Official Title:
A randomized, placebo-controlled trial of minocycline added to serotonin reuptake inhibitors in pediatric OCD: Examining the effects on clinical symptoms and on brain glutamate levels using MRS imaging

NCT Number:
NCT01695291

Document Date:
IRB Approved 03/23/2018

Protocol Title:
Novel Medication Strategies Targeting Brain Mechanisms in Pediatric OCD

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Protocol Number:
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Clinic:
Children's Day Unit

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Lawrence Kegeles, MD

Research Chief:
Moira Rynn, MD

Cover Sheet

Choose ONE option from the following that is applicable to your study
If you are creating a new protocol, select "I am submitting a new protocol." As 5 Year Renewals are no longer required, this option remains for historical purposes.
I am submitting an annual continuation without modifications

Division & Personnel

Division

What Division/Department does the PI belong to?
Child Psychiatry
Within the division/department, what Center or group are you affiliated with, if any?
Pediatric Anxiety and Mood Research Clinic/Children's Day Unit

Unaffiliated Personnel

List investigators, if any, who will be participating in this protocol but are not affiliated with New York State Psychiatric Institute or Columbia University. Provide: Full Name, Degrees and Affiliation.

Dikoma Shungu, Ph.D., who is the co-investigator at Weill Cornell Medical Center.

Moira Rynn, MD (Consulting Professor and Chair, Department of Psychiatry and Behavioral Sciences, Duke University Medical Center)

Application for Continuation of Research

Status

Current Status of Study:
All research interventions were completed. Only data analysis is ongoing.

Summary of Experiences to Date

Please provide a summary of scientific progress of the study and the experience of research participants, to date. This requirement is designed to allow for the investigator and the IRB to reassess the study's risks and benefits in terms of developments in the field, changing practice patterns, and new IRB policies and procedures.
We have completed recruitment and data collection for this study. In total, we enrolled 33 participants. There are no participants in the active or 3-month follow-up phase of the study, with the last participant completing the 3-month follow-up phase in May 2017. The research team is completing data analyses at this time.

Funding

Have there been any changes in funding status since the prior approval?
No
Have the principal investigator and other investigators made all required disclosures of financial interest in the study sponsor/product?
Yes

Summary

Have there been any study findings, recent literature, or untoward events occuring here or at other sites in the past year which might affect the analysis of the safety, risks or benefits of study participation?
No
Have there been any serious adverse events (serious and/or unanticipated problems involving risks to subjects or others at this site which occured in the past year)?
No
Have all study staff with a significant role in the design or implementation of the human subject components of this study received required training in human research subject protections?
Yes
Is the study covered by a certificate of confidentiality?

No

Overall Progress

Approved sample size
45
Total number of participants enrolled to date
33
Number of participants who have completed the study to date
24
Have there been any significant deviations from the anticipated study recruitment, retention or completion estimates?
No
Comments / additional information

Sample Demographics

Specify population
Children, adolescents and young adults
Total number of participants enrolled from this population to date
33
Gender, Racial and Ethnic Breakdown
Gender
-Male: 16
-Female: 17

Ethnicity
-White: 26
-Asian: 3
-African American: 1
-American Indian: 1
-Other: 2

Summary of Current Year's Enrollment and Drop-out

Number of participants who signed consent in the past year
0
Did the investigator withdraw participants from the study?
No
Did participants decide to discontinue study involvement?
No

Procedures

To create the protocol summary form, first indicate if this research will include any of the following procedures

✓ Psychiatric Assessment
✓ Collection of Biological Specimens
✓ Medication Trial
✓ Use of Placebo or Sham Treatment
✓ MRI
✓ Use of Investigational Drug or Device

Population

Indicate which of the following populations will be included in this research

✓ Children (ages 8-12)
✓ Children (ages 13-17)
✓ Adults

Research Support/Funding

Will an existing internal account be used to support the project?
No
Is the project externally funded or is external funding planned?
Yes
Select the number of external sources of funding that will be applicable to this study

Funding Source #1

Is the PI of the grant/contract the same as the PI of the IRB protocol?
Yes
Select one of the following
The grant/contract is currently funded
Source of Funding
Federal
Institute/Agency
NIMH
Grant Name
Novel medication strategies targeting brain mechanisms in pediatric OCD
Grant Number
#1R34MH095502-01
Select one of the following
Multicenter(NYSPI is the lead site)

Business Office
RFMH
Does the grant/contract involve a subcontract?
Yes
Subcontracted?
From
Name institution(s)

Columbia University

Study Location

Indicate if the research is/will be conducted at any of the following
✓ NYSPI
This protocol describes research conducted by the PI at other facilities/locations
Yes
✓ Hospital, clinics and other healthcare facilities

Hospitals,clinics and other healthcare facilities

Select from the list
✓ Weill Cornell Medical Center
or type in location(s)..

Lay Summary of Proposed Research

Lay Summary of Proposed Research
This study will examine the feasibility and potential efficacy of augmenting SRIs with minocycline, a drug with a novel mechanism of action for OCD. The study will additionally assess whether the addition of minocycline leads to measurable changes in striatal glutamate (Glu) levels and whether either baseline striatal Glu levels or changes in striatal Glu levels are associated with response to minocycline. This study will recruit up to 45 youth ages 8-20 diagnosed with clinically significant OCD who have demonstrated no more than partial response to SRI treatment and are currently on a stable dose of SRI medication for at least 12 weeks. Additionally, on a case-by-case basis, the study will accept participants who are unwilling to take SRI medication, but are still interested in enrolling in the minocycline trial. Participants will be randomized to receive either 12 weeks of minocycline treatment or placebo. Randomization will be 2:1 so that 2 of 3 participants receive minocycline and will be stratified by age (8 to 11 years; 12 to 15 years; 16 to 20 years). Participants will undergo MRS scans to measure striatal Glu levels prior to randomization, and again immediately following the treatment period. Participants that are randomized to receive placebo during the blinded treatment phase are given the option of starting minocycline during the 3-month follow-up period. Should any of these participants have a significant response to the minocycline treatment, he or she will be given the option of undergoing a third MRS scan to measure changes in striatal glutamate (Glu) levels since

the Week 12 scan. During the treatment period, participants will meet every other week with the study psychiatrist. All participants will be offered three months of open medication treatment following participation. The clinical trial will only be conducted at NYSPI and the MRS scans may be conducted at Weill Cornell Medical Center or NYSPI depending on scanner availability.

Background, Significance and Rationale

Background, Significance and Rationale

With a lifetime prevalence of 2-3% and half of all cases beginning by age 19, obsessive-compulsive disorder (OCD) is a major health concern for children and adolescents and is a leading cause of illness-related disability. SRI medication and cognitive-behavioral treatment represent front-line treatments for pediatric OCD, but lead to symptom remission in only 54% of youth with OCD. This study will examine the feasibility and potential efficacy of augmenting SRIs with minocycline, a drug with a novel mechanism of action for OCD. The study will additionally assess whether the addition of minocycline leads to measurable changes in striatal glutamate (Glu) levels and whether either baseline striatal Glu levels or changes in striatal Glu levels are associated with response to minocycline. The study will also examine minocyline as a mono-therapy treatment for pediatric OCD in a small subset of participants that are unwilling to take SRI medication. The study will measure changes over time in the striatal glutamate (Glu) levels of these participants as well. Minocycline is a second-generation tetracycline that has been shown to modulate glutamate and to have anti-oxidant and anti-inflammatory properties. There is growing evidence from animal studies and human clinical trials of neurological diseases (including Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease, and ischemia) that minocycline has neuroprotective effects.

Specific Aims and Hypotheses

Specific Aims and Hypotheses

Hypothesis 1: When added to SRI medication, or taken as mono-therapy, minocycline will be superior to pill placebo in reducing OCD symptoms.

Hypothesis 2: Adding minocycline (but not placebo) to an SRI, or taking minocycline (but not a placebo) without an SRI, will reduce glutamate levels in the head of caudate.

Hypothesis 3: Reduction in glutamate levels will be associated with reduction in OCD severity.

Description of Subject Population

Sample #1

Specify subject population
OCD Participants
Number of completers required to accomplish study aims
45
Projected number of subjects who will be enrolled to obtain required number of completers
45
Age range of subject population
8-20 inclusive

Gender, Racial and Ethnic Breakdown

Based on our experience and the demographics of the catchment area served by our institution, we expect the subject racial distribution to be approximately 73% White, 18% Black, 9% Asian, and for the ethnic distribution to be approximately 22% Hispanic. We expect the sample to be 50% female.

