Massachusetts General Hospital
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VI. Pharmacological Treatment of Autism

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Anti-Glutamate Agent: Memantine Hydrochloride

- Memantine hydrochloride is a:
  - moderate-affinity
  - non-competitive
  - NMDA receptor antagonist
- Memantine is approved by the U.S. Food and Drug Administration for the treatment of moderate to severe Alzheimer's disease.
- Memantine improves or delays the decline in cognition (attention, language, visuo-spatial ability), as well as functioning in adults with dementia

A Prospective Open-Label Trial of Memantine Hydrochloride for the Treatment of Social Deficits in Intellectually Capable Adults With Autism Spectrum Disorder

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Abstract: This prospective 12-week open-label trial evaluates the tolerability and efficacy of memantine hydrochloride for the treatment of core social and cognitive deficits in adults with high-functioning autism spectrum disorder (ASD). Measures for assessment of therapeutic response included the Social Responsiveness Scale-Adult Research Version (SRS-A), disorder-specific Clinical Global Impression scales, Behavior Rating Inventory of Executive Functioning–Adult Self-Report, Diagnostic Analysis of Nonverbal Accuracy Scale, and Cambridge Neuropsychological Test Automated Battery. Eighteen adults (mean age, 28 ± 9.5 years) with high-functioning ASD (SRS-A raw score, 99 ± 17) were treated with memantine (mean dose, 19.7 ± 1.2 mg/d; range, 15–20 mg), and 17 (94%) completed the trial. Treatment with memantine was associated with significant reduction on informant-rated (SRS-A, −28 ± 25; $P < 0.001$) and clinician-rated (Clinical Global Impression-Improvement subscale ≤2, 83%) measures of autism severity. In addition, memantine treatment was associated with significant improvement in ADHD and anxiety symptom severity. Significant improvement was noted in nonverbal communication on the Diagnostic Analysis of Nonverbal Accuracy Scale test and in executive function per self-report (Behavior Rating Inventory of Executive Functioning–Adult Self-Report Global Executive Composite, −6 ± 8.8; $P < 0.015$) and neuropsychological assessments (Cambridge Neuropsychological Test Automated Battery). Memantine treatment was generally well tolerated and was not associated with any serious adverse events. Treatment with memantine appears to be beneficial for the treatment of ASD and associated psychopathology and cognitive dysfunction in intellectually capable adults. Future placebo-controlled trials are warranted.

Key Words: autism spectrum disorder, memantine, adults, treatment, psychopharmacology

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comorbid psychopathology including attention-deficit/hyperactivity disorder (ADHD), mood and anxiety disorders, and cognitive dysfunction.[2–4] Although there are drugs to treat irritability and hyperactivity in ASD, to date, no medications have been shown to reliably improve core features of the disorder.[5,6]

Emerging evidence on the safety and efficacy of glutamatergic agents for the treatment of social deficits in ASD is encouraging. Glutamate (Glu) dysregulation has been documented in ASD. Serological, postmortem brain, genetic, and spectroscopic neuroimaging research suggests increased Glu activity in ASD.[7–12] Significantly increased spectroscopic levels of Glu have been documented in the anterior cingulate cortex of adolescent males with high-functioning ASD (HF-ASD) versus controls.[13] The empirical evidence of Glu-modulating agents lamotrigine, amantadine, and D-cycloserine as potential treatments for the core symptoms of ASD is modest at best.[14–16] Memantine hydrochloride is a moderate-affinity, noncompetitive, *N*-methyl-D-aspartate receptor antagonist. Memantine is approved by the US Food and Drug Administration to treat moderate to severe Alzheimer disease.[17] Memantine has also been explored as a treatment for psychiatric disorders including obsessive-compulsive disorder (OCD), bipolar disorder, and ADHD.[18] Open-label trials (OLTs) of memantine report improvement in symptoms of ADHD and executive dysfunction (ED) in adults with ADHD.[19,20] To date, with the exception of a single pediatric trial that included a small number of adults,[21] memantine trials in ASD are limited to children and adolescents; these trials report acceptable tolerability with improvement in attention, hyperactivity, irritability, language, social interaction, and repetitive behaviors.[22–25] Evidence in intellectually capable populations of adults with ASD is lacking. The primary aim of this study was to evaluate the efficacy, safety, and tolerabil-

