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Utilizing precision medicine to treat Alcohol Use Disorder: A commentary on the α1 receptor antagonist

Carolina L. Haass-Koffler, PharmD, PhD

Department of Psychiatry and Human Behavior, Warren Alpert Medical School; Department of Behavioral and Social Sciences, School of Public Health; Center for Alcohol and Addiction Studies; Carney Institute for Brain Science, Brown University, Providence RI.

Pharmacological targets for the development of medications to treat alcohol use disorder (AUD) are difficult to identify, not only because alcohol binds to a large number of receptors and activates and/or inhibits multiple biological systems, but also because the constellation of the AUD endophenotype is extremely complex. Therefore, advancing precision medicine and developing biomarkers able to monitor drug response represent an exploitable resource in the development of AUD pharmacotherapy (Witkiewitz et al., 2019).

Preliminary data of randomized controlled trials (RCTs) administering α1 receptor antagonists have provided promising results (Fox et al., 2012, Simpson et al., 2018), however, conflicting evidence has emerged regarding their ability to decrease alcohol consumption and craving (Wilcox et al., 2018). One aspect that emerged from those studies, is that the noradrenergic system may be affected by different factors, such as: hemodynamic parameters (Haass-Koffler et al., 2017), pharmacogenetics (Zhang et al., 2019), family history of AUD (Kenna et al., 2016), sex differences (Guinle and Sinha, 2020) and alcohol withdrawal symptoms (Sinha et al., 2021). Those factors may individually, an/or in combination, be in part responsible for different (or lack of) responses to AUD treatment (Litten et al., 2010). The results from those trials, targeting the noradrenergic system, highlight the need to develop pharmacotherapies that are tailored for different endophenotypes within the AUD spectrum, and to identify biomarkers that can be utilized for monitoring medication response (Haass-Koffler et al., 2018).

A recent RCT utilizing prazosin (an α1 receptor antagonist) amongst US soldiers on active duty presented by Raskind and colleagues (PMID), suggests additional evidence in favor of applying precision medicine approaches for the treatment of individuals with AUD. In this new study, alcohol outcomes did not significantly differ between prazosin and placebo in the sample as a whole. The effect of prazosin in reducing alcohol craving or consumption, however, was significant in a subgroup of patients with clinical features suggestive of increased noradrenergic activation, specifically elevated blood pressure and heart rate, along mild alcohol withdraw symptoms and with a post-traumatic stress disorder (PTSD) diagnosis. The overall results from this study extend support to other trials conducted

Correspondence: carolina_haass-koffler@brown.edu.

Conflicts of Interest

The author has nothing to disclose.

previously portraying that reducing noradrenergic activation in the central nervous system (CNS) with a brain penetrant α1 receptor antagonist may have regulated sympathetic nervous system overflow (i.e. peripheral proxy for central adrenergic tone) (Reid, 1986), and improved AUD outcomes.

The results for this recent prazosin trial (PMID), showed that in patients with elevated baseline hemodynamic parameters (i.e. blood pressure and heart rate), there was a significant reduction of alcohol consumption compared to placebo. In patients with neuropsychiatric disorders, blood pressure, as a clinical biomarker for assessing α1 receptor antagonism response (Haass-Koffler et al., 2017, Raskind et al., 2016), has been previously evaluated with two medications that are highly lipophilic (partition coefficient, LogP<3) and have high brain permeability (Haass-Koffler et al., 2017). First, it was tested by administering prazosin in patients with PTSD (with a primary outcome of reducing PTSD symptoms) (Raskind et al., 2016), and later by administering doxazosin in patients with AUD (with a primary outcome of reducing alcohol consumption) (Haass-Koffler et al., 2017). Taken together, the recent work by Raskind and colleagues (PMID), replicated and confirmed that elevated blood pressure represents a biomarker to identify patients who will respond better to α1 receptor antagonism. As such, this trial further supports the opportunity to utilize an easily accessible clinical biomarker (i.e. blood pressure) to monitor medication efficacy on neuropsychiatric disorders.

Mild to moderate alcohol withdrawal can also affect noradrenergic and sympathetic nervous system activations as it is characterized by irritability, dysphoria and an increase in anxiety and heart rate. A subgroup of patients within this trial who exhibited those symptoms, benefited from prazosin administration, compared to placebo (PMID). This observation, however, was not substantiated by other assessments for withdrawal (e.g.: clinical institute withdrawal assessment of alcohol scale revised, CIWA-AR) (Perkinson, 2002). Also, previous studies that involved the administration of doxazosin, cannot further support this observation as the enrolled patients, whilst patients seeking AUD treatment, were not required to abstain from alcohol (Kenna et al., 2016).

Similar to a previous study that involved 13 Department of Veterans Affairs Medical Centers (Raskind et al., 2018), this RCT showed that there was no statistically significant difference in improving PTSD symptoms between patients taking prazosin, compared to placebo. However, it is possible that prazosin's lack of effect on PTSD symptoms was due to the fact that many patients enrolled in this trial did not endorse severe PTSD symptoms. Moreover, the results from this trial further support the beneficial therapeutic response of prazosin in patients with PTSD (Raskind et al., 2016) that was observed in another study that demonstrated that prazosin, compared to placebo, was able to reduce PTSD symptoms in soldiers recently returned from combat. Those soldiers endorsed more traumatic experience and intense nightmares which may have contributed to higher adrenergic activation.

In this RCT, prazosin was able to significantly reduce alcohol craving only in patients with PTSD, a disorder that is highly comorbid with AUD in this population. This noteworthy observation may highlight that α1 antagonism may be efficacious in patients with other comorbidities. In fact, prazosin was able to alleviate co-occurring depression and emergent

depressive symptoms, results that are consistent with previous RCTs (Raskind et al., 2007, Sinha et al., 2021). The role of noradrenergic activation in anxiety and depressive disorders is corroborated by a CNS interaction between noradrenergic and corticotropin releasing factor (CRF) system (Dunn and Swiergiel, 2008). Anxiety and depressive disorders are influenced by the activation of the feed-forward loop between projections, from/to the noradrenergic/CRF-containing neurons, between the locus coeruleus (A6) and the paraventricular nucleus of the hypothalamus (PVN), which activates α1 receptors (Aston-Jones et al., 1991). The presence of a comorbidity as a possible marker for drug response is one of the most striking observations and should be further evaluated in clinical research addressing neuropsychiatric disorders, as it is often an exclusionary criterion in many RCTs.

Finally, the utilization of a medication targeting the noradrenergic system should be considered as an adjunct therapy in an alcohol recovery program. Unfortunately, this specific approach could not be demonstrated in this trial, due to the small sample size and also because patients were required when entering into the alcohol treatment program and therefore their baseline alcohol consumption was already low (which contributed to a flooring effect). The clinical observations from this study, however, suggest that prazosin may be a beneficial adjunct pharmacotherapy for mitigating excessive noradrenergic activation. Therefore, it is possible that α1 receptor antagonist medications, such as prazosin or doxazosin, by lowering adrenergic response, may reduce anxiety, depressive or stress-induced craving and reduce the risk of alcohol recurrence.

Conclusion and Future Directions

This work should be evaluated as an example of precision medicine for AUD. Precision medicine differs from personalized medicine, as the latter focus on a therapeutic approach specifically designed for one individual patient, rather than a treatment that is developed on population-based elements which includes both phenotypic and genotypic differences, including comorbidities. This work has substantiated preliminary studies on AUD pharmacological interventions, highlighting that possible comorbidities (or endophenotypes), rarely addressed in RCT protocols, can be utilized as population-based intervention.

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