Buspirone treatment of anxiety in individuals with Williams syndrome

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Research Plan:
A. SPECIFIC AIMS:

Williams syndrome (WS) is a genetic disorder caused by a hemizygous microdeletion spanning 1.5 to 1.8 million base pairs containing 26 to 28 genes at chromosome 7q11.23. The prevalence of WS is estimated to be 1/7500 to 1/10,000. Multiple organ systems are affected by this microdeletion and there is a highly variable range and severity of cognitive and medical problems. Common medical comorbidities include cardiovascular disease, connective tissue abnormalities, growth abnormalities, and endocrine problems. In addition to the medical comorbidities associated with WS, many persons with WS experience high levels of psychiatric symptomatology including inattention, hyperactivity, and anxiety.

One of the areas receiving surprisingly little attention in WS is the diagnosis and treatment of anxiety. While children, adolescents, and adults WS frequently experience symptoms of anxiety, it has not yet been fully characterized. There are currently no published prospective studies on the pharmacologic treatment of anxiety in WS. There continues to be an urgent need for additional studies aimed at the treatment of anxiety in persons with WS.

The **long-term goal** of this research is to advance the evidence-base behind the pharmacological treatment of WS by studying medications that reduce maladaptive symptoms and improve the quality of life of the individual and his/her family members. The **primary objective** of this study is to conduct a preliminary prospective, open-label trial of buspirone for the treatment of anxiety associated with WS. The principal investigator (PI) and colleagues have completed a retrospective case series of buspirone, a serotonin $(5\text{-HT})_{1A}$ receptor partial agonist and dopamine (D3 and D4) antagonist, for the treatment of generalized anxiety disorder in three individuals with WS and believe this to be a promising new treatment for the target symptom of anxiety.

The **central hypothesis** of this project is that buspirone will improve anxiety when administered to children, adolescents, and adults with WS. We also hypothesize that buspirone will be safe and well tolerated. This study will provide much needed pilot data regarding the effectiveness and tolerability of buspirone for these symptoms in WS and is a necessary first step prior to conducting a larger, more definitive randomized controlled trial.

We plan to provide preliminary evidence supporting the central hypothesis and accomplish the objectives of this study by pursuing the following specific aims:

1. **Determine whether buspirone shows preliminary evidence of effectiveness, safety, and tolerability in children, adolescents, and adults with WS.** This aim addresses our central hypothesis that buspirone will be effective and safe in the treatment of anxiety in persons with WS.
    - For preliminary evidence of effectiveness, we will require a significant decrease in mean PARS score from baseline and a ninety-five percent confidence interval for the effect size estimate consistent with a standardized effect size (difference in sixteen-week score from baseline divided by standard deviation at baseline) of one.
    - For preliminary evidence of safety, we will require no observation of serious or severe adverse effects possibly, probably, or definitely associated with buspirone.
    - For preliminary evidence of tolerability, we will require that the 95% confidence interval for drop-out rate due to side effects of the drug be consistent with a rate of 20% or exclude values >=20%.
2. **Determine which semi-structured interviews and existing anxiety rating scales would be most useful for characterizing participants and assessing anxiety treatment effects.** A variety of outcome measures of anxiety will be used to better assess their applicability and feasibility in the WS population. The relative performance of the scales will be evaluated based on their sensitivity to change, their percent of item-level missing data, and any feedback on the appropriateness or ease of use of the scales from participants or study personnel.

B. IMPACT AND RELEVANCE:

The presence of anxiety in people with WS has consistently been identified in population studies of affected adolescents and adults (Blomberg, Rosander, & Andersson, 2006; Cherniske et al., 2004; Dykens, 2003; Einfeld, Tonge, & Rees, 2001; O. T. Leyfer, Woodruff-Borden, Klein-Tasman, Fricke, & Mervis, 2006; O. Leyfer, Woodruff-Borden, & Mervis, 2009; Royston, Howlin, Waite, & Oliver, 2017; Woodruff-Borden, Kistler, Henderson, Crawford, & Mervis, 2010). A recent meta-analysis of anxiety disorders in WS demonstrated that individuals with WS were significantly more likely to have an anxiety disorder than individuals with heterogenous intellectual disability (ID) (RR 4.0, 95% CI 2.27-7.06, $p<0.0001$) (Royston et al., 2017). The most common anxiety disorders identified were specific phobia and generalized anxiety disorder (GAD) (Royston et al., 2017). Common phobias included noise; blood, injury, or infection; thunderstorms; and lightning. A longitudinal study of anxiety in WS demonstrated that in many cases, anxiety disorders persisted over a 5-year follow-up period. Furthermore, of the patients with at least one anxiety disorder, 72.2% developed additional anxiety disorders over time (Woodruff-Borden et al., 2010).

