

Title: Pilot Studies Defining N-acetyl Cysteine as a Treatment for Inhibiting Prurogenic Stimuli

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INFORMED CONSENT FORM AND AUTHORIZATION FOR RESEARCH

Pilot Studies Defining N-acetyl Cysteine as a Treatment for Inhibiting Prurigenic Stimuli

PI: Craig A. Rohan, M.D.

Departments of Pharmacology & Toxicology and Dermatology

About This Research Study

You are asked to participate in a research study. Scientists do research to answer important questions which might help change or improve the way we do things in the future. This consent form will give you information about the study to help you decide if you want to participate. The study staff will discuss this study with you and explain everything in detail. We ask that you read this form and ask any questions you may have before agreeing to be in the study.

This study is being conducted by: Dr. Craig Rohan, MD, Assistant Professor of Pharmacology & Toxicology assisted by Dr. Jeffrey B. Travers, MD, PhD, Chair of Pharmacology & Toxicology

This study is being funded by: The study will be funded by Wright State University Department of Pharmacology and Toxicology

Key Information

The purpose of this consent form is to give you information about this research study. It is up to you to decide whether to take part in this study. If you choose not to participate your decision will not affect your current or future relationship with Wright State Physicians. If you decide to participate, you are free to withdraw at any time without affecting that relationship.

You are invited to take part in this research study testing how a N-acetyl cysteine, a modified amino acid supplement, will affect your skin's response to mild irritants. N-acetyl cysteine has a long history of use in liver diseases and as dietary supplement, where it is known to function as an antioxidant and has a good safety profile.

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

- Forearms will be photographed
- Forearms will be exposed to the mild skin irritants capsaicin and histamine
- Pain and itch scale questionnaires
- Medication tolerance questionnaire

Your participation in this study will take a minimum of 45 days and up to a total of 75 days.

Potential risks you may experience include:

- Potential risks of N-acetyl cysteine include allergic reaction, headache, nausea, and diarrhea
 - The chemical irritants, histamine and capsaicin, may cause some allergic reaction, pain, and discomfort
- Additional risks can be found on page 5

You may not benefit by participating in this study. However, the information gained may be helpful to others.

The alternative to participating in this study is to choose not to participate. Your participation is completely voluntary.

Why is This Study Being Done?

The purpose of this study is to 1) test the use of N-acetyl cysteine as a treatment to limit skin irritation and itching sensation, and to 2) better understand how well N-acetyl cysteine supplementation is tolerated.

Why Am I Being Asked to Participate in This Research Study?

You were selected as a possible participant because you are 18 to 40 years old and are generally healthy.

How Many People Will Take Part?

If you agree to participate, you will be one of twenty participants aged 18-40 who will be taking part in this study.

Taking Part in this Study is Voluntary

You may choose not to take part in this study or choose to leave the study at any time. Deciding to not participate, or deciding to leave the study later, will not result in any penalty or loss of benefits to which you are entitled.

Your decision whether or not to participate in this study will not affect your current or future relationship with Wright State Physicians, nor will it affect your health care. If you decide to participate, you are free to withdraw at any time without affecting that relationship. Please read this entire consent form and take your time to make your decision. We encourage you to talk to your doctor, your family, and/or your friends before you decide.

What Will Happen During the Study?

This research will take place at the Pharmacology Translational Unit at the Wright State Physicians Building. If you agree to be in this study, we will ask you to do the following things:

SCREENING PROCEDURES VISIT 1/DAY 0 (1-2 HOURS)

You will need to have the following exams, test or procedures to find out if you can be in the study. These items will take about 1-2 hours to complete:

- A pregnancy test if you are capable of becoming pregnant.
- Review of medications and supplements you are currently taking.
- Answer any questions you may have.
- Schedule all follow-up appointments.

If the screening exams, tests or procedures show that you can continue to be in the study, and you choose to take part, then the following will be done.

