NCT01850355

Study Protocol: An open-label trial of buspirone for the treatment of anxiety in youth with autism spectrum disorders

Gagan Joshi, MD
Massachusetts General Hospital
Clinical and Research Program in Pediatric Psychopharmacology

1. BACKGROUND AND SIGNIFICANCE

INTRODUCTION

Pervasive developmental disorders (PDD) are lifelong neurodevelopmental disorders characterized by core features of impaired communication, socialization, and behavioral problems [1]. The term PDD encompasses autistic disorder, Asperger's disorder and PDD-NOS – together also referred to as autism spectrum disorders (ASD). An increasingly higher prevalence of ASD is documented in each successive epidemiological survey, and ASD is now estimated to affect more than 1% of youth [2].

In addition to the core features of impaired communication, social deficits, and repetitive behaviors, youth with ASD manifest comorbid symptoms of anxiety and mood dysregulation that contribute to the morbidity and impairment associated with ASD [3-6]. In fact, anxiety-related difficulties are so frequently exhibited in children with ASD that the DSM-IV highlights anxiety-like responses as a common, ''associated feature'' of autism [7].

Anxiety is a very common concern in children and adolescents with ASD, with recent studies suggesting that nearly half of children with ASD meet criteria for an anxiety disorder [8-9], especially social phobia, generalized anxiety disorder, separation anxiety, and obsessive-compulsive disorder [10].

In a study of our clinically referred population of youth with ASD, we observed high rates of psychiatric comorbidities [11]. Multiple anxiety disorders (≥2) were present in more than half (61%) of the youth with ASD. Among the anxiety disorders, separation anxiety disorder, generalized anxiety disorder, and agoraphobia were concurrently present in more than a third of the youth with ASD (37%, 35% and 35%, respectively) and social phobia in more than a quarter of subjects (28%).

The high rate of comorbidity with anxiety disorders in our youth with ASD is consistent with several previous uncontrolled studies that reported equally high prevalence rates of anxiety disorder(s) in referred populations of youth with ASD (43–84%) [8,12-14]. Our findings also concur with previous studies reporting high prevalence rates of various specific anxiety disorders [13-16] and higher levels of anxiety symptom severity in samples of referred populations with ASD [17-18].

Underscoring the importance of targeting anxiety symptoms in these youth, children with ASD have been found to present with higher rates of anxiety symptoms, including social anxiety, than either typically developing children or children with other types of impairments (e.g., specific language impairments) [19].

Child anxiety has been associated with numerous impairments in social and academic functioning, including poorer self-image, lower rates of peer acceptance, and poorer performance on academic achievement tests [20]. If left untreated in childhood, anxiety disorders have been shown to persist through adolescence and adulthood and can become more severely impairing [21-23]. Moreover, child anxiety predicts the development of later psychiatric comorbidities, including major depression [24],

substance use disorders [25], and disruptive behavior disorders [26]. The present impairment and risk of future psychopathology and psychosocial dysfunction posed by these disorders highlights the importance of finding effective interventions for childhood anxiety.

The presence of anxiety symptoms in youth with ASD may be especially impairing to their functioning. Such symptoms are associated higher levels of repetitive behaviors and poorer social reciprocity in youth with ASD [14]. Anxieties and fears are also associated with behavioral problems in youth with ASD at rates higher than those found in children with similar mental and chronological ages [19]. Children with ASD may also be especially vulnerable to the negative impact of anxiety symptoms, as associated avoidance behaviors may further compromise social interactions and limit opportunities for the development of appropriate social behaviors and peer relationships. Given the high prevalence of anxiety symptoms in children with ASD and the potential for very poor outcomes in children who experience these comorbid symptoms, it is important to develop effective interventions for these youth.

Anxiety disorders are common in typically developing children and adolescents, with prevalence rates varying from 6 to 20% [27]. Substantial evidence supports the use of selective serotonin reuptake inhibitors (SSRIs) in the treatment of pediatric anxiety disorders. SSRIs have emerged as the medications of choice for pediatric anxiety disorders based on several controlled trials in youth with moderate to severe anxiety symptoms [28-30]. Furthermore, compared to its antidepressant and anti-OCD effects, the anti-anxiety efficacy of SSRIs appears greatest in pediatric populations [31].

Compared to typically developing populations, youth with ASD exhibit a less robust response to psychotropic medications, with higher rates of adverse effects to both medication and placebo. Such research suggests individuals with ASD may have an atypical response to psychotropic medications and higher susceptibility to adverse effects [32-35].

There is increasing empirical support for the use of SSRIs in children with ASD, although there also remains a great need for controlled trials of these medications. Limited case series and open-label studies have suggested that while SSRIs are effective in reducing symptoms of anxiety in youth with ASD, they are less well tolerated by youth with ASD. Sertraline is the only SSRI that has been evaluated by an open-label trial and found to be effective for the treatment of transition-related anxiety in children with autistic disorder [36]. In this trial, Steingard et al. investigated the use of open-label sertraline in 9 children with ASD and found that 89% had a positive response in their mood and anxiety. Though sertraline was well tolerated at lower doses (<50 mg/day), it was associated with behavioral worsening at higher doses. Similarly, in two case series, citalopram was found to be effective in treating anxiety but was associated with treatment limiting adverse events in nearly a quarter of the youth with ASD [37-38].

Buspirone is a serotonin (5-HT) receptor type 1A agonist that is widely used as an anxiolytic in adults and to treat generalized anxiety disorder in children. Buspirone has also been reported to be effective in treating ADHD features in typically developing individuals with ADHD [39,40].

Buspirone appears to be of particular interest for the ASD population because of its benign adverse effect profile, including the absence of significant sedative properties and complicated interactions with other psychotropic agents. In addition, the serotonin agonist activity of the drug may be useful in the treatment of ASD as serotonin deregulation is implicated in the etiology of ASD [41-42].

