Thieme

# Comparing Efficacy and Side Effects of Memantine vs. Risperidone in the Treatment of Autistic Disorder

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## ABSTRACT

**Introduction:** This study was aimed to compare the efficacy and side effects of memantine, an antagonist of the NMDA receptor of glutamate, with risperidone given the fact that glutamate has been noted for its possible effects in the pathogenesis of autism. Risperidone, an atypical antipsychotic, has been approved by FDA for the management of irritability associated with autism.

**Methods:** 30 children, aged 4–17 years, entered an 8-week, randomized trial. Patients were randomly assigned to receive either risperidone or memantine. Autism Behavior Checklist (ABC), Childhood Autism Rating Scale (CARS), Clinical Global Impressions – Improvement (CGI-I) and Clinical Global Impression-Severity (CGI-S) scales were used to assess behavioral symptoms of the patients.

**Results:** Both risperidone and memantine reduced the scores of 4 subscales of ABC as well as the 10-item and the total score of CARS significantly. However, differences between the 2 drugs in the scores of each evaluating scale were not found to be significant. Relatively, larger number of patients on risperidone showed "very much improvement" when assessed by CGI-I scale when compared with those on memantine.

**Discussion and conclusion:** The present study suggests that memantine may have beneficial effects in the treatment of many core symptoms of autism. Therefore, memantine may be considered as a potential medication in the treatment of those autistic children who do not respond or cannot tolerate side effects of risperidone.



## Introduction

Autistic Disorder (AD) is a life-long chronic disorder that manifests early in childhood and may result in the development of some neurologic disorders [1, 2]. In the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR), AD was a discrete disorder under Pervasive Developmental Disorders (PDDs) and was characterized by defects in 3 areas of social interaction, communication, as well as stereotyped and restricted, repetitive patterns of behavior activities and interests [3]. The prevalence of AD is about 0.1 % in different parts of the world, and it is more prevalent in boys [2]. Several indecisive mechanisms have been proposed for the pathogenesis of autism, and 1 of them is abnormalities in the function of some neurotransmitters such as serotonin, dopamine, and glutamate [4, 5]. Glutamate has been noted for its potential influential effects in the pathogenesis of autism. Different glutamate receptors (GluRs) such as GluR6, GluR8, and N-Methyl-D-Aspartate (NMDA) receptor and some of the glutamatergic neurotransmission pathways have shown altered function in the autistic patients [5–7]. Aldred et al. reported that serum concentrations of glutamic acid in 12 patients with AD and in 11 patients with Asperger's syndrome as well as in their first relatives were higher than that in the control group [8]. Increased function of NMDA has been noted in models of AD [5, 6]. Some of the NMDA antagonists such as lamotrigine, dextromethorphan, amantadine, and memantine have been studied in AD [9–11], and some of them showed improvement in some symptoms of AD such as hyperactivity, speech problems [10, 11], social withdrawal, and stereotypy [11]. In a limited number of studies, memantine has shown bene-

ficial effects on behavioral problems and language function in PDDs patients [12–18].

Several drugs with different mechanisms of actions have been studied in the treatment of autism, but only 2 atypical antipsychotics (risperidone and aripiprazole) have been approved by Food and Drug Administration (FDA) for the management of irritability associated with autism [3, 19]. However, these 2 antipsychotics are also frequently associated with side effects [20]. Finding other drugs with broader efficacy and fewer side effects may help management of AD tremendously. A few studies have suggested that glutamate may have a role in the etiology of autism, and several reports have noted positive effects of memantine in PDDs patients. Authors of this study aimed to conduct a trial that prospectively evaluated memantine in reducing irritability (as the primary outcome) and defects in social communication and interaction and stereotypic behaviors (as the secondary outcomes) in comparison to risperidone.

