to identify other AEs.

Statistical analysis

Distributional characteristics of outcome measures were examined to evaluate similarity to the normal distribution. DPW had a skewness and kurtosis slightly in excess of two; consequently, the data were transformed using a square root transformation. The mixed model procedure, which accommodates cases with missing data, was used to assess medication effects on outcomes with time nested under subjects. The baseline value of each particular dependent measure was added as a covariate. Additionally, as the two groups differed in racial make-up (Table 1), race was added as a covariate to ensure that any differences on outcome variables between groups were not accounted for by race difference. Chi-squared tests were conducted to assess if demographic characteristics, medication adherence or AEs differed between doxazosin and placebo groups. Moderator analyses for FHDA and ADS were conducted using a median split

Table 1 Participant characteristics at baseline [mean ± (standard deviation) or percentage (%)].

	Doxazosin (n = *20)*	*Placebo* (n = *21)*
Age	42.1 (10.2)	42.1 (7.5)
Women (%)	30	29
Hispanic/Latino (%)	10	5
Race (%):		
American/Alaskan Indian	0	5
African–American	25	43
White[a]	65	33
Other	0	5
More than one race	10	14
Drinking per week	69.0 (33.1)	75.6 (71.2)
Heavy drinking days	5.3 (1.6)	5.1 (1.8)
Obsessive compulsive drinking scale score	18.3 (6.4)	14.8 (7.6)
Obsessive drinking scale subscore	7.7 (3.7)	6.0 (4.5)
Compulsive drinking scale subscore	10.6 (3.2)	8.9 (3.7)
Family history density of alcoholism (%)	52	38
Cigarette smokers (%)	70	71
Urine drug screen positive for cannabis (%)	10	29
Systolic blood pressure supine	126 (21)	124 (11)
Diastolic blood pressure supine	81 (13)	79 (10)
Systolic blood pressure standing	124 (16)	124 (12)
Diastolic blood pressure standing	83 (13)	83 (9)
Systolic blood pressure (BP)Δ	2.5 (12.9)	–0.3 (12.1)

[a]χ^2 [(1, $n = 41$) = 4.11, $P = 0.04$]; no other significant baseline differences between groups were found [*Ps* > 0.05].

[consistent with (Rhemtulla, Brosseau-Liard & Savalei 2012), who confirmed the conventional wisdom that, with just two to four categories, continuous methodology is generally not recommended] while gender was already a dichotomous variable. Consistent with recent recommendations (Falk *et al*. 2010), the previous data showing a prazosin effect at the target dose (Simpson *et al*. 2009) and the doxazosin titration scheduled (Supporting Information Table S2), a grace period was applied for the first 4 weeks of medication to account for titration to peak pharmacological effect; therefore, except for the baseline comparisons, medication adherence and AE analyses, all other analyses were conducted for the target dose (16 mg) period only. Standard errors were reported for mixed model analyses; standard deviations were reported for *t*-tests. All participants with at least one valid outcome data point were included in the modified intention-to-treat analysis. SPSS version 21 (IBM Corp., Armonk, NY, USA) was used to conduct the analyses.

RESULTS

Participant characteristics

Of 197 individuals pre-screened by phone, 52 signed the informed consent and were screened in-person; 11 were ineligible, while 41 were eligible and randomized (doxazosin, $n = 20$: placebo, $n = 21$). Thirty participants (doxazosin = 15) completed the treatment phase and 28 (doxazosin = 14) completed the follow-up (Supporting Information Fig. S1). Participants' baseline characteristics are shown in Table 1.

Drinking outcomes

There were no significant differences between groups in DPW ($F_{1,36} = 0.43$, $P > 0.05$) and HDD ($F_{1,35} = 1.03$, $P > 0.05$), although there was a small reduction in DPW and HDD in the doxazosin group compared with placebo (effect sizes $d = 0.23$ and 0.35, respectively). There was no significant time or medication by time interaction for either of the two outcomes (*Ps* > 0.05). (See Supporting Information Table S5 for results for all terms in the model for these two dependent variables.)