Limited trials suggest that buspirone is effective in decreasing anxiety and irritability/aggression in ASD individuals [43]. More importantly, these limited trials suggest that buspirone is well tolerated by the ASD participants.

Rationale

Functionally impairing anxiety is highly prevalent in individuals with ASD. Therapeutic options for alleviating anxiety in this population are, at best, limited. Buspirone, with its known anxiolytic effect in adults and children, its suggested anxiolytic effect in individuals with ASD and anxiety, and its benign adverse effect profile, holds promise for the treatment of anxiety in youth with ASD. Buspirone could also be effective in treating emotional dysregulation (irritability/aggression) and inattention/hyperactivity, which often coexist with ASD. Moreover, as a serotonergic agent, buspirone may be effective in improving core features of ASD.

Primary Hypothesis

Our central hypothesis is that buspirone therapy will be safe, well tolerated, and efficacious in the treatment of anxiety in youth with ASD.

Secondary Hypothesis

Buspirone will be effective in treating core features of ASD and associated features of mood dysregulation (irritability/aggression) and ADHD in youth with ASD.

2. SPECIFIC AIMS

The main objective of this open-label 8-week pilot study is to evaluate the safety and efficacy of buspirone for the treatment of anxiety in youth (ages 6-17 years) with autism spectrum disorders. The study results will be used to generate hypotheses for a larger randomized-controlled trial with explicit hypotheses and sufficient statistical power.

3. LENGTH OF STUDY

The study will last up to 11 weeks (it could take up to three weeks to schedule and complete the initial screening process). Once subjects have completed the screening process, they will begin the 8-week open-label phase. Subjects will be assessed on measures of efficacy and safety every week for the first 4 weeks (at weeks 1, 2, 3, and 4) and thereafter biweekly until the end of the study (at weeks 6 and 8).

4. SOURCE OF SUBJECTS

We plan to enroll 15 youth in order to achieve the goal of exposing 10 subjects to the study medication. We will recruit subjects both internally and externally. Participants will be recruited from the pool of existing patients and new referrals to the Pediatric Psychopharmacology Program and the Alan and Lorraine Bressler Clinical and Research Program for Autism Spectrum Disorders at the MGH, as well as from the Child and Adolescent Psychiatry Department at MGH.

The Bressler clinic is a specialized ambulatory care program, devoted to the assessment and treatment of youth and adults with ASD. The patient population served by the MGH derives from Boston and its suburbs. Approximately 50% of referrals have never been diagnosed or treated. The 3,000 youth that use this clinic make approximately 9,000 visits each year.

If a potential subject's clinician ascertains that the patient has an interest in study participation, the clinician will offer contact information for the study to the patient and/or their parent/guardian. The patient and/or their parent/guardian can then contact the study coordinator for more information on the study. If the patient's physician is a

member of study staff, the patient and his/her family will also be offered the opportunity to speak with another study physician who is not their treating clinician to review study details and consider participation. Clinical records are not scanned in order to recruit subjects.

Subjects may also be recruited from our department's screening protocol entitled, "A General Screening Protocol for Child and Adolescent Research Studies in the Pediatric Psychopharmacology Program", (#2014-P-001103). After participating in the general screening protocol, subjects may be identified as potentially eligible for this study and will be contacted via telephone by our study staff within 7 business days to assess their interest and to complete a specific phone screen for this study. When a member of our study staff telephones the potential subject they will use the already IRB-approved Buspar OL Telephone script. 5 attempts will be made to reach the potential subject before they will be considered uninterested and will not be contacted again by our program regarding this study. Participants, and their parent, who meet eligibility criteria will then be brought in to meet with a study clinician who will explain the study in detail and complete the informed consent process.

Additionally, subjects who have completed other protocols through our program may be eligible to participate in this study, as described in the Study Design section. These subjects will only be recruited if they have agreed to be contacted for future studies and will be contacted via telephone by a research assistant during the duration of our recruitment period. 5 attempts will be made to reach the potential subject before they will be considered uninterested and will not be contacted again by our program regarding this study. We also plan to recruit through advertising in local and regional media via print ads, Internet ads, and advertising posters. Clinical records are not scanned in order to recruit subjects.

5. SUBJECT ENROLLMENT

Informed consent will be obtained prior to the performance of any protocol procedures and prior to subjects receiving the study drug. The informed consent and assent documents will be used to explain in simple terms the risks and benefits of study participation to the subject and/or their parent/guardian. The nature of the study will be fully explained to the subject and/or their parent/guardian by a board-certified physician who is either the primary investigator or co-investigator. The subject and/or their parent/guardian will be encouraged to ask questions pertaining to their participation in the study and the subject and/or their parent/guardian may take as much time as they feel necessary to consider their participation in the study as well as consult with family members or their physician. Participation in this study is voluntary and the subjects and/or their parent/guardian may withdraw from the study at any time. The IRB-approved informed consent documents will be signed and dated by the subject and the physician obtaining consent.

6. SUBJECT SELECTION CRITERIA

Inclusion Criteria

- Male or female participants between 6 and 17 years of age
- Fulfills diagnosis of autism spectrum disorders by meeting DSM-IV-TR PDD diagnostic criteria of autistic disorder, Asperger's disorder, or PDD-NOS as established by clinical diagnostic interview
- Participants with a score of ≥13 on the Pediatric Anxiety Rating Scale (PARS)

- Participants with a score of ≥60 or more on the Anxiety/Depression subscale of CBCL and CGI-Anxiety severity of ≥ 4
- Subjects can be taking psychotropic medications if they have been on the medication for at least 4 weeks prior to initiating study treatment and if they are on a stable dose, provided the medication is not listed in the Concomitant Medications section of the protocol.
- Subjects with disruptive behavior disorders, mood, or psychosis will be allowed to participate in the study provided they do not meet any exclusionary criteria

