


ORIGINAL ARTICLE

An Investigation on Cognitive and Behavioral Effects of Donepezil on Autistic Children in Winter 2020 in Gorgan's Taleghani Pediatric Hospital

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Abstract

Objectives

The present investigation has been done to study the behavioral effects of donepezil in autistic children, given that not much research has been carried out concerning using this drug for treating autism.

Materials & Methods

A cross-sectional and analytic-descriptive study was done on twenty patients with autism, aged 4-17, who visited the neurology clinic of Gorgan's Taleghani Pediatric Hospital and Yasha Pediatric Autism Clinic, Iran from 2019 to 2020. Demographic information, including sex, age, father's education, mother's education ,patient's education, family status, other problems, and ethnicity, were documented using a checklist, having been filled in during interviews with the parents. Before the trial, ABC cognitive and behavioral tests were taken to determine the children's current status. After the tests, these children received a daily dose of donepezil (10mg) before sleep for three months. At the end of the three months, the cognitive and behavioral tests were taken from the children once again. In order to analyze the effects of different factors on the studied variables, including irritability, lethargy, stereotypic behavior, hyperactivity, and inappropriate speech before and after the administration of donepezil in patients, a generalized linear model and to test the effects of donepezil on the studied variables, paired t-test was used.

Results

In this study, twenty patients were registered for the investigation, 12 (60%) male and eight (40%) female. Age groups 5-6 had the highest frequency, and age group 17 had the lowest. Regarding the parents'

education, the highest frequency was for bachelor's degrees, and the lowest was for less-than-high school education and master's degree. The highest frequency for the patients' education was kindergarten (60%), and then groups without education (20%) and elementary school-level education (15%). Most of the studied patients (80%) did not have other problems besides autism, and only 20% had other problems besides autism. The family status of 15% of the families was 'separated,' and ethnically, most patients (80%) were Fars, while the rest (20%) were Turkmen. None of the analyzed factors (age, sex, father's education, mother's education, patient's education, other problems, family status, and ethnicity) had a significant effect on the studied variables after the administration of donepezil. Among the studied variables prior to the administration of donepezil and among the analyzed factors, the father's education, the patient's education, other problems, and family status had only a significant effect on stereotypic behavior. The present research findings of the present research indicated that all the studied variables, including irritability, lethargy, stereotypic behavior, hyperactivity, and inappropriate speech, were significantly decreased toward the desired goal. The decreased amounts in irritability, lethargy, stereotypic behavior, hyperactivity, and inappropriate speech after the administration of donepezil were, respectively, 38%, 44%, 54%, 41%, and 54% and on average, these behaviors were reduced by 46%.

Conclusion

The present investigation has shown that all the studied variables, including irritability, lethargy, stereotypic behavior, hyperactivity, and inappropriate speech, were significantly decreased towards the desired goal by 46%. This significant decrease is indicative of the effectiveness of the treatment of autism patients with donepezil, and therefore, this drug can be placed as a prominent and essential part of the medical therapy of autism.

Keywords: Autism, Children, Donepezil, Gorgan

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Introduction

Autism ('Autos' meaning self, and '-ism' meaning condition) is a neurodevelopmental disorder (1)

and is, in fact, a brain growth disorder (related to social interaction) that is characterized by unusual communicative and verbal behavior. The

signs of this disorder appear before the age of 3. Autism affects many parts of the brain, and how this exactly occurs is not yet clear. This prevalence in boys is 1 in 42, and in girls, it is 1 in 189. In other words, the prevalence of autism is four times higher in boys (2). The 6.26 prevalence in 10,000 5-year-old children in Iran is similar to European countries. However, due to a lack of proper screening or diagnosis, this figure does not seem all that accurate (3). Economic status, social status, lifestyle, and the parents' education level do not affect the incidence of autism. This disorder affects the brain's natural development with social interactions and communication skills. Autistic children and adults have problems in verbal and non-verbal communication, social interactions, and activities like play. This disorder makes it challenging to communicate with others and the outside world. In some cases, self-harm and aggression are also witnessed. In this population, repetitive behavior (e.g., clapping, jumping, and the like), unusual responses to people, preoccupation with certain objects or resistance to change are also seen. Possibly, specific unusual sensitivities in their five senses exist. The main key feature of this disorder is trouble communicating. Experts consider modern lifestyle and its consequent effects, such as stress, responsible for its rising trend. Treatment of autism in children includes both medical and non-medical methods. Antipsychotics such as haloperidol and risperidone are the most widely used drugs worldwide to treat autism. Despite little experimental data, some drugs have been recommended due to their safety and positive effects. Some have been theoretically recommended, such as SSRIs and naltrexone, with limited effect. Stimulants help lower hyperactivity and improve concentration but are accompanied by