Craving, anxiety and stress

There was a significant main effect for medication on the ODS subscale ($F_{1,33} = 4.92$, $P = 0.034$; Fig. 1). There were no significant medication effects on total OCDS ($F_{1,35} = 2.55$, $P > 0.05$), CDS ($F_{1,36} = 0.87$, $P > 0.05$), HAMA ($F_{1,36} = 0.46$, $P > 0.05$), PSS ($F_{1,36} = 0.46$, $P > 0.05$) or POMS-TA ($F_{1,34} = 0.34$, $P > 0.05$) scales. There were no significant main effects for time or medication by time interaction for these outcomes (*Ps* > 0.05).

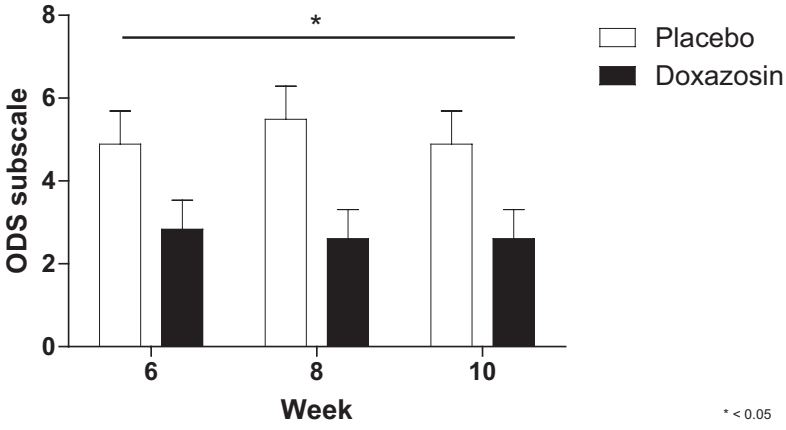

Figure 1 Significant effect for doxazosin on the obsessive craving (ODS) subscale

