Study Protocol

NCT Identifiers: NCT02189213
Protocol ID: 6884
Title: Treatment of Pediatric Anxiety Disorders by Predicting Treatment Response Through Bicellular Markers and Sleep Module (This is the most up to date protocol Dated 5/20/2020)

07/17/2021

New York State Psychiatric Institute

Institutional Review Board

May 15, 2020

To: Dr. Amir Levine

From: Dr. Edward Nunes, Co-Chair
Dr. Agnes Whitaker, Co-Chair

Subject: Approval Notice: Continuation*** expedited per 45CFR46.110(b)(1)(f)(8c)

Your protocol # **6884** entitled: **TREATMENT OF PEDIATRIC ANXIETY DISORDERS BY PREDICTING TREATMENT RESPONSE THROUGH BIOCELLULAR MARKERS AND SLEEP** Protocol version date 05/15/2020 has been approved by the New York State Psychiatric Institute - Columbia University Department of Psychiatry Institutional Review Board from **May 15, 2020 to February 23, 2021.**

Consent requirements:
√ Not applicable: Data Analysis Only
☐ 45CFR46.116 (f)(3) waiver of consent
☐ Signature by the person(s) obtaining consent is required to document the consent process
☐ Documentation of an independent assessment of the participant's capacity to consent is also required.

Approved for recruitment of subjects who lack capacity to consent: ☐ No ☐ Yes

Field Monitoring Requirements: ☐ Routine ☐ Special: _____

✓ Only copies of consent documents that are currently approved by the IRB may be used to obtain consent for participation in this study.
✓ A progress report and application for continuing review is required 2 months prior to the expiration date of IRB approval.
✓ Changes to this research may not be initiated without the review and approval of the IRB except when necessary to eliminate immediate hazards to participants.
✓ All serious and/or unanticipated problems or events involving risks to subjects or others must be reported immediately to the IRB. Please refer to the PI-IRB website at http://irb.nyspi.org for Adverse Event Reporting Procedures and additional reporting requirements.

*** Please note, only remote procedures may be conducted at this time. All in-person procedures are on hold until further notice, due to COVID-19 guidance. Please contact your Division Chief to discuss your specific protocol plan and contact the IRB prior to commencing any in-person procedures.

EN/AHW/alw

Signed copy on file at IRB

Protocol Title:
Treatment of Pediatric Anxiety Disorders by Predicting Treatment Response Through Biocellular Markers and Sleep

Version Date:
05/15/2020

Protocol Number:
6884

Clinic:
Children's Day Unit

First Approval:
04/15/2014

Expiration Date:
02/23/2021

Contact Principal Investigator:
Amir Levine, MD
Email: ama146@columbia.edu
Telephone: 646 481 2655

Co-Investigator(s):
Laura Mufson, PHD
Moira Rynn, MD
Pablo Goldberg, MD
Eleanor McGlinchey, PHD

Research Chief:
Jeremy Veenstra-VanderWeele

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?
Psychiatry
Within the division/department, what Center or group are you affiliated with, if any?
Child and Adolescent Psychiatry

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.
There are no investigators who are not affiliated with New York State Psychiatric Institute or Columbia University.

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.
In the past year, we have continued with data analysis. There has been no participant involvement. We found some potential mechanism for SSRI action via lipid metabolism and certain lipid metabolites that could potentially predict treatment response in children adolescents and young adults. We are going to continue with the data analysis in the next year as well. The ongoing work does not have an effect on the experience of the study participants. The study will potentially offer future tools to assess response to sertraline prior to treatment initiation and could enhance safety and efficacy by offering a precision medicine tool in pediatric psychiatry.

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
60
Total number of participants enrolled to date
14
Number of participants who have completed the study to date
7
Have there been any significant deviations from the anticipated study recruitment, retention or completion estimates?
No
Comments / additional information

Sample Demographics

Specify population
N/A
Total number of participants enrolled from this population to date
N/A
Gender, Racial and Ethnic Breakdown
No subject recruitment has been done this past year.

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
✓ Studies of DNA

✓ MRI
✓ Internet-based Data Collection or Transmission

Population

Indicate which of the following populations will be included in this research
✓ Children (ages 8-12)
✓ Children (ages 13-17)
✓ Medically and Psychiatrically Healthy Subjects
✓ Adults
✓ Employees or Students
✓ Inpatients

Research Support/Funding

Will an existing internal account be used to support the project?
Yes
Describe internal account

The Division of Child and Adolescent Psychiatry will be matching funds.

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
1

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
Other
Sponsor
External, Irving Institute, Columbia University; 2013 Irving Institute/Clinical Trials Office (CTO) Pilot Award
Select one of the following
Single Site
Business Office
CU
Does the grant/contract involve a subcontract?

No

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
No

Lay Summary of Proposed Research

Lay Summary of Proposed Research

The process of treatment with selective serotonin reuptake inhibitors (SSRIs) is arduous. Several months are required to determine response to SSRIs for anxiety, and in the best treatment scenario, when people are treated with adequate doses, only 50%-60% will respond. The purpose of this study is to advance the treatment of anxiety in children, adolescents, and young adults (CAAYA) by examining possible mechanisms of treatment response.

Primary Aim
Our goal is to identify a biomarker via a blood, saliva, or urine test that will determine who will respond well to SSRIs, a class of antidepressant known for its efficacy for pediatric anxiety, and who will not have robust response to medication treatment, before the onset of treatment. To achieve this goal, we will search for biomarkers that predict treatment response to SSRIs for anxiety in CAAYA. More specifically, we plan to examine relationships among telomere length, mRNA in whole blood, allelic variations of candidate genes regulating functional output, metabolomics in blood, urine, and saliva, and response to SSRIs. We are funded to perform this research by the 2013 Irving Institute/Clinical Trials Office (CTO) Pilot Award. We will be concentrating our study on candidate immediate early genes which encode transcription factors and other regulatory elements that react very quickly to changes in the environment and then regulate and orchestrate the expression of a whole program of downstream effector genes, proteins, and metabolites. This genetic process is believed to be responsible for the eventual phenotypic/symptomatic changes. These genes are most likely to change their expression rapidly, at the very onset of treatment, before we observe changes in symptoms, and thus may enable us to predict treatment outcome.

Secondary Aim
Additionally, we aim to identify an endophenotype related to treatment response in pediatric and young adult anxiety. Our hypothesis is that sleep difficulties (insomnia plus circadian rhythm abnormalities) will correlate with the expression of specific genes in the blood among individuals with and without symptoms of these disorders. Hence, for this secondary aim we plan to enroll both CAAYA with clinically impairing anxiety, as well as normal controls to identify the unique biomarkers associated with disturbed sleep in

CAAYA with these disorders. In addition, de-identified data may be used in the future to conduct secondary data analyses and we may use these data to answer questions beyond those described in this protocol.

Tertiary Aim

Dopamine levels have been found to be low in individuals with social anxiety disorder (Tiihonen, et al. 1997; Schneier, et al. 2000; Schneier, et al. 2008), but these levels can be difficult to measure without the use of PET scanning, which is limited in pediatric populations to cases of medical necessity due to concerns over the effects of radiation exposure in this age group. Neuromelanin is created from cytosolic dopamine as part of a scavenger system, and will accumulate in the brain throughout one's lifetime (Rabey and Hefti, 1990). Because of this, neuromelanin is being considered as a biomarker for dopaminergic activity in both healthy individuals and in those with disorders involving dopaminergic dysregulation (Nakamura, et al. 2014; Clewett, et al. 2016; Yamashita, et al. 2016). Unlike dopamine, neuromelanin can be measured using MRI, which is an established and safe tool for research use in children.

Recent research has suggested that neuromelanin levels as measured using MRI can serve as a metric for dopaminergic neuronal density, with an accuracy comparable to that of dopamine transporter PET imaging (Kuya, et al. 2016; Kawaguchi, et al. 2016). Neuromelanin has also routinely demonstrated promise as a diagnostic biomarker for Parkinson's disease (Kitao et al. 2013; Ohtsuka et al. 2014; Reimão, et al. 2015; Castellanos, et al. 2015; Kawaguchi, et al. 2016). Neuromelanin levels have also been found to correlate with changes in dopaminergic activity associated with disease progression in patients with schizophrenia (Watanabe 2014; Yamashita, et al. 2016). To date, the use of MRI to measure neuromelanin has not been reported in pediatric populations. By instituting an optional MRI scan for study participants, we are seeking to provide the proof of concept that neuromelanin can be reliably imaged in the developing brain and can potentially be used as a prognostic biomarker for treatment response.

Design Summary

A. Population: Anxiety Disorder Group

Children, adolescents, and young adults ages 8 to 25 years old with anxiety will enroll in the study for a maximum of 12 weeks. All participants will have their sleep and circadian rhythms monitored at baseline and end of treatment via an accelerometer. At the discretion of the study doctors, patients may be offered the opportunity to undergo one optional MRI scan. If participant is offered the opportunity to undergo an MRI scan, the participant and study doctor can choose to conduct the scan on any one of the visits scheduled for the study.

Outpatient participants who are identified as having clinically impairing anxiety will be required to visit the outpatient program of the Pediatric Anxiety and Mood Research Clinic for a total of 12 study visits. For inpatient participants, study visits will also occur at PAMRC:

1. Screening visit (Week -1).
2. Baseline visit (Week 0) and first administration of SSRI.
3. Medication management phase, which will include scheduled visits at Weeks 1, 2, 3, 5, 7, 9, and 12.
4. **Biological specimens will be collected at Weeks 1, 3, 5, and 12.**
5. Voluntary 6 month and 12 month follow-up visits.

Additional phone contact and visits are allowed based on judgment of the study physician in response to concerns regarding side effects or possible deterioration in clinical status.

Enrolled participants will be required to take the SSRI treatment daily beginning the evening of the Baseline Visit (beginning of Week 0 of treatment), or the morning after, according to doctor's direction, and continuing through to Week 12.

