This supplement contains the following items:

1. Original protocol, final protocol, summary of changes
2. Original statistical analysis plan, final statistical analysis plan, summary of changes
ORIGINAL PROTOCOL

A Double-Blind, Placebo-Controlled Study of N-Acetyl Cysteine in Pathologic Skin Picking

Jon E. Grant, M.D., J.D, M.P.H.

University of Minnesota School of Medicine
Minneapolis, MN

IRB Code #1002M77897

Protocol Version
25 January 2010

TASCS# 100028 assigned to this protocol
A Double-Blind, Placebo-Controlled Study of N-Acetyl Cysteine in Pathologic Skin Picking

This project will take place at the University of Minnesota, Department of Psychiatry. Dr. Jon E. Grant, MD, JD, MPH is the Principal Investigator and can be phoned at 612-273-9736, email at grant045@umn.edu or by mail at 2450 Riverside Avenue, Minneapolis, MN 55454.

This clinical trial will be conducted in the spirit of Good Clinical Practice (GCP) and in accordance with this IRB approved protocol. No deviation from the protocol will be implemented without the prior review and approval of the IRB except where it may be necessary to eliminate an immediate hazard to a research subject. In such a case, the deviation will be reported to the IRB as soon as possible.

Investigational Agent
N-acetyl cysteine (NAC) – 600mg by mouth twice a day for three weeks; 1200mg by mouth twice a day for three weeks; 1200mg by mouth each morning and 1800mg by mouth every afternoon for three weeks. Dosages will be increased based on clinical severity and improvement as determined by the investigator.

Dosing Regimen (BID dosing throughout study)
Week 0 (Visit 1) – Week 3 (V2):  1200mg/day (600mg po qam and 600mg po qpm)
Week 3 (V2) – Week 6 (V3):  2400mg/day (1200mg po qam and 1200mg po qpm)
Week 6 (V4) – Week 12 (V5):  3000mg/day (1200mg po qam and 1800mg po qpm)

Population
The population to be studied for this trial are men and women ages 18-65 who have a current diagnosis of Pathologic Skin Picking (PSP).

Diagnostic Criteria
The following diagnostic criteria for PSP will be utilized. Although PSP is not formally recognized in the Diagnostic and Statistical Manual for Mental Disorders (DSM-IV), the following criteria have been proposed and widely used for the diagnosis of pathologic skin picking (1):

1) current picking at or otherwise manipulating the skin that results in noticeable damage to the skin;
2) an increasing sense of tension, or an unpleasant emotional or physical state, immediately before picking the skin, or when trying to resist picking;
3) pleasure, gratification or relief at the time of picking;
4) the disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of function;
5) the skin picking is not due to a general medical condition; and
6) the skin picking is not better accounted for by another mental disorder (e.g., body dysmorphic disorder, obsessive compulsive disorder, delusion disorder, substance use disorder).
**Project Goals**

The goal of the proposed study is to evaluate the comparative efficacy of N-acetyl cysteine to placebo in pathologic skin picking. Thirty subjects with pathologic skin picking will receive 12 weeks of double-blind treatment with N-acetyl cysteine or matching placebo. The hypothesis to be tested is that N-acetyl cysteine will be more effective than placebo in patients with pathologic skin picking. The proposed study will provide needed data on the treatment of an often disabling disorder that currently lacks a clearly effective treatment.

**Background and Significance**

Pathologic skin picking involves repetitive, ritualistic, or impulsive picking of otherwise normal skin leading to tissue damage, personal distress, and impaired functioning (1). Although skin picking has been described in the medical literature for over one-hundred years, it remains a poorly understood psychiatric issue and often goes undiagnosed and untreated (2, 3).

Picking behavior does not by itself suggest a psychiatric disorder. Pathology exists in the focus, duration and extent of the behavior, as well as the reasons for picking, associated emotions, and resulting problems. Patients with PSP report thoughts of picking or impulses to pick that are irresistible, intrusive and/or senseless (1). These thoughts, impulses, or behaviors also cause marked distress for patients and significantly interfere with other activities (1). Unlike normal picking behavior, the pathologic form of skin picking is recurrent and usually results in noticeable skin damage.

Although there have been no population-wide epidemiological studies of PSP, it has an estimated prevalence rates of 2.0%-5.4% in the general population (4-5). People who engage in this behavior typically spend a significant amount of time picking. Most often they pick their face, but any body part may be the focus – for example, lips, arms, hands, or legs. They may pick at blemishes, pimples, scars or healthy skin. Although some use their hands and fingernails to pick, other may use instruments such as pins, tweezers, razor blades, or knives.

Although individual episodes of picking may only last a few minutes, many patients have multiple episodes of picking each day. In fact, some patients may pick for as long as 12 hours each day (2, 6). This often leads to significant scarring and even disfigurement. In one study, 90% of patients had at least minor tissue damage, 61% suffered from infections, and 45% had “deep craters” due to picking (2).

Shame after picking episodes often leads to covering the lesions with clothing or make-up as well as social avoidance (5). Significant social and occupational impairment, as well as hospitalizations, have been reported (3, 5, 7). Functional impairment may result from a number of factors, such as the extensive amounts of time spent picking and avoidance of people because of the resulting disfigurement.

Although a number of medications have been used to treat neurotic excoriation in case reports, only SRIs and one anti-epileptic medication, lamotrigine, have been formally tested. A 10-week, double-blind study with 10 patients assigned to fluoxetine and 11 to placebo demonstrated, in an intent-to-treat analysis, that fluoxetine (mean dose 53.0 ± 16.4 mg/d) was significantly more beneficial than placebo in reducing picking behavior on only one of three measures used to rate improvement (a self-report visual analog scale assessing change in skin-
picking behavior) (8). A 12-week, double-blind study of lamotrigine in PSP recently completed, failed to demonstrate significant improvements in PSP compared to placebo.

Data on neurotic excoriation’s treatment response to SRIs are limited, and more treatment data are needed. Given that NAC may have a number of advantages over SRIs in treating repetitive behaviors, and is an all-natural supplement, it is a very promising treatment for neurotic excoriation.

**METHODS**

The study will consist of 12 weeks of double-blind treatment with N-acetyl cysteine compared to placebo (1:1) in 30 subjects with PSP. Subjects will be seen every three weeks throughout the course of the study for a total of 5 visits. Study drug will be randomized by the Investigational Drug Services (IDS) Pharmacy who can be reached at 612-273-6212. Randomization of drug will be conducted in blocks of four. The blind will be assessable to the study subject at all times by calling the pharmacy number listed on the medication bottle. The IDS pharmacy will follow proper accountability procedures in regards to both randomization of the study drug and holding of the blind.