Exclusion Criteria

- I.Q. < 70
- DSM-IV-TR PDD diagnoses of Rett's disorder, and childhood disintegrative disorder
- History of active seizure disorder (EEG suggestive of seizure activity and/or history of seizure in last 1 month)
- Subjects with a medical condition or treatment that will either jeopardize subject safety or affect the scientific merit of the study, including:
  - Pregnant or nursing females
  - Organic brain disorders
  - Uncorrected hypothyroidism or hyperthyroidism
  - Clinically significant abnormalities on ECG (e.g., QT prolongation, arrhythmia)
  - History of renal or hepatic impairment.
- Clinically unstable psychiatric conditions or judged to be at serious suicidal risk
- Current diagnosis of schizophrenia or bipolar disorder
- History of substance use (except nicotine or caffeine) within past 3 months or urine drug screen positive for substances of abuse
- Current treatment with medication with primary central nervous system activity (as specified in the Concomitant Medication section of the protocol)
- A non-responder or history of intolerance to buspirone, after treatment at an adequate dose and duration as determined by the clinician
- Subjects currently taking monoamine oxidase inhibitors (MAOI) and/or CYP3A4 inducers or inhibitors including nefazodone, diltiazem, verapamil, erythromaycin, itraconazole, or rifampin.

7. DESIGN

This proposal seeks to complete an 8-week open-label trial to study the efficacy, tolerability, and safety of buspirone for the treatment of the features of anxiety in youth with ASD. In this study, we propose to examine ASD youth ages 6-17 years with significant anxiety features.

Outcome measures

Primary outcome measures: Efficacy will be assessed by reduction in anxiety symptom severity as measured by change from baseline on the PARS and CGI-Anxiety-Improvement scores. Responders are defined as ≥ 30% reduction on the PARS and a score ≤ 2 on the improvement subscale of CGI-Anxiety, i.e., "much" or "very much improved."

Secondary outcome measures will assess the impact of buspirone therapy on the following parameters:

I. Safety and tolerability assessed by monitoring:

1. For treatment-emergent adverse events
2. Vital signs (blood pressure, height and weight)

3. Electrocardiogram (ECG)
4. Hematological parameters
5. For the emergence or worsening of:
    a. Anxiety symptoms assessed by PARS and CGI-Anxiety
    b. Depressive symptoms assessed by CDRS-R and CGI-Depression
    c. Irritability/mania symptoms assessed by YMRS and CGI-Mania
    d. Inattention/hyperactivity symptoms assessed by CGI-ADHD
    e. Repetitive/ritualistic behaviors assessed by CY-BOCS-PDD and CGI-OCD

II. Core features of ASD assessed by SRS-2, CY-BOCS-PDD, and MGH-SECS-C and -I
III. Associated features of ASD assessed by YMRS, CDRS-R, and respective CGI-Improvement subscale
IV. Cognitive functioning assessed by BRIEF and DANVA 2.

This study plans to recruit 15 subjects with ASD between 6-17 years of age with clinically significant and functionally impairing features of anxiety as rated by parent (significant score on the Child Behavior Checklist [CBCL] subscales for anxiety/depression) and clinician (a ≥ 4 on severity subscale of Clinical Global Impression Scale [CGI] for anxiety).

We anticipate that subjects may enter this trial following completion of/withdrawal from other protocols in our office, and that there may be procedural overlap. So as to not burden subjects/parents/guardians with redundant time commitments, we will use the following *diagnostic* data previously collected: If a subject has completed an evaluation with one of the study clinicians within the previous three years or an informant has completed the SRS-2 within the six months prior to entrance into this study, subjects will not be asked to repeat any overlapping diagnostic procedures. We will use the study diagnostic data that had been previously collected so as to not burden the subject with redundant time commitments. However, the study clinician will review the interval time period to assess for clinically significant medical or psychiatric history, to ensure that the subject meets appropriate study entrance criteria.

If the subset of scales assessing intelligence (WASI-II) in the neuropsychological battery has been completed within 12 months prior to entrance into this study, subjects will not be asked to repeat these procedures. We will use the diagnostic data previously collected so as not to burden the subject with redundant time commitments.

Although every effort will be made to encourage subjects to keep regularly scheduled appointments, in the event that a subject is unable to come into the office within a reasonable timeframe of a scheduled visit, and the treating research clinician feels that subject safety will not be jeopardized by doing so, the clinician can conduct the visit with the subject and parent/guardian over the phone. The clinician will complete the phone visit form for all phone visits that occur. This will ensure that each subject will be continuously monitored by the clinician throughout the course of the study despite unforeseen scheduling circumstances. The study evaluation visit, the baseline visit or the final study visit may be not conducted over the phone. Additionally, phone visits may not occur for two consecutive visits.

Evaluation and Characterization: Week 99

After providing study information and obtaining IRB-approved informed consent and assent, participants will undergo an initial screening assessment consisting of a brief demographic interview (collecting information regarding socioeconomic status and history of head injury or trauma), psychiatric and medical history, and assessment

measures (CBCL, PARS, and CGI-Anxiety). Eligible subjects will be administered a detailed assessment battery consisting of diagnostic measures (complete psychiatric evaluation including MGH-ASD-SCL), cognitive assessments (WASI-II and DANVA 2), measures of psychosocial functioning (SAICA and M-FES), and physical assessment measures (complete physical examination including height, vitals, ECG, urine screens, and blood tests). Screening (week 99) procedures can occur over 2 days (within the three week screening window).

Washout Period

After the screening period, subjects who are currently taking prohibited medications (refer top section on the, "Concomitant Medications/Treatments") must discontinue the use of their medication to be eligible for participation in this study. Medication washout is recommended by our clinicians to participants, their parent/guardian, and current providers – this is done according to a case-by-case assessment, considering the duration on drug, the dose, and the adverse effects associated with the treatment and effects of stopping that medication/treatment. Our office does not take over care for the patient, but remains available during this time period. The washout schedule will be discussed with the participant, their parent/guardian, and current providers.