60 participants will be included in the anxiety group.

Given that this is a new area of research we would like to be able to obtain as much statistical power for our biomarker analysis as possible and we may revise this number once we have a better idea of the feasibility of recruiting this particular patient population.

B. Population: Healthy Control Group

Similarly, participants who are recruited as controls (matched by age and gender) will be required to visit the CDU for 5 study visits to match all of the evaluation visits that the anxiety group participates in. This will be so we can make a statement about the generalizability of the biomarkers to these disorders versus a healthy population. This might also enable us to identify a population with anxiety before ever having to do a psychiatric evaluation. So little is known about this area, hence the need to see if there is more or less variance over time between the anxious and control groups. At the doctor's discretion, healthy controls may also be offered the opportunity to undergo **or two optional MRI scans**. If participant is offered the opportunity to undergo the scan(s), the participant and study doctor can choose to conduct the scan on any one of the visits scheduled for the study.

The following visits will take place for the control group:

1. Week -1 will be a Screening visit
2. Baseline visit (Week 0) and **first biological specimen collection.**
3. Weeks 1, 3, 5, and 12 for the **collection of biological specimens.**
4. Voluntary 6 month and 12 month follow-up visits.

30 participants will be included in the control group.

Background, Significance and Rationale

Background, Significance and Rationale

Summary of Significance and Rationale

In the past several years, telomere length has become a marker for biological aging and has been found to respond to various environmental conditions. Most recently, telomere length has been found to be significantly affected by anxiety (Teyssier et al., 2012), and poor sleep (Prather et al., 2011). Other studies

suggest that certain genes may also change their expression in peripheral cells in response to treatment of SSRIs (Cattaneo et al., 2011; Matuzany-Ruban et al., 2010). Several studies report a significant decrease in expression of the genes such as BDNF (Cattaneo et al., 2011), GRK2 (Matuzany-Ruban et al., 2010), CREB and HDAC5 (Iga et al., 2007) mRNA levels in leukocytes of people with depression. The expression of these genes responded to SSRI treatment and normalized to the control level. Importantly, BDNF, HDAC5 and CREB have also been shown to play a role in the pathophysiology of depression and sleep deprivation in the brains in mice. So it seems that there are correlates between the function of genes in the pathophysiology of anxiety, depression and sleep difficulties in the brain and their expression in immune white blood cells. This study may support the use of such biomarkers in personalized treatment for anxiety disorders in CAAYA.
Using the medication procedures established by the CAMS treatment study of anxious youth (Walkup et al., 2008), this is the first study to examine the mechanisms of anxiety disorders in CAAYA and the biomarkers involved in treatment response and observable phenotypes.

Background

Treatment Background

Pediatric anxiety disorders comprise the most common psychiatric conditions in children and adolescents with a prevalence of more than 10% in the pediatric population (Fisher et al., 2006; Keeton et al., 2009). Generalized anxiety disorder (GAD), Separation Anxiety disorder (SAD) and Social Phobia (SoP) are the most frequently diagnosed childhood anxiety disorders. While all children may become anxious in stressful or unfamiliar situations, anxiety disorders manifest as excessive anxiety, which may be accompanied by physical symptoms (e.g., headache, restlessness, and gastrointestinal distress) and impaired daily functioning (e.g., social, emotional, and academic; (Fisher et al., 2006)). Moreover, sleep disturbance is a core feature across pediatric anxiety disorders (Fisher et al., 2006). Left untreated, pediatric patients with anxiety disorders may suffer from physical, emotional, academic, and social impairment. Furthermore, significant anxiety symptoms in children and adolescents may evolve into anxiety and depressive disorders and a higher frequency of substance abuse as older adolescents and adults (Pine et al.,1998; Kaplow et al., 2001). SSRIs are first line pharmacotherapy for all anxiety disorders (Strawn JR et al. 2014). The treatment options for GAD, SAD and SoP are similar as these conditions are related and frequently co-morbid. However, little is known concerning the biological mechanisms that connect these disorders, what phenotypes are associated with specific biomarkers, and the relationship to treatment outcome.

Current evidence-based psychiatric treatment for anxiety disorder in CAAYA involve a trial and error process. Child psychiatrists start with the first line treatments (i.e. serotonin reuptake inhibitors (SSRIs) and/or psychotherapy), which can take at least 4-8 weeks to show any effect. There is a long interval between treatment initiation and response with only 50-60% likelihood that the treatment chosen will succeed in reducing symptoms (Walkup et al., 2008). There is no way to predict, based on clinical or biological patient baseline data, who will respond to medication or psychotherapy treatment. Additionally, there is limited access to specialized psychotherapy for anxiety in CAAYA and often medication treatment is used as the only available option.

Biomarkers Background
Studies have demonstrated a correlation between cellular markers in white blood cells and psychiatric disorders, suggesting that certain genes change their expression in peripheral blood in response to treatment with SSRIs. Several studies report a significant decrease in expression of key genes that are involved in the pathophysiology of anxiety and depression in the brain, such as BDNF, CREB and HDAC5 levels in leukocytes of people with mood and anxiety disorders (Cattaneo, et al., 2011; Matuzany-Ruban, et al., 2010). The levels of BDNF, HDAC5 and CREB in white blood cells then respond to treatment and do not differ from the matched controls after treatment with SSRIs (Catteneo, et al., 2011, Iga et al., 2007). The increase accessibility to sequencing technology allows us to survey more potential biomarkers than what was possible just several years ago. This may enable us to formulate a test that will predict, based on biocellular markers, treatment outcome in anxiety for CAAYA before, or rapidly after the initiation of treatment. By finding molecular markers that can predict treatment success from the onset, we can improve treatment outcomes considerably compared to current standard treatment practices. This kind of personalized medicine will advance the treatment of adolescent anxiety and improve the physician's ability to better advise the parent and/or the patient about treatment options and treatment outcome. Moreover, identifying a potential phenotype associated with biocellular markers may eventually lead to preventative efforts aimed at identifying prodromal symptoms before they become full illness episodes.

Sleep Background
Sleep difficulties are a core feature of anxiety (American Psychiatric Association, 2013). Moreover, sleep and mood complaints are commonly reported to originate in the adolescent years and recent research suggests that primary insomnia in adolescence significantly predicts future psychiatric symptoms (Johnson et al., 2006). Additionally, clinical trials of treatments for anxiety in adolescence have shown that insomnia and other sleep complaints are the most common residual symptoms (e.g., Kennard et al., 2006; Walkup et al., 2008). In the largest treatment study of pediatric anxiety disorders, sleep difficulties were also the most commonly reported side effect of sertraline treatment (Walkup et al., 2008). Little research has focused on sleep problems in adolescent anxiety disorders and whether sleep difficulties contribute to a poor illness course or to relapse after successful treatment. Moreover, we have very little knowledge on whether there are biomarkers related to sleep problems in psychiatric disorders.

MRI Background
Dopamine levels have been found to be low in individuals with social anxiety disorder (Tiihonen, et al. 1997; Schneier, et al. 2000; Schneier, et al. 2008), but these levels can be difficult to measure without the use of PET scanning, which is limited in pediatric populations to cases of medical necessity due to concerns over the effects of radiation exposure in this age group. Neuromelanin is created from cytosolic dopamine as part of a scavenger system, and will accumulate in the brain throughout one's lifetime (Rabey and Hefti, 1990). Because of this, neuromelanin is being considered as a biomarker for dopaminergic activity in both healthy individuals and in those with disorders involving dopaminergic dysregulation (Nakamura, et al. 2014; Clewett, et al. 2016; Yamashita, et al. 2016). Unlike dopamine, neuromelanin can be measured using MRI, which is an established and safe tool for research use in children.

Recent research has suggested that neuromelanin levels as measured using MRI can serve as a metric for dopaminergic neuronal density, with an accuracy comparable to that of dopamine transporter PET imaging

(Kuya, et al. 2016; Kawaguchi, et al. 2016). Neuromelanin has also routinely demonstrated promise as a diagnostic biomarker for Parkinson's disease (Kitao et al. 2013; Ohtsuka et al. 2014; Reimão, et al. 2015; Castellanos, et al. 2015; Kawaguchi, et al. 2016). Neuromelanin levels have also been found to correlate with changes in dopaminergic activity associated with disease progression in patients with schizophrenia (Watanabe 2014; Yamashita, et al. 2016). To date, the use of MRI to measure neuromelanin has not been reported in pediatric populations. By instituting an optional MRI scan for study participants, we are seeking to provide the proof of concept that neuromelanin can be reliably imaged in the developing brain and can potentially be used as a prognostic biomarker for treatment response.

Specific Aims and Hypotheses

Specific Aims and Hypotheses

Aim
To identify biological markers in peripheral blood, saliva, or urine that will predict treatment response in CAAYA subjects with anxiety.

Hypothesis
We predict that CAAYA who respond to medication treatment have a unique set of DNA, RNA, and protein signatures and associated sleep phenotype compared to treatment non-responders and healthy controls.

Primary Study Goals
Our long-term goal is to establish a biological test that will provide personalized treatment recommendations for children suffering from impairing anxiety based on their individual biological profiles and phenotypes. The specific objective of this proposal is to identify DNA, RNA and protein markers that will predict treatment outcomes of anxiety to SSRIs. The central hypothesis is that telomere length, RNA expression profile of specific genes, and an epigenetic signature in peripheral blood will predict treatment response in adolescents with anxiety. This hypothesis is based on multiple reports in the literature of a strong connection between various molecular biomarkers such as telomere length, and gene expression with anxiety (Teyssier et al., 2012). There are also multiple studies that demonstrate an association between RNA gene expression and response to SSRI treatment (Cattaneo et al., 2011 and Matuzany-Ruban et al., 2010). In addition, our basic science studies reveal differences in histone acetylation of stressed mice compared to non-stressed mice and increase in histone acetylation in the cortex of stressed mice following fluoxetine treatment (Levine et. al., 2012), which is also manifested systemically (Hobara et. al., 2010). In addition, de-identified data may be used in the future to conduct secondary data analyses. We may use these data to answer questions beyond those described in this protocol.