**Study Location**

This is a single-site trial in the United States, with a total of 30 subjects aged 18-65. The Principal Investigator for this study is:

Jon E. Grant, J.D., M.D., M.P.H.
Associate Professor of Psychiatry
University of Minnesota
2450 Riverside Avenue, Minneapolis, MN 55454
Phone: 612-273-9736; Fax: 612-273-9779; email: grant045@umn.edu

All subjects will be seen in the Department of Psychiatry’s Ambulatory Research Center at 606 24th Avenue South, Suite 602, Minneapolis, MN 55454. These offices are connected to the Department of Psychiatry and provide confidential interview rooms and facilities specifically designed for the proper conduct of clinical research.

**Subject Recruitment**

All potential subjects for this study will be recruited through newspaper advertising and posters throughout the Minneapolis/St. Paul area. No subjects will be approached directly to solicit interest in the study.

**Subjects:**

*Inclusion criteria:*
1) Men and women age 18-65;
2) Current diagnosis of pathologic skin picking as determined by criteria proposed by Arnold et al. (2001) for at least 6 months duration
Exclusion criteria:
1) Unstable medical illness or clinically significant abnormalities on prestudy laboratory tests or physical examination;
2) History of seizures;
3) Myocardial infarction within 6 months;
4) Current pregnancy or lactation, or inadequate contraception in women of childbearing potential;
5) Need for medication other than NAC with possible psychotropic effects or unfavorable interactions with NAC;
6) Clinically significant suicidality (score of 3 or 4 on item 3 of the Hamilton Depression Rating Scale);
7) Lifetime history of DSM-IV bipolar disorder type I, dementia, or schizophrenia or any other DSM-IV psychotic disorder;
8) Current or recent (past 3 months) DSM-IV substance abuse or dependence;
9) Illegal substance use within 2 weeks of study initiation;
10) Initiation of pharmacotherapy, psychotherapy, or behavior therapy from a mental health professional within 3 months prior to study baseline for the treatment of pathologic skin picking;
11) Previous treatment with N-acetyl cysteine;
12) Treatment with investigational medication or depot neuroleptics within 3 months, with fluoxetine within 6 weeks, or with other psychotropics within 2 weeks prior to study baseline;
13) Asthma (given possible worsening of asthma due to NAC)

Assessments:
Before beginning N-acetyl cysteine, all subjects will receive a psychiatric, medical, and family history evaluation as well as the Structured Clinical Interview for DSM-IV (SCID-P) for Axis I disorders and the Body Dysmorphic Disorder Questionnaire (BDDQ). At the screening visit, female patients will undergo a urine pregnancy test and all subjects will receive a physical examination. Subjects will also complete neurocognitive testing at the first and final visit of the study in order to assess measures of impulsivity and compulsivity.

The following instruments will be completed at each visit throughout the study: 1) Yale-Brown Obsessive Compulsive Scale Modified for Neurotic Excoriation, a semi-structured clinician-administered scale that assesses current severity of picking; 2) Skin Picking Symptom Assessment Scale (SP-SAS), a reliable and valid self-report measure of picking symptoms; 3) the 17-item Hamilton Rating Scale for Depression (HAM-D); 4) the Hamilton Rating Scale for Anxiety (HAM-A); 5) Clinical Global Impression scale; 6) the Sheehan Disability Inventory Safety evaluations, including pulse and blood pressure, and assessment of side effects will be done at each visit.

In addition to these scales, at the screening and final visit, subjects will also complete: 1) the Quality of Life Inventory; 2) the Perceived Stress Scale; 3) the Barratt Impulsiveness Scale; and 4) the Eysenck Impulsiveness Questionnaire.
Safety Assessments:
Safety assessments (sitting blood pressure, heart rate, adverse effects, and concomitant medications) will be documented at each visit. In terms of vital signs, those subjects with abnormal blood pressures will be assessed for symptoms of hypo- or hypertension. Asymptomatic subjects will be evaluated each visit for changes in vital signs. In the case of hypertensive emergencies (BP greater than 210/120), appropriate referral to the emergency room will be made. In the case of hypotension (BP less than 90/60), participants will be evaluated for symptoms of hypotension and if symptomatic, appropriate interventions will be made. Subjects who endorse suicidal thoughts at any time during the study will be removed from the study and appropriate clinical intervention (e.g. hospitalization) will be arranged. A urine pregnancy test will be performed at the screening visit. Assessment of side effects will be done at each visit. Participants will be advised concerning the risk of allergic reactions to NAC: skin rash, skin flushing, drop in blood pressure, irregular heart beat, and respiratory distress. Participants will be advised to visit an emergency room for symptoms suggestive of anaphylactoid reactions.

Adverse Event Reporting:
Unanticipated (unexpected) problems/events, those that are not already described as potential risks in the consent form, or not part of an underlying disease, will be reported to the IRB as soon as possible. The same will be done for serious problems/events and, in the opinion of the investigator, are possibly, probably or definitely related to the research procedures. A follow-up report will also be submitted to the IRB with any documentation related to a previously submitted adverse event.

Randomization and Procedures:
Thirty (30) subjects will be randomized to either N-Acetyl Cysteine (NAC) or placebo in a 1:1 double-blind fashion. All blinding of study medication will be done by the Investigational Drug Services (IDS) office at the University of Minnesota Medical Center, Fairview. IDS will hold the blind information and, in the event of an emergency, both subjects and study personnel will be able to access this information 24 hours a day, 7 days a week via a helpline phone number. N-Acetyl Cysteine will be the only study medication dispensed to subjects for this study. Subjects will be told to take the first dose of study medication after waking up each day (this takes into account 2nd or 3rd shift workers who may not have the same sleep schedule as a day-shift worker) and the second dose in the afternoon. Subjects will be told to monitor and report any side effects experienced to the study staff at each visit or immediately if they wish (via one of the multiple telephone numbers for the study physician and study staff given to them at each visit).

Psychotherapy of any form (including cognitive-behavioral therapy) will not be initiated during the study.

Subjects will be evaluated with the Yale Brown Obsessive Compulsive Scale modified for PSP (NE-YBOCS), SP-SAS, CGI, HAM-D, HAM-A and the Sheehan Disability Inventory at screening and at each visit for the remainder of the study. Medication side effects will be evaluated at each study visit. A tablet count will be kept for each dose of medication taken.
Dosing Regimen for N-Acetyl Cysteine (NAC)
The proposed dose range for NAC in this study will be 1200mg-3000mg/day. This dose range is higher than previously used in our pilot study of pathological gamblers (9) and double-blind study of trichotillomania subjects (10). Because adverse events were mild and few, and some subjects failed to respond at lower doses, we have proposed a higher dose range in this study. This dose range, although higher than suggested as a supplement (1200mg/day), has demonstrated safety in HIV positive subjects who have taken it as an antioxidant and safety in cocaine dependent subjects. In previous studies of NAC (a liquid form used by dissolving NAC in water), approximately 19% reported adverse events, most commonly nausea, indigestion, headache and abdominal pain. Our low rates of adverse events may have been due to route of administration (gel capsule instead of liquid) or the slow titration of NAC. In addition, in our pilot study of pathological gamblers, adverse events were reported during the first week of treatment and did not increase with increasing dosage. Therefore, we expect that the higher dose range proposed in this study, using a slow titration again, will not result in notably worse adverse events. However, the adverse events will be monitored closely throughout the course of the study.