12-week Open-label Trial of Memantine Hydrochloride for the Treatment of Social Deficits in Intellectually-intact Adults with Autism

Demographic Characteristics

Participants	
Total participants	18
Gender *(male)*	14 (78%)
Ethnicity *(Caucasian)*	18 (100%)
Age *(years)*	
Mean	28 ±9.6
Range	18-47
Full Scale IQ	
Mean	106 ±15
Range	75 - 125

Study Medication

- Memantine hydrochloride: 5 mg & 10 mg tablets
- Taken in divided dosage (AM & Afternoon)

Flexible Dose Titration Schedule

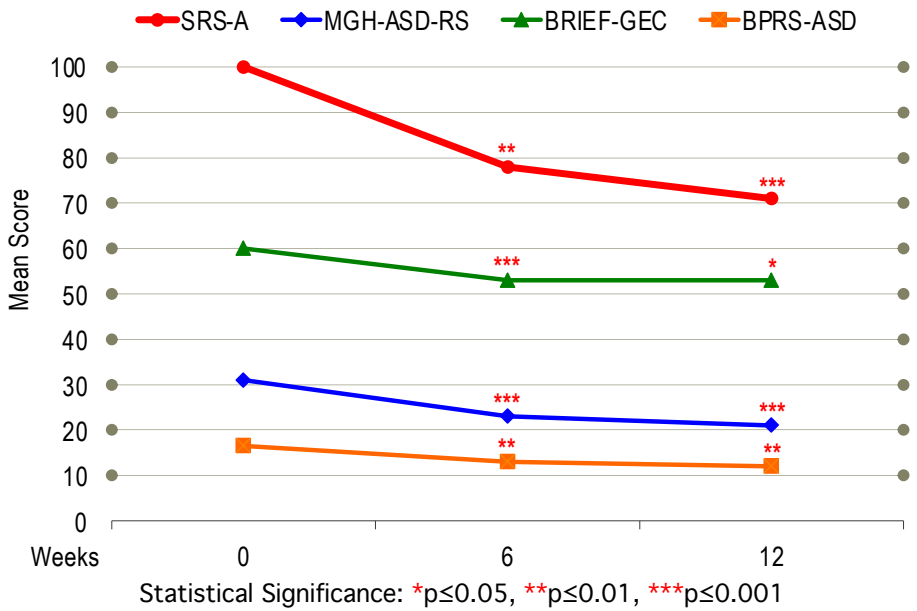
Duration *(Weeks)*	Maximum Dose
0-1	5 mg/day
1-2	10 mg/day
2-3	15 mg/day
4-12	20 mg/day

Study Medication (Memantine)	
Mean dose [Range]	19.7 ±1.2 [15-20] mg/day
At dose 20 mg/day	17 (94%)
At dose 15 mg/day	01 (6%)

