Title: Clinical Trial for Alcohol Use Disorder and Post Traumatic Stress Disorder (PTSD)
ClinicalTrials.gov Number: NCT02966873
Consent Date: April 6, 2021
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Medical University of South Carolina
CONSENT TO BE A RESEARCH SUBJECT

TITLE OF RESEARCH: A Randomized Controlled Trial of N-Acetylcysteine for Alcohol Use Disorder and Comorbid PTSD

A. PURPOSE OF THE RESEARCH

You are being asked to volunteer for a research study. Research studies are voluntary and include only people who choose to take part. Please read this consent form carefully and take your time making your decision. As your study doctor or study staff discusses this consent form with you, please ask him/her to explain any words or information that you do not clearly understand.

The purpose of this study is to evaluate the efficacy of the medication *N*-acetylcysteine (NAC) in combination with Cognitive Behavior Therapy for reducing alcohol use in persons dealing with Post Traumatic Stress Disorder (PTSD). NAC has been approved by the Food and Drug Administration (FDA) for use in adults and children for other uses (such as chronic lung conditions and an overdose in acetaminophen (Tylenol®)) but has not been approved by the FDA for treatment of alcohol use disorder (AUD). The use of NAC is investigational for the purpose of this study, meaning that we are studying whether or not this medication is effective for helping people with PTSD reduce the severity of their AUD.

You are being asked to participate in this study because you are a person who may have AUD and symptoms of PTSD. The study is sponsored by the National Institute on Alcohol Abuse and Alcoholism. The investigators in charge of this study are Drs. Elizabeth Santa Ana, Sudie Back and Kevin Gray. The study is being done at the Medical University of South Carolina and approximately 200 people will take part.

B. PROCEDURES

If you agree to be in this study, the following will happen:

I. Screening and Baseline Phase

Screening: You will complete a screening visit to see if you qualify for the study. This visit will include a brief medical history, review of medications, and a physical exam to include your vitals (checking your pulse, blood pressure, temperature, and weight). Your regular medications should be continued during the study unless otherwise directed by the study team.

A urine sample will be collected to test for drugs, alcohol and nicotine in your system. This information is for research purposes only. In addition, females will be required to take a pregnancy test. The pregnancy test will be completed prior to the drug testing. Females testing positive or those who plan to become pregnant during the study period cannot participate in the study and no further study procedures will be completed.

For Women of Childbearing Potential: Being a part of this study while pregnant may expose the unborn child to significant risks. Therefore,

pregnant women will be excluded from the study. If you are a woman of childbearing potential, a urine pregnancy test will be performed, and it must be negative before you can continue in the study. If you are planning to become pregnant or are recently pregnant and breastfeeding, you should not participate in this study. If you have unprotected sex or you become pregnant during this study, you must inform your study doctor immediately. Should you decide to pursue study participation, you agree to use birth control (any form of hormonal contraception such as Depo-Provera, daily oral contraception, non-iron intrauterine device, transdermal patch, or Nuva-ring, or double barrier contraception- which is a combination of any two methods of: condoms, spermicide, or diaphragm) to avoid pregnancy.

During this screening visit, you will also be asked questions and given questionnaires to complete about your general substance use (alcohol, nicotine, and other drugs), mood, behaviors, sleep, and thinking abilities.

If you complete the screening visit, it could take 3-4 hours. After staff has reviewed all the information collected, you will be contacted to inform you of your eligibility status. If you are found eligible and you wish to continue in the study, a randomization visit will be scheduled. If you are not found eligible and/or do not wish to continue in the study, additional community resources can be made available to you upon request.

Randomization Visit: You will be asked to complete some questionnaires and tasks much like those completed at screening visit.

The study medication you receive will be determined by chance. You will have a 50:50 chance (like the flip of a coin) of receiving either NAC or placebo (a pill with no medicine given in the same form as the active drug). Neither you nor your study team will know which study medication you are receiving; however, the researchers can find out what you are taking if there is a need to do so. You will take 2 capsules of study medication twice a day (2 capsules in the morning and 2 capsules in the evening).