Data Analysis:
Primary analyses will be intent-to-treat with last observation carried forward. The NE-YBOCS will be the primary outcome measure. For both primary and secondary measures, random regression analyses will be conducted using the MIXREG program.

Ethical Considerations
This study will be conducted according to US and international standards of Good Clinical Practice (FDA regulations 21 CFR 312 for IND studies and FDA guidance E6) for all studies. Applicable government regulations and University of Minnesota research policies and procedures will also be followed.

This protocol and any amendments will be submitted to the University of Minnesota Institutional Review Board (IRB) for formal approval to conduct the study. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB. The formal consent of a subject, using the IRB-approved consent form, will be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

Data Handling and Record Keeping
All subject data will be maintained by the study personnel under the supervision of the principal investigator. Subjects will be seen in the University of Minnesota Ambulatory Research Center at 606-24th Avenue South, Suite 602, Minneapolis, MN 55454. Patient binders will be kept in a locked room only accessible to research staff.
Finance and Insurance
All research will be paid for by the internal departmental funds of the Department of Psychiatry at the University of Minnesota.
In the event that this research activity results in an injury, treatment will be available, including first aid, emergency treatment and follow-up care as needed. Care for such injuries will be billed in the ordinary manner to the subjects’ insurance company. If the subject believes that they have suffered a research related injury, they will be instructed to inform the principal investigator immediately.

Time Line
Recruitment for the proposed study will begin as soon as study drug is available. It is anticipated that all subjects would be entered into the study within approximately 12 months, and that the study would be completed within 15 months of initiation.

REFERENCES
Appendix A

Diagnostic Criteria for Skin Picking

A. Recurrent picking at or otherwise manipulating the skin that results in noticeable damage to the skin.

Have you ever repeatedly picked, scratched or squeezed your skin or engaged in frequent peeling off of “dead skin”? Do you bite your nail cuticles?

IF YES: Did or does the picking, scratching, squeezing, peeling or biting create noticeable damage to the skin, or create scratches, sores, scabs or infection?

NOTE: THROUGHOUT THE REST OF THE INTERVIEW USE THE PATIENT’S OWN TERM FOR DESCRIBING THE ACTIVITY THAT DAMAGES THE SKIN: E.G., PICKING, SCRATCHING, SQUEEZING, PEELING, BITING, OR OTHER TERM.

When did you last do this?
For how many days, weeks or months did that period last?

Which area or areas of your skin do you (pick)? (Picking at or biting nail cuticles is considered skin picking.) ____________

What do you use to (pick) your skin? (fingernails, instruments such as tweezers, nail files, pins or knives).

B. An increasing sense of tension, or an unpleasant emotional or physical state, immediately before picking the skin, or when trying to resist picking.

How do you feel immediately before you start (picking)? Do you feel tense or nervous? Do you feel angry, depressed, guilty, bored?

Does your skin itch, burn, crawl, tingle, prickle, feel dry or hurt before you pick?

C. Pleasure, gratification, satisfaction or relief at the time of picking.

How do you feel while you are (picking) at your skin? Do you feel pleasure, satisfaction or relief when you are (picking) your skin?

Do you find that you “zone out” or lose track of time when you are (picking)?

Do you find that you have spent time doing it without being aware that you were?
D. The picking is not better accounted for by another mental disorder, and is not due to a general medical condition (e.g., a dermatological or systemic condition).

By inspection and brief history taking, the clinician should rule out neuropsychiatric conditions such as Alzheimer’s disease, pervasive developmental disorder, Prader-Willi syndrome, stereotypic movement disorders and Tourette’s Disorder.

Do you have a medical condition or skin problem that causes you to pick your skin? (What is the name of that condition? Possibilities include: eczema, psoriasis, diabetes, liver or kidney disease, Hodgkin’s disease, polycythemia vera, systemic lupus).

Do you pick your skin in order to get rid of bumps or blemishes or other problems or defects that you feel make you look especially unattractive or ugly? (Rules out Body Dysmorphic Disorder).

Do you pick your skin to get rid of parasites or insects that are beneath the surface of the skin? (Rules out Delusional Disorder, Somatic Type [delusions of parasitosis])

Do you pick because of chemical or other contamination, or concerns about germs or infections, and wash the skin area repeatedly? (Rules out OCD)

Do you hear voices that tell you to pick your skin? (Rules out schizophrenia).

Do you pick your skin only when you are high on an illicit drug such as cocaine or methamphetamine or some other street drug? (Rules out drug-induced skin picking).

Cutting or burning the skin suggests Borderline Personality Disorder.

E. The skin picking causes clinically significant distress or impairment in social, occupational, or other important areas of function.

Does the skin picking cause you significant distress or upset you a lot? Has your skin picking ever caused you to miss work or school, or withdraw socially, for example by canceling or avoiding important events or social time with friends?

Do you take steps to hide or cover up or camouflage the damage to your skin, for example by using cosmetics or by wearing clothes that hide the area?

SKIN PICKING CHRONOLOGY*

IF UNCLEAR: During the past month have you picked (scratched, squeezed, peeled, bit – USE THE SUBJECT’S OWN WORDS) your skin?
Has met symptomatic criteria for Skin Picking during the past month.

Over the past week, how many days did you pick your skin?

Over the past week, on days when you have picked your skin, about how much total time did you spend picking each day?

What is the longest period of days, weeks or months during which you have often done this to your skin?

When was this period?

When did you last have (any symptoms of skin picking)?

Number of months prior to interview when the subject last had a symptom of skin picking._______

INDICATE CURRENT SEVERITY:

1. **Mild**: Few, if any symptoms in excess of those required to make the diagnosis are present, and symptoms result in no more than minor impairment in social or occupational functioning.

2. **Moderate**: Symptoms or functional impairment between “mild” and “severe” are present.

3. **Severe**: Many symptoms in excess of those required to make the diagnosis, or several symptoms that are particularly severe, are present, or the symptoms result in marked impairment in social or occupational functioning.

IF CURRENT CRITERIA NOT FULLY MET (OR NOT AT ALL):

4. **In Partial Remission**: the full criteria for the disorder were previously met but currently only some of the symptoms or signs of the disorder remain.

5. **In Full Remission**: There are no longer any symptoms or signs of the disorder, but it is still clinically relevant to note the disorder.

