Study Protocol: Memantine for the Treatment of Social Deficits in Youth with Disorders of Impaired Social Interactions: A Randomized-Controlled Trial

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Version Date: AME 33, submitted to the IRB on 05/19/22
Last Modified: 05/19/22

I. BACKGROUND AND SIGNIFICANCE

One of the most impairing and heart wrenching dysfunctions associated with autism spectrum disorder (ASD) are the impaired interpersonal relationships with colleagues, superiors, and family members referred to as deficits in social cognition. Children and adolescents who have difficulties with social cognition often suffer in the presence of other children as well as effective social communication with adults[1].

To date, there is no treatment available for the management of deficits in social functioning. Our group has studied the role of a glutamate modulating agent, memantine, for improving social functioning in adults and youth suffering from High-Functioning Autism Spectrum Disorder (HF-ASD)[2-7]. In addition, we have documented abnormal brain glutamate in individuals with ASD and brain changes towards normalization of glutamate activity with memantine treatment[8].

Memantine: Memantine hydrochloride is a moderate-affinity, non-competitive, NMDA receptor antagonist. Memantine treatment in adults with Alzheimer's disease improves cognition, as well as functional and behavioral symptoms[9-10]. Available data from limited retrospective and prospective treatment studies of memantine in individuals with ASD report an acceptable tolerability profile with improvement in a range of behavioral impairments including attention, hyperactivity, language, eye contact, social interaction and withdrawal, and repetitive behaviors[11-12].

Our group found promising results in a previous open-label trial of memantine in high-functioning (IQ: mean=106 ±15) adults (N=18) with ASD[13]. Of the 18 participants exposed, only one participant discontinued trial due to treatment-limiting adverse events (AEs). All the participants who completed the 12-week trial (N=17) were receiving maximum study dose of 20 mg/day. The maximum dose of memantine in one participant who completed through week 6 of the trial was limited to 15 mg/day due to cognitive dullness. Memantine treatment was generally well tolerated and was not associated with any serious AEs. In general, AEs were transient and considered mild or moderate. The most commonly reported AE was headache (N=2). There were no clinically significant changes in the safety measures (vital signs) following memantine therapy. Treatment with memantine was associated with significant improvement of autism severity. Significant improvement was noted in nonverbal communication for reading low-intensity facial emotions on Diagnostic Analysis of Nonverbal Accuracy Second Edition (DANVA2) ($p=0.03$) and in the cognitive dysfunction specifically in executive domains of cognitive flexibility, emotional control, and planning and organization. In addition, memantine treatment was associated with significant improvement in attention deficit hyperactivity disorder (ADHD) and anxiety symptom severity.

In an ongoing memantine randomized control trial (RCT) for children and adolescents with HF-ASD, the interim analysis suggests good tolerability. 25 adolescents (mean age 14 ±3 years; males: 80%) with ASD of moderate-severe impairment were randomized to either

memantine (N=11; mean dose=20 mg/day) or placebo (N=12). Memantine was well tolerated (no serious AEs reported). AEs were mild-moderate and transient with the exception of 2 participants who experienced a treatment limiting AE of nausea. Headache was the most common AE though no AEs were reported at significantly higher rate with memantine vs. placebo. RCT findings suggest that treatment with memantine is reasonably well tolerated and appears to be effective in improving features of ASD in intellectually capable children and adolescents.

Given the lack of medication treatments for improving social functioning and based on these encouraging preliminary findings, we propose to build upon our initial results and study the efficacy and tolerability of memantine for the treatment of social deficits in youth suffering from HF-ASD.

Telemedicine: Just as telemedicine has reformed clinical care, it is expected to reform clinical trials[14]. The outpatient psychiatry clinics at Massachusetts General Hospital have used telemedicine for routine clinic appointments for qualifying patients after an in-person consultation. Telemedicine significantly lessens patient burden, as the patient does not have to come into the office for appointments, but still receives the same level of clinical care through the face-to-face video conference. As such, we propose the inclusion of a number of telemedicine visits in this study protocol.

