

Comparison of the effects of different doses of memantine in combination with methylphenidate in children affected by ADHD

Forough Riahi, Ashraf Tashakori, Maryam Enayatollahi

Summary

Introduction: Children with Attention-Deficit/ Hyperactivity Disorder (ADHD) respond differently to methylphenidate treatment. Memantine has been considered for the treatment of these patients and its prescriptive dose is discussed by researchers. The aim of present study was to investigate the effect of adding different doses of memantine to methylphenidate in the treatment of children with children with ADHD.

Material and Methods: In a double blind clinical trial, 72 patients with ADHD were evaluated. Patients randomly divided into two groups. Group one received lower doses of memantine (0.1-0.25 mg/kg) and Methylphenidate; group two received higher doses of memantine(0.25-0.5 mg/kg) and Methylphenidate for six weeks. 39 patients who continued the study until the end, at the week zero, second, fourth and sixth, their demographic and clinical information were assessed by demographic questionnaire and Conners Parent Questionnaire. SPSS version 20 was used for statistical analysis.

Results: The mean age of patients was 9.51 ± 2.29 years and their weight was 27.38 ± 8.31 kg and 12.8% of them were female. A total of 16 patients in group one and 23 patients in group two completed the study. Two patients of group one and three patients of group two were excluded due to drug complications, which, all of whom were male. The mean score of the Conners at the baseline of study was 23.84 ± 2.44 and in the sixth week, it was 12.58 ± 2.89 . Moreover, no significant difference was found at any time range: baseline ($p=0.275$), second week ($p=0.921$), fourth week ($p=0.7$) and sixth week ($p=0.966$). The Conners score in both groups was significantly reduced over a 6-week period of treatment. also, the mean heart rate of the patients in group two in the 4th week ($p=0.01$) and the 6th week ($p=0.02$) was significantly lower than group one while the systolic blood pressure in group two after six weeks of treatment was significantly increased ($p=0.01$).

Conclusion: Memantine was effective in the treatment of patients with hyperactivity disorder, and constantly reduced patients' Conners score over a 6-week period. However, no significant difference was observed between patients receiving higher dose of memantine and patients given lower dose of memantine. Therefore, given the increased risk of the related side effects, it is advisable to prescribe a lower dose of memantine along with methylphenidate.

ADHD, memantine, methylphenidate, conners scale, ADHD

Forough Riahi, Ashraf Tashakori, Maryam Enayatollahi: Department of Psychiatry, Golestan Hospital, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

Correspondence address: karami.9926@gmail.com

INTRODUCTION:

Attention-deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder that is most

commonly diagnosed by pediatricians. According to the 2011 guideline of the American Children's Academy, incidence of ADHD diagnosis is prevalent among preschool children and adolescents aged 4 to 18. As specified by DSM-V, ADHD is a disorder marked by an ongoing pattern of inattention and/or hyperactivity-impulsivity [1]. A study conducted in Iran demonstrated that the prevalence of ADHD is 3 to 6 percent. The estimated prevalence of ADHD as diagnosed by DSMIV-TR is also reported to be 3 to 7 percent among school-age children. Relatives of people with ADHD have a higher risk of developing ADHD. This ailment is more commonly diagnosed in males, with the sex ratio ranging from 2:1 to 9:1 [1, 2].

Despite the fact that ADHD is associated with alterations in dopaminergic and noradrenergic function, the underlying neurobiology of this disorder is not fully understood yet. The findings also point to genetics and heredity to 75% as causes of ADHD. ADHD results from a dysfunction in neurochemical and neuroanatomical systems of the brain. This is approved by data derived from family, twin, adoption, neurotransmitters, and genetic studies [1, 3].

The most common behavioral problems in school-age or preschool children with ADHD include attention deficit, restlessness and impulsivity. These children at school and at home are not able to appropriately carry out instructions and require more attention from their teachers and parents. They are aggressive and irritable yet disobedient to their parents. A poor self-image and a feeling of inadequacy are also prevalent in these children, secondary depression is also seen [1, 2, 4, 5].