You will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance (like pulling numbers out of a hat). A computer program will place you in one of the study groups. Neither you nor your doctor can choose the group (also referred to as an "arm") you will be in. You will have an equal chance of being placed in any group first. You will cross over to the opposite treatment arm later in the study, completing both treatment arms.

- Arm A: N-acetyl cysteine (also called NAC)—take two 750 mg tablets twice daily for 7 days then follow-up

- Arm B: placebo—take two placebo tablets twice daily for 7 days then follow-up

After completing the first 7-day treatment arm medication, N-acetyl cysteine or placebo, you will return for your first follow-up visit (see details below).

Visit 2/Day 8 (1-2 hours)

- We will pick one area on each forearm to perform the following procedures:
 - Both volar (underside) forearms will be photographed
 - We will perform a skin prick histamine test on the volar aspect of one forearm. A small lancet will be used to make a slight prick on the skin, then a drop of a histamine solution will be placed over the site of the skin prick.
 - i. Measurements of redness and swelling over the site will be taken every 5 minutes for 60 minutes or until symptoms return to normal
 - We will apply a capsaicin ointment treatment using two fingertip units (approximately 1 gram) to cover an area slightly larger than the size of a quarter (3 cm diameter circle) on the opposite arm of the histamine test
 - After capsaicin and histamine have been applied, you will be asked to rate your sensation of pain and itch on these two sites once every minute for 20 minutes, then every 5 minutes for a total of 60 minutes.
 - i. To rate pain and itch, you will be asked to draw a line on a paper diagram (0 mm to 100 mm) to visually represent your sensation
 - a. 0 mm being no pain or itch
 - b. 100 mm being the worst pain or itch imaginable
 - We will also ask you to complete a questionnaire regarding your tolerance of the medication

Washout Period (30-60 days)

After visit 1 you will enter a minimum 30-day washout period where you will not be taking any medication associated with this study. This “washout period” must last for at least 30 days and may be as long as 60 days.

Treatment Arm Crossover (7 days)

Following the washout period, you will be switched into the opposite treatment arm of your original assignment (e.g., if you initially completed seven days of N-acetyl cysteine supplementation, then you would now begin the seven-day placebo period). After this seven-day period you will return for the second, and final round, of skin testing.

Visit 3/ Day 45 (up to day 75) (1-2 hours)

- We will pick one area on each forearm to perform the following procedures:
 - Both volar (underside) forearms will be photographed
 - We will perform a skin prick histamine test on the volar aspect of one forearm. A small lancet will be used to make a slight prick on the skin, then a drop of a histamine solution will be placed over the site of the skin prick.
 - i. Measurements of redness and swelling over the site will be taken every 5 minutes for 60 minutes or until symptoms return to normal
 - We will apply a capsaicin ointment treatment using two fingertip units (approximately 1 gram) to cover an area slightly larger than the size of a quarter (3 cm diameter circle) on the opposite arm of the histamine test
 - After capsaicin and histamine have been applied, you will be asked to rate your sensation of pain and itch on these two sites once every minute for 20 minutes, then every 5 minutes for a total of 60 minutes.

- i. To rate pain and itch, you will be asked to draw a line on a paper diagram (0 mm to 100 mm) to visually represent your sensation
 - a. 0 mm being no pain or itch
 - b. 100 mm being the worst pain or itch imaginable
- o We will also ask you to complete a questionnaire regarding your tolerance of the medication

What Steps Are Being Taken to Reduce Risk of Coronavirus Infection?

The following steps are being taken to address the risk of coronavirus infection:

Screening: If you show potential symptoms of COVID-19 (fever, cough, shortness of breath, etc.) then you will NOT participate in this study at this time.

Physical distancing: Whenever possible, we will maintain at least 6 feet of distance from you while conducting the study.

Mask/Covering: We will wear a mask and you will be required to shield your mouth and nose with a cloth face cover or mask during the study, even when maintaining at least 6 feet of distance. If you do not have a mask, one will be provided when entering the building. Tissues will be available to cover coughs and sneezes.

