Official title: ***Lidocaine Infusion as a Treatment for Cocaine Relapse and Craving***

NCT number: ***NCT01929343***

Document date: ***May 21, 2015***

The University of Texas Southwestern Medical Center at Dallas
Institutional Review Board

Protocol Template (for Investigator Initiated Studies)

1. Title
Lidocaine Infusion as a Treatment for Cocaine Relapse and Craving

2. Principal Investigator and Co-Investigator
PI: Bryon Adinoff, M.D.
Co-Investigators: Edson Brown M.D., Ph.D.; Francesca Filbey, Ph.D.; Enas Kandil, M.D.; Alina Suris, Ph.D.

3. Sponsor of the Study
NIH-NIDA

4. Investigational New Drug (IND)/Investigational Device Exemption (IDE)
IND 119175 for Lidocaine Hydrochloride Injection

5. Purpose of the Study, Including the Hypothesis to be Tested
Pharmacologic approaches have been generally unsuccessful in decreasing cocaine use in addicted patients and behavioral approaches have limited utility. While some medications and novel approaches show promise, there are presently no FDA approved drugs for the treatment of cocaine addiction. Furthermore, pharmacologic approaches directly targeting monoamine, GABAergic, and NMDA receptors have not been fruitful. Thus, the need for novel targets and approaches for cocaine addiction is imperative.
Primary Aim 1: Assess the effects of lidocaine in reducing cue-induced cocaine craving.

Hypothesis P1: Cue-induced craving assessed one week after infusion will be less in patients administered lidocaine+cue-induced relative to those given saline+cue-induced craving or lidocaine alone.

Hypothesis P1b: Physiologic responses to cue-induced craving assessed one week after infusion will be significantly less in patients administered lidocaine relative to those administered saline.

Primary Aim 2: Assess the effects of lidocaine on cocaine use [as measured by urine drug screen (UDS)] and craving for four weeks following lidocaine or saline administration.

Hypothesis P2a: Cocaine use will be significantly less in the patients administered lidocaine [+cue-induced craving] compared to those administered saline+cue-induced craving or lidocaine alone.

Hypothesis P2b: Craving will be significantly less in the patients administered lidocaine+cue-induced craving compared to those administered saline+cue-induced craving or lidocaine alone.

If our hypotheses are proven correct, these findings will (1) demonstrate the feasibility of interfering with reconsolidation memories in substance-dependent patients, (2) support a role for lidocaine in the treatment of cocaine addiction, and (3) guide the development of a larger study to assess treatment outcome with lidocaine.

6. Background and Results of Previous Related Research

A novel treatment approach is to disrupt the neural processes involved in cue-related memories (memory links between the external stimuli associated with drug use and the subjective drug effect). These engrained memories, when reactivated by cues, elicit craving and a return to drug use. Each cue re-exposure, however, requires the re-remembering (or reconsolidation) of the drug cue. Key molecular processes required for memory reconsolidation are NMDA receptor activation, the induction of nitric oxide (NO) synthesis and increased extracellular signal-regulated kinase (ERK) activity. In rodent models, blocking these processes changes the cue-related memory; the cue loses its potency to induce a return to drug self-administration. Lidocaine is an FDA approved medication that inhibits activation of NMDA receptors and suppresses production of NO and ERK. Lidocaine, like cocaine, is a local anesthetic with potent effects as a sodium-channel blocker. Unlike cocaine, lidocaine is essentially devoid of activity at monoamine re-uptake transporters and has no rewarding or addictive properties. As lidocaine suppresses the molecular processes required for drug cue reconsolidation and has relatively specific effects upon the striatal regions necessary for drug cue reconsolidation, lidocaine may offer a novel approach for interfering with memory reconsolidation. Two other Na^+ channel blockers have also decrease craving and/or substance use in substance-dependent subjects. We propose that the systemic administration of lidocaine following the induction of cue-induced craving, relative to saline plus cue-induced craving or lidocaine without cue-induced craving, will block the reconsolidation of cue memories. This will lead to a reduction in cue-induced craving upon repeated testing as well as subsequent cocaine use and basal craving. If our hypotheses are proven correct, these findings will 1) support a role for lidocaine in cocaine addiction treatment, 2) demonstrate the feasibility and efficacy of attenuating cue-induced memories, and 3) guide the development of a larger study with lidocaine.