Treatment Trial Phase: Weeks 0 through 8

Participants who fulfill the inclusion and exclusion criteria will be treated with buspirone for a period of 8 weeks. Subjects will be evaluated at weekly intervals during titration phase (4 weeks from baseline) and thereafter every 2 weeks during the maintenance phase of the trial. Study visits will have a visit window of +/- 2 days to facilitate scheduling. Each visit will assess drug efficacy (CGIs and GAF), tolerability (assessing for treatment-emergent adverse-events), and safety (vital signs including weight). At baseline, midpoint (week-4), and endpoint, the PARS, MASC, SRS-2, MGH-SECS-C and -I, BRIEF, CDRS-R, YMRS, CY-BOCS-PDD, and PQ-LES-Q assessment measures will be administered. The CBCL will also be administered at weeks 4 and 8/drop-visit. At endpoint (completion/drop-visit), participants will be reevaluated on cognitive (DANVA 2) and physical assessment measures (complete physical examination including vitals, ECG, blood tests, and urine screening).

Study Discontinuation

Participants will be withdrawn from the study if they experience significant worsening of symptoms, or if the subject or their family decides to withdraw. A subject may be withdrawn from the study at any time if any of the following conditions are met:

- Worsening of PDD, ADHD, OCD, anxiety, depression, or mania, as reflected by respective Clinical Global Improvement score of 6 (Much worse) or 7 (Very Much Worse) for 2 visits in a row.
- Subjects who experience intolerable adverse effects, and/or clinically significant laboratory values inconsistent with continuation in the study.
- Unstable psychiatric condition that clinically requires 1) a change in stable dose of concomitant psychotropic medications or 2) subjects requiring inpatient psychiatric admission.
- Emergent suicidality
- Active substance abuse

- Pregnancy
- Allergic drug reaction
- Non-compliance (less than 70% compliance for 2 visits or longer)
- Failure to return medication or dosing diary for 2 consecutive visits
- Failure to keep study appointments for more than 2 consecutive visits without justification
- Clinical judgment of the investigator
- Withdrawal of consent

If study participation is discontinued for safety reasons, participants will be offered three follow-up clinical visits, allowing adequate time for appropriate psychiatric referrals to treaters in their communities.

Study Medication

At each visit, measures of safety and effectiveness will be administered. Buspirone will be titrated to the maximum daily dose during the first four weeks of the trial (dose titration phase). Week-4 onwards, subjects will be maintained on maximum achieved dose till the end of the trial (dose maintenance phase).

Dose titration phase: Titration of buspirone will follow the flexible titration schedule with an option for slower titration, holding at lower dose, or lowering the dose based on tolerability and response to buspirone as per clinician judgment. Dose will be adjusted upward per titration schedule provided the treatment is well tolerated and the response is insufficient (CGI-Improvement>2).

Dose maintenance phase: During the maintenance phase, buspirone will be maintained on the maximum achieved dose. As a one-time option during the maintenance phase, the dose of the study medication can be decreased by a maximum of 10 mg based on tolerability to buspirone per clinician judgment.

Buspirone will be administered in divided dosage. During the titration phase, the total dose of buspirone will be increased at each visit and on the 4th day after each visit by 5 mg.

The study buspirone titration schedule, detailed below, is based on treatment guidelines described in the Physicians' Desk Reference [45].

Buspirone Flexible Titration Schedule

Visit	Week	Day	Maximum Total Dose (mg/day)
1	0	1	10
	0.5	5	15
2	1	8	25
	1.5	12	30
3	2	15	40
	2.5	19	45
4	3	22	55
	3.5	26	60
5	4	28	Maintained on the maximum achieved dose

Buspirone will be available in four different strengths: 5,10,15, and 30 mg. Ten days worth of study medication will be dispensed for weekly visits and 20 days worth of medication will be dispensed for biweekly visits. To assess and ensure drug

accountability and compliance, study medication will be returned, counted, and re-dispensed every visit by the study coordinator.

Concomitant Medications / Treatments

A detailed past and present treatment history (pharmacological / non-pharmacological) will be taken as part of initial evaluation. Following are the concomitant medications/treatments guidelines:

- Participants on stimulant medication must be on a stable dose for at least 2 weeks prior to baseline.
- Subjects may take melatonin (up to 3mg) or Benadryl (up to 50 mg) at bedtime as needed (prn) for insomnia.
- Non-pharmacological treatments such as supportive individual, family, or group therapy will be permitted provided they were in place for a substantial period of time (> 1 month) prior to study participation and remain unchanged during the course of the trial.
- No new non-pharmacological treatments may be initiated during the course of the trial.
- Subjects may not take monoamine oxidase inhibitors (MAOI) and CYP3A4 inducers or inhibitors including: nefazodone, diltiazem, verapamil, erythromycin, itraconazole, rifampin or grapefruit juice

8. ASSESSMENTS (see protocol schedule)

A. Diagnostic Assessments

Administered at Week 99

- MGH ASD Symptom Checklist (MGH-ASD-SCL): The spectrum of ASD symptoms will be screened by using clinician administered MGH-ASD-SCL. This screening instrument adopted items from DSM-IV diagnostic criteria for PDD and assesses for the individual core domains and associated features of ASD.

B. Psychosocial Assessment Measures

Administered at Week 99

- Social Adjustment Inventory for Children and Adolescents (SAICA): The SAICA is an assessment administered to parents that measures social functioning in children 6 to 18 years old. Content areas include activities, peer relations, family relations, and academic performance.
- Moos Family Environment Scale (M-FES): We will use the M-FES as a measure of general family conflict. The M-FES assesses the quality of interpersonal relationships among family members and consists of 90 true-false items completed by the parent(s). The M-FES has high internal and test-retest reliability and population norms. Ten aspects of the family environment are assessed, permitting an evaluation of the degree of stress in the family environment and of parental discord. In divorced/separated families, this instrument will be used to evaluate the biological family prior to the divorce, as well as the current family environment. Following procedures previously used by our group, families will be categorized into "high" and "low" conflict family environments, based upon their scores on the conflict, cohesion, and expressiveness subscales.

