Title:

Lemborexant Augmentation of Naltrexone for Alcohol Craving and Sleep: A Randomized, Double-Blind, Placebo- Controlled Study

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Background

Alcohol is one of the most popular substances used worldwide for thousands of years. Globally, harmful alcohol use continues to be a major public health and economic burden. The World Health Organization global status report attributed harmful alcohol use to 3 million deaths in 2016.(*Global Status Report on Alcohol and Health 2018*, n.d.) In the United States, alcohol is the most used substance by people over the age of 12, with alcohol use disorder (AUD) affecting 14.5 million people in this age group. Hazardous alcohol use is associated with emergency room visits, overdose, driving fatalities and chronic medical conditions such as liver disease, heart disease, and hypertension.(*Alcohol Facts and Statistics | National Institute on Alcohol Abuse and Alcoholism (NIAAA)*, n.d.)

Pharmacological interventions for AUD have expanded over the past few decades, including FDA approved and off-label medications such as naltrexone that have demonstrated efficacy in reducing alcohol cravings, consumption, and likelihood of relapse.(Swift & Aston, 2015; Zindel & Kranzler, 2014) However, the significant variability in response to treatment fuels ongoing interest in novel pharmacotherapy for AUD. A common approach involves repurposing readily available medications based on our understanding of AUD pathophysiology. In this study, we focus on the orexin system, which has been implicated in behaviors such as feeding, sleep-wake cycle, motivation, and reward associated with food, sex and substances including alcohol.(Li et al., 2016) The brain neuropeptides orexin A and orexin B originate in the hypothalamus and project throughout the central nervous system, activating G-protein-coupled receptors orexin 1 and 2 (OX1R and OX2R). While both orexin receptors are involved in addictive behaviors, OX1R signaling has a stronger association with reward processes whereas OX2R promotes arousal. Chronic alcohol exposure may lead to neuroadaptations in the orexin system, as observed in studies showing a positive correlation between orexin levels and severity of alcohol dependence and distress during alcohol withdrawal.(Goltz et al., 2009; Ziółkowski et al., 2016) Moreover, multiple animal studies have demonstrated efficacy of orexin antagonists in reducing alcohol craving, self-administration, and reinstatement of alcohol use induced by cues and stress.(Moorman, 2018)

The orexin antagonist lemborexant is FDA approved for treatment of insomnia. Lemborexant acts on both OX1R and OX2R and has shown efficacy in sleep initiation and maintenance compared to placebo on polysomnography and patient-report.(Rosenberg et al., 2019) It has demonstrated long-term safety and effectiveness without physical dependence or rebound insomnia.(Murphy et al., 2017; Yardley et al., 2021) Compared to suvorexant, another orexin antagonist, lemborexant has greater selectivity and stronger binding for orexin receptors. Suvorexant has secondary effects on the adenosine receptor and dopamine transporter whereas lemborexant only has weak binding to melatonin 1. These differences may increase risk of misuse for suvorexant more than lemborexant.(Asakura et al., 2021) In addition, Lemborexant's longer half-life (17-19h) may be advantageous for reduction of cravings during the day.(Landry et al., 2021)

In people with AUD, insomnia is a common problem that is associated with alcohol craving and relapse.(He et al., 2019) Standard treatment for AUD with naltrexone improves cravings and other AUD outcomes, but does not improve sleep. In some cases, naltrexone may have a detrimental effect on sleep.(Anton et al., 2006; Panin & Peana, 2019) Lemborexant may be able to target both alcohol craving/urges and insomnia when added to standard treatment with naltrexone.

Aims and hypothesis

Our primary goal is to evaluate the effects of naltrexone plus lemborexant augmentation compared to naltrexone plus placebo on cue-induced and non-cued alcohol craving scores. Our secondary goals are to evaluate the effects of this combination on sleep quality using actigraph data.

> **Hypotheses**: H1: we hypothesize that the group receiving naltrexone plus lemborexant augmentation will have a greater decrease in cue-induced and non-cued alcohol craving scores than naltrexone plus placebo. H2: we hypothesize that the group receiving naltrexone combined with lemborexant will experience a greater improvement on objective sleep measures.

Significance of the problem

Alcohol use disorder (AUD) and insomnia are highly comorbid in our psychiatric inpatients. In people with AUD, insomnia may be persistent and is associated with alcohol craving and relapse. Standard treatment for AUD with naltrexone improves cravings and other AUD outcomes, but does not improve sleep. In some cases, naltrexone may have a detrimental effect on sleep. Insomnia is associated with higher severity of depression, anxiety, and suicidality. Adequate treatment of both alcohol cravings and insomnia may improve overall outcomes.