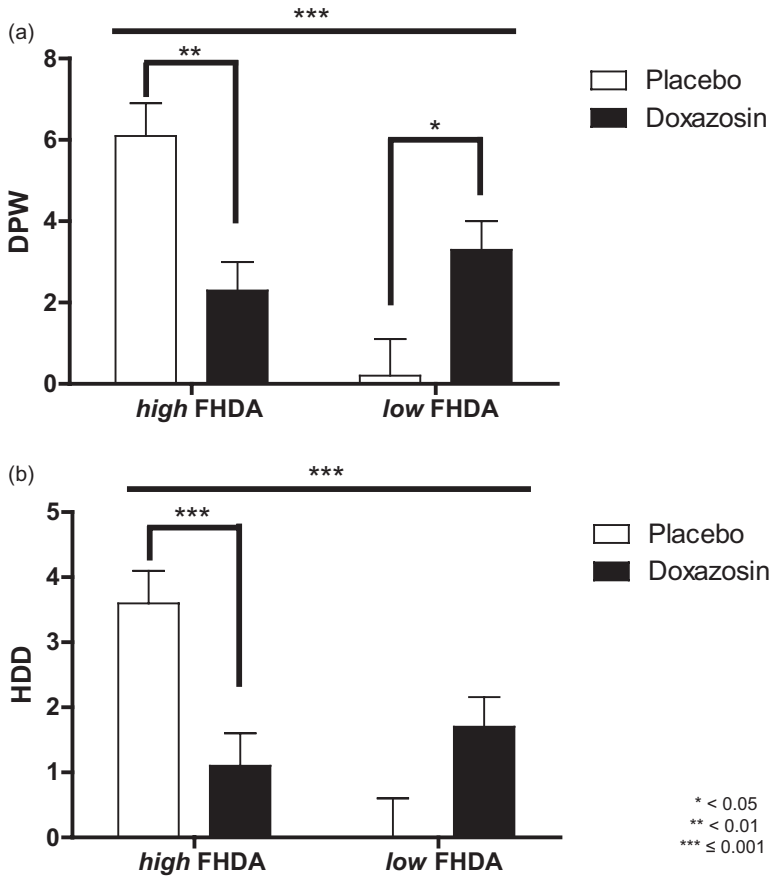

Figure 2 (a) Significant effect for doxazosin on drinks per week (DPW), family history density for alcoholism (FHDA) × medication interaction; (b) significant effect for doxazosin on heavy drinking days (HDD) per week, FHDA × medication interaction. Horizontal lines indicate significant interactions and brackets indicate *post hoc* analyses with significant findings

(See Supporting Information Tables S6 and S7 for results for all terms in the model for these dependent variables.)

Moderators

Analyses for the three potential moderators (FHDA, ADS and gender) of the two primary drinking outcomes were conducted using an alpha corrected by a factor of 6 (3 × 2).

There were main effects of FHDA on DPW ($F_{1,35} = 9.48$, $p_{corrected} = 0.024$) and HDD ($F_{1,34} = 13.38$, $p_{corrected} = 0.005$), as well as significant FHDA × medication interactions for both DPW ($F_{1,35} = 17.35$, $p_{corrected} = 0.001$) and HDD ($F_{1,34} = 25.29$, $p_{corrected} = 0.00009$). *Post hoc* analyses showed a significant medication effect for *high* FHDA in the expected direction (i.e. reduction of drinking) for DPW ($t_{31} = 3.47$, $p_{corrected} = 0.003$; Fig. 2a) and HDD ($t_{31} = 3.84$, $p_{corrected} = 0.0004$; Fig. 2b). Large effect sizes were reported for both DPW ($d = 1.18$) and HDD ($d = 1.30$) with *high* FHDA as moderator (Table 2). Notably, there was a significant reverse medication effect for *low* FHDA on DPW ($t_{29} = 2.59$, $p_{corrected} = 0.04$; Fig. 2a)

Table 2 Family history density of alcoholism (FHDA) as moderator of the primary drinking outcomes [mean ± (standard error)].

		Drinks per week		*Heavy drinking days*	
FHDA	High FHDA	4.2 (0.5)		2.3 (0.3)	
	Low FHDA	1.8 (0.6)		0.7 (0.4)	
	$p_{corrected}$	0.024		0.005	
		Doxazosin	Placebo	Doxazosin	Placebo
FHDA × medication	High FHDA	2.3 (0.7)	6.1 (0.8)	1.1 (0.5)	3.6 (0.5)
	Low FHDA	3.3 (0.7)	0.2 (0.9)	1.7 (0.4)	0.0 (0.6)
	$p_{corrected}$	0.001		0.00009	
High FHDA × medication effect size (*d*)		1.18		1.30	

and trend for a reverse medication effect for *low* FHDA on HDD ($t_{29} = 2.40$, $p_{corrected} = 0.08$; Fig. 2b). FHDA was not related to differences in age, gender, race, ethnicity or baseline DPW or HDD. There were no significant effects for ADS or gender on the two main outcomes (data not shown).

Exploratory analyses

Based on the earlier results for FHDA, additional analyses were performed to investigate the extent to which effects in secondary outcomes were also moderated by FHDA. Given the exploratory nature of these analyses, results are presented with uncorrected alpha levels (Table 3). There were significant main effects of FHDA on craving scales (total OCDS: $F_{1,34} = 6.25$, $P = 0.017$; ODS: $F_{1,35} = 6.97$, $P = 0.012$; CDS $F_{1,34} = 5.45$, $P = 0.026$), anxiety (HAMA: $F_{1,34} = 5.13$, $P = 0.030$) and mood (POMS-TA: $F_{1,32} = 7.44$ $P = 0.010$), but not PSS ($P > 0.05$). There were significant FHDA by medication interactions for craving (total OCDS: $F_{1,35} = 10.06$, $P = 0.003$; ODS: $F_{1,35} = 5.23$, $P = 0.028$; CDS: $F_{1,35} = 11.08$, $P = 0.002$) and anxiety (HAMA: $F_{1,32} = 9.76$, $P = 0.004$).

