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Title:
An Open-Label Trial of Epidiolex in the Treatment of Obsessive Compulsive Disorder: Proof of Concept Study (NCT04978428)

This project will take place at the University of Chicago. Dr. Jon E. Grant, MD, JD is the Principal Investigator and can be phoned at 773-834-1325 or reached by email at jgrant4@bsd.uchicago.edu.

This clinical trial will be conducted in the spirit of Good Clinical Practice 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.

Objective

The primary objective of the proposed study is to evaluate the safety and efficacy of Epidiolex (cannabidiol) in adults with obsessive compulsive and related disorders (OCRDs). OCRDs include obsessive compulsive disorder (OCD), trichotillomania, skin picking, tourettes disorder, body dysmorphic disorder (BDD), and hoarding disorders. These disorders appear linked in terms of phenomenology and possibly biology. Fifteen subjects with OCRDs will be treated in an open-label fashion with Epidiolex (2.5 mg/kg twice daily for one week followed by 5mg/kg twice daily) for two total weeks of active treatment. The hypothesis to be tested is that Epidiolex will result in reduction in symptoms of OCRDs (improvement in symptoms will be indicated by lower scores on established outcome measures of OCRDs symptoms that have been used in prior studies).

Background

OCRDs as a group are some of the most common psychiatric illnesses with lifetime prevalence of 1–5 %. Although onset of illness is possible across the lifespan, the age at the onset of OCRDs generally appears to be bimodal with onset either during childhood (approximately 10 years of age) or during adolescence/young adulthood (approximately 21 years of age). If untreated, OCRDs are chronic illnesses, resulting in a poor overall quality of life and high social costs due to the high rates of unemployment and disability associated with OCRDs. The World Health Organization has identified at least one of the OCRDs (e.g., OCD) as a leading global cause of nonfatal illness (Grant, 2014). Many patients are undertreated despite functional impairments and personal and social difficulties leading to a poor quality of life (Blanco et al., 2006).

Current treatments for OCRDs are often inadequate. Cognitive behavioral therapy has been shown to reduce OCRDs but finding trained psychologists is difficult. Currently available medications include selective serotonin reuptake inhibitors (SSRIs), but as many as 40-60% of patients with OCRDs do not respond to typical SSRI/SRI treatments (Ravizza et al., 1995).

Choice of Medication

Epidiolex has been approved by the US Food and Drug Administration for the treatment of seizures associated with Dravet syndrome and Lennox–Gastaut syndrome in patients aged ≥ 2 years and for the treatment of seizures associated with tuberous sclerosis complex (TSC) in patients 1 year of age and older. Epidiolex contains a highly purified form of cannabidiol (CBD) that comes from the cannabis plant. The active ingredient is nearly 100% CBD.

The pathophysiology of OCRDs includes the involvement of different neurotransmitter systems, the most important being the serotoninergic system. Interestingly, in case reports, OCRDs has improved with the use of cannabinoids. Possible underling mechanisms of beneficial effects of cannabinoids in OCRDs can be speculated as being related to the complex interplay between

cannabinoids and serotonin (5-HT) function. In *in vivo* and *in vitro* studies, it has been demonstrated that cannabinoids modulate the activity of the 5-HT system at several levels. Thus, based on the serotonin hypothesis of OCRDs, it can be speculated that cannabinoid may improve OCRDs by modulating the serotoninergic system. However, one might also speculate that OCRDs is caused by a dysfunction within the endocannabinoid system. Accordingly, cannabinoids might ameliorate OCRDs *via* direct activation of the endocnnabinoid system or indirectly by reducing anxiety.

The aim of the present study is to examine the efficacy and safety of Epidiolex in adults with OCRDs.

Study Design/Methodology

Fifteen adults with OCRDs will be recruited for an open-label proof of concept study in which Epidiolex will be administered for 2 weeks. All 15 subjects will have a current OCRD per DSM-5 criteria. Following baseline measures, subjects will receive Epidiolex (2.5 mg/kg twice daily for one week followed by 5mg/kg twice daily for one week). Participants will be seen each week during the 2-week period. At week 2, subjects will be discontinued from medication. Efficacy and safety measures will be performed at each visit.

Study Population/Sample Size

15 male and female outpatients aged 18-65 with a current primary diagnosis of an OCRD.