Handwashing: We will wash hands before/during examination or use a hand sanitizer. We will ask you do the same.

Disinfecting materials: When feasible, we will clean and disinfect surfaces before your visit, using an EPA-registered disinfectant for hard materials and by laundering soft materials. Disinfected materials will be handled using gloves, paper towel, plastic wrap or storage bags to reduce the chance of re-contamination of materials.

Electronics: Alcohol-based wipes or sprays will be used to disinfect shared touch screens, mice, keyboards, etc. Surfaces will be dried to avoid pooling of liquids.

We comply with all federal, state, and local health mandates relating to COVID-19.

How Long Will I Be in This Research Study?

If you choose to take part, you will be on the study for up to 75 days (minimum of 45 days) from the first Screening Visit through the final follow-up procedures.

Can I Stop Being in This Research Study? What Happens if I Change My Mind?

If you decide to participate, you are free to withdraw your consent and discontinue participation at any time without any penalty. Your decision will not affect your ability to receive medical care for your disease and you will not lose any benefits to which you would otherwise be entitled. If you withdraw from the study, or the study medication is stopped for any reason:

- There are no anticipated consequences of discontinuing the study drug
- There are no specific termination procedures beyond stopping the medicine. We request that you return any unused study drug to the Pharmacology Translational Unit.

The principal investigator or study staff may also withdraw you from the study, without your consent for one or more of the following reasons

- Failure to follow the instructions of the research study staff.
- Pregnancy.

- You need treatment not allowed in the study.
- The study is cancelled.
- The principal investigator believes it is in your best interest.

Is There Any Way Being in This Study Could Be Bad for Me? What are the Risks?

This research may hurt you or cause discomfort in the following ways:

- **N-acetyl cysteine supplementation:** This is an over-the-counter medicine that is widely used, including the doses proposed for this study. Potential risks include allergic reaction to the active medicine or its components, headache, nausea or diarrhea.
- **Histamine treatment:** Histamine is routinely used as a positive control on routine allergy skin testing, potential risks include bleeding, infection, itching and pain.
- **Capsaicin treatment:** Capsaicin is commonly used in various concentrations including at over-the-counter strengths, but potential risks include allergic reaction, irritation of skin, pain or itching
- **Photograph and Pain/Itch Scales:** There are no risks to photography nor pain/itch scales. Photographs will not allow the subject to be recognizable.
- **Loss of Privacy:** A risk of this research is a loss of privacy (revealing to others that you are taking part in this study) or confidentiality (revealing information about you to others to whom you have not given permission to see this information). The researchers have procedures in place to lessen the possibility of this happening. See the section, titled “How Will my Information be Protected.”

In addition to these risks, this research may hurt you in ways that are unknown. These may be a minor inconvenience.

What Do I Need to Know About Reproductive Health and/or Sexual Activity if I Am in This Study?

You should not be or become pregnant, father a baby, breastfeed, or donate eggs/sperm while on this research study. Once you complete the study, there is not a set amount of time you should wait before becoming pregnant or father a child.

If you are sexually active, both men and women should use at least one effective means of birth control while participating in this research study. According to the World Health Organization and the United States Center for Disease Control and Prevention, the most effective forms of birth control include complete abstinence, surgical sterilization (both male and female), intrauterine devices (IUDs), and the contraceptive implant. The next most effective forms of birth control include injectables, oral contraceptive pills, the contraceptive ring, or the contraceptive patch. Acceptable but least effective methods of birth control include male condoms (with or without spermicide) and female condoms.

If you or your partner become pregnant while participating in this research study, it is important that you tell the study doctor or other research team member immediately. You may be required to stop participation in this study.

What are the Potential Benefits of Taking Part in the Study?

There are no direct benefits to you. More broadly, this study may help the researchers learn more about the management of diseases that involve skin itching and skin pain. This may help future populations with similar issues and may help future researchers design interventions to help with skin irritation.

Will I Receive My Research Results?