II. SPECIFIC AIMS

Primary Aim

Aim 1: To examine the clinical efficacy and tolerability of memantine for the treatment of social impairment in youth with HF-ASD. We will study the short- and long-term clinical effects of memantine in 60 children and adolescents with HF-ASD by conducting a 12-week randomized-controlled trial (RCT).

III. LENGTH OF STUDY

This study may take up to 16 weeks from enrollment (allowing up to four weeks to schedule and complete the initial screening process and baseline visit). Once participants have completed the screening process and baseline characterization, HF-ASD participants will then begin the 12-week randomized-controlled trial.

IV. PARTICIPANT SELECTION CRITERIA

Inclusion Criteria

1. Male and female participants ages 8-17 years (inclusive).
2. DSM-5 ASD diagnostic criteria as established by clinical diagnostic interview
3. At least moderate severity of social impairment as measured by a total raw score of ≥85 on the parent/guardian-completed **Social Responsiveness Scale-Second Edition (SRS-2)**[15] and a score of ≥4 on the clinician-administered **Clinical Global Impression-Severity scale (CGI-S)**[18].

Exclusion Criteria

1. Impaired communicative speech
2. Participants currently treated with the following medications (known to impact glutamate levels):
   a. Lamotrigine
   b. Amantadine
   c. N-acetylcysteine
   d. D-cycloserine
3. Participants treated with a psychotropic medication not listed above on a dose that has not been stable for at least 4 weeks prior to study baseline.
4. Co-administration of drugs that compete with memantine for renal elimination using the same renal cationic system, including hydrochlorothiazide, triamterene, metformin, cimetidine, ranitidine, quinidine, and nicotine
5. Initiation of a new psychosocial intervention within 30 days prior to randomization.
6. Participants who are pregnant and/or nursing.
7. Participants with a history of non-febrile seizures without a clear and resolved etiology.
8. Participants with a history of or a current liver or kidney disease.
9. Clinically unstable psychiatric conditions or judged to be at serious suicidal risk.
10. Participants who have current alcohol or drug dependence or abuse, as established by clinical diagnostic interview. If the participant has a recent history of substance abuse, there will be a two-week washout period before initiating the trial as an added precaution. There are no known safety issues relating to memantine and recent history of substance abuse.
11. Serious, stable or unstable systemic illness including hepatic, renal, gastroenterological, respiratory, cardiovascular (including ischemic heart disease), endocrinologic, neurologic, immunologic, or hematologic disease.
12. Participants with severe hepatic impairment (LFTs > 3 times ULN).
13. Participants with genitourinary conditions that raise urine pH (e.g., renal tubular acidosis, severe infection of the urinary tract).
14. Known hypersensitivity to memantine.
15. Severe allergies or multiple adverse drug reactions.
16. A history of intolerance or adequate exposure to memantine, as determined by the clinician.

17. Investigator and their immediate family defined as the investigator's spouse, parent, child, grandparent, or grandchild.

V. SOURCE OF PARTICIPANTS

We propose to enroll up to 60 participants with HF-ASD, in order to expose to medication 40 participants who exhibit marked social impairment. Participants will be recruited from the referral pool of existing and new patients at three different MGH sites – the Bressler Program for ASD, the Lurie Center for Autism, and the Child Psychiatry Outpatient Clinic – and from the general public by flyers and internet advertisements. In addition, if any clinician or provider ascertains that one of their patients has an interest in participating in this study, the clinician/provider may provide the patient and their parent/guardian with the study coordinator's contact information. The patient and their parent/guardian may then contact the study coordinator for more information about the study. Potential participants will be screened for eligibility by the study coordinator over the phone using an IRB-approved script prior to enrollment.

School representatives in the Boston areas (e.g., principals or heads of the parent teacher organization/association) will also be approached via telephone or email and asked if study advertising materials can be brought to their school or placed in their school communications (e.g., newsletter). Only upon hearing back from the school representative will any recruitment materials be provided.