7. Concise Summary of Project:

In this proof-of-concept approach for the treatment of cocaine addition (modeled on a paradigm developed by our group to assess pharmacologic disruptors of PTSD-related trauma memories), the effect of lidocaine infusion following cue-induced craving will be assessed in treatment-seeking, cocaine-addicted outpatients. Immediately following the induction of cue-induced craving, lidocaine or saline will be administered in a double-blind, randomized design. A third arm will also assess lidocaine in the absence of cue-induced craving. One week following the infusion, cue-induced craving will be assessed. Cocaine use and craving (non cue-induced) will be monitored for four weeks.

8. Study Procedures:

66 participants with active cocaine use disorder will be studied. After consent and screening, on Study Day 1, participants will describe scenarios in which they experience cocaine cravings. Participants will also be asked to describe scenarios that they find relaxing. This study session lasts approximately one hour. On Study Day 2, participants will be checked in overnight at Zale Hospital. If the participant is not currently on a residential treatment unit, they may be asked to stay overnight for 3 days prior to Study Day 2. Upon arrival the participants will have a physical exam and drug and pregnancy tests. The following day, scripts will be read to participants and lidocaine (n=22) or saline (n=22) will be administered immediately following craving reactivation. Since lidocaine may be effective in the absence of craving induction, a third group of subjects (n=22) will be given lidocaine but not a craving script. One week later (Study Day 3), craving intensity and physiologic activation following cue-induced craving will be assessed. Costs incurred from these visits will be covered by the research team's funding for this study. Follow-up sessions post-infusion will include 3 times weekly UDS for 4 weeks. Weekly therapy visits conducted for all outpatient participants will be audio recorded for research purposes only. Recordings will not be used for commercial purposes.

If participant is attending a residential treatment program, Study Day 2 will take place one week prior to discharge from their program. Study Day 3 will take place immediately following discharge from their treatment program.

Due to sex differences in craving (106), randomization will be stratified by sex.

9. Sub-Study Procedures:

NA

10. Criteria for Inclusion of Subjects:
Inclusion criteria: All participants must be 25-60 years old, of either sex, and of any race. The relatively small sample size necessitates that variability be limited. Participants will be either outpatient and treatment seeking or attending a residential treatment program at the VA Medical Center or Homeward Bound, Inc (a local public-sector treatment facility). If attending a residential treatment facility, participants will be studied just prior to discharge. Patients must meet DSM-IV criteria for cocaine dependence (by Structured Clinical Interview DSM-IV Lifetime) and must identify cocaine as their primary present and lifetime drug of abuse. Participants must live close enough to the sites and have reliable transportation such that they can attend all assessments, study sessions, and follow-up and treatment sessions.

11. Criteria for Exclusion of Subjects:
Patients with active DSM-IV other Substance Dependence (except nicotine) within the previous three months, Affective Disorder, Schizophrenic Disorders, or significant cognitive impairment (WTAR<70). Due to the complicating presentation of substance-induced mood or psychotic disorders, these disorders will only be cause for exclusion if symptoms persist upon cocaine abstinence. Patients concomitantly using tricyclic anti-depressants, benzodiazepines, cimetidine, mood stabilizers, opioids, lithium, sympathomimetics, anticonvulsants that act on sodium and L-type channels similar to lidocaine, sedative/hypnotics, β-blockers, or dopamine agonists will be excluded from the study. Participants on stable doses of SSRIs and SNRIs for at least two weeks will not be excluded. Medical conditions that might limit cooperation (e.g. dementia) or put the patient at medical risk (i.e. significant hematologic, hepatic, renal, or cardiovascular pathology – particularly arrhythmias) will be excluded. Patients with congenital or idiopathic methemoglobinemia or patients taking medications associated with increased risk of methemoglobinemia (including sulfonamides, acetaminophen, acetanilid, aniline dyes, benzocaine, chloroquine, dapsone, naphthalene, nitrates and nitrites, nitrofurantoin, nitroglycerin, nitroprusside, pamaquine, paraaminosalicylic acid, phenacetin, phenobarbital, phenytoin, primaquine, quinine) will be excluded. Patients with past or present neurologic disorders (i.e. severe head trauma, transient ischemic attacks, stroke, tumor, etc.) will be excluded. Active suicidal ideation, pregnant or nursing women, and prisoners will be excluded from the study.

