A Double-Blind, Placebo-Controlled Study of Dronabinol in Trichotillomania and Other Body focused Repetitive Behaviors

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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 and Dosing

Dronabinol 5mg to 15mg po qday

Population

The population to be studied for this trial is 50 men and women ages 18-65 who have a current DSM-5 diagnosis of trichotillomania or other body focused repetitive behavior (BFRB) (e.g., skin picking disorder).

Project Goals

The goal of the proposed study is to evaluate the efficacy and safety of dronabinol in trichotillomania. 50 subjects with DSM-5 trichotillomania or other BFRB will receive 10 weeks of double-blind dronabinol or placebo. The hypothesis to be tested is that dronabinol will be effective and well tolerated in patients with trichotillomania or other BFRBs compared to placebo. The proposed study will provide needed data on the treatment of disabling disorders that currently lacks a clearly effective treatment.

Background

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). Although discussed in the medical literature for over one hundred years, and affecting all strata of society, there have been no epidemiological studies detailing how common trichotillomania is and there are no clear treatment approaches for everyone with trichotillomania. Behavioral therapy is generally regarded as the first-line treatment but trained therapists are difficult to find. In addition, there is no medication currently approved by the Food and Drug Administration for trichotillomania. Trichotillomania is related clinically to other BFRBs, specifically skin picking disorder. In fact, it appears that trichotillomania and skin picking disorder may in fact share a common neurobiology. Other BFRBs such as skin ppicking disorder also lack any agreed upon medication intervention, but evidence suggests that both skin picking disorder and trichotillomania may respond to the same interventions.

The Trichotillomania Impact Project survey showed that only 15% of adults in the community with trichotillomania reported experiencing significant improvement with treatment of their symptoms (2). This may be because of the ongoing difficulty of finding a therapist

experienced in trichotillomania treatments. More than 55% of persons in this survey believed that their clinician did not have sufficient knowledge of the disorder, and less than one-third were receiving evidence-based treatments for trichotillomania (2).

A recent meta-analytic study of randomized treatment trials in adults demonstrated that behavioral treatments, mainly habit reversal therapy, have the greatest efficacy in treatment of trichotillomania and skin piking disorder (3). Selective serotonin reuptake inhibitors (SSRIs) are the most widely used treatment for adults with trichotillomania and skin picking disorder, despite evidence that their efficacy is no greater than placebo (3).

Instead of using SSRIs, we conducted an open-label study of dronabinol a synthetic form of tetrahydrocannabinol (THC) approved by the FDA as an appetite stimulant for people with AIDS and antiemetic for people receiving chemotherapy, in 14 women with trichotillomania and found that 9 (64.3%) responded to treatment and that the mean effective dose was 11.6 ± 4.1 mg/day (4).

Recent studies using diffusion tensor imaging demonstrated that both trichotillomania and skin picking subjects exhibited significantly reduced fractional anisotropy in anterior cingulate, pre-supplementary motor area, and temporal cortices (5). These data suggest that the disorganization of white matter tracts in motor habit generation and suppression may underlie the pathophysiology of these disorders (5). Neurochemically, motor habits may rely partially on the endocannabinoid system. CB1 receptors are highly expressed in the basal ganglia nuclei, the hippocampus, cerebellum, and neocortex (6-7) and are implicated in attenuating glutamatergic exocitotoxic damage by suppressing the neuronal release of glutamate via inhibition of calcium channels (8-10). The activation of CB1 receptors reduces glutamate release in the dorsal and ventral striatum [possibly through an interaction with brain-derived neurotrophic factor (11)], thereby modulating neurotransmission in the basal ganglia and mesolimbic reward system (12). Stress-induced anxious behavior has been associated with the loss of CB1 receptor function in the striatum (13).

Glutamatergic dysfunction has been implicated in the pathophysiology of trichotillomania (14-15). Pharmacotherapies, such as dronabinol, that target excessive glutamatergic drive through its effects on CB1 Receptors may, therefore, be expected to correct the underlying pathophysiology and symptoms of trichotillomania.

In the USA, dronabinol is FDA-approved for the treatment of anorexia associated with weight loss in patients with AIDS and nausea and vomiting associated with cancer chemotherapy. In our previous study examining dronabinol for trichotillomania, doses between 5 and 15mg/day were well tolerated and beneficial (4). This lack of significant side effects is consistent with other studies of dronabinol where it has been associated primarily with central nervous system-related adverse events (for example, confusion, dizziness, euphoria, and somnolence), but these adverse events are generally mild to moderate in severity and generally reversible upon dose modification (16-17).

