

Trial of Naproxen Sodium for the Treatment of OCD in Children With PANDAS

NCT04015596

03/06/2026

**PARTNERS HUMAN RESEARCH COMMITTEE
DETAILED PROTOCOL**

**Double-Blind, Randomized, Placebo-Controlled Trial of Naproxen Sodium for the
Treatment of Obsessive-Compulsive Symptoms in Pediatric Autoimmune
Neuropsychiatric Disorder Associated with Streptococcal infections (PANDAS)**

Version Date: 5/5/2023

I. BACKGROUND AND SIGNIFICANCE

The pathogenesis of Obsessive-Compulsive Disorder (OCD) remains unknown, though this debilitating disorder affects approximately 1-2% of children worldwide. Recent neuroimaging data has shown inflammation in the brains of adults with OCD compared to healthy controls,¹ suggesting that brain inflammation and brain-derived immune cells may play an etiological role in the development of OCD symptoms. This is central to the hypothesized pathogenic mechanism involved in Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal infections (PANDAS) and Pediatric Acute Onset Neuropsychiatric Disorder (PANS); namely, that neuroinflammation and immune-mediated processes, following infection, is sufficient to provoke OCD symptoms in children.² Therapies designed to decrease brain inflammation have reported mixed efficacy in a small number of controlled trials in PANDAS patients,³ though recent open-label studies suggest that naproxen sodium, a non-steroidal anti-inflammatory (NSAID) medication, may decrease OCD symptoms in a significant portion of PANDAS patients.⁴ NSAIDs, while commonly prescribed as over-the-counter analgesics, have been reported to produce beneficial effects on mood and anxiety in a number of clinical trials across multiple psychiatric conditions,^{5,6} including OCD symptoms in adults.⁷ Importantly, naproxen sodium readily crosses the blood brain barrier and has a suppressive effect on inflammatory cells within the brain.⁸ In accordance with the extant literature from open-label cohort and case-report studies,⁴ we have witnessed a marked reduction in obsessive compulsive symptoms in children diagnosed with PANDAS and treated with naproxen sodium within our clinic at Massachusetts General Hospital. To date, no blinded, placebo-controlled trials evaluating the effect of naproxen sodium in the treatment of OCD symptoms in children with PANDAS, PANS, or non-PANS/PANDAS OCD have been conducted. If empirically-validated, naproxen sodium has the potential to be an etiologically-based therapy for the treatment of inflammatory-related OCD symptoms in children with PANDAS, PANS, and non-PANS/PANDAS OCD. Accordingly, we propose to conduct the first placebo-controlled trial of naproxen sodium in children with PANDAS, PANS, or pediatric OCD. Our findings will directly inform treatment guidelines for PANDAS, PANS, and pediatric OCD patients, as well provide insight into the pathophysiology of OCD symptoms in children.

II. SPECIFIC AIMS

Aim 1. Evaluate the efficacy of naproxen sodium (dosed at 10mg/kg, PO, BID) to treat OCD symptoms in patients with PANDAS, patients with PANS, and patients without PANS/PANDAS.

Hypothesis 1. Subjects receiving naproxen sodium from all three groups will display a significant decrease in OCD severity from baseline to the 8-week time point, compared to those receiving placebo, as evaluated by the change in CY-BOCS-II total score. Additionally, we hypothesize that a significantly higher number of subjects receiving naproxen sodium, compared to those receiving placebo, will qualify as treatment responders (³25% reduction in CY-BOCS symptoms).

Aim 2. Evaluate the safety and tolerability of naproxen sodium compared to placebo in subjects with and without PANS/PANDAS.

Hypothesis 2. We hypothesize that naproxen sodium will be well-tolerated by PANDAS, PANS, and non-PANS/PANDAS participants, with an equal prevalence of side-effects in the active treatment and placebo cohorts. Complete blood count, comprehensive metabolic panel including liver enzymes, blood electrolytes, kidney function, streptococcal antibodies, stool for presence of blood, and vital signs (blood pressure, heart rate, weight) will be measured throughout the study and compared between the active treatment and placebo cohorts.

III. SUBJECT SELECTION

We propose to acquire completed data on 44 children with PANDAS for this pilot study with 22 participants randomized to the active treatment condition and 22 participants randomized to the placebo condition. With a hypothesized attrition rate of 40-50%, we plan to enroll 70 participants. Participants will be recruited for this study through postings of IRB approved advertisements on (1) the PANDAS network website and (2) on the MGH clinical trials website as well as (3) through clinic referrals. This study will also be registered on Clinicaltrials.gov. Eligible patients who contact the Pediatric Neuropsychiatry and Immunology Program (PNIP) at Massachusetts General Hospital (MGH)/Harvard Medical School who indicate they are interested in research will also be contacted for potential recruitment. Prospective participants will be contacted about enrolling in the study PRIOR to initiating treatment with Dr. Williams or any PNI Clinic provider. Current or former patients of Dr. Williams in the PNIP will not be approached to participate in the study. The study will be initially presented to the parents by the research coordinator or research assistant, and not the PI (Dr. Williams). Last year, the PNIP program evaluated over 100 new patients with suspected PANDAS. Furthermore, over 80% of our evaluated families have stated they are willing to be contacted regarding research studies.

