Silymarin Treatment of Trichotillomania in Children and Adults: A Double-Blind, Placebo-Controlled, Cross-Over Study

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Project Goals

The goal of the proposed study is to evaluate the efficacy and safety of silymarin (milk thistle) in children and adults with trichotillomania. The hypothesis to be tested is that silymarin will be more effective and well tolerated in children and adults with trichotillomania compared to placebo. The proposed study will provide needed data on the treatment of a disabling disorder that currently lacks a clearly effective treatment.

Specific Aims

The primary aim of this application is to conduct a randomized placebo-controlled pharmacotherapy trial using silymarin (milk thistle) in 25 participants with trichotillomania. The study will consist of three phases: a 6 week active treatment phase with milk thistle, a 6 week placebo phase, and a 1 week wash-out period between the two 6 week phases. The subjects will be randomized to either receive active or placebo treatment in the first 6 weeks, and the other during the remaining 6 week phase.

This will be one of few studies assessing the use of pharmacotherapy for the treatment of trichotillomania in children and adults. Assessing the efficacy and safety of silymarin (milk thistle), will help inform clinicians about additional treatment options for children and adults suffering from this disorder.

The antioxidant, milk thistle, offers a unique mechanism to address the inability to control a behavior as seen in trichotillomania. Cognitive research suggests that trichotillomania is characterized as a disorder of response inhibition. Although many people may pull a hair occasionally, the inability to stop the pulling once it has started is the hallmark of trichotillomania. Milk thistle appears to increase dopamine in the prefrontal cortex and thereby improve a range of cognitive functions, such as planning, response flexibility, and response inhibition. The proposed study will allow us to investigate baseline cognitive aspects of children and adults with trichotillomania and examine the impact of drug treatment on tasks of cognitive control.

Aim 1: We will examine the effects of milk thistle versus placebo in children and adults with trichotillomania. By targeting deficits in cognitive control, milk thistle may offer a unique mechanism to address compulsive behaviors. We hypothesize that milk thistle will be more effective than placebo in reducing hair pulling behavior during an acute treatment period.

Aim 2: Because lack of cognitive control may underlie a range of body-focused repetitive behaviors, and improvement in related systems may be secondary to greater control, we will examine levels of cognitive control using cognitive tasks pre- and post-treatment. This study will examine cognitive deficits across a range of prefrontal-dependent domains which have been associated with trichotillomania – response inhibition, working memory, cognitive flexibility and planning ability - as possible predictors of treatment and as possible biomarkers for underlying pathophysiology of hair pulling behavior. We hypothesize that improvement in response inhibition will be greater in participants who receive milk thistle compared with placebo.

Background and Significance

Pathological hair-pulling, trichotillomania, has been defined as repetitive, intentionally performed pulling that causes noticeable hair loss and results in clinically significant distress or functional impairment (1). Trichotillomania appears relatively common with an estimated prevalence between 1-3% (2). Data on the pharmacological treatment of trichotillomania is limited to case reports and conflicting double-blind studies of serotonin reuptake inhibitors (3). One positive double-blind study of N-acetyl cysteine in adults was not successful when examined for children and adolescents (4-5). Available data on the treatment of trichotillomania in children are therefore limited.

Silymarin, a flavonoid and a member of the Asteraceae family, is extracted from the seeds of milk thistle (*Silybum marianum*) and is known to have antioxidative and anti-apoptotic properties. Furthermore, it has been demonstrated that its anti-oxidative activity is related to the scavenging of free radicals and activation of anti-oxidative defenses: increases in cellular glutathione content and superoxide dismutase activity. Milk thistle has been used for a range of psychiatric disorders including methamphetamine abuse and obsessive compulsive disorder. The flavonoid complex silymarin in preclinical studies has been found to increase serotonin and dopamine levels in the cortex (6). In the frontal cortex one of the functions of dopamine is to increase the signal to noise ratio, increased dopamine correlating with increased frontal performance (7). Studies have shown that the higher cortical dopamine levels are associated with improved frontal cortical cognitive performance (8). Cortical inhibition is felt to be the basis for top-down control of motivated behaviors. A recent randomized controlled study with milk thistle was conducted in Iran Thirty five participants with moderate OCD were randomly assigned to 200 mg of milk thistle leaf extract or 10 mg of fluoxetine three times daily for eight weeks. Results revealed no significant difference in treatment effects between milk thistle and fluoxetine from baseline to endpoint as both interventions provided a highly significant reduction in symptoms (9). Silymarin or Milk Thistle may therefore offer promise for the treatment of individuals with trichotillomania.