worsening behavioral problems, weight loss, and stereotypy (4).

Donepezil is a centrally-acting acetylcholinesterase inhibitor. The use of this drug in moderate and severe stages of Alzheimer's has been approved. This drug does not affect neural degeneration and only improves perception, cognitive ability, memory, concentration, social interaction, thinking, ability to speak, and the patient's daily activities. Considering related studies that are mentioned in the discussion and the fact that there has been no published study concerning the use of donepezil to treat autism in Iran, the current study has been conducted to evaluate the long-term effects of donepezil on cognitive and behavioral functions in autistic children.

Materials & Methods

This is a cross-sectional and clinical trial study.

The subjects of this study were 7-14-year-old autistic patients who had visited the specialized neurology clinic of Gorgan's Taleghani Hospital and Yasha Autism Clinic in the year 2020. All the visiting patients diagnosed with autism using diagnostic methods such as history taking and psychological tests were then treated with donepezil after filling in the questionnaire, which was the inclusion criteria, were entered into the study. Before the trial, cognitive and behavioral Autism Behavior Checklist (ABC) tests were taken to evaluate the current state of the children. After the test, the children received two separate daily doses (5 mg per dose) of donepezil for three months. At the end of three months, the cognitive and behavioral ABC test was again taken. The ABC test is a 58-question questionnaire designed to evaluate the presence and severity of destructive behavior in these patients. This tool evaluates five

classes of behavioral and cognitive abnormalities, three of which are the domains in which the main defects of autism are present (lethargy, stereotypic behavior, and inappropriate speech), and the remaining two (hyperactivity and irritability) are pertinent to related disorders.

The data collected from this study have been entered into Excel software, and the statistical analysis has been done using SAS (2003) software. To compare the means of the measured variables before and after the administration of the drug at different times, the researchers used the paired t-test with a 5% significance level. To account for the effects of different variables (sex, age, level of education in father and mother, education of patient, other problems, family status, and ethnicity) on the measured variables, the General Linear Model of SAS (2003) was used.

This study incurred no physical, psychological, or financial harm to the subjects of this study. All the participants have given their informed consent to participate in this study. This study was approved by the Ethics Committee of Golestan University of Medical Sciences.

Results

Relative Frequency of the Studied Variables in Patients

Relative frequencies of different variables are shown in Figures 1 through 8. As shown in Figure 1, the frequency of boys in the studied patient is larger than in girls. Regarding age, five and six-year-olds had the more significant frequency, and the 17-year-old group had the most minor (Figure 2). Regarding the parents' education level (Figures 3 and 4), the most prominent frequency was for bachelor's degrees, and the smallest was for, respectively, below high school and master's

degrees. The most considerable frequency concerning patients was for preschool (60%) and then groups without education (20%) and primary school (15%) (Figure 5). Most of the studied patients (80%) had no other problems and only 20% had other problems besides autism (Figure 6). Concerning family status, 15% of families were separated, and concerning ethnicity, most of the patients were Fars, and the rest (20%) were Turkmen. (Figures 7 and 8)

As Table 1 shows, there is a downward trend in all the measured variables after the administration of donepezil. The amount of decrease in variables such irritability, lethargy, stereotypic behavior, hyperactivity, and inappropriate speech after the administration of donepezil were, respectively, 38%, 44%, 54%, 41%, and 54%. Therefore, on average, there has been a 46% decrease in such behaviors. The coefficients of variation of the studied variables, specifically with regard to stereotypic behavior after administering the drug and inappropriate speech before and after administering donepezil, were high (Table 1).

