STUDY PROTOCOL INCLUDING STATISTICAL ANALYSIS PLAN

OFFICIAL TITLE: Modeling Stress-precipitated Smoking Behavior for Medication Development

BRIEF TITLE: Stress and smoking behavior (Sherry McKee, PhD, PI)

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

Guanfacine is an alpha2a adrenergic receptor agonist known to attenuate stress-induced reinstatement to nicotine 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.

STUDY OBJECTIVE

To conduct a Phase II human laboratory study evaluating the effect of guanfacine on smoking behavior. Using a double-blind, placebo-controlled, we randomized adults with nicotine dependence to guanfacine (3mg/day or placebo) to evaluate whether guanfacine increases the ability to resist smoking. Following titration to steady state medication levels over a 3-week period, subjects completed two laboratory sessions to evaluate drinking smoking behavior.

STUDY DESIGN AND METHODS

This study was a double-blind, placebo controlled, parallel-group design, to compare immediate release guanfacine (3.0mg/day) to placebo (0mg/day) in adults meeting criteria for nicotine dependence. This study consisted of an intake session, a physical exam, and two laboratory sessions following titration to steady state levels. Ability to resist smoking was modelled as the delay to start smoking in exchange for monetary reinforcement. Primary outcome measure time to delay smoking.

ELIGIBILTY

Minimum Age: 18 Years

Maximum Age: 60 Years

Sex: All

Gender Based:

Accepts Healthy Volunteers: Yes

Criteria:

Inclusion Criteria:

- ages 18-60
- able to read and write in English

- smokers

Exclusion Criteria:

- any significant current medical conditions that would contraindicate smoking
- current Diagnostic and Statistical Manual IV (DSM-IV) abuse or dependence of other substances, other than nicotine (or caffeine) dependence
- positive test result at intake appointments on urine drug screens conducted for opiates, cocaine, or benzodiazepines
- women who are pregnant or nursing
- suicidal, homicidal or evidence of severe mental illness
- participants prescribed any psychotropic drug in the 30 days prior to study enrollment
- blood donation within the past 6 weeks
- participants who have engaged in a quit attempt in the past 3 months
- specific exclusions for administration of guanfacine not already specified include: Hypotensive individuals with sitting blood pressure below 90/50 mmHG; EKG evidence at baseline screening of any clinically significant conduction abnormalities, including a Bazett's corrected QT interval (QTc) >450 msec for men and QTc>470 msec for women; known intolerance for guanfacine

STATISTICIAL CONSIDERATIONS

PRIMARY HYPOTHESIS: During the laboratory session, 3mg/day guanfacine vs placebo will increase the time to resist smoking. Anova of medication condition was used to evaluate time to delay smoking.