STUDY PROTOCOL INCLUDING STATISTICAL ANALYSIS PLAN

OFFICIAL TITLE: Guanfacine Clinical Trial for Smoking Cessation

BRIEF TITLE: Guanfacine Clinical Trial for Smoking Cessation (Sherry McKee, PhD, PI)

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Identifying effective medications for the treatment of tobacco dependence remains a high priority as the vast majority of smokers fail to maintain long-term abstinence even with FDA approved pharmacotherapies. One promising, yet relatively unexplored avenue for medication development for smoking cessation are medications which target stress-reactivity. Several lines of evidence suggest that stress is a primary mediator of smoking maintenance and relapse. Preclinical research demonstrates that noradrenergic pathways are involved in stress-induced reinstatement to nicotine, as well as nicotine-related reinforcement and withdrawal, and that their manipulation may be of potential therapeutic benefit for smoking cessation.

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 clinical trial evaluating the efficacy of guanfacine for smoking cessation. Using a double-blind, placebo-controlled, parallel group design, we randomized adult daily smokers to guanfacine (6mg/day ER, or placebo) combined with brief behavioral support for an 8-week treatment period.

STUDY DESIGN AND METHODS

This Phase II, clinical trial is a double-blind, placebo-controlled, parallel group study. Adult daily smokers motivated to quit smoking were be randomized to guanfacine (6mg day ER) or placebo Sex will be a stratification variable (50% female). Following eligibility screening and randomization, participants were titrated to steady state medication levels over a 3-week period. Participants completed an 8-week treatment period combining medication with brief behavioral support and were followed 6 months post-treatment to assess the durability of medication effects. The primary outcome measure was rates of prolonged smoking abstinence at the end of the 8-week treatment phase.

ELIGIBILTY
Minimum Age: 18 Years

Maximum Age: 65 Years

Sex: All

Gender Based:

Accepts Healthy Volunteers: Yes

Criteria:

Inclusion Criteria:

Age 18-65

Able to read, write and comprehend English

Smoker

Able to take oral medications and willing to adhere to a medication regimen

Provide evidence of a stable living residence in the last 2 months, have reasonable transportation to the study site, and have no plans to move within the next 3 months or unresolved legal problems

Exclusion Criteria:

Any significant current medical conditions that would contraindicate smoking

Current Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) abuse or dependence of other substances, other than nicotine dependence or alcohol abuse

Positive test results at intake appointment on urine drug screen for illicit drugs

Past 30 days use of any psychoactive drugs including anxiolytics and antidepressants

Women who are pregnant or nursing

Suicidal, homicidal or evidence of current mental illness such as schizophrenia, bipolar disorder or major depression, or anxiety disorders

Meeting DSM-IV criteria for current attention deficit hyperactivity disorder (ADHD)

Individuals who are currently taking medications known to be effective for smoking cessation or are regular users of other tobacco products in the past 30 days

Only one member per household can participate in the study

Specific exclusions for administration of guanfacine not already specified include:

EKG evidence at baseline screening for 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

Impaired liver (as indicated by aspartate aminotransferase (AST), alanine aminotransferase (ALT) >3x normal)

Renal function (as indicated by estimated creatinine clearance <60cc/min)

Treatment with any antihypertensive drug or any alpha-adrenergic blocker

Use of any central nervous system depressant (e.g., phenothiazines, barbiturates, benzodiazepines)

Use of strong cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ketoconazole) or inducers (e.g., rifampin), or consumption of grapefruit juice

Subjects may not have donated blood in the past 8 weeks or have been involved in other investigational studies that involve substantial blood draws or medications unknown to us

STATISTICIAL CONSIDERATIONS

PRIMARY HYPOTHESIS: Guanfacine vs placebo will increase rates of prolonged abstinence during weeks 3 to 8 of the 8-week treatment period. Logistic regression was used to evaluate medication effects on the abstinence outcome.