12. Sources of Research Material:
Initial screening will consist of questionnaires, routine blood chemistry and cell blood count, EKG, pregnancy test and urine tests for illicit drug use. Questionnaires will include lifetime use of substances (drugs and alcohol), personal psychiatric history, psychiatric history of family members, demographic and medical information, and development of craving script. Subjective measures of craving, mood, and anxiety and physiological measures will be obtained during infusion and reactivation sessions. Measures of craving, mood and urine tests for illicit drug use will be obtained upon follow-up. All measures will be used for research purposes only.

13. Recruitment Methods and Consenting Process:
Subjects will be recruited from the VA substance dependence program, flyers, Internet and newspaper ads, and links to our Website. Participants will be evaluated after they contact us expressing an interest in study participation. General information about the study and brief screening will be provided over the phone. Interested participants will be scheduled for further evaluation and obtaining informed consent. Assessment will then include a history and medical evaluation, routine laboratory tests, EKG, urine drug screen (UDS), Wechsler Test of Adult Reading (WTAR) (107) and urine pregnancy test. Structured Clinical Interview for DSM-IV (SCID) (108) will be used for diagnosis. Subjects meeting inclusion/exclusion criteria will be further assessed with demographic/clinical variables (including menstrual phase), Time Line Follow Back (109) to determine lifetime and previous 90 days cocaine use (number of days used, amount used in $), the Inventory of Drug Use Consequences (InDUC) (110) and the SF-36 Health Survey assessing quality of life (111).

14. Potential Risks:

The insertion of an intravenous catheter may cause a slight pain when inserted. A bruise may form temporarily at the spot where the catheter is inserted. There is a slight chance of inflammation of the vein and/or clot formation, but this is rare.

Lidocaine is FDA approved as a local anesthetic (applied intradermally) and for cardiac arrhythmias and status epilepticus (11). Lidocaine may commonly (1-10%) cause central nervous system symptoms such as numbness and tingling, dizziness, drowsiness, anxiety and nervousness. Rare side effects (0.01 to 0.09%) include dizziness, a metalic taste, lightheadedness, nervousness, apprehension, euphoria, confusion, ringing in the ear, blurred vision, nausea and vomiting, sensations of heat, cold or numbness, twitching, tremors, and convulsions. Rarely, irregular heart beats and/or slowed heart rate may progress to respiratory depression and heart attack. At the injection site, you may experience a burning sensation, pain, skin irritation, or swelling. Rarely (0.01 to 0.09%), an allergic reaction can be experienced, including hives, difficulty breathing, swelling of face, lips, tongue, or throat.

A report from Stanford University Pain Management Center reports on the use of lidocaine infusion for chronic pain. No serious adverse events were reported in over 3000 lidocaine infusions (121). Other reviews also note the safety of lidocaine infusion at doses similar to that being used in the present study (12). A recent Cochrane review of 395 patients receiving lidocaine during surgery notes that lidocaine did not result in toxicity or clinically significant adverse events (49).

