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Higher pretreatment blood pressure is associated with greater alcohol drinking reduction in alcohol-dependent individuals treated with doxazosin

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Abstract

Background—Preclinical and clinical research suggest that the α_1 receptor antagonist prazosin reduces alcohol consumption. Furthermore, clinical studies indicate a role of prazosin in treating Post-Traumatic Stress Disorder (PTSD) symptoms, while a recent trial suggested that pre-

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Authors Contribution

LL, RMS and CLH-K were responsible for the concept and design of this study analysis. CLH-K, KG, WHZ and MM performed and/or assisted with the statistical analyses. CLH-K, KG, PMW, SE, VL, NJL, RMS, GAK and LL assisted with data analysis and interpretation of findings. CLH-K wrote the first draft of the manuscript. KG, SE, MM, PMW, VL, NJL, RMS, GAK and LL provided critical revision of the manuscript for important intellectual content. All authors critically reviewed content and approved final version for publication.

Conflict Of Interest

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

treatment blood pressure (BP) predicts therapeutic response for prazosin in PTSD patients. Whether pre-treatment BP may predict response to α_1 blockers in alcohol-dependent (AD) patients is unknown. We previously reported a randomized controlled trial (RCT), where doxazosin, an α_1 receptor antagonist with a more favorable pharmacokinetic profile than prazosin, reduced drinks per week (DPW) and heavy drinking days (HDD) in AD patients with a *high* family history density of alcoholism. In this study, we tested pre-treatment BP as another potentially valuable clinical moderator of doxazosin's response on alcohol consumption.

Methods—This was a double-blind placebo-controlled RCT testing doxazosin up to 16 mg/day in AD treatment-seeking patients ($N = 41$). The hypothesized moderator effect of baseline standing systolic and diastolic BP on DPW and HDD was tested.

Results—With pre-treatment standing diastolic BP as a moderator, there were significant BP $\times$ medication interactions for both DPW [$**p = 0.009$, $d = 0.80$] and HDD [$*p = 0.018$, $d = 1.11$]. *Post-hoc* analyses indicated significant doxazosin effects in patients with *higher* standing BP in reducing both DPW and HDD.

Conclusion—These findings suggest that higher standing diastolic BP at baseline (pre-treatment) may represent a predictor of doxazosin's response on alcohol consumption in AD patients. These results further elucidate the possible efficacy and mechanisms of action of α_1 receptor antagonism in AD individuals.

Keywords

alcohol use disorder; aldosterone; α_1 adrenoreceptor; blood pressure; cortisol; doxazosin

1. INTRODUCTION

Progress in the understanding of the neurobiological pathways that regulate the development and maintenance of alcohol use disorder (AUD) (Koob et al., 2009) has led to the development of novel pharmacotherapies. However, the Food and Drug Administration (FDA)-approved medications, *i.e.*, disulfiram, naltrexone, and acamprosate, have shown efficacy limited to subgroups of AUD patients (Edwards et al., 2011). Therefore, identifying personalized medicine approaches and biomarkers of medication response are crucial steps in medication development for AUD (Heilig and Leggio, 2016).

Targeting the norepinephrine system is a promising pharmacological approach to treat AUD. Norepinephrine transmission innervates key limbic areas for arousal, reinforcement, and stress – processes involved in the development and maintenance of AUD (Koob, 2008). Specifically, rodent work suggests that noradrenergic α_1 receptor antagonism may be a potentially effective pharmacological approach to AUD treatment (Koob, 2008; Trzaskowska et al., 1986; Walker et al., 2008). For example, the α_1 blocker prazosin, approved by the FDA for hypertension and benign prostatic hyperplasia, has been shown to reduce alcohol self-administration in ethanol-dependent rats (Walker et al., 2008), ethanol drinking in ethanol-preferring (P) rats (Froehlich et al., 2015; Rasmussen et al., 2009), and to block stress-induced reinstatement of ethanol seeking in ethanol-dependent rats (Le et al., 2011). Two small double-blind placebo-controlled studies have provided translational evidence of the previous rodent work by showing that prazosin given three times a day (4

mg, 4 mg and 8 mg) reduced alcohol consumption (Simpson et al., 2015; Simpson et al., 2009) and decreased both stress- and cue-induced alcohol craving (Fox et al., 2012) in alcohol dependent (AD) patients.