Description of subject population
We plan to recruit approximately 45 individuals ages 8-20 in this study. Participants will have a current diagnosis of OCD and will be currently taking SRI medication. SRI dosage must be stable for at least 12 weeks prior to study participation.

Recruitment Procedures

Describe settings where recruitment will occur
Recruitment for this study was completed in 2016.

The study recruited participants from the Anxiety Disorders Clinic (ADC), directed by Dr. Simpson, as well as the CAPES Evaluation Service and the Children's Day Unit (CDU), which are directed by Dr. Rynn. The ADC screens over 200 adults (≥ 18) with OCD a year. More than half are on medication (predominantly SRIs). The CAPES/CDU provides free expert consultation, evaluation, and treatment referrals for children and adolescents suffering from mood and anxiety disorders. In past years, CAPES/CDU evaluated as many as 30 children and adolescents with OCD, of whom approximately one-third were on SRIs only. OCD self-help organizations such as the International OCD Foundation were contacted to further publicize the existence of this study.

Participants (ages 8-20) and their parent/caregiver were assessed by an IRB-approved phone screen. For participants ages 18-20, the research team obtained permission from the participant before speaking to his/her parent/caregiver. We do not communicate to families that we will destroy their screening

information if they do not come in for a study visit. Regardless of study participation, we enter the information from the phone screens into a deindentifed and password protected database.

How and by whom will subjects be approached and/or recruited?
Research staff on the CDU and ADC may approach and discuss the research study with potential participants who have given permission to be contacted about research. Drs. Rynn, Simpson, and Goldberg will be responsible for fully explaining the details of the study, answering any questions, and consenting the participants if they are interested in the study.
How will the study be advertised/publicized?
IRB-approved radio/newspaper/web advertisements and flyers were used to recruit participants
Do you have ads/recruitment material requiring review at this time?
No
Does this study involve a clinical trial?
Yes
Please provide the NCT Registration Number
01695291

Concurrent Research Studies

Will subjects in this study participate in or be recruited from other studies?
Yes
Describe concurrent research involvement
Participants may be recruited from the following ongoing studies:
· EVALUATION AT THE CHILD AND ADOLESCENT PSYCHIATRY EVALUATION SERVICES (CAPES) OF THE CHILDREN'S DAY UNIT (CDU)," IRB #7058R (formally 6019R)
· "MRS Glutamate Measurement in Healthy Controls and People with OCD", IRB #6218

Inclusion/Exclusion Criteria

Name the subject group/sub sample
OCD participants
Create or insert table to describe the inclusion criteria and methods to ascertain them

CRITERION	METHOD OF ASCERTAINMENT
1) Participants must be ages of 8-20 at the time of consent.	Inquiry at time of consent by trained research staff
2) Participants must weigh at least 25kg.	Weight assessed by study nurse
3) Participants and a parent/guardian must be able to read and understand English.	Inquiry at time of consent by trained research staff
4) Participants must meet diagnostic	Clinical Interview; CYBOCS administration

criteria for primary obsessive-compulsive disorder with score ≥ 16 on the Children's Yale-Brown Obsessive Compulsive Scale (CYBOCS).	
5) Participants must be on a stable and minimal adequate dose of serotonin reuptake inhibitor (SRI) medication as defined by the literature for a minimum of 12 weeks, and have a documented history of intolerable adverse effects at a higher dose or strong preference to stay at that dose. Congruent with the literature, minimal adequate SRI doses to treat OCD are as follows: Clomipramine 75 mg/day; Fluoxetine 20 mg/day; Paroxetine or Paroxetine CR 20 mg/day; Sertraline 50 mg/day; Fluvoxamine 100 mg/day; Citalopram 20 mg/day; Escitalopram 10 mg/day for a minimum of 12 weeks. If a potential participant is on a minimal adequate SRI dose, the research team will collaborate with the participant's treating psychiatrist to determine if participation in the trial is clinically indicated. OR Participants must be unwilling to take SRI medication due to reasons such as having a history of adverse side effects from SRI medication.	Phone screen, Clinical interview, medical records by research team.

6) If taking SRI medication, report of at least minimal response to current SRI medication to warrant ongoing SRI treatment.	Inquiry at time of consent by trained research staff; consultation with referring clinician and the CGI-I
7) For participants younger than 18, written informed assent by the participant and consent by the parent. For participants 19 and older, written consent by the participant and permission for legal guardian/parent to provide information.	Consent Interview by study psychiatrist

Create or insert table to describe the exclusion criteria and methods to ascertain them

CRITERION	METHOD OF ASCERTAINMENT
1) Lifetime diagnosis of: psychotic disorder, bipolar disorder, eating disorder, pervasive developmental disorder, mental retardation, or substance/alcohol dependence.	Clinical Interview
2) Current diagnosis of major depressive disorder, Tourette's/Tic Disorder, or substance/alcohol abuse.	Clinical Interview
3) Active suicidal ideation.	Clinical Interview
4) Females who are pregnant, nursing, or using hormonal birth control.	Medical evaluation conducted by study psychiatrist
5) Any major medical or neurological problem (e.g., unstable hypertension, seizure disorder, severe renal deficiency, and head trauma).	Medical history obtained by study psychiatrist
6) Positive urine screen for illicit drugs.	Urine toxicology assessment
7) Presence of metallic device or dental braces.	Inquiry at time of consent by trained research staff
8) IQ <80	Wechsler Abbreviated Scale of Intelligence (WASI) administration.
9) OCD patients with primary symptoms of hoarding (determined by CYBOCS/ YBOCS checklist).	Clinical Interview
10) Current or past diagnosis of pediatric autoimmune neuropsychiatric disorders associated with streptococcus (PANDAS). This will be defined by the following criteria: abrupt onset of OCD symptoms (often with comorbid tics) with a relapsing–remitting symptom course, a temporal association between symptom exacerbations and a Group-A beta-hemolytic streptococcal (GAS)	Clinical Interview

infection, association with neurological abnormalities during exacerbations (adventitious movements, motoric hyperactivity, urinary hesitancy), and prepubertal age of onset.	
11) Individuals who are currently receiving Exposure and Response Prevention therapy and are in the acute phase of treatment. Participants may receive ongoing supportive therapy and school counseling as long the treatment was initiated and remained stable for at least 6 weeks prior to enrollment in the study. The intensity and frequency of therapy should remain unchanged throughout the trial.	Inquiry at time of consent by trained research staff
12) Documented history of hypersensitivity or intolerance to tetracycline antibiotics	Medical history obtained by study doctor
13) Use of medications that are contra-indicated with minocycline (e.g., concomitant use of antacids, iron, calcium, magnesium, aluminum, zinc salts as they impair minocycline absorption; of anti-coagulant drugs as minocycline has been shown to depress plasma prothrombin activity; of other antibiotics or Accutane due to the rare side effect of Pseudotumor cerebri)	Medical evaluation conducted by study doctor
14) Inability of participant or parent/guardian to read or understand English.	Inquiry at time of consent by trained research staff

Waiver of Consent/Authorization

Indicate if you are requesting any of the following consent waivers
Waiver of consent for use of records that include protected health information (a HIPAA waiver of Authorization)
No
Waiver or alteration of consent
Yes
Waiver of documentation of consent
No
Waiver of parental consent
No

Consent Procedures

Is eligibility screening for this study conducted under a different IRB protocol?
No
Describe procedures used to obtain consent during the screening process
Prior to initiating screening procedures, Drs. Rynn, Simpson, or Goldberg, will obtain consent from the participant's parent/legal guardian by describing the purpose and nature of this research study. Families will have a chance to review the consent form thoroughly and ask any questions prior to signing.
Describe Study Consent Procedures

Drs. Rynn, Simpson, or Goldberg, will answer any questions the participant's parent/legal guardian may have and will obtain written consent. The participant's parent/legal guardian will receive a copy of the signed consent.