Subjects

Inclusion criteria:

1) Men and women age 18-65
2) Primary diagnosis of OCRD
3) YBOCS score of at least 18 at baseline for those with OCD; for those with other OCRDs, moderate level of severity as indexed by the Clinical Global Impression Scale score of 4 or greater
4) Ability to understand and sign the consent form.

Exclusion criteria:

1) Unstable medical illness based on history or clinically significant abnormalities on baseline physical examination or labs
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 psychiatric disorder other than an OCRD
5) Illegal substance use based on urine toxicology screening
6) Initiation of psychological interventions within 3 months of screening
7) Use of any other psychotropic medication
8) Previous treatment with epidiolex
9) Cognitive impairment that interferes with the capacity to understand and self-administer medication or provide written informed consent

Advertisements will target this study population. Interested individuals will be asked to contact a study coordinator or complete an online survey expressing interest. Individuals will then undergo a phone screen before being scheduled for a first appointment. After being screened, potential

subjects will be scheduled for a first appointment in which we will confirm medical and psychiatric history, laboratory tests, and inclusion/exclusion criteria.

Drugs, Dosages, and Regimens

All subjects who are enrolled will receive Epidiolex (2.5 mg/kg twice daily for one week followed by 5mg/kg twice daily for one week). Subjects will be seen each week for 2 weeks. Dosage changes and reductions will not be permitted. After study conclusion (week 2), the dose will be discontinued.

Treatment Duration, Visit Frequency, and Procedures

This is a 2-week study (2 weeks of acute treatment). Subjects will be seen at baseline and then each week thereafter for a total of 3 visits.

Diagnostic Evaluation

Psychiatric evaluation will use the MINI International Neuropsychiatric Interview.

Assessments at Each Visit

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, Family history data, Medical evaluation including physical examination, liver function tests, EKG, weight, and vital signs, Urine pregnancy test (for women of childbearing years) and urine drug screen, and a psychiatric evaluation (using the following measures: MINI International Neuropsychiatric Interview (Sheehan et al., 1998); Depressive symptoms will be rated with the 24-item Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960); Anxiety symptoms will be assessed using the Hamilton Anxiety Rating Scale (HAM-A) (Hamilton, 1959); Psychosocial functioning will be evaluated using the patient-rated version of the Sheehan Disability Scale (SDS) (Sheehan, 1983); Quality of Life Inventory (QOLI) (Frisch et al., 1993); Autism Spectrum Quotient (AQ-10); Epworth Sleepiness Scale (EPS); Pittsburgh Sleep Quality Index (PSQI); and the Columbia Suicide Severity Rating Scale (C-SSRS)).

Efficacy evaluation

The primary outcome measure will be the change from baseline using the Clinical Global Impression Scale (CGI-severity).

Secondary measures

For OCD and skin picking, we will also use the Yale Brown Obsessive Compulsive scale (YBOCS) and the YBOCS modified for skin picking (SPD-YBOCS). The YBOCS is a 10-item scale that assesses OCD symptoms during the last seven days. The first five items comprise the urge/thought subscale and items 6–10 comprise the behavior subscale. The YBOCS has demonstrated excellent preliminary psychometric properties. Both YBOCS subscales will be evaluated as secondary efficacy measures.

For hair pulling, we will use the NIMH TTM severity scale. For hoarding disorder, we use the Hoarding Rating Scale. For Tourettes we will also use the Yale Global Toc Severity Scale. Other secondary efficacy measures include the change in the Hamilton Depression and Anxiety Rating Scales, SDS, and QOLI.

Cognitive assessments
All participants will complete a series of cognitive tasks at baseline and again at the end of week-2 visit. The cognitive assessments will include the following tasks:

Tower of London Task. On each trial of the task, subjects observe two sets of pockets each containing three colored balls on-screen. On 'move' trials, subjects attempt to work out 'in mind' the minimum number of moves required to move the balls in one set of pockets to match a goal arrangement also shown in the other set of pockets. After working on this minimum number, subjects indicate responses by pressing one of four buttons. On 'counting' trials, volunteers see similar visual stimuli but count the number of balls in each array, again indicating their responses using the button box. Subjects are instructed to count the number of colored balls in each of the two arrays displayed on the screen and then to subtract the number in the lower array from the number in the upper array. Responses are made using a button box. For both tasks, problems with correct responses of 2, 3, or 4 only were used in the scanner.