Individuals who express interest in the study, will be screened for eligibility by the study coordinator or a research assistant via phone. If their answers to the IRB approved phone screen indicate that they may be eligible for the study, the parent/guardian will be asked to complete the Social Responsiveness Scale – Second Edition (SRS-2) online via RedCap, a secure online data capture system.

The study coordinator will send a link to complete the SRS-2 electronically to the parent/guardian via REDCap. An online consent statement will appear, prompting parents to indicate their agreement to participate in the online questionnaire portion of the study. If the parent/guardian indicates their agreement, the data capture system will proceed to the SRS-2.

After completing the SRS-2, eligible participants based on inclusion and exclusion criteria will either be scheduled to speak with a study clinician via phone to obtain informed consent (and assent as necessary) prior to completing further screening and baseline study procedures via virtual visit.

VI. PARTICIPANT ENROLLMENT

Prior to the completion of any study procedures, the study clinician will remotely conduct informed consent procedures with the participant and their parent/guardian. The study clinician will be a licensed physician and either the Principal Investigator or a co-investigator. The informed consent and assent forms will be used to explain, in simple terms, the nature of the study. The risks and benefits of and alternatives to study participation will be fully explained to the participant and their parent/guardian. The participant and their parent/guardian will be encouraged to ask questions pertaining to their participation in the study and the participant and their parent/guardian may take as much time as they feel necessary to consider their participation in the study, as well as to consult with family members or their physician.

Study staff will schedule a time for the study clinician to conduct informed consent procedures with the participant and their parent/guardian via telephone call. Study staff will provide the participant and their parent/guardian with an IRB-approved consent form and assent form (as applicable) via Adobe Sign or courier mail service. This correspondence will include information about why they are receiving the consent form and directions to inform study staff when the consent form has been received. The study clinician will call the participant and their parent/guardian at the scheduled time and conduct informed consent procedures.

If the participant and their parent/guardian decide to participate in this study, they will sign the consent form and assent form (as applicable) via Adobe Sign or on paper. The signed form(s) will then be sent via Adobe Sign or courier mail service to the study clinician who performed the informed consent procedures for signature. The signed form(s) will then be sent to the study coordinator via Adobe Sign or courier mail service. The study coordinator will perform a completeness check prior to the start of any study procedures and provide the participant and their parent/guardian a copy of the signed form(s) via Adobe Sign or courier mail service.

Participation in this study is voluntary and the participant and/or their parent/guardian may withdraw the participant from the study at any time. The IRB-approved informed consent and assent documents will be signed and dated by the participant's parent/guardian, the participant, and the study clinician obtaining informed consent.

VII. STUDY PROCEDURES

This study is a 12-week randomized-controlled trial of memantine for the treatment of HF-ASD. All study visits and study procedures (excluding informed consent procedures) will be conducted via the MGH telemedicine platform, TeleHealth, which is maintained by Partners HealthCare. In the event that TeleHealth malfunctions or the participant and their parent/guardian do not have access to a device compatible with the TeleHealth platform, the study visit will be completed via Zoom or telephone call instead.

If at any point during a telemedicine study visit, the participant or their parent/guardian endorses any safety concerns or any acute clinical issues emerge, the study clinician will

take the necessary steps to ensure the participant receives the appropriate follow-up clinical care.

The Screening Visit (Week 99) will be conducted in two parts and may take place over multiple days, as necessary. First, informed consent procedures will be conducted via telephone by the study clinician. After the study coordinator has received the signed form(s) via Adobe Sign or courier mail service, the Screening Visit (Week 99) will be scheduled, and the following Week 99 study procedures will be completed.

Clinician:
- Eligibility Checklist (Inclusion/Exclusion Criteria)
- Clinical Interview
- Reproductive Potential Form
- MGH ASD DSM-5 Symptom Checklist
- CGIs (ASD: Social Interaction, ASD: Social Communication, ASD: Mannerisms, ASD: Global, Irritability, ADHD, Anxiety, MDD, Global)

Participant and/or Parent/Guardian:
- Vital Signs (optional)
- Urine pregnancy screen (if applicable)
- Demographic Interview
- SRS-2 (pre-screening)

The collection of the vital signs (blood pressure, pulse, height, weight) will be considered optional. The study coordinator will ask the parent/guardian to report the participant's vital signs on the same day as the study visit via telephone call or email. The study coordinator will note that these data points were provided by parent/guardian report, rather than study staff measurement.

