STUDY PROTOCOL INCLUDING STATISTICAL ANALYSIS PLAN

OFFICIAL TITLE: **Does Guanfacine Attenuate Stress-Induced Drinking?**

BRIEF TITLE: **Does Guanfacine Attenuate Stress-Induced Drinking? (Sherry McKee, PhD, PI)**

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Identifying effective medications for the treatment of alcohol use disorders remains a high priority as problems associated with alcohol use continues to be major public health problem. One promising, yet relatively unexplored avenue for medication development for alcohol use are therapeutics that target stress-reactivity. Several lines of evidence suggest that stress is a primary mediator of alcohol use and relapse. Preclinical research demonstrates that noradrenergic pathways are involved in stress-induced consumption and reinstatement to alcohol, as well as alcohol-related reinforcement and withdrawal, and that their manipulation may be of potential therapeutic benefit for alcohol use.

Guanfacine is an alpha2a adrenergic receptor agonist known to attenuate stress-induced reinstatement to alcohol and other drugs of abuse in preclinical studies. Guanfacine rescues the prefrontal cortex from detrimental effects of stress and improves working memory, attention, and behavioral control. In a study evaluating 3mg/day guanfacine for smoking cessation, we demonstrated that guanfacine was well tolerated, attenuated the effects of stress on smoking, reduced smoking-related reinforcement, improved cognition, and significantly reduced smoking during a brief treatment phase.

STUDY OBJECTIVE

To conduct a Phase II human laboratory study evaluating the effect of guanfacine on alcohol consumption. Using a double-blind, placebo-controlled, dose-ranging parallel group design, we randomized non-treatment seeking adults with alcohol use disorders (DSM-IV dependence or abuse) to guanfacine (3mg/day, 1.5mg/day, or placebo) to evaluate whether guanfacine reduces alcohol self-administered in the laboratory. Following titration to steady state medication levels over a 3-week period, each subject will complete two laboratory sessions to evaluate drinking during a 2-hour alcohol self-administration paradigm.

STUDY DESIGN AND METHODS

This study was a double-blind, placebo controlled, parallel-group design, to compare immediate release guanfacine (1.5, 3.0mg/day) to placebo (0mg/day) in adults meeting criteria for DSM-IV alcohol use disorders. This study consisted of an intake session, a physical exam, and two laboratory sessions following titration to steady state levels. Ad-lib alcohol consumption was assessed during the 2-hour session. Doses designed to raise alcohol to 0.12 g/dL were provided. Following the medication taper, subjects were assessed for an additional two weeks. Primary outcome measures include mls consumed during the self-administration sessions, and secondarily, the frequency and severity of adverse events during the titration period.

ELIGIBILTY

Minimum Age: 21 Years

Maximum Age: 65 Years

Sex: All

Gender Based:

Accepts Healthy Volunteers: Yes

Criteria:

Inclusion Criteria:

Age 21-65

Able to read and write English

Meets Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for current (past 6 months) alcohol abuse or alcohol dependence

Exclusion Criteria:

Participants with any significant current medical conditions, seizures, delirium or hallucinations, or other unstable medical conditions including HIV

Current DSM-IV abuse or dependence on substances, other than alcohol abuse, alcohol dependence, or nicotine dependence

Women who are pregnant or nursing

Suicidal, homicidal or evidence of current (past 6-month) mental illness

Meet DSM-IV criteria for current (past-6 month) attention deficit hyperactivity disorder (ADHD)

Specific exclusions for administration of guanfacine not already specified include: EKG evidence at baseline screening of any clinically significant conduction abnormalities or arrhythmias; known intolerance for guanfacine or any alpha blocker; history of fainting, syncopal attacks, heart failure or myocardial infarction, or impaired liver as indicated by aspartate aminotransferase (AST), alanine aminotransferase (ALT) > 3x normal or renal function (estimated creatinine clearance <60 cc/min); treatment with any antihypertensive drug or any alpha-adrenergic blocker; use of any central nervous system (CNS) depressant (e.g., phenothiazines, barbiturates, benzodiazepines)

Subjects likely to exhibit clinically significant alcohol withdrawal during the study.

Individuals who are seeking treatment for drinking

STATISTICIAL CONSIDERATIONS

PRIMARY HYPOTHESIS: During the laboratory component, 3mg/day guanfacine and 1.5mg/day guanfacine vs placebo will reduce alcohol consumption. Linear mixed models with medication condition, lab session, and time were used to evaluate mls consumed.