An Open Label Study of Glutathione in Children with Autism Spectrum Disorder

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This project will take place at the University of Chicago, Department of Child and Adolescent Psychiatry. Dr. Karam Radwan, M.D., is the Principal Investigator and can be contacted at 773-834-6686, email at kradwan@yoda.bsd.uchicago.edu or by mail at 5841 South Maryland Ave (MC 3077), Chicago, IL 60637.

This clinical trial will be conducted in the spirit of Good Clinical Practice (GCP) and in accordance with an IRB approved protocol. No deviation from the protocol will be implemented without the prior review and approval of the IRB except where it may be necessary to eliminate an immediate hazard to a research subject. In such a case, the deviation will be reported to the IRB as soon as possible.

Population
The population to be studied for this trial are children and adolescents, both male and female, ages 4-17 that have a current diagnosis of Autism Spectrum Disorder (ASD).

Diagnostic Criteria (1)
The following diagnostic criteria for ASD will be utilized. Criteria are defined by the Diagnostic and Statistical Manual for Mental Disorders (DSM-5) for a diagnosis of Autism Spectrum Disorder (1):

A. Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history (examples are illustrative, not exhaustive, see text):

1. Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation; to reduced sharing of interests, emotions, or affect; to failure to initiate or respond to social interactions.
2. Deficits in nonverbal communicative behaviors used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures; to a total lack of facial expressions and nonverbal communication.
3. Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behavior to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers.

Specify current severity: Severity is based on social communication impairments and restricted repetitive patterns of behavior.

B. Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least two of the following, currently or by history (examples are illustrative, not exhaustive; see text):

1. Stereotyped or repetitive motor movements, use of objects, or speech (e.g., simple motor stereotypies, lining up toys or flipping objects, echolalia, idiosyncratic phrases).
2. Insistence on sameness, inflexible adherence to routines, or ritualized patterns or verbal nonverbal behavior (e.g., extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat food every day).
3. Highly restricted, fixated interests that are abnormal in intensity or focus (e.g., strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interest).
4. Hyper- or hyporeactivity to sensory input or unusual interests in sensory aspects of the environment (e.g., apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement).

Specify current severity: Severity is based on social communication impairments and restricted, repetitive patterns of behavior.

C. Symptoms must be present in the early developmental period (but may not become fully manifest until social demands exceed limited capacities or may be masked by learned strategies in

later life).

D. Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.

E. These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay. Intellectual disability and autism spectrum disorder frequently co-occur; to make comorbid diagnoses of autism spectrum disorder and intellectual disability, social communication should be below that expected for general developmental level.

Note: Individuals with a well-established DSM-IV diagnosis of autistic disorder, Asperger's disorder, or pervasive developmental disorder not otherwise specified should be given the diagnosis of autism spectrum disorder. Individuals who have marked deficits in social communication, but whose symptoms do not otherwise meet criteria for autism spectrum disorder, should be evaluated for social (pragmatic) communication disorder.

Specify if:

- With or without accompanying intellectual impairment
- With or without accompanying language impairment
- Associated with a known medical or genetic condition or environmental factor
- Associated with another neurodevelopmental, mental, or behavioral disorder
- With catatonia

Project Goals

The goal of the proposed study is to evaluate the safety and feasibility of oral Glutathione in children and adolescents who have Autism Spectrum Disorder. Twenty-four subjects with ASD will receive 12 weeks of oral Glutathione reduced. The hypothesis to be tested is that: Oral Glutathione will be effective in increasing the blood level of Glutathione, which may help to decrease some problem behaviors and irritability in this particular ASD population. The second aim of this study is to evaluate the tolerability of oral Glutathione. The proposed study may provide needed data for future studies aimed at the treatment of aggressive behaviors that can be seen in this patient population.