Given the serious personal consequences associated with trichotillomania and skin picking disorder, and the likelihood of success of dronabinol in treating both disorders, the aim of the present study was to examine the efficacy and safety of dronabinol vs placebo in adults with trichotillomania or skin picking disorder using a double-blind, placebo-controlled design.

We hypothesize that dronabinol will be more effective than placebo in reducing the frequency of hair pulling and skin picking and in improving overall psychosocial functioning after 10 weeks of treatment when compared to baseline.

Primary Aim/Objective

The aim of the present study is to examine the efficacy and safety of dronabinol vs placebo in adults with trichotillomania and skin picking disorder.

Co-Primary Endpoint(s):

The co-primary efficacy measures will be the change in hair pulling or skin picking frequency and urges to pull hair or pick skin for the past week as indicated by change in total score on the *NIMH Trichotillomania Symptom Severity Scale* (for TTM) or Skin Picking Symptom Assessment Scale (for SPD), reliable and valid clinician-administered measures (18-19), as well as the same scale modified for skin picking disorder, and the change in psychosocial functioning over the same time period using the Sheehan Disability Scale (20). The co-primary efficacy end points will be the change in these measures from baseline to week 10.

Secondary Aim/Objective

A secondary aim of the study is to examine the effects of dronabinol vs placebo on self-report measures of hair pulling, skin picking, quality of life, and measures of mood and anxiety.

Secondary Endpoint(s):

Secondary efficacy measures include the change in number of days per week pulling, the Clinical Global Impressions–Improvement Scale (CGI-I) rated global improvement of symptoms over time (results will be dichotomized as improved [CGI-I ratings of 1 or 2 very much/much improved] or not improved [CGI-I ratings of 3-7]) (20), the self-report Massachusetts General Hospital Hairpulling Scale (22), the Skin Picking Symptom Assessment Scale, the Quality of Life Inventory (23), the Hamilton Depression Rating Scale (24), the Hamilton Anxiety Rating Scale (25), and the Tridimensional Personality Questionnaire

Methodology

50 individuals with trichotillomania or skin picking disorder will be recruited for a double-blind, placebo-controlled pilot study in which dronabinol or placebo is administered in a 1:1 fashion. All 50 subjects will have trichotillomania or skin picking disorder per DSM-5 criteria. Following baseline measures, all subjects will be randomized to either dronabinol or placebo and seen every 2 weeks for the first four weeks and every 3 weeks for the remainder of the 10-week period.

Participants will be started at 5mg po qday for 2 weeks, then 5mg po bid for 2 weeks and then 5mg TID for the remaining 6 weeks. Participants will only go up to the full dose if clinically needed. Efficacy and safety measures will be performed at each visit.

The study will be conducted in accordance with the International Conference on Harmonization Guideline for Good Clinical Practice, all local ethical and legal requirements, and the World Medical Assembly (Declaration of Helsinki). The study protocol and procedures will be approved by the University of Chicago's institutional review board prior to any recruitment. Written informed consent will be required for study participation.

Randomization of drug will be conducted in blocks of eight. The blind will be assessable to the study subject at all times by calling the pharmacy number listed on the medication bottle. The investigational pharmacy will follow proper accountability procedures in regards to both randomization of the study drug and holding of the blind.

Subjects:

Inclusion criteria:

1) men and women age 18-65;
2) current DSM-5 trichotillomania or skin picking disorder; and
3) Ability to understand and sign the consent form.

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Exclusion criteria:

1) Unstable medical illness based on history or clinically significant abnormalities on baseline physical examination
2) Current pregnancy or lactation, or inadequate contraception in women of childbearing potential
3) Subjects considered an immediate suicide risk based on the Columbia Suicide Severity rating Scale (C-SSRS) (www.cssrs.columbia.edu/docs)
4) Past 12-month DSM-5 diagnosis of psychosis, major depressive disorder, bipolar disorder, mania, or a substance or alcohol use disorder
5) Illegal substance use based on urine toxicology screening
6) Stable dose of medications for at least the past 3 months
7) Previous treatment with dronabinol
8) Cognitive impairment that interferes with the capacity to understand and self-administer medication or provide written informed consent

Baseline Assessments:

Those subjects who appear appropriate for the study, based on telephone screening, will be invited for a baseline assessment. The duration of the baseline assessment will be approximately 90 minutes and will include the following: informed consent, demographic data, concomitant medications (no psychotropic medications will be allowed), and family history data. There will also be a physical examination (including weight, and vital signs, urine pregnancy test for women of childbearing years and urine drug screen, as well as a baseline blood draw to assess nutritional status. The blood draw is optional to the subject and will administered at the PI's discretion). Finally, the subjects will undergo a psychiatric evaluation (using the MINI International Neuropsychiatric Interview).