In a previous study assessing the rCBF effects of procaine infusion in cocaine-addicted subjects, participants were followed (including urine drug screen) for three months after the study, at one week, one month, and three months post-infusion (37). This follow-up was conducted to assure that there were no long-term, untoward and unexpected adverse effects to procaine infusion. Seven of 12 patients (58%) had not relapsed at three months. One patient was abstinent at two weeks and then moved out of town. Four patients relapsed by two weeks following treatment. These relapse rates are comparable to those observed in clinical drug trials.

Subjects will be assessed for pregnancy and cocaine use prior to lidocaine infusion. If participants report cocaine use within previous 72 hours or their UDS is positive for cocaine, lidocaine will not be administered and the session will be rescheduled. If a participant is positive upon rescheduling, they will be terminated from the study and referred for care. If a female is positive for pregnancy, study participation will end and she will be referred for care.

CBT is an efficacious behavioral treatment for cocaine dependence. Since there are no FDA approved medications for cocaine dependence, even subjects receiving placebo infusion will receive an acceptable, albeit limited, treatment.

Some of the questions that are asked may make participants feel uncomfortable.

15. Subject Safety and Data Monitoring:

All subjects will be carefully assessed prior to participation in the studies, including psychiatric and medical history (as appropriate), laboratory tests, and examination by a board-certified physician (Dr. Kandil). Subjects with medical or psychiatric problems that would increase risk for participation will be excluded from the study.

Craving will likely be increased during script development, lidocaine/saline infusion session, and craving reactivation. During craving induction, participants will be monitored at all times. A neutral imagery session will follow all craving imagery followed by a 20-min muscle relaxation session. Persistent craving that occurs following the craving reactivation session will be referred to the treating therapist (the first CBT session follows craving reactivation). Any participant who demonstrates need for additional intervention due to serious psychiatric/medical symptoms will be referred to emergency psychiatric services located in the VA Medical Center (if eligible for care) or other public sector (Homeward Bound, Inc.) or private (Presbyterian Medical Center) treatment programs. Participants demonstrating severe psychiatric/medical symptomology will be walked or transported by shuttle bus or taxi to one of those centers, as determined by the PI.

Participants will be provided a car service to and from Study Session 2. If the participant is outpatient they will be picked up and dropped off at home. If the participant is attending a residential facility they will be transported back to the treatment program.

All lidocaine/saline infusions will be supervised by Dr. Enas Kandil, an anesthesiologist and co-investigator. Either Dr. Kandil or an ACLS certified nurse will be in attendance during throughout the infusion. Heart rate, including EKG rhythm strip, will be monitored continuously throughout the infusion and blood pressure will be obtained every 15 minutes, and more frequently if indicated. If the participants' hemodynamics (heart rate and blood pressure) change by more than 20% (typically a consequence of cardiac arrhythmias) the infusion will be stopped. The more serious toxic effects of lidocaine (e.g. unconsciousness, confusion, convulsions, respiratory arrest) are preceded by numbness of the tongue, lightheadedness, visual disturbances and muscle twitching; infusions will be terminated if the subject reports of any of these latter signs or symptoms and they persist for more than two minutes. The infusion may also be stopped at any time per physician discretion. A checklist of signs and symptoms will be obtained every 15 minutes. Subjects will be observed for at least two hours (approximately one half-life of lidocaine) following the cessation of lidocaine (or saline) infusion. Dr. Kandil must approve discharge for all participants on the infusion study day. There is a crash cart in the CRU and a 24-hour code team in the hospital.

Lidocaine labels carry warnings and precautions for use in patients with various cardiac conditions, notably conduction abnormalities (e.g., heart block, QT prolongation). Cardiac conditions will be identified by ECG, medical history and physical exam. Participants with any medical history of cardiac disease (e.g. myocardial infarction, congestive heart failure, cardiac arrhythmia) or an abnormal ECG (including any arrhythmia, heart block, QT prolongation) will be excluded. Lidocaine labels carry warnings and precautions regarding the dangers its use in patients with significant renal disease, due to the risk of accumulating active metabolites. Renal impairment will be identified through medical history and physical exam as well as laboratory measures of creatinine and BUN, electrolyte panel, and urinalysis. Participants with abnormal levels of creatinine or BUN will be excluded. Participants with any evidence of renal insufficiency identified by laboratory measures or medical history or physical exam will be excluded from the study.

