Tolcapone Treatment of Obsessive Compulsive Disorder:

A Double-Blind, Placebo-Controlled, Cross-Over Pilot Study

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Project Goals

The goal of the proposed study is to evaluate the efficacy and safety of tolcapone in adults with obsessive compulsive disorder (OCD). The hypothesis to be tested is that tolcapone will be more effective and well tolerated in adults with OCD compared to placebo. The proposed study will provide needed data on the treatment of a disabling disorder where current treatments are often ineffective.

Specific Aims

The primary aim of this application is to conduct a randomized placebo-controlled pharmacotherapy trial using tolcapone in 20 participants with OCD. The study will consist of two phases: a 2 week active treatment phase with tolcapone, a one-week wash-out phase, and a 2 week placebo phase. The subjects will be randomized to either receive tolcapone or placebo treatment in the first 2 weeks, and the other during the remaining 2 week phase.

This will be one of few studies assessing the use of pharmacotherapy for the treatment of OCD in adults. Assessing the efficacy and safety of tolcapone will help inform clinicians about additional treatment options for adults suffering from this disorder.

Several brain structures and functions have been implicated in OCD. Studies have consistently shown hyperactivity in the orbitofrontal cortex and caudate (1-2). Other key implicated regions (suggesting abnormalities in functional or structural connections) include the anterior cingulate cortex, thalamus, amygdala, and parietal cortex (3-5). Neuropsychological studies involving patients with OCD have shown deficits in cognitive abilities that are linked to the functioning of the frontal lobe and its related frontosubcortical structures, such as executive functioning, impulsivity in motor function, and cognitive inflexibility (i.e., not changing behavior on the basis of new information) (6-7).

If OCD is untreated, the course is usually chronic, often with waxing and waning symptoms. Without treatment, remission rates among adults are low (approximately 20%) (8). With appropriate treatment (serotonin reuptake inhibitors [SRIs]), patients report substantially higher rates of symptom response and remission (9). However, only approximately one-third of patients with OCD receive appropriate pharmacotherapy, and fewer than 10% receive evidence-based psychotherapy (10). In addition, even with appropriate treatment, approximately 30-35% of people with OCD fail to find any relief from SRIs (11), and thus more treatment options are needed.

In the frontal lobes, low levels of dopamine reuptake transporters and Catechol-O-methyltransferase (COMT) are responsible for the regulation of synaptic dopamine and its inactivation (12). The COMT effect on prefrontal cortical efficiency has been robust (i.e. significant by meta-analysis; see 13), although associations with behavior have been less convincing. Tolcapone, a COMT inhibitor, has shown benefit in improving executive

functioning and the efficiency of cortical information processing in healthy volunteers (14). Therefore, we hypothesized that tolcapone would decrease OCD symptoms and augment prefrontal dependent neural circuitry via improvement in executive functioning.

The proposed study will allow us to investigate baseline cognitive aspects of adults with OCD and examine the impact of drug treatment on tasks of cognitive dysfunction. We will examine the effects of tolcapone versus placebo in adults with OCD. By targeting deficits in cognitive deficits, tolcapone may offer a unique mechanism to address OCD symptoms. We hypothesize that tolcapone will be more effective than placebo in reducing OCD symptoms.

Background and Significance

The hallmark of OCD is the presence of obsessions, compulsions, or both. Obsessions are repetitive and persistent thoughts (e.g., of contamination), images (e.g., of violent scenes), or urges (e.g., to stab someone). Obsessions are intrusive, unwanted thoughts that cause distress or anxiety. The person attempts to ignore or suppress these obsessions with another thought or action (i.e., a compulsion). Compulsions (or rituals) are repetitive behaviors (e.g., washing) or mental acts (e.g., counting) that the person feels driven to perform in response to an obsession. Compulsions are meant to neutralize or reduce the person's discomfort or to prevent a dreaded event.

Tolcapone, a catechol-O-methyl-transferase (COMT) inhibitor, is currently approved by the FDA for the treatment of Parkinson's disease. Tolcapone's mechanism of action is unlike any pharmacological agent currently available. The methylation enzyme COMT regulates dopamine levels in the prefrontal cortex. Lower dopaminergic activity in the prefrontal cortex may be considered as a common biological substrate of a predisposition to be unable to inhibit and stop behaviors. In the frontal cortex, optimal dopamine modulation of prefrontal cortical networks appears to be necessary for a variety of cognitive functions, including planning, attention, and response flexibility (15-16). Studies of naturally occurring COMT isozymes with differential enzymatic activity have shown that the higher cortical dopamine levels associated with reduced COMT activity results in improved frontal cortical cognitive performance (17-19). Preclinical and clinical research has demonstrated that tolcapone improves improves executive functioning in normal controls (20). Cortical control is felt to be the basis for top-down control of motivated behaviors (21-22). As the only CNS penetrant COMT inhibitor, tolcapone offers a unique mechanism to address cognitive deficits associated with OCD. Tolcapone has shown benefit in improving executive functioning, the efficiency of cortical information processing in healthy controls (23). A COMT inhibitor, such as tolcapone, should increase prefrontal cortical dopamine, enhance prefrontal efficiency, and improve executive functioning and cognitive flexibility; this in turn should improve cognitive control. Tolcapone may therefore offer promise for the treatment of individuals with OCD.