In addition, the following instruments will be completed at the screening visit: 1) NIMH Trichotillomania Symptom Severity Scale (or the same scale modified for skin picking); 2) Sheehan Disability Scale; 3) Massachusetts General Hospital Hairpulling Scale; 4) the 17-item

Hamilton Rating Scale for Depression (HAM-D); 5) the 17-item Hamilton Rating Scale for Anxiety (HAM-A); 6) Clinical Global Impression (Improvement and Severity) scale; 7) Cambridge Caffeine Use Questionnaire; 8) The Dietary Fat and Free Sugar Questionnaire and 9) the Quality of Life Inventory; 10) Cambridge-Chicago Trait Scale (12); the Skin Picking Symptom Assessment Scale (SP-SAS); and the Body Focused Repetitive Behavior Broad Assessment Measure (BFRB-BAM), a new scale being added for validation purposes. In addition, subjects will undergo cognitive assessments at baseline and study endpoint.
Cognitive Assessments: Assessments of cognitive control will be comprised of several valid paradigms (See below). These tasks are designed to probe dissociable neural circuitry and cognitive processes likely to be implicated in the pathophysiology of addictions. Task order was chosen arbitrarily and will be applied consistently across subjects, to minimize possible confounding factors of differences in task order across participants.

The following tasks will be administered at baseline and final visits:

-Stop Signal Task of Inhibitory Control (SST)
-Intra-dimensional/Extra-dimensional Set Shift Task (ID/ED task)
-One Touch Stockings Task (OTS)
-Rapid Visual Processing Task (RVP)
-Spatial Working Memory Task (SWM)
-Cambridge Gambling Task (CGT)

Following-Up Visit Assessments

All follow-up visits will include all psychiatric measures (except the MINI which will be done at baseline only) and safety measures (adverse events, vital signs, C-SSRS). There will be four follow up visits for a total of five visits.

Subject Compensation

Subjects will be compensated $20 per visit, for a total of $100. Compensation will be given in the form of a check at the end of the study, as per University of Chicago protocol.

Safety Assessments

Safety and tolerability will be assessed using spontaneously reported adverse events data, Columbia–Suicide Severity Rating Scale (C-SSRS), vital signs, and by evaluating premature termination. Safety assessments (C-SSRS, sitting blood pressure, heart rate, adverse effects, and concomitant medications) will be documented at each visit. Subjects who are an immediate suicide risk will be removed from the study and appropriate clinical intervention (e.g. hospitalization) will be arranged. Urine pregnancy tests will be performed at the initial visit. Subjects who have a positive urine pregnancy test will be excluded from the study. Assessment of side effects will be done at each visit. AEs will be coded by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (Med- DRA) Version11.1. The incidences of all AEs will be summarized descriptively. 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.

Seizure and seizure-like activity have been reported in patients receiving dronabinol. Therefore, history of seizures will be an exclusion criterion. If a seizure occurs, dronabinol will be discontinued. Participants will be advised to discontinue dronabinol and contact a healthcare provider immediately if they experience a seizure.

Although the seizure risk needs to be taken seriously, the occurrence of new seizures from dronabinol, when excluding patients with a seizure disorder, appears to be fairly low even in medically compromised patient (25). In the proposed study, our dose of dronabinol is only up to a total of 15mg each day and patients with trichotillomania are on average quite healthy. This may explain why we saw only a small amount of mild side effects in our previous study (4).

Table 1 outlines adverse events that occurred in subjects with AIDS –related anorexia and chemotherapy-related nausea as well as not medically compromised subjects with trichotillomania (4).