The current pilot study examines the tolerability and efficacy of milk thistle in the treatment of trichotillomania in children and adults. We hypothesize that milk thistle will reduce the severity of symptoms related to trichotillomania and improve patients' overall functioning.

Methodology

The proposed study will consist of a 13 week double-blind cross-over study trial of milk thistle in 25 people (ages 10-65). The study will be divided into an initial 6 week phase, a 1 week wash-out phase, and a second 6 week phase, with one of the 6 week phases consisting of active treatment with milk thistle, and one of the 6 week phases consisting of inactive placebo treatment. Participants will be randomized to receive either milk thistle or placebo during the first 6 week phase on a 1:1 basis. This blinding will be maintained by the IDS pharmacy at the University of Chicago.

Subjects:

Inclusion criteria:

1) Males and females age 10-65;
2) Diagnosis of current trichotillomania (TTM) based on DSM-5 criteria and confirmed using the clinician-administered Structured Clinical Interview for DSM-5 (SCID);
3) Hair-pulling behavior within 2 weeks prior to enrollment;
4) If under 18, child able and willing to provide active assent for participation;
5) If under 18, legal guardian available to provide consent for participation.
6) If 18 or older, able to provide written consent for participation.

Exclusion criteria:

1) Infrequent hair-pulling (i.e. less than one time per week) that does not meet DSM-5 criteria for trichotillomania;
2) Unstable medical illness as determined by the investigator;
3) History of seizures;
4) Current use of stimulants coinciding with onset or exacerbation of trichotillomania symptoms or other current medications coinciding with exacerbation or onset or trichotillomania symptoms;
5) Clinically significant suicidality (defined by the Columbia Suicide Severity Rating Scale);
6) Baseline score of $\geq$17 on the Hamilton Depression Rating Scale (17-item HDRS);
7) Lifetime history of bipolar disorder type I or II, schizophrenia, autism, any psychotic disorder, or any substance use disorder;
8) Initiation of psychotherapy or behavior therapy within 3 months prior to study baseline;
9) Previous treatment with milk thistle;
10) Any history of psychiatric hospitalization in the past year;
11) Currently pregnant (confirmed by urine pregnancy test)

Consent Procedures

As part of the target population is a vulnerable population, additional procedures will be in place to ensure enrollment and consent processes. During the consent processes, each child will be asked to provide active verbal or written assent to participate in the study. A refusal to respond or inaction will be taken as a denial of assent. The child will also be asked to complete a separate assent form, including simplified language to describe the study. Additionally, a legal guardian for each child will be asked to read and sign an accompanying consent form to participate in the study. It will be made clear to the child and his/her guardian that they are free to withdraw from the study at any time if they wish to withdraw their assent to participate.

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 $10 per visit to be paid in the form of one ten dollar (US$10.00) bill at the completion of each visit. Parking vouchers will also be provided for subjects as-needed.

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.

Study Design

The study is a 13-week, double-blind, placebo-controlled, pilot study of the safety and efficacy of milk thistle for children and adults with trichotillomania. All eligible study subjects will go through a 6-week treatment phase during which they will begin milk thistle at 300mg twice a day. Subjects will be given a matching placebo during the 6-week placebo phase. Subjects will be seen for scheduled study visits every two weeks during the 6-week blinded phases, with an additional visit one week after the end of the first 6 week phase, corresponding with the end of the 1 week wash-out period. Subjects will be randomized to either receive either the active of placebo condition during the first 6-week phase, and the remaining condition during the second 6-week phase. All efficacy and safety assessments will be performed at each visit. Subjects who are not compliant with their use of study medication (i.e. failing to take medication for three or more consecutive days) will be discontinued from the study. Patients who experience a clinically significant adverse event will also be discontinued from the study.