## Methods

This study was an 8 week, randomized, open-label trial conducted between April 2012 and March 2013 in Tehran, Iran. The protocol was approved by ethics committee of Tehran University of Medical Sciences (TUMS). Written informed consent was obtained from parents of patients. All patients, between 4 to 17 years of age with diagnosis of autistic disorder based on DSM-IV-TR criteria participated in this study. Patients who had not received any drug for the treatment of autism or had not responded satisfactorily to their previous treatments could enter this study. Those with unsatisfactory response to drug therapy had to go through a 2-week washout period prior to the initiation of the study. The study protocol allowed epileptic patients who did not have any seizure attack for at least 1 month to enter this trial. Patients were excluded from the study if they suffered from any neurologic disorder except for controlled epilepsy, defined as having no seizure attack for at least 1 month before entering the trial, had a history of substance abuse, neuroleptic malignant syndrome, severe allergic reactions to risperidone or memantine, any cardiac disease, hematologic malignancy, acute kidney or liver failure, consumed stimulant drugs and were pregnant.

### Sample size calculation

Sample size was obtained from formula for calculating the sample size for comparing a continuous outcome between 2 groups:

$$n = 2(Z\,1-\alpha/2 + Z\,1-\beta)2\,S^2/d^2$$

$\alpha$ is the type I error and assumed 0.05. $\beta$ is the type II error and assumed 0.2. S is the baseline standard deviation of the primary outcome (which was change in the score of the irritability subscale of ABC) that determined based on previous studies. d is the minimum change in the score of the primary outcome that is valuable.

Ultimately, considering $S = 8.18$ and $d = 6$, the calculated sample size was 30.

Patients were randomly allocated to receive risperidone or memantine based on simple, balanced, blocked randomization.

### Risperidone dose

Risperidone was started at 0.02 mg/kg/day then increased to 0.04 mg/kg/day at week 2 and ultimately to 0.06 mg/kg/day at the third week. The maximum daily dose of risperidone was 3 mg/day. Drug was prescribed once daily at night.

### Memantine dose

Memantine was started at about 0.2 mg/kg/day then increased to 0.3 mg/kg/day at the second week and ultimately to 0.4 mg/kg/day at the third week. The maximum daily dose of memantine was 20 mg/day. Memantine was prescribed once daily at night unless patients could not tolerate the entire daily dose at 1 time or encountered sleep disturbances.

### Assessment

4 scales were utilized to assess patients as following: Childhood Autism Rating Scale (CARS), Aberrant Behavior Checklist (ABC), Clinical Global Impression-Improvement (CGI-I) scale, and Clinical Global Impression-Severity (CGI-S) scale. Patients were assessed by CARS, ABC, and CGI-S at baseline, by ABC and CGI-I at the end of week 4, and by CARS, ABC, and CGI-I at the end of week 8.

CARS is a questionnaire with 15 items, each is scored 1 through 4 based on the severity of behavior problem, and higher scores indicate more severe symptoms. The total score ranged from 15 to 60. This questionnaire is a reliable and sensitive scale for diagnosis and outcome measures in patients with AD [21, 22].

ABC has 5 subscales, which totally include 58 items. Each item can be scored from 0 to 3. Higher scores on each subscale show more severity of symptoms. ABC is a sensitive instrument for evaluating treatment effects in the intellectually disabled patients as well as in patients with PDDs [23].

CGI is a scale that is used for global assessments in the psychiatric disorders. CGI-S and CGI-I are used for evaluation of severity of symptoms and improvement relative to the baseline state, respectively [24].

### Safety evaluation

Patients and their parents were questioned about any experienced side effects at the end of weeks 4 and 8.