We will not be obtaining any results from this study's activities that could be important to your health or well-being.

Will I Be Told About New Information That May Affect My Decision to Participate in This Research Study?

During the course of the study, you will be informed of any significant new research information (either good or bad), such as changes in the risks or benefits resulting from participation in the research or new alternatives to participation, that might cause you to change your mind about continuing in the research. If new information is provided to you, you may be asked to sign a consent form that includes the new information.

Will I be Paid to Participate in the Research?

You will receive up to \$150 as payment for your participation. You will be given this payment at study completion by check. You will be given partial payment if you are unable to complete the entire study as outlined below:

Day 0-Visit 1:	Informed Consent	\$20
Day 7-Visit 2:	First treatment arm	\$20
	Noxious Stimuli Testing #1	\$40
Day 45-Visit 3:	Second treatment arm	\$20
	Noxious Stimuli Testing #2	\$40
	Completion of all Skin and Pain Itch scales	\$10
Maximum Compensation:		\$150

Will It Cost Me Anything to Participate?

There is no cost to you for taking part in this study.

Who Will Pay for My Treatment If I Am Injured?

If you feel that you have been injured as a result of participating in the research, contact the researcher Dr. Craig Rohan or Dr. Jeffrey Travers at (937)-245-7500 to talk to them about your illness or injury.

Emergency Contact (24) hour: [REDACTED] or Wright State Physicians Pharmacology Translational Unit (937)-245-7500

If you feel that you have been injured as a result of participating in the research, contact the research office at (937)-245-7500 to talk about your illness or injury. If you are injured by being in this research study, you will be treated appropriately with no physician cost from Dr. Rohan/ Dr. Travers, though a pharmacy fee could be incurred if prescriptions are required. Also, it is your responsibility to determine the extent of your health care coverage. The study sponsor does not plan to provide other forms of compensation (such as lost wages or pain and suffering) to you for research related illness or injury. By signing this form, you will not give up any legal rights.

How Will my Information Be Protected?

The people who will know that you are a research subject are members of the research study staff, and if appropriate, your physicians and nurses. No information about you, or provided by you, during the research, will be disclosed to others without your written permission, except if necessary to protect your rights or welfare or if required by law.

The information that you give in the study will be handled confidentially. Your information will be assigned a code number.

Your data/subject chart will be stored in locked cabinets and a secure cloud-based storage system. This informed consent form will be kept for a minimum of 6 years after the study is complete.

It is unlikely, but possible, that others responsible for research oversight may require us to share the information you give us from the study to ensure that the research was conducted safely and appropriately. Organizations, in addition to the Wright State Institutional Review Board (IRB) and research investigators, that may inspect your research records include Wright State Physicians. We will only share your information if law or policy requires us to do so. If the researchers learn that you are abusing/neglecting/going to engage in self-harm/intend to harm another, state law requires the researchers report this behavior/intention to the authorities. Finally, confidentiality could be broken if materials from this study were subpoenaed by a court of law.

FDA Clinical Trial Registry

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

Authorization to Use and Disclose Your Health Information

State and Federal laws, including the Health Insurance Portability and Accountability Act (HIPAA), require researchers to protect the privacy of your health information. This section of the consent form describes how researchers, with your authorization (permission), may use and release (disclose or share) your protected health information (PHI) for this research study. **Please read this section of the consent form carefully.**

If you sign this document, you give permission to Dr. Craig Rohan and the Wright State Physicians Pharmacology Translational Unit research team to use or disclose (release) the following protected health information:

- Your medical records for past medical conditions and medications related to your skin health/condition
- All information (research records and medical records) created during your participation in this research study
- All information related to illness or hospitalizations that occur during your participation in this study

The research team needs this information to conduct the study. This is a study to test how N-acetyl cysteine, a modified amino acid supplement, will affect your skin's response to mild irritants.

To maintain the integrity of this research, you might not have access to any health information developed as part of this study until it is completed. At that point, you generally would have access to your health information.