Table 1
Adverse events associated with dronabinol

	Pooled trial data from studies of subjects with AIDS-related anorexia and chemotherapy-related nausea[a]	**Trichotillomania study participants (*n* = 14)**			
Adverse event	Dose range (5–20 mg/day)	2.5 mg/day (*n* = 14)	5 mg/day (*n* = 13)	10 mg/day (*n* = 12)	15 mg/day (*n* = 7)
Light-headed/dizzy	3–10%	2 (14.3%)	1 (7.7%)	1 (8.3%)	–
"High" (i.e., easy laughing, elation, and heightened awareness)	8–24%	–	1 (7.7%)	2 (16.7%)	–
Sedation	3–10%	1 (7.7%)	1 (7.7%)	–	–
Dry mouth	Frequency not specified	–	1 (7.7%)	1 (7.7%)	–
Constipation	Frequency not specified	–	1 (7.7%)	–	–
Headache	<1%	–	–	1 (7.7%)	–
Nausea/vomiting	3–10%	–	1 (7.7%)	–	–
Abdominal pain	3–10%	–	–	–	–
Paranoia	3–10%	–	–	–	–

	Pooled trial data from studies of subjects with AIDS-related anorexia and chemotherapy-related nausea[a]	Trichotillomania study participants ($n = 14$)			
Any side effect	Frequency not specified	3 (21.4%)	6 (46.2%)	5 (41.7%)	0

[a] http://www.fda.gov/ohrms/dockets/dockets/05n0479/05N-0479-emc0004-04.pdf

and http://www.merckmanuals.com/professional/lexicomp/dronabinol.html

Subject Withdrawal

If a subject withdraws from the study, all instruments administered at the screening visit will be completed at the final visit. These will be conducted when the subject is able to come in for an early termination visit. Withdrawn subjects will be given the phone number of the principal investigator as well as the phone numbers of local resources for trichotillomania and skin picking.

Data and Safety Monitoring Plan

1. Responsibility for Data and Safety Monitoring
   The PI will have overall responsibility for monitoring the integrity of study data and participant safety.
2. Procedures for Monitoring Participant Safety
   The PI will implement the following procedures to ensure data integrity and the safety of participants during the study.
   - A number of elements of the research plan are intended to minimize the risks of study participation. If subjects become actively suicidal with intent and plan to kill themselves, the PI will evaluate them and refer them for immediate non-study treatment. Any participant endorsing suicidal thoughts with intent and plan will be immediately evaluated by the PI and referred to a higher level of care if clinically indicated.
   - The PI will evaluate patient safety and resolve any safety issues if necessary, as such issues arise. The PI will also be responsible for preparing written summary reports of adverse events and will prepare a written report summarizing any decisions that are made pertaining to participant disposition.
   - Data integrity and confidentiality will be safeguarded as discussed above in the Data Management and Statistical Analysis section under Research Methods.

Monitoring Committee

We will establish a monitoring committee and define in detail its role, its composition, and its operating procedures for reviewing patient safety and data from this study. The monitoring committee, comprised of three individuals independent of personnel involved in the study,

including a psychiatrists and a statistician, will come together via conference call yearly. The committee will use a standardized approach employing contemporary bio statistical, psychiatric/psychological, and ethical principles to review study design and interim data every year. The committee will audit the records from the study and will ensure the data are being collected, managed and protected. The committee will have the ability to ask for more frequent reviews at any time if they deem it necessary. In addition, the PI will inform the committee of any serious adverse event.
The PI will prepare a specific report for the committee in advance of each meeting. Attention will be given to data quality and timeliness, recruitment, risk versus benefit, adverse events and other factors that could affect study outcome.

3. **Reporting Adverse Events**
    - Any serious adverse event will be reported to the Institutional Review Board (IRB) at the University of Chicago in a full written report within 10 working days of the event. For fatal/life-threatening serious adverse events, the PI will notify the IRB Chair by phone immediately.
    - Any moderate adverse event which appears definitely, probably, or possibly related to study participation will be reported to the University of Chicago IRB in writing within 20 working days.
    - Any mild adverse event will be summarized in the IRB annual progress reports.

Statistical Analysis

Design/Randomization
The study is a double-blind, placebo-controlled study. Participants will be randomized (1:1) to receive dronabinol or placebo by the University of Chicago Investigational pharmacy in block sizes of eight, using computer-generated randomization with no clinical information.

Due to the pandemic of COVID19, study participants can perform their baseline and follow-up visits online using encrypted Zoom instead of in person visits. All inventories will be assessed. Blood samples and urine toxicology, however, will be at the discretion of the study PI. In cases where they are considered medically necessary, the participant can have them drawn locally and submitted to the study team.

