STUDY PROTOCOL INCLUDING STATISTICAL ANALYSIS PLAN

OFFICIAL TITLE: Combining Varenicline and Guanfacine for Smoking Cessation

BRIEF TITLE: Varenicline and Guanfacine 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. For this study, we tested whether the combination of guanfacine and varenicline (and FDA approved medication for smoking cessation) produced preferable outcomes to varenicline alone. There is significant preclinical data identifying that the noradrenergic and acetylcholine systems interact at the cellular and molecular level, and combined treatment with guanfacine and varenicline may produce additive effects on smoking cessation.

STUDY OBJECTIVE

The novel design of this study combines a laboratory paradigm to evaluate stress-induced smoking behavior and smoking-related reinforcement, followed by a 12-week treatment phase to evaluate clinical outcomes.

STUDY DESIGN AND METHODS

This Phase II, clinical trial is a double-blind, placebo-controlled, parallel group study. Adults who smoked daily and were motivated to quit smoking were be randomized to guanfacine (6mg day ER) + varenicline (2mg/day) or varenicline only. Following eligibility screening and randomization, participants were titrated to steady state medication levels over a 3-week period, and then completed a laboratory session to evaluate the effect of stress on smoking. Participants then completed a 12-week treatment period combining medication with brief behavioral support. The primary outcome measure was the ability to resist smoking following stress.

ELIGIBILTY

Inclusion Criteria:

1. Age 18+
2. Able to read and write English
3. SMOKER: 10 or more cigarettes per day for at least the past year, Carbon Monoxide (CO) > 10 ppm at intake
4. Able to take oral medications and willing to adhere to medication regimen
5. Provide evidence of a stable living residence in the last 2 months prior to randomization, have reasonable transportation arrangements to the study site, have no plans to move within the next 3 months, and have no unresolved legal problems
6. Motivated to quit smoking (8 or greater on the Contemplation Ladder)

Exclusion Criteria:

1. Subjects with any significant current medical conditions (neurological, cardiovascular [including hypertension or hypotension: sitting BP >160/100 or <90/60mmHg at baseline screening], endocrine, thyroid, renal, liver), seizures, delirium or hallucinations, or other unstable medical conditions
2. Current Diagnostic and Statistical Manual of Mental Disorders (DSM-V) alcohol or substances use disorders, other than mild alcohol use disorder or tobacco use disorder
3. Subjects who have a positive test result at intake appointment on urine drug screens conducted for illicit drugs
4. Past 30 day use of psychoactive drugs excluding anxiolytics and antidepressants (however, see #10; barbiturates, benzodiazepines are exclusionary)
5. Women who are pregnant or nursing, or fail to use one of the following methods of birth control unless she or partner is surgically sterile or she is postmenopausal (hormone contraceptives [oral, implant, injection, patch, or ring], contraceptive sponge, double barrier [diaphragm or condom plus spermicide], or IUD)
6. Suicidal, homicidal or evidence of current (past 6-month) severe mental illness such as schizophrenia or bipolar disorder
7. meeting DSM-V criteria for current (past-6 month) attention deficit hyperactivity disorder (ADHD)
8. Individuals who are currently taking medications known to be effective for smoking cessation (e.g., FDA smoking cessation medications, nortriptyline, clonidine) or are regular users of e-cigarettes or other tobacco projects (pipe, cigar, smokeless tobacco) in the past 30 days
9. Only one member per household can participate in the study
10. Specific exclusions for administration of guanfacine not already specified: 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 (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-blocker; use of any central nervous system (CNS) depressant (e.g., phenothiazines, barbiturates, benzodiazepines)
11. Specific exclusions for the administration of varenicline not already specified: known intolerance to varenicline or taking H2blockers (e.g., Cimetidine), quinolones, or trimethoprim.

STATISTICIAL CONSIDERATIONS

PRIMARY HYPOTHESIS: Guanfacine+varenicline vs varenicline will increase the ability to resist smoking following stress. Random effects regression was used to evaluate medication effects on the latency to smoke.