Screening Assessments

1. Demographic data and clinical characteristics will be recorded for each subject (baseline visit).
2. Formal screening psychiatric interview for each subject including the Mini International Neuropsychiatric Inventory (10) (baseline visit).
3. Symptom severity at baseline and follow-up visits will be examined using reliable and valid scales:
    a. *Massachusetts General Hospital Hairpulling Scale* (MGH-HPS) (11) (each visit)

b. *Trichotillomania Scale for Children, Child Version* (TSC-C) (12) (each visit) (only for children under the age of 18 who are participating in the study)
c. *Trichotillomania Scale for Children, Parent Version*(TSC-P) (12) (each visit) (only for parents of children under the age of 18 who are participating in the study)
d. *NIMH Trichotillomania Symptom Severity Scale* (TSS) (13) (each visit)
e. *Clinical Global Impression severity and improvement scales* (14) (each visit)
f. *Sheehan Disability Scale* (15) (baseline and final visit)
g. *Hamilton Anxiety Rating Scale* (HAM-A) (16) (each visit)
h. *Hamilton Depression Rating Scale* (HAM-D) (17) (each visit)
i. *Lie Acceptability Scale (Baseline)*
j. *The Narcissistic Personality Inventory 16 (Baseline)*
k. *The Social Desirability Scale (Baseline)*

Massachusetts General Hospital Hair Pulling Scale (MGH-HPS) (11). The MGH-HPS is a 7-item, self-report scale that rates urges to pull hair, actual amount of pulling, perceived control over behavior, and distress associated with hair pulling over the past seven days. Analysis of the MGH-HPS has demonstrated two separate factors with acceptable reliability for both: "severity" and "resistance and control."

Trichotillomania Scale for Children (TSC-C & TSC-P) (Parent and Child Versions) (12). The TSC is a validated measure of trichotillomania symptom severity in children. These scales assess parent and child reports of frequency of pulling behavior as well as other facets of severity and impairment. (Tolin et al., 2008)

NIMH Trichotillomania Severity Scale (NIMH-TSS) (13). The NIMH scale is a 5-item, clinician-administered scale that rates hair pulling symptoms during the past week. The items assess pulling frequency (both on the previous day and during the past week), urge intensity, urge resistance, subjective distress, and interference with daily activities. Four items are rated from 0 (none) to 5 (most severe) and the final item is rated from 0 to 4. A total score is calculated by summing all the item scores. The NIMH-TSS has demonstrated sensitivity to changes in symptom severity.

Clinical Global Impression- Severity and Improvement (CGI) (14). The CGI consists of a reliable and valid 7-item Likert scale used to assess severity and improvement in clinical symptoms. The CGI severity scale was used at each visit and ranges from 1 = "not ill at all" to 7 = "among the most extremely ill." The CGI Improvement scale was used at each follow-up visit and ranges from 1 = "very much improved" to 7 = "very much worse."

Sheehan Disability Scale (SDS) (15). The SDS is a three-item, reliable and valid self-report scale that assesses functioning in three areas of life: work, social or leisure activities, and home and family life. Scores on the SDS range from 0 to 30.

Hamilton Anxiety Rating Scale (HAM-A) (16). The HAM-A is a reliable and valid, clinician-administered, 14-item scale that provides an overall measure of global anxiety.

Hamilton Depression Rating Scale (HAM-D) (17).The HAM-D is a valid and reliable, 17-item, clinician-administered rating scale assessing severity of depressive symptoms.

Cambridge-Chicago Trait Scale (Cambridge CHI-T Scale) (18). The CHI-T scale is a 16-item self-report scale that measures compulsivity.

Lie Acceptability Scale (Goosie, 2014): An 11-item self-report questionnaire which assesses an individual's perception of the acceptability of lying across several dimensions.

The Narcissistic Personality Inventory 16 (Raskin & Terry, 1988): The NPI-16 is a short measure of subclinical narcissism that has shown meaningful face, internal, discriminant, and predictive validity. It can serve as an alternative measure of narcissism when situations do not allow the use of longer inventories.

The Social Desirability Scale (Crowne & Marlowe, 1960): A 33-item self-report questionnaire which assesses the degree to which individuals report the outcome that is most socially desirable using true/false questions.