Anxiety represents a common and interfering symptom cluster among individuals with developmental disorders. Anxiety may play a role in challenging behaviors including elopement, aggression, self-injury, and reclusive/avoidant behavior, that impact participation in school, day programs, and vocational sites. All these symptoms/behaviors also contribute to caregiver stress. Untreated anxiety may lead to decreased effectiveness of behavior therapy interventions impacting the overall trajectory of achieved independence with activities of daily living and other life skills. One study demonstrated an association between high anxiety and attention allocation away from eye regions of threatening facial expressions WS (Kirk, Hocking, Riby, & Cornish, 2013). Another study demonstrated that anxiety was associated with diminished anger recognition among adults with WS compared to typically developed controls (Ng, Bellugi, & Järvinen, 2016). Taken together, these studies suggest that anxiety may adversely affect social functioning in individuals with WS.

Despite documented elevated rates of anxiety in individuals with WS, our current knowledge of efficacious, safe, and tolerable pharmacologic treatments for anxiety among individuals with WS remains limited. Empirical evidence on psychopharmacologic treatment options for co-morbid anxiety in WS is limited to retrospective case series; no prospective studies have been completed. A case series including two adult patients with WS reported that the use of low doses of a low-potency first generation antipsychotic (levomepromazine) was helpful for the treatment of insomnia and anxiety. Both patients in this case series subsequently developed depressive symptoms which responded to a selective serotonin reuptake inhibitor (SSRI) (Urgeles, Alonso, & Ramos-Moreno, 2013). Our group completed a retrospective case series describing symptoms of GAD in three adolescents/young adults with WS and their course of treatment with buspirone. Treatment with buspirone was well-tolerated and resulted in sustained response in all three cases. (Thom, Keary, Waxler, Pober, & McDougle, 2019).

Buspirone, a non-benzodiazepine, generally non-sedating anxiolytic, is a 5-HT_{1A} receptor agonist and D3/D4 antagonist. It has a Food and Drug Administration (FDA) indication for the treatment of GAD in adults and is currently available as a generic. Multiple double-blind, placebo-controlled trials have demonstrated the efficacy of buspirone for treating symptoms of GAD in adults (Feighner, Merideth, & Hendrickson, 1982; Pecknold et al., 1989; Sramek, Frackiewicz, & Cutler, 1997). Although rare, side effects can include headache, nausea, dizziness, and muscle tension (Schatzberg & DeBattista, 2015).

Our group was the first to report on the potential role of buspirone for the treatment of anxiety in WS (Thom et al., 2019). Based upon our clinical experience, we have found it helpful for a variety of anxiety symptoms associated with WS. Our case series is limited by small sample size, retrospective report, open-label treatment, and no control group. Furthermore, in some cases patients received psychotherapy, changes in the school or living environment, and optimization of medical conditions in conjunction with buspirone. Our knowledge base on the effect of buspirone for the treatment of anxiety in WS would be enhanced by a prospective study with a larger

sample size, standardized enrollment procedures and dose titration, and prospective assessments of treatment outcomes.

In summary, anxiety frequently occurs in WS yet no prospective treatment studies have been conducted which can guide treatment. Buspirone appears promising in the treatment of anxiety disorders in WS. A prospective, pilot study is urgently needed to address this large gap in treatment knowledge. This project is extremely relevant to advancing the knowledge about WS and its treatment. The proposal will characterize anxiety in a sample of individuals with WS and each participant will receive open-label treatment with buspirone

C. INNOVATION

Studying the treatment of anxiety in WS is highly novel. Anxiety is a common co-morbidity in WS though it hasn't received attention in terms of characterization or treatment. This trial when completed will be the first prospective study of a medication for the treatment of anxiety in WS. Buspirone itself has a unique mechanism with a benign side effect profile and appears promising in treating anxiety in WS.