Joshi et al., 2016

ASD Features: Treatment Response

Self-, Informant-, & Clinician-Rated Measures

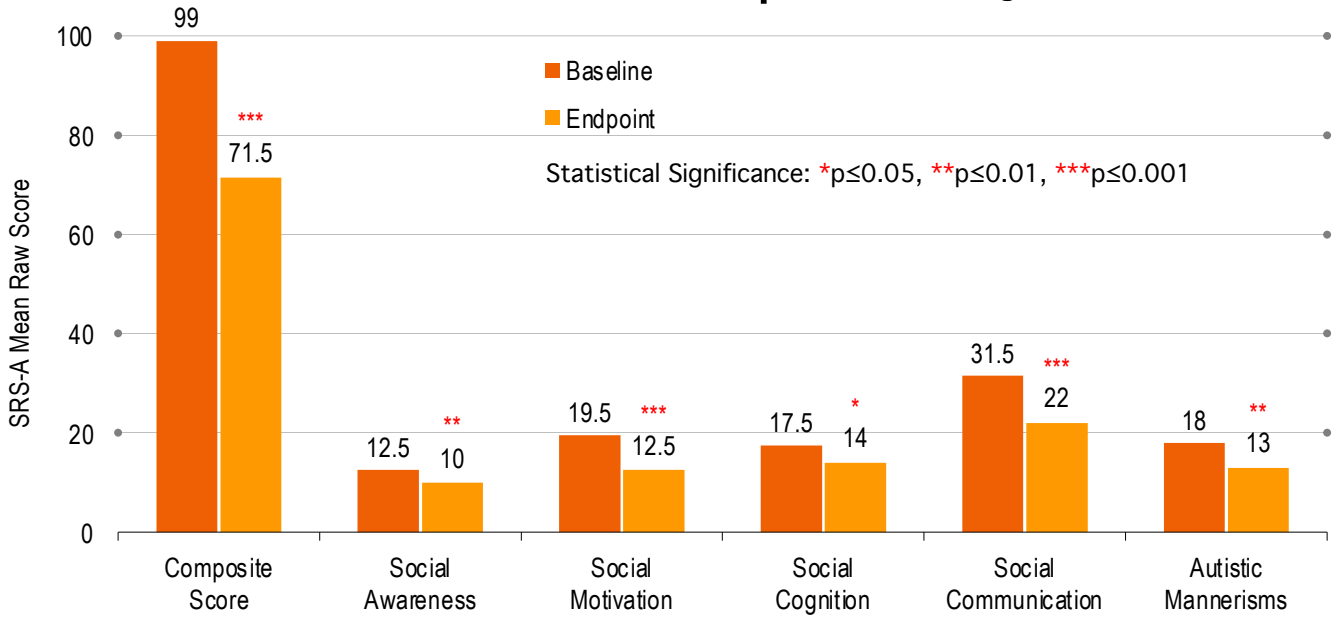


Significant improvement in social behaviors with memantine treatment

Joshi et al., 2016

ASD Features: Treatment Response

SRS-A Mean Response by Domains



Significant improvements observed in various domains of social functioning

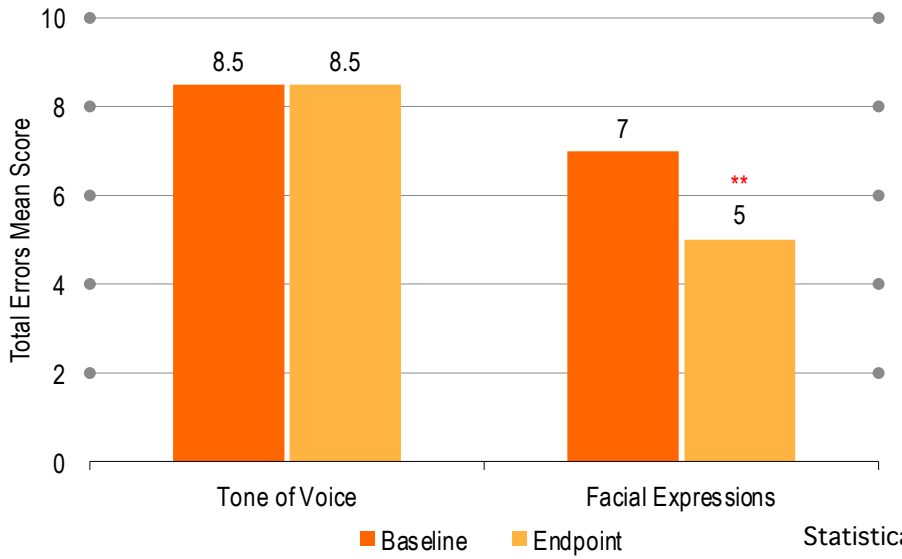
Joshi et al., 2016

Non-verbal Communication: Treatment Response

Reading Non-Verbal Emotional Cues: DANVA2 Performance



Errors in Reading Non-verbal Emotions



Statistical Significance: **p≤0.01



Significant improvement in reading facial expressions

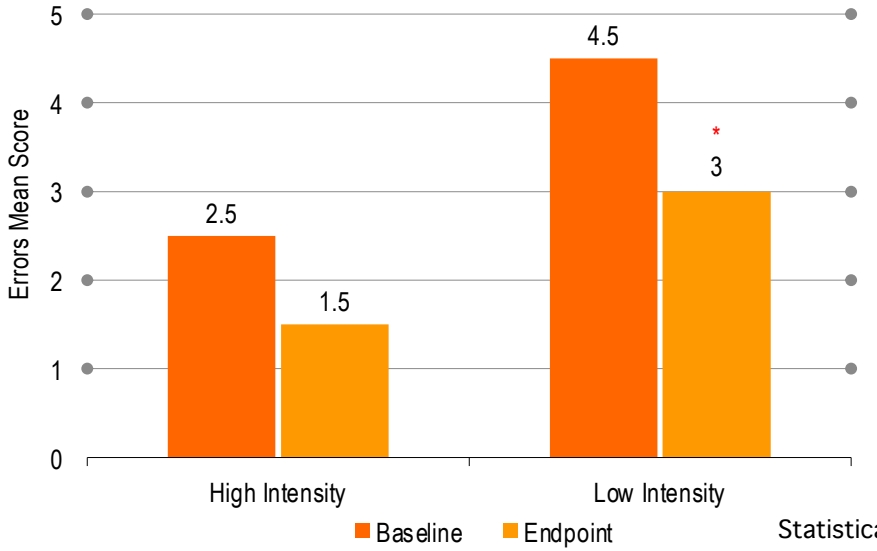
Joshi et al., 2016

Non-verbal Communication: Treatment Response

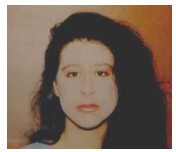
Reading Non-Verbal Emotional Cues: DANVA2 Performance