Exploratory Study Goals

1. To explore the biomarkers involved in symptoms of anxiety, including clinically impairing worry, rumination, social avoidance, inhibitory control and tolerance for frustration.

2. To explore the effect of sleep on the above symptoms, given the known effects of sleep disturbance on symptoms of anxiety (Yoo et al., 2009).
3. To examine whether neuromelanin can be reliably imaged using MRI in the brain of children and adolescents.
4. To test whether neuromelanin levels differ between patients and healthy controls, and/or if neuromelanin levels among patients differ according to type of anxiety disorder.

Description of Subject Population

Sample #1

Specify subject population
Children, adolescents, and young adults (CAAYA) with clinically impairing anxiety
Number of completers required to accomplish study aims
60
Projected number of subjects who will be enrolled to obtain required number of completers
80
Age range of subject population
8-25

Sample #2

Specify subject population
Healthy children, adolescents, and young adults (CAAYA) with no psychiatric disorder
Number of completers required to accomplish study aims
30
Projected number of subjects who will be enrolled to obtain required number of completers
40
Age range of subject population
8-25

Gender, Racial and Ethnic Breakdown

Based on the community from which we will be drawing patients and proportions to those encountered during previous clinical trials at this site, we expect the sample to be approximately 10% African-American,

44% Hispanic, 40% Caucasian, and 6% Other or Unknown. It is expected that the sample will be approximately 1:1 = male:female.

Description of subject population

Participants in this trial will be 60 children, adolescents, and young adults ages 8-25 who have clinically impairing anxiety symptoms based on a Children's Global Assessment Scale (CGAS) score of less than 65 for children and adolescents, or a Global Assessment Scale (GAS) score of less than 65 for young adults; and a healthy control group (N=30), ages 8-25 with no psychiatric illness.

Recruitment Procedures

Describe settings where recruitment will occur
Recruitment will draw from the broadest possible population with respect to gender and ethnic origin. IRB-approved radio/newspaper/web advertisements and flyers will be used to recruit both clinical and control participants. Recruitment will also be done on social media websites such as Craigslist, Facebook, Columbiapsychiatry.org (research studies page), Twitter, LinkedIn and Clinician email listserves.(materials to be submitted). **Prior to the scheduling of the Week -1 in-person screen, potential participants may undergo a telephone interview, and may complete a pre-screening self-report questionnaire through the Valant patient portal.** CAAYA will be enrolled through the PAMRC outpatient program on the Children's Day Unit (CDU) and the Children and Adolescent Psychiatric Evaluation Service (CAPES), located on the second floor of the New York State Psychiatric Institute. CAAYA and their families will be seen in the CDU for study visits. The CAPES/the PAMRC provides free expert consultation, evaluation, and treatment referrals for CAAYA suffering from mood and anxiety disorders.
How and by whom will subjects be approached and/or recruited?

Study participants may be recruited from the Child and Adolescent Psychiatric Evaluation Service (CAPES) located in the PI on the second floor (IRB # 7058R, PI Moira Rynn, M.D.). Drs. Levine Ellie McGlinchey, Pablo Goldberg, and Moira Rynn will be responsible for explaining the details of the study and consenting the participants if they are interested.

Participants ages 8-17 and their parent/caregiver may be assessed by an IRB-approved CAPES phone screen and **a self-report questionnaire completed through the Valant online portal. Participants ages 18-25 may be assessed individually, without a parent, by an IRB-approved CAPES phone screen and through a self-report questionnaire completed through the Valant online portal.**

How will the study be advertised/publicized?

Craigslist
Participants will be recruited through the volunteers section of the Craigslist website. We will post advertisements on this website bi-weekly with a brief description of our study (see attached recruitment notice). Advertisements will be targeted towards parents of potential pediatric patients ages 8-17, or

potential young adult patients ages 18-25 themselves. We will not be targeting minors through the ads, nor will be speak to minors without permission from their parents or guardians. Interested parents that contact us will be given more detailed information to assess further their interest in the study. If a parent agrees to participate, the staff member will request permission to administer the screening questionnaire in order to determine eligibility for our study.

Brochures

Brochures for patients will be distributed in New York and New Jersey to colleges and private schools (counseling services), mental health clinicians (psychiatrists, psychologists, social workers), university health clinics**,** and community health organizations. Recruitment of patients also occurs by potential patients themselves as well as their families, who learn about the study via the Internet, from their counselors or clinicians, by word of mouth, and from informational presentations in the community, including community health centers/organizations, conferences (i.e. Columbia's annual conference) and family organizations (NAMI).

Web/Social Media/Email listserves

Participants will also be recruited via Facebook (www.facebook.com), an on-line networking community to participate in our studies. We will post a description of our study on a page created for our study, as well as on the pages of other groups that are interested in anxiety. Facebook will be utilized as a recruitment method by posting a description of our study to inform treatment providers, support group leaders, parents and guardians of the research being conducted under this protocol. Facebook will not be utilized to inform children of our studies. Facebook will not be used to contact children. Despite precautionary measures enacted to deter children from responding to our postings, if a child does respond to a Facebook posting, he/she will be asked to speak with his/her parent or guardian regarding his/her interest in participation in the study who may then contact us.

We aim to use free internet resources, such as Twitter, LinkedIn and a website blog, for advertising that direct people to either the Facebook site or to our study information listed on the Columbia Psychiatry research studies site. We will use only IRB-approved text that directs individuals to the website, and by not offering any clinical advice or consultation over the internet. Text that the IRB approves for web use may also be used in emails to let clinicians in the community know about this study through emails on listserves that many of our clinicians at Columbia belong to, such as the CUPP (Columbia University psychopharmacology Forum), CHIPER (Child Psychiatry list serve at Columbia University), and the Downtown Clinician’s Collective (DTCC). This IRB approved text will also be used to describe the study on any bios listed of the PI (Amir Levine, MD), such as a faculty/staff website at Columbia University, and could include a link to a webpage giving further information about the study, such as the study Facebook site or the Columbia psychiatry research studies site. Any new text to be posted on social media sites, such as twitter, will be submitted to Dacia Morris who will review text before it is posted.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. The NCT number will be added to this protocol upon receipt.

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
NCT02189213

Concurrent Research Studies

Will subjects in this study participate in or be recruited from other studies?
Yes
Describe concurrent research involvement

At this point in time we're not anticipating that our participants will be in any other concurrent study. However, if a participant is referred to the study, who is presently involved in another protocol in the institution, we would like to be able to enroll them in our study, providing that the concurrent study is a non-treatment study that involves minimal burden to the participant (e.g. just filling out simple questionnaires). We are not aware of any concurrent research protocol that any of our participants would be interested in.

Inclusion/Exclusion Criteria

Name the subject group/sub sample
CAAYA with an Anxiety disorder
Create or insert table to describe the inclusion criteria and methods to ascertain them

CRITERION	ASCERTAINMENT METHOD
1) Participants aged 8-25 years inclusive at the time of the consent/assent, either outpatient or inpatient if hospitalization is required for one of the following reasons: • It is presently unsafe for subject to stay at home because he/she may run away • Subject needs closer monitoring while being started on medications • Subject needs a level of care that is greater than once a week outpatient treatment and is willing to participate in the study.	Phone screen by research staff
2) Participants age 8-17 must have a parent or legally authorized representative (LAR) who can provide signature of informed consent, and there must be documentation of assent by the participant.	Consent interview by study doctor

Participants aged 18 - 25 will provide their own signature of informed consent.	
3) Participant meets Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) or Fifth Edition (DSM-V) criteria for a clinically impairing anxiety disorder based on detailed psychiatric evaluation at screening including completion of the Anxiety Disorders Interview Schedule for DSM-IV or DSM-V Child Version (ADIS-C) and a Children's Global Assessment Scale (CGAS) score less than 65.	Interview and assessment by study doctor. ADIS evaluation by independent evaluator
4) Participants who are female of child-bearing potential (defined as ≥9 years of age or if <9 years of age are post-menarchal) must have a negative urine pregnancy test at the Baseline Visit. Females of child-bearing potential must abstain from sexual activity that could result in pregnancy or agree to use acceptable methods of contraception. Condoms should be used with the following acceptable contraceptives: • Intrauterine devices, • Hormonal contraceptives (oral, depot, patch, injectable, or vaginal ring). • Other acceptable contraceptive methods are double barrier methods (e.g., condoms and diaphragms with spermicidal gel or foam).	Urine pregnancy test; interview and assessment by study doctor.