6. **Prior History**: There is a history of the criteria having been met for the disorder, but the individual is considered to have recovered from it.
AGE AT ONSET

IF UNKNOWN: How old were you when you first started picking your skin to the point of causing noticeable damage, scratches, sores, scabs or infection?
FINAL PROTOCOL

A Double-Blind, Placebo-Controlled Study of N-Acetyl Cysteine in Pathologic Skin Picking

Jon E. Grant, M.D., J.D, M.P.H.

University of Chicago Medical Center
Chicago, IL

IRB Code # 12-1340

Protocol Version
15 October 12
A Double-Blind, Placebo-Controlled Study of N-Acetyl Cysteine in Pathologic Skin Picking

This project will take place at the University of Chicago, Department of Psychiatry. Dr. Jon E. Grant, MD, JD, MPH is the Principal Investigator and can be phoned at 773-834-1325, email at jongrant@uchicago.edu or by mail at 5841 South Maryland Avenue, Chicago, IL 60637.

This clinical trial will be conducted in the spirit of Good Clinical Practice (GCP) and in accordance with this IRB approved protocol. No deviation from the protocol will be implemented without the prior review and approval of the IRB except where it may be necessary to eliminate an immediate hazard to a research subject. In such a case, the deviation will be reported to the IRB as soon as possible.

Investigational Agent
N-acetyl cysteine (NAC) – 600mg by mouth twice a day for three weeks; 1200mg by mouth twice a day for three weeks; 1200mg by mouth each morning and 1800mg by mouth every afternoon for three weeks. Dosages will be increased based on clinical severity and improvement as determined by the investigator.

Dosing Regimen (BID dosing throughout study)
Week 0 (Visit 1) – Week 3 (V2): 1200mg/day (600mg po qam and 600mg po qpm)
Week 3 (V2) – Week 6 (V3): 2400mg/day (1200mg po qam and 1200mg po qpm)
Week 6 (V3) – Week 12 (V5): 3000mg/day (1200mg po qam and 1800mg po qpm)

Study Drug Needed
V1: 1200mg = 2(600mg) pills x 21 days = 42 pills
V2: 2400mg = 4(600mg) pills x 21 days = 84 pills
V3: 3000mg = 5(600mg) pills x 21 days = 105 pills
V4: 3000mg = 5(600mg) pills x 21 days = 105 pills
V5: none dispensed (end of study)
TOTAL PILLS for 30 subjects = 10,080 pills / 2 = 5040 NAC and 5040 placebo capsules

Population
The population to be studied for this trial are men and women ages 18-65 who have a current diagnosis of Pathologic Skin Picking (PSP).

Diagnostic Criteria
The following diagnostic criteria for PSP will be utilized. Although PSP is not formally recognized in the Diagnostic and Statistical Manual for Mental Disorders (DSM-IV), the following criteria have been proposed and widely used for the diagnosis of pathologic skin picking (1):

1) current picking at or otherwise manipulating the skin that results in noticeable damage to the skin;
2) an increasing sense of tension, or an unpleasant emotional or physical state, immediately before picking the skin, or when trying to resist picking;
3) pleasure, gratification or relief at the time of picking;
4) the disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of function;
5) the skin picking is not due to a general medical condition; and
6) the skin picking is not better accounted for by another mental disorder (e.g., body dysmorphic disorder, obsessive compulsive disorder, delusion disorder, substance use disorder).

**Project Goals**
The goal of the proposed study is to evaluate the comparative efficacy of N-acetyl cysteine to placebo in pathologic skin picking. Thirty subjects with pathologic skin picking will receive 12 weeks of double-blind treatment with N-acetyl cysteine or matching placebo. The hypothesis to be tested is that N-acetyl cysteine will be more effective than placebo in patients with pathologic skin picking. The proposed study will provide needed data on the treatment of an often disabling disorder that currently lacks a clearly effective treatment.

**Background and Significance**
Pathologic skin picking involves repetitive, ritualistic, or impulsive picking of otherwise normal skin leading to tissue damage, personal distress, and impaired functioning (1). Although skin picking has been described in the medical literature for over one-hundred years, it remains a poorly understood psychiatric issue and often goes undiagnosed and untreated (2, 3).

Picking behavior does not by itself suggest a psychiatric disorder. Pathology exists in the focus, duration and extent of the behavior, as well as the reasons for picking, associated emotions, and resulting problems. Patients with PSP report thoughts of picking or impulses to pick that are irresistible, intrusive and/or senseless (1). These thoughts, impulses, or behaviors also cause marked distress for patients and significantly interfere with other activities (1). Unlike normal picking behavior, the pathologic form of skin picking is recurrent and usually results in noticeable skin damage.

Although there have been no population-wide epidemiological studies of PSP, it has an estimated prevalence rates of 2.0%-5.4% in the general population (4-5). People who engage in this behavior typically spend a significant amount of time picking. Most often they pick their face, but any body part may be the focus – for example, lips, arms, hands, or legs. They may pick at blemishes, pimples, scars or healthy skin. Although some use their hands and fingernails to pick, other may use instruments such as pins, tweezers, razor blades, or knives.

Although individual episodes of picking may only last a few minutes, many patients have multiple episodes of picking each day. In fact, some patients may pick for as long as 12 hours each day (2, 6). This often leads to significant scarring and even disfigurement. In one study, 90% of patients had at least minor tissue damage, 61% suffered from infections, and 45% had “deep craters” due to picking (2).

Shame after picking episodes often leads to covering the lesions with clothing or make-up as well as social avoidance (5). Significant social and occupational impairment, as well as hospitalizations, have been reported (3, 5, 7). Functional impairment may result from a number
of factors, such as the extensive amounts of time spent picking and avoidance of people because of the resulting disfigurement.

Although a number of medications have been used to treat neurotic excoriation in case reports, only SRIs and one anti-epileptic medication, lamotrigine, have been formally tested. A 10-week, double-blind study with 10 patients assigned to fluoxetine and 11 to placebo demonstrated, in an intent-to-treat analysis, that fluoxetine (mean dose 53.0 ± 16.4 mg/d) was significantly more beneficial than placebo in reducing picking behavior on only one of three measures used to rate improvement (a self-report visual analog scale assessing change in skin-picking behavior) (8). A 12-week, double-blind study of lamotrigine in PSP recently completed, failed to demonstrate significant improvements in PSP compared to placebo.

There have been previous studies that have shown the effectiveness of NAC in disorders similar to pathological skin picking (please see section entitled “Dosing Regimen for N-Acetyl Cysteine (NAC)” for other uses of NAC in humans). One such disorder is Trichotillomania, an impulse control disorder that is similar to pathological skin picking as they both are grooming disorders which involve repetitive, ritualistic, or impulsive qualities, though Trichotillomania concerns hair pulling. A study done with NAC and Trichotillomania found that those who received NAC had significantly reduced hair pulling symptoms compared to those who had the placebo (9). Due to the similarity of these two disorders, we believe the outcome will be similar in reducing the impulsive qualities that both disorders possess.

