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

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Introduction

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.

Background

- There is considerable evidence for a role of the nicotinic system in the rewarding effects of alcohol. Varenicline is a nicotinic partial agonist currently approved for smoking cessation, and pre-clinical and clinical studies suggest that varenicline may attenuate the motivation for, as well as the rewarding effects of alcohol. Varenicline may have clinical utility in the pharmacotherapy of alcohol use disorder (AUD) (Litten, 2013).
- The brain reward system, particularly the striatum, has demonstrated activation during anticipation of working for reward, including alcohol. The Monetary Incentive Delay (MID) task has been used extensively to study reward processing. The BOLD signal change in the striatum during anticipation for monetary reward is thought to measure the incentive salience of reward cues (Knutson, 2001; Bjork, 2004), and may serve as a brain biomarker of the effectiveness of medications that target the reward system in AUD.
- Self-administration is a hallmark of all addictive drugs, including alcohol. Human experimental models using intravenous alcohol self-administration (IV-ASA) assess alcohol seeking and consumption behavior (Zimmermann, 2013), and may be sensitive to medications that target the rewarding effects of alcohol.

Objectives

This study examined the effects of varenicline in heavy drinkers using experimental 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.

Study Design

- Randomized, double-blind study in 36 male and female, smoking and non-smoking, heavy drinkers, aged 21-58 years.

Study procedure	IV Alcohol self-administration	Dosing begins			fMRI scan (AFID task)	IV Alchohol self-administration
Day	0	1	4	7	14	21
Dose	0	0.5mg 1x day	1mg 1xday	1mg 2xday		1mg 2x day

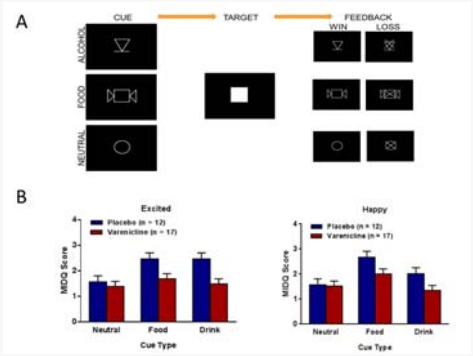
Subject Characteristics

n = 29*	Placebo						Varenicline					
	Non Smoker (n = 6)		Smoker (n = 6)		Total (n = 12)		Nonsmoker (n = 9)		Smoker (n = 8)		Total (n = 17)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Male/Female	5/1		6/0		11/1		8/1		6/2		14/3	
Age (Years)	37.3	16.6	38.5	11.3	37.9	13.5	27.6	8.1	32.3	10.6	29.8	9.4
Timeline Followback (90 days)												
Drinking Days	66.2	17.8	65.3	14.7	65.8	15.6	59.1	19.3	79.7	12.1	68.1	19.2
Drinks/ Drinking Day	5.7	2.3	8.2	2.6	6.9	2.7	6.7	3.4	5.7	2.9	6.2	3.1
Heavy Drinking Days	34.5	11.5	54.3	19.7	44.4	18.5	34.2	21.6	51.1	29.7	42.2	26.4
AUDIT	12.5	4.2	14.3	6.9	13.4	5.5	12.2	3.4	16.4	5.6	14.2	4.9

*2 subjects in Varenicline group and 5 subjects in Placebo group were excluded from analysis due to insufficient data.

Results

Alcohol-Food Incentive Delay Task



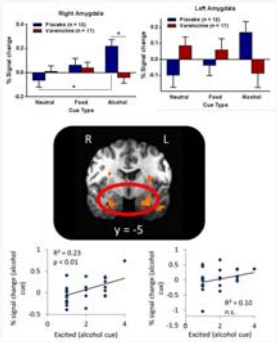
Panel A shows the visual cues for alcohol (intravenous alcohol infusion), food (highly palatable snacks) or neutral (no rewards) conditions as well as the task sequence. Panel B shows a significant main effects of medication for the items Excited ($F1,25 = 8.16$, $p = 0.009$) and a trend for a main effect of medication Happy ($F1,25 = 3.79$, $P = 0.063$). The varenicline group showed lower scores compared to the placebo group across cue types. Error bars represent SEM.

Brain Activation during Reward Anticipation

Ventral Striatum

A cluster in the right putamen showed a significant treatment-by-cue-type interaction. The placebo group showed greater activation to alcohol cues relative to neutral cues, whereas the varenicline group showed equivalent activation for both cue types. Individuals with higher putamen activity during the alcohol cue also reported greater excitement when viewing the alcohol cue (R^2=0.23, p=0.009). Error bars represent SEM.

Amygdala

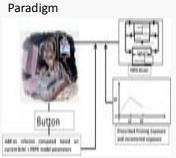


Clusters in the bilateral amygdala showed significant treatment-by-cue-type interactions, where the placebo group showed increased activity in response to an alcohol cue relative to a neutral cue, but the varenicline group did not show increased activity in response to an alcohol cue. In the right amygdala cluster, post-hoc analysis showed that the varenicline group had significantly less activation in response to an alcohol cue relative to the placebo group. Activity in the right amygdala cluster during an alcohol cue was positively correlated with self-reported excitement when viewing the alcohol cue (R^2=0.23, p=0.009). Error bars represent SEM.

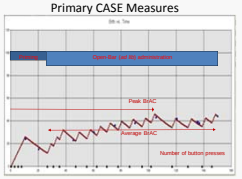
IV-Alcohol Self-Administration (IV-ASA)

Computer-Assisted Self-infusion of Ethanol (CASE) Method

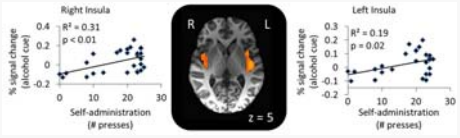
Schematic of CASE Paradigm



Typical CASE Session Data Output Showing Primary CASE Measures



Relationship between IV-ASA and Brain Activation



There were no main effects of varenicline on IV-ASA measures. Results of a voxel-wise analysis of correlation between the number of self-infusions during the second visit (button presses). The analysis revealed a positive association between button presses and activity in the bilateral posterior insula in response to the alcohol cue (right: R2=0.31, p=0.006; left: R2=0.19, p=0.02).

Conclusions

- Varenicline decreased activation in striato-cortico-limbic regions associated with motivation and incentive salience of alcohol reward in heavy drinkers.
- 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.
- The AFID task demonstrates robust striatal responses to alcohol cues, indicating its potential utility as a brain biomarker of motivation and incentive salience of alcohol (and possibly other rewards), as well as of the effect of medications on the neural correlates of these reward processes.
- Medication repurposing of varenicline could be targeted towards reward-drinkers seeking treatment for AUD. Human experimental models of alcohol seeking and consumption may facilitate development of pharmacotherapies for AUD.

References

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