The consequences of ADHD are an indicative of the importance of immediate treatment when symptoms occur. ADHD requires pharmacological and non-pharmacological interventions. Drug therapy is a major part of ADHD treatment. Sympathomimetic drug treatment is widely used for children with ADHD since the central nervous system stimulants are proven to be highly effective with potentially mild side effects, including short-acting and sustained-release methylphenidate, dextroamphetamine and amphetamine salts combined with dexmethylphenidate. Bupropion, venlafaxine, and alpha agonists (for exam-

ple clonidine) make the second-line of ADHD treatment [4].

Non-pharmacological therapies for ADHD may involve psychosocial interventions. Psychosocial treatments have a tremendous impact on homework performance, organizational skills, and parent-reported ADHD diagnosis [6].

Many investigations have suggested that central nervous system stimulants such as methylphenidate remain first-choice drug treatment for children and young people with ADHD [1, 3]. Approximately 75% of ADHD children under drug treatment with methylphenidate have indicated remarkable improvement in school performance and on-task behavior. Methylphenidate was also shown to improve academic performance of ADHD children [4].

Children with ADHD respond differently to methylphenidate treatment. Side effects associated with methylphenidate might also cause patients to stop taking the medicine as prescribed. In many studies the alternative drugs of Methylphenidate have been evaluated including: bupropion, clonidine, guanfacine, theophylline, modafinil, amantadine, selegiline and venlafaxine. Using these alternative medicines may increase patients' potential for treatment response. Many researchers are still looking for a drug with high effectiveness, low or no side effects, no harmful effect while being affordable for many patients [7, 8].

Memantine acts as noncompetitive antagonist of voltage-dependent NMDA receptors with moderate affinity and direct impact on phencyclidine site of the NMDA receptors. It blocks the NMDA receptor channel and the neurotransmitter glutamate activity in the brain [9-12].

Many studies have also shown that the use of memantine (20 mg/day for 8 weeks) can be effective in the treatment of ADHD children aged 6-12 years. Memantine can improve the ADHD symptoms as well as neurophysiological performance in patients. Furthermore, no serious adverse effects (mortality and suicide) have been reported for the use of memantine by patients; only some mild side effects (constipation, headache and dizziness) might be observed during the first week [7].

Some researchers have prescribed memantine with a daily dose of 10 mg [14] while some have gone with a daily dose of 20mg. However, there

has not been any investigation showing which dosage benefits the patients more and has better impacts on them [13-15]. So, the purpose of this comparative study was to investigate the effects of adding different doses of memantine to methylphenidate in children with ADHD. The survey results may help identify an appropriate drug dosage to add to the standard treatment for ADHD children.

MATERIAL AND METHODS

This study was a double blind clinical trial. In the present study, patients referred to Golestan Hospital of Ahvaz who were diagnosed with hyperactivity disorder (based on DSM-V), were included in the evolution. The diagnosis was confirmed by two psychiatrists and a specialist psychiatric assistant. Baseline demographic data of the patients were also recorded.

Inclusion criteria 1) Children aged 6-12 years old, 2) Hyperactivity and Attention Deficit disorder based on DSM-V and 3) Conner's score equal to and above 20.

Exclusion criteria: Children were excluded if they had been previously diagnosed with a serious psychiatric disorder (such as schizophrenia, bipolar disorder, severe depression and mental disability). Additional exclusion criteria were history or current diagnosis of seizure and medical conditions such as cardiovascular problems, diabetes, history of allergy to memantine, history of lack of response to memantine, history of severe side effects associated with memantine and methylphenidate and voluntary withdrawal at each stage of the study.

Randomization: Individuals were randomly divided into two equal groups using randomized four block method.

Blinding: The patient, the patient's parent, nurse and the evaluator were not aware of the amount of memantine dose taken by each patient.

Study design

It should be noted that all patients in this study were receiving Methylphenidate.

Patients were divided into two groups. Group one received memantine with doses of 0.1 to 0.25

mg/kg. The trial in group one began with memantine at a minimum dose of 0.1 mg/kg plus Methylphenidate; and gradually over a 2-week period, the dose was increased to the max, provided that there was no prohibition on dose increase. In this group, Methylphenidate was given as a fixed dosage. This means that in the first week a quarter of the pill was given twice daily. Then, the second week, half the pill was given twice daily, and in the third week, three-quarters of the pill was also given twice daily. During the fourth week, one pill was given twice daily and it remained the same way until the end of the study. In case of any side effects, the dosage was adjusted again; and in case of severe complications and drug intolerance, the patient was excluded from the trial.