Background and Significance

Autism Spectrum Disorder is a complex neurodevelopmental disorder, which can involve impaired social interaction, impaired language and communication, limited interest, repetitive/ritualistic behaviors and sometimes aggressive behavior (3). Although Autism Spectrum Disorder has been described in medical literature for years, it remains poorly understood and the exact etiology and neurobiology are not quite clear. However, an emerging topic in research is the imbalance between bodily oxidative systems and anti-oxidative stress in Autism Spectrum cases (i.e. redox systems). Glutathione is involved in neuro-protection against oxidative stress and play a major role in our anti-oxidative stress systems, which may mean that decreasing oxidative stress over time could be a possible treatment for some problem behaviors that are seen in Autism Spectrum Disorder (3).

Glutathione is a vital antioxidant agent, necessary for neutralizing reactive oxygen species (i.e. free radicals) and it is needed for optimal detoxification or removal of toxic substances from the human body (5, 7). There is evidence that indicates that children with Autism Spectrum Disorder have lower levels of plasma reduced Glutathione than in typically developing children (5). This finding has been observed across several neuropsychiatric conditions. The lower levels of glutathione that are seen in this population appear to be due to abnormalities found in the transsulfuration pathway, a pathway that is key for Glutathione production (5). The decreased or diminished levels of Glutathione can potentially lead to accumulations of reactive oxidative species which may cause functional changes in DNA, RNA, protein, lipid and carbohydrate systems, leading to cellular dysfunction (4). This redox variance appears to be involved in the pathogenesis of ASD and has been proposed by other studies (4).

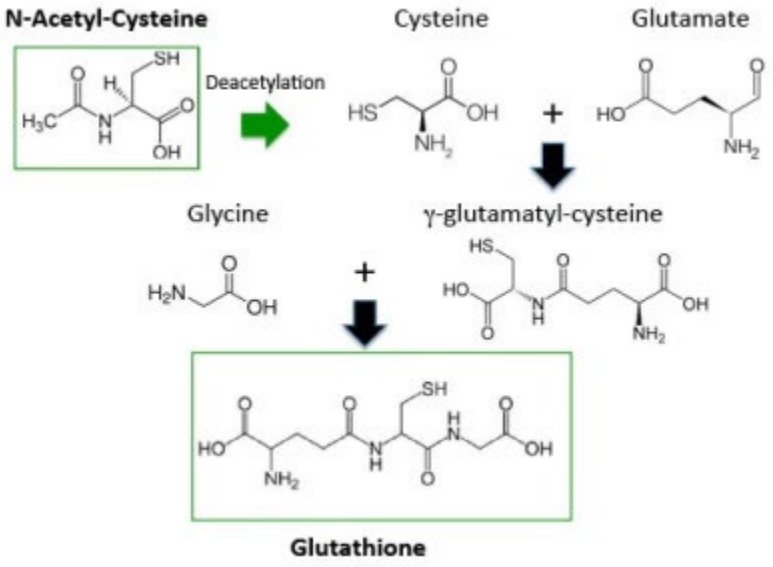
According to the Centers for Disease Control, the prevalence of Autism Spectrum Disorder in 2014 was about 1 in 59 children (aged 8) in 11 communities across the US and has been increasing (2). The disorder occurs in all racial, ethnic and socioeconomic groups; and it is about 4 times more common among males than females (2). The concern over the last several years has been how to effectively treat patients with ASD and especially those with significant social impairments and behavioral dysregulation. Some children who have ASD can present with irritability, which refers to vocal and motoric outbursts demonstrating anger, frustrations and/or distress, often referred to “temper tantrums,” “rages,” or “meltdowns” (8). Along with irritability, some children may also present with problem behaviors, which refers to physical acts of aggression that have a high potential to result in harm to themselves, other people or property (8). The severity of the irritability or problem behaviors can have a significant impact on how the child is perceived

by the outside world and can hinder their socialization with others even further. Other very important concerns are how the behaviors can jeopardize educational placements and can possibly lead to inpatient psychiatric admissions or long-term residential placements (8).