Doxazosin is another α_1 blocker that is FDA-approved for hypertension and benign prostatic hyperplasia and has an improved pharmacological profile when compared to prazosin, *i.e.*, longer half-life that allows for once a day dosing with fewer associated side effects (Akduman and Crawford, 2001; Leggio and Kenna, 2013). Recently, we tested doxazosin's effects on drinks per week (DPW) and heavy drinking days (HDD) among treatment-seeking AD patients (Kenna et al., 2016). This randomized controlled trial (RCT) indicated that doxazosin reduced alcohol consumption in a sub-group of individuals seeking treatment for AUD, specifically in those with high family history density of alcoholism (*FHDA*) (Kenna et al., 2016).

A recently proposed biomarker of α_1 -blockade response in neuropsychiatric disorders is pre-treatment blood pressure (BP). Specifically, a RCT testing prazosin in patients with post-traumatic-stress disorder (PTSD) showed that baseline (pre-treatment) standing BP predicts prazosin's efficacy on PTSD symptoms, suggesting that prazosin works better in those PTSD patients with higher pre-treatment standing BP (Raskind et al., 2016). Standing BP is regulated by norepinephrine activation via α_1 receptors in peripheral arterioles and it may represent a peripheral surrogate for α_1 receptor central tone (Reid, 1986). Whether pre-treatment BP may moderate response to α_1 blockers in alcohol-dependent (AD) patients is unknown. Given the involvement of noradrenergic activity during alcohol consumption and alcohol dependence (Sinha, 2007), and based on the recent RCT testing prazosin in PTSD patients (Raskind et al., 2016), here we examined the role of pre-treatment standing BP as a moderator of doxazosin's effects on alcohol drinking outcomes in AD patients. Additionally, given the important role of norepinephrine transmission in alcohol drinking, stress, and anxiety (Koob, 2008), we explored additional secondary outcomes from our RCT, namely alcohol craving, anxiety, and stress levels. Finally, in order to explore whether the putative moderator effect of BP may also relate to peripheral neuroendocrine biomarkers, we also assessed blood levels of cortisol and aldosterone. In fact, both hormones may play a role in BP tone (Lyngso et al., 2016; Ullian, 1999), as well as in excessive alcohol drinking (Helms et al., 2014; Leggio et al., 2008; Spencer and Hutchison, 1999).

In summary, the goal of this secondary analysis was to test the hypothesis that pre-treatment standing BP acts as a moderator of doxazosin's response on alcohol drinking outcomes in patients with AD.

2. METHODS AND MATERIALS

2.1 Parent Study

The parent study was a 10-week between-subject double-blind placebo-controlled proof-of-concept RCT testing doxazosin up to 16 mg/day in individuals seeking outpatient treatment for AUD (Kenna et al., 2016). The study was conducted at the Brown University Center for Alcohol and Addiction Studies ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01437046): NCT01437046) and approved by the

Brown University Institutional Review Board. Doxazosin, or matching placebo, were titrated up during the first four weeks of dosing.

All patients signed an informed consent prior to participation. Individuals were enrolled accordingly to the DSM-IV diagnosis of alcohol dependence; and heavy drinking (average 4 standard drinks per day for women or 5 standard drinks per day for men) during the 90-day period before screening, as assessed by the Timeline Follow-Back (TLFB) (Sobell et al., 1988). The study consisted of four phases: telephone pre-screening, in-person screening, 10-week treatment, and 2-week follow-up. During the 10-week treatment, participants were seen at weeks 2, 3, 4, 6, 8 and 10: clinical and research assessments were performed, and study medication and medical management sessions were provided. We titrated the medication up to the highest dose (16 mg/day) because a goal of this proof-of-concept study was to assess the maximum tolerated dose (MTD) of doxazosin in an AUD population. The choice of testing the highest dose was also consistent with the prazosin alcohol trial (Simpson et al., 2009), where the highest dose of prazosin was tested (16 mg/day). Consistent with the recommended titration schedule, doxazosin was titrated up to 16 mg daily (or MTD) during the first 4 weeks; a 1-week downward titration was also included for safety reasons. No episodes of hypotension occurred during the study.

2.2 Moderator Analysis

Consistent with recent work (Raskind et al., 2016), we *a priori* chose baseline (pre-treatment) standing BP as the moderator to be tested. Blood pressure was assessed using the same auto cuff Dinamap Adult Vital Signs Monitor machine for all patients during the entire duration of the study. The vital signs were measured by the same research staff throughout the study.