In the second group, memantine was given with doses of 0.25 to 0.5 mg/kg. In this group, memantine treatment was started off at a dose of more than 0.25 mg/kg along with methylphenidate; and within two weeks, the dosage was gradually increased to the max, provided that there was no prohibition on dose increase. Both groups received high dose of medication for four weeks straight. The second group also received methylphenidate at a fixed dose. That means that in the first week, a quarter of the pill was given twice daily. Then, in the second week, half a pill was given twice daily, and in the third week, three-quarters of the pill was also given twice a day. During the fourth week, one pill was given twice daily and it remained the same way until the end of the study. In case of any side effects, the dosage was adjusted again; and in case of severe complications and drug intolerance, the patient was excluded from the trial.

In case the patients' guardian did not agree to pursue the study, it was attempted to obtain their consent following appropriate training and explanations during the investigator's briefings. Likewise, in the absence of a timely referral, the patient was contacted on the phone numbers which were received prior to the trial. (A landline number and both parents' cell phone numbers)

Patients in both groups were evaluated for the response rate and side effects at baseline and at weeks 2, 4, and 6. The mean score of the Conners test was also recorded.

Ethics statement

This study was approved by Ahvaz University of Medical Sciences, through the institution’s research ethics board approval number IR.AJUMS.REC.1396.543. Moreover, this research was conducted in compliance with the research ethics standards.

STATISTICAL ANALYSIS

SPSS software (version 20; IBM Company) was used to carry out the statistical analysis. The data were expressed as mean and standard deviation for quantitative variables and frequency and percentage for qualitative variables. Chi-square, t-test and multiple linear regression were used for data analysis. P-value less than 0.05 was considered significant.

RESULTS

A total of 72 patients were divided in two groups (36 in each group). 33 patients were excluded from the trial due to showing side effects or unwillingness to pursue the study. Of these, 5 patients (two subjects from group one and three from group 2) were excluded due to showing adverse effects. Ultimately, 16 patients from group one and 23 patients from group two completed the study and received follow-up treatment. The mean age of the residual subjects in the study was 9.51±2.29 years. The mean age of group one was 7.79±2.15 years and the mean age of the second group was 10.57±1.67 years which was significantly higher than group one (p<0.001). Also, 34 subjects were identified as male and 5 as female. The average weight of the remaining individuals at the baseline of the study was 27.38±8.31 kg; in the second week it was 28.20±8.44 kg, in the fourth week it was 28.79±8.41 kg and in the sixth week it was 28.84±8.63 kg. The mean weight of the participants in group two was significantly higher than group one (p<0.001).

Table 1. Patient’s characterizations on the first evaluation of week zero

Variable	Group	Indices					P-value
		Number	Minimum	Maximum	Mean	SD	
Age	One	16	5	12	7.79	2.155	<0.001
	Two	23	6	12	10.57	1.674	
Weight	One	16	13.00	40.00	22.0000	5.69210	<0.001
	Two	23	26.00	64.00	31.1304	7.84685	
Heart rate	One	16	70.00	98.00	81.6875	7.62206	0.057
	Two	23	66.00	82.00	76.4348	4.23004	
Systolic BP	One	16	80.00	110.00	103.7500	7.41620	0.525
	Two	23	90.00	120.00	105.2174	7.30477	
Diastolic BP	One	16	60.00	90.00	67.5000	8.56349	0.582
	Two	23	60.00	70.00	65.2174	5.10754	

The average heart rate of the subjects remaining in the study was 78.58±6.33 beats per minute; in the second week 79.07±5.75 beats per minute; in the fourth week 79.42±5.57 beats per minute; and in the sixth week 79.39±7.17 beats per minute. The average heart beat rate of the second group was significantly lower during the fourth (p=0.01) and sixth week trial (p=0.02).

The mean systolic blood pressure of the remaining subjects at the baseline was 104.61±7.28 mmHg, the second week was 105.00±7.07 mmHg, in the fourth week it was 105.78±6.31 mmHg, and in the sixth week it was 105.92±6.24 mmHg. There was not any significant difference between the two groups with regard to systolic blood pressure.