Cognitive Assessments: In addition, subjects will undergo cognitive assessments at baseline and study endpoint. Assessments of cognitive control will be comprised of several valid paradigms (Table 1). These tasks are designed to probe dissociable neural circuitry and cognitive processes likely to be implicated in the pathophysiology of body-focused repetitive behaviors. Task order will be chosen arbitrarily and will be applied consistently across subjects, to minimize possible confounding factors of differences in task order across participants.

Table 1.Neurocognitive Tasks

Task	**Target Cognitive Process**
MOT	Training Task.
Intra-dimensional/Extra-dimensional Set Shift Task (ID/ED task)	Intra- and extra-dimensional thinking ability. Assesses cognitive flexibility.
Stop-Signal Task of Inhibitory Control	Motor impulsivity and response inhibition.
Tower of London Task	Problem solving and logic task.
Cambridge Gamble Task	Decision making and risk adjustment.
RVP	Visual processing abilities.
SWM	Spatial working memory abilities.

Efficacy Assessments

The primary outcome measure will be the *NIMH Trichotillomania Severity Scale (NIMH-TSS)*. The NIMH-TSS is a reliable and valid scale that is frequently used in research to assess symptom severity.

Secondary efficacy measures include

- *The Clinical Global Impression-Improvement and Severity scales (CGI)*
- *Massachusetts General Hospital Hair Pulling Scale (MGH-HPS)*

- *Trichotillomania Scale for Children (TSC-C & TSC-P) (Parent and Child Versions)*
- *Sheehan Disability Scale (SDS)*
- *Hamilton Anxiety Rating Scale (HAM-A*)
- *Hamilton Depression Rating Scale (HAM-D)*.
- *Cambridge-Chicago Trait Scale (Cambridge CHI-T Scale)*

Safety Assessments

Safety assessments (sitting blood pressure, heart rate, adverse effects, and concomitant medications) will be documented at each visit.

Suicidality will be assessed using the Columbia Suicide Severity Rating Scale. This scale will be performed at every visit. 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.

The investigator will record use of concomitant medications in terms of daily dosage, start and stop dates, and reason for use. Adverse events will be recorded at each study visit and as they become known to the study staff. Medication compliance will be ascertained through weekly pill count of investigational medication.

Risks and Benefits

Risks

Potential risks during the study include side effects from the active milk thistle. The most common side effects include:

- Upset stomach
- Diarrhea
- Headaches
- Bloating

In rare cases, other side effects may occur. In the event of one of these changes, participants and guardians will be instructed to contact the study doctor immediately:

- A skin rash
- Respiratory distress.

It is also possible that the questions regarding symptoms related to trichotillomania, depression, or mental health may be distressing, especially for children. Special precautions will be taken to allow the child to adjust to the study environment and provide opportunities for the child to check in with study staff about any current discomfort. There may be other risks that could arise which are not reasonably foreseeable. If new information becomes available, study staff will make this information available to participants and legal guardians immediately.

Benefits

Potential benefits include a possible direct medical benefit. Specifically, the study drug may help curb the severity of symptoms related to trichotillomania, but there can be no guarantee that this will be the case.

This research provides substantial benefit for current treatments for trichotillomania, particularly in children. As there is currently little to no research in this area, the current study could offer significant advancement in possible treatments for this disorder.

Data Analysis

Demographic and baseline visit characteristics for milk thistle and placebo groups will be compared using chi-square and analysis of variance to determine if group differences existed at ranodmization. Given the crossover design, both the placebo and the active milk thistle groups will contain an N of 25. Primary and secondary measures will be examined using repeated-measures ANOVA modeling analyses (PROC MIXED, SAS/STAT Software for Windows, Version8.2, SAS Institute Inc., Cary, NC, USA). The baseline value of the measure being analyzed will be used as a covariate. A time trend (linear) will be included in all models. 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 as well as for the completers. All available post-randomization data will be first analyzed and a secondary, supportive analysis of completers will be performed. All comparison tests will be two-tailed and an alpha level of .05 will be used to determine statistical significance given the exploratory nature of the study.

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.

Special attention will be paid to ensuring that the participants feel comfortable in the study settings. Children will be given the option of having a guardian sit in on study visits, or asking them to wait in a designated area. Should significant problems arise, the legal guardian will be made aware of issues on behalf of the child in question.

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