Indicate which of the following are employed as a part of screening or main study consent procedures
✓ Consent Form

Justification for Waiver or Alteration of Consent

Waiver of consent is requested for the following
A waiver or alteration of consent is needed in order to obtain verbal consent from potential participants during the study phone screen. Please refer to 45CFR46.116(d) for justification of this waiver.
Explain why your research can not be practicably carried out without the waiver or alteration
As it is not practical to get written consent prior to conducting the phone screen, we instead get verbal consent from participants and/or their parents at the beginning of each phone screen. The staff member conducting the phone call documents that verbal consent was obtained.
Describe whether and how subjects will be provided with additional pertinent information after participation
N/A

Assent Procedures

Describe procedures by which subject assent will be assessed and/or recorded

Drs. Rynn, Simpson, or Goldberg will describe the purpose and nature of the research study. The participant will have a chance to review the assent form thoroughly and ask any questions prior to signing. If they decide to participate in the study, they will also receive a copy of the signed assent form.

Persons designated to discuss and document consent

Select the names of persons designated to obtain consent/assent
Goldberg, Pablo, MD
Kegeles, Lawrence, MD

Rynn, Moira, MD
Simpson, Helen, MD
Type in the name(s) not found in the above list

Dikoma Shungu, Ph.D., who is the co-investigator at Weill Cornell Medical Center.
Pablo Goldberg, MD
Moira Rynn, MD
Paula Yanes-Lukin, PhD

Study Procedures

Describe the procedures required for this study

Overview:
Children's Day Unit:
The clinical trial will be conducted at the Children's Day Unit (CDU). The CDU is an outpatient clinic and a research day treatment program that provides services for the psychiatric and educational needs of children and adolescents participating in research protocols at NYSPI. Most of the children have either failed or not completely responded to first line treatments for mood, OCD, or other anxiety disorders. School services are provided by PS186X, a New York City public school located on the unit during the academic year from September through June. In addition, during the 6 week summer program in July and August, the CDU provides educational tutoring. This unit provides continued clinical care for children and adolescents after their participation in an IRB approved protocol at no cost. Led by Dr. Rynn, the staff consists of a research medical director, Dr. Pablo Goldberg, a research nurse, a social worker, psychologists, and trainees. Although this protocol is an outpatient protocol, if an adolescent requires additional support or requires a higher level of care, the adolescent may be admitted to the CDU partial program that runs Monday through Friday from 8:30 am to 2:20 pm where the adolescent can be closely monitored, receive educational credit, and additional supportive services. For children under the age of 12, the CDU team is available for the child and the parent to come in for daily check-in visits for support and monitoring, but it does not have educational programming for children under 12.

Screening
Upon consenting, participants will complete all screening procedures. Screening may last from 1 to 4 weeks to allow sufficient time to obtain thorough medical and psychiatric history to ensure the patient's safety and eligibility/ineligibility in the study. Screening procedures include:

- Diagnostic Assessment: Anxiety Disorders Interview Schedule - Child/Parent version (The child version will be administered to all participants. The parent version will be administered to parents of all participants ages 8-17, and to parents of participants ages 18-20 with their permission); OCD onset form; Clinical Global Inventory – Severity Scale; Family History Screen and Isolated Tics/Tic Disorder Assessment questions
- Feasibility and Safety Assessment: Columbia Suicide-Severity Rating Scale; Pediatric Adverse Event Rating Scale

- Efficacy Assessment: Children's Yale-Brown Obsessive Compulsive Scale (CYBOCS)
- Intelligence Assessment: Wechsler Abbreviated Scale of Intelligence (WASI)
- Medical: Medical evaluation; Tanner Scale, physical exam, EKG, labs, including a Thyroid Function Test, and vital signs

Baseline Evaluation
After completing the screening procedures, eligible participants will proceed to the baseline evaluation. Baseline evaluation procedures include:

- MRS scan except for participants who have MRS incompatible dental braces
- Efficacy Assessments: Children's Yale-Brown Obsessive Compulsive Scale (CYBOCS); Child Obsessive-Compulsive Impact Scale – Revised (COIS-R); Hamilton Depression Scale (HAM-D)
- Feasibility and Safety Assessment: Columbia Suicide-Severity Rating Scale; Pediatric Adverse Event Rating Scale; Medication Adherence

Randomization
Randomization to minocycline or placebo treatment will occur following the baseline evaluation. Randomized assignments will be generated using a random number generator in SAS. We will randomize minocycline versus placebo in a 2:1 ratio to gather more data about minocycline's clinical effect. To balance the minocycline-placebo groups with respect to age, randomization will be stratified with respect to age ranges (8 to 11 years; 12 to 15 years; 16 to 20 years).

Post-randomization
Once randomized, the study psychiatrist will conduct the week 1 check-in via phone. After that, participants will be seen by the study psychiatrist every two weeks for a total of 12 weeks. Visits will last 30 minutes, except the first, which will last 60 minutes. The study psychiatrist will offer support and monitor the patient's medication and side effects. To monitor for unexpected pregnancy, females will have a blood pregnancy test at screening and a urine pregnancy test at each study visit. A manual for medication procedures is provided in Appendix A. Clinician adherence to this manual will be formally assessed using the Clinician Adherence to Pharmacotherapy form as described in the manual.

Ongoing SRI treatment: Participants will enter on an SRI (at a stable dose for ≥ 12 weeks). The study psychiatrist will continue to prescribe this SRI. To confirm ongoing SRI adherence, SRI pill counts will be conducted at each psychiatrist visit. In addition, SRI blood levels will be assessed at baseline and week 12 (or early termination). For each participant and at each time point, blood will be drawn at the same time of day and in a constant temporal relationship to their last SRI dose. The goal is to verify a stable SRI dose in each participant during the trial and thereby exclude the possibility that any therapeutic effect is due to a change in SRI level. A small sample of participants will enroll in the study without being on a dose of SRI medication. For these participants, we will not monitor SRI adherence nor assess SRI blood levels.

At each treatment visit, medication adherence will be assessed. In addition, the C-SSRS will be administered at each treatment visit to assess for suicidality, the Pediatric Adverse Event Rating Scale (PAERS) will be administered to assess for the presence of adverse events, and the Clinical Global Impression Scale (CGI-S) will be administered to assess symptom severity and improvement. Vital signs will also be taken at each treatment visit, and pregnancy tests will be administered to female participants.

Week 4, 8 & 12 IE Visits: Efficacy measures will be re-administered by the independent evaluator at Weeks 4, 8, and 12 of treatment to assess for change in OCD symptoms. The following measures will be administered at these visits:

- Children's Yale-Brown Obsessive Compulsive Scale (CYBOCS)
- Child Obsessive-Compulsive Impact Scale – Revised (COIS-R)
- Hamilton Depression Scale (HAM-D)

The following staff members are designated independent evaluators for this study: Anthony Puliafico, PhD, Chiaying Wei, MA, Paula Yanes-Lukin, PhD.

Post-treatment Assessment: At Week 12, in addition to the Week 12 IE assessments, the following assessments will be administered:

- Medical Evaluation including the Tanner Scale, physical exam, EKG, labs and vital signs
- Client Satisfaction Questionnaire (CSQ)
- Previously endorsed modules on the ADIS-C/P

Follow-up Treatment
Upon completion of the 12-week clinical trial, participants will be offered an additional 3 months of open medication management as clinically indicated based on their treatment history and response during the study. Participants and their families will be unblinded to their treatment assignment at this point. In the event they prefer to be treated elsewhere, they will also be provided referrals to community providers. With their permission, all participants will be assessed every 4 weeks for OCD severity (using the CYBOCS and CGI-S by the IE) and safety (PAERS by the MD). The 1-month and 2-month follow-up assessments will be conducted **in person, or if necessary,** by phone, and the 3-month assessment will be conducted in person.This will be pilot data to help us evaluate patient satisfaction (e.g. proportion who choose to continue minocycline), ongoing safety, and maintenance of response. Participants that begin taking, and respond to, minocycline during the follow-up period may also have the option of undergoing a third MRS scan.

Clinical Deterioration *(please see Appendix A and Protection of Human Subjects)*
A clinical management issue of major significance is the referral of unimproved or deteriorating adolescents for a clinical evaluation. In particular, any patient who is evaluated by the study clinician to be much worse (CGI-I score of 6) for two consecutive visits will be discontinued from the protocol. If the adolescent begins to show clinical deterioration during the study and further continuation under such circumstances would be detrimental to the adolescent, a referral will be made for a clinical evaluation by an independent evaluator to determine whether the adolescent should be withdrawn from the study. If the adolescent is withdrawn from the protocol, the adolescent will be eligible for no cost treatment on the Children's Day Unit. If the participant or the participant's parent/guardian would prefer outside referrals, arrangements will be made by the research staff. The psychiatrist has full responsibility and authority to refer the adolescent for this clinical evaluation at any time regarding the adolescent's suitability for remaining in the study. Additionally, participants who experience severe reaction to the study medication will be unblinded to their treatment assignment following the adverse event.