Our group has published a case series with this drug in adolescents/young adults with WS. We continue to use it clinically at our neurodevelopmental disorders center, often as the first-line pharmacotherapy for interfering anxiety in WS. Over the years, we have found buspirone to be particularly effective as a first-line agent for the treatment of disabling anxiety. This project represents a novel avenue of study and we expect that it will advance knowledge on how best to treat anxiety in WS. This data could also be used to obtain future funding for a more definitive randomized controlled trial.

D. RESEARCH STRATEGY

Study Design:

A 16-week, flexibly-dosed, open-label trial of buspirone was chosen as the optimal way of gathering quality preliminary data. Participants will be seen at screen, baseline, and following 4, 8, 12, and 16 weeks of treatment. The duration of the trial will allow us to adjust the dose of study drug over the first 12 weeks and allow for stable dosing during the final 4 weeks of the trial. We may complete visits remotely utilizing Partners approved secure videoconferencing platforms such as Zoom or by phone.

Participants:

Twenty children, adolescents, and adults, 5 to 65 years of age, with a genetic or clinical diagnosis of WS exhibiting clinically significant anxiety on standardized rating scales will be recruited for this trial. All caregivers calling for an appointment at our Center are asked if they have any interest in participating in research. The Lurie Center's IRB-approved research registry will also be searched to identify participants eligible for this project. The approved study research invitation letter will be sent will also be sent via patient gateway to Mass General Brigham patients diagnosed with Williams syndrome and meeting age criteria utilizing a queried list from the Mass General Brigham Research Patient Data Registry (RPDR). Given the size of the Lurie Center, we do not expect significant difficulty in recruiting 20 subjects over the 3 years of the project.

Subjects and their legal guardians interested in participating in the study will have a face-to-face interview with the PI and/or the research coordinator/assistant where the nature of the project, the risks, the benefits, and the alternatives to participation in the project are discussed. Prior to engaging in research, formal written consent will be obtained from the parent(s)/legal guardian(s) on an IRB-approved consent form. An IRB-approved assent form will also be used for the subjects under the age of 18 years of age. The only exception will be for younger children with lower developmental levels who are assessed as incapable of participating in even a simplified discussion of benefits, risks, and alternatives.

Inclusion Criteria:

1. **Age 5 to 65 years of age**
2. **Diagnosis of WS** confirmed via genetic testing or a clinical diagnosis made by a clinician with significant experience treating patients with WS
3. **Clinically significant anxiety as evidenced by a Pediatric Anxiety Rating Scale (PARS) score of 10 or greater (5-item scale).** The PARS ("The Pediatric Anxiety Rating Scale (PARS): Development and psychometric properties." 2002) was chosen as an inclusion criterion (and outcome measure) since it assesses severity across common anxiety disorders in children including generalized anxiety, social anxiety, separation anxiety, and transition-associated anxiety. In addition, it is an instrument that allows the clinician to incorporate both child and parent report into a final clinician-rated score for each item.
4. **A Clinical Global Impression Severity Item score ≥ 4 (moderate) for anxiety** symptoms at Screen and Baseline.

Exclusion Criteria:

1. **Diagnosis of OCD, posttraumatic stress disorder, major mood disorder, psychotic disorder, or substance use disorder.** These disorders are exclusionary since the primary treatment of these disorders may require acute psychosocial treatments or other medications that would confound the assessments.
2. **Presence of any past or present conditions that would make treatment with buspirone unsafe.** This includes allergy to buspirone, liver or kidney disease, and pregnancy (or being sexually active without using acceptable methods to prevent pregnancy).
3. **Use of selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), benzodiazepines, antihistamines (as needed use of an antihistamine for the treatment of allergies will be permitted), or antipsychotics.** Subjects will need to be off medications from these classes for at least 5 elimination half-lives prior to beginning the trial.
4. **Use of other psychotropic medications which are ineffective, poorly tolerated, or sub-optimal in terms of dose.** A board-certified child and adolescent psychiatrist will assess any other psychotropic medications being used and determine whether they are effective, tolerated, and optimal in terms of dose. Concurrent use of a psychotropic medication (other than SSRIs, SNRIs, benzodiazepines, antihistamines, or antipsychotics) will be allowed if the dose has been stable for 30 days and if they meet the criteria of effectiveness, tolerability, and dose.
5. **Previous adequate trial of buspirone.** An adequate trial will be defined as a total daily dose of ≥20 mg for at least 4 weeks. In addition, subjects who developed significant adverse effects during a trial of buspirone at any dose or duration will be excluded.
6. **Severe or profound intellectual disability based on clinical assessment and review of standardized assessment of cognitive skills.** Subjects will undergo standardized testing and be evaluated by study staff to determine cognitive capabilities. Participants determined to have severe or profound intellectual disability will be excluded.

Baseline Characterization:

All subjects will have a baseline psychiatric diagnostic evaluation done to gather a thorough developmental, medical, and psychiatric history, as well as a mental status exam and height and weight will be obtained for subjects evaluated in the clinic, and additionally provided by a caregiver at the week 16 visit if completed remotely. The medical history and exam will be aimed at ruling out other medical conditions that could exacerbate anxiety or behavioral symptoms (e.g., chronic gastrointestinal disease, obstructive sleep apnea, thyroid disease). The following standardized scales and testing will also be conducted.

1. **Stanford-Binet Intelligence Scales, Fifth Edition (SB-5)**. The SB-5 will be used to calculate an abbreviated battery IQ. The abbreviated IQ was chosen to limit subject burden given that a number of other measures will be conducted at screening and can be administered remotely.
2. **The Weschler Abbreviated Scale of Intelligence, Second Edition (WASI-II).** The WASI-II can also be administered remotely and will be used for subjects depending on age and ability.
3. **Developmental Profile, Fourth Edition (DP-4).** If patients are unable to obtain a valid score on the SB-5 ABIQ or WASI-II due to constraints of a virtual visit, significantly delayed cognitive skills, or inability of participant to cooperate with testing, the Cognitive and Adaptive Behavior subscales of the Developmental Profile (DP-4) Parent/Caregiver Interview Form will be administered.

Buspirone Treatment:

Subjects will receive buspirone 2.5 mg each morning at the start of the trial. The dose will be increased by 2.5 mg per week in two divided doses daily depending on effectiveness and tolerability. During the first 12 weeks, patients will be seen monthly with additional telephone visits conducted in between clinical visits for additional monitoring of adverse effects and for dosing adjustment as necessary. The optimal dose will be reached by week 12 of treatment. A final visit will be conducted at week 16. The minimum starting dose will be 2.5 mg and the maximum total daily dose will be 30 mg. Buspirone is prepared in 5 mg tablets and will be dosed twice daily due to the short half-life (2-3 hours) of this medication (see example of dosing schedule below).

Example Dosing Schedule*		
	Morning Dose (mg)	Afternoon Dose (mg)
Week 1	2.5	None
Week 2	2.5	2.5
Week 3	5	2.5
Week 4	5	5
Week 5	7.5	5
Week 6	7.5	7.5
Week 7	10	7.5
Week 8	10	10
Week 9	12.5	10
Week 10	12.5	12.5
Week 11	15	12.5
Week 12	15	15
Week 13-16	Stable dose for last 4 weeks of study	
**The schedule is a guide and may be adjusted depending on tolerability and effectiveness.*		

Outcome Measures:

1. **Pediatric Anxiety Rating Scale (PARS)**. The PARS will be the primary outcome measure. It will be conducted at screening, baseline, and each follow-up visit.
2. **Child and Adolescent Symptom Inventory (CASI) Anxiety Items**. These include 20 parent-rated items from the Child and Adolescent Symptom Inventory. It will be conducted at baseline and each follow-up visit.
3. **Screen for Childhood Anxiety Related Emotional Disorders (SCARED)**. The SCARED (Birmaher et al 1999) is a 41-item scale that includes both a child/self-report and parent-report form. It is used to screen for symptoms of panic disorder, separation anxiety disorder, social phobia, and generalized anxiety disorder, as well as school phobias. It will be conducted at baseline and each follow-up visit.