### Statistical analysis

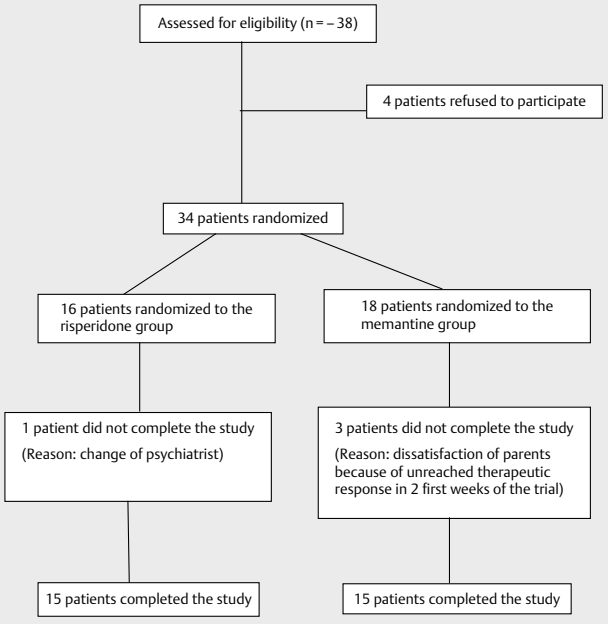
Baseline numerical data were compared by independent sample t-test. Continuous data were compared by the chi-square test or Fisher's exact test as needed. Scores of ABC and CARS were analyzed by 1-way repeated measure analysis of variance (ANOVA) for comparing the 2 groups. Comparison of CARS scores between baseline and after 8 weeks of treatment for each group was done by paired sample t-test. ABC scores at baseline as well as at weeks 4 and 8 after the initiation of the treatment were compared by repeated measure ANOVA in each group. Results were considered significant when P-value was $\leq 0.05$.

## Results

### Baseline characteristics

▶ **Fig. 1** shows the flow chart of participants in the trial. Of 38 patients initially screened, 34 were randomly assigned to the ris-

peridone (16 patients) or memantine (18 patients) group. In the risperidone group, 1 patient left the study due to changing his psychiatrist, and 3 patients discontinued medication in the memantine group because of their parents' will (they believed that their children did not show any behavioral improvement during the first 2 weeks of therapy). Ultimately, 30 patients completed the trial. The mean age of patients was 6.7 ± 3.2 years old, and 23 patients (76.7 %) were males. Before enrollment in the study, 6 patients were receiving risperidone, 2 patients were receiving aripiprazole, and 3 were on sodium valproate. Demographic data of patients did not differ significantly between the 2 groups. Severity of symptoms based on the mean scores of the ABC subscales and total score of CARS was similar between the 2 groups (▶ **Table 1**). Based on CGI-S scale, 3 patients were found to be moderately ill (20 %), 6 patients markedly ill (40 %), and 6 patients severely ill (40 %) in the risperidone group. In the memantine group, 1 patient was mildly ill (6.66 %), 1 patient was moderately ill (6.66 %), 8 patients were found to be markedly ill (53.33 %), and 5 patients severely ill (33.33 %). There was no significant difference between the 2 groups regarding this variable (P = 0.6).




▶ **Fig. 1** Flow chart of participants in the study.