II. Treatment Phase

Medication start

Weekly Study Visits: Over the next 12 weeks, you will come to the study center to complete each weekly visit in person or meet via home-based telehealth (HBT) for routine checks of your overall health and wellbeing. HBT allows a therapist and patient who are not in the same room together to communicate. This is usually done over the computer using MUSC-approved teleconferencing applications. At these visits, you will complete questionnaires and tasks much like the ones completed at earlier visits. Study personnel will review your medication use, inspect blister packs, and perform pill counts to monitor the amount of medication you are taking. You will be provided additional medication between your weekly visits.

During certain visits over the 12 weeks, you will have urine collected to measure your medication compliance, as well as alcohol, drug and nicotine use. A Urine sample will be collected at baseline, randomization, week 6, week 12 and each follow up visit (3 and 12 months after treatment phase). Vital signs will be collected at

baseline and at weeks 6 and 12. A breathalyzer will be done during each in-office visit. For HBT participants, a saliva test will be performed at the start of each HBT visit/therapy session.

These weekly visits will also include individual counseling (Cognitive Behavior Therapy) to help with reducing your alcohol use. Topics discussed during counseling include coping with craving, drink refusal skills, enhancing your social support network.

Weekly visits will take approximately 1.5-2 hours to complete.

Telehelath

If there is anything that makes it difficult for you to come to the MUSC, you may choose to complete this study via home-based telehealth (HBT). In order to complete sessions via HBT, you will need to have internet or cellular access in your home and a computer, tablet, or smartphone capable of accessing the internet. If you complete study appointments via telehealth, biological measures and specimens will not be collected at those appointments, however you will be required to provide a recent documentation of your blood pressure at your baseline appointment (up to 6 weeks before your baseline appointment). You have the option of taking your own blood pressure if you or someone you know has a blood pressure cuff, getting your blood pressure measurement from a medical provider or an automated machine (for example, those that can be found and pharmacies or grocery stores), or the study staff may view a recent blood pressure in your EPIC record. Pregnancy tests and alcohol saliva tests, and study medication will be shipped to you. Females will be required to provide a verbal confirmation of a negative pregnancy test at the baseline visit, prior to enrollment and at week 6 and 12.

In the event you are unable to make it to the office for your study visit, the study team may send you study medication via United Parcel Service (UPS). We would like your consent to ship study medication to the address provided on your contact information form.

Please indicate your choice below, *or scroll down to the bottom of the screen and select your choice electronically:*

____Yes, I would like study medication shipped to my residence if I am unable to make my appointment, or in the event MUSC is closed.

____No, I would *not* like study medication shipped to my residence if I am unable to make my appointment, or in the event MUSC is closed.

You will be asked to provide information of individual(s) that may be contacted (up to three times) in an emergency or in the event that you cannot be reached. The study team will reach out to designated individuals if you are not responsive to three contact attempts.

III. Follow-Up Phase

Follow-Up Visits (3and 12 months): At these visits, you will be asked to complete questionnaires and discuss your progress since completing medication with study personnel. Much like previous visits, your overall health and wellbeing will

be reviewed along with similar samples of urine collected. No additional counseling will be provided at these visits, and therefore it would be expected that these visits would last about 1-1.5 hours. These visits may also be conducted via telehealth (urine sample will not be collected).

You may withdraw from the study at any time. If you decide to stop participating in the study, you are encouraged to talk to study staff first so that you can stop taking medication and withdraw safely. Another reason to tell study staff that you are thinking about stopping is to discuss what follow-up care could be most helpful to you.

You may be withdrawn from this study without your consent if the researchers believe it is in your best interest or if you fail to follow study procedures.

C. DURATION

Participation in the study could include up to 16 visits (either in person or via telehealth) over a period of 15 months.