4. **Aberrant Behavior Checklist (ABC-2)**. The ABC-2 is a 58-item questionnaire with 5 subscales derived by factor analysis: Irritability, Social Withdrawal, Stereotypy, Hyperactivity, and Inappropriate Speech. It has been extensively used in psychopharmacological studies of autism and other developmental disorders and assesses many symptoms that are either central to autism (Social Withdrawal, Stereotypy, Inappropriate Speech) or frequently a target of treatment (Irritability, Hyperactivity). It will be conducted at baseline and each follow-up visit.
5. **Pittsburgh Sleep Quality Index (PSQI).** The PSQI is a self-rated 19 item questionnaire which assesses sleep quality and disturbances over a one-month time interval (Buysse et al., 1989). It will be used to assess the sleep quality of study participants by parent/caregiver report.
6. **Clinical Global Impressions (CGI)**. A trained clinician will perform the CGI. The CGI is designed to take into account all factors to arrive at an assessment of severity and response to treatment, including parent report, parent-rated measures, and clinician-rated measures (as described below). The CGI Severity (CGI-S) item is rated on a scale from 1 to 7 (1 = normal, not at all ill; 2 = borderline ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; 7 = among the most extremely ill patients). The CGI Global Improvement (CGI-I) item is also rated from 1 to 7 (1 = very much improved; 2 = much improved; 3 = minimally improved; 4 = no change; 5 = minimally worse; 6 = much worse; 7 = very much worse). Subjects receiving a CGI-I rating of 1 or 2 will be classified as **responders** to treatment. The severity ratings will be conducted at screen, baseline and the last follow-up visit. The improvement ratings will be conducted at each follow-up visit.

Safety Monitoring:

According to the buspirone package insert, common adverse events associated with the use of buspirone not seen at an equivalent incidence among placebo-treated patients include dizziness, nausea, headache, nervousness, lightheadedness, and excitement. Treatment-emergent adverse events in placebo-controlled clinical trials occurring at a rate of at least 1% of patients taking buspirone include tachycardia, drowsiness, insomnia, decreased concentration, anger/hostility, confusion, depression, blurred vision, dry mouth, abdominal/gastric distress, diarrhea, constipation, vomiting, musculoskeletal pain, numbness, paresthesia, incoordination, tremor, skin rash, fatigue, and sweating/clamminess. Adverse events will be collected via a structured side effect rating scale completed with the participant and their primary caregiver. This will include a list of adverse experiences that have been reported with buspirone at a rate greater than 1% including but not limited to dizziness, drowsiness, nausea, headache, nervousness, fatigue, insomnia, xerostomia, impaired concentration, hostility, confusion, blurred vision, diarrhea, abdominal pain, numbness, and weakness. Each of these side-effects plus any additional complaints will be rated at baseline on a 4-point scale by the caregiver as follows: 0 = none; 1 = mild; 2 = moderate; 3 = severe. This scale is similar to that used by the RUPP Autism Network. Suicidality will be assessed at each visit by directly asking the subject (when verbal skills are sufficient) and the caregiver about any thoughts or behaviors that directly or indirectly might indicate suicidality (e.g., morbid thoughts, self-injury, statements about life not worth living), when indicated by positive responses. At baseline, the Columbia-Suicide Severity Rating Scale (C-SSRS) will be administered per the instructions at www.cssrs.columbia/ed/clinical_trials.html. The C-SSRS will also be administered at each subsequent visit following the first report of suicidality. Subjects and caregivers will also have information on how to contact the on-call physician from our practice group who provides coverage 24 hours/day and 365 days/year. Physicians taking call are familiar with research protocols and can contact the principal investigator at any time.