## Results after enrollment in the study

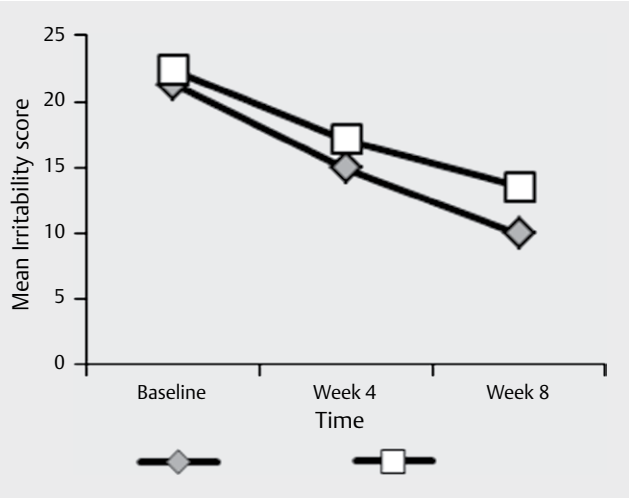
Results of ABC showed that both drugs significantly reduced the scores of "Irritability" (▶ **Fig. 2**), "Lethargy/social withdrawal", "Inappropriate speech", and "Hyperactivity" subscales, but differences between the 2 groups for each subscale were not found to be significant (P = 0.134, P = 0.82, P = 0.5, and P = 0.23, respectively). Effects of the medications on the ABC subscales are presented in ▶ **Table 2**. Results obtained based on CARS indicated that both drugs significantly reduced the scores of "Relating to people", "Emotional response", "Body use", "Object use", "Visual response", "Listening response", "Verbal communication", "Activity level", "Adaptation to change", and "Overview" items and total score of CARS. But differences between the 2 groups were not significant for each item (P = 0.87, P = 0.58, P = 0.59, P = 0.38, P = 0.10, P = 0.33, P = 0.77, P = 0.23, P = 0.06, P = 0.84, and P = 0.77, respectively). Changes in the scores of the CARS items and the total score after treatment are presented in ▶ **Table 3**.

Results of the CGI-I scale after 4 weeks of treatment showed that in the risperidone group, 3 patients (20 %) were reported with very much improvement, 9 patients (60 %) with much improvement, 2 patients (13.3 %) with minimal improvement, and 1 patient (6.7 %) with no change. In the memantine group, 1 patient (6.7 %) was reported with very much improvement, 7 patients (46.7 %) with much improvement, 5 patients (33.3 %) with minimal improvement, and 2 patients (13.3 %) with no change, and differences between the 2 groups did not reach a statistical significance (P = 0.42).

Results of the CGI-I scale after 8 weeks of treatment with risperidone showed 4 patients (26.7 %) as very much improved, 7

▶ **Table 1** Baseline characteristics of patients.

| Characteristic | Risperidone (N:15) | Memantine (N:15) |
|---|---|---|
| Age (years) † | 6.56 ± 3.51 | 6.83 ± 2.98 |
| Sex (male number/total number) (%) | 10/15 (66.7) | 13/15 (86.7) |
| Weight (kg) † | 25 ± 13.33 | 23.6 ± 12.41 |
| Previous drugs (number/total number) (%) | | |
| Risperidone | 2/15 (13.33) | 4/15 (26.66) |
| Aripiprazole | 0/15 | 2/15 (13.33) |
| Score of ABC subscale † | | |
| Irritability | 21.26 ± 6.85 | 22.40 ± 11.16 |
| Lethargy/social withdrawal | 17.53 ± 9.66 | 22.13 ± 7.17 |
| Stereotypy | 5.66 ± 5.97 | 5.66 ± 5.7 |
| Inappropriate speech | 6 ± 2.97 | 6.27 ± 4.4 |
| Attention deficit/hyperactivity | 27.53 ± 12.03 | 30.40 ± 9.47 |
| Total CARS score † | 40.16 ± 5.52 | 42.56 ± 6 |
| † Data are presented as mean ± SD | | |
| ABC: Aberrant Behavior Checklist, CARS: Childhood Autism Rating Scale | | |




▶ **Fig. 2** Changes in the score of "Irritability" subscale of ABC.

patients (46.7 %) as improved, and 3 patients (20 %) as minimally improved while 1 patient (6.6 %) had no change. In the memantine group, 1 patient (6.7 %) was very much improved, 7 patients (46.7 %) much improved, and 3 patients (20 %) minimally improved while 4 patients (26.7 %) had no change, and differences between the 2 groups did not reach a statistical significance (P = 0.33).

### Side effects

Increase in appetite was the most reported side effect of risperidone that happened in 8 patients (53 %). Other side effects included somnolence in 5 patients (33.3 %), fever in 4 patients (26.7 %), indifference to self-defense in 3 patients (20 %), enuresis in 2 patients (13.3 %), drooling in 1 patient (6.7 %), nasal congestion in 1 patient (6.7 %), and fatigue in 1 patient (6.7 %).