Errors in Reading Facial Expressions



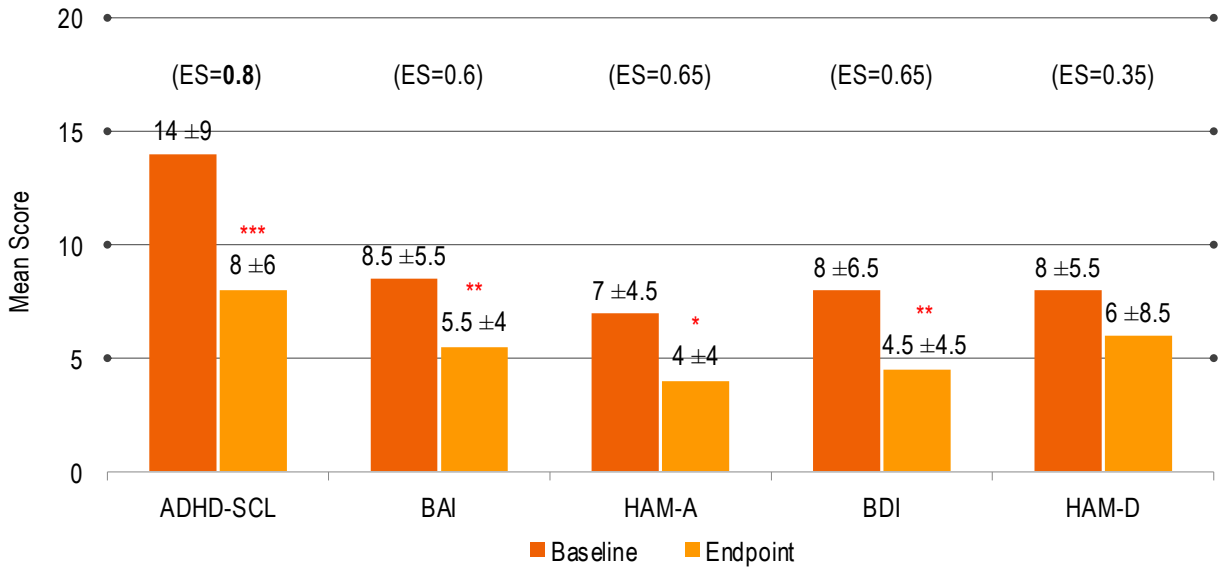
Statistical Significance: *p≤0.05



Significant improvement in reading subtle facial expressions

Joshi et al., 2016

Associated Psychopathology: Treatment Response



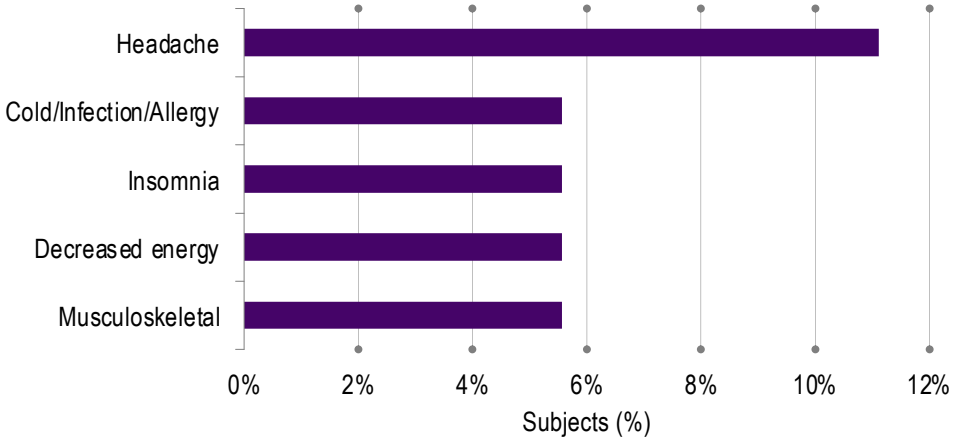
Statistical Significance: *p≤0.05, **p≤0.01, ***p≤0.001
Clinician-rated measures: ADHD Symptom Checklist (ADHD-SCL); Beck Anxiety Inventory (BAI); Beck Depression Inventory (BDI)
Self-rated measures: Hamilton Anxiety Scale (HAM-A); Hamilton Depression Scale (HAM-D)

Additional improvements in symptom severity of ADHD, Anxiety, and Depression

Joshi et al., 2016

Adverse Events

Adverse Events (reported >1 visit)