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

CRITERION	ASCERTAINMENT METHOD
1) Participant has a current co-morbid psychiatric diagnosis of a bipolar disorder, psychosis, a pervasive developmental disorder other than Asperger's Syndrome, an eating disorder, substance abuse disorder or sleep disorder of narcolepsy and/or sleep apnea.	Interview and assessment by study doctor.; ADIS evaluation by independent evaluator; CHSQ
2) Participant as any condition or illness which, in the opinion of the study doctor, represents as an inappropriate risk to the participant and/or could confound the interpretation of the study.	Phone screen by research staff; interview and assessment by study doctor.
3) Participant has received any evidence-based psychosocial intervention in the past 6 weeks. i.e. Individual Cognitive Behavioral Therapy, Group Cognitive Behavioral Therapy, or Social Effectiveness Training.	Phone screen by research staff; interview by study doctor.
4) Participant is unwilling or unable to provide blood, urine, and/or saliva samples at designated visits.	**Phone screen by research staff; interview and assessment by study**

	doctor.
5) Participant is female and is pregnant or is currently lactating.	Urine pregnancy test; interview and assessment by study doctor
6) Participant is currently considered at risk for suicide in the opinion of the study doctor, has previous made a suicide attempt in the past 6 months, or is currently reporting active suicidal ideation. Participants with intermittent passive suicidal ideation are not necessarily excluded based on the assessment of the study doctor.	Phone screen by research staff; interview and assessment by study doctor.
7) Participant has had a substance use disorder within the past 6 months.	Phone screen by research staff; medical history self-report; urine toxicology
8) Participant has a clinically important abnormality on drug and alcohol screen at the Screening Visit or Baseline Visit.	Urine toxicology
9) Participant has started or changed the dosage of a medication (including herbal supplements) that has anxiogenic, anxiolytic, or CNS effects within the past 3 months.	Phone screen by research staff; interview and assessment by study doctor; urine toxicology
10) Participant has a known or suspected allergy, hypersensitivity, or clinically significant intolerance to any components found in the study drug.	Phone screen by research staff; interview and assessment by study doctor.
11) Participant has had several failed attempts with SSRI treatment.	Phone screen by research staff; interview and assessment by study doctor.
12) Participant has an acute illness and/or is taking short term medication at the time of initiation of the study.	Interview and assessment by study doctor.
13) Participants failed screening or was previously enrolled in this study.	Phone screen by research staff; interview and assessment by study doctor
14) Participant is unable to read.	Phone screen by

	research staff

Inclusion/Exclusion Criteria #2

Name the subject group/sub sample
Healthy Control CAAYA
Create or insert table to describe the inclusion criteria and methods to ascertain them

CRITERION	ASCERTAINMENT METHOD
1) Outpatient participants aged 8-25 years inclusive at the time of the consent/assent.	Phone screen by research staff
2) Participants age 8-17 must have a parent or legally authorized representative (LAR) who can provide signature of informed consent, and there must be documentation of assent by the participant. Participants aged 18 - 25 will provide their own signature of informed consent.	Consent interview by study doctor
3) Participant does not meet Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) or Fifth Edition (DSM-V) criteria for any psychiatric disorder.	Interview and assessment by study doctor; ADIS evaluation by independent evaluator
4) Participants who are female of child-bearing potential (defined as ≥9 years of age or if <9 years of age are post-menarchal) must have a negative urine pregnancy test at the Baseline Visit. Females of child-bearing potential must abstain from sexual activity that could result in pregnancy or agree to use acceptable methods of contraception. Condoms should be used with the following acceptable contraceptives: • Intrauterine devices, • Hormonal contraceptives (oral, depot, patch, injectable, or vaginal ring). • Other acceptable contraceptive methods are double barrier methods (e.g., condoms and diaphragms with spermicidal gel or foam).	Urine pregnancy test; interview and assessment by study doctor

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

CRITERION	ASCERTAINMENT METHOD
1) Has a current psychiatric diagnosis or sleep disorder.	Interview and assessment by study doctor; ADIS evaluation by

	independent evaluator; CHSQ
2) Participant as any condition or illness which, in the opinion of the study doctor, represents as an inappropriate risk to the participant and/or could confound the interpretation of the study.	Phone screen by research staff; interview and assessment by study doctor
3) Participant has received any psychosocial intervention in the past 6 weeks.	Phone screen by research staff; interview and assessment by study doctor
4) Participant is female and is pregnant or is currently lactating.	Urine pregnancy test; interview and assessment by study doctor
5) Participant is unwilling or unable to provide blood, urine, and/or saliva samples at designated visits.	**Phone screen by research staff; interview and assessment by study doctor.**
6) Participant is currently considered at risk for suicide in the opinion of the study doctor, has previous made a suicide attempt in the past 6 months, or is currently reporting active suicidal ideation. Control participants with any suicidal ideation will not be eligible for the study.	Phone screen by research staff; interview and assessment by study doctor.
7) Participant has a clinically important abnormality on drug and alcohol screen at the Screening Visit or Baseline Visit.	Urine toxicology
8) Participant has started or changed the dosage of a medication (including herbal supplements) that has anxiogenic, anxiolytic, or CNS effects within the past 3 months.	Phone screen by research staff; interview and assessment by study doctor; urine toxicology
9) Participant has an acute illness and/or is taking short term medication at the time of initiation of the study.	Interview and assessment by study doctor
10) Participant is unable to read.	Phone screen by 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

No
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

Only M.D.s will obtain assent/consent for CAAYA with an anxiety disorder. For anxiety group participants, prior to initiating screening procedures, Drs. Levine, Goldberg, Rynn or Delaney will obtain consent from the participant (for participants ages 18-25), or from the participant's parent/legal guardian (for participants 8-17), by describing the purpose and nature of this research study. Young adult patients and/or families will have a chance to review the consent form thoroughly and ask any questions prior to signing.

For healthy control participants, prior to initiating screening procedures, Drs. Levine, McGlinchey, Goldberg, Rynn or Delaney will obtain consent from the participant (for participants ages 18-25), or from the participant's parent/legal guardian (for participants 8-17) by describing the purpose and nature of this research study. Young adult participants will have a chance to review the consent form thoroughly and ask any questions prior to signing.

Describe Study Consent Procedures
For anxiety patients, Drs. Levine, Goldberg, Rynn or Delaney will answer any questions the participant (for participants ages 18-25), or the participant's parent/legal guardian (for participants ages 8-17) may have and will obtain written consent. Young adult participants or minor participants' parent/legal guardian will receive a copy of the signed consent.

For healthy control participants, Drs. Levine, McGlinchey, Goldberg, Rynn or Delaney will answer any questions the participant (for participants ages 18-25), or from the participant's parent/legal guardian (for participants 8-17) may have and will obtain written consent. Young adult participants or minor participants' 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

Assent Procedures

Describe procedures by which subject assent will be assessed and/or recorded
For anxiety patients ages 8-17, Drs. Levine, Goldberg, Rynn or **Delaney** will describe the purpose and nature of this 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.

For healthy control participants ages 8-17, Drs. Levine, McGlinchey, Goldberg, Rynn or **Delaney** will describe the purpose and nature of this 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
Levine, Amir, MD
McGlinchey, Eleanor, PHD
Mufson, Laura, PHD
Type in the name(s) not found in the above list

Independent Assessment of Capacity

You have indicated that your study involves subjects who MAY LACK capacity to consent.
Does this study require an independent assessment of capacity?
No

Study Procedures

Describe the procedures required for this study

Study Location

Children's Day Unit at the Pediatric Anxiety and Mood Research Clinic
The study will be conducted at the Pediatric Anxiety and Mood Research Clinic (PAMRC) which consists of the Children's Day Unit (CDU) and CAPES. The PAMRC has 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.

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 a child or adolescent patient requires

additional support or requires a higher level of care, the participant may be admitted to the CDU day treatment program that runs Monday through Friday from 8:30 am to 3:30 pm where the 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. Pediatric participants ages 8-17, as well as young adult participants ages 18-25, will have their screening and outpatient visits conducted at PAMRC. However, only participants ages 8-17 may be eligible to enroll in the CDU day treatment program.

Prescreening (Telephone Contact)

Trained research staff will conduct a telephone screen with the parents of prospective study participants. After providing a brief overview of the study, the research staff will ask the prospective study participant's permission to ask screening questions and obtain identifying information. Verbal consent to ask these questions will be documented by the research staff circling the response and signing his/her name prior to asking questions. The study doctor will be available to answer questions about the study. **Potential participants may also complete a pre-screening questionnaire through the Valant patient portal.**

Screening Visit

Prior to entering the Treatment Period, all criteria for enrollment will be evaluated during the Screening (Week -1) Visit. The participant will be asked to come to the PAMRC where written informed consent from participant will be obtained (if ages 18-25), or written informed consent from their parent/guardian and written informed assent from the participant will be obtained (if ages 8-17); before any other study procedures are conducted. Clinical interviews and secondary measured will be administered to assess eligibility and/or baseline function. Week -1 will take approximately **5** hours to complete. Procedures to be done at Screening Visit include:

- Consent and assent obtained prior to any other procedures
- Any baseline symptoms reported will be recorded from the time informed consent is obtained
- Demographic information
- Medical history
- Vital signs, including: oral temperature, respiratory rate, supine blood pressure (BP) and pulse (after 5 minutes of rest), and standing BP and pulse (after 2 minutes of standing from supine position), height and weight
- Historical/concomitant medications will be recorded. This includes as follows all lifetime psychoactive medications and other medications used during the 30 days prior to screening.
- Lifetime non-pharmacological interventions for anxiety will be recorded.
- If available, family psychiatric history for the participant's immediate family will be obtained.
- "Baseline" version of the Columbia Suicide Severity Rating Scale (C-SSRS) will be administered to screen for suicidality.
- Urine pregnancy, drug and alcohol screen.

- Diagnostic interview (for both groups) and Anxiety Disorders Interview Schedule for DSM-IV or DSM V Child Version- Clinician Severity Rating Scale (ADIS-C CSR).
- Tanner Self-report scale (if applicable), Pediatric Sleepiness Scale (PDSS), Clinical Global Impressions (CGI), ADIS-C CSR, Screen for Child Anxiety Related Disorders (SCARED), Children's Sleep Habits Questionnaire, Affective Reactivity Index (ARI), Mood and Feelings Questionnaire Long Version (MFQ)

At the completion of the screening assessment, the individual and/or their family will be informed of their study eligibility. CAAYA who do not meet eligibility criteria for the study's anxiety disorder population will be referred for appropriate ongoing mental health treatment. Participants will not receive a physical exam and will not be excluded based on a medical evaluation.