Side effects of memantine included somnolence in 2 patients (13.3 %), insomnia in 2 patients (13.3 %), apnea at the beginning of speaking in 2 patients (13.3 %), deterioration of stuttering in 1 patient (6.7 %), decrease in appetite in 1 patient (6.7 %), and nausea in 1 patient (6.7 %).

### Aggravation of the symptoms

Memantine caused aggravation of some symptoms, which included throwing objects (in 2 patients), impulsive behaviors (in 2 patients), hyperactivity (in 1 patient), agitation (in 1 patient), and pertinacity (in 1 patient).

## Discussion

This study was designed to compare efficacy of risperidone with memantine in the management of AD across 3 core symptoms of autism: stereotyped behaviors, impairment in social interactions, and communication skills. The results show that 2 core symptoms of autism, impairment in social interactions and communication skills, improved significantly in the both groups. However, these improvements were not significantly different between the 2 groups. Interestingly, only verbal communication skills improved in both groups. Statistical analysis of scores of "Inappropriate

▲ **Table 2** Comparison of the scores of ABC subscales after 4 and 8 weeks of treatment.

| | Risperidone | | | Memantine | | | F | Effect size† |
|---|---|---|---|---|---|---|---|---|
| **ABC Subscale** | **Baseline** | **After 4 weeks** | **After 8 weeks** | **Baseline** | **After 4 weeks** | **After 8 weeks** | | |
| Irritability | 21.26 ± 6.85 | 14.93 ± 5.29 * * * | 9.36 ± 6.29 * * * | 22.4 ± 11.16 | 17.13 ± 9.7 * * * | 13.5 ± 10.63 * * * | 2.38 | 0.63 |
| Lethargy/social withdrawal | 17.6 ± 9.74 | 14.1 ± 7.46 * * | 10.96 ± 6.9 * * * | 22.13 ± 7.17 | 17.7 ± 7.51 * * * | 14.7 ± 8.4 * * * | 0.06 | 0.1 |
| Stereotypy | 5.06 ± 6.06 | 4.2 ± 4.76 | 3.4 ± 3.86 | 5.66 ± 5.7 | 5 ± 5.2 | 4.6 ± 5.06 | 1.1 | 0.13 |
| Inappropriate speech | 5.69 ± 2.83 | 4.15 ± 2.3 * * | 3.73 ± 3.07 * | 6.27 ± 4.4 | 5.36 ± 3.8 | 4.09 ± 3.44 * | 0.62 | 0.07 |
| Hyperactivity | 28 ± 12.22 | 20.33 ± 9.24 * * * | 14.53 ± 8.3 * * * | 30.4 ± 9.47 | 24.83 ± 8.58 * * * | 20.3 ± 10.04 * * * | 1.5 | 0.37 |

* $P \leq 0.05$, * * $P \leq 0.01$, * * * $P \leq 0.001$

† For calculation of effect size, the mean score at 8 weeks was subtracted from the baseline score for each group. Then, the difference in the change from baseline between the 2 groups was divided by the pooled standard deviation of the difference scores

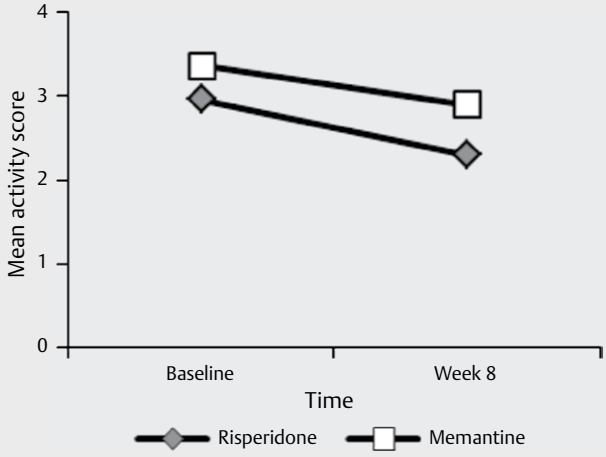
▶ **Table 3** Comparison of the scores of CARS items after 8 weeks of treatment.