Sex

As shown in Table 2, the sex of the patient had no statistically significant effect on the studied variables (irritability, lethargy, stereotypic behavior, hyperactivity, and inappropriate speech) after the administration of the drug ($p > 0.05$)

Age

As indicated in Table 2, the age of the patient had no statistically meaningful effect on the studied variables (irritability, lethargy, stereotypic behavior, hyperactivity, and inappropriate speech) after the administration of the drug ($p > 0.05$).

The Education Level of the Father

According to the data (Table 2), the education level of the father had a significant effect on stereotypic

behavior before the administration of the drug ($p < 0.05$). The highest and the lowest means of stereotypic behavior before the administration of donepezil were, respectively, for fathers with below-high school levels (11.33) and associate degree levels (7). Among fathers with bachelor's and high-school diplomas, no significant difference was witnessed with regard to this variable compared with other groups ($p > 0.05$).

Education Level of the Mother

According to Table 2, the education level of the mothers of the patients had no statistically meaningful effect on the studied variables (irritability, lethargy, stereotypic behavior, hyperactivity, and inappropriate speech) after the administration of the drug ($p > 0.05$).

Education Level of the Patient

According to the collected data, shown in Table 2, the patient's education level had a statistically significant effect only on the stereotypic behavior of the patient ($p < 0.05$). The highest and lowest means of stereotypic behavior before the administration of donepezil were for, respectively, patients with no education (11.75) and elementary education (6.33). Among patients with a preschool level of education (8.31), there was no statistically significant difference with regard to this variable compared with the two other groups ($p > 0.05$).

Other Problems

Other problems of the patient had a statistically significant effect only on the stereotypic behavior of the patient ($p < 0.05$). Patients with other problems, with a mean of 14.5, had a less favorable situation than patients without other problems, with a mean of 7.25, regarding stereotypic behavior before the administration of donepezil (Table 1).

Family Status

According to the data (Table 2), the family status of the patient had a statistically significant effect only on the stereotypic behavior of the patient ($p < 0.05$). Patients with separated parents, with a mean of 11.66, had a less favorable condition than children with separated parents, with a mean of 8.17.

Ethnicity

The ethnicity of the patient had no statistically significant effect on the studied variables (irritability, lethargy, stereotypic behavior, hyperactivity and inappropriate speech) after the administration of the drug ($p > 0.05$).

The Effect of Donepezil on the Studied Variables

In order to evaluate the effect of donepezil on the studied variables, the paired t-test was used. As indicated in Table 1, the value of the studied variables (irritability, lethargy, stereotypic behavior, hyperactivity, and inappropriate speech) were statistically favorably reduced ($p < 0.05$).

Descriptive statistics of the studied variables are shown in Table 1.

Table 1. Descriptive statistics of the studied variables

	Number of Observations	Mean	Standard Deviation	Minimum	Maximum	Coefficient of Variation (%)
Variable						
Irritability before donepezil	20	18.2	7.48	2	31	41.10
Irritability after donepezil	20	11.35	5.75	2	26	50.66
Lethargy before donepezil	20	22.10	8.04	8	35	26.38
Lethargy after donepezil	20	12.30	6.85	4	33	55.69
Stereotypic behavior before donepezil	20	8.70	5.08	2	16	58.39
Stereotypic behavior after donepezil	20	4	3.74	0	12	93.50
Hyperactivity before donepezil	20	27.15	9.21	10	43	33.92
Hyperactivity after donepezil	20	15.95	9.27	4	40	58.12
Inappropriate speech before donepezil	20	3.50	2.54	0	8	72.57
Inappropriate speech after donepezil	20	1.60	1.19	0	3	74.38

The Effect of Different Factors on the Studied Variables

Table 2. Effects of different factors on studied variables

Variable	Level of Significance (P Value)							
	Sex	Age	Father Education	Mother Education	Patient Education	Other Problems	Family Status	Ethnicity
Irritability before donepezil	0.7760	0.6357	0.5377	0.4798	0.9829	0.5325	0.3557	0.4931
Irritability after donepezil	0.9089	0.7097	0.6384	0.6491	0.9609	0.4542	0.4192	0.3965
Lethargy before donepezil	0.5002	0.3950	0.3413	0.5861	0.3955	0.1490	0.2736	0.3868