Inclusion Criteria for PANDAS cohort: Enrolling children with PANDAS allows for verification of a specific infection and putative trigger (*Streptococcus pyogenes*) which precedes the onset of OCD symptoms. The inclusion criteria for the PANDAS cohort are identical to a recent clinical trial of immune modulating therapy in children with PANDAS,³ and are: (1) significantly interfering OCD symptoms (as measured by a CY-BOCS-II score greater than 16), (2) ages 6- to 15-years-old, (3) new-onset of OCD symptoms within the previous 18 months, (4) sufficient fluency of English to understand study staff, procedures and

questionnaires, and (5) parent/legal guardian who can provide informed consent. Patients must also meet all criteria for PANDAS, which are: 1) prepubertal symptom onset; 2) acute onset of symptoms (from no/minimal symptoms to maximum severity within 24-48 hours) and/or an episodic (relapsing-remitting) course; 3) temporal association between symptomatic periods and infections with Group A Streptococcus (GAS) infection; and 4) presence of neurological abnormalities (e.g. handwriting deterioration, choreiform movements).⁹ The onset/exacerbation of OCD symptoms must also be accompanied by at least three of the following clinical signs and symptoms, some of which have been shown to differentiate between children with PANDAS and childhood-onset OCD,¹⁰ including:

- a. Markedly increased level of anxiety, particularly new onset of separation anxiety
- b. Emotional lability, irritability, aggressive behavior and/or personality change
- c. Sudden difficulties with concentration or learning
- d. Developmental regression (“baby-talk”, temper tantrums).
- e. Sleep disorder (insomnia, night terrors, refusal to sleep alone)
- f. Handwriting deterioration or other sign of motoric dysfunction (including new onset of motor hyperactivity, presence of choreiform finger movements, pronator drift or truncal instability)
- g. Urinary frequency or increased urge to urinate; daytime or night-time secondary enuresis

These co-occurring symptoms must be “severe” or “dramatic” and proceed from no/minimal symptoms to maximum severity within the same 24-48 hour interval during which the OCD symptoms arose. In addition to these inclusion criteria, PANDAS subjects will be required to provide documentation of a positive GAS infection via medical records. As the time between a documented GAS infection and the onset of PANDAS symptoms has not been defined in the PANDAS diagnostic criteria, we will use a guideline of approximately six weeks or less between a documented GAS infection and the onset of OCD symptoms for inclusion into the study.⁹ Liver, kidney, and blood-clotting function must be deemed normal by the study physician based on laboratory results from the screening visit.

Inclusion Criteria for PANS cohort: The inclusion criteria are: (1) significantly interfering OCD symptoms (as measured by a CY-BOCS-II score greater than 16), (2) ages 6- to 15-years-old, (3) new-onset of OCD symptoms within the previous 18 months, (4) sufficient fluency of English to understand study staff, procedures and questionnaires, (5) parent/legal guardian who can provide informed consent, and (6) liver, kidney, and blood-clotting function must be deemed normal by the study physician based on laboratory results from the screening visit. Patients must also meet all criteria for PANDAS, which are: 1) prepubertal symptom onset; 2) acute onset of symptoms (from no/minimal symptoms to maximum severity within 24-48 hours) and/or an episodic (relapsing-remitting) course; and 3) temporal association between symptomatic periods and a documented infection (not

streptococcal). The onset/exacerbation of OCD symptoms must also be accompanied by at least three of the following clinical signs and symptoms, including:

- a. Markedly increased level of anxiety, particularly new onset of separation anxiety
- b. Emotional lability, irritability, aggressive behavior and/or personality change
- c. Sudden difficulties with concentration or learning
- d. Developmental regression (“baby-talk”, temper tantrums).
- e. Sleep disorder (insomnia, night terrors, refusal to sleep alone)
- f. Handwriting deterioration or other sign of motoric dysfunction (including new onset of motor hyperactivity, presence of choreiform finger movements, pronator drift or truncal instability)
- g. Urinary frequency or increased urge to urinate; daytime or night-time secondary enuresis

Inclusion Criteria for non-PANS/PANDAS OCD cohort: The inclusion criteria are: (1) significantly interfering OCD symptoms (as measured by a CY-BOCS-II score greater than 16), (2) ages 6- to 15-years-old, (3) new-onset of OCD symptoms within the previous 18 months, (4) sufficient fluency of English to understand study staff, procedures and questionnaires, (5) parent/legal guardian who can provide informed consent, (6) liver, kidney, and blood-clotting function must be deemed normal by the study physician based on laboratory results from the screening visit, and (7) may not meet criteria for PANS/PANDAS.

Exclusion Criteria for all cohorts: (1) child who is acutely psychotic or suicidal; (2) child has a serious neurological disorder or impairment (e.g. brain damage, blindness, deafness), an intellectual disability, or autism, (3) history of immune modulating therapies (e.g. IVIG, steroids) for OCD/PANDAS symptoms, (4) pre-existing liver, kidney, GI bleeding or clotting disorders (GFR <75 mL/min/1.73m²), (5) history of ulcers in the digestive system, (6) history of restricted fluid intake, as this could exacerbate side effects,⁴ (7) concurrent antibiotic treatment or antibiotic treatment within approximately one-week of baseline, (8) pregnant or becomes pregnant, (9) currently engaged in an intensive outpatient CBT treatment program (more than weekly), (10) concurrent SSRI or other psychoactive medication treatment **except and unless** the dose has been stable for at least 6 weeks approximately (i.e. no recent titration, initiation, or change in dosage), (11) concurrent medications that do not meet the above criteria (e.g., other psychotropic medications or anti-inflammatory agents), (12) history of severe asthma or currently uncontrolled asthma, (13) is currently taking NSAIDs for PANDAS/PANS/OCD, and (14) has had IVIG or steroids for PANDAS/PANS/OCD previously. Patients who do not meet criteria due to their currently prescribed medications will be ineligible for the study and no taper to meet inclusionary criteria will be allowed. No exclusions will be made based upon gender or minority status.

Children who are not able to swallow pills may still be included. They may open the capsule and mix the drug with food or liquid.