As determined by the Reproductive Potential Form, women of child-bearing potential will complete a urine pregnancy test as part of the Week 99 study visit. If indicated by the Pregnancy Monitoring Form, a urine pregnancy test will also be completed as part of the Week 0, Week 6, and Week 12 study visits.

Study staff will mail a urine pregnancy test directly to the participant's home address. The test will be mailed in advance to ensure delivery prior to the Week 99 study visit. On the same day as the study visit, the study coordinator, the participant, and their parent/guardian will complete the test while connected via telephone call. During the telephone call, the study coordinator will review the proper procedure for completing the test. The participant will complete the test while the parent/guardian remains on the line. The result will be verbally reported to the study coordinator. In addition, the participant's parent/guardian will provide the study coordinator with visual confirmation of the result via email.

In the event that a urine pregnancy test is positive, the study clinician will advise the parent/guardian to follow up with the participant's pediatrician. Study staff will not enter a positive urine pregnancy test into the participant's medical record; this result will be documented in study records only.

If two parents/guardians of the participant are available, we will ask them both to independently complete an SRS-2 form. Both forms will be scored, and the form with the higher score will be used to determine participant eligibility in order to reduce the possibility of under-recognition of social impairment.

We anticipate that participants may enter this study following completion of/withdrawal from other protocols in our office, and that there may be procedural overlap. If a participant has completed an evaluation with one of the study clinicians in the three years prior to entrance into this study, they 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 participant 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 participant meets appropriate study entrance criteria.

All data will be collected and entered into REDCap, an electronic data capture system that streamlines data collection and ensures data integrity. REDCap software allows researchers to design and implement study surveys electronically for collecting, storing, retrieving, and manipulating data.

Parents/guardians and/or research staff will enter survey responses into electronic assessment forms. The responses will then be transmitted securely via an encrypted connection and stored in a secured database. Electronic data capture eliminates the need for subsequent data entry by staff, thus minimizing human error. However, in the event that REDCap is unavailable or malfunctioning, study staff will email all study instruments to the parent/guardian.

12-Week RCT: Participating children and adolescents with HF-ASD who meet the eligibility criteria will be randomly assigned to either memantine or placebo for the course of the 12-week RCT. Participants will be assessed tri-weekly during throughout the 12 weeks (Baseline [Week 0], Week 3, Midpoint [Week 6], Week 9, Endpoint [Week 12]). The same parent/guardian most familiar with the participant's day-to-day behavior will participate in the assessment of behavioral symptoms at all visits. Study visits will have a visit window of +/- 3 days to facilitate scheduling.

Randomization: The MGH Clinical Trials Pharmacy will prepare the blinded memantine and placebo capsules for the study. Participants will be randomized to either active memantine or placebo in a 1:1 ratio after they have been determined to meet all eligibility criteria. Randomization lists stratified by gender and racial/ethnic minority status (minority vs. Caucasian) will be generated by the statistician and passed to the investigational pharmacy for assignment.

Washout Period: Participants who are currently being treated with prohibited psychotropic medications as listed in the exclusion criteria 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 based on 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 but remains available during this time period. The washout schedule – which will span two weeks or more – will be discussed with the participant, their parent/guardian, and current providers. Individuals taking a medication that is effectively and safely treating their symptoms will not be taken off of such medication for the purpose of enrolling in this study.

Trial Phase (Weeks 0-12): Participants will be prescribed study medication for the period of 12 weeks. Study medication will be ordered from and dispensed by the MGH Clinical Trials Pharmacy (CTP). Study staff will pick the study medication up from the MGH CTP and, on the same day, send it via courier mail service directly to the participant's home address. The study medication will be ordered and shipped in advance to ensure delivery prior to the Baseline (Week 0) and Midpoint (Week 6) study visits. Enough study medication will be dispensed to last until Midpoint (Week 6) and Endpoint (Week 12), respectively.