| CARS item | Risperidone | | Memantine | | F | Effect size |
|---|---|---|---|---|---|---|
| | Baseline | After 8 weeks | Baseline | After 8 weeks | | |
| Relating to people | 3.4 ± 0.6 | 2.53 ± 0.58 * * * | 3.56 ± 0.65 | 2.63 ± 0.66 * * * | 0.027 | 0.1 |
| Imitation | 1.9 ± 1.02 | 1.7 ± 1.01 | 2.1 ± 1.25 | 1.66 ± 0.91 * | 1.55 | 0.26 |
| Emotional response | 2.83 ± 0.81 | 2.2 ± 0.70 * * * | 3.13 ± 0.99 | 2.56 ± 1.06 * * | 0.3 | 0.07 |
| Body use | 1.96 ± 1 | 1.56 ± 0.72 * * | 2.9 ± 0.5 | 2.33 ± 0.64 * * * | 0.29 | 0.26 |
| Object use | 2.63 ± 1.04 | 2.26 ± 0.92 * * | 3.2 ± 0.9 | 2.66 ± 0.91 * * | 0.79 | 0.2 |
| Adaptation to change | 3.33 ± 0.89 | 2.60 ± 0.78 * * * | 2.76 ± 1.08 | 2.43 ± 1.09 * | 3.83 | 0.44 |
| Visual response | 2.06 ± 0.88 | 1.86 ± ± 0.81 * | 2.23 ± 0.88 | 1.73 ± 0.59 * | 2.73 | 0.44 |
| Listening response | 2.56 ± 0.84 | 2.13 ± 0.81 * * | 2.26 ± 0.86 | 2.03 ± 0.78 * | 0.96 | 0.26 |
| Taste, smell, and touch response | 2.56 ± 1.32 | 2.20 ± 1.08 | 3.23 ± 0.75 | 2.5 ± 0.8 * * * | 2.11 | 0.4 |
| Fear or nervousness | 2.66 ± 1.19 | 2.36 ± 1.1 | 2.63 ± 1.17 | 2.36 ± 1.09 | 0.001 | 0.028 |
| Verbal communication | 2.80 ± 0.97 | 2.36 ± 0.95 * | 3.1 ± 0.66 | 2.56 ± 0.75 * * | 0.08 | 0.12 |
| Nonverbal communication | 1.7 ± 1.06 | 1.5 ± 0.86 | 1.6 ± 0.92 | 1.43 ± 0.75 | 0.05 | 0.038 |
| Activity level | 2.9 ± 0.8 | 2.26 ± 0.82 * * * | 3.36 ± 0.66 | 2.9 ± 0.76 * * * | 1.5 | 0.23 |
| Level and consistency of intellectual response | 2.60 ± 1.02 | 2.46 ± 1 | 2.63 ± 1.17 | 2.63 ± 1.17 | 1.9 | 0.13 |
| Overview | 3.4 ± 0.43 | 2.56 ± 0.65 * * * | 3.43 ± 0.59 | 2.83 ± 0.58 * * * | 0.08 | 0.4 |
| Total score | 42.85 ± 4.6 | 35.2 ± 5.6 * * * | 42.56 ± 6 | 34.9 ± 5.64 * * * | 0.08 | 0.001 |

* $P \leq 0.05$, * * $P \leq 0.01$, * * * $P \leq 0.001$

CARS: Childhood Autism Rating Scale

† For calculation of effect size, the mean score at 8 weeks was subtracted from the baseline score for each group. Then, the difference in the change from baseline between the 2 groups was divided by the pooled standard deviation of the difference scores




▶ **Fig. 3** Changes in the score of "Activity level" item of CARS.

speech" subscale of ABC showed that risperidone influenced verbal skills earlier (at the end of week 4) than did memantine (at the end of week 8). However, the effects of risperidone and memantine were not significantly different on verbal skills after 8 weeks of treatment. Furthermore, none of the study drugs found to significantly improve stereotypic behaviors.