Picking can be extremely detrimental to an individual and with no prior treatment studies with double-blind support, an effective treatment is urgently needed. Data on neurotic excoriation’s treatment response to SRIs are limited, and more treatment data are needed. Given that NAC may have a number of advantages over SRIs in treating repetitive behaviors, and is an all-natural supplement, it is a very promising treatment for neurotic excoriation. We hope with the past effectiveness in a related impulse control disorder that NAC will show effectiveness in those with pathological skin picking.

Aims
1) We will examine the effects of NAC versus placebo in pathological skin picking. Evidence suggests that NAC may modulate glutamate within the nucleus accumbens and thereby reduce urges to pick. We hypothesize that NAC will be more effective than a placebo in patients with pathological skin picking.

2) Because lack of inhibitory control may underlie a range of impulse control behaviors, and improvement in impulsive symptoms may be secondary to greater control, we can examine improved levels of inhibitory control using cognitive tasks pre- and post-treatment. We expect to see greater inhibitory control in those skin pickers who receive NAC. By assigning half of the group to placebo, we can begin to explore what contributions NAC makes to the improvement in inhibitory control. We hypothesize that improvement in cognitive tasks will be greater in those pathological skin pickers who receive NAC compared to placebo.
METHODS
The study will consist of 12 weeks of double-blind treatment with N-acetyl cysteine compared to placebo (1:1) in 60 subjects with PSP (30 were enrolled in a previous study at the University of Minnesota run by the same PI, which is now closed; a total of 30 will be recruited at University of Chicago). Subjects will be seen every three weeks throughout the course of the study for a total of 5 visits. Randomization of drug will be conducted in blocks of four. The blind will be assessable to the study subject at all times by calling the pharmacy number listed on the medication bottle. The IDS pharmacy will follow proper accountability procedures in regards to both randomization of the study drug and holding of the blind.

Study Location
This is a single-site trial in the United States, with a total of 30 subjects aged 18-65. The Principal Investigator for this study is:

Jon E. Grant, J.D., M.D., M.P.H.
Professor of Psychiatry
University of Chicago
5841 South Maryland Avenue, Chicago, IL, 60637

All subjects will be seen in the Department of Psychiatry at the University of Chicago Medical Center at 5841 South Maryland Avenue. The offices are connected to the Department of Psychiatry and provide confidential interview rooms and facilities specifically designed for the proper conduct of clinical research.

Subject Recruitment
All potential subjects for this study will be recruited through newspaper advertising and posters throughout the Chicago area. No subjects will be approached directly to solicit interest in the study.

Subjects:
Inclusion criteria:
1) Men and women age 18-65;
2) Current diagnosis of pathologic skin picking as determined by criteria proposed by Arnold et al. (2001) for at least 6 months duration
3) YBOCS-NE score of more than 16 points.

Exclusion criteria:
1) Unstable medical illness or clinically significant abnormalities on physical examination;
2) History of seizures;
3) Myocardial infarction within 6 months;
4) Current pregnancy or lactation, or inadequate contraception in women of childbearing potential;
5) Need for medication other than NAC with possible psychotropic effects or unfavorable interactions with NAC;
6) Clinically significant suicidality (score or 3 or 4 on item 3 of the Hamilton Depression Rating Scale);
7) Lifetime history of DSM-IV bipolar disorder type I, dementia, or schizophrenia or any other DSM-IV psychotic disorder;
8) Current or recent (past 3 months) DSM-IV substance abuse or dependence;
9) Illegal substance use within 2 weeks of study initiation;
10) Initiation of pharmacotherapy, psychotherapy, or behavior therapy from a mental health professional within 3 months prior to study baseline for the treatment of pathologic skin picking;
11) Previous treatment with N-acetyl cysteine;
12) Treatment with investigational medication or depot neuroleptics within 3 months, with fluoxetine within 6 weeks, or with other psychotropics within 2 weeks prior to study baseline;
13) Asthma (given possible worsening of asthma due to NAC)

**Assessments:**
Before beginning N-acetyl cysteine, all subjects will receive a psychiatric, medical, and family history evaluation as well as the Structured Clinical Interview for DSM-IV (SCID-P) for Axis I disorders. At the screening visit, female patients will undergo a urine pregnancy test and all subjects will receive a physical examination. Subjects will also complete neurocognitive testing at the first and final visit of the study in order to assess measures of impulsivity and compulsivity.

The following instruments will be completed at each visit throughout the study: 1) Yale-Brown Obsessive Compulsive Scale Modified for Neurotic Excoriation, a semi-structured clinician-administered scale that assesses current severity of picking; 2) Skin Picking Symptom Assessment Scale (SP-SAS), a reliable and valid self-report measure of picking symptoms; 3) the 17-item Hamilton Rating Scale for Depression (HAM-D); 4) the Hamilton Rating Scale for Anxiety (HAM-A); 5) Clinical Global Impression scale; 6) the Sheehan Disability Inventory Safety evaluations, including pulse and blood pressure, and assessment of side effects will be done at each visit.

In addition to these scales, at the screening and final visit, subjects will also complete: 1) the Quality of Life Inventory; 2) the Perceived Stress Scale; 3) the Barratt Impulsiveness Scale; and 4) the Eysenck Impulsiveness Questionnaire.

**Note on SP-SAS and YBOCS-NE:**
The YBOCS-NE is a modified scale based off the YBOCS created for OCD testing. It is a semi-structured clinician-administered scale that assesses the current severity of a subject’s skin picking based on both thoughts/urges and activities. This modification of the YBOCS has previously been used in a treatment study of pathological skin picking and has shown satisfactory psychometric properties (10,11). The YBOCS-NE is the primary outcome of the study, used to track the subject’s skin picking behaviors and
difficulties over the course of the study. To address the aims of the study, the severity of the subject’s skin picking must be assessed. For the purposes of accepting a subject into the study and to assess primary outcome, it must be determined if the subject has severe enough skin picking habits that can be potentially treated with noticeable effects. A subject that has extremely mild symptoms might not benefit from treatment and therefore not determine the effectiveness of NAC, as stated in our aims. In addition, by using this scale, we can determine the overall effectiveness of the NAC, especially comparing the end results to the baseline. The SP-SAS (the self report scale) is being used for the same purpose, although it is being used for secondary outcome measures. There are currently not many of assessment scales for skin picking, therefore we must use the specific scales that are found to be valid and reliable and target skin picking.

Note on additional measures:

Depression symptom severity will be assessed using the Hamilton Depression Rating Scale (HAM-D). This will be used as an outcome measure over the course of the study as well as a general assessment measure. This measure relates to AIM #1 as we will be able examine whether improvement in picking is due to a direct affect or simply due to improvement in mood.

Anxiety symptom severity will be assessed using the Hamilton Anxiety Rating Scale (HAM-A). This will be used as an outcome measure over the course of the study as well as a general assessment measure. This measure relates to AIM #1 as we will be able examine whether improvement in picking is due to a direct affect or simply due to improvement in anxiety.