Although a number of medications have been used to treat comorbidities associated with ASD such as neuroleptic agents, antidepressants, stimulants and anxiolytics, there is limited evidence about direct pharmacologic treatment of ASD alone. However, complementary and alternative medicine has been showing some potential promise in treatment options for this patient population. There have been some placebo-controlled trials of N-acetylcysteine (NAC) in ASD patients directed toward the treatment of irritability, aggression, self-injurious behavior and tantrums (11). Harden et al. (2012), found a significant reduction in irritability symptoms that were measured by the Aberrant Behavior Checklist in a placebo-controlled pilot trial of NAC in children with ASD (4). Another 12-week randomized, double-blind, placebo-controlled trial of oral NAC in children with ASD; found NAC to be safe; however, it was not noted to have a significant impact on core social impairment seen in ASD, but the authors did indicate that larger scaled trials are needed in order to predict a good treatment response (11).

N-acetylcysteine is an antioxidant agent and glutamatergic modulator, it is also a precursor to Glutathione via cysteine production. Glutathione is found naturally in the human body and produced by the liver; it is a 3-amino acid (tripeptide) that is composed of cysteine linked to glutamate and followed by glycine attachment (Figure 1). When N-acetylcysteine is de-acetylated, cysteine is provided to feed into the transsulfuration pathway, leading to the production of Glutathione (9). Glutathione is also found in plants, all mammalian tissue, fungi and some bacteria; and it is considered a key determinant of redox signaling, vital in detoxification of xenobiotics, regulates cell proliferation, apoptosis and immune function (6, 7). As mentioned, there is some evidence that antioxidant agents may be beneficial in reducing irritability or aggression in children with ASD. Therefore, we believe that by testing the feasibility of using oral Glutathione directly, and examining the anticipated changes in Glutathione blood level, as we are bypassing the transsulfuration pathway and providing Glutathione supplementation to the body, may be beneficial for ASD patients. Given that Glutathione may have various advantages over other pharmacological agents in treating children with ASD, and it is an all-natural supplement, it can be a promising treatment for irritability and problem behaviors seen in this population and may play a role in correcting the lower levels of plasma reduced Glutathione often observed in children with ASD.

Figure 1: Image NAC de-acetylation and formation of Glutathione (9)



Aims

1) To determine whether Glutathione given over a 12-week period increases plasma Glutathione level in a sample of 24 children aged 4-17 years old with a history of Autism Spectrum Disorder.
2) To determine the feasibility of using oral Glutathione in this patient population
3) To test whether oral administration of Glutathione supplement is well tolerated as a medical food in children with ASD.

Overall, we will examine the effects of Glutathione in children with Autism Spectrum Disorder. Evidence suggests that Glutathione may reduce reactive oxygen species that can accumulate in patients with ASD and thereby may help to decrease significant problem behaviors seen in this population. We hypothesize that oral Glutathione will be safe and well tolerated in patients with Autism Spectrum Disorder.

METHODS

The study will consist of **12 weeks of open label trial** with treatment of oral Glutathione in 24 subjects with ASD; the subjects will be recruited at the University of Chicago. Subjects will be seen every two weeks for the first month and then every four weeks for the remaining two months with one final visit at the end of the study for a total of 5 visits.

Study Location

This is a single-site trial in the United States, with a total of 24 subjects aged 4-17. The Principal

Investigator for this study is:

Karam Radwan, M.D.
Professor of Child and Adolescent Psychiatry
University of Chicago
5841 South Maryland Avenue, Chicago, IL, 60637

All subjects will be seen in the Department of Child and Adolescent Psychiatry at the University of Chicago Medical Center at 5841 South Maryland Avenue. The offices are connected to the Department of Psychiatry and provide confidential interview rooms and facilities.

Investigational Agent
Glutathione (GSH) Reduced (Oral Capsules - Jarrow Brand)
– for patients 40kg or less: 500 mg by mouth twice a day for two weeks, then 1000 mg by mouth twice a day for ten weeks.
– for patients greater than 40 kg: 500 mg by mouth twice a day for two weeks, then 1000 mg by mouth twice a day for two weeks, then 1000 mg by mouth each morning and 2000 mg by mouth every afternoon for eight weeks.
– Dosages will be increased based on tolerability and the monitoring of any potential GI side effects as determined by the investigator.