Intra-Extra Dimensional Set Shift Task. This task examines cognitive flexibility. Subjects are presented with four boxes: two contain pink shapes and two are blank. Using a rule set by the computer, subjects are notified that one of the displayed shapes is correct and the other is incorrect. Individuals must learn this rule and then select the correct shape in as many trials as possible. Once the subject chooses a number of correct shapes the computer switches the rule to introduce a new "correct" shape. The subject must adapt; this is the intra-dimensional set shift. Following this portion of the task the computer introduces a set of white shapes overlaying the pink shapes. The new correct shape is one of the white shapes. Again, the subject must identify the correct shape as chosen by the computer. This addition of stimuli is the extra-dimensional set shift (ED).

Stop Signal Response Task. This task measures response inhibition. Subjects are presented with a series of directional arrows that appear one at a time on the screen. The subject must immediately press the corresponding arrow computer key matching the direction of the arrow as fast as they are able. When a buzzer sounds after the directional arrow is displayed the subject must resist pressing the computer key. The estimated time it takes for the subject to suppress the already triggered response when the buzzer sounds is calculated as the 'stop signal reaction time.'

Cambridge Gambling Task. The CGT examines decision-making. During each trial subjects are presented with ten blocks, a portion of which are red and a portion of which are blue. A token randomly resides under one of these ten boxes. Subjects must decide if they think the token resides under a red or blue box. After a decision is made they are given an opportunity to bet a certain amount by pressing a box showing decreasing values on the screen. After a time, the box shows incrementing or decrementing values and the subject must again decide how much they want to bet. The outcome measures of interest is the total proportion of points gambled, the quality of decision-making, and risk adjustment.

Spatial Working Memory Task. The SWM tests ability to remember spatial information and to use working memory in that process. Colored boxes are presented on a screen, one containing a blue box in it. Subjects click the boxes in order to find the blue box. Once they find it, they can use process of elimination to find all of the other blue boxes until a column on the right of the screen is filled. The number of boxes in each trial increases over time. SWM total errors is the number of times the subject clicks a box that is known not to contain a blue box

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 OCRD treatment.

Subject Termination

If a subject fails to take the medication for a consecutive three-day period or fails to attend weekly visits, they will be terminated from the study. In this case, the procedures for Subject Withdrawal will be followed (see above).

Safety Assessments

Safety and tolerability will be assessed using spontaneously reported adverse events data, C-SSRS, vital signs, and by evaluating premature termination. Safety assessments (sitting blood pressure, heart rate, adverse effects, concomitant medications, and motor tolerability using the Abnormal Involuntary Movement Scale) 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. Study team members are mandated reporters and as such, will arrange for the subject to be taken to the emergency room if any intent to harm themselves is expressed. 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.

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.

Risks

Participants may experience side effects while taking the drugs used in this study. Side effects are usually reversible when the drug is stopped but occasionally continue and may cause serious complications, if subjects experience any side effects, they will be asked to contact the study doctor immediately.

There may be other risks that could arise which are not reasonably foreseeable. If new information becomes available which could influence their willingness to continue, this new information will be discussed with the participant.

While taking the study drug, the subject's condition may remain the same or worsen due to no effect of the study drug.

Risks of Epidiolex

*T*he following important adverse reactions may occur:

• Hepatocellular Injury
• Somnolence and Sedation

• Suicidal Behavior and Ideation
• Hypersensitivity Reactions

Risks of blood draws
Needle sticks can cause discomfort, pain, burning sensation or bruising.

Data Analysis
Data analysis will involve all visits during the 2-week open-label treatment phase.

All enrolled subjects will be included in the analyses of baseline demographics and safety according to an intent-to-treat (ITT) principle. 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-baseline 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 follow-up safety assessment.

Primary analysis will use a last observation carried forward approach. Variables that were collected at baseline and final visit will be analyzed using a paired *t* test or the nonparametric Wilcoxon test. The total score on the CGI-Severity scale is the primary endpoint measure. The nonparametric Cochran Q test will be used to analyze the binary responder variable. The remaining variables will be analyzed using a repeated measures general linear model (GLM) analysis with polynomial contrasts across the repeated visits. This being a pilot study, all tests of hypotheses used a significance level of 0.05.

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 at the University of Chicago. Patient binders will be kept in a locked room only accessible to research staff.

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 in the 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 two individuals independent of personnel involved in the study, including a psychiatrist and a statistician, will come together via conference call every 6 months. The committee will use a standardized approach employing contemporary bio statistical, psychiatric/psychological, and ethical principles to review study design and interim data. 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.

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.

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