Psychosocial functioning will be evaluated using the patient-rated version of the Sheehan Disability Scale (SDS. This will be used as a secondary outcome measure over the course of the study as well as a general assessment measure. It relates to Aim #1.

Quality of Life Inventory (QOLI). The QOLI is a 16-item self-administered rating scale that assesses life domains such as health, work, recreation, friendships, love relationships, home, self-esteem and standard of living. This will be used as a secondary outcome measure over the course of the study and relates to Aim #1.

Clinical Global Impression (CGI) (Severity) scale will be used by the clinician to assess overall severity of skin picking at baseline. This will be used as a secondary outcome measure over the course of the study and relates to Aim #1.

The Perceived Stress Scale (PSS) is a self-report questionnaire used to determine levels of stress in the subject. This will be used as a secondary outcome measure over the course of the study and relates to Aim #1.
The Barratt Impulsiveness Scale (BIS) and Eysenck Impulsiveness Questionnaire (EIQ) are both self-report questionnaires used to determine levels of impulsiveness as well as levels in certain categories such as adventuresomeness, general impulsivity as well as empathy. This will be used as a secondary outcome measure over the course of the study and they relate to Aim #2.

CANTAB cognitive tasks (see below under Cognitive Testing are the outcome measures related to Aim #2).

**Study Population/Sample Size**

60 male and female outpatients aged 18-64 with a primary diagnosis of pathological skin picking.

*Note on sample size:* The sample size is low due to this is a pilot study, the data will likely be used for future grant applications. There also is no external sponsor, therefore internal funding limits the number of subjects. 30 subjects have already been seen in Minnesota, though the study has been discontinued at that site.

Sample size calculation, using baseline NE-YBOCS total scores reported in a previous study (mean score of 19.5 (SD 6.2)), is based on a simple test of mean differences. For this study, we assume 15% and 40% decreases for placebo and for NAC groups, respectively, by week 12, leading to mean scores of 17.8 and 11.7. Normal distribution is assumed. To detect a mean difference of 6.1 with 80% power and 5% significance level in a two-sided test, 36 subjects will be needed.

**Participant Exclusion:**

For this study, children under the age of 18 will be excluded. The rationale for this is that we do not know the safety of the study drug on development. There may be side effects, known or unknown, that could potentially be dangerous for those under the age of 18. For their safety, we exclude these from participating in the study. Additionally, adults over the age of 64 will be excluded from the study. Due to the possibility of more cognitive decline within this age range, there is a possibility of interference with consent and completion of tasks.

**Safety Assessments:**

Safety assessments (sitting blood pressure, heart rate, adverse effects, and concomitant medications) will be documented at each visit. In terms of vital signs, those subjects with abnormal blood pressures will be assessed for symptoms of hypo- or hypertension. Asymptomatic subjects will be evaluated each visit for changes in vital signs. In the case of hypertensive emergencies (BP greater than 210/120), appropriate referral to the emergency room will be made. In the case of hypotension (BP less than 90/60), participants will be evaluated for symptoms of hypotension and if symptomatic, appropriate interventions will be made.
who endorse suicidal thoughts at any time during the study will be removed from the study and appropriate clinical intervention (e.g. hospitalization) will be arranged. A urine pregnancy test will be performed at the screening visit. Assessment of side effects will be done at each visit. Participants will be advised concerning the risk of allergic reactions to NAC: skin rash, skin flushing, drop in blood pressure, irregular heart beat, and respiratory distress. Participants will be advised to visit an emergency room for symptoms suggestive of anaphylactoid reactions.

**Adverse Event Reporting:**
Unanticipated (unexpected) problems/events, those that are not already described as potential risks in the consent form, or not part of an underlying disease, will be reported to the IRB within 10 business days. The same will be done for serious problems/events and, in the opinion of the investigator, are possibly, probably or definitely related to the research procedures. A follow-up report will also be submitted to the IRB with any documentation related to a previously submitted adverse event.

**Randomization and Procedures:**
Thirty (30) subjects will be randomized to either N-Acetyl Cysteine (NAC) or placebo in a 1:1 double-blind fashion. The blinding center will hold the blind information and, in the event of an emergency, both subjects and study personnel will be able to access this information 24 hours a day, 7 days a week via a helpline phone number.

N-Acetyl Cysteine will be the only study medication dispensed to subjects for this study. Subjects will be told to take the first dose of study medication after waking up each day (this takes into account 2nd or 3rd shift workers who may not have the same sleep schedule as a day-shift worker) and the second dose in the afternoon. Subjects will be told to monitor and report any side effects experienced to the study staff at each visit or immediately if they wish (via one of the multiple telephone numbers for the study physician and study staff given to them at each visit).

Psychotherapy of any form (including cognitive-behavioral therapy) will not be initiated during the study.

Subjects will be evaluated with the Yale Brown Obsessive Compulsive Scale modified for PSP (NE-YBOCS), SP-SAS, CGI, HAM-D, HAM-A and the Sheehan Disability Inventory at screening and at each visit for the remainder of the study. Medication side effects will be evaluated at each study visit. A tablet count will be kept for each dose of medication taken.

**Dosing Regimen for N-Acetyl Cysteine (NAC)**
The proposed dose range for NAC in this study will be 1200mg-3000mg/day. This dose range is higher than previously used in our pilot study of pathological gamblers (12) and double-blind study of trichotillomania subjects (9). Because adverse events were mild and few in our previous work, and some subjects failed to respond at lower doses, we have proposed a slightly higher dose range in this study. This dose range is within the range previously used in pilot studies of individuals with cocaine dependence or in studies of HIV positive individuals (range of 1200mg to 3600 mg) (14-15). In addition, this dose range, although higher than suggested as an antioxidant supplement (1200mg/day), has demonstrated safety in these other patient populations.
(14-15). In previous studies of NAC (a liquid form used by dissolving NAC in water), approximately 19% reported adverse events, most commonly nausea, indigestion, headache and abdominal pain (16). We have reported lower rates of adverse events and this may have been due to route of administration (gel capsule instead of liquid) or the slow titration of NAC (12). In addition, in our trichotillomania study, adverse events were non-existent and rates did not increase with increasing dosage (9). Therefore, we expect that the higher dose range proposed in this study, using a slow titration again, will not result in notably worse adverse events. However, the adverse events will be monitored closely and appropriate interventions made.

**Table 3. Patients With Trichotillomania Reporting Any Adverse Drug Experiences**

<table>
<thead>
<tr>
<th>Adverse Drug Event</th>
<th>Placebo Group (n=25)</th>
<th>N-Acetylcysteine Group (n=25)</th>
<th>P Value a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>1 (4)</td>
<td>0</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (8)</td>
<td>0</td>
<td>.49</td>
</tr>
<tr>
<td>Cough</td>
<td>1 (4)</td>
<td>0</td>
<td>&gt;.99</td>
</tr>
</tbody>
</table>

* a Fisher exact test.