Dosing Regimen for ≤40kg group (BID dosing throughout study)
Week 0 (Visit 1) – Week 2 (Visit 2): 1000mg/day (500mg po qam and 500mg po qpm)
Week 2 (V2) – Week 12 (V5): 2000mg/day (1000mg po qam and 1000mg po qpm)

Dosing Regimen for ≥40kg group (BID dosing throughout study)
Week 0 (Visit 1) – Week 2 (Visit 2): 1000mg/day (500mg po qam and 500mg po qpm)
Week 2 (V2) – Week 4 (V3): 2000mg/day (1000mg po qam and 1000mg po qpm)
Week 4 (V3) – Week 12 (V5): 3000mg/day (1000mg po qam and 2000mg po qpm)

Maximum Amount of Study Drug Needed
V1: 1000mg = 2 (500mg) pills x 14 days = 28 pills
V2: 2000mg = 4 (500mg) pills x 14 days = 56 pills
V3: 3000mg = 6 (500mg) pills x 28 days = 168 pills
V4: 3000mg = 6 (500mg) pills x 28 days = 168 pills
V5: none dispensed (end of study) total per subject: 420 pills
TOTAL PILLS for 24 subjects = ~10,080pills maximum (based on recruiting patients ≥40kg)

SUMMARY OF DATA COLLECTION AND STUDY PROCEDURES BY VISIT		
		Visit

	Screening	1	2	3	4	5	6
Consent Forms:	X						
Medical Procedures on Child							
Blood draw		X					X
Heart rate		X	X	X	X	X	X
Blood pressure		X	X	X	X	X	X
Parent Reports on Child							
Aberrant Child Checklist	X	X	X	X	X	X	X
Social responsiveness Scale	X	X	X	X	X	X	X
Clinical Global Impression Scale	X	X	X	X	X	X	X
PRAS ASD	X						X
Vineland-3	X						X
Side effects checklist		X	X	X	X	X	X

Subject Recruitment
All potential subjects for this study will be recruited through the Child and Adolescent Psychiatry Department Neurodevelopmental clinic and by Neuropsychological referral.

Subjects:
Inclusion criteria:
1) Boys and girls ages 4-17;
2) Current diagnosis of Autism Spectrum Disorder as determined by criteria in DSM-5
3) Parents of Children ages 4-17 with a current diagnosis of Autism Spectrum Disorder as determined by criteria in DSM-5

Exclusion criteria:
1) Unstable medical illness or clinically significant abnormalities on physical examination;
2) History of seizures;
3) History of Hematological disorders;
4) Myocardial infarction within 6 months;
5) Current pregnancy or lactation, or inadequate contraception in girls of childbearing potential;
6) Current or recent (past 3 months) DSM-5 substance abuse or dependence;

7) Illegal substance use within 2 weeks of study initiation;

8) Previous treatment with Glutathione;

9) Current treatment with N-acetylcysteine, milk thistle, Vitamin C, Vitamin B, Grape Seed Extract, Amino Acids, or Zinc (known to interfere with Glutathione level)

11) Current treatment with Dextromethorphan, D-cycloserine, Amantadine, Memantine, Lamotrigine or Riluzole (known to have glutamatergic properties)

12) Asthma (given this is rare, but possible worsening of asthma symptoms due to Glutathione)

Assessments:
Existing Data
Before beginning Glutathione, all subjects will have a psychiatric, medical, and family history evaluation completed as part of their standard clinical care.

New Data Collection
At the screening visit, all subjects will receive a physical examination. For all subjects, at the initial visit, blood work will be obtained for a baseline Glutathione level. Glutathione level will also be obtained at study completion. Total amount of blood to be obtained will be 4 teaspoons. PI will obtain neuropsychological evaluations report if it is available.