IV. SUBJECT ENROLLMENT

Participants will be screened for eligibility by research staff via phone screen. If eligible, participants will be scheduled for a screening study visit at 185 Cambridge Street or at the Charlestown Navy Yard Campus where consent will be obtained before the initiation of any study procedures by a licensed study physician, with the study PI available by page to answer any questions. Some to all of the screening study visit may occur remotely. A parent/guardian will provide written consent. Children ages 7 years through 15 years will be asked to provide written assent on the PHRC approved Assent Form. Assent for subjects 14 through 15 years of age will be documented in writing using the PHRC approved Consent Form. Children age 6 years will provide verbal assent. When assent is not obtained, the PI will document his rationale in the research records. It is anticipated that obtaining written informed consent will take approximately 15-25 minutes, on average. Comprehension of the consent information will be assessed via solicitation of answers to questions throughout the process. If comprehension appears to be limited, participants will be actively queried to determine whether they need further explanation. Subjects will be given unlimited time to make a decision regarding enrollment and may wish to have the consent forms for further review at home-and call back if they wish to participate. Should a potential subject wish to make a decision at a later date, their parking will be reimbursed and they will be scheduled for a future study visit.

Randomization will occur by random number generator, and research staff will be blind to treatment assignment. The randomization key will be maintained by the pharmacy that issues the study medication, and the blind can be broken when necessary based on medical necessity and when each participant completes the trial.

V. STUDY PROCEDURES

A. Assessments:

Demographic and Diagnostic, and Symptom Measures.

(1) *Demographic Information Sheet* assesses general information of both parents and children, including age, gender, SES, education, family history of psychiatric and medical illness, and treatment history.

(2) *PANDAS Diagnostic Checklist* is a checklist to ensure subjects meet all PANDAS diagnostic criteria and is completed by a physician.

(3) *Yale Global Tic Severity Scale (YGTSS)*¹¹ is an interview to assess the presence and severity of tics.

(4) *Schedule for Affective Disorders and Schizophrenia for School-Age Children- Present and Lifetime Version (KSADS-PL)*¹² is a clinician-administered diagnostic interview for DSM-V childhood disorders. To allow for increased social distancing during the COVID-19 pandemic, in some circumstances the web-based computerized version (KSADS-COMP) will be used instead of the KSADS-PL.¹³

(5) *Clinical Global Impressions Scale-Severity (CGIS)*¹⁴ is a clinician-rated scale of the patient's global level of functioning.

- (6) *Children's Yale-Brown Obsessive-Compulsive Scale-Parent Report (CY-BOCS-PR)*¹⁵ is an adaptation of the original clinician-administered CY-BOCS that is designed to be completed by the parent. It is a 10-item scale of pediatric OCD symptoms and severity.
- (7) *Treatment Expectancy* for both placebo and active treatment conditions will be evaluated prior to initiating treatment by both subjects and parents.¹⁶
- (8) *Screen for Childhood Anxiety Related Disorders (SCARED)* is a 41-item questionnaire with self-report and parent-report versions to assess the child's anxiety symptoms and level of symptom severity.¹⁷
- (9) *Family Accommodation Scale for Obsessive-Compulsive Disorder Self-Rated Version (FAS-SR)* is a self-report measure for parents that assesses the degree to which the parent observes and/or is incorporated into their child's compulsive rituals.¹⁸
- (10) *Family Accommodation Scale-Anxiety (FASA)* is a self-report measure for parents that assesses the degree to which the parent participates in/observes their child's anxiety-related symptoms.¹⁵
- (11) *NICHQ Vanderbilt Assessment Scales (Vanderbilt)* is a parent-report measure to assess patient symptoms, primarily as they pertain to Attention Deficit Hyperactivity Disorder (ADHD).¹⁹
- (12) *Coercive Disruptive Behavior Scale for Pediatric OCD (CD-POC)* is an 18-item parent-report measure that assesses the degree of coercion by the child for the parent or other family members to engage in compulsive or accommodation behaviors.¹⁵
- (13) *Children's Florida Obsessive Compulsive Inventory (C-FOCI)* is a self-report questionnaire to assess symptom severity of OCD symptoms in children.²⁰
- (14) *The Caregiver Burden Inventory (CBI)* is a 24-item questionnaire to assess the caregiver's feelings and demands places on them while caring for an ill loved one.²¹ This measure has recently been validated in this population.²²
- (15) *The Columbia Impairment Scale (CIS)* is a 13-item scale to assess impairment in interpersonal relations and functioning in school and work as well as psychopathology and use of leisure time.²³
- (16) *The Columbia Depression Scale (CDI)* is a self-report scale that assess depression symptoms in adolescents ages 11 years and older.²⁴
- (17) *The Eating Disorders in Youth Questionnaire (EDY-Q)* is a self-report instrument assessing early-onset restrictive eating disturbances in children ages 8-13 years.²⁵
- (18) *The Modified Overt Aggression Scale (MOAS)* is a four-item questionnaire to assess nature and prevalence of aggression.²⁶
- (19) *Yale-Brown Obsessive Compulsive Severity Scale and Checklist-Child Version (CY-BOCS)* is a measure of OCD symptom severity and description of symptoms.²⁷

Cognitive Assessments.

(1.) *The Beery-Buktenica Developmental Test of Visual-Motor Integration (VMI)* – An untimed developmental sequence of geometric forms to be copied with paper and pencil. It is

designed to assess the extent to which individuals can integrate their visual and motor abilities.²⁸

(2.) *Grooved Pegboard Test (pegs)*– a manipulative dexterity test, containing 25 holes with randomly

positioned slots. Pegs, which have a key along one side, must be rotated to match the hole before the peg can be inserted. This test requires complex visual-motor coordination.²⁹

Primary Outcome Measure. *Children's Yale-Brown Obsessive-Compulsive Scale, 2nd Edition (CY-BOCS-II)*³⁰ is a clinician-administered interview with the parent and child of OCD symptoms and severity. It will be administered by an independent rater (i.e., study staff who is not the subject's study physician) blind to treatment condition.

Adherence Measures and Adverse Effects.