Minocycline versus Pill Placebo
Participants will be randomized to receive the addition of either minocycline or pill placebo. The medications will be identical in appearance and made by the NYSPI pharmacy. Those randomized to minocycline will receive approximately 2 mg/kg/day, the FDA-approved dose for minocycline and the dose used in our pilot study (<35 kg: 50 mg/day; 35-55 kg: 50 mg BID; >55-75 kg: 75 mg BID; >75kg: 100 mg BID). Participants will be asked to take the tablet with food, in an upright position, and with 4 to 8 ounces of water in order to lessen gastric side effects. After randomization, participants will receive child proofed bottles that contain enough study medication until the next visit with an additional 3 days coverage in case of scheduling issues. Drs. Rynn and Goldberg will prescribe the study drug, which will be dispensed by the NYSPI pharmacy. All participants will have a minocycline level drawn at week 12 to confirm treatment adherence. In the absence of a laboratory that can perform a minocycline level, participants' serum and plasma will be collected and stored in a -80 degree Celsius freezer at NYSPI until an alternate laboratory can be located to do this test. Minocycline is FDA-approved in those ages 8 and above for treatment of infections and acne and has a favorable risk-benefit profile.

MR Neuroimaging Methodology
All MR imaging data will be acquired on a GE 3T SIGNA whole-body MR system and a standard quadrature single-channel head coil in a total examination time of approximately 45 min, including scan setup. At baseline, after 12 weeks of treatment, and for a subset of the sample, after the 3-month follow-up period, subjects will undergo MR imaging at either NYSPI or at Weill Cornell Medical Center. Participants will continue to take their prescribed SRI medication (if applicable) and minocycline or placebo when they undergo the 12-week MR imaging. Subjects will be escorted to the imaging procedure by a project coordinator. Female participants will be given a urine pregnancy test prior to scanning in addition to the blood pregnancy test at screening. There will be a 72-hour window between pregnancy testing and MRS scan. The team at Cornell will receive a signed copy of the negative urine pregnancy test in order to proceed with the scan. First, a standard T1-weighted volumetric MRI series will be acquired for use in estimating the proportions of gray matter, white matter and CSF content of the head of the caudate through tissue segmentation. Second, glutamate (Glu) levels will be recorded from the head of the caudate using MRS. The recorded 4D raw data set will be processed using standard procedures. The striatal voxels will be selected from the spectroscopic imaging grid after acquisition and post-processing, and then analyzed for Glu content using versatile software, XsOSNMR, developed in Dr. Shungu's laboratory (see Resources). The rationale for focusing on the striatum and the head of the caudate in particular is described above (Section C5.h). The Glu data will be quantified as peak area ratios relative to the robust unsuppressed water resonance (W) in a spectroscopic imaging data set that will be acquired in just 4 min using the same spatial parameters as in the PRESS SI sequence.

You can upload charts or diagrams if any

Criteria for Early Discontinuation

Criteria for Early Discontinuation
Clinical deterioration *(please see Appendix A and Protection of Human Subjects):* A clinical management

issue of major significance is the referral of unimproved or deteriorating adolescents for a clinical evaluation. In particular, any patient who is evaluated by the study clinician to be much worse (CGI-I score of 6) for two consecutive visits will be discontinued from the protocol. If the adolescent begins to show clinical deterioration during the study and further continuation under such circumstances would be detrimental to the adolescent, a referral will be made for a clinical evaluation by an independent evaluator to determine whether the adolescent should be withdrawn from the study. If the adolescent is withdrawn from the protocol, the adolescent will be eligible for no cost treatment on the Children's Day Unit. They will also have the option to attend the school program on the CDU. If the participant or the participant's parent/guardian would prefer outside referrals, arrangements will be made by the research staff. The psychiatrist has full responsibility and authority to refer the adolescent for this clinical evaluation at any time regarding the adolescent's suitability for remaining in the study.

Blood and other Biological Samples

Please create or insert a table describing the proposed collection of blood or other biological specimens

A blood sample, approximately one tablespoon (15 cc's) of blood, will be taken at screening and at study completion (or withdrawal, if earlier) for a total of two tablespoons (30 cc). These samples will be used to measure minocycline and SRI levels and for safety monitoring, including Chemistry Screen and CBC. The samples for drug assay will be forwarded to a centralized laboratory for analysis. Participants may experience a bruise at the site of venipuncture. EMLA cream may be used to minimize the discomfort of venipuncture.

Assessment Instruments

Create a table or give a brief description of the instruments that will be used for assessment
Diagnostic Assessments:
Anxiety Disorders Interview Schedule for Children for DSM-IV (ADIS-C/P Revised): This will be administered to the subject (and parent/caretaker for those <18 and those 18-20 with permission) by the independent evaluator (IE) at screening to confirm the diagnosis of OCD and its age of onset. At the week 12 post-treatment assessment, previously endorsed modules on the ADIS-C/P will be administered to measure changes in diagnoses and symptomatology.

Wechsler Abbreviated Scales of Intelligence (WASI): This estimates Full Scale IQ with excellent reliability and validity for ages 6-90. It consists of four subtests: Vocabulary, Similarities, Block Design, and Matrix Reasoning. The Vocabulary and Matrix Reasoning subtests will be administered by the protocol manager at screening.

Family History Screen (FHS): This screens for the presence of 15 psychiatric disorders among the participant's biological relatives. It is administered to a family informant (for those ages 8-17) or to the

subject (ages 18-20), who reports on himself/herself and on other biological relatives. It will be administered by the MD at screening.

Isolated Tics/Tic Disorder Assessment: The parent(s) of the participant will be asked five questions about family history of isolated tics and Tic Disorder. The questions were developed by investigator Blair Simpson and are administered as an addendum to the FHS.

Medication Evaluation: The study psychiatrist and study nurse will conduct a medical history, laboratory tests, physical exam, (including weight, height, and EKG), pregnancy test at each visit, at screening and Week 12.

The Tanner Scale: This is a scale of physical development based on external primary and secondary sex characteristics. Participants look at pictures of pubertal stages and identify their pubertal stage.

Feasibility Assessments:
Pediatric Adverse Event Rating Scale (PAERS): This self-report questionnaire assesses the severity of 48 potential adverse events, each on a five-point Likert scale (0–4). It is filled out by the participant at each medication visit (and parent/caretaker for those <18 and those 18-20 with permission). It is reviewed by the study psychiatrist to determine final severity and relationship to treatment or illness.

Columbia Suicide-Severity Rating Scale (C-SSRS): This is a semi-structured clinician rating of suicidal behavior, suicide attempts, and presence and intensity of suicidal ideation. The assessment will be administered by study psychiatrists at screening, baseline and each study visit except the phone interview at week 1.

Client Satisfaction Questionnaire (CSQ): Used in prior studies, this scale includes questions about satisfaction with treatment condition (CSQ). It will be completed by the participant (and parent/caretaker for those < 18 and those 18-20 with permission) at week 12 and used to assess the acceptability of minocycline augmentation. For children under the age of 12, the Research Assistant (RA) will be present in case of reading comprehension questions.

Medication Adherence: The participant and psychiatrist will review the dosing procedures and use of a dosing diary with the parent/caretaker. Adherence to medication will be assessed by: 1) direct query of the participant and parent/caretaker; 2) pill count; 3) review of the dosing diary that participants return at each study visit; and 4) SRI and minocycline blood levels (as described above). A log will document the number of SRI and study medication tablets provided and what is returned at the next visit, with 70% or greater accuracy considered adherent. Number of sessions attended will also be recorded.

Attrition: The proportion of patients who drop out at each assessment will be used as a measure of attrition. Specific reasons for discontinuation will be documented. Every attempt will be made to obtain all assessments at all time points from all study participants, even if they terminate early from the study.

Efficacy Assessments:
Yale-Brown Obsessive Compulsive Scale, Child version (CYBOCS): The CYBOCS is a semi-structured measure of OCD severity with excellent inter-rater reliability, internal consistency, and test-retest reliability.