As for the TLFB-based drinking outcomes, we chose the same primary drinking outcomes selected for the parent study (Kenna et al., 2016): drinks per week (DPW) and heavy drinking days (HDD). As expected, the drinking outcomes DPW and HDD were highly correlated in the sample [$r_{197} = 0.860$, *** $p < 0.001$].

In addition, we conducted exploratory analyses to look at the potential moderator effects of standing BP on craving, anxiety, and stress. Alcohol craving was assessed using the Obsessive-Compulsive Drinking Scale (OCDS), including the total, obsessive (ODS) and compulsive (CDS) craving scores (Anton et al., 1995). Anxiety and stress were assessed using the Hamilton Anxiety Scale (HAMA) (Hamilton, 1959), the Anxiety-Tension Subscale of the Profile of Mood States (POMS-TA) (Pollock et al., 1979), and the Perceived Stress Scale (PSS) (Cohen et al., 1983).

2.3 Serum Hormones Analysis

Blood samples were collected at approximately 12:00 hour at baseline on the enrolment day (Week 01) and at the same time on the last day of the study (Week 10). Samples were stored at -80°C and serum cortisol and aldosterone levels were processed by East Side Clinical Laboratory (Providence, RI) via chemiluminescence assays.

2.4 Statistical Analysis

Distributional characteristics of outcome measures were examined to evaluate similarity to the normal distribution. As described in the parent study (Kenna et al., 2016), DPW had a skewness and kurtosis slightly in excess of two; consequently, the data were transformed using a square root transformation. Difference between groups were analyzed using χ^2 -square.

Consistent with the parent study (Kenna et al., 2016), and based on recommendations to apply a grace period to titrate medications to reach the target dose in RCTs (Falk et al., 2010), the statistical analyses included only data after the 4th week of treatment. Standing diastolic BP was dichotomized for the following three reasons: 1) from a clinical standpoint, a categorical approach for BP provides information that is easier to communicate to clinicians. That is, our approach resulted in a median split of standing diastolic BP of 80.5 mmHg. This matches well with clinical practice where diastolic BP $\leq$ 80 mmHg reflects normal BP, while diastolic BP $>$ 80 mmHg reflects a pre-hypertensive or hypertensive status; 2) from a statistical standpoint, consistent with previous reports (Rhemtulla et al., 2012), categorical variables are less influenced by outliers and are preferred for a smaller sample size; and 3) from a methodological standpoint, this approach is consistent with the parent study (Kenna et al., 2016). We used a linear mixed model analysis to investigate the potential moderator effect of standing BP on the two primary drinking outcomes (DPW and HDD) that were collected weekly (weeks 5–10). Mixed effects models only require that each subject has at least one data point, in contrast to analysis of variance (ANOVA) or generalized estimating equation (GEE) models; thus, mixed effects models include all subjects and accommodate missing data. The following covariates were added: 1) the baseline value of each dependent measure; 2) race, as its distribution differed between the two groups (Kenna et al., 2016); and 3) smoking, as nicotine is a well-known factor affecting BP (Falk et al., 2008) and there is high comorbidity between AUD and smoking (Grucza and Bierut, 2006), as also seen in this sample (approximately 70% of our alcohol-dependent patients were smokers) (Kenna et al., 2016). Then, we conducted *t*-tests as *post hoc* analysis to probe direction and nature of moderator effect. Lastly, we analyzed the main effects of standing BP as a moderator for DPW and HDD.

Standard errors (*SE*) were reported for linear mixed model analyses; standard deviations (*SD*) were reported for *t*-tests. SPSS version 21 (NY, U.S.) was used to conduct the analyses and GraphPad Prism (v.5) was used to generate figures (La Jolla, CA, USA).