Administered Weeks 99, 4 and 8/drop-visit

- Child Behavior Checklist (CBCL): The CBCL is a parent-report measure that assesses maladaptive emotional and behavioral problems in children ages 6-18. Several subcategories are assessed including social withdrawal, somatic complaints,

anxiety and depression, destructive behavior, social problems, thought problems, attention problems, aggressive behavior, and delinquent behaviors.

Administered Weeks 0, 4, and 8/drop-visit

- Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q): The PQ-LES-Q is a self-report measure that assesses quality of life from the point of view of the subject. Subjects are instructed to consider each item and indicate their response scaled 1-5.

Administered Weeks 0-8

- DSM-IV Global Assessment of Functioning (GAF): The GAF will assess global functioning using a scale from 1 (worst) to 100 (best). This scale will be used at baseline to characterize the sample as well as at each visit to assess change.

C. Neuropsychological Battery

Administered at Week 99

- Wechsler Abbreviated Scale of Intelligence Scale (WASI-II) Vocabulary and Matrix Reasoning subtests: This scale meets the demand for a quick reliable measure of intelligence in clinical, educational, and research settings and will provide a Full Scale IQ.

Administered at Weeks 99 and 8/drop-visit

3. Assessment of Social Cognition

- Diagnostic Analysis of Nonverbal Accuracy Scale (DANVA 2): Child Faces and Child Paralanguages subtests. This assessment consists of 2 tasks of social competence assessing participant ability for recognizing feelings expressed through faces and paralanguage by children: Both subtests have been standardized and have acceptable internal consistency and reliability. This test can be administered for testing social competence in children as young as 3 years of age.

D. Quantitative Scalar Assessments

Administered Weeks 0-8/drop-visit

Severity assessment of ADHD, PDD, Psychosis, Mania, Depression, Anxiety, and OCD

- NIMH Clinical Global Impression Scale (CGI): The CGI is a measure of illness severity, improvement, and efficacy of treatment. The score for severity ranges from 1 (normal, not at all ill) to 7 (among the most extremely ill subjects). Improvement ranges from 1 (very much improved) to 7 (very much worse). And lastly, the effectiveness index measures to what extent the subject is experiencing therapeutic effects as well as the level of adverse events. The CGI scales will be used for the assessment of PDD, ADHD, OCD, psychosis, mania, depression, and anxiety.

Severity assessment of Anxiety

Administered at screening (Week 99), baseline (Week 0) midpoint (Week 4), & endpoint (Week 8/drop-visit)

- Pediatric Anxiety Rating Scale (PARS): The PARS is a clinician-rated scale, to be used with parent and children. It has 2 sections: a symptom checklist and severity items. The symptom checklist is used to determine the child's repertoire of symptoms during the past week. The 7 severity items are used to determine severity of symptoms and the PARS total score. The total score for the PARS is derived by summing the 7 severity items; total score ranges from 0 to 35.

Administered at baseline (Week 0), midpoint (Week 4), and endpoint (Week 8/drop-visit)

- Multidimensional Anxiety Scale for Children (MASC): We will ask all parents and children (ages 8-19) to complete the MASC, a 39-item scale, distributed into four major factors: physical symptoms, social anxiety, harm avoidance, and separation anxiety. It has been shown to distinguish between anxiety and depression, as well as among anxiety disorders [44].

Administered at baseline (Week 0), midpoint (Week 4), and endpoint (Week 8/drop-visit)

Severity assessment of Autism Spectrum Disorder – Core Features

- Social Responsiveness Scale-Second Edition (SRS-2): The SRS-2 is a 65-item rating scale completed by the parent or guardian. This scale measures the severity of autism spectrum symptoms as they occur in natural social settings.
- MGH Social-Emotional Competence Scale [Clinician-Rated Measure] (MGH-SECS-C): Severity of ASD will be assessed by administering the clinician rated MGH-SECS-C. This is a 37-item scale that assesses for the severity of core and associated symptoms of ASD in a Likert scale from 0 to 8.
- MGH Social-Emotional Competence Scale [Informant-Rated Measures] (MGH-SECS-I): is a 37-item scale that assesses for the severity of core and associated symptoms of ASD in a Likert scale from 0 to 6. This scale is to be completed by the parent or guardian measuring the severity of autism spectrum symptoms as they occur in natural social settings.

Severity assessment of Executive Function Deficits

- Behavior Rating Inventory of Executive Function (BRIEF): An 86-item rating scale to assess level of executive function deficits.

Severity assessment of Compulsive/Repetitive Behaviors

- Children's Yale Brown Obsessive Compulsive Scale modified for PDD (CY-BOCS-PDD): CY-BOCS is a clinician-rated 10-item scale (total range from 0 to 40), with subtotals for obsessions (items 1-5) and compulsions (items 6-10). The CY-BOCS includes a Symptom Checklist of over 60 examples of obsessions and compulsions. CY-BOCS-PDD is modified and validated version of CY-BOCS for use in children with PDD. CY-BOCS-PDD consists of following modifications: 1) the Obsessions checklist and severity scales are dropped because of the well-known cognitive and communication limitations in this population, 2) the compulsions checklist is retained from the original CY-BOCS and expanded to include repetitive behaviors commonly seen in children with PDD, 3) given that parents are the primary informant for children with PDD, selective alterations are made on the probes for Compulsion severity items.

Severity assessment of Depression

- Children's Depression Rating Scale-Revised (CDRS-R): The CDRS-R is modeled after the Hamilton Depression Rating Scale for adults, and assesses the presence and severity of depressive symptoms in children ages 6 and older. It includes questions relevant to youth, such as questions about school, family, and peer functioning. We will administer this measure to parents and directly to the child. 17 symptom areas associated with depression are assessed. It has been widely used in treatment outcome studies of childhood depression and BPD.