In our study, both drugs significantly reduced the scores of "Irritability" and "Hyperactivity" subscales of ABC and "Activity level" item of CARS. There were no significant interactions between the study groups and time in these domains. However, depicted plot of "Activity level" item of CARS for the 2 drugs had a steeper slope for risperidone (▶ **Fig. 3**), and the amount of decrease in the mean score of the item by risperidone was more than that of memantine (▶ **Table 3**). It should be noted that there are different targets for reducing "level of activity" by risperidone vs. memantine. For instance, risperidone causes more sedation while memantine may improve memory function and attention more. When considering other symptoms of AD, both risperidone and memantine significantly reduced fear or nervousness and improved listening as well as visual and emotional responses; however, no significant differences were noted between the 2 drugs. In addition, memantine also significantly decreased the score of "Taste, smell, and touch response" item of CARS.

There are a few studies that support the beneficial effects of risperidone or memantine in AD. McCracken et al. reported significant reduction in scores of "Stereotypy", "Hyperactivity", and "Irritability" subscales of ABC in an 8 week, placebo-controlled trial of risperidone in 101 autistic patients who were between 5 to 17 years of age [25]. Secondary outcome analysis of the results of this study was done by McDougle et al., who reported that risperidone effectively improved "Sensory motor behavior", "Sensory response", and "Language" subscales of Ritvo-Freeman Real Life Rating Scale (RF-RLRS) [26].

In another study, Pandina et al. noted that risperidone significantly improved "Social withdrawal", "Hyperactivity" and "Irritability" subscales of ABC in an 8-week, double-blind, placebo-controlled study in 55 autistic children between 5 to 12 years of age [27].

Zuddas et al. conducted an open-label trial of risperidone in 11 PDDs patients between 7 to 17 years of age for 6 months and optional continuation to 12 months. 9 out of 11 patients were diagnosed with AD. This study showed significant improvement in "Social impairment" and "Negative emotion" factors of CARS and "Hyperactivity" factor of Child Psychiatric Rating Scale (CPRS) after treatment with risperidone [28].

An open-label study designed by Masi et al. evaluated the effects of 16 weeks of treatment with risperidone on 24 children between 3.6 to 6.6 years of age with PDDs (19 with AD and 5 with PDD-Not Otherwise Specified [PDD-NOS]). This trial showed that risperidone significantly improved symptoms evaluated by "Withdrawal", "Unspontaneous relation to examiner", "Hyperactivity", "Angry affect", and "Rhythmic motions" factors of CPRS as well as "Relating to people", "Non-verbal communication", "Taste, smell, and touch response", "Emotional response", "Fear or nervousness", and "Activity level" items of CARS [21].

McDougle et al. compared risperidone with placebo in the treatment of 31 adults with AD or PDD-NOS. This double-blind, placebo-controlled trial showed improving effects of risperidone on the stereotypy and irritability symptoms. Risperidone significantly improved "Sensory motor behaviors" and "Affectual reactions" by reducing the scores of these subscales of RF-RLRS [29].

Shea et al. reported that 8 weeks of treatment with risperidone in 79 PDDs patients between 5 to 12 years of age significantly reduced scores of all subscales of ABC [30].

There are fewer studies on the effects of memantine in patients with AD. In an open-label trial, Chez et al. studied memantine as an adjunctive drug on 151 patients with PDDs (105 patients with autism and 46 with PDD-NOS). Improvement in language function was seen in 82.7 % of patients, and changes began between the second and fourth weeks of the treatment. Relationship with others and cooperation with home and school schedules and directions were improved in 79.3 % of the patients. Improvement in the self-stimulatory stereotypic behaviors was noted in 15.5 % of patients [12].