Study medication adherence

Percentages of days of medication adherence were as follows: doxazosin = 85.7 (24.0) percent-days adherent and placebo = 75.6 (32.7) percent-days adherent, ($t_{39} = 1.13$, $P = 0.27$). The two groups did not differ on medication adherence ($P > 0.05$).

Drug titration

There were no statistical differences between doxazosin and placebo groups during the drug titration phase and maximum tolerable dose. Of the 28 who completed the study, 24 participants reached 16 mg (12 doxazosin; 12 placebo), and four completed the study at a lower dose (maximum tolerable dose of doxazosin: one remained at 4 mg and one reached 16 mg for a week then returned to 8 mg; maximum tolerable dose of placebo: one remained at 4 mg and one at 2 mg). Of the 13 who did not complete the study, six participants reached 16 mg (three received doxazosin; three received placebo) and seven never reached 16 mg (three received doxazosin, however, one completed the 10-week study at 4 mg but did not return for follow-up; four received placebo).

AEs

Four AEs were more frequent in the doxazosin group versus placebo: dizziness, depression or other mood disturbance, trouble urinating ($Ps < 0.05$) and headache ($P < 0.01$; Supporting Information Table S3). Particular attention was also given to BP, given doxazosin's expected hypotensive effects, assessed as systolic and diastolic BP changes (BPΔ; average supine minus average standing reading). No baseline differences were observed between the two groups (Table 1). No significant differences in BPΔ were observed between the two groups during treatment (Supporting Information Table S4).

DISCUSSION

This study provides preliminary yet promising results on the potential role of doxazosin in the treatment of AD. Specifically, findings from this relative small sample do not support a role for doxazosin in reducing alcohol use in a general AD population; however, doxazosin may be effective in reducing drinking and craving in AD patients with *high* FHDA. While this trial was developed based only on the previous pre-clinical and clinical literature related to prazosin in AD, a subsequent pre-clinical study (O'Neil *et al.* 2013) showed that doxazosin decreased voluntary alcohol consumption in P rats without affecting total fluid intake, locomotor activity or alcohol clearance. The positive effects of doxazosin in P rats are consistent with our clinical findings where doxazosin significantly reduced drinking only in patients with *high* FHDA. In fact, the P rat line is a well-characterized model of excessive voluntary alcohol drinking and these lines are based on repeated generations of selective breeding for alcohol preference (Li *et al.* 1979). An additional pre-clinical observation consistent with the present clinical findings

Table 3 Family history density of alcoholism (FHDA) as moderator of the secondary aims [mean ± (standard error)].

	Total OCDS		*ODS*		*CDS*		*HAMA*		*POMS-TA*	
FHDA										
High FHDA	11.1 (1.3)		5.3 (.6)		6.8 (.6)		2.4 (.3)		5.5 (.6)	
Low FHDA	3.4 (1.4)		1.3 (.7)		4.5 (.6)		4 (.3)		2.8 (.6)	
P	< 0.001		< 0.001		0.009		< 0.001		0.004	
FHDA × medication	Doxazosin	Placebo	Doxazosin	Placebo	Doxazosin	Placebo	Doxazosin	Placebo	Doxazosin	Placebo
High FHDA	5.5 (1.7)	16.8 (1.8)	3.5 (0.8)	7.2 (0.9)	3.8 (0.8)	9.9 (0.8)	1.8 (0.4)	3.1 (0.4)	7.0 (0.8)	3.9 (0.8)
Low FHDA	5.8 (1.7)	1.0 (2.1)	1.3 (0.8)	1.3 (0.9)	5.6 (0.8)	3.3 (0.8)	1.0 (0.4)	0.0 (0.5)	2.8 (0.8)	2.8 (1.0)
P	< 0.001		0.010		< 0.001		0.004		0.078	

Obsessive compulsive drinking scale: total score (OCDS) and obsessive (ODS) and compulsive (CDS) subscales; Hamilton anxiety scale (HAMA); anxiety-tension subscale of the profile of mood states (POMS-TA).

is that, in another set of experiments, prazosin was more potent in ethanol-dependent rats than in non-dependent rats (Walker *et al.* 2008).