The following instruments will be completed at each visit throughout the study: 1) Aberrant Behavior Checklist [ABC], a 58-item parent report subjective scale used for assessing problem behavior in subjects with intellectual and developmental disabilities; 2) Social Responsiveness Scale [SRS], a 65-item parent report questionnaire designed to use with children ages 4-17, providing age- and gender-referenced ranges and assessing social deficits pertaining to autism and

other domains; and 3) the Clinical Global Impression scale [CGI]; 7 point scale to measure symptom severity. Also, readings of patients' heart rates and blood pressures will be obtained; and assessment of side effects will be done at each visit.

Note on ABC and SRS:
The ABC is a standardized scale used for assessing problem behaviors in subjects with developmental and intellectual disabilities. The items are divided into five subscales: 1) Irritability; 2) Lethargy/Social Withdrawal; 3) Stereotypic Behavior; 4) Hyperactivity; and 5) Inappropriate Speech. High scores are indicative of severe behavioral symptoms. The ABC will be used to track the subjects' problem behaviors and difficulties over the course of the study. The severity of the subjects' problem behaviors must be assessed and examined its relationship with a baseline blood level of glutathione. In addition, by using this scale, we can observe the overall effect of oral Glutathione on problem behaviors, especially comparing the end results to the baseline.

The SRS is being used for the same purpose, although it is being used for secondary outcome measures. It is a parent report questionnaire designed for use with children aged 4-17 and provides age- and gender-referenced, as well as raw scores for the following domains: total score (reflecting severity of social deficits pertaining to autism); receptive, expressive, cognitive and motivational aspects of social behavior; and autistic preoccupations. High scores are also indicative of severe behavioral symptoms.

Note on additional measures:
Clinical Global Impression (CGI) (Severity) scale will be used by the clinician to assess overall severity of problem behaviors in Autism Spectrum Disorder subjects at baseline. This will be used as a secondary outcome measure over the course of the study and relates to Aim #1.

Study Population/Sample Size
24 male and female outpatients aged 4-17 with a primary diagnosis of Autism Spectrum Disorder.

-*Note on sample size*: The sample size is low due to this being a pilot feasibility study and the primary aim of the study is not to examine the effectiveness of oral glutathione as a treatment but rather examine the functionality of providing oral glutathione on the blood level, the data will likely be used for future studies on treatment or grant applications. There also is no external sponsor, therefore internal funding limits the number of subjects.

Participant Exclusion:
For this study, children under the age of 4 and adults over the age of 17 will be excluded. The rationale for this is that the study population of interest are pediatric subjects in the children and adolescent age ranges.

Data Analysis:
Primary analyses will be intent-to-treat with last observation carried forward. Changes in the blood level of glutathione will be the primary outcome measure. For both primary and secondary measures, random regression analysis will be conducted using the MIXREG program
Demographic and baseline visit characteristics of the Glutathione treatment patients will be documented. Primary and secondary measures will be examined using analysis of variance modeling analyses (SPSS). The difference in the overall level of posttreatment values, the main effect for treatment, will be the test of primary interest. Analyses will be performed on all available data by the use of an intention-to-treat population (last observation carried forward). All patients who return for at least 1 follow-up visit will be included in the intention-to-treat population. Effect sizes will also calculated using the Cohen effect size index d. A d of 0.2 is considered a small effect size, 0.5 is medium, and 0.8 is large. Partial eta squared ($\eta 2$), which is the proportion of the effect + error variance that is attributable to the effect, will be calculated. Interpretation of $\eta 2$ is that greater than 0.2 is a large effect size, greater than 0.1 is a medium effect size, and greater than 0.05 is a small effect size.

The CGI severity scale will be used to assess clinically significant change after treatment. For someone to have a clinically significant change, her or his final CGI severity score had to be less than the cutoff score, and her or his change from baseline had to be greater than the reliable change index

The study will end once 24 subjects have been recruited and have completed the study visits. At this point, the data analysis will then begin.