3. RESULTS

3.1 Participant Characteristics

We pre-screened 197 individuals by phone; 52 individuals were screened in-person after written consent was obtained; and 41 were randomized (doxazosin, $n = 20$; placebo, $n = 21$). Participants were male or female, 18 years old, with a diagnosis of AD based on the DMS-IV and a desire to reduce or quit alcohol consumption. Baseline characteristics were extensively described in the parent study (Kenna et al., 2016). At baseline, there were no differences in BP values between the two medication groups [standing systolic: 105–162

mmHg; median split 121.5 mmHg; standing diastolic: 72–114 mmHg; median split: 80.5 mmHg; ($p's > 0.05$)). In this study, we excluded patients with significant alcohol withdrawal symptoms, *i.e.*, Clinical Institute Withdrawal Assessment for Alcohol score (CIWA-Ar) 10. There were no significant differences on the baseline CIWA-Ar scores between the two groups. The BP range of the participants was 105–162 mmHg for systolic (median split: 121 mmHg), and 72–114 mmHg for diastolic (median split: 80.5 mmHg). There was no difference of systolic and diastolic BP values at baseline among the two medication groups ($p's > 0.05$) (Kenna et al., 2016).

3.2 Standing Blood Pressure as moderator of the drinking outcomes

There was a significant standing diastolic BP $\times$ medication interaction both on DPW ($F_{1,34} = 7.555$, $**p = 0.009$; Figure 1A) and HDD ($F_{1,34} = 6.232$, $*p = 0.018$, Figure 1B). *Post-hoc* analyses showed a significant medication effect for *higher* diastolic BP in the hypothesized direction (*i.e.*, reduction of drinking) for both DPW [$t_{32} = -2.299$, $*p = 0.028$] and HDD [$t_{32} = -3.216$, $**p = 0.003$]. Large effect sizes were reported for both DPW ($d = 0.80$) and HDD ($d = 1.11$) when comparing the medication groups with *higher* standing diastolic BP. *Post-hoc* analyses for *lower* diastolic BP showed no significant difference in the medication effect for either DPW or HDD [$p's > 0.05$]. There were no effects on standing systolic BP $\times$ medication interaction ($p's > 0.05$). There were also main effects of standing diastolic BP on both DPW ($F_{1,34} = 5.941$, $*p = 0.020$) and HDD ($F_{1,34} = 8.817$, $**p = 0.005$) and of standing systolic BP on both DPW ($F_{1,35} = 13.839$, $***p = 0.001$) and HDD ($F_{1,35} = 13.960$, $***p = 0.001$). We can interpret that the main effect of BP on drinking indicated that individuals with higher BP consumed significantly more alcohol when compared to individuals with lower BP, regardless of whether or not they were taking medication [DPW: *lower* BP $M = 2.05 \pm 0.56$; *higher* BP $M = 4.0 \pm 0.53$; HDD: *lower* BP $M = 0.86 \pm 0.35$; *higher* BP $M = 4.0 \pm 0.53$]. Blood pressure was not related to differences in age, gender, race, AUD severity, or baseline of the dependent variables. In addition, standing diastolic BP was not related to high family history density of alcoholism, the moderator tested in the parent study (Kenna et al., 2016) as reflected by non-significant χ^2 -square analyses [$p > 0.05$], therefore indicating that standing diastolic BP acted as an independent moderator.

Since smoking was included as an additional covariate in this analysis, but not in the parent study, we confirmed the results when smoking was removed as a covariate from the model. We found a significant standing diastolic BP $\times$ medication interaction [$F_{1,34} = 7.809$, $**p = 0.008$] on DPW and a significant standing systolic BP $\times$ medication interaction [$F_{1,34} = 4.346$, $*p = 0.045$] on HDD. Similarly, the main effects remained when smoking was removed as a covariate: there were main effects of standing diastolic BP on both DPW $F_{1,34} = 6.034$, $*p = 0.019$] and HDD [$F_{1,34} = 7.663$, $**p = 0.009$] and of standing systolic BP on both DPW [$F_{1,35} = 13.743$, $***p = 0.001$] and HDD [$F_{1,35} = 13.740$, $***p = 0.001$]. Finally, we tested drinks per drinking days (DPDD) as an additional drinking outcome and for both for systolic and diastolic standing BP, we did not find BP $\times$ medication interactions [$p's > 0.05$].

3.3 Exploratory analyses: craving, anxiety, stress and hormone serum levels

For both for systolic and diastolic standing BP, we did not find BP $\times$ medication interactions on craving, anxiety or stress [p 's > 0.05]. There was a main effect of diastolic BP on craving [OCDS compulsive: $F_{1,32} = 5.21$, *** $p < 0.029$; OCDS total: $F_{1,32} = 5.45$, *** $p < 0.026$]. Individuals with higher diastolic BP had less of a reduction in craving [OCDS compulsive: *lower* BP $M = 3.37 \pm 0.84$, *higher* BP $M = 6.08 \pm 0.79$; OCDS total: *lower* BP $M = 6.27 \pm 1.53$, *higher* BP $M = 11.29 \pm 1.44$].