The mean diastolic blood pressure of the subjects remaining in the study at the baseline was 66.15±6.73 mmHg, the second week was 67.10±6.53 mmHg, the fourth week was

64.21±5.00 mmHg and the sixth week was 65.00±5.06 mmHg. There was not any significant difference between the two groups regarding diastolic blood pressure.

Table 2. Conner's Score in both group from week zero to week 6

Time	Group	Indices					P-value
		Number	Minimum	Maximum	Mean	SD	
Week zero	One	16	20.00	28.00	23.3750	2.44609	0.275
	Two	23	17.00	31.00	24.1739	2.75767	
Week 2	One	16	14.00	25.00	19.0000	3.20416	0.921
	Two	23	13.00	24.00	18.7826	2.90699	
Week 4	One	16	11.00	22.00	15.6875	3.13515	0.7
	Two	23	10.00	21.00	15.2174	2.90699	
Week 6	One	16	8.00	18.00	12.6875	3.07069	0.966
	Two	23	7.00	19.00	12.5217	2.84237	

The mean scores of the participants on Conners questioner at the baseline was 23.84±2.44. In the second week it was 18.87±2.99, the fourth week was 15.41±2.97 and the sixth week was 2.89±12.5. Again, there was no significant difference between the two groups in their Conners test scores.

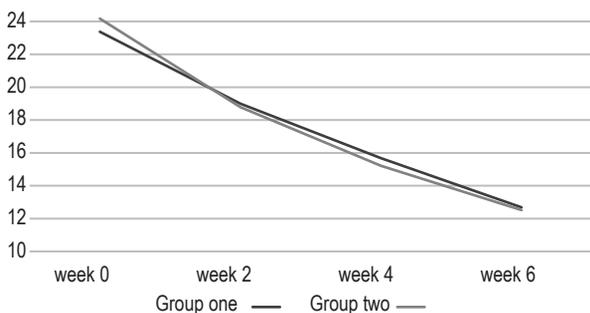


Figure 1. Conner's Score in both group from week zero to week 6

DISCUSSION

ADHD is a neurobehavioral disorder with symptoms that include poor attention, restlessness and impulsive acts [16]. Despite the well-established efficacy and safety of stimulants for ADHD, alternative medications are still needed for several reasons [17]. Almost 10 – 30% of those who are affected with ADHD may not respond

to stimulants or may not be able to tolerate the associated adverse effects [18]. So, this study was conducted to evaluate the effect of adding different amounts of memantine to methylphenidate in children with ADHD.

The results of this study showed that, 39 patients completed the study. Of these, 16 belonged to group one and 23 were in group two. The mean age of the patients was 9.51 ± 2.29 years. In a study conducted by Mohammadi et al., the number of patients participating in the study was 40 and the mean age was estimated 9.09±1.94 years, which is close to the present investigation [7].

A study by Tashakori and Mohammad Beigi on 36 patients with an average age of 8.6 years also suggests similar results to those of the present study [15]. However, Findling et al studied 16 patients with an average age of 8.1 years which is less than the average age of the subjects in the current study.

The gender examination of the patients in Findling's study showed that the prevalence of boys was much higher than girls so that only 12.8% of the patients (5 persons) were girls [14]. In a study by Mohammadi et al., the participants were also made of 6 girls and 34 boys that are almost similar to the present study [7]. Nevertheless, Tashakori and Mohammad Beighi included 41.7% female patients in their trial, which is much higher than the female patients in the present study [15]. Moreover, In the study of Find-

ling et al., girls accounted for 43.8% of the population, which is much higher than the present study [14].

Also, the average weight of the patients participating in the study was 27.38 ± 8.31 kg. According to the study's method, predictably significant increase was observed in group two. This statistical significant difference remained intact through the 6-week treatment. Also, the patients' weight in group one, except for the fourth week, was significantly increased in all stages of the study compared to its previous stage. And in group two also, significant increase was observed during treatment regarding the patients' weight. In the study conducted by Mohammadi et al., the mean weight of patients was 32.4 ± 10.46 kg which is slightly higher than the mean weight of the subjects in the current study (30.41 ± 9.4 kg) [7]. However, it is worth pointing out that in these studies, the weight fluctuations of patients were not studied or reported during each steps of the trial. Therefore, reporting on the weight changes of the participants could be regarded as strength of this study.