Potential Risks and Benefits:
The study supplement Glutathione may help to decrease problem behaviors and irritability that can be seen in children with Autism Spectrum Disorder. It is also postulated that the information learned from this study will benefit other individuals and children and adolescents with problem behaviors related to Autism Spectrum Disorder in the future.

Most supplements can cause side effects, but are typically safe. Side effects are usually reversible when the supplement is stopped. The most common side effects associated with Glutathione include; upset stomach, diarrhea, dizziness, dry mouth or headaches and sometimes, but rarely a skin rash, skin flushing or respiratory distress can be seen. As such, patients with asthma or allergies that have resulted in respiratory distress in the past will not be included in this study to ensure safety.

Safety Assessments:
Safety assessments (sitting blood pressure, heart rate, adverse effects, and concomitant medications) will be documented at each visit. In terms of vital signs, those subjects with abnormal blood pressures will be assessed for symptoms of hypo- or hypertension. Asymptomatic subjects will be evaluated each visit for changes in vital signs. In the case of hypertensive emergencies (BP greater than 210/120), appropriate referral to the emergency room will be made. In the case of hypotension (BP less than 90/60), participants will be evaluated for symptoms of hypotension and if symptomatic, appropriate interventions will be made. Subjects who endorse suicidal thoughts at any time during the study will be removed from the study and appropriate clinical intervention (e.g. hospitalization) will be arranged.

At the initial visit, blood work will be obtained for a baseline Glutathione level and an end point Glutathione level will also be obtained at study completion. Assessment of side effects will be done at each visit. Participants will be advised concerning the risk of allergic reactions to Glutathione: skin rash, skin flushing, drop in blood pressure, irregular heartbeat, and respiratory distress. Although is it extremely rare but participants will be advised to visit an emergency room for symptoms suggestive of anaphylactoid reactions.

Adverse Event Reporting:
Unanticipated (unexpected) problems/events, those that are not already described as potential risks in the consent form, or not part of an underlying disease, will be reported to the IRB within 10 business days. The same will be done for serious problems/events and, in the opinion of the investigator, are possibly, probably or definitely related to the research procedures. A follow-up report will also be submitted to the IRB with any documentation related to a previously submitted adverse event.

Procedure:
Twenty-four (24) subjects will be recruited to receive oral Glutathione reduced in this open-label trial. All parents of the subjects will be provided with informed consent forms and verbal assent from subjects $\geq$ 6 years of age will be obtained after an age appropriate version of the informed consent forms are read to them. The Child Psychiatry clinicians/nurses, patients and parents will be aware of the medication name and dosing schedules as indicated. The clinic nurse will obtain vitals at each visit. Glutathione will be the only study medication dispensed to subjects for this study. Subjects will be told to take the first dose of study medication after breakfast each day and the second dose in the evening after dinner. Subjects will be told to monitor and report any side effects experienced to the study staff at each visit or immediately if they wish (via one of the

multiple telephone numbers for the study physicians and study staff given to them at each visit).

Psychotherapy of any form (including cognitive-behavioral therapy) will be reported to the PI during the study.

Subjects will be evaluated with the Aberrant Behavior Checklist (ABC), Social Responsiveness Scale (SRS) and CGI at screening and at each visit for the remainder of the study. Medication side effects will be evaluated at each study visit. A tablet count will be kept for each dose of medication taken to monitor adherence.

Dosing Regimen for Glutathione

The proposed dose range for Glutathione in this study will be 1000mg-3000mg/day based on the subject's weight. A previous observational study of children with Cystic Fibrosis showed that this population responded well and were able to absorb Glutathione with a daily dose of 65mg/kg (10).

As Cystic Fibrosis is a condition that typically results in malabsorption of fats and other products, it is our thought that subjects with normal gastrointestinal (GI) systems may also absorb Glutathione effectively and at a slightly lower milligram starting dose, which is proposed to be ~32.5mg/kg. No adverse events were noted in the above mentioned study; however, to ensure tolerability in subjects with normal functioning GI systems, starting at a low dose and titrating up accordingly will be the most conservative and safe method.