Efficacy Analysis
For statistical analysis, the full-analysis set will be defined as all participants who took at least 1 dose of the study drug and had at least 1 post-randomization primary efficacy assessment. The safety-analysis set will be defined as all randomized participants who took at least 1 dose of the study drug and completed at least 1 post-randomization safety assessment. Participants with trichotillomania and skin picking disorder will be grouped as one BFRB group.

We will compare the baseline characteristics of both groups using Fisher's exact test for categorical variables and the t test for continuous variables. We will calculate adherence to treatment, based on the number of pills returned at each visit, as the number of pills taken divided by the number of days in the study × 100%.

Primary endpoint analysis

The primary outcome measure will be the change from first randomization visit to study endpoint in total composite score on the NIMH Trichotillomania Symptom Severity Scale(s) and the Sheehan Disability Scale.

The primary analysis of efficacy for continuous measures will be analysis of variance (ANOVA), with terms for treatment to assess differences between treatment groups in the change from first randomization visit to endpoint using the last observation carried forward. The primary analysis for global improvement and response categories will be the Cochran-Mantel-Haenszel test using the last observation carried forward. The primary analysis for ≥5% reduction in weight will be Fisher's exact test using the last observation carried forward.

Secondary endpoints analyses
Secondary outcome measures will include the change from first randomization visit to study endpoint in CGI severity and improvement scales, self-reported hair pulling behavior using the MGH-HPS, self-reported skin picking behavior using the SP-SAS, the change in depressive and anxiety symptoms, change in quality of life, and impacts on personality markers. We will use a longitudinal analysis comparing the rate of change of the outcome during the treatment period between groups. The difference in rate of change will be estimated by random regression methods. The model for the mean of the outcome will include terms for treatment, time, and treatment-by-time interaction. To account for the correlation of observations within participants, we will use SAS procedure MIXED with a first-order antedependence covariance structure. The longitudinal analyses will use all available observations from all time points from all participants who completed a randomization visit evaluation.

Safety analyses
We will evaluate differences between groups in the incidence of treatment-emergent adverse events using Fisher's exact test. Descriptive statistics will be used to evaluate changes in laboratory values, blood pressure and heart rate.

Sample Size
The sample size was calculated for the co-primary endpoint of change from randomization. For 80% power to compare the change from randomization, assuming a true effect size of 0.5 between treatment group and the placebo group, 50 participants with a BFRB will be needed in each treatment group based on a 2-group t test at the .05 level of significance. Given the low rates of adverse events expected with dronabinol, we expect few drop-outs from the study and therefore a smaller sample is needed.

Data Management Plan
Data collected will consist of demographic data, subjective (self-report questionnaires, interview responses, ratings), and physiological (weight, heart rate and blood pressure). Access to individually identifiable private information about human subjects will be limited to Dr. Grant and their staff and will be collected specifically for the proposed research project. All collected data will be stored utilizing a 4-digit subject identification code, linked to separately stored identifying information via a coded log only available to the PI.

The gender ratio of trichotillomania and skin picking disorder have been estimated to be approximately 3:1 (female:male). We will also make every effort to include a racially/ethnically diverse study population. The year 2010 Chicago census is 2,695,598 (US Census Bureau, 2011). The year 2010 Chicago race distribution is as follows: white 47.1%, African/African-American 33.9%, Asian/Asian-American 6.2%, Native American 1.0%, or other race/not identified (11.8%). A total of 28.9% of the population also identified as Hispanic/Latino allowing for a diverse population sample (year 2010, US Census Bureau, Chicago, IL). We will make every effort to ensure that members of both genders and diverse racial, ethnic, and socioeconomic groups are adequately represented in the proposed study.

The PI will implement the following procedures to ensure data integrity and the safety of participants during the study: A number of elements of the research plan are intended to minimize the risks of study participation. For example, the study exclusion criteria exclude patients who are experiencing clinically significant suicidality or require a higher level of care than outpatient. If this is indicated, the PI will evaluate them and refer them for immediate non-study treatment (for example, inpatient or additional pharmacologic treatment). The PI will carefully monitor ratings on the Columbia Suicide Severity Rating Scale and the Hamilton Depression rating Scale; any participant endorsing suicidal thoughts, will be immediately evaluated by the PI and referred to a higher level of care if clinically indicated. The PI will evaluate patient safety at each visit and resolve any safety issues more frequently if necessary, as such issues arise. The PI will also be responsible for preparing written summary reports of adverse events and will prepare a written report summarizing any decisions that are made pertaining to participant disposition.

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 and the investigator-designated research professional obtaining the consent.

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