Severity assessment of Mania symptoms

- Young Mania Rating Scale (YMRS): The YMRS is an 11-item interview which queries the core symptoms of mania in the child, including elevated mood, irritability, psychomotor agitation, hypersexuality, and aggressive behavior. The YMRS score

ranges from 0-60. Questions are asked about the last week. We will administer this measure separately to parents and children. Originally designed for use with bipolar adults, the YMRS has recently been adapted for use with children. The YMRS has shown acceptable internal consistency and good discriminative validity. It is considered one of the best available instruments for assessing pediatric mania, and has been widely used in phenomenologic and treatment outcome studies of youth with BPD.

E. Safety Assessment Measures

Administered Weeks 0-8/drop-visit

- Adverse Experiences: We will record any adverse health events experienced during the study, along with duration, severity, cause, treatment, and outcome.
- Vital Signs: Blood pressure, pulse, and weight

Completed at screening (Week 99) and endpoint (Week 8/drop-visit)

- Physical Examination
- Blood Tests: Comprehensive metabolic panel including complete blood count, total electrolyte count, liver function test, thyroid function test, and random glucose levels
- Urine Drug Screen (for subjects ≥12 years old)
- Urine Pregnancy Test (for menstruating female subjects
- ECG

9. DATA ANALYSIS

Considering our open-label single group design, we will rely on comparisons of the participants' performances at baseline (week 0) prior to the initiation of treatment relative to their scores at the last assessment (week 8). Thus, statistics for paired samples will be utilized. This design largely protects against the bias introduced by confounding factors. That is, since the same participants are tested on two occasions, all static confounding factors are perfectly balanced, and can have no impact on the findings. Bias can still result from time-varying factors that are not associated with the outcomes, but we are confident that any such factors will have a minimal impact on this study, considering the duration of the trial. Specifically, we will employ Wilcoxon signed rank tests for continuous or discrete outcome measures, and McNemar's test for binary outcomes. These tests are free from assumptions regarding the distribution of the outcome variables, which is appropriate since the scales we are proposing to utilize are not considered to have Gaussian distributions, and will not be amenable to parametric methods.

10. SAFETY

The principal investigator (PI) will be responsible for the safety of all research subjects. The PI will supervise all study activities including ratings, laboratory tests, and vital signs. Consistent with good clinical practice, safety will be monitored by each subject's assigned clinician at each study visit. This clinician will be available 24 hours a day by page.

If a subject is withdrawn from the study due to adverse events, lack of response, or as a decision by the clinician, they will be offered open treatment for three months, giving adequate time for appropriate psychiatric care to be arranged.

Blood draw: A topical anesthetic cream (EMLA) will be offered to subjects before blood draws. The dose of EMLA cream will not exceed administration guidelines based on subject age and weight. Subjects with sensitivity to local topical anesthetics will not receive EMLA cream. If an infection does occur, it will be treated.

Study Medication: Safety will be monitored through treatment-emergent adverse events and measuring change in vital signs through laboratory analyses. All adverse events will be recorded. A subject may be dropped from the study or dosage may be decreased and timing of medication changed at any time due to adverse events. All adverse events will be reported to the PHRC according to PHRC guidelines.

11. CONFIDENTIALITY

All research-related records, initiated as a result of a subject's participation in this study that reveal the subject's identity, will remain confidential except as may be required by law. While the results of the clinical laboratory blood testing will become part of a subject's Massachusetts General Hospital medical record, they will not link the subject to participation in any research. Subjects will only be contacted regarding future studies if they indicate that they are interested in being contacted by initialing in the specific section of the consent form.

When voice recordings are used, they will be labeled with the subjects' code name and number, and only the study coordinator and study clinicians will have access to the recordings. These recordings will be used to monitor the completeness of study evaluations and the similarities and differences between different raters. These recordings will be saved securely using a password-protected database and maintained for 1 year after completion of the study for the purpose of verifying data and maintaining study reliability and will then be deleted after this time.

12. RISKS AND DISCOMFORTS

Blood Draw: There may be some discomfort during the blood draws. Subjects may have a bruise and/or bleeding at the needle site. Occasionally a subject may feel faint when blood is drawn. Rarely, an infection may develop. If an infection does occur, it can be treated. EMLA cream will be regularly offered to any subject to numb the site of the draw.

Study Medication - Buspirone: The most common side effects reported with use of buspirone are: nausea, vomiting, headache, dizziness, drowsiness, fatigue, weakness, numbness, nervousness, lightheadedness, upset stomach, stomach pain, constipation, diarrhea, dry mouth, difficulty sleeping, depression, and excitement.

Other side effects include: skin rash, itching, fast or irregular heartbeat, blurred vision, and unusual movements of the head or neck muscles.

All subjects will be closely monitored for serious adverse reactions and drug-drug interactions with any ongoing concomitant medications. All serious unexpected adverse experiences of a research subject will be reported to PHRC.

13. POTENTIAL BENEFITS

There may be no direct benefit to subjects participating in this study. Potential benefits to the participants include education about ASD, a trial of medication that could

be continued after the study, and the opportunity to contribute to medical science and thus help others with ASD.

Protocol Schedule

	Evaluation	Titration								Maintenance				
Week	99	0		1		2		3		4		6		8
Day		0	5	8	12	15	19	22	26	29	36	43	50	57
Buspirone Dosing (Total mg/day)		10	15	25	30	40	45	55	60	***	***	***	***	***
Consenting (Parent & Subject)	X													
Procedures														
Demographic Interview	X													
Psychiatric Evaluation & Medical History	X													
Physical Examination	X													X
Height	X													X
Vital Signs (BP, pulse & weight)	X	X		X		X		X		X		X		X
Urine pregnancy test (menstruating females)	X													X
Urine drug screen (subjects ≥12 years old)	X													X
Hematological tests	X													X
ECG	X													X
Cognitive Tasks														
Neuropsychological Battery*	X													
DANVA-2	X													X
Clinician Rated Scales														
MGH-ASD-SCL	X													
PARS	X	X								X				X
CGI**	X	X		X		X		X		X		X		X
GAF		X		X		X		X		X		X		X
Adverse Event Log		X		X		X		X		X		X		X
Concomitant Medication Log		X		X		X		X		X		X		X
CY-BOCS-PDD		X								X				X
MGH-SECS-C		X								X				X
CDRS-R		X								X				X
YMRS		X								X				X
Patient/Parent-Rated Scales														
SAICA	X													
M-FES	X													
CBCL	X									X				X
MASC		X								X				X
SRS-2		X								X				X
BRIEF-Parent		X								X				X
MGH-SECS-I		X								X				X
PQLESQ		X								X				X