Disclosure of your protected health information

If you sign this form, the researchers may share your health information during the conduct of the study with:

- Non-Wright State Physicians researchers or organizations working with Wright State Physicians researchers.
- Law enforcement or other agencies, when required by law
- Wright State University Institutional Review Board, which oversees our research
- The sponsor (the organization paying for) of this research study: Wright State University Department of Pharmacology and Toxicology
- Representatives of government agencies in the United States and other countries (i.e. Food and Drug Administration and the Office of Human Research Protection)
- Other authorized Wright State Physicians Officials who oversee research and clinical care

The people listed above will use and share your health information to review the quality, safety, and results of the research and may also do additional research.

Please understand that these persons/organizations who may receive your health information may not be required by U.S. Federal privacy laws (such as HIPAA) to protect it and may share your information with others without your permission.

This authorization does not have an expiration date.

However, you can change your mind and cancel this authorization at any time. To cancel this authorization, you must write to the principal investigator at 725 University Blvd., Fairborn, OH 45234.

If you cancel this authorization, you will no longer be allowed to take part in the research study. If you cancel this authorization, health information you had already allowed us to obtain may still be used and disclosed by researchers in order to maintain the integrity and reliability of the research, and to report any adverse (bad) effects that may have happened to you.

If all information that does or can identify you is removed from your health information, the remaining information will no longer be subject to this authorization and may be used or disclosed for other purposes.

Right to refuse to sign this Authorization

You have the right to refuse to sign and give your authorization. If you do not sign this form, your non-research related treatment, payment or enrollment in any health plans, or your eligibility for other medical benefits at Wright State Physicians will not be affected in any way.

However, if you do not sign this form, you will not be able to participate in this research study.

Will My Information Be Used for Research in the Future?

Information collected from you may be used for future research studies or shared with other researchers for future research. If this happens, information which could identify you will be removed before any information is shared.

Who Should I Call with Questions?

If you have questions about the research study itself, please contact the Principal Investigator at (937)-245-7500. If you have questions about your rights as a research volunteer or would simply like to speak with someone other

than the research team about concerns regarding this study, please contact the Wright State IRB Office at (937) 775-4462 or irb-rsp@wright.edu. All reports or correspondence will be kept confidential.

You will be given a copy of this information to keep for your records.

What Are My Rights/Responsibilities As A Research Subject?

As a subject, your responsibilities include:

- Follow the instructions of the research study staff.
- Take the study drug as instructed
- Keep your study appointments. If it is necessary to miss an appointment, please contact the research study staff to reschedule as soon as you know you will miss the appointment.
- Tell the research study staff about any side effects, doctor visits, or hospitalizations that you may have.
- Tell the research staff if you believe you might be pregnant or have gotten your partner pregnant.
- Keep the study drug in a safe place, away from children and for your use only.
- Complete your questionnaires as instructed.
- Ask questions as you think of them.
- Tell the research staff if you change your mind about staying in the study.

While participating in this research study, you should not take part in any other research project without approval from the research staff of each study.

Statement of Consent

I have read (or someone has read to me) the above information provided in this form. I have had the opportunity to ask questions and have my questions answered. In consideration of all information provided in this form, I give my consent to participate in this research study and authorize the use and disclosure of my protected health information for this study. I will be provided with a copy of this form to keep for my records.

I agree

I disagree

The researcher may take photographs of me to aid with data analysis.
The researcher will not share these photographs with anyone outside of the immediate study team.

The researcher may take photographs of me for use in scholarly presentations or publications. My identity may be shared as part of this activity, although the researcher will attempt to limit such identification. I understand the risks associated with such identification.

The researcher may contact me in the future to see whether I am interested in participating in other research studies by the Principal Investigator of this study.

Signature of Subject

Your signature documents your permission to take part in this research. You will be provided a copy of this signed document.

Signature of Participant

Date

Printed Name of Participant

Signature of Person Obtaining Consent

Date

Printed Name of Person Obtaining Consent