Erikson et al. designed a retrospective open-label study of memantine in 18 PDDs patients, out of whom 13 had AD. Patients were between 6 to 19 years of age. It was reported that social interactions improved clinically in all participants. However, improvement was not significant in 6 patients, who were evaluated by ABC. Memantine also had positive effects on "Hyperactivity" subscale of ABC [15].

Effects of memantine on 14 PDDs children aged between 3 to 12 years old were evaluated in an 8-week, open-label trial performed by Owley et al. Memantine significantly reduced scores of "Irritability", "Lethargy/social withdrawal", and "Inappropriate speech" subscales of ABC. Although this study reported the modest effects of memantine in improving hyperactivity, 5 patients experienced increased hyperactivity as a side effect of memantine [17].

Because Risperidone and Memantine have different clinical effects, the possible effects of an add-on treatment were evaluated by Ghaleiha et al. in a 10-week placebo controlled study. In this trial, 40 children aged between 4 to 12 years old were randomly assigned to either risperidone plus memantine or risperidone plus placebo. After 10 weeks of treatment, scores of irritability, stereotypic behavior, and hyperactivity/noncompliance subscales of ABC-Community rating scale were significantly reduced in the memantine group in comparison to the placebo group. The most reported side effects were nausea or sedation in the memantine group and dizziness, nausea, sedation, and increase in appetite in the placebo group [31].

Reported side effects of risperidone in the present study included increase in appetite, somnolence, fever, indifference to self-defense, enuresis, drooling, nasal congestion, and fatigue in the descending order. Those side effects of risperidone that were observed in our study have been in accordance with the reported side effects of this medication in the literature [21, 25, 27, 28, 30]. However, to the best of the author's knowledge, indifference to self-defense has not been reported in the literature.

Reported side effects of memantine in our study were somnolence, insomnia, apnea at the beginning of speaking, agitation, deterioration of stutter, decrease in appetite, and nausea in the decreasing order. Reported side effects of memantine in the literature included hyperactivity, irritability, and lethargy [14, 15, 17].

It should be emphasized that even though our study showed some beneficial effects of memantine in the treatment of autism, some symptoms were deteriorated by this drug and can limit its use. These symptoms include throwing objects, impulsive behaviors, hyperactivity, agitation, and pertinacity. Likewise, Chez et al. has related mild worsening of some behavioral symptoms (such as hyperactivity, irritability, and manic) to the consumption of memantine [12].

## Study limitations

The overall design of the study has limitations such as open-label design, small sample size, and short length of time for following up the participants. These limitations certainly influence the results.

When participants are not blinded to the assigned standard medication may feel that they are deprived from new treatments, and those who receive new treatment may become anxious about unproven efficacy and unknown side effects of the new drug. In this study, the patients were not directly engaged in their assessments as we asked their parents; however, judgment of the parents about changes in behaviors of their child might be affected by knowledge of the type of the medication. If investigators are not blinded, their attitude about drugs may affect their judgments about changes in behaviors of patients. In the present study, only the 2 psychiatrists (JA and MT) directly assessed the participants and presented their point of view by scoring CGI scales. In contrast, rating other scales was done only based on the responses of the parents; judgment of the investigator (NN) did not affect scoring.

Memantine administration for a longer time may have resulted in more improvement in some symptoms of autism such as social interactions and relationship to others.

In conclusion, from the view point of clinical effects, the results of the present trial suggest that memantine may be as effective as risperidone in the management of many main symptoms of autism. These findings can propose that memantine has a potential to be used in those autistic children who are unresponsive to risperidone or cannot tolerate its side effects.

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## Conflict of Interest

The authors declare no conflict of interest.

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