Level of Significance (P Value)								
	Sex	Age	Father Education	Mother Education	Patient Education	Other Problems	Family Status	Ethnicity
Lethargy after donepezil	0.9329	0.7282	0.5332	0.6972	0.7232	0.3112	0.3817	0.2979
Stereotypic behavior before donepezil	0.2462	0.0605	0.0367	0.0613	0.0378	0.0120	0.0369	0.0887
Stereotypic behavior after donepezil	0.4695	0.7087	0.6729	0.4802	0.6445	0.9499	0.7155	0.2920
Hyperactivity before donepezil	0.4395	0.2435	0.2641	0.2539	0.4245	0.0907	0.1115	0.9018
Hyperactivity after donepezil	0.8793	0.5950	0.5539	0.5130	0.7828	0.2374	0.7832	0.8244
Inappropriate speech before donepezil	0.8660	0.3873	0.5037	0.4671	0.3264	0.9201	0.4555	0.2660
Inappropriate speech after donepezil	0.6992	0.7349	0.9913	0.6579	0.8160	0.9490	0.6313	0.3995

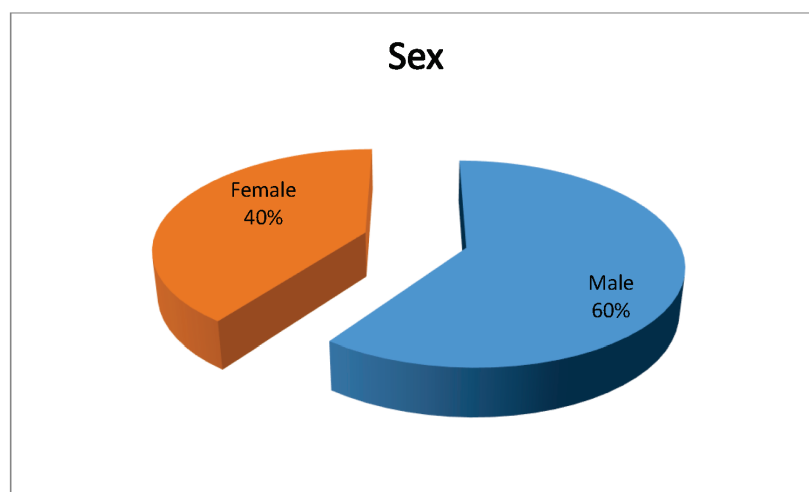


Figure 1. Frequencies of different sexes in studied patients

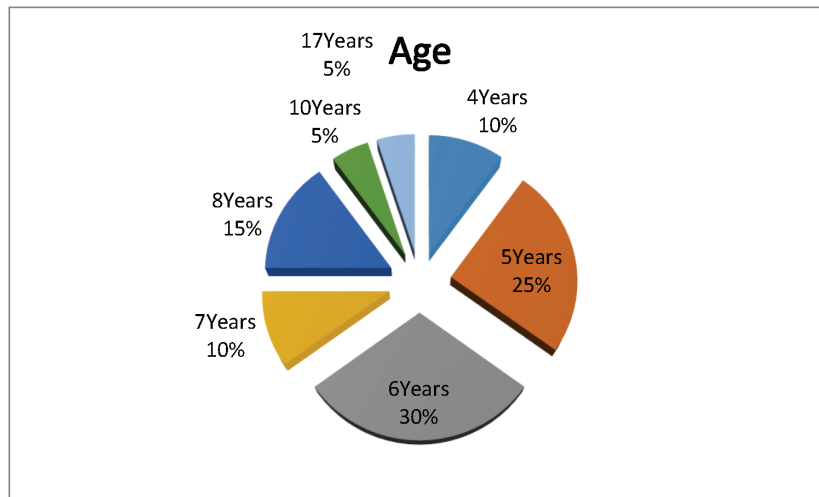