All adverse events picked up on the rating scale as new will be recorded by the physician. The physician will also ask about any visits to the doctor, new medication use (e.g. OTC cold medicine), or any other complaints, in order to be confident that most adverse events are uncovered. The physician will keep a running log of adverse events that will record the date of onset, date of resolution, seriousness, severity, and relationship to study intervention

(e.g., definite, probable, possible, remote, or none) as well as whether the adverse event led to a change in study intervention or other treatment.

A physician will review vital signs as they become available. All significant adverse events as well as the progress of the study will be reviewed and discussed in detail at the biannual meetings of the **Data and Safety Monitoring Board (DSMB)**. The DSMB includes rotating members of MGH faculty and/or affiliates including physicians, researchers, and a biostatistician familiar with the study population and design. All serious or unexpected AEs that are possibly related to drug treatment will be reported to the MassGeneral Brigham IRB within 5 working days from notification of the event.

Sample Size Considerations:

Taking into account a likely placebo response, we consider a clinically meaningful decrease in mean PARS score 16 weeks after the start of buspirone to be equivalent to a standardized effect size (mean change/baseline standard deviation) of 1.0. Assuming a standardized effect size of 1.0, a correlation between baseline and week 16 measurements of 0.5, and a total loss to follow up of 30% (resulting in 14 participants providing complete data), a sample size of 20 participants provides greater than 90% power to detect a decrease in mean PARS score from baseline. In addition, for a standardized effect size of 0.2, a sample size of 20 provides nearly 80% power to rule out an effect size as large as 1.0.

For safety outcomes, if there is a serious or severe adverse event associated with buspirone treatment in the population that occurs with a frequency of 10% or more, we will have an 85% or greater chance of observing it in the study and concluding there are safety concerns with buspirone use in the population, assuming at least 90% (n=18) of participants remain in the study long enough to experience the event.

For tolerability, for discontinuation rates due to side effects of 50% or greater, a sample size of 20 provides 80% power to detect a difference from 20%, assuming no more than 10% dropout for unrelated reasons (n=18). All sample size calculations assume two-sided testing with alpha=0.05.

Statistical Analysis Plan:

Demographic and clinical characteristics of the sample will be tabulated using means (SDs) for continuous characteristics and clinical scale scores treated as continuous and frequencies and percents for categorical and ordinal variables.

Change in PARS 5-item total score between baseline and week 16 will provide our primary preliminary estimate of efficacy. To estimate changes in PARS score and all other clinical outcomes but the CGI-I between baseline and week 16, we will use repeated measures linear regression models, as implemented in PROC MIXED in SAS and fit using REML estimation, with repeated measurements of clinical scores as outcomes and time, in categories, as the predictor. Our primary interest will be only in the difference between baseline and week 16 scores, but all observed scores will be included as outcomes, given that partially observed scores may be informative for estimation. We will obtain an estimate of 16-week change and corresponding 95% CI using a contrast of the week 16 and baseline model parameters. A contrast of the same parameters will provide a statistical test of the null hypothesis that there was no change in outcome between baseline and 16 weeks. For the CGI-I, we will estimate the percentage who respond to treatment and corresponding 95% CI using the proportion of participants with CGI-I scores <=2 at 16 weeks. For this calculation, participants who withdrew prior 16 weeks due to side effects will be included as non-responders, and participants who withdrew for other reasons will be excluded. Sensitivity to change will be compared between scales using standardized effect sizes, calculated using the estimated 16-week change in each outcome divided by the SD of the outcome at baseline. We will also tabulate and compare the percent of item-level missing data for each scale.

Frequency of all side effects and adverse events and corresponding 95% CIs will be tabulated. Tolerance and corresponding 95% CI will be estimated using the proportion of participants who did not withdraw from the study before 16 weeks due to reasons other than side effects or an adverse event who discontinue treatment due to side effects or an adverse event. We will also use the 16-week study retention rate and corresponding 95% CI, calculated as the proportion of the participants enrolling in the study who remain in the study for 16 weeks, as a measure of feasibility.

Confidence intervals for binomial proportions will be calculated using Wilson's method. Confidence intervals and statistical tests will be two-sided, with test-wise alpha=0.05.