*Please see Section 8 (Assessments) for details.
**CGIs: (Only CGI-Anxiety completed at wk. 99) PDD, PDD-SI, PDD-SC, PDD-M, Anxiety, ADHD, OCD, Psychosis, Depression, Mania
***Maximum achieved dose

References:

1. Association AP, DSM-IV Sourcebook. Vol. 1. 1994, Washington, DC: American Psychiatric Association.
2. Autism and Developmental Disabilities Monitoring Network Surveillance Year 2008 Principal Investigators; Centers for Disease Control and Prevention. Prevalence of autism spectrum disorders--Autism and Developmental Disabilities Monitoring Network, 14 sites, United States, 2008. MMWR Surveill Summ. 2012;61(3):1-19. PMID: 22456193.
3. Strayhorn J, N Rapp, W Donina, and P Strain. Randomized trial of methyphenidate for an autistic child. Journal of the American Academy of Child and Adolescent Psychiatry; 1988. 27: p. 244-247.
4. Fankhauser MP, VC Karumanchi, ML German, A Yates, and SD Karumanchi. A double-blind, placebo-controlled study of the efficacy of transdermal clonidine in autism. Journal of Clinical Psychiatry; 1992. 53(3): p. 77-82.
5. Cook EH, Rowlett, R., Jaselskis, C., Leventhal, B.L. Fluoxetine treatment of children and adults with autistic disorder and mental retardation. Journal of the American Academy of Child and Adolescent Psychiatry; 1992. 31(4): p. 739-745.
6. Kolmen B, H Feldman, B Handen, and J Janosky. Naltrexone in young autistic children: A double-blind, placebo-controlled crossover study. Journal of the American Academy of Child and Adolescent Psychiatry; 1995. 34(2): p. 223-231.
7. American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders: DSM-IV. 4th ed. 1994, Washington, DC: American Psychiatric Association. 886.
8. de Bruin EI, RF Ferdinand, S Meester, PF de Nijs, and F Verheij. High rates of psychiatric co-morbidity in PDD-NOS. J Autism Dev Disord; 2007. 37(5): p. 877-86.
9. Simonoff E, A Pickles, T Charman, S Chandler, T Loucas, and G Baird. Psychiatric disorders in children with autism spectrum disorders: prevalence, comorbidity, and associated factors in a population-derived sample. J Am Acad Child Adolesc Psychiatry; 2008. 47(8): p. 921-9.
10. White SW, D Oswald, T Ollendick, and L Scahill. Anxiety in children and adolescents with autism spectrum disorders. Clin Psychol Rev; 2009. 29(3): p. 216-29.
11. Joshi G, C Petty, J Wozniak, A Henin, R Fried, M Galdo, M Kotarski, S Walls, and J Biederman. The Heavy Burden of Psychiatric Comorbidity in Youth with Autism Spectrum Disorders: A Large Comparative Study of a Psychiatrically Referred Population. J Autism Dev Disord; 2010. 40(11): p. 1361-70.
12. Muris P, P Steerneman, H Merckelbach, I Holdrinet, and C Meesters. Comorbid anxiety symptoms in children with pervasive developmental disorders. J Anxiety Disord; 1998. 12(4): p. 387-93.
13. Leyfer OT, SE Folstein, S Bacalman, NO Davis, E Dinh, J Morgan, H Tager-Flusberg, and JE Lainhart. Comorbid psychiatric disorders in children with autism: interview development and rates of disorders. J Autism Dev Disord; 2006. 36(7): p. 849-61.
14. Sukhodolsky DG, L Scahill, KD Gadow, LE Arnold, MG Aman, CJ McDougle, JT McCracken, E Tierney, S Williams White, L Lecavalier, and B Vitiello. Parent-rated anxiety symptoms in children with pervasive developmental disorders: frequency and association with core autism symptoms and cognitive functioning. J Abnorm Child Psychol; 2008. 36(1): p. 117-28.