Timeline:

Recruitment for the proposed study will begin as soon as the study drug is available and IRB approval is confirmed. It is anticipated that all subjects would be entered into the study within approximately 6 months, and that the study would be completed within 12 months of initiation.

Ethical Considerations:

This study will be conducted according to US and international standards of Good Clinical Practice (FDA regulations 21 CFR 312 for IND studies and FDA guidance E6) for all studies. Applicable government regulations and University of Chicago research policies and procedures will also be followed.

This protocol and any amendments will be submitted to the University of Chicago Institutional Review Board (IRB) for formal approval to conduct the study. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator.

Parents of all subjects for this study will be provided a consent form describing this study and providing sufficient information for parents to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB. The formal consent of parents of subjects, using the IRB- approved consent form, will be obtained before that subject is submitted to any study procedure. This consent form must be signed by the parents of subjects or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

Data Handling and Record Keeping

All subject data will be maintained by the study personnel under the supervision of the principal investigator. All subjects will be seen in the Department of Child and Adolescent Psychiatry at the University of Chicago Medical Center at 5841 South Maryland Avenue. Patient folders will be kept in a locked cabinet only accessible to research staff.

Finance and Insurance

All research will be paid for by the internal departmental funds of the Department of Child and Adolescent Psychiatry at the University of Chicago.

In the event that this research activity results in an injury, treatment will be available, including first aid, emergency treatment and follow-up care as needed. Care for such injuries will be billed in the ordinary manner to the subjects' insurance company. If the parents of subjects believe that they have suffered a research related injury, they will be instructed to inform the principal investigator immediately.

Compensation

Participation in this study will be completely voluntary and no monetary compensation will be offered.

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Appendix A

Diagnostic Criteria for Autism Spectrum Disorder (1)

The following diagnostic criteria for ASD will be utilized. Criteria are defined by the Diagnostic and Statistical Manual for Mental Disorders (DSM-5) for a diagnosis of Autism Spectrum Disorder (1):

A. Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history (examples are illustrative, not exhaustive, see text):

1. Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation; to reduced sharing of interests, emotions, or affect; to failure to initiate or respond to social interactions.
2. Deficits in nonverbal communicative behaviors used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures; to a total lack of facial expressions and nonverbal communication.
3. Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behavior to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers.

Specify current severity: Severity is based on social communication impairments and restricted repetitive patterns of behavior.

B. Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least two of the following, currently or by history (examples are illustrative, not exhaustive; see text):

1. Stereotyped or repetitive motor movements, use of objects, or speech (e.g., simple motor stereotypies, lining up toys or flipping objects, echolalia, idiosyncratic phrases).
2. Insistence on sameness, inflexible adherence to routines, or ritualized patterns or verbal nonverbal behavior (e.g., extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat food every day).
3. Highly restricted, fixated interests that are abnormal in intensity or focus (e.g., strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interest).
4. Hyper- or hyporeactivity to sensory input or unusual interests in sensory aspects of the environment (e.g., apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement).

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C. Symptoms must be present in the early developmental period (but may not become fully manifest until social demands exceed limited capacities or may be masked by learned strategies in later life).

D. Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.

E. These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay. Intellectual disability and autism spectrum disorder frequently co-occur; to make comorbid diagnoses of autism spectrum disorder

and intellectual disability, social communication should be below that expected for general developmental level.

Note: Individuals with a well-established DSM-IV diagnosis of autistic disorder, Asperger's disorder, or pervasive developmental disorder not otherwise specified should be given the diagnosis of autism spectrum disorder. Individuals who have marked deficits in social communication, but whose symptoms do not otherwise meet criteria for autism spectrum disorder, should be evaluated for social (pragmatic) communication disorder.

Specify if:

- With or without accompanying intellectual impairment
- With or without accompanying language impairment
- Associated with a known medical or genetic condition or environmental factor
- Associated with another neurodevelopmental, mental, or behavioral disorder
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