Data Management:

When a participant is enrolled in the study, he or she will be assigned a unique identification number that is used to identify all data associated with that person, including hard copy, and computerized data. Data will be collected on hard-copy forms and then verified by data entry personnel. All of the hard copy research data is kept in locked file cabinets at the Lurie Center. Only the PI and primary research assistants will have access to these files, ensuring security of the hard copy records.

Once data is obtained, the clinician will review the form to make sure that all required items are completed and to clarify any ambiguous notations before giving it to the research assistant responsible for data entry. Several quality control measures are built into our computerized data management. Data entry forms have been designed that correspond to the measures used in this study. These forms are configured so that out-of-range values cannot be entered; data entry prompts appear in the correct order, including skipping questions when appropriate; and entered values cannot be inadvertently overwritten. Immediately after data entry, a series of logic check programs are run automatically, indicating any entered values that appear incorrect and the reason why. Logic check reports will be reconciled with the hardcopy and, if necessary, the clinician. Changes will then be entered, and the logic check programs executed again in order to detect any new errors resulting from the changed values. The process will continue until no further errors are detected by the logic check programs.

Project Milestones:

Year 1: The trial will be initiated after obtaining IRB approval. Eight subjects will enroll into the protocol.

Year 2: Trial enrollment continues. An additional 8 subjects will be enrolled into the protocol.

Year 3: Trial enrollment continues. The final 4 subjects will be enrolled into the protocol. Data will be analyzed.

Schedule of Measures:

Table 1. Schedule of Measures		Treatment Phase							
Measure	Screen	Baseline	Week 2*	Week 4	Week 6*	Week 8	Week 10*	Week 12	Week 16
Parent Ratings [1]									
Demographics	X								
PARS [2]	X	X		X		X		X	X
SCARED [3]		X		X		X		X	X
CASI Anxiety [4]		X		X		X		X	X
ABC-2 [5]		X		X		X		X	X
PSQI [6]		X		X		X		X	X
Subject Assessments									
Height, Weight	X								
Urine Pregnancy Test [7]	X								

PARS**	X	X		X		X		X	X
SCARED**		X		X		X		X	X
Stanford-Binet-5 (SB-5), WASI-II [8], or Developmental Profile-4 (DP-4)	X								
Treating Clinician									
WS Diagnosis [9]									
Diagnostic Exam including medical/psychiatric History	X								
Health/Behavior Review	X								
Adverse Effects Review		X	X	X	X	X	X	X	X
CGI-Severity [10]	X	X							X
CGI-Improvement [11]				X		X		X	X
Suicide Assessment [12] / C-SSRS* [13]	X*	X*	X	X*	X	X*	X	X*	X*
Concomitant Treatments	X	X	X	X		X	X	X	X
Concomitant Medications	X	X	X	X		X	X	X	X

Telephone Visit; [1] Parent or primary caretaker ratings; [2] PARS = Pediatric Anxiety Rating Scale; [3] SCARED = Screen for Child Anxiety Related Disorders; [4] CASI Anxiety = Child & Adolescent Symptom Inventory; [5] ABC-2 = Aberrant Behavior Checklist, Second Edition; [6] PSQI = Pittsburgh Sleep Quality Index; [7] Females of child-bearing potential only; [8] WASI-II = Weschler Abbreviated Scale of Intelligence, Second Edition; [9] genetic testing or clinical diagnosis; [10] CGI-S = Clinical Global Impression for Severity; [11] CGI-1 = Clinical Global Impression for Improvement [12] Suicide Assessment included in Adverse Effect Review; [13] Columbia-Suicide Severity Rating Scale (C-SSRS) will be administered to participant and/or parent if any positive suicidal ideation is reported during clinical assessment. Each visit following the first report of suicidal ideation will include the administration of the C-SSRS.; ** when subject's communication abilities allows

F. ENVIRONMENT

The performance site is the Lurie Center in Lexington, Massachusetts. It serves as the major referral site for children, adolescents, and adults with autism and other neurodevelopmental disorders from throughout the State of Massachusetts, as well as neighboring states. Research is a major focus of the Center's mission. Approximately 20 patients with WS are seen annually for an initial evaluation, thus ensuring an adequate sample from which to recruit.

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