Utility of Human Laboratory Models for Screening of Pharmacotherapeutics for Alcohol Use Disorder: The Case of Varenicline

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Question Being Addressed:

Alcohol use disorder is associated with tremendous cost and negative impact to the affected individual and society. This underscores the critical and unmet need for more efficacious pharmacotherapeutic agents that can help improve treatment outcomes in individuals with AUD. Pre-clinical models can help identify novel targets for AUD treatment and clinical trials can provide evidence of clinical efficacy; however, there is a need for approaches to screen these new targets in humans prior to larger proof-of-concept studies.

This study aimed to evaluate the effects of varenicline, a partial nicotinic receptor agonist, in a human laboratory model of alcohol response and motivation as well as neuroimaging-based correlates of these behaviors. This study examines the utility of the approach of using human lab models to evaluate potential new medications on alcohol response measures to provide early indicators of potential future clinical effectiveness of novel medications for AUD treatment.

ABSTRACT:

INTRODUCTION: Alcohol use disorder (AUD) is a chronic disease that has a tremendously negative impact on affected individuals, and a substantial burden on society as a whole. FDA-approved medications for AUD have been shown to reduce hazardous drinking and improve health; however the effect sizes for existing medications are small, and clinical utilization is low. Thus, there is a great need to expand the range of therapeutics and develop personalized treatment approaches. Human laboratory models provide an important translational approach to developing initial evidence of novel pharmacological targets, thus facilitating the screening of promising new therapeutics prior to proof-of-concept phase-II trials.

Pre-clinical and emerging clinical evidence suggest that varenicline, a nicotinic partial agonist approved for smoking cessation, attenuates alcohol seeking and consumption. This study examined the effects of varenicline in heavy drinkers using human laboratory models of motivation and consumption of alcohol including: (1) a novel Alcohol–Food Incentive Delay (AFID) functional magnetic resonance imaging (fMRI) task to examine brain activation associated with incentive salience of alcohol reward cues, and (2) an intravenous alcohol self-administration (IV-ASA) paradigm.

METHODS: In this double-blind, placebo-controlled, randomized trial, 29 participants, aged 21-60 years, received varenicline (2 mg/day) or placebo for 3 weeks. After 2 weeks of treatment, participants underwent an fMRI scan while performing the AFID task. At baseline and at 3 weeks of treatment, participants underwent a 2-hour IV-ASA session where they could press a button to receive short standardized alcohol infusions up to a maximum blood alcohol concentration (BAC) of 0.12%.

RESULTS: Results from the fMRI task showed that cues signaling alcohol reward were associated with significant brain activation in the nucleus accumbens, amygdala and posterior insula in the placebo, but

not in the varenicline group (all $p<0.05$). Varenicline also attenuated subjective feelings of happiness and excitement in response to alcohol cues compared to placebo. Participants with higher insula response to alcohol cues showed higher IV-ASA behavior across treatment groups ($R2=0.26$). Varenicline did not affect IV-ASA measures, possibly due to a ceiling effect on maximal BAC.

CONCLUSIONS: Varenicline decreased activation in brain regions associated with motivation and incentive salience of alcohol reward in heavy drinkers. These findings along with results of other clinical trials indicate the potential utility of varenicline in treatment for AUD. These human experimental models provide insight into potential biobehavioral mechanisms underlying varenicline effect and the fMRI measures may have utility as a brain marker of potential effectiveness of novel pharmacotherapies for AUD.

DISCLOSURES: The authors report no conflicts of interest for this work.