Pregnancy Testing

As part of the Screening visit, participants who are female and have had their first period will have her urine tested for pregnancy, and again before she is given medication if more than one week has passed. A urine pregnancy test will also be given to females who have been offered and agree to undergo the optional MRI scan, on the day of the scan, to establish eligibility prior to undergoing the scan. Participants age 18-25 will be informed if they test positive, while participants age 8-17 will have their parent/legal guardian informed if they test positive. If the test shows that the participant is pregnant, she will not be able to participate in the study. The Study Doctor will discuss with her where she can go to get further treatment. If the participant thinks she is pregnant at any time during the study, she will be informed that she must stop taking the study medication and tell the Study Doctor right away. She will be offered the opportunity to have a confidential pregnancy test (one where no one but the participant will be told what the results are) outside of the pediatric clinic. We will offer to help the participant find a clinic where they do such testing, although if she does obtain a confidential pregnancy testing outside of the pediatric clinic, or if the participant is pregnant, or becomes pregnant, she may not participate in the study and we will refer her for treatment for her anxiety in a clinic near where she lives.

Sleep/Activity Monitoring

Those who are eligible will be given a device early in the study that measures sleep and locomotor activity to wear on his/her wrist. This is an actigraphy watch, which is worn just like a wristwatch and is the same size as a regular wristwatch. The participant will wear the device on his/her non-dominant wrist for one week at the beginning of the study and then again from week 11 to week 12 of treatment. The actiwatch is the size of a large wrist watch. We do not expect wearing this on the non-dominant arm to cause discomfort and participants will be compensated for wearing the device for the duration of a week. In order to keep CAAYA engaged in completing the sleep study portion of the protocol and to collect additional information about how sleep and mood interact, participants will also be asked to complete a daily sleep and mood diary consisting of gold standard questions used in sleep research (Carney et al., 2012). For inpatient participants, we will continue to monitor sleep in the same way, but will use inpatient status as a covariate in our analyses, because inpatient sleep is necessarily different from outpatient baseline sleep.

Valant Patient Portal

Once enrolled in the study, participants will be offered the option to enroll in the Valant

online patient portal. As part of this registration, participants will be instructed on the option to use Valant to communicate with the study staff, to complete study questionnaires ahead of time, and to view appointments as well as set reminders for upcoming appointments.

Baseline Visit

At the Baseline Visit, if the participant meets all eligibility criteria, he or she will give a baseline blood draw/urine/saliva to assess biomarkers. At the study doctor's discretion, patients (and their parents for minors) will be offered the opportunity to undergo one optional MRI scan. Those who agree will first be screened for eligibility to undergo the MRI scan using the MRI Screening Questionnaire, which includes questions regarding MRI-specific inclusion/exclusion criteria, including the presence of ferromagnetic implants, pubertal status, and pregnancy. Participants will be offered the option of training in the MRI simulator before initiating the scan. An additional pregnancy test will be given to post-menarchal females prior the the MRI scan, and a negative result will be required to undergo the procedure. The scan can occur at the baseline visit or any other study visit that the doctor and patient agree to. Week 0 will take approximately **1 hour** to complete. Procedures to be done at Baseline Visit include:

- Re-evaluate inclusion/exclusion criteria to ensure participant continues to meet eligibility criteria * Adverse events will be assessed and compared to symptoms at baseline
- Urine drug and alcohol testing will be conducted to confirm eligibility.
- The “Since the Last Visit” version of the C-SSRS will be administered at the Baseline Visit (Week 0) and every visit thereafter until the end of the study
- Eligible anxiety group participants will take their first dose of medication product in the evening of the Baseline Visit, or the following morning, as directed by the doctor.
- Blood Draw/urine/saliva sample (see section on collection of blood.
- At the doctor's discretion, MRI Screening Questionnaire and Baseline MRI scan with optional training in the MRI simulator (optional - can be baseline or any other mutually agreed upon study visit)

Sleep Monitoring Period

Beginning after the screening visit, all participants will have their sleep and daily locomotor activity monitored via accelerometer. Participants will also fill out a daily sleep and mood diary. Following screening, participants will wear an actiwatch for one week. We do not anticipate this being difficult for participants given that the actiwatch is the same size as a regular wristwatch. Early in the study participants will return the sleep diary actiwatch after wearing it continuously for one week, and wear it again at the end of treatment (actiwatch will be received at week **9**) with instructions to wear it from weeks 11-12. Watch will be returned at Week 12).

Actigraph Watch

Actigraphs are small wrist watch-like devices that provide an objective estimate of the sleep/wake cycle via movement. Within is a sensor, a processor and memory. The processor samples physical motion and translates it to numerical digital data. It summarizes the frequency of motions into epochs of specified time

duration and stores the summary in memory. These data are then downloaded to a computer and analyzed to generate various sleep and circadian rhythm parameters.

7-Day Sleep Diary

The sleep diary allows for the measurement of the following subjectively estimated variables: Timing of sleep, Sleep onset latency (SOL), number of awakenings (nWAKE), amount of time awake after sleep onset (WASO), total sleep time (TST), sleep relevant emotions such as sleep quality and mood. (See appendix for example of text message sleep questions) (Carney et al., 2012). After receiving the sleep diary early in the study, patients will complete one week of entries and return it soon after. Patients will complete another one at the end of treatment (Sleep Diary will be received on Week 9 with instructions to fill it out from weeks 11-12. Diary will be returned at Week 12.)

MRI Scan Procedures

Mock Scanner or MRI Simulator

Individuals offered the opportunity to undergo the MRI scan will also have the option to undergo training for the MRI scan in an MRI simulator in order to help the participant acclimate to the scanning procedure. In the simulator, SimFx and Motrack are used to simulate the MRI experience. SimFx is used to simulate the scanner sound and scanning noise. Motrack monitors how much a participant moves through a sensor attached to the participant's head.

MRI Scan

The participant will be instructed to lie in the magnet while being as still as possible for 25 minutes. All precautions and protections will be given to the participant to ensure that they are as safe and comfortable as possible. If the participant appears nervous or anxious, a trained member of the research staff will remain with them inside the scanning suite for the duration of the scan. All of the MRI procedures will be conducted on the 3-Tesla MRI scanner at the New York State Psychiatric Institute. A qualified Magnetic Resonance Technologist will conduct the procedure.

Primary and Secondary Outcome Measures

1. The primary outcome measure for our study is the CGI-I.

2. The remaining measures are secondary, including:
    - ADIS-C CSR
    - Tanner Staging
    - SCARED
    - MFQ
    - ARI
    - CHSQ
    - PDSS
    - PAERS

- Sleep/Activity Monitoring

Based on clinical need of the participant and judgment of the study doctors, participants may begin treatment either at the first combined screening/baseline visit, or several weeks after screening. Secondary measures may be completed within the first few weeks of the study. Treatment will not be delayed beyond baseline visit. Most of the subjects are going to be started one week after screening. However, one reason to have a one-week gap is to obtain a better assessment of measurements. Some participants improve through the evaluation process, so it is appropriate have this time lapse. However, those patients who have significantly impairing anxiety symptoms in addition to secondary comorbid symptoms, such as depression, may warrant earlier treatment. These early starters will not be the majority of the sample.

Treatment Visits

After considering all aspects of study participation as presented during the study entry procedures, subjects and/or families must agree in writing to "full participation" in the study. Full participation is further defined as agreement to comply with the requirements of the treatment plan and of all assessment procedures. At the beginning of the treatment phase, families will be asked to review all the requirements for each component of the study. We will reiterate the importance of compliance with the medication, the blood/saliva/urine tests and the sleep measures. We will also reiterate that all of the research is voluntary and they can withdraw participation at any point, which will not affect their receiving treatment here.

Patients will have one research physician throughout the study who, in addition to monitoring clinical status and medication effects, will offer general encouragement regarding the expected benefits from treatment. Patients will be monitored in person initially weekly then every other week for medication adjustment based on a standardized escalating dose schedule (see below). The SSRI will be administered with the goal of achieving a CGI rating of 2 or less. Participants whose CGI remains above 2 will have the dose of SSRI increased to the maximum recommended dose that they can tolerate.

The first treatment will begin at baseline and denotes Week 0 of treatment with SSRI. Except for the baseline and exit visits, all pharmacotherapy visits will last 30-45 minutes. At each visit, the research physician will inquire first about general benefits, and then about specific levels of any improvements in the participant's symptoms identified on the Goal Attainment Scale (GAS) and associated distress and dysfunction, and general functioning. Parents will have completed a Patient Medication Diary that will allow the research physician to assess medication compliance. The research physician will then inquire about side effects before initiating (at baseline visit) or adjusting (subsequent visits) medication using the following general question: “Any health or other problems this week?” Having explored the nature of these problems, including potential medication side effects, the research physician will complete an adverse event form only for those symptoms reported by the patient that met adverse event reporting criteria. On the adverse event form (PAERS form), the research physician will then indicate his/her opinion as to whether the reported adverse event was medication related, the strength of this opinion and whether and what if any changes in medication (e.g. dose, timing) were made. At the conclusion of the visit, the research physician

will emphasize that medication will likely help the patient feel better during the coming week unless the patient is already normalized in which case the expectation is for continued benefit.

Consistent with good medical practice, every effort will be made to use the most effective, best tolerated dose of SSRI. Dose increases will be delayed or doses reduced for clinically significant side effects, e.g. side effects producing both distress and dysfunction, for which the clinician and the patient/parent believe dosage reduction is indicated. The dosing schedule uses a fixed- flexible dose schedule, adjusting the dose upward according to CGI Severity score and down as a function of side effects within a fixed dosing range.

Treatment Visit Schedule

Visits are scheduled at weeks 0, 1, 2, 3, 5, 7, 9, and 12, and twice voluntarily after 6 and 12 months after the final treatment assessment visit. Additional phone contact and visits are allowed based on judgment of the study physician in response to concerns regarding side effects or possible deterioration in clinical status. 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 and I) will be administered to assess symptom severity and improvement. The following procedures will be completed at all treatment visits:

- CGI, C-SSRS
- Adverse events will be assessed via the CDU side effects form (PAERS) and through open ended inquiry.
- The study doctor's decision to either titrate to the next dose level, remain on the current dose, or to down titrate to the previous dose level for each participant will be recorded.
- Medication use and compliance will be reviewed. Participants will be provided prescriptions for their medication and instructed to bring in their medication bottle with each visit so that adherence can be evaluated and tracked.