(1) Parents will provide verbal reports of medication adherence over the previous 4 weeks.

(2) *Frequency and Intensity and Burden of SIDE Effects Rating Scale (FIBSER)*³¹ is a 3-item self-rated measure of medication side effects used in the STAR*D study.

B. Procedure.

Phone Screen. First, a brief phone screen with the parent will be conducted by research staff to ensure eligibility of the child. If the child meets inclusion criteria and the family is willing to participate in the described study, they will be asked to obtain medical records pertinent to GAS infections (should any exist) and will be scheduled for an initial screening visit.

Visit 1 (Screening).

Informed consent will be obtained by a licensed study physician; the study PI will be available either on site or by phone to answer any questions which may arise during the consenting process. Children age 7 and above will be given an assent form and will be required to sign the assent form prior to enrollment. Children under the age of 7 will be required to give verbal assent after the study procedures have been explained to them. All parents and/or guardians of potential study participants will be required to read and sign the consent forms. Participants and their family members will be informed that their participation is entirely voluntary, and they may withdraw from the study at any time without penalty. The study physician will conduct a brief medical and psychiatric history, review the provided medical records, and complete the CGIS. An independent rater will administer the CY-BOCS, CY-BOCS-II, YGTSS, and KSADS. Parents will be asked to complete measures related to their children's symptoms (CY-BOCS-PR, MOAS, FASA, FAS-SR, Vanderbilt, SCARED, CIS, CBI, CDPOC), a family history questionnaire, and a demographic information sheet. Children will be asked to complete questionnaires regarding their symptoms (C-FOCI, SCARED, CDI, EDY-Q). Both parents and children will be asked to complete a measure of treatment expectancy. If the participant endorses suicidality at any point throughout enrollment in the project, a licensed clinician or the study physician will be immediately informed by study staff and will assess and triage any expressions of suicidality from subjects.

Children will also provide a urine sample and complete a blood draw to assess liver, kidney, and blood-clotting function as well as streptococcal antibodies; these tests include a complete blood count with hematocrit/hemoglobin, ALT/AST, urine electrolytes, hsCRP, creatinine, BUN, iron metabolism, and PT/INR. Additional blood (5-10mL) will be collected for later analysis of inflammatory cytokine measurements. The human blood products may be sent to an external partner that has a data-sharing agreement with MGB (e.g., OLink) for analysis. Transportation of samples may include the use of a courier service (i.e. UPS, FedEx) or may be transported by study staff in their personal vehicle. Samples will be de-identified to maintain privacy and confidentiality of participants. In the rare occurrence that laboratory results are not achieved (e.g., laboratory tests were inconclusive, samples could not be processed), subjects will be required to return to have an additional blood draw. Subjects will be provided materials for fecal occult blood testing (FOBT to be returned and tested at Visit 2. We anticipate that the screening assessment will take approximately 3 hours. At the completion of the clinic visit, participants will be debriefed. If the participant meets all eligibility requirements, and if the result of their laboratory tests for kidney, clotting, FOBT, and liver function are within normal limits, they will be randomized to active treatment or placebo conditions. We anticipate 24-48 hours will be required to receive and review the results of the kidney and liver function tests. These tests will be reviewed by two physicians on the study staff (Dr. Kyle Williams and Dr. Dan Geller), both of whom have extensive training in pediatric medicine and one who has completed a pediatric residency and is board certified in pediatric medicine (Dr. Geller). If any abnormal results are obtained on the laboratory testing, these two study physicians will determine if they are clinically significant and would prevent participation in the trial. Should any clinically significant findings on these tests be discovered, the potential subject will be informed that they are unable to participate in the study, and the laboratory results will be shared with the parents of the potential participants and (if the parents desire) the subjects' pediatrician or primary care provider in order to determine if clinical intervention is necessary. We intend to use the Millers Compounding & Homecare Pharmacy to provide the active medication (dosed at 10mg/kg, PO, BID) and placebo pills for this trial. The pharmacy will hold the randomization key and blind the medication, and all research staff and participants will remain blinded to study condition. Due the requirement of assessing normal clotting, liver, and kidney function laboratory tests, we anticipate the time between screening and randomization to be approximately 1 week.

Virtual component in light of the COVID-19 pandemic- To minimize in-person contact, portions of the screening visit may be performed virtually. Specifically, written informed consent and assent will be obtained virtually by a licensed study physician over during a video call. Families will be sent a private survey link to access the informed consent/assent form in REDCap. The survey link will contain a blank PDF upload of the informed consent/assent form, as well as an attached PDF for download. Families will have the opportunity to follow along with the physician obtaining consent in reviewing the document. REDCap survey options, including checkboxes designating "Yes" or "No", as well as signature lines in which families can sign off with their computer mouse, will allow the study to obtain and document informed consent and assent. When the family has no further questions and have documented consent/assent appropriately, the physician will receive authorization in REDCap to acknowledge they obtained consent by signing their name, as well as inputting their encrypted Partners username and password. Study staff will then import signed informed consent/assent into REDCap eDC and the electronic study regulatory binder and email the participant and family copies of their signed informed consent/assent.

Additionally, subjects will consent for the pharmacy to hold the address of participants in order to mail study medications directly to patients to reduce in-person contact in subsequent visits. Study questionnaires and interviews will be conducted over a secure video call and through a Partners approved data collection portal (Studytrax). Subjects will be provided materials for fecal occult blood testing (FOBT) to be returned and tested at Visit 2 and Visit 3. In-person procedures for blood and urine sample collection and neurocognitive assessments will be reduced to approximately 1-hour visits.