Since lidocaine can increase cocaine lethality (122), participants with a positive UDS for cocaine (or amphetamine) or who report stimulant use within the previous 72 hours will not receive an infusion. Women with a positive pregnancy test or who report unprotected heterosexual sex since their previous menses not receive an infusion and will be referred for appropriate care. If an infusion is not administered due to cocaine use, the subject may be rescheduled for another session (at the PIs discretion). If the rescheduled infusion cannot be performed (due to stimulant use or pregnancy), the subject will be terminated from the study and referred for care. In addition, subjects will be observed for at least two hours (approximately one half-life of lidocaine) following the cessation of lidocaine (or saline) infusion. Participants will be advised of the potential for increased cocaine toxicity for 24 hours after lidocaine administration and will be discharged to the care of a family member or friend. All participants will receive a 24-hour call-in number to contact research staff in the advent of problems. An IND for the use of lidocaine (administered over one hour in outpatient cocaine-addicted patients during a neuroimaging paradigm) has recently been approved by the FDA using a similar paradigm, including the two-hour wait prior to discharge (IND 115555).

Investigators, other research staff, therapists, and other clinical care staff will be blind to the status of the subjects in the study. If necessary, the blind can be broken by the VHANTX research pharmacist. Breaking the blind would be unlikely, however, as any adverse event experienced during the infusion will be treated acutely with the assumption that the participant is receiving active drug.

As lidocaine is not FDA approved for the treatment of cocaine addiction or to attenuate memory reconsolidation, an IND will be obtained from the FDA for its use in this proposal. In addition, the DSMB will obtain interim unblinded primary outcome measures following the assessment of 15 participants (n=5/group) and 30 participants (n=10/group) (see Section IV.E.4).

At the final follow-up session, all outpatient participants will receive a referral list of local substance use intervention centers, both public sector and private. If a participant's substance use worsens during the study and more intensive treatment is required, the participant will be referred for more intensive treatment and terminated from the study.

All adverse events that occur at any time point will be reported (SAEs within 48 hours) to the UTSW and VA IRB (the HRRC) and to the Project Officer.

The proposed study is placebo-controlled and conducted in a group of patients with cocaine dependence. Given the potentially vulnerable nature of the participants, in addition to monitoring and review by the UT Southwestern and VA North Texas Health Care System (VANTHCS) IRB, we have implemented an additional data and safety monitoring plan that includes the formation of a Data and Safety Monitoring Board (DSMB).

Informed Consent Process

1) All investigators and research assistants and other staff (including administrative staff) will receive training in the protection of human research subjects in the form of a UT Southwestern and/or VANTHCS required on-line tutorial.
2) All persons obtaining informed consent will, in addition to the training above, attend a UT Southwestern-sponsored day-long symposium on the informed consent process, ethical conduct of research, and patient safety.
3) A psychiatrist (PI or a co-I) will, in all cases, be involved in the informed consent process providing additional information about the study, including risks, benefits and alternatives, and to answer questions.
4) All investigators and staff involved with patient care will remain updated on issues related to patient rights and safety through educational programs and updates provided by UT Southwestern and the VANTHCS IRB.

Data Handling/Confidentiality

1) Training outlined above addresses issues of confidentiality in research.
2) All subjects are immediately assigned a 3-letter unique ID upon entry into the study. All Personal Health Information (PHI) that is linked to the unique ID is entered into a spreadsheet in the VANTHCS server. This spreadsheet can only be accessed by the PI's administrative assistant. No PHI is linked with the unique ID in electronic form or hard copies other than on the spreadsheet noted.
3) Hard copies with PHI are kept in a locked file cabinet separate from research files using the unique ID.
4) All patient records for the research study will be maintained on the UT Southwestern or VANTHCS Health Care campus in locked file cabinets or computers with password-protected access.
5) To ensure accuracy, data will be checked and reviewed by both research assistants and investigators involved in the study.