15. Steinhausen HC and CW Metzke. Differentiating the behavioural profile in autism and mental retardation and testing of a screener. Eur Child Adolesc Psychiatry; 2004. 13(4): p. 214-20.
16. Green J, A Gilchrist, D Burton, and A Cox. Social and psychiatric functioning in adolescents with Asperger syndrome compared with conduct disorder. J Autism Dev Disord; 2000. 30(4): p. 279-93.
17. Gadow KD, CJ Devincent, J Pomeroy, and A Azizian. Comparison of DSM-IV symptoms in elementary school-age children with PDD versus clinic and community samples. Autism; 2005. 9(4): p. 392-415.
18. Russell AJ, D Mataix-Cols, M Anson, and DG Murphy. Obsessions and compulsions in Asperger syndrome and high-functioning autism. Br J Psychiatry; 2005. 186: p. 525-8.
19. Evans DW, K Canavera, FL Kleinpeter, E Maccubbin, and K Taga. The fears, phobias and anxieties of children with autism spectrum disorders and Down syndrome: comparisons with developmentally and chronologically age matched children. Child Psychiatry Hum Dev; 2005. 36(1): p. 3-26.
20. Strauss CC, CL Frame, and R Forehand. Psychosocial impairment associated with anxiety in children. Journal of Clinical Child Psychology 1987. 16(3): p. 235-239.
21. Keller MB, PW Lavori, J Wunder, W Beardslee, CE Schwartz, and J Roth. Chronic course of anxiety disorders in children and adolescents. J Am Acad Child and Adolesc Psychiatry; 1992. 31(4): p. 595-599.
22. Otto MW, MH Pollock, JF Rosenbaum, GS Sachs, and RH Asher. Childhood history of anxiety in adults with panic disorder: Association with anxiety sensitivity and comorbidity. Harvard Review of Psychiatry; 1994. 1(5): p. 288-293.
23. Otto M, MH Pollack, KM Maki, RA Gould, JJ Worthington, JW Smoller, and J Rosenbaum. Childhood history of anxiety disorders among adults with social phobia: Rates, correlates, and comparisons with patients with panic disorder. Depression and Anxiety; 2001. 14: p. 209-213.
24. Brady EU and PC Kendall. Comorbidity of anxiety and depression in children and adolescents. 1992. 111(2): p. 244-255.
25. Weissman MM, S Wolk, P Wickramarante, RB Goldstein, P Adams, S Greenwald, ND Ryan, RE Dahl, and D Steinberg. Children with prepubertal-onset major depressive disorder and anxiety grown up. Archives of General Psychiatry; 1999. 56: p. 794-801.
26. Angold A, J Costello, and A Erkanli. Comorbidity. Journal of Child Psychology and Psychiatry; 1999. 40(1): p. 57-87.
27. Costello EJ, HL Egger, and A Angold. The developmental epidemiology of anxiety disorders: phenomenology, prevalence, and comorbidity. Child Adolesc Psychiatr Clin N Am; 2005. 14(4): p. 631-48, vii.
28. (AACAP) AAoCaAP, Practice parameter for the assessment and treatment of children and adolescents with ADHD. 2007: Washington, D. C.
29. Compton S, J Piacentini, J Walkup, and e al. Child/adolescent anxiety multimodal study (CAMS):acute phase efficacy and safety results. in 48th Annual NCDEU Meeting. 29 May 2008. Phoenix.
30. Beidel DC, SM Turner, FR Sallee, RT Ammerman, LA Crosby, and S Pathak. SET-C versus fluoxetine in the treatment of childhood social phobia. J Am Acad Child Adolesc Psychiatry; 2007. 46(12): p. 1622-32.
31. Bridge JA, S Iyengar, CB Salary, RP Barbe, B Birmaher, HA Pincus, L Ren, and DA Brent. Clinical response and risk for reported suicidal ideation and suicide

attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials. JAMA; 2007. 297(15): p. 1683-96.
32. Campbell M, P Adams, R Perry, EK Spencer, and JE Overall. Tardive and withdrawal dyskinesia in autistic children: A prospective study. Psychopharmacology Bulletin; 1988. 24(2): p. 251-255.
33. Handen BL, CR Johnson, and M Lubetsky. Efficacy of methylphenidate among children with autism and symptoms of attention-deficit hyperactivity disorder. J Autism Dev Disord; 2000. 30(3): p. 245-55.
34. Aman MG, MDL Arnold, CJ McDougle, B Vitiello, L Scahill, M Davies, JT McCracken, E Tierney, PL Nash, DJ Posey, S Chuang, A Martin, B Shah, NM Gonzalez, NB Swiezy, L Ritz, K Koenig, J McGough, JK Ghuman, and RL Lindsay. Acute and long-term safety and tolerability of risperidone in children with autism. J Child Adolesc Psychopharmacol; 2005. 15(6): p. 869-84.
35. Posey DJ, RE Wiegand, J Wilkerson, M Maynard, KA Stigler, and CJ McDougle. Open-label atomoxetine for attention-deficit/ hyperactivity disorder symptoms associated with high-functioning pervasive developmental disorders. J Child Adolesc Psychopharmacol; 2006. 16(5): p. 599-610.
36. Steingard RJ, B Zimnitzky, DR DeMaso, ML Bauman, and JP Bucci. Sertraline treatment of transition-associated anxiety and agitation in children with autistic disorder. J Child Adolesc Psychopharmacol; 1997. 7(1): p. 9-15.
37. Couturier JL and R Nicolson. A retrospective assessment of citalopram in children and adolescents with pervasive developmental disorders. J Child Adolesc Psychopharmacol; 2002. 12(3): p. 243-8.
38. Namerow L, P Thomas, J Bostic, J Prince, and M Monuteaux. Use of citalopram in pervasive developmental disorders. J Dev Behav Pediatr; 2003. 24(2): p. 104-8.
39. Niederhofer H. An open trial of buspirone in the treatment of attention-deficit disorder. Hum Psychopharmacol; 2003. 18(6): p. 489-92.
40. Malhotra S and PJ Santosh. An open clinical trial of buspirone in children with attention deficit/hyperactivity disorder. Journal of the American Academy of Child and Adolescent Psychiatry; 1998. 37(4): p. 364-371.
41. Chandana SR, ME Behen, C Juhasz, O Muzik, RD Rothermel, TJ Mangner, PK Chakraborty, HT Chugani, and DC Chugani. Significance of abnormalities in developmental trajectory and asymmetry of cortical serotonin synthesis in autism. Int J Dev Neurosci; 2005. 23(2-3): p. 171-82.
42. Chugani DC, O Muzik, M Behen, R Rothermel, JJ Janisse, J Lee, and HT Chugani. Developmental changes in brain serotonin synthesis capacity in autistic and nonautistic children. Ann Neurol; 1999. 45(3): p. 287-95.
43. Buitelaar JK, RJ van der Gaag, and J van der Hoeven. Buspirone in the management of anxiety and irritability in children with pervasive developmental disorders: results of an open-label study. J Clin Psychiatry; 1998. 59(2): p. 56-9.
44. Dierker LC, KR Merikangas, and P Szatmari. Influence of parental concordance for psychiatric disorders on psychopathology in offspring. J Am Acad Child Adolesc Psychiatry; 1999. 38(3): p. 280-8.
45. *Physicians' desk reference*. (66th ed.). (2011). Montvale, NJ: Thomson PDR.