Visit 2 (Baseline). The study physician will provide the study medication for the initial 4 weeks. The study physician will assess concomitant medications and treatments. The study physician will also complete the CGIS. The independent rater will administer the CY-BOCS and YGTSS. Parents will be asked to complete the CY-BOCS-PR. The study physician will provide detailed, written instructions on how to administer the study medication (twice a day, roughly twelve hours apart, with food). The study physician will provide information about possible side effects and will be available by page 24 hours a day should symptoms worsen, or side effects emerge. The parents of participants will be provided detailed instructions on how to page Dr. Williams with concerns regarding study medication side effects or adverse events. In light of COVID-19 pandemic, all or some of this visit may be conducted virtually via video (i.e., evaluation, questionnaires, and interviews). In these circumstances, medication will be mailed to participants directly from the pharmacy. Instructions on administering the study medication would be sent electronically.

Visit 3 (4 weeks post-baseline). The study physician will conduct a medical evaluation and assess ongoing safety for continuation in the trial. He will provide the patients and parents with the remaining 4 weeks of study medication. The study physician will complete the CGIS, and parents will be asked about treatment adherence. The independent rater will administer the CY-BOCS and YGTSS. Parents will be asked to complete the CY-BOCS-PR, and together with their child, will complete measures assessing side effects (FIBSER). Participants will also be provided with a fecal occult blood test (FOBT) to return at visit 4 for screening to test for gastrointestinal bleeding. If participants test positive on the FOBT test, they will be removed from the study and advised to stop taking the study medication. Participants and their parents who have a positive FOBT test will be contacted by a study physician within 24 hours to discuss any needed clinical follow-up and further assessment due to this positive test. Any needed clinical follow-up will be coordinated with the participants' pediatrician or primary care physician. In light of COVID-19 pandemic, all or some of this visit may be conducted virtually via video (i.e., evaluation, questionnaires, and interviews). In these circumstances, medication will be mailed to participants directly from the pharmacy. Fecal blood tests will be obtained at the beginning of the trial and completed at home by the parents during the third study visit. Results of the tests would be shown to study personnel during the video call and a screenshot of the result taken by study staff.

Visit 4 (8 weeks post-baseline). The study physician will conduct a medical evaluation and assess safety. Parents will be asked to turn in all unused study medication. The study physician will

complete the CGIS. The independent rater will administer the CY-BOCS, CY-BOCS-II and YGTSS. Parents will be asked to complete measures related to their children's symptoms (CY-BOCS-PR, MOAS, FASA, FAS-SR, Vanderbilt, SCARED, CIS, CBI, CDPOC), a family history questionnaire, and a demographic information sheet. Children will be asked to complete questionnaire regarding their symptoms (C-FOCI, SCARED, CDI, EDY-Q) and well as neurocognitive tasks related to fine motor skills (VMI, pegs). Parents and participants will undergo a debriefing session on their experience in the trial, and the blind will be broken and discussed with the participants and family to review future treatment options. Patients will also undergo a blood draw. In the rare occurrence that laboratory results are not achieved (e.g., laboratory tests were inconclusive, samples could not be processed), subjects will be required to return to have an additional blood draw. Additional blood (5-10mL) will be collected for later analysis of inflammatory cytokine measurements. Patients will also complete another dipstick urinalysis and if results are positive, the PI will be informed. At the conclusion of the study, all patients will be invited to enroll in the Pediatric Neuropsychiatry and Immunology Program for continuity if their insurance is accepted at MGH or receive referrals for follow-up care and medication management elsewhere. In light of COVID-19 pandemic, portions of this visit may be conducted virtually via video (i.e., evaluation, questionnaires, and interviews).

Below is the schedule of study procedures:

	1 (Screen)	2 (Baseline)	3 (4 weeks)	4 (8 weeks)	Event Based
Assessment/Procedure					
Consent/Assent	X				
KSADS	X				
Demographics	X				
Family History	X				
PANDAS Diagnostic Checklist	X				
Treatment Expectancy	X				
Concomitant Medication Log	X	X	X	X	
Concomitant Treatment Log	X	X	X	X	
CY-BOCS, CY-BOCS-II/YGTSS/CGIS	X	X	X	X	
CY-BOCS-PR (Parent)	X	X	X	X	
FAS-SR/FASA (Parent)	X			X	
MOAS (Parent)	X			X	
C-FOCI (Child)	X			X	
EDY-Q (Child)	X			X	
Vanderbilt (Parent)	X			X	
SCARED (Parent/Child)	X			X	
CDI (Child)	X			X	
CIS (Parent)	X			X	
CBI (Parent)	X			X	
CDPOC (Parent)	X			X	
VMI/pegs	X			X	
FIBSER			X	X	X

Serious Adverse Event Form					X
Medication Adherence			X	X	
Vital Signs	X			X	X
Physical Exam	X				X
Blood draw	X			X	X
Urinalysis	X			X	X
FOBT		X	X		X

C. Physical and Laboratory monitoring.

A physical exam will be completed at screening either in-person or during a video telehealth visit. During the screening and 8-week study visits, a small blood draw (4 tubes, approximately 14mL total) will be obtained at the MGH Pediatric Group Practice or by a research phlebotomist in Simches or Spaulding Rehabilitation Hospital Boston to assess for liver functioning (LFTs), kidney functioning (CHEM-7), and bleeding disorders (PT/INR), and streptococcal antibodies; these tests include hematocrit/hemoglobin, ALT/AST, urine electrolytes, hsCRP, creatinine, BUN, iron metabolism, and PT/INR. A urine sample will also be tested for urinalysis at the screening and at the 8-week study visits. If the visit is conducted remotely, results of in-home testing will be shown to study staff during video call and a screenshot will be taken of the result. Vital signs (blood pressure, heart rate, and weight) will be monitored at each in-person visit or obtained by the patient's parent during video sessions, when feasible. Participants will complete a fecal occult blood test at baseline and the 4-week follow-up visit. Should a participant show signs of acute liver injury, gastrointestinal bleeding, or kidney dysfunction based on week lab tests, they will be contacted immediately by Dr. Williams, informed to stop taking the study medication, and will be removed from the study. Follow-up care will then be discussed, as needed, by Dr. Williams and the participant's parents. As part of the urine test conducted at study visit 1, a pregnancy test will be completed for all female subjects who have begun menstruation. If the test is positive, the subject will not be able to participate in the study and will be given a referral for local treatment. The study doctor will inform the child if the test is positive and will inform the child's parent/guardian as well if the child agrees. Even if the child does not agree, the study doctor may still decide to inform the parent/guardian based on the child's age, maturity, or medical condition.