Neither cortisol nor aldosterone serum levels significantly changed from baseline to the end of the treatment (Week 10) [p 's > 0.05]. There were no significant differences in either cortisol or aldosterone serum levels between the doxazosin and placebo groups at baseline or after treatment at week 10 [p 's > 0.05]. Furthermore, there were no differences in either cortisol or aldosterone plasma levels between standing diastolic *lower* versus *higher* BP sub-groups [$p > 0.05$].

4. DISCUSSION

This study provides preliminary evidence supporting the potential role of pre-treatment standing BP as a moderator of the α_1 receptor antagonist, doxazosin's response on alcohol drinking in individuals seeking treatment for AUD. These results also suggest that standing BP may represent a biomarker of doxazosin's response in AUD. To further validate our results, we confirmed that standing BP was not a proxy of *FHDA* (Kenna et al., 2016), but an independent moderator. The specificity of our results was strengthened by the observation that in patients with *lower* BP, doxazosin not only did not reduce alcohol consumption, it appears there was a trend towards increased drinking compared to placebo. This suggests that the beneficial effects of doxazosin are specific for a sub-type of AUD patients and, if confirmed by future studies, these results may represent an example of a personalized medicine approach.

While our results are the first suggesting a role of standing BP as a moderator for the use of the α_1 blocker doxazosin in AUD, they are consistent with recent data that indicated that pretreatment BP moderated the effects of the α_1 receptor antagonist prazosin in improving PTSD symptoms in combat active duty soldiers (Raskind et al., 2016). Taken together, these studies suggest that pre-treatment BP may represent a moderator of α_1 blockers' effects on clinical outcomes related to the specific population under treatment, *e.g.*, alcohol use in AUD patients and PTSD symptoms in PTSD patients. Indeed, given the high comorbidity between AUD and PTSD (Ralevski et al., 2014), future studies should explore the potential role of pre-treatment BP as a moderator of α_1 blockade's effects on patients with both disorders.

While this study is not able to provide causal information on how pre-treatment standing BP may predict doxazosin's response in AUD patients, some considerations are worth noting. In the central nervous system, α_1 receptors regulate both arteriolar resistance and venous capacitance and thus contribute to BP (Reid, 1986); furthermore, norepinephrine stimulation increases BP. Standing BP has been proposed as a surrogate for α_1 receptor central tone (Reid, 1986) and as an index of autonomic nervous system activity (Tulen et al., 1999).

Speculatively, these considerations suggest that patients with *higher* standing BP may have a higher α_1 receptor central tone, which in turn may result in a better response to α_1 blockade via doxazosin. In addition, this observation supports the hypothesis that doxazosin's response on drinking outcomes are mediated directly by its engagement to the α_1 receptor and are specific to alcohol drinking, at least in this population of AUD patients without PTSD or anxiety comorbidity.

Consistent with this hypothesis, standing BP moderated doxazosin's effects on alcohol consumption without moderating secondary outcomes like craving, anxiety, or stress, which possibly rules out that doxazosin's responses were due to non-specific effects on anxiety and/or stress-related pathways (*e.g.*, via the HPA axis), rather than a specific central effect mediated by its action on the α_1 receptor. However, it is important to keep in mind that the sample studied here did not have other comorbidities like PTSD and/or anxiety disorders, so it was unlikely to observe a medication effect on these secondary outcomes. It is possible that, in patients with such comorbidities, α_1 receptor blockade may prevent the increase in anxiety due to alcohol deprivation, which in turn may represent a mechanism for relapse prevention, as recently observed in alcohol-preferring (P) rats (Rasmussen et al., 2016).