It is validated in those starting at age 7 and used in studies up to age 20. The CYBOCS differs from the adult YBOCS only in its use of simpler language. The CYBOCS will be administered by IEs at screening, baseline, and weeks 4, 8, and 12 and will be the primary outcome measure. As secondary outcomes, response will be defined as a CYBOCS decrease of ≥ 30% and excellent response as a CYBOCS of ≤ 10 following the Pediatric OCD Study (2004). The CYBOCS checklist will be used to determine symptom dimensions.The CYBOCS will be administered by the IE at screen, baseline, weeks 4, 8, and 12.

Hamilton Depression Scale (HAM-D, 17-item): This semi-structured interview which assesses the severity of depressive symptoms is validated for use in ages 7 and above. It will be administered by the IE at baseline, weeks 4, 8, and 12.

Child Obsessive-Compulsive Impact Scale-Revised (COIS-R): This 27-item self-report questionnaire measures OCD-specific functional impairment. The COIS-R-C is a 3-factor structure youth-report form. The COIS-R-P is a 4-factor structure parent-report measure (completed by the parent/caretaker for those <18 and those 18-20 with permission). Both will be completed at baseline, weeks 4, 8, and 12.

Family Accommodation Scale (FAS) (5 minutes): This scale consists of 12 items to assess the areas and the level of family accommodation to the patient's OCD symptoms. It will be completed by the parent at baseline, week 4, week 8, and session 12 or early termination in this study.
Please attach copies, unless standard instruments are used

Off label and investigational use of drugs/devices

Choose from the following that will be applicable to your study
✓ Drug
Select the number of drugs used in this study
1

Drug #1

Name of the drug
Minocycline
Manufacturer and other information
Other name: Minomycin, Minocin, Arestin, Aknemin, Solodyn and Dynacin
Manufacturer: Watson
Approval Status
No IND is required
Choose one of the following options
FDA conditions are met (see 'Rules')
Explain

According to 21 CFR 312.2(b)(1), the clinical investigation of a marketed drug or biologic does not require submission of an IND if all six of the following conditions are met:

(i) it is not intended to be reported to FDA in support of a new indication for use or to support any other significant change in the labeling for the drug;

We are not intending to report the results to the FDA in support of a new indication or change in labeling.

(ii) it is not intended to support a significant change in the advertising for the product;
There will be no support to change advertising for this product.

(iii) it does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.

There is no change in the route of administration or dosage level in this subject population and does not increase the risks for this specific population or decrease the acceptability of the risks associated with the use of the drug product for this particular disorder.

(iv) it is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively];
Yes

(iv) it is conducted in compliance with the requirements concerning the promotion and sale of drugs [21 CFR 312.7];
Yes

(vi) it does not intend to invoke 21 CFR 50.24.
Yes

Research Related Delay to Treatment

Will research procedures result in a delay to treatment?
Yes
Maximum duration of delay to any treatment
For all enrolled participants, the maximum delay in initiating augmentation treatment will be 14 weeks. Participants will be randomized to either minocycline or placebo upon completing the baseline evaluation. Two of every three participants will be randomized to minocycline and will begin treatment immediately after randomization, and approximately 1-4 weeks after the screening process began. Participants who are randomized to placebo will be offered medication management at no cost following the 12-week acute treatment phase of the study. All participants will be advised of their alternatives to participation (e.g., seeking alternative SRI augmentation treatments such as the addition of cognitive-behavioral therapy, an atypical antipsychotic, or clomipramine) before consenting to participate.
Maximum duration of delay to standard care or treatment of known efficacy
For enrolled participants, the maximum delay in beginning a treatment of known efficacy is 14 weeks. Participants in both the minocycline and placebo groups will be offered medication management following

the 12-week acute treatment phase of the study.
Treatment to be provided at the end of the study
Upon completion of the acute treatment period, participants will be offered three additional months of medication management at no cost. Medication management will be offered to all participants regardless of response during the acute study treatment period because all participants will enter the study on a stable SRI dose. For participants requiring continued medication management following this three-month follow-up treatment period, the research staff will refer the patient to his or her previous psychiatrist or will assist the participant and his/her family in identifying a psychiatrist.

Clinical Treatment Alternatives

Clinical treatment alternatives
Currently cognitive-behavioral treatment involving exposure and response prevention (CBT/ERP) and serotonin reuptake inhibitor (SRI) medication are considered the first line treatments for OCD. However, pharmacotherapies have relatively modest effects in OCD. CBT/ERP treatment is the mainstay of the treatment for OCD. Yet, CBT/ERP alone results in response rates of anywhere between 60% and 80%, and fear of non-adherence to ERP is hypothesized to contribute to the lack of ERP efficacy across age groups.

Risks/Discomforts/Inconveniences

Risks that could be encountered during the study period
1) Distress from discussion about emotional symptoms; 2) blood sampling; 3) delay in initiation of other medication augmentation options for OCD patients; 4) medication-related adverse events and side effects for those randomized to minocycline; 5) placebo risks; 6) risks from chronic SRI treatment; 7) risks associated with MR imaging.

1) Distress from thoughts or discussion about emotional symptoms: Some participants may experience distress or anxiety related to participating in these procedures. Participants will be monitored throughout the procedures, and they will be encouraged to report any concerns. A psychiatrist will be available to assist the participant if needed, and participants will be removed from the protocol if their distress or anxiety becomes intolerable. Participants and their legal guardians will be informed that their continued treatment at NYSPI will not be impacted if at any point they choose to no longer participate.

2) Risks of blood sampling: A blood sample, approximately one tablespoon (15 cc's) of blood, will be taken at screening and at study completion (or withdrawal, if earlier) for a total of two tablespoons (30 cc). These samples will be used to measure minocycline and SRI levels and for safety monitoring, including Chemistry Screen and CBC. The samples for drug assay will be forwarded to a centralized laboratory for analysis. Participants may experience a bruise at the site of venipuncture. EMLA cream may be used to minimize the discomfort of venipuncture.

3) Delay in Initiating Other Augmentation Treatment for Participants: All participants must be on active treatment, an SRI, which has known efficacy from the beginning of the study and all patients must have experienced at least minimal response to this SRI**.** Participants will be randomized to minocycline or

placebo (2:1). We do not expect pill placebo to have effects. Therefore, for all the participants enrolled, the maximum delay in initiating augmentation treatment will be 14 weeks. All subjects will be advised before entering of their alternatives to participation (e.g., seeking alternative SRI augmentation treatments such as the addition of cognitive-behavioral therapy, an atypical antipsychotic, or clomipramine).

Because minocycline may not benefit participants and placebo is assumed to have no effects, there is the potential for participants to not improve from baseline or even to experience a worsening of symptoms. Participants will be monitored closely for the development of depressive symptoms, intolerable suicidal thinking or behaviors, and/or a decline in function. If, at any time it is clinically determined that it is unsafe for a participant to continue in the study (e.g., no longer meets inclusion/exclusion criteria that are focused on safety), the participant will be discontinued from the study and provided three months of treatment at no cost.

4) Minocycline Risks: Minocycline is a semi-synthetic derivative of tetracycline with a large volume of distribution. The drug is completely absorbed from the gastrointestinal tract and 60-75% is bound to plasma proteins. Food does not interfere with the absorption of minocycline. Most of minocycline is concentrated in the liver and excreted, by way of the bile, into the intestine, from which the drug is partially reaabsorbable. Its half life is about 18 hours. Approximately 11% of minocycline is excreted by the kidneys. Minocycline is highly lipid soluble and penetrates the CNS. It is found in high concentration in the tears, saliva and breast milk. Drug interactions with minocycline include various antacids, calcium, and iron supplements. It is active against many tetracycline resistant strains of bacteria like staphylococci, streptococci, and E. Coli. Minocycline is commonly used to treat acne and is available for prescription to children and adolescents aged 8 years and older. It is generally well tolerated both acutely and chronically. Minocycline is not recommended for use for under the age of 8 because it may lead to permanent tooth discoloration. The most common side effects in children and adolescents are nausea, headache, and dizziness.

In a study of 700 patients (ages 13 to 48) receiving minocycline for acne, 13% reported adverse effects, all of which were rated as mostly benign. Gastrointestinal disturbances and vestibular disturbances were the most common, each occurring in about 2% of patients. Vestibular adverse effects including dizziness or vertigo may occur particularly in women. Participants will be advised not to drive or operate machinery if affected. Chronic administration of minocycline over two years to Huntington' Disease patients revealed no side effects related to long term administration. Unlike other tetracyclines, minocycline does not appear to accumulate in those with impaired renal function. However, when used in individuals with impaired renal function, the recommendation is to reduce the dose or extend the time intervals between doses.