Prior to shipping the study medication, study staff will obtain consent from the participant and their parent/guardian to share their name and mailing address with the courier mail service. They will also ensure that the participant's parent/guardian will be available to receive the shipment. This will be documented in a Note to File and placed in the participant's study binder.

After shipping the study medication, study staff will inform the participant and their parent/guardian of the name of the courier mail service, the package tracking number, and the anticipated delivery date and time. Study staff will also follow up with the participant and their parent/guardian to receive acknowledgement that the study medication was received and that it is in good condition. This will be documented in a Note to File and placed in the participant's study binder with the shipping receipt and tracking number.

In order to minimize study staff presence at MGH, study medication orders for participants from this and other studies within this department will be coordinated so that they can be picked up and mailed in bulk. The study coordinator retrieving the bulk study medication orders will receive prior approval to return to MGH and will be listed as a member of study staff on all applicable studies.

Per standard research procedure, the study clinician will record parent/guardian-reported medication compliance in the applicable Chart Note. After the completion of study participation, the participant's parent/guardian will mail the leftover study medication and bottles to the study coordinator via mail. The study coordinator will complete a thorough capsule count at that time and maintain the study medication until it can be returned to MGH and discarded in a biohazard container.

At Baseline (Week 0), Week 3, Midpoint (Week 6), Week 9, and Endpoint (Week 12) the following study procedures will be completed:

Clinician:
- Chart Note
- CGIs (ASD: Social Interaction, ASD: Social Communication, ASD: Mannerisms, ASD: Global, Irritability, ADHD, Anxiety, MDD, Global)
- Adverse Events
- Concomitant Medications

Participant and/or Parent/Guardian:
- BRIEF Parent Form

At Baseline (Week 0), the following additional study procedures will be completed:

Clinician:
- Pregnancy Monitoring Form

Participant and/or Parent/Guardian:
- Vital Signs (optional)
- Urine Pregnancy Screen (if applicable)
- Child Behavior Checklist

At Midpoint (Week 6), the following additional study procedures will be completed:

Clinician:
- Pregnancy Monitoring Form

Participant and/or Parent/Guardian:
- Vital Signs (optional)
- Urine Pregnancy Screen (if applicable)
- SRS-2

At Endpoint (Week 12), the following additional study procedures will be completed:

Clinician:
- Pregnancy Monitoring Form

Participant and/or Parent/Guardian:

- Vital Signs (optional)
- Urine Pregnancy Screen (if applicable)
- SRS-2
- Child Behavior Checklist

For a complete schedule of assessments, refer to Table I (page 13).

In cases where issues with the scheduled dose titration arise, participants may schedule additional study visits outside of Weeks 99, 0, 3, 6, 9, and 12. Adverse Events and Concomitant Medications will be documented, and a Chart Note will be completed at such visits.

Dose Titration Phase (Weeks 1-4): Study medication will be initiated at 2.5 mg/day, raised to 5 mg/day on day 4, and gradually up-titrated by 5 mg/week to a maximum dose of 20 mg/day. Titration of the study medication will be guided by the (following) forced titration schedule with an option for slower titration or holding at lower dose per clinician judgment. Memantine will be administered in twice daily divided dosages with a total daily dose of ≥2.5 mg/day.

Study Medication Dosing: Study medication (memantine/placebo) will be titrated to the maximum daily dose during the first 4 weeks of the trial (dose titration phase). Participants will follow the following forced titration schedule until Week 4 when participants will be maintained on maximum achieved dose until the end of the trial (dose maintenance phase; Weeks 5-12). During the dose maintenance phase, there will be a one-time option to decrease the dose of the study medication.

Memantine Forced Titration Schedule

Day	*Maximum Total Dose Prescribed (mg/day)*
1	2.5
5	5
8	10
15	15
22	20
28	Maintain maximum achieved dose

Primary Outcome Measure of Efficacy: Clinician-rated CGI-Improvement (CGI-I) subscale and the parent-rated SRS-2. Treatment responders will be defined as those who demonstrated improvement of ≥25% on the SRS-2 total raw score *and* a score of 2 or 1 on the CGI-I subscale ("much" or "very much improved").