Biomarker Collection

Biological samples will be collected at Week 0, 1, 3, 5, and 12.

- Blood will be drawn for the analysis of biomarkers and for measuring SSRI levels. **Blood will not be collected from children or adolescents (ages 8-17) on Week 1.**
- A saliva sample will be taken in a tube and urine in a cup at the same visits as the blood draws. The amount of saliva will be 2 milliliters and urine will be a minimum of 4 milliliters.

Medication Treatment

SSRI medication will be provided and distributed at no cost to all participants. All patients and their parents will be given explicit verbal and written (medication diary) instructions on when and how to take their medication. They will also be instructed to return their unused medication when they come for each clinic visit. Study medication will be dispensed only as directed by this protocol. Every effort will be made to encourage patient adherence with the dosage regimen as per protocol. Adherence will be monitored with pill counts of returned bottles during each visit, with immediate feedback provided for deviations from prescribed dosing. Specific procedures for each treatment session regarding safety, handling of adverse

events, the administration of other medications and other procedures will adhere to a pharmacotherapy manual adapted from the CAMS study (see below). Treatment providers are not blind to treatment status. The PAMRC team will review the clinical status of each child in rotation at weekly clinic meetings.

Dosing Schedule

All medication will be administered once daily, usually in the morning, in a "fixed-flexible" fashion. The dose is increased as scheduled in the event the patient remains symptomatic with minimal side effects. Specifically, to best reconcile dose-response and time-action effects, this study will follow the CAMS strategy, which used a fixed-flexible dosing schedule that is dependent on the research physician-assigned CGI-S score and the ascertainment of clinically significant side effects. Relative to normal functioning for an age, race, gender and community matched peers, the CGI-Severity (CGI-S) score will be anchored as follows: 1=normal, not at all ill, 2=borderline mentally ill, 3=mildly ill, 4=moderately ill, 5=markedly ill, 6=severely ill, 7=among the most extremely ill. Specifically, the dose of sertraline may be increased by 25 to 50 mg/day according to the following CGI-S schedule. If the CGI-S score = 1 or 2, no change in dose. If the CGI-S score = 3, the clinician has the option to leave the dose the same or increase it to the next higher dose to account for time-response considerations (the expected time to onset of benefits or resolution of side effects). If the CGI-S score is > 4, the research physician (absent limiting side effects) must increase to the next higher dose in a 25 or 50 mg/day increment, depending on the week of treatment and on the presence of dose-limiting side effects. In subjects with CGI-S=3, the dose may be increased by 25 or 50 mg/day, depending on the starting dose and side effects, to a maximum of 200 mg/day at the end of the week 6 visit. The starting dose will be 50mg. At week 7 and beyond, the dose may be reduced only for clinically significant side effects. Dose increases may be delayed or doses reduced for clinically significant side effects, e.g., side effects producing both distress and dysfunction, for which the clinician and the patient/parent believe dosage stabilization or reduction is indicated. Given no evidence for age related differences in dosing and because we allow for dose adjustment in response to clinical status and side effects, the same dosing schedule is used for younger and older subjects.

For the SSRIs Fluoxetine and Escitalopram, we will follow the dosing schedules laid out by The Texas Children's Medication Algorithm (Hughes, Emslie 2007), where a CGI-S score of > 4 reflects a clinical status of "symptomatic" or "minimally responsive", a CGI-S score = 3 reflects a "partial response", a CGI-S score = 2 reflects "response", and a CGI-S score = 1 reflects "remission".

SSRI Dosing Schedule

Week	Visit Type	Dose **(Sertraline)**	Dose **(Fluoxetine)**	Dose **(Escitalopram)**
0	Office	25 mg/day	10 mg/day	10 mg/day
1	Office	50 mg/day	20 mg/day	10 mg/day
2	Office	50 mg/day	20 mg/day	10 mg/day
3	Office	100 mg/day	20 mg/day	10 mg/day
4	Phone	100 mg/day	20 mg/day	10 mg/day
5	Office	150 mg/day	40 mg/day	20 mg/day
6	Phone	150 mg/day	40 mg/day	20 mg/day

7	Office	200 mg/day	40 mg/day	20 mg/day
8	Phone	200 mg/day	40 mg/day	20 mg/day
9	Office	200 mg/day	40 mg/day	20 mg/day
10	Phone	200 mg/day	40 mg/day	20 mg/day
11	Phone	200 mg/day	40 mg/day	20 mg/day
12	Office	200 mg/day	40 mg/day	20 mg/day

Follow-up Phase

The voluntary follow-up takes place 6 and 12 months after the final treatment visit (Week 12). All participants will be asked to return to the CDU for safety assessments and completion of the same behavioral tasks. The Follow-up Period consists of 2 study visits. We are also requesting permission to re-contact patients if they might be eligible for future studies.

Final Assessments (Week 12)

Procedures to be performed at final visit (Week 12):

- If applicable, urine pregnancy test
- Urine drug and alcohol screen
- Blood/saliva/urine draw
- Weight and height
- Vital signs
- Tanner self-report scale (if applicable), C-SSRS, Pediatric Sleepiness Scale (PDSS), Clinical Global Impressions (CGI), ADIS-C CSR, Screen for Child Anxiety Related Disorders (SCARED), Child Sleep Habits Questionnaire, Affective Reactivity Index (ARI), Mood and Feelings Questionnaire Long Version (MFQ)
- Assessment for new AEs or SAEs and changes in concomitant medications
- Study drug will be dispensed and a referral will be given to the anxiety group participants. 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. For participants requiring continued medication management following this three-month follow-up treatment period, the research staff will assist the participant and his/her family in identifying a psychiatrist. Participants will also be given referrals for therapy if desired by one of the CDU social workers who will work with each family who desires a referral to find a therapist convenient to their home and if possible, within their insurance network.

Procedures for Healthy Controls

30 participants will be included in the control group and will be matched to the anxiety group on age and gender. Participants who are identified as controls will be required to visit the PAMRC for 5 study visits and 2 additional follow-up visits. The same procedures will be followed as in the anxiety group, with the exception of treatment visits and treatment administration. The visits will be as follows:

1. Week -1 will be the same Screening visit with pregnancy test included (consent/assent before any other procedures administered).
2. 7 days of Sleep/Activity Monitoring will occur at the beginning and the end of the assessment where participants will wear the actigraphy watch and complete the sleep and mood diary.
3. Week 0 will be the same Baseline visit with behavioral tasks and first blood draw/saliva/urine. At the doctors' discretion, participants will be offered the opportunity to undergo **one or two** optional MRI scan. If the participant (and their parents if they are a minor) agree, they will then be assessed for MRI eligibility using the MRI Screening Questionnaire. Participants will be offered the option of training in the MRI simulator before initiating the scan. Post-menarchal females will be given an additional pregnancy test prior to the scan and a negative result will be required to undergo the scan.
4. Study visit at Week 1, 3, and 5 to obtain a blood/saliva/urine sample **(minors will provide urine and saliva only on Week 1).**
5. Study visit at Week 12 for final assessment to obtain another blood/saliva/urine sample and return the actiwatch and sleep and mood diary.
6. Voluntary study visits at the 6 and 12 month follow-up to assess sleep and complete the behavioral tasks.

Adverse Events (AE)

Adverse Event Monitering
The Children's Day Unit adverse monitoring form will be utilized via interview by the study doctor during each visit as a prompt to inquire about the occurrence of the most common side effects of psychiatric drugs. Any symptoms/conditions reported by the participant through the use of the interview or any other method will be assessed to determine if the reported experience qualifies as an AE if it leads to functional impairment.

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.

You can upload charts or diagrams if any

Blood and other Biological Samples

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

Children and Adolescents (Ages 8-17)

Specimen	Total # Collections	Sample Volume	Total Volume Collected
Whole Blood for DNA	1	4 ml	4 ml
Plasma (incl. SSRI levels)	4	14 ml	28 ml

Total per draw: 14-18 ml **Study total:** 60 ml

Young Adults (Age 18-25)

Specimen	Total # Collections	Sample Volume	Total Volume Collected
Serum	5	10 ml	50 ml
Whole Blood for DNA	5	4 ml	20 ml
Plasma (incl. SSRI levels)	5	14 ml	70 ml

Total per draw: 28 ml **Study total:** 140 ml

Blood

We will draw blood from participants as part of biomarker collection, as well as to measure SSRI levels in the treatment group. **The amount and timing of the blood draws will differ between minor and adult participants.** Within each age group, the amount of blood drawn will be the same for the treatment and control groups. Blood collection will not occur more frequently than 2 times per week for either of the groups.

- **Children and Adolescents: Participants age 8-17 will provide blood samples at Weeks 0, 3, 5, and 12. At week 0, we will draw approximately 1.5 tablespoons (18 ml) of blood. At weeks 3, 5, and 12 (or withdrawal, if earlier), we will draw approximately 1 tablespoon (14 ml) of blood.**
- **Young Adults: A blood sample, approximately two tablespoons (28 ml) of blood, will be taken at Weeks 0, 1, 3, 5, and 12 (or withdrawal, if earlier) for a total of 140 ml. These samples will be used to measure SSRI levels and biomarkers of treatment response.**

Urine and Saliva

At weeks 0, 1, 3, 5, and 12, participants will provide a saliva sample and a urine sample. The amount of saliva collected will be 2 milliliters and urine will be 4 milliliters minimum.