D. Reliability Review.

To ensure diagnostic accuracy, an independent reviewer (i.e., study staff who is not the subject's study physician) with extensive knowledge of both PANS/PANDAS and childhood-onset OCD will be asked to review the Diagnostic Checklist for each screened subject and assign a diagnosis of PANDAS, PANS, or non-PANDAS/PANDAS OCD. Inter-rater reliability will be calculated between the diagnoses made by study physicians and the independent reviewer.

VI. BIOSTATISTICAL ANALYSES

We computed power for a between subject (Group=Naproxen, Placebo) and within subject (3 Timepoints: Baseline, 4 week, 8 week) repeated measures ANOVA assuming an alpha of 0.05, and employing a Huynh-Feldt correction for correlated error. Power for the test of the Group X Timepoint interaction was of primary interest. A test-retest correlation of $r=0.5$ was also assumed based on pilot data, with a first order autoregressive decay in the correlations. Also, based on pilot data, the within Group-Timepoint error standard deviation was set at 9. The effect size considered minimally substantively important to detect was specified as a mean decline from Baseline to 8 weeks of $[(27-21)/7]$ 85% of the within cell standard deviation for the Placebo Group, contrasted with a mean decline of a little over 2 $[(27-11)/7]$ within cell standard deviations for the Naproxen Group. Based on these specifications, power for the Group X Time interaction was computed to be 0.819 with 22 subjects per group. A post-hoc analysis will be conducted to determine if treatment effects are moderated by diagnostic group.

With a maximum hypothesized attrition rate of 40-50%, we plan to enroll 70 participants to obtain 44 complete data sets. Prior to outcome analysis, we will examine the distributions of the outcome variable (i.e. CY-BOCS-II total score), and transform the data if normality is not reasonable. We will also verify the functional form of continuous covariates (i.e. test if a linear model is appropriate). If missing data is substantial and we have reason to believe that the assumption of missingness at random (MAR) is violated, we will utilize multiple imputation (MI) to replace missing values with simulated values. The results from multiple imputations of the missing data will then be combined and analyzed by standard methods to produce estimates and confidence intervals that incorporate missing-data uncertainty. The groups will be compared on baseline demographic and clinical variables using ANOVAs or Mann-Whitney tests for continuous variables; chi-square for categorical variables. If significant baseline group imbalance is detected on a particular variable and that variable is correlated with outcome at $r > .30$, then it will be included as a covariate in the inferential analyses. In a similar manner, dropouts and completers will be compared on baseline variables using ANOVAs, as well as Mann-Whitney tests. Each of the statistical tests above will use a two-tailed alpha-level of .05. Interrater reliability of PANDAS diagnosis will be assessed using weighed Kappas. A mixed model will be used to compare the change in CY-BOCS scores between groups. All analyses will be conducted using SPSS 24.0.³²

VII. RISKS AND DISCOMFORTS

Naproxen sodium is typically well-tolerated and approved by the FDA to treat rheumatological conditions in children.³³ However, common side-effects of naproxen sodium may include indigestion, gastrointestinal pain, bruising, and less-commonly, bleeding, allergic reaction, acute kidney disease, myocardial infarction, and stroke. Studies of adults with NSAID use showed chronic use (one year or more) increased risk of GI complications, renal failure, stroke/myocardial infarction, and exacerbation of chronic medical issues.^{34,35} Studies of children showed increased GI disorders, ulcers, and hypertension following at least one year of treatment.³⁶ NSAID-exacerbated respiratory

disease (NERD) is a hypersensitivity to NSAIDs that causes respiratory-related symptoms such as bronchospasms, acute asthma exacerbation, and severe asthma morbidity. A recent Taiwanese population-based study found children with asthma using an anti-asthmatic agent in combination with NSAIDs showed a higher rate of asthma-related hospitalization (9.3%) compared to those not taking NSAIDs (6.7%).³⁷ Therefore, children with a history of severe asthma, defined as an emergency department presentation for asthma-related issues, or currently uncontrolled asthma will be excluded, and patients with a history of asthma or reactive airway disease or those taking anti-asthmatic medication will receive additional counseling regarding risk and warning signs of NERD. All patients will also be counseled not to use NSAIDs for typical management of pain during the course of the study, but to use acetaminophen if needed or other non-medicinal measures, such as an ice pack. Study dosing will also be limited to a maximum dose of 500mg.³⁸

A previous randomized control trial of medication versus placebo in patients with pediatric OCD have documented patients in the placebo condition experienced mild weight gain, small increases in blood pressure, hyperkinesia, and nervousness.³⁹ Children in the placebo condition may not have a decrease in OCD symptoms over the course of the study, and may experience an increase in OCD symptoms.

Common effects of blood draws with needles include pain, bruising, swelling at the site of blood collection, and fainting for a short period. Uncommon effects include nerve damage or infection at the needle insertion site. In line with Partners recommendations (<https://www.partners.org/Assets/Documents/Medical-Research/Clinical-Research/Blood-Sampling-Guidelines.pdf>), pediatric subjects will be offered the use of the topical anesthetic EMLA Cream (lidocaine 2.5% and prilocaine 2.5%) to numb the skin prior to venipuncture. Local side effects include blanching and erythema but this preparation is widely accepted as safe and well tolerated in children over three months of age.⁴⁰

The questions regarding psychiatric symptoms may make some children uncomfortable. They will be allowed to skip any questions or discontinue the questions at any time.

