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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 for prazosin in treating Post-Traumatic Stress Disorder (PTSD) symptoms and a recent trial suggested that pre-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 x 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.

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

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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 effect 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: 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 h 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