**Data Analysis:**
Primary analyses will be intent-to-treat with last observation carried forward. The NE-YBOCS will be the primary outcome measure. For both primary and secondary measures, random regression analyses will be conducted using the MIXREG program.

Demographic and baseline visit characteristics of the N-acetylcysteine and placebo groups will be compared using $\chi^2$ and $t$ tests to determine whether group differences existed at randomization. Differences in response between the placebo and N-acetylcysteine groups will be adjusted for baseline disparities by use of the baseline score as a covariate. Primary and secondary measures will be examined using analysis of variance modeling analyses (SPSS). The difference in the overall level of posttreatment values, the main effect for treatment, will be the test of primary interest. Analyses will be performed on all available data by the use of an intention-to-treat population (last observation carried forward). All patients who return for at least 1 postrandomization visit will be included in the intention-to-treat population. Because 7 dependent variables are to be examined, a Bonferroni correction will be used; tests will be 2-tailed, and $\alpha = .007$ ($0.05 / 7 = .007$) will be used to determine statistical significance.

Effect sizes will also calculated using the Cohen effect size index $d$. A $d$ of 0.2 is considered a small effect size, 0.5 is medium, and 0.8 is large. Partial eta squared ($\eta^2$), which is the proportion of the effect + error variance that is attributable to the effect, will be calculated. Interpretation of
\( \eta^2 \) is that greater than 0.2 is a large effect size, greater than 0.1 is a medium effect size, and greater than 0.05 is a small effect size.

Clinically significant change will be determined using the approach developed by Jacobson and Truax (17). The CGI severity scale will be used to assess clinically significant change after treatment. For someone to have a clinically significant change, his or her final CGI severity score had to be less than the cutoff score, and his or her change from baseline had to be greater than the reliable change index.

The study will end once 30 subjects have been recruited and have completed the study visits. At this point, the data analysis will begin.

**Cognitive Testing**

Cognitive testing will be conducted using two previously validated tests taken from CANTABeclipse software (18). The choice of cognitive challenges is based on the clinical features of PSP. The compulsive and repetitive behaviors seen in PSP resemble those seen in trichotillomania (TTM) and possibly obsessive compulsive disorder (OCD). The overwhelming urges to pick coupled with a sense of relief or calm after engaging in the behavior reported by those with PSP are very similar to the urges to engage in compulsive acts reported by those with TTM or OCD. Tests of neurocognitive functioning have been examined in TTM and OCD (19). Significant deficits of motor inhibition (Stop-signal task) were noted in both the TTM and OCD groups but only the OCD group showed deficits in extra-dimensional set-shifting (19). Due to the clinical similarities of PSP to TTM, we chose cognitive tasks that would best reflect the underlying impulsivity and cognitive flexibility of PSP. All testing will be conducted in the same controlled environment to minimize confounding variables across subjects. The order of the tasks will be fixed. The stop-signal task will be used to assess motor inhibition (20-21). On this test, subjects will be instructed to respond to a left- or right-facing arrow which appeared on a computer screen in a rapid fashion. Corresponding motor responses will be measured as will be the subjects’ ability to inhibit responses when an auditory “beep” (stop-signal) sound occurred on a subset of trials. Through an algorithm, the time taken to internally suppress prepotent motor responses will be measured, i.e. Stop-Signal Reaction Times (SSRT). Key outcome variables are SSRT, mean reaction time on ‘go’ trials, and the total number of directional errors made. Inhibitory control on this task, as indexed by SSRT, has been shown to be dependent on distributed neural circuitry including the right inferior frontal gyrus (22). Cognitive flexibility, i.e. set-shifting, was measured using the using the Intra-dimensional/ Extra-dimensional Shift Test (ID/ED task), developed from the Wisconsin Card Sorting Test assessing frontal lobe integrity (23). This test involves nine stages using multidimensional stimuli presented as a visual discrimination task. On the task, subjects will be presented with two stimuli on-screen for each trial, and attempted to learn an underlying ‘rule’ about which stimulus is correct. After each choice, the task provides the subject with feedback (right/wrong). After meeting learning criterion (6 consecutive correct choices), the rule is changed by the computer. Where learning criterion was not obtained within 50 trials, the task terminates. Key outcome variables will be the
number of errors made on the task overall (total errors, and total corrected errors) along with total errors for the Intra-dimensional (ID) and Extra-dimensional (ED) stages of the task. The ‘total corrected errors’ measure accountes for errors that would have been made had the subject completed all stages of the task. Cognitive flexibility, as measured by this task, has been found to be dependent on prefrontal cortex integrity (24).

**Time Line**

Recruitment for the proposed study will begin as soon as study drug is available and IRB approval is confirmed. It is anticipated that all subjects would be entered into the study within approximately 12 months, and that the study would be completed within 15 months of initiation.

**Ethical Considerations**

This study will be conducted according to US and international standards of Good Clinical Practice (FDA regulations 21 CFR 312 for IND studies and FDA guidance E6) for all studies. Applicable government regulations and University of Chicago research policies and procedures will also be followed.

This protocol and any amendments will be submitted to the University of Chicago Institutional Review Board (IRB) for formal approval to conduct the study. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB. The formal consent of a subject, using the IRB-approved consent form, will be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

**Data Handling and Record Keeping**

All subject data will be maintained by the study personnel under the supervision of the principal investigator. All subjects will be seen in the Department of Psychiatry at the University of Chicago Medical Center at 5841 South Maryland Avenue. Patient binders will be kept in a locked room only accessible to research staff.

**Finance and Insurance**

All research will be paid for by the internal departmental funds of the Department of Psychiatry at the University of Chicago.

In the event that this research activity results in an injury, treatment will be available, including first aid, emergency treatment and follow-up care as needed. Care for such injuries will be billed in the ordinary manner to the subjects’ insurance company. If the subject believes that they have suffered a research related injury, they will be instructed to inform the principal investigator immediately.
Compensation
For participating in the study, participants will receive $20 per visit to be paid in the form of a check at the end of the study. Upon completion of the study, participants will receive an additional $50 for completing all visits, making for a total compensation of $150.

REFERENCES


Appendix A

Diagnostic Criteria for Skin Picking

A. Recurrent picking at or otherwise manipulating the skin that results in noticeable damage to the skin.

Have you ever repeatedly picked, scratched or squeezed your skin or engaged in frequent peeling off of “dead skin”? Do you bite your nail cuticles?

IF YES: Did or does the picking, scratching, squeezing, peeling or biting create noticeable damage to the skin, or create scratches, sores, scabs or infection?

NOTE: THROUGHOUT THE REST OF THE INTERVIEW USE THE PATIENT’S OWN TERM FOR DESCRIBING THE ACTIVITY THAT DAMAGES THE SKIN: E.G., PICKING, SCRATCHING, SQUEEZING, PEELING, BITING, OR OTHER TERM.