Although a breach of confidentiality is possible, all study data will be maintained with study codes and will not have identifying information. Forms containing identifying information, such as the consent forms, will be maintained by the PI in a locked filing cabinet or in password protected documents that are only accessible to study staff. Healthcare Secure Zoom will be used for all virtual visits, as per Partners HealthCare recommendations.

Children who are not able to swallow pills may mix the inside of the capsule with food/drink. It is recommended that this drug is taken with a full glass of water, regardless of pill versus crushed tablet form. There are no known additional risks of drug administration via crushed tablet versus pill form.

VIII. POTENTIAL BENEFITS

We anticipate that most children will experience a decrease in symptoms of OCD. The non-PANS/PANDAS OCD group will have the possible benefit of reduced OCD symptoms. We expect a reduction in symptoms for both children who receive naproxen sodium and those who receive placebo, although we hypothesize that the rate of remission of symptoms will be higher for those receiving active treatment.

The parents or guardian of participants will be paid \$50 at the completion of the 4th study visit.

The proposed study will advance our understanding of effective treatments for children suffering from PANDAS, PANS, and non-PANS/PANDAS OCD. Our primary aim for this area of research is to provide the first randomized, placebo-controlled trial of naproxen sodium in PANDAS, PANS, and pediatric OCD to directly inform treatment guidelines and improve patient care.

IX. MONITORING AND QUALITY ASSURANCE

Should side-effects occur, participants and their families will be instructed to page the study physician who will evaluate and document the severity of the side-effects and determine the appropriate course of action. A study physician (either Dr. Williams or Dr. Geller) will be available via page 24 hours a day, seven days a week, to handle emergencies or urgent medical questions which arise; participants parents will be given the pager number and contact information for study staff at the baseline visit and informed that they can and should contact us with any medical urgencies or emergencies which arise. If adverse events present as any more than a mild risk, then both study physicians will consult regarding whether it is safe for the participant to continue the trial. Participants' parents will be advised on the appropriate course of action by the study physician; this may include study-drug termination, breaking the blind/removal from the study, and potentially, evaluation in a local emergency department for severe or ongoing symptoms. All side-effects will be documented, and Serious Adverse Events will be reported to the Partners IRB within 24 hours of their report to study staff. Ongoing psychiatric care will be offered to the participants and families of any participant who is removed from the study. Should medical care be necessary due to side-effects or Serious Adverse Events from the use of study medication, appropriate referrals for medical care will be provided. Parents will be asked to sign a release of information form in order to co-ordinate care with the child's PCP as and when necessary.

Confidentiality will be maintained through the use of password-protected databases accessible only to study staff.

The study principal investigator, Kyle Williams MD, PhD., will regularly monitor the protocol and conduct quality assurance reviews quarterly.

X. REFERENCES

1. Attwells, S. *et al.* Inflammation in the Neurocircuitry of Obsessive-compulsive Disorder. *JAMA Psychiatry* **74**, 833–840 (2017).
2. Williams, K. A. & Swedo, S. E. Post-infectious autoimmune disorders: Sydenham's chorea, PANDAS and beyond. *Brain Res.* **1617**, 144–154 (2015).
3. Williams, K. A. *et al.* Randomized, Controlled Trial of Intravenous Immunoglobulin for Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections. *J. Am. Acad. Child Adolesc. Psychiatry* **55**, 860-867.e2 (2016).
4. Spartz, E. J. *et al.* Course of Neuropsychiatric Symptoms After Introduction and Removal of Nonsteroidal Anti-Inflammatory Drugs: A Pediatric Observational Study. *J. Child Adolesc. Psychopharmacol.* **27**, 652–659 (2017).
5. Nery, F. G. *et al.* Celecoxib as an adjunct in the treatment of depressive or mixed episodes of bipolar disorder: a double-blind, randomized, placebo-controlled study. *Hum. Psychopharmacol. Clin. Exp.* **23**, 87–94 (2008).
6. Müller, N. *et al.* The cyclooxygenase-2 inhibitor celecoxib has therapeutic effects in major depression: results of a double-blind, randomized, placebo controlled, add-on pilot study to reboxetine. *Mol. Psychiatry* **11**, 680 (2006).
7. Shalbakfan, M. *et al.* Celecoxib as an adjuvant to fluvoxamine in moderate to severe obsessive-compulsive disorder: a double-blind, placebo-controlled, randomized trial. *Pharmacopsychiatry* **48**, 136–140 (2015).
8. Imbimbo, B. P., Solfrizzi, V. & Panza, F. Are NSAIDs useful to treat Alzheimer's disease or mild cognitive impairment? *Front. Aging Neurosci.* **2**, 19 (2010).
9. Swedo, S. E. *et al.* Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: clinical description of the first 50 cases. *Am. J. Psychiatry* **155**, 264–271 (1998).
10. Bernstein, G. A., Victor, A. M., Pipal, A. J. & Williams, K. A. Comparison of clinical characteristics of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections and childhood obsessive-compulsive disorder. *J. Child Adolesc. Psychopharmacol.* **20**, 333–340 (2010).
11. Storch, E. A. *et al.* Reliability and validity of the Yale Global Tic Severity Scale. *Psychol. Assess.* **17**, 486 (2005).
12. Sheehan, D. V. *et al.* Reliability and validity of the mini international neuropsychiatric interview for children and adolescents (MINI-KID). *J. Clin. Psychiatry* (2010).