Adverse Events

1) Exclusion criteria include active suicidal ideation, pregnant or nursing women, or prisoners to minimize the risk to vulnerable populations or adverse events.
2) All adverse events will be discussed with and evaluated by a physician or psychologist investigator as soon as the event is reported by the participant.
3) All adverse events will be reported to the IRB and DSMB. Serious adverse events (e.g., death of a participant) will be reported within 48 hours to the IRB, DSMB and NIDA program official. As part of this reporting process the PI evaluates the severity of the adverse event, its relationship to the study, and whether changes in the protocol are warranted.
5) The PI, co-investigators involved with clinical care, and the research assistant will be available 24 hours each day to patients and other investigators should an emergency arise.
6) At the completion of the study participants will be given referrals for further treatment of cocaine dependence.
8) The PI will submit an annual safety and adverse event report to the NIDA program official.

Data and Safety Monitoring Board

In addition to the safeguards listed above, we will form a Data and Safety Monitoring Board that will periodically review the project. This board will consist of Dr. Matt Byerly M.D.(chair), Dr. Joan Reisch, and one additional board member to be determined.

None of the proposed members is a co-investigator or consultant on the proposed grant. Thus, the board will provide an independent review and oversight of the study. The board will meet immediately prior to the initiation of enrollment in the study and again after 10 and 30 participants have been enrolled and at the end of the study. The study's research assistant will present safety data to the board for review, including changes in cocaine use/craving and dropouts prior to cue-memory reactivation and during follow-up. The PI (Dr. Adinoff) will also attend the meeting. In addition, materials provided to the IRB, including serious adverse events leading to death, hospitalization, or ER visits will be forwarded to board members. The board will review preliminary data on adverse events and outcomes. As lidocaine has not previously been assessed for use in the treatment of cocaine addiction or to attenuate memory reconsolidation, the study statistician (Dr. Leonard) will conduct a blinded analyses of the primary outcome measures after 15 and 30 subjects have been assessed. If notable differences are observed between treatment groups, the research pharmacist will unblind the groups for the DSMB (see Letter from DSMB Chair, Dr. Byerly). If a pattern begins to emerge and the Board feels that protocol modifications are needed, based on a preponderance of adverse events occurring in a particular treatment group or lidocaine is increasing cocaine craving and/or cocaine use (the opposite of what is hypothesized), it will have the authority to recommend modifications of safety procedures and recommend temporarily or permanently discontinuation of enrollment. However, the final decision on these matters will rest with the local IRBs and NIDA.

16. Procedures to Maintain Confidentiality:

Subject confidentiality will be maintained at all times. Results of the urine drug screens and all other research tests will be strictly confidential. The investigative team will retain all of the information obtained in this research. None of the data will be presented in any publications in such a way to identify a particular subject. All data and copies of executed consent forms will be maintained in the offices of the study personnel at the UT Southwestern Medical Center or VA Medical Center. A Certificate of Confidentiality will be obtained for the study.

17. Potential Benefits:

Direct Benefit to Participants: The assessment, including a history and physical, routine labs, and diagnostic interview may be some direct benefit to participants. All subjects will receive CBT, which is a beneficial treatment for cocaine dependence. Frequent follow-up visits with study staff have also been shown to have a positive effect on treatment outcome. If lidocaine is effective in disrupting cocaine-cue memories, the group given lidocaine will directly benefit from this intervention.
Direct Benefit to Others: This study may provide the basis for both a new pharmacological treatment (lidocaine) and new approach (disruption of memory reconsolidation) cocaine dependence.

18. Biostatistics: (omit this section for peer-reviewed research such as cooperative group, or NIH-sponsored studies, and for industry-sponsored research which has been submitted to FDA)
Study is funded by NIDA.