Design and methods

The study will be a randomized, double-blind, placebo-controlled clinical trial of naltrexone plus placebo versus naltrexone plus lemborexant conducted at The Menninger Clinic on inpatients with alcohol use disorder. Recruitment will occur on patients admitted to a Menninger inpatient unit over a 12-month period. Because the average length of stay at The Menninger Clinic is 2 to 4 weeks, the study period will last 2 to 4 weeks depending on the patient's length of stay. We plan to enroll 10 patients and randomize half to lemborexant plus naltrexone and half to placebo plus naltrexone using a computer-generated randomization scheme.

All participants will receive a standard treatment program with pharmacotherapy for their psychiatric conditions, CBT, DBT, individual therapy, and group therapy during their inpatient admission. Subjects will be randomly assigned to either naltrexone plus placebo or naltrexone plus lemborexant. For all patients, naltrexone will be given at 50 mg/day. For the lemborexant augmentation group, lemborexant will be given at 10mg at bedtime. Dose reductions due to tolerability will be permitted at the discretion of the investigator. Blinding will be ensured by use of a matching placebo for lemborexant 10mg using over-encapsulation. Participants and study personnel will be blinded to the study drug. Medications will be administered by nursing staff. All participants will be exposed to alcohol-related cues using virtual reality technology at baseline, at the end of week 2 or end of week 4.

Safety: Safety assessments will be collected weekly throughout the study. These assessments will consist of monitoring and recording of adverse events and periodic measurement of vital signs.

Assessment and Outcomes Measures (Tables 1 and 2): As part of the Menninger Clinic inpatient evaluation, each patient will be given a medical examination, including physical exam and laboratory testing on admission. Assessments will include baseline EKG, CBC, BMP, liver profile, pregnancy test (females), and urine drug screen. This information is part of the health record and will be collected for screening and analysis.

Clinical diagnoses including alcohol use disorder will be assessed using the structured clinical interview for DSM-5 (SCID-5). Alcohol use disorder severity will be measured using the alcohol dependence scale (ADS). We will also be using an actigraph to measure total sleep time and wake after sleep onset. Cue-induced alcohol cravings will be assessed using the Alcohol Urge Questionnaire (AUQ) and non-cued alcohol craving will be assessed using the Penn Alcohol Craving Scale (PACS).

Table 1: Initial Assessment, Sleep, Mood, and Suicide risk

Measure	**Instrument**	**Screening**	**Daily**	**Weekly**	**Discharge**
DSM-5 Diagnoses (including Alcohol use disorder)	Structured Interview for DSM-5 (SCID-5)	X			
Alcohol Use Disorder Severity	Alcohol Dependence Scale (ADS)	X			
Total Sleep Time, wake after sleep onset	ActiGraph wGT3X-BT	X		X	X

Table 2: Alcohol Craving Measures

Measure	Instrument	Baseline	Week 1	Week 2	Week 3	Week 4
Cue-induced alcohol craving	Alcohol Urge Questionnaire (AUQ)	X	x	x	x	x
Non-cued alcohol Craving	Penn Alcohol Craving Scale (PACS)	X	X	X	X	X

Statistical Analysis: Descriptive statistics and bivariate tests will be used to inspect distributional properties of sample demographics and clinical outcomes at baseline, within the sample and between participant subgroups (e.g., gender, age, AUD severity). All outcome measures and safety assessments will be summarized weekly over the study period. Additionally, variables that significantly differ between participants who dropped out of the study and those who did not will be controlled statistically in our hypothesis testing to minimize any systematic bias due to attrition. Hierarchical linear modeling (HLM) will be conducted to examine the effects of receiving naltrexone plus lemborexant augmentation versus naltrexone plus placebo, while properly accounting for (a) the dependency of observations—i.e., correlation of repeated measurements (level 1) within participants (level 2) and (b) any difference due to receiving the treatments in a different group. Appropriate covariance structures will be determined in a preliminary analysis (i.e., intercept-only model) based on model fit (e.g., adjusted Akaike Information Criterion, Bayesian Information Criterion). Statistical significance will be determined at 0.05 alpha level.

Sample Size and Power: The study is a pilot trial with a purpose of obtaining *unbiased* effect sizes for naltrexone plus lemborexant augmentation prescribed to a small number of adult patients with AUD. No formal power calculation is

applicable because this is a first-in-human study and relevant data is not available in the literature.

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