Assessment Instruments

Create a table or give a brief description of the instruments that will be used for assessment

Anxiety Disorders Interview Schedule for Children (ADIS-C): The ADIS-C is a diagnostic interview of both the participant and parent/legal guardian designed to establish the presence of SAD, GAD, or SOP, based on a Composite Clinical Severity Rating of e4. The interview also establishes whether any exclusion diagnoses are present (i.e. bipolar disorder, psychosis, a pervasive development disorder other than Asperger's Syndrome, an eating disorder, or substance abuse disorder), in which case the participant is not eligible for entry into the study.

Anxiety Disorders Interview Schedule for DSM-IV Child Version-Clinician Severity Rating Scale (ADIS-C CSR): The ADIS-C CSR is an index of symptom severity and disability of GAD, SAD, and SoP symptoms. It is administered by an independent evaluator through interviewing the participant and the parent or guardian. Following the establishment of a Baseline ADIS-C CSR, this assessment represents the level of severity and disability at the point in time the assessment interview is conducted.

Clinical Global Impressions (CGI-S, CGI-I) (5 minutes): CGI-I/S is a clinical rating based upon the complete clinical presentation and will be used as an efficacy measure and permits a global evaluation of the participant's severity over time.

Tanner Staging Form: a quick, commonly used self-report measure of pubertal development. The Tanner Staging Scale is a self-report form on which youth indicate which of a series of illustrations of pubertal development most closely represents their own body.

Self Report for Childhood Anxiety Related Disorders (SCARED): The SCARED assessment is a parent and participant completed tool used to measure symptoms of anxiety, including the most common symptoms of GAD, SAD, and SoP.

Mood and Feelings Questionnaire Long Form (MFQ): The MFQ is a 33-item self-report questionnaire that assesses 17 symptom areas related to depression, including those that serve as criteria in the DSM-IV. It provides an overall index of severity of depression.

Affective Reactivity Index (ARI): is a 6-item clinician-administered questionnaire with good inter-rater reliability and validity that provides an overall index of severity of irritability.

Childhood Sleep Habits Questionnaire (CSHQ): The CSHQ was designed by clinical researchers at Brown University for children to screen for the most common sleep problems in children. The CSHQ is not intended to be used to diagnose specific sleep disorders, but rather to identify sleep problems and the possible need for further evaluation. A higher score is indicative of more sleep problems. The responses are scored on a 3-point scale: Usually, Sometimes, Rarely and can indicate if this behavior is a problem.

Columbia Suicide Severity Rating Scale (CSSRS): The C-SSRS is a semi-structured interview that captures the occurrence, severity, and frequency of suicide-related thoughts and behaviors during the assessment period. The interview includes definitions and suggested questions to solicit the type of information needed to determine if a suicide-related thought or behavior has occurred.

Pediatric Daytime Sleepiness Scale (PDSS): The PDSS is used to assess daytime sleepiness in participants prior to and during the treatment period. The PDSS is a self-report scale suitable for middle-school-age children that was designed to be easy to administer, to score and to interpret. All 8 questions were developed based on behavior frequently engaged in by this age group, and sleepiness-related questions were based on previous research regarding situations that may be sensitive to sleep loss (eg, falling asleep during class). The questions are scored from 0-4 (never = 0; seldom = 1; sometimes = 2; frequently = 3; always = 4), based on Likert-scale ratings. In order to reduce the possibility of response bias, response to item number 3 are reverse scored. The total PDSS scores range from 0-32.
Children's Global Assessment Scale (CGAS): The CGAS is a clinician-rated scale that assesses overall functioning and impairment in all aspects of the child's life. It has been found to be a reliable instrument for assessing impairment in children with psychiatric disorders. Scores range from 1-100, with scores over 70 indicating normal adjustment, and scores below 50 indicating moderate to severe impairment.

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.

Self-Report Questionnaires in Valant Patient Portal: The Valant patient portal provides the option for clinicians to assign patients self-report questionnaires from a list of non-proprietary, peer-reviewed psychiatric measures. Based on clinical need, the study doctor may decide to assign a patient one or more additional questionnaires to complete through the Valant patient portal, so that their specific symptoms can be better tracked, and their unique needs be better addressed.

Please attach copies, unless standard instruments are used

Research Related Delay to Treatment

Will research procedures result in a delay to treatment?
Yes
Maximum duration of delay to any treatment
Medication monotherapy is an acceptable treatment approach for pediatric anxiety. However, during the study participants cannot receive evidence-based psychotherapy targeting their anxiety symptoms. Participants will be made aware of other options during the consent procedures. For all enrolled participants, the maximum delay in initiating augmentation treatment will be 13 weeks. All participants will be advised of their alternatives to participation (e.g., seeking alternative augmentation treatments such as the addition of cognitive-behavioral therapy) before consenting to participate.
Maximum duration of delay to standard care or treatment of known efficacy
For actively enrolled participants, the maximum delay in beginning a treatment of known efficacy is 13 weeks. Participants 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. For participants requiring continued medication management following this three-month follow-up treatment period, the research staff will assist the participant and his/her family in identifying a psychiatrist.

Risks/Discomforts/Inconveniences

Risks that could be encountered during the study period

In clinical trials of sertraline and other SSRIs, the following side effects are considered to be related to the study drug: gastrointestinal complaints (nausea, pain, diarrhea, and constipation), dizziness, allergic reactions, increased anxiety or irritability, increased activation/restlessness, sleep changes (increased or decreased), sexual side effects, appetite changes (increase or decreased), unusual thoughts, sweating, fatigue, suicidal ideation/attempts/and or behaviors.

In addition to these issues, the participants and their families (for participants ages 8-17) will be made aware of the Food and Drug Administration advisory that the use of antidepressants like the SSRIs may lead to suicidal thinking/attempts in depressed youths and that the FDA has placed product warning label with information highlighting the need for close observation for worsening of depression and the emergence of suicidality in children and young adults treated with these medications. This information will be a part of the consent process for the study so that families are aware of these issues when considering participation in the study.

There are other risks associated with the study drug and participation in the study. Some of these risks are not known at this time. Other risks in the study include:

Worsening and Non-improvement Risk: There is a chance that the study drug may not help the participant's symptoms or that his or her symptoms might worsen.

Allergy Risk: The participant could experience an allergic reaction with the use of SSRI. Allergic reactions are serious and could be life threatening if not treated promptly.

Blood Draw Risks: The participant may have pain, bleeding, swelling, or bruising around the vein where his or her blood is collected. There may be a risk of infection from any blood draw. The participant may feel dizzy or may feel faint.

Magnetic Resonance Imaging: Both the FDA and the NYSPI IRB have deemed MRI Scanning on the GE 3 Tesla MRI Scanner at the New York State Psychiatric Institute to be classified as a non- significant risk.

Urine Saliva Risks: There are no known risks to providing a saliva or urine sample.

Pregnancy and Breastfeeding: It is not known whether the study drugs affect pregnant women, unborn children or children of nursing women. Because of these unknown risks, the participant may not enter the study if she is pregnant, breastfeeding, or trying to become pregnant. A pregnancy test will be done before the participant enrolls in the study. During the study, the participant should not become pregnant, and she should not nurse a baby.

Testing: The thinking tasks and questionnaires in this experiment are explicitly designed to induce emotion. We are doing this to learn about the relationship between anxiety emotion and behavior and the physiology that underlies emotion in CAAYA. Although we expect the emotions invoked will be mild and short-lived, there is a small chance that a participant could become significantly distressed. Were this to occur, we would immediately end the session and take every step to help soothe the participant, and direct they or their family (for participants ages 8-17) to appropriate services, if necessary.

Abrupt Discontinuation and Withdrawal Risk: SSRI discontinuation syndrome, refers to a unique set of symptoms that can develop after people stop taking an SSRI. It most often occurs in those who abruptly quit the medication. About one in five people who take an SSRI for six or more weeks will experience withdrawal symptoms if they suddenly stop taking the medicine. Tapering down the medication slowly usually helps to avoid the following potential symptoms: Anxiety, irritability, depression and mood swings, light-headedness, dizziness and balance problems, electric shock sensations, fatigue, flu-like symptoms, headache, loss of coordination, muscle spasms, nausea, nightmares, tremors, trouble sleeping, vomiting. SSRIs haven't been described to have acute withdrawal risks and the medication could be stopped abruptly, however, where withdrawal is experienced the mediation will be tapered off gradually in collaboration with the study physician.

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. For further specific measures of minimizing risk please refer to the pharmacotherapy manual, pages 12-24.

There is no benefit to completing the cognitive or sleep tasks apart from closer monitoring of the participant's wellbeing. Although we expect the emotions invoked will be mild and short-lived, there is a small chance that a participant could become significantly distressed. Were this to occur, we would immediately end the session and take every step to help soothe the participant, and direct them and/or their family to appropriate services, if necessary.

Methods to Protect Confidentiality

Describe methods to protect confidentiality

The study doctor and research team will collect, retain, and use personal health information about the participant to conduct the study. This may include the participant's initials, date of birth, medical history,

and information from study visits. The participant's name and other personal identifying information will also be stored in an electronically secure database at New York Psychiatric Institute. Information about the results of the study procedures will also be collected. To protect the participant's identity, the study staff will assign a unique, confidential code number to each participant. This number helps the study staff identify each participant's research records for this study. **In addition, participants may have information transmitted and/or stored through the Valant online portal system. We are contracted to work with Valant through a Business Associates Agreement under which Valant has agreed to abide by all HIPAA requirements for Business Associates, including the Security Rule and the implementation of appropriate safeguards with respect to PHI. The use of this system has been approved for use in our study by Amy Bennett-Staub.**

We will take all reasonable steps to make sure that the personal information in each participant's medical record is kept confidential. However, we cannot guarantee total privacy. A participant's personal information may be shared with others if required by applicable law or regulation. In addition, study information collected about the participant and his or her medical record (which may include his or her name) may be directly accessed and copied by the following people:
* Government health and regulatory agencies
* Independent ethics committees

To the extent allowed by law and regulation, all information that is collected about the participant and leaves the clinic will have his or her name, address, contact details, and any other information that could identify him or her removed so that he or she cannot be recognized by it.