Safety and Tolerability Outcome Measures: The safety and tolerability of memantine treatment will be monitored by recording AEs and asking participants to self-report vital signs.

Concomitant Medications/Treatments: As part of the initial psychiatric evaluation, a detailed history of past and present treatments (pharmacological and non-pharmacological) will be obtained. At each study visit, participants will be assessed for the use of concomitant medication. Participants will be allowed to take melatonin (up to 3 mg) or Benadryl (up to 50 mg) at bedtime as needed (pm) 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 the study participation and remain unchanged during the course of the trial. No new non-pharmacological treatments are to be initiated during the course of the trial.

Drop Criteria: A participant may be withdrawn from the study at any time if any of the following conditions are met:

- Worsening of ASD, ADHD, or anxiety as reflected by respective Clinical Global Improvement score of 6 (Much worse) or 7 (Very Much Worse) for 2 visits in a row.
- Participants who experience intolerable adverse effects, and/or clinically significant laboratory values inconsistent with continuation in the study as determined by PI.
- Unstable psychiatric condition that clinically requires 1) treatment with prohibited concomitant psychotropic medications or 2) inpatient psychiatric admission.
- Emergent suicidality
- Active substance abuse
- Pregnancy
- Allergic drug reaction
- Non-compliance (less than 70% compliance for 2 visits or longer based on parent report)
- 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 due to safety reasons, participants will receive three follow-up visits, giving adequate time for appropriate psychiatric referrals to treaters in their community. If emergent suicidality were to occur during the course of the study, the supervising clinician will then directly assess the level of risk and take the appropriate action (including contacting treatment providers, working on a safety plan, arranging for emergency evaluation via an ER, calling 911, etc.) The clinician will document the actions taken, and it will be noted in the participant's file. Participants who discontinue due to non-compliance with the protocol will receive a referral to HF-ASD treaters in the area.

Subjects who discontinue study participation before the completion of the study will be asked to complete all tasks scheduled to take place on the final study visit at the time of study discontinuation. These tasks may be scheduled as an additional visit, called a study drop-out visit.

VIII. ASSESSMENTS (see Table I)

Characterization Assessments

- *Demographic Interview:* A brief demographic interview will be conducted with the participant's parent to estimate socioeconomic status, as well as collect information about any educational accommodations and past head injuries and/or trauma.

Rating Scales

Informant-Rated:

- *Social Responsiveness Scale – Second Edition (SRS-2)*[15]: A 65-item rating scale completed by the parent used to measure the severity of autism spectrum symptoms as they occur in natural settings.
- *Behavior Rating Inventory of Executive Function (BRIEF-Parent)*[16]: A 78-item rating scale to assess level of executive function deficits.
- *Child Behavior Checklist (CBCL)*[17]: A parent-report questionnaire that evaluates maladaptive behavioral and emotional problems, both internalizing and externalizing, in children ages 6-18.

Clinician-Rated:

- *Clinical Global Impression Scale (CGI)*[18]: The CGI is a measure of illness severity, improvement, and efficacy of treatment (National Institute of Mental Health, 1985). The score for severity ranges from 1 (normal, not at all ill) to 7 (among the most extremely ill participants). Improvement ranges from 1 (very much improved) to 7 (very much worse). And lastly, the effectiveness index measures to what extent the participant is experiencing therapeutic effects as well as the level of adverse events they are experiencing. The CGI scale will be used for the assessment of global functioning. Additionally, the following disorder-specific CGIs will also be administered: ASD, Irritability, ADHD, Anxiety, and MDD.
- *Massachusetts General Hospital-Autism Spectrum Disorder-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-5 diagnostic criteria for ASD and assesses for the individual core domains and associated features of ASD.

Safety Assessments

- *Adverse Experiences*: to record any adverse health events experienced during the study, along with duration, severity, cause, treatment, and outcome.
- *Concomitant Me*dications: to record additional medications taken during the study.