Experienced any AEs: 6 (33.3%)

Serious AEs: None

Treatment Limiting AEs: N=1

Decreased energy, emotional numbness, feeling dissociated, feeling on edge (resolved on d/c)

Memantine treatment was very well tolerated by adults with Autism

Joshi et al., 2016

12-Week Randomized-Controlled Trial of Memantine Hydrochloride (Namenda) in Intellectually-intact Adolescents with Autism

Clinical Trials Registration @ ClinicalTrials.gov
Registration Number: NCT01972074
URL: https://clinicaltrials.gov/ct2/show/NCT01972074?term=namenda+and+autism&rank=6

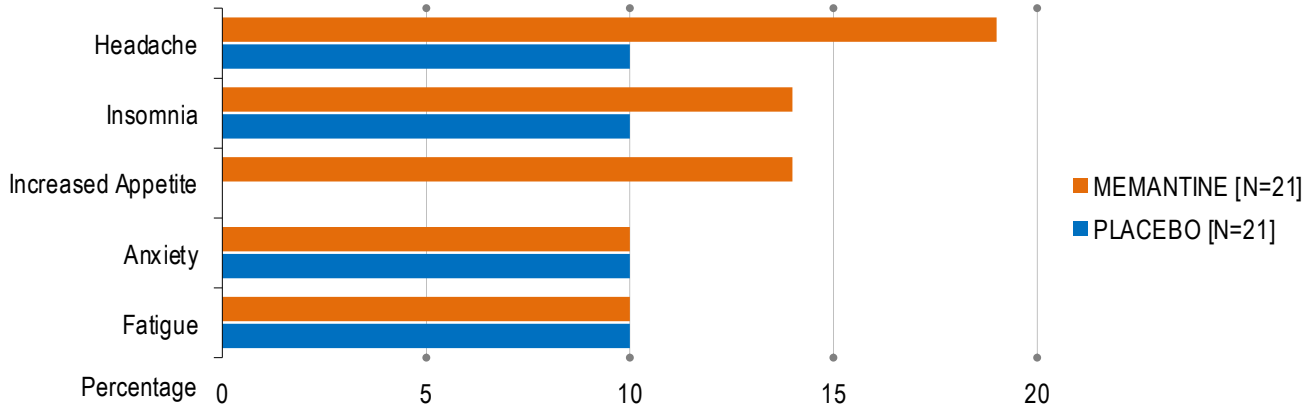
Study Approved by: Partners Human Research Committee Institutional Review Board