Figure 2. Frequencies of different ages in studied patients

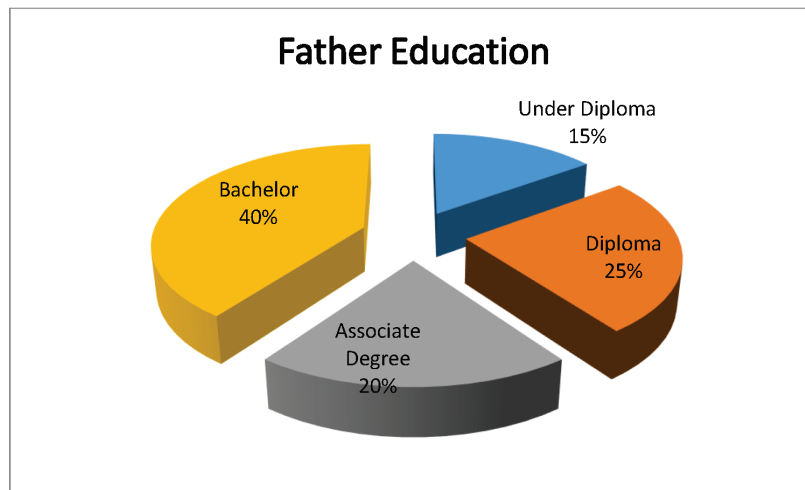


Figure 3. Frequencies of father education level in studied patients

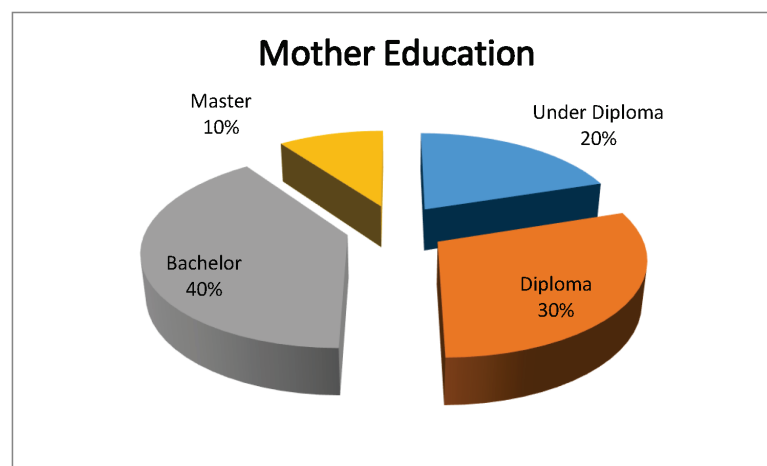


Figure 4. Frequencies of mother education level in studied patients

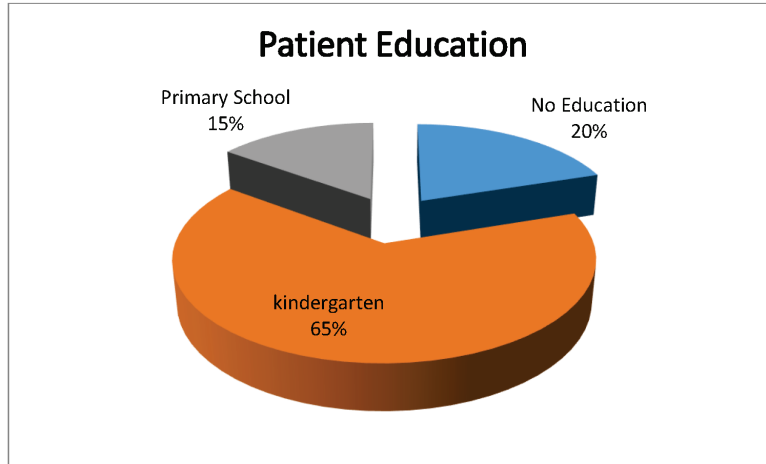


Figure 5. Frequencies of patient education level

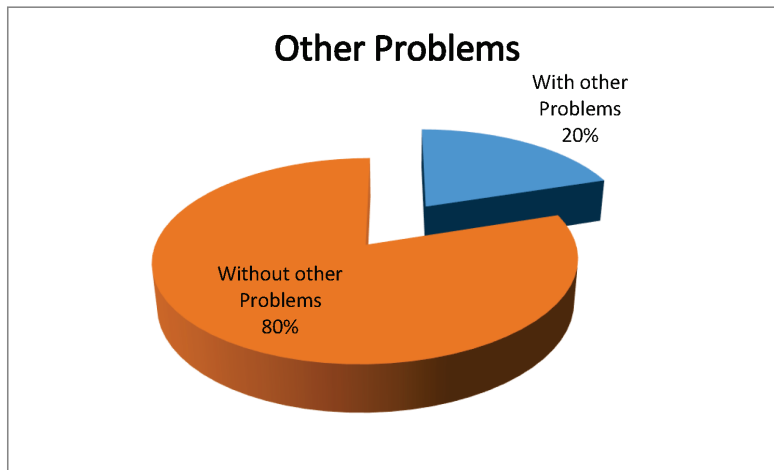


Figure 6. Frequencies of other problems in studied patients

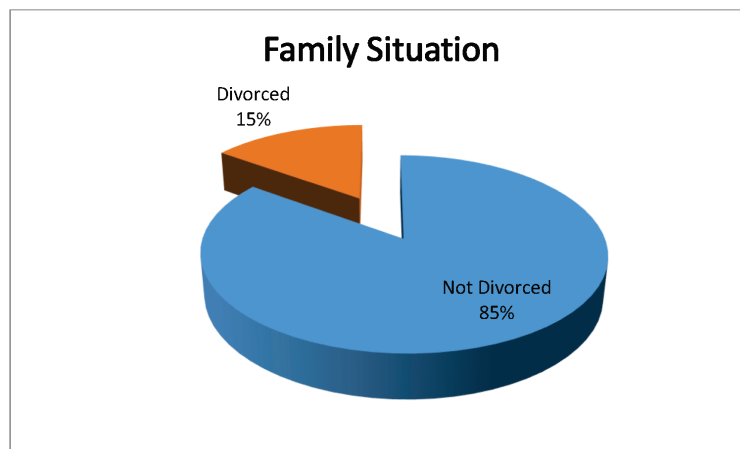


Figure 7. Frequencies of family situation in studied patients

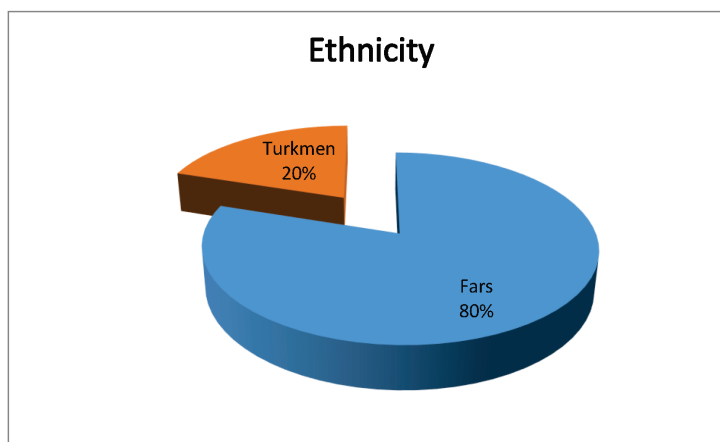


Figure 8. Frequencies of ethnicity in studied patients

Discussion

This descriptive-analytic study was done on 4-17-year-old autistic children who had visited the neurology clinic of Gorgan's Taleghani Pediatric Hospital and Yasha Pediatric Autism Clinic in 2020. All the children whose autism diagnosis were confirmed using diagnostic methods such as history taking and psychological tests and were treated with donepezil after completing the questionnaire were entered into the study as consistent with the criteria. Before the test, ABC cognitive and behavioral tests were taken to evaluate the children's current condition. After preliminary tests, these children received two separate doses of donepezil (10 mg) daily for three months. At the end of three months, ABC cognitive and behavioral tests were retaken from the children. In this study, twenty autistic patients were entered, 12 (60%) male and eight (40%) female. Therefore, according to the studied population in the current study, the frequency of this condition was higher in boys than in girls. The results of the Christensen (2016) study also showed that the frequency of autism is higher in boys than in girls. According to this report, the frequency of this condition is

