Pharmacogenetic Trial of Noradrenergic Medication for Treatment of Cocaine Abuse

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Title	**Pharmacogenetic Trial Of Noradrenergic Medication for Treatment of Cocaine Dependence**
Protocol #	**H-32926, Baylor College of Medicine IRB**
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Grant #	**VA-funded CDA**

Background and Objectives

Cocaine use disorders are a significant cause of morbidity and mortality throughout the world. Cocaine has been shown to significantly worsen symptoms of hyperarousal among Vietnam combat veterans with post-traumatic stress disorder (PTSD), a disorder which affects approximately 14% of all previously deployed U.S. military personnel. Noradrenergic antagonism reduces cocaine use. Noradrenergic treatment for cocaine use can also reduce anxiety (PTSD) symptoms.

Original goals of proposed research were: (1) To investigate the intersection between cocaine dependence and anxiety disorders such as PTSD, given the common involvement of the noradrenergic system in the neuropathogenesis of these disorders; (2) To apply pharmacogenetics to identify subpopulations of cocaine dependent individuals that respond preferentially to pharmacologic treatments affecting the noradrenergic system.

However, due to a reduced sample size from 150 to 43 individuals (see Data Analysis section), the final goal was reduced to only determining whether Doxazosin was an effective agent in reducing cocaine use. No further level of analysis was possible due to the reduced sample size.

Data Analysis

In our original proposal we anticipated randomizing N = 150 in a 1:1 ratio to two conditions (n = 75 per condition). However, due to significant difficulties in recruitment in this population, total recruitment goal was reduced to 43 individuals with approximately equal distribution into active vs placebo arms for this study. Analysis will be made via a Bayesian analysis using a posterior predictive distribution.

Rather than serving as the definitive trial of doxazosin for treatment of cocaine use disorder, the aim of this CDA was to examine whether or not the compound warrants further investigation in a larger scale, phase IIb/III trial. Developing effective pharmacotherapy requires incremental investigation of biologically plausible treatments based on systematically accruing data. Bayesian statistical inference provides a principled approach to answer this question. Bayesian statistical reasoning lends itself particularly well to evaluating evidence in this context. Indeed, addressing the so-called “Pipeline Problem” in developing clinical applications, the FDA has indicated that Bayesian statistics offers one avenue of improved methodological efficiency.[i,ii,iii,iv,v,vi] Decision-making based on an initial trial of a compound for a new indication is assisted by estimates of the probability of an effect of some specified magnitude. These statements, not part of the conventional, Frequentist statistical lexicon, are accessible via Bayesian approaches, even with small sample sizes.[vii,viii]

Strengths of the Bayesian analysis are as follows:
1) Present the strengths of using a Bayesian approach to obtain probabilistic estimates of the effect sizes that exist, given our current data.

2) Stipulate prior distributions for analysis of the current data (prior to examining the data). These priors will include: a) weak, diffuse priors and b) empirically-based informative priors derived from a sample drawn from the same general population.

3) Stipulate a decision-rule that, prior to examining the data, will articulate the necessary threshold of evidence that will warrant further consideration of the current test compound in future trials. This decision-rule requires two parts: a) specification of an effect that would merit continued investigation, and b) specification of the posterior probability that this effect, or one larger, exists that would be sufficient to warrant future trials. The decision rule we will initially propose to the DSMB is that if, after analysis with empirically-derived informative priors, the drug compound (doxazosin) demonstrates a posterior probability >0.66 (2 in 3 chance) of a >15% increase in sustained 2-week abstinence at the end of treatment, then the drug warrants further investigation.

Risk/Benefits Ratio

The primary benefit of participation in this study is the potential for reduction of cocaine use through the study medication as well as through access to the guided cognitive behavioral therapy (CBT) option. If the treatment is found to be effective, other individuals with similar problems may benefit from the findings of this study. The psychological and laboratory assessments confer minimal risks and these are minimized through confidentiality procedures and the use of skilled personnel to administer the assessments. The medication treatment confers potential risk, but Doxazosin has been found to be safe in previous studies. Careful screening of physical health prior to study entry and close daily monitoring of patients during the study should reduce these risks. This proposed study may help to develop new and more effective treatments for stimulant dependence. Given that the risks are managed appropriately and the societal benefits are substantial, the ratio of this study appears greatly weighted towards benefit.

Procedures

Recruitment will be by word-of-mouth and fliers posted in VA clinics. Interested candidates will be scheduled for a phone screen with a qualified investigative staff member and receive an explanation of the study purpose and requirements in lay language. The study procedures will select individuals more likely to comply with study requirements by requiring subjects to attend clinic visits and submit a minimum number of urine samples during the screening period. During the initial interview, the interviewer will not ask questions in a manner that reveals the eligibility criteria for study entry. If still interested in participating after receiving an explanation of the study, candidates will be given an opportunity to review, inquire about, and sign and date the study informed consent form (ICF). Any candidate who has difficulty understanding the information contained in the ICF will reread the misunderstood portion(s) of the consent and discuss it with a trained and qualified research staff member until s/he shows complete understanding of the information discussed in the consent form, and may thus give full consent. Any candidate who is unable to demonstrate understanding of the information contained in the ICF will be excluded from study participation. Candidates who are excluded, or who decline participation, will be given referrals to substance abuse treatment programs such as the VA.