13. Townsend, L. *et al.* Development of three web-based computerized versions of the Kiddie Schedule for affective disorders and schizophrenia child psychiatric diagnostic interview: preliminary validity data. *J. Am. Acad. Child Adolesc. Psychiatry* **59**, 309–325 (2020).
14. Guy, W. *ECDEU Assessment Manual for Psychopharmacology*. (US Department of Health, Education, and Welfare Public Health Service Alcohol, Drug Abuse, and Mental Health Administration, 1976).
15. Lebowitz, E. R., Vitulano, L. A. & Omer, H. Coercive and disruptive behaviors in pediatric obsessive compulsive disorder: A qualitative analysis. *Psychiatry Interpers. Biol. Process.* **74**, 362–371 (2011).
16. Devilly, G. J. & Borkovec, T. D. Psychometric properties of the credibility/expectancy questionnaire. *J. Behav. Ther. Exp. Psychiatry* **31**, 73–86 (2000).
17. Birmaher, B. *et al.* Psychometric properties of the Screen for Child Anxiety Related Emotional Disorders (SCARED): a replication study. *J. Am. Acad. Child Adolesc. Psychiatry* **38**, 1230–1236 (1999).
18. Calvocoressi, L. *et al.* Family accommodation of obsessive-compulsive symptoms: instrument development and assessment of family behavior. *J. Nerv. Ment. Dis.* **187**, 636–642 (1999).
19. Wolraich, M. L. *et al.* Psychometric properties of the Vanderbilt ADHD diagnostic parent rating scale in a referred population. *J. Pediatr. Psychol.* **28**, 559–568 (2003).
20. Storch, E. A. *et al.* Children’s Florida obsessive compulsive inventory: psychometric properties and feasibility of a self-report measure of obsessive–compulsive symptoms in youth. *Child Psychiatry Hum. Dev.* **40**, 467–483 (2009).
21. Novak, M. & Guest, C. Application of a multidimensional caregiver burden inventory. *The gerontologist* **29**, 798–803 (1989).
22. Farmer, C. *et al.* Psychometric evaluation of the caregiver burden inventory in children and adolescents with PANS. *J. Pediatr. Psychol.* (2018).
23. Bird, H. R., Shaffer, D., Fisher, P. & Gould, M. S. The Columbia Impairment Scale (CIS): Pilot findings on a measure of global impairment for children and adolescents. *Int. J. Methods Psychiatr. Res.* (1993).
24. Zuckerbrot, R. A. *et al.* Adolescent depression screening in primary care: feasibility and acceptability. *Pediatrics* **119**, 101–108 (2007).
25. Hilbert, A. & van Dyck, Z. Eating Disorders in Youth-Questionnaire. (2016).

26. Kay, S. R., Wolkenfeld, F. & Murrill, L. M. Profiles of aggression among psychiatric patients: I. Nature and prevalence. *J. Nerv. Ment. Dis.* (1988).
27. Scahill, L. *et al.* Children's Yale-Brown obsessive compulsive scale: reliability and validity. *J. Am. Acad. Child Adolesc. Psychiatry* **36**, 844–852 (1997).
28. Beery, K. E. *The Beery-Buktenica developmental test of visual-motor integration: Beery VMI, with supplemental developmental tests of visual perception and motor coordination, and stepping stones age norms from birth to age six.* (NCS Pearson Minneapolis, MN, 2004).
29. Kløve, H. Clinical neuropsychology. *Med. Clin. North Am.* **47**, 1647–1658 (1963).
30. Storch, E. A. *et al.* Development and Psychometric Evaluation of the Children's Yale-Brown Obsessive-Compulsive Scale Second Edition. *J. Am. Acad. Child Adolesc. Psychiatry* **58**, 92–98 (2019).
31. Wisniewski, S. R. *et al.* Self-rated global measure of the frequency, intensity, and burden of side effects. *J. Psychiatr. Pract.* **12**, 71–79 (2006).
32. IBM Corp. *IBM SPSS Statistics for Windows.* (IBM Corp., 2016).
33. Falkner, B. *et al.* The Effects of Celecoxib or Naproxen on Blood Pressure in Pediatric Patients with Juvenile Idiopathic Arthritis. *Clin. Med. Insights Pediatr.* **9**, CMPed-S20720 (2015).
34. Marcum, Z. A. & Hanlon, J. T. Recognizing the risks of chronic nonsteroidal anti-inflammatory drug use in older adults. *Ann. Long-Term Care Off. J. Am. Med. Dir. Assoc.* **18**, 24 (2010).
35. Laine, L., Curtis, S., Cryer, B., Kaur, A. & Cannon, C. Risk factors for NSAID-associated upper GI clinical events in a long-term prospective study of 34 701 arthritis patients. *Aliment. Pharmacol. Ther.* **32**, 1240–1248 (2010).
36. Sobel, R. E. *et al.* Safety of celecoxib and nonselective nonsteroidal anti-inflammatory drugs in juvenile idiopathic arthritis: results of the phase 4 registry. *Pediatr. Rheumatol.* **12**, 29 (2014).
37. Lo, P.-C., Tsai, Y.-T., Lin, S.-K. & Lai, J.-N. Risk of asthma exacerbation associated with nonsteroidal anti-inflammatory drugs in childhood asthma: A nationwide population-based cohort study in Taiwan. *Medicine (Baltimore)* **95**, e5109–e5109 (2016).
38. Frankovich, J. *et al.* Clinical Management of Pediatric Acute-Onset Neuropsychiatric Syndrome: Part II—Use of Immunomodulatory Therapies. *J. Child Adolesc. Psychopharmacol.* **27**, 574–593 (2017).

39. GELLER, D. A. *et al.* Fluoxetine Treatment for Obsessive-Compulsive Disorder in Children and Adolescents: A Placebo-Controlled Clinical Trial. *J. Am. Acad. Child Adolesc. Psychiatry* **40**, 773–779 (2001).
40. Russell, S. C. S. & Doyle, E. A Risk-Benefit Assessment of Topical Percutaneous Local Anaesthetics in Children. *Drug Saf.* **16**, 279–287 (1997).