Also, the mean heart beat rate (78.58 ± 6.33 pulses per minute) was examined and the second group was found to show significantly lower heart beat rate during the fourth and sixth weeks compared to group one. These changes, however, were significantly increased in the second week in group two and not significant during the fourth and sixth week. Further to this, systolic (104.61 ± 7.28 mmHg) and diastolic (66.15 ± 6.73 mmHg) blood pressure changes recorded in patients were another strength of this paper as it demonstrated that in group two, systolic blood pressure after six weeks of treatment was significantly increased. With less attention being paid by other studies to this variable, further investigations are recommended.

the effect of medication on ADHD in this study was conducted as the main objective using Conners questionnaire and it was found that the average Conners score of the eligible subjects at the baseline of the trial was 23.84 ± 2.44 , showing no significant difference between two groups. The Conners test score of both groups showed a significant decrease at each stage of the study compared to its previous stage; and in both groups this decrease happened in a similar manner. This implies that there was no sig-

nificant difference between the two groups during the second, fourth, and sixth weeks of intervention, since in both of them Conners test score decreased significantly during each week compared to the previous week.

Examining patients' complications in both groups indicated no significant difference between them as in the second group three patients were excluded from the study after showing side effects while in the first group two patients were removed due to the same problem.

It is necessary to state that these complications were reported following methylphenidate administration. In the study by Mohammadi et al. on comparing the effect of memantine and methylphenidate on ADHD children, it was reported that methylphenidate had a significant effect on scoring results at week 6 while side effects in the memantine group was most commonly observed. They also reported the most common side effects of memantine to be decreased appetite, headache, vomiting, nausea, and fatigue. They concluded that although the effectiveness of memantine is less than methylphenidate, it can be used as an alternative treatment [7].

In the present study, the complications of nausea and vomiting were also observed in the patients. However, in the Mohammadi et al study only one group received memantine, but in the current study both groups received different doses of memantine, and we observed these complications in both groups, although they were slightly prevalent.

Tashakori and Mohammad-Beigi examined the combined effect of memantine and methylphenidate vs. methylphenidate on ADHD children. The mean Conners score in the methylphenidate group with placebo at the beginning of the study was 4.22 and in the methylphenidate plus memantine group was 22.3. The mean Conners scores in the methylphenidate group with placebo decreased from 22.4 to 13.5; and in the methylphenidate group with memantine it decreased from 3.22 to 10. Also, comparing the two groups, the mean Conners score was not statistically significant at the baseline and at the first week. However, during the second, third and fourth weeks the methylphenidate group with memantine indicated a significant decrease compared to the methylphenidate group with placebo. There was also no significant difference

between two groups in terms of complications. They finally concluded that memantine combined with methylphenidate is more effective in the treatment of children with ADHD than methylphenidate alone, showing the same drug side effects [15]. However, the reduction of Conner score in that study was similar and consistent with the present study. The difference in the methodology of two studies based on the lack of allocation of placebo group in the present study (non-prescription of methylphenidate alone) led to the fact that in the present study, we could not report the difference in complications in the presence or absence of memantine.

Moreover, Findling et al in 2007 examined the safety, tolerability, pharmacokinetics and effectiveness of memantine in pediatric patients with ADHD. The results of their study showed that 20mg dosage of memantine is effective in the treatment of children with ADHD. It can be concluded that the drug is effective for the treatment of ADHD patients while being associated with little side effects [14].

CONCLUSION

The results of this study showed that memantine, an NMDA receptor antagonist, provides improvement in symptoms of patients with ADHD, leading to a constant decrease in patients' Conners test score over a 6-week period. However, the increase in the drug dosage had no significant impact on the patients' Conners score in both groups. Therefore, given the increased risk of drug side effects, it is advisable to prescribe a low dosage of memantine as an add-on to methylphenidate.

Limitations

The main limitation of the present study is a lack of comparison group receiving only methylphenidate treatment. So; this makes it difficult to infer whether there is any additional advantage of adding memantine. Therefore, it should be considered when designing research in this area in the future.

Acknowledgements

The present research article has been extracted from the "Assistant Thesis" conducted as a research project funded by the grant number of U-96114 provided by Research Deputy of Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran. We are thankful and grateful to everyone who has cooperated to conduct this study.

Conflicts of interests

The authors declare that they have no conflicts of interests.