D. RISKS AND DISCOMFORTS

There are risks involved with participating in this study, including risks associated with *N*-Acetylcysteine (NAC), study procedures, and loss of confidentiality.

All medications may cause side effects and there are several known risks and discomforts associated with NAC. Your condition will be monitored closely by the medical clinician associated with the study. If the medical clinician or you decide to stop your participation in the study due to unwanted experiences or side effects, you will receive appropriate follow-up care as determined by the medical clinician.

1) Adverse Effects of *N*-acetylcysteine (NAC)

In this study, you may be taking NAC orally (by mouth). The most common side effects seen when NAC is taken by mouth include diarrhea, nausea, vomiting, and headache. These side effects are usually mild and go away even with continued use of NAC. There is also a risk of a skin reaction, such as flushing, itching, or rash. The dose of NAC (2400 mg daily) used in this study is much less than the dose patients receive for acetaminophen overdose. In addition, NAC has been used up to 3500 mg in adult subjects orally in the treatment of Alzheimer's disease. Although we have observed mostly mild side effects of 2400 mg NAC in our studies involving marijuana using adolescents and adults, and no significant differences in side effects between NAC and placebo, it does not rule out the possibility that more serious side effects may occur.

Some patients who have taken intravenous NAC (liquid NAC in a vein) for the treatment of acetaminophen overdose have had more serious reactions. Allergic reactions have occurred in about 5% of patients taking intravenous NAC. These reactions may be mild, consisting of flushing, rash, and itching. Less common side effects include trouble breathing, low or high blood pressure, fever, and hives. If untreated, such a reaction

could lead to death. Even more rare serious side effects of intravenous NAC are irritability, confusion, and seizures. These reactions (severe allergic reaction or seizures) have never been reported when NAC is taken orally (by mouth), as it will be in this study.

It is highly unlikely (probably less than one chance in several thousand) that you will have a severe allergic reaction to NAC. In the event that you begin to experience mild itching or localized rash, we will advise you to take an antihistamine medicine, like Benadryl (diphenhydramine). If you have trouble breathing, the emergency medical system (EMS – call 911) should be called, and you should be transported to the nearest emergency room for immediate treatment.

The likelihood of a seizure is probably even less than the likelihood of a serious allergic reaction.
Because NAC has not been evaluated in combination with many other medications, it will be important for you to report to the research staff any medications you may be taking before, during, or after the treatment phase. Medications include prescription medications from a doctor, over-the-counter medications that you may buy in a drug store, herbal medications that you may buy in a health food store, or "street" drugs.

It is unknown how the drugs in this research study will affect an unborn baby. If you are a female able to have children, you should not become pregnant or nurse a baby while in this research study. If you become pregnant during the study, you must notify the research staff immediately. The research staff will wish to follow the outcome of any pregnancy and condition of any newborn and report this to the study sponsor. In addition, if you are a female able to have children, you must agree to use at least one of the following methods of birth control:

- oral contraceptives (birth control)
- contraceptive patch
- barrier (diaphragm or condom)
- intrauterine contraceptive system
- levonorgestrel implant
- medroxyprogesterone acetate contraceptive injection
- complete abstinence from sexual intercourse
- hormonal vaginal contraceptive ring

<u>2) Riboflavin</u>
Your study medication will also contain a small amount of riboflavin, a vitamin that is found in many foods and in multivitamins. Your urine will be tested for riboflavin while you are in the study to confirm that you are taking study medication as instructed. You will be asked not to take multivitamins that contain riboflavin while taking study medication. There are no known health risks of taking riboflavin, though it may cause your urine to appear bright yellow.

3) Randomization Risk
You will be assigned to the study medication by chance. The study medication you receive may prove to be less effective or to have more side effects than the other study medication or other available treatments.

4) Placebo Risk
If you are in the group that receives placebo, your condition will go without active medication treatment for 12 weeks.