Skin pigmentation may occur in up to 4% of patients. Three patterns of skin pigmentation have been described: blue-black macules occurring in areas of inflammation and scarring and possibly due to an iron chelate of minocycline within macrophages; blue-grey macules or hyperpigmentation affecting normal skin and which may be due to a breakdown product of minocycline; or a grayish-brown discoloration occurring particularly in sun-exposed areas of skin ('muddy skin syndrome'), apparently due to melanin deposition. Skin pigmentation appears to resolve slowly upon discontinuing the drug, although recovery may be incomplete. Diffuse pigmentation tends to occur at doses greater than 100 mg and may resolve with reduction of dose; however, localized pigmentation does not appear to be dose related. There are rare reports of photosensitivity, which is manifested by an exaggerated sunburn; participants will be advised to avoid extensive exposure to sunlight. Study participants will be carefully monitored for the development of any

skin pigmentation, and if it were to develop, the participant will be withdrawn from the study.

Rare adverse effects include erythema nodosum, hepatitis, and systemic lupus erythematosus and have been usually in patients taking the drug long-term for acne. Rare hypersensitivity reactions may include arthralgia, myalgia, pulmonary infiltration, and anaphylaxis. Other rare adverse effects include alopecia, myocarditis, vasculitis**,** pseudotumor cerebri and decreased hearing. Esophageal ulceration has occurred rarely and may be a particular problem if capsules or tablets are taken with insufficient fluid or in a recumbent posture. The true incidence of these rare adverse events and whether minocycline directly causes any of them is not clear given the widespread use of this drug. Adverse events due to minocycline treatment are being followed by the FDA Adverse Event Reporting System (AERS) to determine if there is any link between the chronic use of minocycline and autoimmune-like symptoms in pediatric patients.

Pregnancy: Minocycline should not be used in pregnancy as the tetracycline class of drug is able to cross the placenta and can have toxic effects on the developing fetus. For this reason, pregnant females are excluded from the study. Any female patient who has reached menarche must demonstrate a negative human chronic gonadotrophin (HCG) test at screening and a negative urine pregnancy test at each study visit. Results will be shared with the participant's parent(s)/legal guardian(s). Females in the study who are capable of becoming pregnant must either be abstaining from sexual intercourse for the duration of the study or be using a medically acceptable form of contraception. Acceptable methods of birth control are the double barrier methods (condom and spermicide) and intra-uterine devices. Given that minocycline can potentially render oral contraceptives less effective, use of oral contraceptive without the additional use of the double barrier method or an intra-uterine device is not considered acceptable as a contraceptive method. Because minocycline may be excreted in human milk, nursing females are also excluded from this study. A negative pregnancy test is required to start, and continue in, the study. In addition to the study required pregnancy tests, confidential pregnancy testing is available outside of our clinic, and referrals will be provided if the participant prefers this, however, the participant would not be able to continue in the study. Although highly unlikely given the careful screening monitoring for pregnancy if a study participant is determined to be pregnant, appropriate antenatal counseling will be offered to the participant for the purpose of explaining the risks to the fetus and risks and benefits for the prospective mother. The pregnant participant will be withdrawn from study participation. The participant will also be referred to appropriate antenatal medical care. The study clinician will continue to offer routine clinical treatment until the participant is carefully transitioned to a mutually agreed upon clinician for longer-term care. If the participant decides to continue with the pregnancy, further referrals, as appropriate for the neonate and mother, will be made. The outcome of the pregnancy will be reported to the IRB and DSMB board.

Minocycline is bacteriostatic and may interfere with the bactericidal action of penicillin. Participants will be advised to immediately inform study doctors about any additional antibiotics prescribed and that the use of penicillin is not advised. Absorption of minocycline is impaired by antacids containing calcium, magnesium, aluminium, zinc salts and iron preparations. Participants will be advised against the use of Accutane, given both compounds have the rare side effect of causing pseudotumor cerebri. Minocycline has been shown to depress plasma prothrombin activity and participants who are treated with anticoagulants may need to have this medication adjusted.

Participants will be monitored closely for adverse events and will be withdrawn from the study if there is evidence of developing these more serious events. In the clinical judgment of the study team, if the

participant has significant neurological complaints, assessment by a pediatric ophthalmologist should be considered. In the event that the study participant can not tolerate the more common side effects (e.g., nausea, dizziness, and headaches) the participant will be withdrawn from the study.

Given the wide spread use of minocycline over the past 30 years and the extensive safety data available for its use for acute and chronic treatment of acne and infections in children and adolescents, it is anticipated that most side effects will be limited and manageable. Those participants randomized to minocycline will receive approximately 2 mg/kg/day, the FDA-approved dose for minocycline and the dose used in our pilot study (<35 kg: 50 mg/day; 35-55 kg: 50 mg BID; >55-75 kg: 75 mg BID; >75kg: 100 mg BID). Participants and their parents/care giver will be instructed to take the tablet with food and with 4-8 ounces of water in order to lessen gastric adverse effects and in an upright position well before retiring to bed. Additionally, participants will be instructed and reminded of the adverse events to be aware of at each study visit such as developing skin pigmentation, always using birth control, avoiding intense direct sun light, and informing the study doctor when prescribed any type of medication such as other antibiotics. Additionally, participants will be advised that they can not take the following: anti-coagulant drugs, antacids containing iron preparations, calcium, magnesium, aluminum, and zinc salts and Accutane. If a participant experiences adverse event or a common side effect that does not resolve and is intolerable, the study doctor will discontinue participant from the study and the patient will be referred for open treatment.

5) Placebo risks: One risk for participants who are randomized to inactive treatment is that they may experience no change from baseline and/or worsening of clinical symptoms. Participants will be monitored by safety evaluations for the development of depressive symptoms, intolerable adverse events, suicidal behaviors, and/or decline in functioning. If, at any time it is clinically determined that it is unsafe for a participant to continue in the study (e.g., no longer meets inclusion/exclusion criteria that are focused on safety), the participant will be withdrawn from the study.

6) Risks from chronic SRI treatment: A review in 2004 by the Food and Drug Administration (FDA) of all pediatric placebo-controlled randomized studies of antidepressant medications found an increased incidence of suicidal thoughts and behaviors in the medication group (4%) versus the placebo group (2%). There were no completed suicides. Based on this finding, the FDA issued a “black-box” warning on all antidepressant medications, stating that their use may increase suicidal thinking and behavior in youth. This has led to the FDA to develop guidelines recommending frequent follow up and careful monitoring for the development of new or worsening of symptoms such as insomnia, increased agitation, anxiety, and depression symptoms, as well as the development of suicidal ideation/ behaviors.

Long-term adverse effects with antidepressants, including SRIs, are similar to those reported in acute trials, including gastrointestinal disturbance, insomnia, and headache. Overall, these adverse effects were mild in severity, diminished as treatment continued, and did not lead to study withdrawal from clinical trials. Discontinuation syndromes associated with SRIs are headache, gastrointestinal distress, dizziness, and irritability or agitation. The participants in this study must be on a stable tolerable dose with at least minimal response for the 12 weeks, and thus should be experiencing minimal to no adverse events.

Adverse events will be carefully tracked with the appropriate medical monitoring with lab work, vital signs, and safety measurement as designated in the research strategy. All adverse events spontaneously reported by the individual throughout the study will be documented and rated in intensity, relationship to study drug and

outcome by the study doctor. The Pediatric Adverse Event Rating Scale (PAERS) will also be used to evaluate for adverse events reported by parent (for those <18) and adolescent (for all 8-20) at every study visit. The PAERS rates the severity of 48 adverse event items on a five-point Likert scale (0–4). It will be reviewed by the clinician at each visit to determine final severity and relationship to treatment or illness.

In addition, suicidal ideation and behaviors will be systematically monitored during study visits using the Columbia Suicide-Severity Rating Scale (C-SSRS) which evaluates and tracks suicidal ideation, suicidal acts, seriousness of acts, medical lethality of act, thoughts of death, and non suicidal self injury.