Results also suggest that for those patients with *low* FHDA, not only did doxazosin not reduce drinking, but it also appears that there was a trend toward *increased* drinking. This is interesting because it further supports the potential selectivity of doxazosin, by suggesting not only a subtype of AD patients (with *high* FHDA) for whom doxazosin could reduce drinking, but also another subtype for whom the use of doxazosin would not be recommended (patients with *low* FHDA). Furthermore, the opposite effects of *high* versus *low* FHDA in moderating doxazosin's effect suggest that, when pooled together, the two effects may cancel each other out, thus the lack of doxazosin's effects on drinking outcomes in the whole general sample.

It is also important to consider the potential confounding by the placebo effect observed in this study as lower alcohol use was reported by placebo-treated subjects with *low* FHDA. In the *high* FHDA group, placebo clearly was not associated with reduced alcohol drinking like it did in the *low* FHDA group, but doxazosin did. It is possible that doxazosin's effect was exhibited in the *high* FHDA group because they expressed adequate drinking to resolve the response, whereas drinking in the *low* FHDA group was so profoundly suppressed by the placebo effect that the interpretation was confounded. It could even be plausibly hypothesized that the *low* FHDA group exhibited a differentially potent placebo effect due to motivating conditions of the clinical trial, that doxazosin treatment could have actually diminished the impact of these conditions and allowed expression of moderate drinking, perhaps through an anxiolytic effect, a potential explanation consistent with what is already observed in non-dependent rats where a low dose of prazosin actually increased alcohol self-administration (Walker *et al.* 2008).

Although this study does not provide definitive answers on the potential biobehavioral mechanism(s) of action, some hypotheses are possible. The effect of doxazosin in reducing alcohol craving in patients with *high* FHDA, in the absence of effects on anxiety and stress, could suggest one potential pathway. Notably, these outpatients were exposed to alcohol cues in their 'real-word' life and these cues might have frequently elicited craving, against which doxazosin may have facilitated its effect in those with *high* FHDA. Taking into account the consistent doxazosin suppression of alcohol craving reflected in the obsessive drinking score and the potential confounding by placebo effect on alcohol consumption discussed earlier, it is possible to speculate that doxazosin treatment may be effective only in subjects that are expressing high voluntary alcohol drinking, a

potential explanation consistent with previous rodents research showing that other drugs working on the noradrenergic system suppress alcohol drinking in high alcohol-drinking but not in low alcohol-drinking rats (Moorman & Aston-Jones 2009). While drawing conclusive findings in this domain is beyond the scope of this research, human laboratory studies assessing doxazosin's effects on craving may be helpful to better investigate this putative mechanism of action.

Another potential mechanism of action is via influence on stress-induced anxiety and stress-induced relapse/reinstatement of alcohol seeking, which are mediated, at least partially, by the norepinephrine system (Koob 2008). However, the present study provides no support for this putative mechanism of action in humans. It is conceivable that an effect of doxazosin on anxiety and/or stress could be detected in a different study design with abstinent AD patients who start doxazosin after an in-patient detoxification phase. Supporting evidence for this includes the fact that brain α_1-adrenergic mechanisms mediate enhanced acoustic startle response (Stevens *et al.* 1994), which is characteristic of abstinent alcoholic individuals (Krystal *et al.* 1997) and outbred rats experiencing prolonged abstinence following long-term chronic daily ethanol consumption and withdrawal (Rasmussen *et al.* 2009).