Inclusion/Exclusion Criteria

Inclusion Criteria

Subject inclusion/selection criteria: 1) Signed informed consent form and HIPAA authorization form 2) Subject is cooperative, understands the risks and benefits, and is willing and able to adhere to study requirements. 3) Any race or ethnic origin 4) Diagnosis of cocaine-dependence according to DSM-IV criteria 5) Between the ages of 18 and 64 6)

Must be current users of cocaine with self-reported use of cocaine within the last 90 days, or at least one cocaine-positive urine during screening. Women of childbearing age are eligible to be included in the study if they have a negative pregnancy test at screening, agree to adequate contraception to prevent pregnancy, to have monthly pregnancy tests, and they understand the risk of fetal toxicity due to medication. 8) Must be in good general health as determined by self-report and/or CPRS-based medical history, general clinical examination conducted by a study physician, and lab tests. HIV testing will be recommended but is not required for participation in this study. 9) Motivated to discontinue or reduce cocaine use during the period of the study, as evidenced both by the judgment of the Investigator or designee and by the subject's compliance level with the requirement for attendance at clinic visits, such that weekly urine sample requirements for inclusion criteria are fully met.

Exclusion Criteria:

Subject Exclusion Criteria: 1) Current diagnosis of other drug dependence, especially alcohol or benzodiazepine dependence, or abuse (other than cocaine, tobacco, or cannabis). 2) Significant medical conditions (e.g., major cardiovascular, renal, endocrine, hepatic disorders) such as abnormal liver function (with laboratory findings of SGOT or SGPT greater than three times normal), hypotension, a current cardiac condition that in the opinion of the investigator would contraindicate Doxasozin treatment, and those having a high risk of cardiovascular disease, seizure disorders, or another significant underlying medical condition which would ontraindicate Doxazosin treatment. 3) Lifetime schizophrenia, bipolar disorder, or other psychotic disorders (excluding substance-induced psychotic disorders). 4) Actively considering plans of suicidality or homicidality 5) Women planning to become pregnant or breastfeed during the study, refusal to use a reliable form of birth control, or refusal of monthly pregnancy testing. 6) Subjects who are prescribed certain anti-hypertension drugs (i.e. doxasozin) will be excluded because these medications may interact with Doxazosin's brain effects in reducing cocaine abuse.7)Subject has participated in another clinical trial or received any other investigational compound within 7 days prior to being randomized into this study These criteria will be assessed through a comprehensive evaluation, including complete physical, neurological, and clinical psychiatric examinations. Routine laboratory studies will include CBC, BUN/creatinine, serum glucose, electrolytes, liver function tests, pregnancy test, urine toxicologies, and ECG. Based on the ECG general medical history and physical exam, those having a high risk of cardiovascular disease will be excluded from participation. A physician will examine each subject and review the laboratory data and ECG. Results of the evaluation will be made available to the subject or subject's personal physician upon request. If any results are positive, subjects will be referred to their personal physician or to a local clinic of their choice.

Cost/Payment

Delineate clinical procedures from research procedures. Will subject's insurance (or subject) be responsible for research related costs? If so state for which items subject's insurance (or subject) will be responsible (surgery, device, drugs, etc). If appropriate, discuss the availability of financial counseling.

There is no cost to the participants in this study.

Dollar Amount:
$ 820

Distribution Plan:
Pmnt Schedule

• Screen: up to $40• Study required weekly visits x 3 visits per week: $15 paid at end of each visit, bonus $20 at the end of visit 3 for each week for no missed visits and bottle return ($65/wk). Total compensation over the course of this 12-wk study, including screening is $820. All payments are made via direct deposit and distributed at the end of each scheduled visit.

Sample Collection
Sample: Blood

- Blood chemistries:
  Chem 19, CBC as well as an EKG and general physical examination will be performed at screening. Blood drawings will occur at screening, and end of the study. These bloods include laboratory evaluation, liver function tests at screening and end of the study.

- For blood draws, specify the amount drawn, in teaspoons, at each visit and across the course of the subjects entire participation time.
  12 ml (2.5 teaspoons) of blood will be collected at screening and at the end of ths study for a total of 24ml or 5 teaspoons.

SAMPLE: Urine

- What is the purpose of the sample collection?
  Urine toxicology monitoring Urine samples will be monitored thrice weekly regardless of treatment group (typically, Monday, Wednesday, Friday) for opioids, cocaine metabolite (benzoylecgonine) and other drugs of abuse (e.g. benzodiazepines, barbiturates). Urines are rated negative if the quantity of drug or metabolite is <300 ng/ml (benzoylecgonine or benzodiazepine metabolites) or <200 ng/ml (opioids). Most opioids, benzoylecgonine, and benzodiazepines appear to be detectable after use for about 3 days. Thus, this frequency of urine monitoring will allow us to detect most drug use, including any regular cocaine use. Pregnancy tests will be conducted at screening, and weeks 4, 8, 12, and 15.

Section R: Advertisements

A PROGRAM FOR COCAINE USERS
You may be eligible to participate in a 3-month research study to test a medication for cocaine abuse. This study is being conducted by the Michael E. DeBakey VA Medical Center and Baylor College of Medicine. We are currently seeking volunteers who will be compensated for study participation.

877-807-3072

All calls are CONFIDENTIAL.

BCM Baylor College of Medicine Michael E. DeBakey VA Medical Center

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References

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[v] Temple, R. How the FDA currently makes decisions on clinical studies. Clinical Trials. 2: 276-281.

[vi] Irony, T. Bayesian Medical Device Clinical Trials in the Regulatory Setting. Bayesian Biostatistics Conference. University of Texas M.D. Anderson Cancer Center. Houston, Tx. 2008.

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[viii]Lilford RJ, Thornton JG, Braunholtz D. Clinical trials and rare diseases: a way out of a conundrum. BMJ 1995;311(7020):1621-1625.