The participant may cancel his or her permission for the researchers to collect or use his or her personal health information. This can be done at any time by writing to the study doctor. If the participant cancels his or her permission, he or she will not be able to stay in the study. The study staff will stop collecting medical information about the participant. They will continue to use the information already collected in order to maintain the reliability of the study's results and to satisfy legal and regulatory requirements.

Regulations may allow the participant to have access to his or her study-related personal health information. The participant has the right to ask his or her study doctor for updated information on what data the study doctor has recorded for him or her and the participant can request corrections of any errors in the recorded data. However, the participant will not have access to his or her study-related personal health information until the study is complete.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify any participants. At most, the Web site will include a summary of the results. All participants can search this website at any time.
Will the study be conducted under a certificate of confidentiality?
No

Direct Benefits to Subjects

Direct Benefits to Subjects

All participants will receive a thorough evaluation of psychiatric symptoms and history provided by the PAMRC. If a participant is not eligible for the study, referrals will be made for the subject.

There may be a direct benefit to the patient if the study drug works as it is intended. The participant's anxiety may improve. However, if the study treatment does not work, he or she may not benefit. Moreover, for the control participants, they may not find any direct benefit. The results of this study may provide information that could help improve available treatment in the future and potentially lead to preventative interventions for anxiety in CAAYA. In this study the control group will benefit by having an assessment in the CDU and gaining information about their sleep and activity patterns.

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 in the anxiety group will be paid a $10 gift certificate per study visit in which they have to give a blood sample (up to $50 or $70 if they also complete the follow-up visits). They will be provided the study drug and psychiatric services at no cost.

Participants in the control group will be paid a $20 gift certificate per study visit (up to $100).
Control young adults or control parents (for participants ages 8-17) will be paid $10 (gift card for young adults, cash for parents) for the initial assessment visit. Controls and parents are being paid more to give them incentive to participate in the study. The anxiety group will already have the incentive of receiving treatment at no cost.

All participants that are offered and complete the MRI scan will receive a $40 gift certificate. **Controls who complete two MRI scans will receive an additional $40 certificate for the second scan.**

All participants will be given a bonus of $10 for wearing the actiwatch both during the screening period and exit (Week 11-12) period.

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Uploads

Upload the entire grant application(s)
Upload copy(ies) of unbolded Consent Form(s)
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Upload copy(ies) of unbolded Assent Form(s)
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HIPAA Child 4-2015-3.pdf
Upload any additional documents that may be related to this study

New York State Psychiatric Institute (NYSPI)
Authorization to Use or Disclose Health Information during a Research Study

Protocol Number: 6884 **Principal Investigator:** Amir Levine, M.D.

Name of Study: Treatment of Pediatric Anxiety Disorders by Predicting Treatment Response Through Biocellular Markers and Sleep

Before researchers can use or share any identifiable health information ("Health Information") about you as part of the above study (the "Research"), the New York State Psychiatric Institute (NYSPI) is required to obtain your authorization. You agree to allow the following individuals and entities to use and disclose Health Information about you as described below:

- New York State Psychiatric Institute (NYSPI), your doctors and other health care providers, if any, and
- The Principal Investigator and his/her staff (together "Researchers"). Researchers may include staff of NYSPI, the New York State Office of Mental Health (OMH), Research Foundation for Mental Hygiene, Inc. (RFMH), and Columbia University (CU), provided such staff is a part of the study, and
- Providers of services for the Research at CU, NYSPI and/or RFMH, such as MRI or PET, or Central Reference Laboratories (NKI), if indicated in the consent form**.**

1. The Health Information that may be used and/or disclosed for this Research includes:

☑ All information collected during the Research as told to you in the Informed Consent Form.
☑ Health Information in your clinical research record which includes the results of physical exams, medical and psychiatric history, laboratory or diagnostic tests, or Health Information relating to a particular condition that is related to the Research.
☐ Additional information may include:

2. **The Health Information listed above may be disclosed to:**

☐ Researchers and their staff at the following organizations involved with this Research:

☐ The Sponsor of the Research,

and its agents and contractors (together, "Sponsor"); and
☑ Representatives of regulatory and government agencies, institutional review boards, representatives of the Researchers and their institutions to the level needed to carry out their responsibilities related to the conduct of the research.
☐ Private laboratories and other persons and organizations that analyze your health information in connection with this study

☐ Other (family members or significant others, study buddies, outside agencies etc.) Specify:

3. By giving permission to release your Health Information as described above, you understand that your Health Information may be disclosed to individuals or entities which are not required to comply with the federal and state privacy laws which govern the use and disclosure of personal Health Information by NYSPI. This means that once your Health

Information has been disclosed to a third party which does not have to follow these laws (e.g., a drug company or the Sponsor of the Research), it may no longer be protected under the HIPAA or NYS Mental Hygiene Law requirements but is subject to the terms of the consent form and may be subject to other state or federal privacy laws or regulations.

4. Please note that:

- You do not have to sign this Authorization form, but if you do not, you may not be able to participate in the study or receive study related care. You may change your mind at any time and for any reason. If you do so, you may no longer be allowed to participate in the study. If you withdraw this Authorization the research staff and the Sponsor, if this is sponsored research, may still use or disclose Health Information containing identifying information they already have collected about you as needed to maintain the reliability of the research. Any request to withdraw this Authorization must be made in writing to (enter name and contact information below):
  Amir Levine, M.D.
  1051 Riverside Drive, Unit #78. New York, N.Y. 10032
- While the Research is going on, you may not be allowed to review the Health Information in your clinical research record that has been created or collected by NYSPI. When this research has been completed you may be allowed to see this information. If it is needed for your care, your Health Information will be given to you or your Doctor.

5. This Authorization does not have an end date.

6. You will be given a copy of this form after you have signed it.

I agree to the use and disclosure of Health Information about me as described above:

_____ _____

Signature of Participant/ Legal Representative Date

_____

Printed Name of Participant

_____

Relationship of Legal Representative to Participant (if applicable)

We also ask you or your legal representative to initial the statements below:

☐ **I have received a copy of the NYSPI/OMH Notice of Privacy Practices.**

New York State Psychiatric Institute (NYSPI)
Authorization to Use or Disclose Health Information during a Research Study
(Child Version)

Protocol Number: 6884 **Principal Investigator:** Amir Levine, M.D.

Name of Study: Treatment of Pediatric Anxiety Disorders by Predicting Treatment Response Through Biocellular Markers and Sleep

Before researchers can use or share any identifiable health information ("Health Information") about your child as part of the above study (the "Research"), the New York State Psychiatric Institute (NYSPI) is required to obtain your authorization. You agree to allow the following individuals and entities to use and disclose Health Information about your child as described below:

- New York State Psychiatric Institute (NYSPI), your child's doctors and other health care providers, if any, and
- The Principal Investigator and his/her staff (together "Researchers"). Researchers may include staff of NYSPI, the New York State Office of Mental Health (OMH), Research Foundation for Mental Hygiene, Inc. (RFMH), and Columbia University (CU), provided such staff is a part of the study, and
- Providers of services for the Research at CU, NYSPI and/or RFMH, such as MRI or PET, or Central Reference Laboratories (NKI), if indicated in the consent form.

1. The Health Information that may be used and disclosed for this Research includes:

☑ All information collected during the Research as told to you in the Informed Consent Form.
☑ Health Information in your child's clinical research record which includes the results of physical exams, medical and psychiatric history, laboratory or diagnostic tests, or Health Information relating to a particular condition that is related to the Research.
☐ Additional information may include:

2. **The Health Information listed above may be used and disclosed to:**

☐ Researchers and their staff at the following organizations involved with this Research:

☐ The Sponsor of the Research,

and its agents and contractors (together, "Sponsor"); and
☑ Representatives of regulatory and government agencies, institutional review boards, representatives of the Researchers and their institutions to the level needed to carry out their responsibilities related to the conduct of the research.
☐ Private laboratories and other persons and organizations that analyze your child's health information in connection with this study

☐ Other (family members or significant others, study buddies, outside agencies etc.) Specify:

3. By giving permission to release your child's Health Information as described above, you understand that your child's Health Information may be disclosed to individuals or entities which are not required to comply with the federal and state privacy laws which govern the use and disclosure of personal Health Information by NYSPI. This means that once your child's Health

Information has been disclosed to a third party which does not have to follow these laws (e.g., a drug company or the Sponsor of the Research), it may no longer be protected under the HIPAA or NYS Mental Hygiene Law requirements but is subject to the terms of the consent form and may be subject to other state or federal privacy laws or regulations.

4. Please note that:

- You do not have to sign this Authorization form, but if you do not, your child may not be able to participate in the study or receive study related care. You may change your mind at any time and for any reason. If you do so, your child may no longer be allowed to participate in the study. If you withdraw this Authorization the research staff and the Sponsor, if this is sponsored research, may still use or disclose Health Information containing identifying information they already have collected about your child as needed to maintain the reliability of the research. Any request to withdraw this Authorization must be made in writing to (enter name and contact information below):
  Amir Levine, M.D.
  1051 Riverside Drive, Unit #78. New York, N.Y. 10032

- While the Research is going on, you may not be allowed to review the Health Information in your child's clinical research record that has been created or collected by NYSPI. When this research has been completed you may be allowed to see this information. If it is needed for your child's care, your child's Health Information will be given to you or your child's Doctor.

5. This Authorization does not have an end date.

6. You will be given a copy of this form after you have signed it.

I agree to the use and disclosure of Health Information about me as described above:

_____ _____

Signature of Parent/ Legal Representative Date

_____

Printed Name of Parent/Legal Representative

_____

Name of child

We also ask you or your legal representative to initial the statements below:

☐ **I have received a copy of the NYSPI/OMH Notice of Privacy Practices.**