IX. BIOSTATISTICAL ANALYSIS

Clinical Data Analysis: Because this is an RCT following participants over a short period of time, missing data are not expected to impact our analyses such that standard statistical tests will be employed. Changes in the primary outcome measures of efficacy (CGI-I and SRS-2) within and between study groups over time will be tested with longitudinal generalized estimating equation (GEE) regression models (RM) estimated using STATA 12.0 within the framework of the general linear model (GLM). For binary outcomes, logistic RMs will be fit with the binomial family and the logit link. For count data, Poisson RMs will be fit with the Poission family and the log link, for normally distributed data, linear RMs will be fit with the Gaussian distribution and identity link. Each model will predict outcome scores from treatment group (memantine vs. PBO), study visit (ordinal predictor), and the group by visit interaction, which is our test of efficacy. Changes in the tolerability outcome measurements will be tested using Chi-squared tests. All analyses will be intention to treat (ITT).

X. RISKS AND DISCOMFORTS

Risks of Taking Memantine: The most frequently observed adverse reactions with memantine are dizziness, confusion, headache, constipation, hypertension, cough, pain, hallucinations, somnolence, vomiting, dyspnea, and fatigue. Serious adverse reactions include Stevens-Johnson syndrome and seizures.

All participants will be closely monitored for serious adverse reactions and drug-drug interactions with their ongoing concomitant medications. All serious unexpected adverse experiences of a participant will be reported to the Partners Human Research Committee.

Problems and side effects not listed above and not known at this time could occur. Participants will be told of any changes in the way the study will be done and any newly discovered risks to which they may be exposed.

Risks of Assessments: Some of the questions asked in this study may make participants feel uncomfortable, and some of the neuropsychological testing may be boring or frustrating. While we hope participants and their parents will answer all questions, they may skip any questions they do not wish to answer.

Adverse events and unanticipated problems will be reported to the PHRC according to current guidelines. We will follow and adhere to all guidelines as defined and outlined on the Partners Human Research Committee web site: (http://healthcare.partners.org/phsirb/adverse_events.htm).

XI. POTENTIAL BENEFITS

There may be no direct benefit to participants participating in this study. Potential benefits to the participants include education about HF-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 the disorder.

XII. REFERENCES

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Table 1. INTERVENTION SCHEDULE

	Pre-Screening	**Week 99 Screening**	**Week 0 Baseline**	**Week 3**	**Week 6 Midpoint**	**Week 9**	**Week 12 Endpoint/ Study Drop Visit**	***Dose Titration Visit**
Informed Consent		X						
Procedures								
Vital Signs		**X	**X		**X		**X	
Urine Pregnancy Screen (WOCBP)		***X	***X		***X		***X	
Pregnancy Monitoring Form			X		X		X	
Characterization Assessments								
Clinical Interview		X						
Demographic Interview		X						
Chart Note			X	X	X	X	X	X
Clinician Rated Scales								
Reproductive Potential Form		X						
MGH-ASD-DSM5-SCL		X						
CGI-ASD-SI		X	X	X	X	X	X	
CGI-ASD-SC		X	X	X	X	X	X	
CGI-ASD-M		X	X	X	X	X	X	
CGI-ASD		X	X	X	X	X	X	
CGI-Irritability		X	X	X	X	X	X	
CGI-ADHD		X	X	X	X	X	X	
CGI-Anxiety		X	X	X	X	X	X	
CGI-MDD		X	X	X	X	X	X	
CGI-Global		X	X	X	X	X	X	
Adverse Events			X	X	X	X	X	X
Concomitant Medications			X	X	X	X	X	X
Informant-Rated Scales								
SRS-2	**X**				X		X	
BRIEF Parent Form			X		X		X	
CBCL			X				X	

* This is an additional in-person study visit that may be scheduled, as needed, in cases of dose titration adjustments.
** Vital signs are optional and will be collected via parent/guardian report.
*** This urine pregnancy screen will be conducted only if indicated by the Reproductive Potential Form or the Pregnancy Monitoring Form.