REFERENCES

1. Visser SN, Bitsko RH, Danielson ML, Ghandour RM, Blumberg SJ, Schieve LA, et al. Treatment of attention deficit/hyperactivity disorder among children with special health care needs. *The Journal of pediatrics*. 2015;166(6):1423-30. e2.
2. CUTLER JL. Kaplan and Sadock's synopsis of psychiatry. LWW; 2016.
3. Schachar R. Genetics of attention deficit hyperactivity disorder (ADHD): Recent updates and future prospects. *Current developmental disorders reports*. 2014;1(1):41-9.
4. Barkley RA. Attention-deficit hyperactivity disorder: A handbook for diagnosis and treatment. 3 ed. New York: Guilford Publications; 2014.
5. Nikolas MA, Elmore AL, Franzen L, O'Neal E, Kearney JK, Plumert JM. Risky bicycling behavior among youth with and without attention deficit hyperactivity disorder. *Journal of child psychology and psychiatry*. 2016;57(2):141-8.
6. Chan E, Fogler JM, Hammerness PG. Treatment of attention-deficit/hyperactivity disorder in adolescents: a systematic review. *Jama*. 2016;315(18):1997-2008.
7. Mohammadi MR, Mohammadzadeh S, Akhondzadeh S. Memantine versus methylphenidate in children and adolescents with attention deficit hyperactivity disorder: a double-blind, randomized clinical trial. *Iranian journal of psychiatry*. 2015;10(2):106-13.
8. Lee XY, Koukouna E, Lim CG, Guan C, Lee TS, Fung DSS. Can We Play with ADHD? An Alternative Game-Based Treatment for Inattentive Symptoms in Attention-Deficit/Hyperactivity Disorder. *Subconscious Learning via Games and Social Media*: Springer; 2015. p. 69-86.
9. Johnson JW, Glasgow NG, Povysheva NV. Recent insights into the mode of action of memantine and ketamine. *Current opinion in pharmacology*. 2015;20:54-63.
10. Povysheva NV, Johnson JW. Effects of memantine on the excitation-inhibition balance in prefrontal cortex. *Neurobiology of disease*. 2016;96:75-83.
11. Vorobeychik Y, Willoughby CD, Mao J. NMDA receptor antagonists in the treatment of pain. *Comprehensive Treat-*

- ment of Chronic Pain by Medical, Interventional, and Integrative Approaches: Springer; 2013. p. 61-7.
12. Badanich KA, Mulholland PJ, Beckley JT, Trantham-Davidson H, Woodward JJ. Ethanol reduces neuronal excitability of lateral orbitofrontal cortex neurons via a glycine receptor dependent mechanism. *Neuropsychopharmacology*. 2013;38(7):1176-88.
 13. Erickson CA, Posey DJ, Stigler KA, Mullett J, Katschke AR, McDougle CJ. A retrospective study of memantine in children and adolescents with pervasive developmental disorders. *Psychopharmacology*. 2007;191(1):141.
 14. Findling RL, McNamara NK, Stansbrey RJ, Maxhimer R, Periclou A, Mann A, et al. A pilot evaluation of the safety, tolerability, pharmacokinetics, and effectiveness of memantine in pediatric patients with attention-deficit/hyperactivity disorder combined type. *Journal of child and adolescent psychopharmacology*. 2007;17(1):19-33.
 15. Tashakori A, Mohammadbeigi D. Comparison of Effectiveness and Side Effects of Combination of Memantine and Methylphenidate with Methylphenidate alone in Treatment of Children with Attention-Deficit/Hyperactivity Disorder. *Jundishapur Sci Med J*. 2014; 13(5):581-8.
 16. Chavez B, Sopko Jr MA, Ehret MJ, Paulino RE, Goldberg KR, Angstadt K, et al. An update on central nervous system stimulant formulations in children and adolescents with attention-deficit/hyperactivity disorder. *Annals of Pharmacotherapy*. 2009;43(6):1084-95.
 17. Dopheide JA, Pliszka SR. Attention-deficit-hyperactivity disorder: an update. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*. 2009;29(6):656-79.
 18. Mohammadi MR, Mohammadzadeh S, Akhondzadeh S. Memantine versus methylphenidate in children and adolescents with attention deficit hyperactivity disorder: a double-blind, randomized clinical trial. *Iranian journal of psychiatry*. 2015;10(2):106.