5) Interviews/Rating Scales (Questionnaires)
The questions that will be asked may be sensitive in nature and make you feel uncomfortable. You may be asked personal questions that you find distressing. You may refuse to answer any question(s) that you do not wish to answer.

6) Risk of Loss of Confidentiality
There is a chance that your personal information may inadvertently not be kept confidential. Some answers you give during the research visits (like whether you use illegal drugs) may put you at risk if other people find out. To keep what you say private, your study records will use a code number instead of your name. We will protect your records to the extent allowed by law by keeping all your materials in locked file cabinets only accessible by research staff and all computer files will be secure password-protected files only accessed by research staff. Your research records are kept separate from your clinic records and will not be shared with your clinical counselor. Only research staff will have access to your private information.
If you are or become pregnant and test positive for illegal drugs, it is a law that the South Carolina Department of Social Services (DSS) must be notified. You and your family will be evaluated by the agency. You could be ordered to mandatory drug treatment, lose custody of your children, or possibly be jailed.

7) Unknown Risks
The experimental treatments may have unknown side effects. The researchers will let you know if they learn anything during the course of the study that might make you change your mind about participating in the study.

E. BENEFITS

You may benefit from participation in this study. However, given the investigational nature of this study, benefit cannot be guaranteed or promised. Information gained from this study may help other investigators have a better understanding of the treatment of alcohol use disorder and PTSD symptoms.

F. MEDICAL RECORDS

Information about your study participation will not be in your medical record. This means that neither your research participation nor any of your research results will be included in any MUSC medical record.

F. DATA SHARING

Information about you (including your identifiable private information and/or any identifiable biospecimens) may have all of your identifiers removed and used for future research studies or distributed to other researchers for future research without additional informed consent from you or your legally authorized representative.

G. DISCLOSURE OF RESULTS

Results from this research study will not be directly disclosed or shared with participants, however you may choose to view the results, which will be published at www.clinicaltrials.gov.

H. COSTS

If you choose to complete your study visits through home-based telehealth (HBT), normal cellular and data rates will apply for use of video streaming services. During the HBT sessions, you will talk with study staff about your overall health, medication compliance and the previous week's substance use. In addition, you will talk to your study therapist for approximately 1 hour. These procedures will be conducted through secure online video chat.

If you choose to receive text messages from the study staff, normal cellular data usage rates will apply.

I. PAYMENT TO PARTICIPANTS

In return for your time and effort, you will be paid for every visit you complete. Maximum payment is received if study visit is completed in full and as scheduled. The following is a schedule of payments for the study:

Visit	Baseline	Randomization	Weeks 1-11	Week 6 Bonus	Week 12	Months 3 & 12
Maximum Possible Compensation ($)	$50	$25	$30	$20	$75	$50

If you complete all the study visits, you could have a total compensation of $610. Compensation/payment is available in the form of cash or check. If you receive compensation in the form of check, you will be asked to fill out a W9. Payment for study visits may also be made using a pre-paid debit card, called a ClinCard. It works like a bank debit card and you may use the card to purchase goods or services everywhere Debit MasterCard is accepted. Should you choose this payment option, you will be given a ClinCard at the beginning of the study. Each time you receive payment for participation in this study, the money will be added to the card, as outlined in the payment schedule above.

Mileage reimbursement is available for individuals who travel more than 50 miles to Charleston. Also, if the baseline visit is four hours or longer, telehealth participants will be offered a meal.

You are also invited to participate in the recruitment of other participants for this study. If you refer an individual to the study and he or she is enrolled, you will receive $10. Participation in this process is completely voluntary, and if you elect not to participate your participation in this study will not be affected in any way.
Payments that you receive from MUSC for participating in a research study are considered taxable income per IRS regulations. Payment types may include, but are not limited to checks, cash, gift certificates/cards, personal property, and other items of value. If the total amount of payment you receive from MUSC reaches or exceeds $600.00 in a calendar year, you will be issued a Form 1099.