The lack of group differences (medication versus placebo groups; *higher* versus *lower* BP groups) in either serum cortisol or aldosterone peripheral levels in this study further supports a central effect of doxazosin via its actions on the α_1 receptor. These latter results are consistent with previous preclinical and clinical observations. For example, preclinical data do not support the concept that unregulated α -adrenergic receptor binding facilitates the potentiation of α -adrenergic-mediated vasoconstriction by corticosteroids or mineralocorticoids (Ullian, 1999). Clinical studies show that cortisol excretion rate does not correlate with BP (Fraser et al., 1999) and studies in animal models have shown that ACTH levels (which in turn stimulates cortisol release) are not affected by α_1 antagonism (Cecchi et al., 2002). Similarly, numerous studies in humans have shown that the α_1 antagonists terazosin (Beretta-Piccoli et al., 1986), prazosin (Falch et al., 1979), and doxazosin (Oliveros-Palacios et al., 1991) reduce BP without any effect on peripheral aldosterone levels. Finally, research has shown that doxazosin administration does not result in sustained changes in either cortisol or aldosterone levels (Whitworth et al., 1987). In addition, the lack of changes in serum cortisol baseline levels may also reflect, at least in part, the absence of clinically-significant alcohol withdrawal during the study (Costa et al., 1996).

Preclinical mechanistic and larger confirmatory clinical studies are needed to determine the role of BP on doxazosin's responses in AUD, and on specific BP cut-offs that may be used in future studies and clinical applications. Nevertheless, it is important to highlight the importance of these preliminary findings, especially in light of their easy translation to clinical practice. In fact, unlike other potential assessments that are self-reported and/or retrospective, BP is an objective and clinically established measurement; therefore, its use as a biomarker of treatment response to α_1 receptor blockade in neuropsychiatric disorders (*e.g.*, AUD and PTSD) may be particularly relevant. In addition, it is important to note that BP measurements are routinely performed in clinical research and medical practice, and represent a very feasible, inexpensive, and easily accessible assessment. As such, this study suggests that standing BP may represent a readily measurable biological parameter to

predict response to an $\alpha 1$ receptor antagonist like doxazosin in AUD patients. Notably, a strength of this study is that we enrolled outpatients seeking treatment for AD, a population close to patients seen in clinical practice settings. In addition, while the small sample represents an important limitation, we used a linear mixed-effects model, an approach that includes all participants and allows for missing values (Bolker et al., 2009). Finally, diastolic blood pressure is primarily a measure of peripheral vascular resistance. Unlike systolic blood pressure, diastolic BP is less affected by atherosclerosis, or other pathology, that reduces compliance and elasticity in blood vessels (Franklin, 2007). An $\alpha 1$ antagonist like doxazosin acts by inhibiting $\alpha 1$ adrenergic receptors in blood vessel smooth muscle from binding norepinephrine, which results in a reduction in peripheral vascular resistance, and thus lowers diastolic BP (Giles and Sander, 2013). Also, while some studies have shown an association between alcohol use disorder and both systolic and diastolic hypertension (Stewart et al., 2008), others have shown a more selective relationship between alcohol dependence and diastolic hypertension (Seppa et al., 1996). In summary, a potential explanation of our findings is that diastolic BP might represent a more accurate physiological marker of response to doxazosin, especially in a population affected by AUD.

In conclusion, this analysis provides additional clinical-relevant evidence for a role of doxazosin in the treatment of AUD, specifically in those AUD patients with higher pre-treatment standing BP. This study supports not only the use of personalized medicine approaches in the treatment of AUD, but also provides preliminary evidence towards identifying possible biomarkers of doxazosin's response in AD patients in order to best identify potential responders versus non-responders.

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HIGHLIGHTS

- Research suggests the α_1 receptor agonists reduces alcohol consumption
- Pre-treatment blood pressure (BP) predicts therapeutic response of prazosin in Post-Traumatic Stress Disorder (PTSD) patients
- Doxazosin reduced alcohol consumption in alcohol-dependent (AD) patients with a *high* family history density of alcoholism (FHDA)

A.

B.

B.

Figure 1. Standing diastolic blood pressure (BP) moderates doxazosin response on alcohol drinking outcomes

(A) On Drinks Per Week (DPW), there was a significant standing diastolic BP $\times$ medication interaction [$F_{1,34} = 7.555$, $**p = 0.009$]. *Post-hoc* analyses indicated a significant medication effect for patients with *higher* diastolic BP in reducing DPW [$t_{32} = -2.299$, $*p = 0.028$]. (B) On Heavy Drinking Days (HDD), there was a significant standing diastolic BP $\times$ medication interaction [$F_{1,34} = 6.232$, $*p = 0.018$]. *Post-hoc* analyses indicated a significant medication

effect for patients with *higher* diastolic BP in reducing HDD [$t_{32} = -3.216$, $**p = 0.003$].
Results are expressed as the $M \pm SEM$, not significant [$p > 0.05$].

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