An open question remains with what may be the potential causes underlying differential doxazosin response by family history of alcoholism. We examined if *high* FHDA was a proxy of another more direct biomarker but found that FHDA was not related to baseline differences, such as age, gender, race, ethnicity or baseline alcohol use. One may speculate that FHDA was a proxy of a potential genetic biomarker that might predict doxazosin response, an intriguing hypothesis that could not be tested in this study, given that genetic sampling was not conducted. Consistent with the growing literature suggesting an important role of pharmacogenetics in AD (Heilig *et al.* 2011; Leggio & Schwandt 2014), future studies will need to investigate potential biological (genetic) markers, such as, e.g., genetic variants that have been associated with the response to doxazosin in hypertensive patients (Lynch *et al.* 2008). These objective biomarkers might allow the identification of more precise and replicable subtypes of AD patients more likely to respond to doxazosin. This future line of inquiry will be important not only because family history of alcoholism is typically self-reported and there is not enough evidence to suggest it as a reliable predictor of response, but also because its implementation in clinical practice may be challenging due to the need to standardize the way how family history of alcoholism is defined, operationalized and assessed.

Given recent findings suggesting a role of doxazosin in posttraumatic stress disorder (PTSD; De Jong *et al.* 2010) and cocaine abuse (Newton *et al.* 2012; Shorter, Lindsay & Kosten 2013), future research exploring the role of doxazosin in the common co-morbidities between AD and both PTSD and cocaine use is worth considering. In this regard, another important consideration is that while this preliminary study aimed at testing the maximum tolerable dose of doxazosin, i.e. up to 16 mg/day, future studies may also be designed as dose-ranging studies, especially considering that lower doses of doxazosin have been used in PTSD (De Jong *et al.* 2010) and cocaine abuse (Newton *et al.* 2012; Shorter *et al.* 2013).

This study provides important information on the safety of doxazosin specifically in the context of alcohol misuse. While this was not a medication–alcohol interaction study in a controlled in-patient setting, these findings support the safety of doxazosin–alcohol interaction in a 'real-word' clinical outpatient setting. This study also presents questions on safety- and efficacy-related differences between doxazosin and prazosin in AD. Within the general safety profile of this class of drugs, doxazosin has been designated as a safer medication compared with prazosin (Akduman & Crawford 2001). The slower onset of action of doxazosin and its relatively long $t_{1/2}$ decreases the likelihood of first-dose postural hypotension compared with prazosin (Kirby *et al.* 1998). In the context of AD patients, Simpson *et al.* (2009) reported one case of clinically significant hypotension out of 24 enrolled patients, while in our study ($n = 41$), no patients presented with clinically relevant hypotension. This is also consistent with the observation that, while effective for lowering BP in hypertensive patients, doxazosin has no significant effect on BP in normotensive patients, thus further decreasing the risk of hypotension (Akduman & Crawford 2001). In summary, the lack of severe AEs or other safety concerns, together with the low number of dropouts (whose rates were similar in the doxazosin and placebo groups), indicate that safety and tolerability of doxazosin in this trial was fair and make it an acceptable medication for AD patients.

In terms of efficacy, in contrast to the prazosin study (Simpson *et al.* 2009), we did not find a main doxazosin effect in the general sample. One possible explanation for this inconsistency is that the prazosin trial overestimated the medication's effect, a potential type I error in small RCTs. Another possibility is that, unlike prazosin, doxazosin only works in patients with significant family history for alcoholism. However, it is unknown if prazosin's effects might be even stronger in patients with *high* FHDA. Only a three-arm RCT (doxazosin versus prazosin versus placebo) would be able to address safety- and efficacy-related differences between the two medications.