When did you last do this?
For how many days, weeks or months did that period last?

Which area or areas of your skin do you (pick)? (Picking at or biting nail cuticles is considered skin picking.) ____________

What do you use to (pick) your skin? (fingernails, instruments such as tweezers, nail files, pins or knives).

B. An increasing sense of tension, or an unpleasant emotional or physical state, immediately before picking the skin, or when trying to resist picking.

How do you feel immediately before you start (picking)? Do you feel tense or nervous? Do you feel angry, depressed, guilty, bored?

Does your skin itch, burn, crawl, tingle, prickle, feel dry or hurt before you pick?

C. Pleasure, gratification, satisfaction or relief at the time of picking.

How do you feel while you are (picking) at your skin? Do you feel pleasure, satisfaction or relief when you are (picking) your skin?

Do you find that you “zone out” or lose track of time when you are (picking)?

Do you find that you have spent time doing it without being aware that you were?
D. The picking is not better accounted for by another mental disorder, and is not due to a
general medical condition (e.g., a dermatological or systemic condition).

By inspection and brief history taking, the clinician should rule out neuropsychiatric conditions
such as Alzheimer’s disease, pervasive developmental disorder, Prader-Willi syndrome,
stereotypic movement disorders and Tourette’s Disorder.

Do you have a medical condition or skin problem that causes you to pick your skin? (What is the
name of that condition? Possibilities include: eczema, psoriasis, diabetes, liver or kidney disease,
Hodgkin’s disease, polycythemia vera, systemic lupus).

Do you pick your skin in order to get rid of bumps or blemishes or other problems or defects that
you feel make you look especially unattractive or ugly? (Rules out Body Dysmorphic Disorder).

Do you pick your skin to get rid of parasites or insects that are beneath the surface of the skin?
(Rules out Delusional Disorder, Somatic Type [delusions of parasitosis])

Do you pick because of chemical or other contamination, or concerns about germs or infections,
and wash the skin area repeatedly? (Rules out OCD)

Do you hear voices that tell you to pick your skin? (Rules out schizophrenia).

Do you pick your skin only when you are high on an illicit drug such as cocaine or
methamphetamine or some other street drug? (Rules out drug-induced skin picking).

Cutting or burning the skin suggests Borderline Personality Disorder.

E. The skin picking causes clinically significant distress or impairment in social,
occupational, or other important areas of function.

Does the skin picking cause you significant distress or upset you a lot? Has your skin picking
ever caused you to miss work or school, or withdraw socially, for example by canceling or
avoiding important events or social time with friends?

Do you take steps to hide or cover up or camouflage the damage to your skin, for example by
using cosmetics or by wearing clothes that hide the area?

SKIN PICKING CHRONOLOGY*

IF UNCLEAR: During the past month have you picked (scratched, squeezed, peeled, bit – USE
THE SUBJECT’S OWN WORDS) your skin?
Has met symptomatic criteria for Skin Picking during the past month.

Over the past week, how many days did you pick your skin?

Over the past week, on days when you have picked your skin, about how much total time did you spend picking each day?

What is the longest period of days, weeks or months during which you have often done this to your skin?

When was this period?

When did you last have (any symptoms of skin picking)?

Number of months prior to interview when the subject last had a symptom of skin picking._______

INDICATE CURRENT SEVERITY:

1. **Mild**: Few, if any symptoms in excess of those required to make the diagnosis are present, and symptoms result in no more than minor impairment in social or occupational functioning.
2. **Moderate**: Symptoms or functional impairment between “mild” and “severe” are present.
3. **Severe**: Many symptoms in excess of those required to make the diagnosis, or several symptoms that are particularly severe, are present, or the symptoms result in marked impairment in social or occupational functioning.

IF CURRENT CRITERIA NOT FULLY MET (OR NOT AT ALL):

4. **In Partial Remission**: the full criteria for the disorder were previously met but currently only some of the symptoms or signs of the disorder remain.
5. **In Full Remission**: There are no longer any symptoms or signs of the disorder, but it is still clinically relevant to note the disorder.
6. **Prior History**: There is a history of the criteria having been met for the disorder, but the individual is considered to have recovered from it.
AGE AT ONSET

IF UNKNOWN: How old were you when you first started picking your skin to the point of causing noticeable damage, scratches, sores, scabs or infection?
PROTOCOL: SUMMARY OF CHANGES

• The amount of study drug needed (number of pills per visit and total number of pills) was added.
• More specific aims were included in the final protocol, which were not in their own section in the original protocol.
• The study location changed from the University of Minnesota to the University of Chicago because Dr. Jon Grant, the PI, moved to the University of Chicago. The contact information was updated in the final protocol to reflect that.
• A note was included about each of the assessments used in the study in the final protocol, including what the scale measures and why it is necessary for the study.
• Study population/sample size was explained more in depth, including the logic used to determine sample size.
• A table with adverse event reporting statistics from a previous study using N-acetyl Cysteine was added.
• The data analysis section gave more detailed information about the data analysis plan in the final protocol. It included which tests would be used and what would determine significance.
• A section on cognitive testing was added to the final protocol. It included which tasks from the CANTAB would be used and the reason for using them.
• A short section on compensation was included in the final protocol, which explained how much money participants would receive per office visit during the study.

ORIGINAL STATISTICAL ANALYSIS PLAN

Primary analyses will be intent-to-treat with last observation carried forward. The NE-YBOCS will be the primary outcome measure. For both primary and secondary measures, random regression analyses will be conducted using the MIXREG program.

FINAL STATISTICAL ANALYSIS PLAN

Demographic and baseline visit characteristics for NAC and placebo groups will be compared using chi-square and t-tests to determine if group differences occurred at randomization. All randomized participants will be included in the analyses of baseline demographics and safety using an intention-to-treat (ITT) principle.

Efficacy analyses will include only individuals who had returned for at least one post-randomization visit. The statistical model for the primary, secondary, and cognitive variables will be a linear mixed-effects regression model (LME) that includes terms for treatment group, time, and treatment-by-time interaction. The analyses will be run using the nlme package on R for Windows (R Foundation, Vienna, Austria; http://www.r-project.org). Literature suggests LME without imputation may provide more accurate and stable results than LME models using fixed and multiple imputation methods for handling missing data, so no imputation will be undertaken for missing outcome data. All tests of hypotheses will be performed by using a two-sided
significance level of 0.05. Rates of treatment response, defined by a CGI-Improvement rating at endpoint of “much” or “very much” improved, will be calculated for those who complete the study and compared between those on NAC and those on placebo.

STATISTICAL ANALYSIS PLAN: SUMMARY OF CHANGES

The data analysis changed substantially based on what our statisticians considered the most up-to-date and rigorous analysis. Primary outcome stayed the same.