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

Methodology

The proposed study will consist of a 5-week double-blind cross-over study trial of tolcapone in 20 people (ages 18-65). The study will be divided into an initial 2 week phase and a second 2 week phase, with one of the 2 week phases consisting of active treatment with tolcapone, and the other 2 week phase consisting of inactive placebo treatment. There will be a one-week wash-out phase between the 2-week treatment phases. Participants will be randomized to receive either tolcapone or placebo during the first 2 week phase on a 1:1 basis. This blinding will be maintained by the IDS pharmacy at the University of Chicago.

Based on a recent single dose tolcapone study for OCD, we should not need longer than two weeks to see an effect (unpublished data). Tolcapone is not an SSRI, so we don't anticipate it taking as long as an SSRI to see an effect. In a study using tolcpone for gambling disorder, effects were shown within the first two weeks of taking the drug (Grant et al., 2013). We do not have enough data to know what the effect size will be. It will likely be underpowered, but 20 active vs. 20 placebo should be sufficient to detect a signal. This will provide data for a future well-powered study.

Subjects:

Inclusion criteria:

1) Males and females age 18-65;

2) Diagnosis of current OCD based on DSM-5 criteria and confirmed using the clinician-administered Structured Clinical Interview for DSM-5 (SCID);

3) Able and willing to provide written consent for participation.

Exclusion criteria:

1) Unstable medical illness, including liver disease, as determined by the investigator and liver function test;

2) History of seizures;

3) Clinically significant suicidality (defined by the Columbia Suicide Severity Rating Scale);

4) Baseline score of ≥17 on the Hamilton Depression Rating Scale (17-item HDRS);

5) Lifetime history of bipolar disorder type I or II, schizophrenia, autism, any psychotic disorder, or any substance use disorder;

6) Initiation of psychotherapy or behavior therapy within 3 months prior to study baseline;

7) Previous treatment with tolcapone;

8) Any history of psychiatric hospitalization in the past year;

9) Currently pregnant (confirmed by urine pregnancy test)

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

The study will consist of 4 visits. For participating in the study, participants will receive $25 per visit to be paid in the form of a check at the completion of the study. 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 5-week, double-blind, placebo-controlled, pilot study of the safety and efficacy of tolcapone for adults with OCD. All eligible study subjects will go through a 2-week treatment phase during which they will begin tolcapone at 100mg twice a day. Subjects will be

given a matching placebo during the 2-week placebo phase. Subjects will be seen for scheduled study visits every two weeks during the 2-week blinded phases. Subjects will be randomized to either receive either the active or placebo condition during the first 2-week phase, and the remaining condition during the second 2-week phase. Study timeline is outlined below.

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. Liver diseases will be assessed at the time of subject entry and at the last visit. Subjects will have their blood drawn at baseline and again at the time of study completion to test for liver function.

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, 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.

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 (24) (baseline visit).
3. Symptom severity at baseline and follow-up visits will be examined using reliable and valid scales:
    a. *Yale Brown Obsessive Compulsive Scale* (YBOCS) (25) (each visit)
    b. *Clinical Global Impression severity and improvement scales* (26) (each visit)
    c. *Sheehan Disability Scale* (27) (baseline and final visit)
    d. *Hamilton Anxiety Rating Scale* (HAM-A) (28) (each visit)
    e. *Hamilton Depression Rating Scale* (HAM-D) (29) (each visit)

Yale Brown Obsessive Compulsive Scale (YBOCS) (25). The YBOCS is a reliable and valid 10-item clinician administered scale assessing urge, behavior, and total severity scores.

Clinical Global Impression- Severity and Improvement (CGI) (26). 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) (27). 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) (28). 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) (29).The HAM-D is a valid and reliable, 17-item, clinician-administered rating scale assessing severity of depressive symptoms.

Cognitive Assessments: In addition, subjects will undergo cognitive assessments at baseline. 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 OCD. 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 *Yale Brown Obsessive Compulsive Scale (YBOCS)*. The YBOCS 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)*
- *Sheehan Disability Scale (SDS)*
- *Hamilton Anxiety Rating Scale (HAM-A*)
- *Hamilton Depression Rating Scale (HAM-D)*.

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.

Liver diseases will be assessed at the time of subject entry and during the final study visit. Subjects will undergo a blood draw by venipuncture. One 8ml sample will be collected for liver function testing. This procedure will be repeated at the time of study completion, during the subject's final visit.

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

Tolcapone has been associated with hepatic failure in some individuals and carries a Black Box warning of hepatotoxicity from the FDA. Given the tolcapone dose of 200mg/day

used in this study is far lower than the 600mg/day dose used in Parkinson's disease and the dose associated with hepatotoxicity, and the fact that participant is only taking the medication for 2 weeks, we feel that the risk of hepatotoxicity is very low. Hepatotoxicity associated with tolcapone has been documented when the medication has been used continuously for at least 16 weeks at total daily doses of 600mg/day and liver function tests were not monitored (30).

Patients will also be assessed for clinical signs of hepatic dysfunction (persistent nausea, fatigue, lethargy, anorexia, jaundice, dark urine, and pruritus).

Other common adverse events associated with tolcapone (nausea, diarrhea, orthostatic hypotension, somnolence, confusion, hallucinations, and rhabdomyolysis are possible, although these have been reported at the dosage used for Parkinson's disease (300-600mg/day) and not the lower dose proposed for this study.

Benefits

Potential benefits include a possible direct medical benefit. Specifically, the study drug may help curb the severity of symptoms related to OCD, but there can be no guarantee that this will be the case. As current options may provide little benefit for many people with OCD, the current study could offer significant advancement in possible treatments for this disorder.

Data Analysis

Demographic and baseline visit characteristics for tolcapone 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 tolcapone groups will contain an N of 20. 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.

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