in boys 1 in 42 and girls 189 (2). In other words, the prevalence of this condition is four times as much in boys compared with girls. The difference in the proportions of males and females in this study was largely due to the size of the studied population and differences in ethnicity. The reason for the higher prevalence of autism in boys is still unclear. This issue may be rooted in the biological differences between the two sexes or due to the current methods of defining and diagnosing autism. Probably, autistic girls can replicate the behavior of their peers to hide their autistic behavior better than boys. Biologically, the gene expression pattern of the brain of the autistic person is closer to the normal male brain than to normal female brains. On the other hand, girls need higher genetic mutation rates to have this condition (Lommes et al., 2017; Gould, 2017) (5, 6).

The coefficient of variation of all the studied variables (irritability, lethargy, stereotypic behavior, hyperactivity, and inappropriate speech), particularly stereotypic behavior after administering donepezil and inappropriate speech before and after administering donepezil was relatively high. One possible reason for the high value for these variables could have been due to

the different answers of the parents due to their education level and experience. The coefficient of variation of these variables being higher after the administration of donepezil as compared to before indicates different reactions to the drug among the patients. Therefore, different medical guidelines may be proposed for different patients for better results.

None of the studied factors (sex, age, father's education, mother's education, and the patient's education, family status, other problems, and ethnicity) had a statistically meaningful impact on the studied variables after the administration of the donepezil. Concerning the studied variables before the administration of donepezil, among the studied factors, the father's education, the patient's education, other problems, and the family status only had a meaningful impact on stereotypic behavior. Generally, with the education level of the father and the patients, a favorable downward trend was witnessed with regard to stereotypic behavior, which can make education an effective factor, both from external and genetic perspectives. In regards to other problems, patients with other problems displayed higher rates of stereotypic behavior, which can indicate the effect of this factor on this behavior, and during treatment, this should be heeded. Patients with separated parents also displayed higher rates of stereotypic behavior. In other research, short practical instruction of the parents was more effective than instructions with long duration and formal education on destructive behavior in autistic patients (Bradshaw et al., 2018; Bearss et al., 2015) (7, 8). Nevertheless, to evaluate the effect of different factors on the behavioral characteristics of autistic patients and for a more comprehensive analysis, studies with much larger populations and longer-term studies

are needed.

The significant decrease in autistic behaviors is indicative of the effectiveness of the treatment of autistic patients with donepezil, and therefore, this drug can be implemented as an essential and primary drug in the treatment course of this condition. Due to the neuropathologic and neurochemical abnormalities in cholinergic pathways in autism, donepezil, increasing available acetylcholine levels, has been proposed as a drug to ameliorate the symptoms of this condition. (Srivastava et al., 2011; Hardan, and Handen, 2002) (9, 10). Rossignol and Frey (2014), in a systematic review on the use of anti-Alzheimer's medication in autistic patients, have written that among the seven studies done on donepezil, five studies have shown improvement in symptoms in areas of expressive language, communication, social interaction, irritability, hyperactivity, attention, and eye contact (11). Handen et al. (2011) in a study on the effects of donepezil in children and adults, have concluded that this drug improves hyperactivity and behavioral and cognitive functions. However, since no statistically meaningful difference was found between the group receiving the medication and the control group, it was declared that , possibly, a short course of treatment with donepezil might have a limited effect on cognitive function in autistic patients, and a longer course of treatment is recommended (12). Chez et al. (2003), in a study done on children with autism by administering hydrochloride donepezil for six weeks, have shown that this drug can decrease autistic behavior and improve speech in patients (13). Buckley et al. (2011), in an investigation to determine the effect of donepezil on enhancing rapid eye movement, and sleep in young children with autism spectrum disorders, have concluded that this drug can

increase the duration of rapid eye movement during sleep (14). Karvat and Kimchi (2014), in research on the mouse as an autism model, have proven the positive effects of donepezil on cognitive features and social deficiency (15).

In Conclusion

The present research has shown that the value of all the studied variables, including irritability, lethargy, stereotypic behavior, hyperactivity, and inappropriate speech, decreased by 54%, on average, favorably and statistically significantly after the treatment course with donepezil. This significant decrease indicates the effectiveness of treating autistic patients with donepezil. Hence, this drug can be implemented as an essential or choice drug in the treatment course of this condition.