Although we did not collect central spinal fluid to measure doxazosin concentrations, there is evidence that doxazosin crosses the blood–brain barrier. Preclinical studies demonstrate central nervous system (CNS) actions of doxazosin administered peripherally (McLeod & Cairncross 1995). In humans, somnolence is a dose-dependent side effect of doxazosin and a pilot study reported that doxazosin reduced PTSD symptoms (De Jong *et al*. 2010). In our trial, three of the four side effects more common in the doxazosin group were CNS-related (dizziness, headache and mood disturbances), further supporting doxazosin's central effects. This is consistent with the fact that doxazosin works on all subtypes, α_{1A}, α_{1B} and α_{1D} (Gross *et al*. 1989). Blockade of the α_{1B} subtypes (located in the brain) by doxazosin contributes to the central side effects thus demonstrating indirectly its actions in the CNS (Akduman & Crawford 2001).

Strengths of this study include that this is the first clinical study of the efficacy of doxazosin in AD and the enrollment of outpatient treatment-seeking AD patients, a population more closely representing the 'real-word' in terms of clinical practice. Limitations include the lack of actual genetic testing, for which future pharmacogenetic work is warranted; the use of riboflavin and ultraviolet light for adherence measurement (Herron *et al*. 2013), thus highlighting the need for better ways to assess adherence in future studies (for review, see Gurvich, Kenna & Leggio 2013) and the small sample. Notably, although the small sample did not allow for describing family history of alcoholism as a tripartite categorization (Rohsenow *et al*. 2007), we calculated family history based on first-degree relatives, an approach consistent with the COMBINE study (the largest pharmacotherapy RCT in the alcoholism field) (Anton *et al*. 2006) and took into account the 'density' of family history, consistent with previous recommendations (Rohsenow *et al*. 2007; Capone *et al*. 2011).

Importantly, this initial clinical study provides a platform for future studies both in terms of safety and power estimation for efficacy and suggests that a follow-up RCT may be designed by *a priori* enrollment of AD patients with *high* FHDA. Considering an RCT with 80 percent power to detect an effect size on DPW and HDD, 20 participants with *high* FHDA per cell would need to be retained. On the other hand, if participants were not screened on FHDA, > 400 participants per cell would need to be retained.

In conclusion, this RCT provides preliminary evidence for a role of doxazosin in the treatment of AD, albeit limited to patients with *high* FHDA. Future studies are warranted to identify possible biomarkers of doxazosin's response in AD patients in order to best identify potential AD patients who are responders or non-responders.

Acknowledgements

This study was funded by the National Institute on Alcohol Abuse and Alcoholism (NIAAA), Grant R21AA019994 (principal investigators: Dr. Leggio and Dr. Kenna). Dr. Leggio's current work is supported by the NIAAA Division of Intramural Clinical and Biological Research and the National Institute on Drug Abuse (NIDA) Intramural Research Program. Dr. Haass-Koffler's work is supported by the 5T32AA007459-28 training grant from NIAAA.

The authors would like to thank Samuel Fricchione (Brown University) for providing technical support and Dr. Melanie Schwandt (NIAAA) for reviewing and commenting on the manuscript.

Disclosure/Conflict of Interest

Dr. Kenna has received consultant fees from CT Laboratories. Dr. Swift has received travel and honorarium from D&A Pharma, Lundbeck and consultant fees from CT Laboratories. The other authors report no biomedical financial interests or potential conflicts of interest.

Authors Contribution

GAK and LL were responsible for the study concept and design. CLH-K, SME and MBB contributed to the acquisition of the data. WHZ performed the statistical analyses. GAK, CLH-K, RMS and LL assisted with data analysis and interpretation of findings. LL drafted the manuscript. GAK, CLH-K and RMS provided critical revision of the manuscript for important intellectual content. All authors critically reviewed content and approved final version for publication.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Figure S1 Study flow-chart.
Table S1 Inclusion and exclusion criteria.
Table S2 Drug titration schedule.
Table S3 Adverse events (AEs) as frequency percentage (%).
Table S4 Blood pressure changes (BPΔ) [M ± (SE)].
Table S5 Full models for drinking outcomes.
Table S6 Full models for craving.
Table S7 Full models for anxiety and stress.