7) Risks associated with MRI Scanning: There are no known long-term biological risks from the use of MRI scanners per se, including the GE 3T scanner for use in this proposal. The 3T GE system proposed in this study is a nonsignificant risk device (per FDA website, U.S. Food and Drug Administration, Center for Devices and Radiological Health, "Guidance for the Submission of Premarket Notifications for Magnetic Resonance Diagnostic Devices", http://www.fda.gov/cdrh/ode/95.html, Nov., 1998). Human studies have been carried out under IRB approval in the US since 1990 under this same evaluation at a variety of institutions throughout the US. More recently, field strengths of 7T and 8T have been approved for research studies in humans at the University of Minnesota and Ohio State University. All MRI studies follow guidelines set by the FDA with regard to specific absorption ratio (SAR), limits on gradient slew rate (dB/dt), and noise. At the same time, possible risks associated with MRI scanning can be classified into one of six areas: a) acoustic noise levels; b) physical discomfort; c) fetal exposure; d) static magnetic fields (leading to the attraction of ferromagnetic metal objects); e) gradient or time-varying magnetic fields (leading to the possible stimulation of peripheral nerves); and f) radiofrequency (RF) magnetic fields (leading to the possible risk of tissue heating).

a) Acoustic Noise Levels: The acoustic noise associated with MR imaging is related to the mechanical movement of the gradient coils during the scanning process.

FDA Guidelines: "The acoustic noise levels associated with the device must be shown to be below the level of concern established by pertinent Federal Regulatory or other recognized standards setting organizations. If the acoustic noise is not below the level of concern, the sponsor must recommend steps to reduce or alleviate the noise perceived by the patient." Current FDA guidelines follow the regulations of the International Electrotechnical Commission (IEC) Standard 601-2-33, which stipulate that for MR equipment used in medicine, hearing protection is required when the system can produce acoustic sound levels above 99 dBA (maximum A weighted r.m.s.) and that the protection should be able to reduce noise levels to below 99 dBA. The FDA has approved systems for which noise levels have been quantified, ranging up to 105 dB RMS for scanners operating at field strengths of 1.5 Tesla. It is important to note that the static magnetic field strength is only one factor, and not necessarily the most important one, in determining acoustic noise. Among the factors listed above, the design and construction of the gradient coils plays a major role in the noise level that MRI scanning produces. Therefore, noise levels are not necessarily greater when scanning at 3.0 T compared with 1.5 T field strengths. It is nevertheless possible that, in some circumstances, our system could produce noise levels higher than 99 dB, as do many clinical systems operating at lower field strengths.

Summary: The acoustic noise levels perceived by human subjects when undergoing MRI examination in our 3.0 Tesla magnet constitutes a non-significant risk; specifically, our system will not be operated in a way that will present more noise to human subjects than is recommended by the FDA.

Plans to Minimize Risk: As suggested by the FDA, we will take steps to reduce the noise levels experienced by subjects. The easiest and most reliable means of preventing hearing loss is to use disposable earplugs, which we will do for all scans. We will also be using acoustically shielded headsets, which further attenuate noise.

b) Physical Discomfort: The physical confinement and isolation produced by the scanner could cause mild to moderate emotional distress, although participants in previous trials, including participants diagnosed with OCD, generally tolerate the procedures remarkably well. All subjects will be able to communicate directly with technologists and study staff to inform them of any emotional or physical distress during the scanning procedure. If they wish, the scan will be terminated immediately and the subject will be removed from the scanner.

c) Fetal Exposure: The risk of MR imaging to the fetus is unknown. Pregnant women are excluded. While there is no known risk of MR scans to the fetus, it is standard practice to exclude women who are pregnant from research MR scans. Therefore to implement this exclusion a pregnancy blood test will be performed at screening and, in addition, a urine pregnancy test will be performed on the day of each MR scan for all female participants.

d) Static Magnetic Fields: The possible risks of static magnetic fields have received much attention in the lay press, but scientific consensus on these risks has yet to be fully reached. The FDA has deemed that systems operating at 8.0 Tesla or less do not pose a significant risk. Moreover, experience with thousands of clinical studies over the past decade, and with multiple human investigations carried out at higher field strengths over this period, have not revealed risks of exposure to higher static magnetic fields. The most significant risk associated with static magnetic fields is that ferromagnetic objects, such as aneurysm clips or heart valves, can interact with the magnetic field of an MRI scanner, causing the device to malfunction or to move, and injuring the subject.

FDA Guidelines: “Studies conducted at 8T or less are not considered significant risk" (FDA Center for Devices and Radiological Health, memorandum 7-14-03).

Summary: This category of risk applies to work conducted around superconducting magnets of any kind (including standard clinical diagnostic MRI units). It is not unique to our 3.0 Tesla facility, which will maintain a safety policy to safeguard subjects and staff members from these incidental risks. Systems with static magnetic field less than 8 Tesla have been considered to represent a nonsignificant risk by the FDA. The static magnetic field of our system (3.0 Tesla) is therefore to be classified as posing nonsignificant risk to human subjects.

Plans to Minimize Risk: The risks outlined above are the same as in other commercially available clinical systems. Like clinical MRI centers, our facility has a complete range of procedures to assure security of the restricted access area, careful screening of potential subjects before they enter the restricted access area, and a metal detector positioned at the doorway leading into the magnet room within the MRI suite. In addition,

access is tightly controlled, allowing only those personnel and research subjects who have legitimate reason to be there. Doors to the unit will be securely locked, with only MR technologists, physicists, or physicians controlling entry of ferromagnetic and other materials that could possibly cause injury to patients, research subjects, personnel, or equipment. In addition, entry-ways to the unit will be labeled with clear visible signs warning of the presence of the magnetic field and the exclusion from entry by individuals with implanted metal objects such as prostheses, pins, clips, IUD's, etc.

e) Time-Varying Magnetic Fields/nerve stimulation: The concern about the time-varying magnetic fields used in MRI is that these can, in some instances, induce stimulation of peripheral nerves, thereby producing sensations such as 'twitching' or 'tingling'. In very rare instances, this nerve stimulation can be painful. Nerve stimulation is particularly likely when subjects are physically positioned in a way that increases the likelihood of inducing stimulation, such as with hands clasped or arms folded. It should be noted that the parameter of interest here, dB/dt (the rate of change in the magnetic field per unit time), is not a function of the strength of the static magnetic field, so evaluating risk in a 3T MRI scanner involves the same considerations as evaluating other MRI systems operating at lower magnetic field strengths (i.e., the same issues apply to all the commercially available, FDA approved scanning systems). Thus, it is the gradient system only that needs to be evaluated to determine the risk of producing nerve stimulation.

FDA Guidelines: The FDA Guidance of 1995 was developed specifically to consider the fact that many clinical systems were capable of exceeding levels of dB/dt that could produce nerve stimulation. It was originally considered that a warning level should be implemented to guard against peripheral nerve stimulation, but the FDA finally concluded that: '... this warning level is not considered critical since there are no harmful effects associated with mild peripheral nerve stimulation.' The current guidelines therefore include monitoring procedures to help avoid painful peripheral nerve stimulation, and without specific dB/dt limitations.

Summary: The gradients used in our 3.0 Tesla MRI system will typically be operated at levels below those considered to be negligible according to FDA guidelines. Our system, like most commercially available, FDA-approved systems, does have the capacity to exceed this level, but it will include the same safeguards that are included in other FDA-approved clinical systems. Furthermore, policies and procedures will be implemented according to FDA guidelines to avoid the possibility of painful peripheral nerve stimulation. Therefore, in all circumstances the system will be operated in a way that poses nonsignificant risk to the participant.

Plans to Minimize Risk: The consent form will provide information about this risk. A record of dB/dt value will also be included with the imaging data to help in analysis of levels of peripheral nerve stimulation possibly perceived by subjects. In addition, we will conduct detailed calculations of the changes in magnetic field over time that our gradient system is capable of, and conservative values will be selected as limits that will be used to determine when special additional monitoring is indicated. In these cases, we will use the monitoring procedures recommended by the FDA. The gradient switching times and strengths will also be monitored together with the routine assessment of all electrical components of the system, as described previously.