Study Funded by: National Institute of Mental Health Career Development Award #K23MH100450

Tolerability

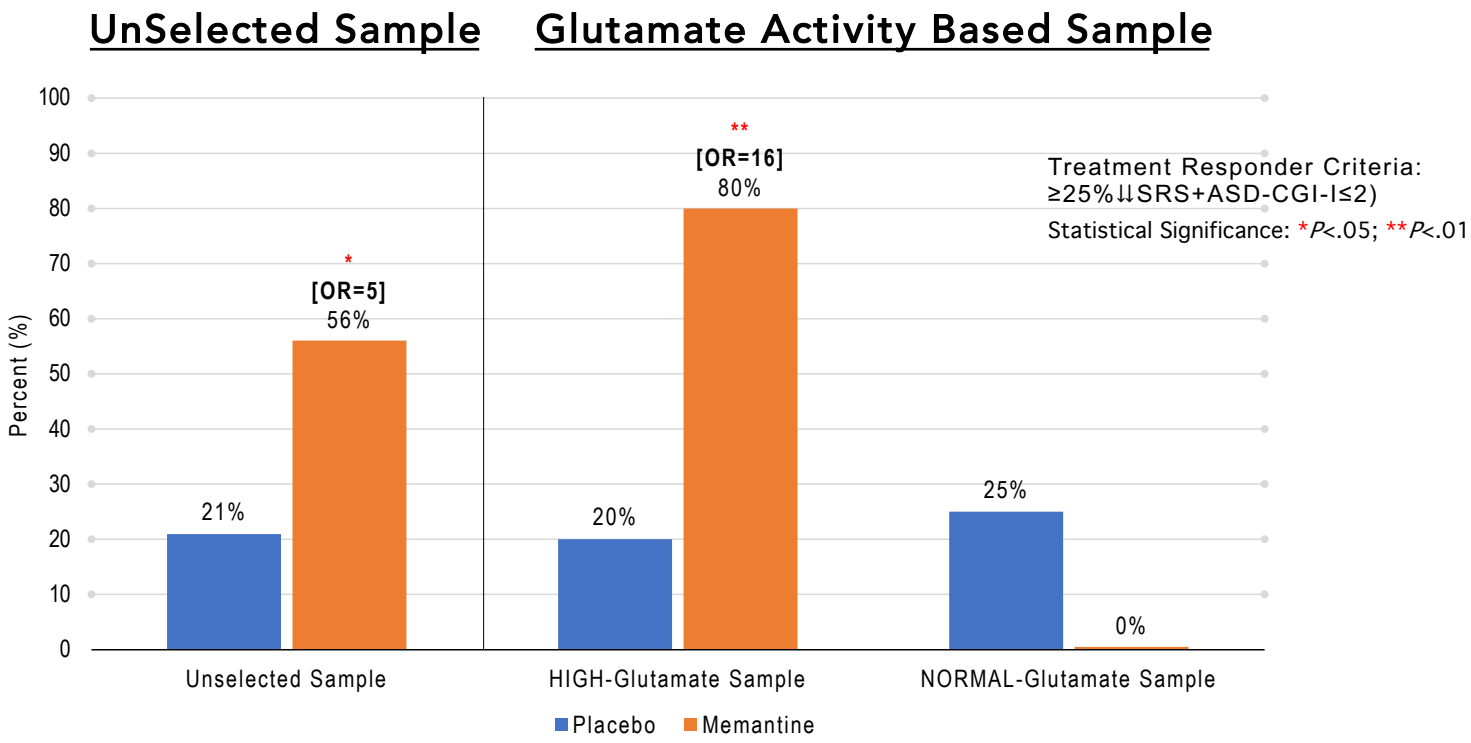
STUDY MEDICATION	MEM[N=21]	PBO[N=21]	p-value [t-statistic]
Dose[Range] *(mg/day)*	19.7 ±1 [15-20]	19 ±3 [10-20]	0.35 [t_{38}=0.94]
@ Maximum Study Dose (20mg/day)	18 (86)	19 (95)	

Adverse Events (Mild-Moderate Severity)



Memantine treatment was very well tolerated by youth with Autism

Memantine Treatment Responders



Significant improvement in social functioning with memantine treatment