J. ALTERNATIVES

This study involves an investigational medication and counseling. You have the option of declining to participate in this study. Alternative treatments for alcohol use disorder and PTSD are available.

K. SIGNIFICANT NEW FINDINGS

If there are significant new findings during the course of the study, you will be notified.

L. STUDENT PARTICIPATION

Your participation or discontinuance will not constitute an element of your academic performance, nor will it be a part of your academic record at this Institution.

M. EMPLOYEE PARTICIPATION

Your participation or discontinuance will not constitute an element of your job performance or evaluation, nor will it be a part of your personnel record at this Institution.

N.CLINICALTRIALS.GOV

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

O. CONTACT

You have the option of receiving appointment reminders and links to study surveys through text messages. Should you elect to receive text messages, normal cellular data usage and rates will apply. Please indicate your choice below, *or scroll down to the bottom of the screen and select your choice electronically:*

____Yes, I agree to be contacted via text message

____No, I do not agree to be contacted via text message

The researcher in charge of this study might like to contact you in the future about other research opportunities. Please indicate your choice below, *or scroll down to the bottom of the screen and select your choice electronically:*

____Yes, I agree to be contacted

____No, I do not agree to be contacted

P. CONFIDENTIALITY

We will take careful precautions to maintain your confidentiality, using procedures that we have successfully employed in similar previous as well as ongoing studies. All study data related to psychological outcomes (i.e., the responses to questionnaires) and demographics will not have any unique identifying data attached in any way. There will be a master list of participants (again, not linked to any participant responses) which will be kept separate from all data and will be available only to Drs. Santa Ana, Back, and Gray and approved study personnel. All data will be stored in a confidential manner (i.e., in locked files or on encrypted computers in the Study Coordinator's or Research Assistant's office). Access to research records (paper and computerized) will be restricted to the project staff, sponsor audit personnel, and MUSC IRB auditors.

CONSENT

Results of this research will be used for the purposes described in this study. This information may be published, but you will not be identified. Information that is obtained concerning this research that can be identified with you will remain confidential to the extent possible within State and Federal law. The sponsor and the Food and Drug Administration (FDA) will receive copies of the research records. The investigators associated with this study, the FDA, and the MUSC Institutional Review Board for Human Research will have access to identifying information. All records in South Carolina are subject to subpoena by a court of law.

In the event of a study related injury, you should immediately go to the emergency room of the Medical University Hospital, or in case of an emergency go to the nearest hospital and tell the physician on call that you are in a research study. They will call your study doctor who will make arrangements for your treatment. If the study sponsor does not pay for your treatment, the Medical University Hospital and the physicians who render treatment to you will bill your insurance company. If your insurance company denies coverage or insurance is not available, you will be responsible for payment for all services rendered to you.

Your participation in this study is voluntary. You may refuse to take part in or stop taking part in this study at any time. You should call the investigator in charge of this study if you decide to do this. Your decision not to take part in the study will not affect your current or future medical care or any benefits to which you are entitled.

The investigators and/or the sponsor may stop your participation in this study at any time if they decide it is in your best interest. They may also do this if you do not follow the investigator's instructions.

Volunteer's Statement

I have been given a chance to ask questions about this research study. These questions have been answered to my satisfaction. If I have any more questions about my participation in this study or study related injury, I may contact Dr. Elizabeth Santa Ana at (843)789-7168. I may contact the Medical University of SC Hospital Medical Director (843) 792-9537 concerning medical treatment.

If I have any questions, problems, or concerns, desire further information, or wish to offer input, I may contact the Medical University of SC Institutional Review Board for Human Research IRB Manager or the Office of Research Integrity Director at (843) 792-4148. This includes any questions about my rights as a research subject in this study.

I agree to participate in this study. I have been given a copy of this form for my own records.

If you wish to participate, please sign below for paper consents or scroll to the bottom of the screen to provide an electronic signature.

Signature of Person Obtaining Consent	Date	Signature of Participant	Date