In addition, MR technologists receive special training to prevent peripheral nerve stimulation. Before any scanning procedure that might stimulate peripheral nerves, a technologist will inform the subject that

peripheral nerve stimulation may occur; describe the nature of the sensation to the subject; instruct subjects not to clasp their hands, since this may create a conductive loop which will increase the possibility of stimulation; maintain constant verbal contact with the subject; instruct subjects to inform the MR technologist if they experience discomfort or pain; terminate the scan if the subject complains of discomfort or pain; complete a report of any incidents involving severe discomfort or pain, including describing the associated circumstances (imaging parameters, dB/dt value, level of pain, etc.), and submit this report immediately to the IRB.

f) Specific Absorption Rate (SAR): MRI scanning induces some heating of body tissues. This specific absorption rate (SAR) that determines heating is the amount of radiofrequency (RF) energy deposited (typically by a coil or "helmet"-like apparatus placed over the subject's head) per unit volume of tissue per unit time. The SAR for RF radiation is primarily related to the amplitude of RF power, duration of the RF pulse, type of RF coil, frequency of RF radiation, resistivity of the tissue, configuration of the anatomical region, and several other parameters.

FDA Guidelines: "The following are levels of concern: A) If SAR 0.4 W/kg whole body; and if SAR 8.0 W/kg spatial peak in any 1 gram of tissue; and if SAR 3.2 W/kg averaged over the head: below level of concern. Or B) If exposure to radiofrequency magnetic fields is insufficient to produce a core temperature increase in excess of 1°C and localized heating to greater than 38°C in the head, 39°C in the trunk and 40°C in the extremities: below level of concern. The parameter SAR cited above must be shown to fall below either of the two levels of concern by presentation of valid scientific measurement or calculation evidence sufficient to demonstrate that SAR is of no concern."

This guideline is based on the calculation of a system that has no thermoregulatory response, and thus it is a very conservative estimate compared with the temperature change that would be experienced in any living subject. Normal diurnal temperature variations in humans, for example, are about +/-1°C from the normal set point 37°C, and healthy people with normal thermoregulatory responses can easily dissipate any excess (or, in this instance, deposited) heat by increasing their peripheral blood flow or sweat rate. Thus, the heating effect of MRI with the SARs used in accord with these guidelines is extraordinarily unlikely to cause any acute effects in healthy human subjects. Furthermore, our scanner console calculates SAR based on the subject's body weight before running any pulse sequence and prohibits running of the sequence if exceeds the FDA-approved limit.

Summary: Because all experiments performed on the 3.0 Tesla system will comply with FDA guidelines with regard to SAR, and because appropriate RF power safety checks are in place, this criterion for classification of nonsignificant risk is satisfied.

Plans to Minimize Risk: The magnitude of temperature increase during MRI scanning is minimal. Increases are always within FDA guidelines, which include core temperature increases less than 1°C , as well as localized heating to less than 38°C in the head, 39°C in the trunk, and 40 °C in the extremities. Our 3.0 Tesla system has in place a means to monitor RF power levels and ensure that energy deposition is sufficiently low to stay well within these guidelines for temperature increases. First, a "system security" unit is employed to integrate the output of the RF amplifiers. This integration takes into account the amplitudes and duty cycle of the transmitter. If system security detects an output that might exceed the guidelines noted above, it automatically shuts down the entire RF power system. Secondly, all pulse sequences are evaluated,

based on calculations and sound scientific measurements, to ensure that SAR remains within FDA-approved guidelines, prior to their use in humans. Any experiment performed on our 3.0 Tesla system will comply with all FDA guidelines with regard to RF power deposition. Proper and routine monitoring of all RF electronics (e.g., coils, transmitters, system security, etc.) will be performed on a regular basis. All pulse sequences will be evaluated (by calculation and by valid scientific measurement) prior to use in humans.
Describe procedures for minimizing risks
All efforts will be made to minimize risks and to ensure participant safety. Participants will be encouraged to relay the emergence of any adverse events to the study team, who will attend to it appropriately.

Methods to Protect Confidentiality

Describe methods to protect confidentiality
Confidentiality will be maintained by assigning unique identifying code numbers to each participant and his/her family. Code numbers, rather than names, will be used on all documents pertaining to the participants. All data will be kept in locked files or on Windows 2003 servers or XP workstations with password access, to which only researchers will have access. These operating systems provide multi-level security restrictions and privileges will only be granted by Drs. Rynn, Simpson and Shungu to others working on the project. All individuals granted access to the database will be issued a password. The portion of the database that connects a person's identifying information and the code numbers will be maintained separately and require a higher level of security clearance on the system. No individual will be named or described with information that could allow him/her to be identified in published reports.

Once the MR data are analyzed, Dr. Shungu will provide Drs. Simpson and Rynn a hard copy of a deindentified database of the key MRS variables for each subject. These MRS variables will be merged by the study data manager into the clinical database to create the final data file that will be stored on a network server securely located behind the NYSPI firewall.

Clinical data will be entered twice into a Microsoft Access relational database, checked for consistency, and merged with MRS data. This database is stored on a network server securely located behind the NYSPI firewall; a username and password are required to access the server and a separate password to access this database. Subjects are identified by numeric codes consistent with HIPAA guidelines; hard copies of data are stored in locked rooms with restricted access. The data manager will perform random data audits to further ensure the integrity of the data. Server backups of study databases are performed nightly; database copies on CD-ROM archive disks are stored separately for safety. Drs. Simpson and Rynn will oversee the operation and scientific integrity of the clinical trial and ensure that the protocol design, instrumentation, patient recruitment, data collection and analysis yield information that achieves the major objectives of the study.

The MR imaging data will be transferred from the scanner to a secure network-attached file storage server, which can be accessed to retrieve the data for further processing. Consistent with HIPAA guidelines, subjects will only be identified by numeric codes. Dr. Shungu is responsible for the scientific integrity of the MR imaging data. Dr. Shungu will provide Drs. Simpson and Rynn the de-identified database of the relevant MRS variables. The MRS data will be merged with the clinical data by the study data manager (Dr. Van Meter, see Personnel) prior to the analyses. This merged file will constitute the final datafile and will be

stored on a network server securely located behind the NYSPI firewall.
Will the study be conducted under a certificate of confidentiality?
No

Direct Benefits to Subjects

Direct Benefits to Subjects
The potential benefit of this study is that the subject may be randomized to minocycline augmentation and may respond to this novel treatment strategy for OCD. In addition, each participant will be receiving a psychiatric evaluation and will be carefully followed in the study. Participants will continue on SRI medication and will only be included in the study if he/she have experienced at least a minimal response to SRI treatment. Participants and their legal guardians will be informed of any clinically significant findings from the clinical assessments and from the MR imaging.

The MRS measurements will not be of direct benefit to subjects. The indirect benefit is the knowledge the study will provide about minocycline's potential effects on the brain and/or about potential biomarkers that might predict who will respond to this novel treatment strategy. Although the risks are greater than minimal given the randomization to placebo and the unknown efficacy of minocycline as an augmentation option, at this time there are no proven medication augmentation treatment strategies for children and adolescents with OCD who continue to have clinically-significant symptoms despite an adequate SRI. Available compounds to augment SRI treatment include stimulants, antipsychotics, or clomipramine, but the data supporting the efficacy of these compounds in pediatric OCD are limited and some have the potential for significant adverse event burden. Moreover, low risk methods for examining putative brain mechanisms of these compounds (e.g., changes in dopamine or serotonergic neurotransmission) are not yet feasible in pediatric populations. Minocycline is FDA approved for children 8 years and older and is well tolerated. MRS methods can be used in pediatric populations to assess the effects of minocycline on striatal glutamate (Glu) levels, one of minocycline's possible mechanisms of action. Thus, it would seem the potential benefits of this study make the potential risks a reasonable consideration for participants suffering from this impairing disorder.

Compensation and/or Reimbursement

Will compensation or reimbursement for expenses be offered to subjects?
Yes
Please describe and indicate total amount and schedule of payment(s).
Include justification for compensation amounts and indicate if there are bonus payments.
Participants will be compensated for $125.00 for each MRI scan and $50 for the evaluations done at the time of the scan. The compensation takes into account the time involved, travel costs and parking in New York City, and meals or snacks.

References

References

N/A

Uploads

Upload the entire grant application(s)
Upload copy(ies) of unbolded Consent Form(s)
Upload copy(ies) of bolded Consent Form(s)
Upload copy(ies) of unbolded Assent Form(s)
Upload copy(ies) of bolded Assent Form(s)
Upload copy(ies) of the HIPAA form
Upload any additional documents that may be related to this study