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Author's Contribution

Yamin Ghareman: Data interpretation and critical revision of manuscript draft

Seyed Ahmad Hosseini: Data collection and participation in manuscript draft preparation

Saeed Hassani, Firouzeh Derakhshanpour: Data analysis and critical revision of manuscript draft

Mohammad Javad Hassani: Data interpretation and critical revision of manuscript draft

Parnian Hosseini, Data collection

Conflicts of interest

The authors declare that they have no conflict of interest.

References

1. Mokhtari, B., Karimzadeh, F. A review on the autism with the most approaches on the critical biomarkers. *Razi Journal of Medical Sciences*, 2018; 24(165):35-46.
2. Christensen, D.L. Prevalence and characteristics of autism spectrum disorder among children aged 8 years autism and developmental disabilities monitoring network, 11 sites, United States. 2016. *MMWR Surveillance Summaries*. 65.
3. Samadi, S.A., and McCkonkey, R. Autism in developing countries: Lessons from Iran. *Autism Research and Treatment*. 2011:1-11.
4. Malone, R.P., Gratz, S.S., Delaney, M.A., and Hyman, S.B. Advances in drug treatments for children and adolescents with autism and other pervasive developmental disorders. *CNS Drugs*. 2005; 19 (11): 923-934.
5. Lommes, R., Hull, L., and Mandy, W.P.L. What is the male-to-female ratio in autism spectrum disorder? A systematic review and meta-analysis. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2017, 56(6):466-474.
6. Gould, G. Towards understanding the under-recognition of girls and women on the autism spectrum. *Autism*. 2017, 21(6):703-705.
7. Bradshaw, J., Bearss, K., McCracken, C., Smith, T., Johanson, C., Lecavalier, L., Swiesy, N., and Scahill, L. Parent education for young children with autism and disruptive behavior: Response to active control treatment. *J. Clin. Child Adolesc. Psychol*. 2018, 47(SUP1): S445-S455.
8. Bearss, K., McAdam, D.B., Mruzek, D.W., and Handen, B. Effect of parent training vs parent education on behavioral problems in children with autism spectrum disorder: A randomized

- clinical trial. *JAMA*.2015, 313(5):1524-1533.
9. Srivastava, R.K., Agarwal, M., and Pundhir, A. Role of Donepezil in autism: Its conduciveness in psychopharmacotherapy. *Case Reports in Psychiatry*.2011, 1-2.
10. Hardan, A.Y., and Handen, B.L. A retrospective open trial of adjunctive Donepezil in children and adolescents with autistic disorder. *Journal of Child and Adolescent Psychopharmacology*. 2002, 12 (3): 237-241.
11. Rossignol, D.A., and Frye, R.E. The use of medications approved for Alzheimer's disease in autism spectrum disorder: a systematic review. *Frontiers in Pediatrics*. 2014, 2 (87): 1-8.
12. Handen, B.L., Johnson, C.R., McAuliffe-Bellin, S., Murray, P.J., and Hardan, A.Y. Safety and efficacy of Donepezil in children and adolescents with autism: Neuropsychological measures. *Journal of Child and Adolescent Psychopharmacology*. 2011, 21 (1): 43-50.
13. Chez, M. G., Buchanan, T.M., Becker, M., Kessler, J., Aimonovitch, M.C., and Mrazek, S.R. Donepezil hydrochloride: a double-blind study in autistic children. *Journal of Pediatric Neurology*. 2003.1(2): 83-88.
14. Buckley, A.W., Sassower, K., Rodriguez, A.J., Jennison, K., Wingert, K., Buckley, J., Thurm, A., Sato, S., and Swedo, S. An open label trial of donepezil for enhancement of rapid eye movement sleep in young children with autism spectrum disorders. *Journal of Child and Adolescent Psychopharmacology*. 2011. 21 (4): 353-357.
15. Karvat, G., and Kimchi, T. Acetylcholin elevation relieves cognitive rigidity and social deficiency in a mouse model of autism. *Neuropsychopharmacology*. 2014. 39: 831-840.

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