PHARMACOLOGICAL TREATMENT IN STABILIZING THE SYMPTOMS IN CHILDREN WITH ADHD SYMPTOMS

HOUSSEIN TOUFIC SEBLANY[1], IULIANA ŞTEFANIA DINU[1*], MONICA SAFER[2], DOINA ANCA PLEŞCA[2]

[1]*University of Medicine and Pharmacy „Carol Davila", 37 Dionisie Lupu street, Bucharest*
[2]*Department of Pediatrics and Pediatric Neurology, „Victor Gomoiu" Children Clinical Hospital, University of Medicine and Pharmacy „Carol Davila", 37 Dionisie Lupu street, Bucharest*
**corresponding author*: *iulyadinu@yahoo.com*

Abstract

Attention-deficit/hyperactivity disorder (ADHD) is a chronic disorder characterized by problems with paying attention, impulsivity and over-activity which influence all the life fields of a child with ADHD. The prevalence of ADHD in children is approximately 7% worldwide, both males and females being affected and with different etiology. A high rate of these patients present neurologic etiology, determined by factors which occurred in different stages of the development process. The consequences of ADHD cause social problems because these children have difficulties regarding family, school and social integration, associating a considerable impairment in the quality of life (QoL). The goal of therapeutic approaches is to improve the QoL by managing the symptoms. There is no treatment for curing ADHD, but there is a pharmacologic treatment used in order to control the symptoms.

The goal of the study was to determine the impact of treatment on symptoms control in ADHD patients. The subjects were administered methylphenidate or atomoxetine. The ADHD symptoms were screened with Child Symptom Inventory-4 scale. Pharmacological treatment and early diagnosis have a positive impact on outcomes, QoL and long-term prognosis.

Rezumat

Tulburarea hiperkinetică cu deficit de atenţie (ADHD) este o afecţiune cronică care apare în copilărie şi este caracterizată prin deficit de atenţie, impulsivitate şi hiperactivitate, simptome care pot afecta toate aspectele vieţii unui copil. Prevalenţa la copii este de aproximativ 7% la nivel mondial, abordând ambele sexe şi având etiologie diferită. Un procent important dintre pacienţi prezintă etiologie neurologică, cauzată de factori ce au intervenit în diverse etape de dezvoltare. Datorită simptomelor, copiii cu ADHD întâmpină dificultăţi de integrare în familie, la şcoală, precum şi în societate, calitatea vieţii fiind astfel compromisă. Dezideratul major în abordarea terapeutică a copiilor cu ADHD este îmbunătăţirea calităţii vieţii prin stabilizarea simptomelor. Nu există tratament curativ pentru ADHD, dar există tratament farmacologic folosit pentru a controla simptomatologia la copii, realizând astfel managementul comportamentului psiho-social.

Studiul a urmărit impactul tratamentului farmacologic asupra controlului simptomelor la copiii cu ADHD. Au fost selectaţi pacienţi care au urmat tratament cu metilfenidat sau atomoxetină, iar grupul de control a fost format din pacienţi care au primit

consiliere specifică pentru pacient şi familie, psihoterapie individuală, educaţie ortogenică. Simptomele au fost evaluate cu ajutorul scalei *Child Symptom Inventory-4* (CSI-4). Studiul întreprins a demonstrat că utilizarea terapiei farmacologice determină o ameliorare a simptomatologiei. Rezultatele obţinute sugerează importanţa diagnosticului precoce şi instituirea unei terapii farmacologice corecte. Terapia iniţiată determină stabilizarea simptomelor şi poate preveni multe din consecinţele nefaste în viaţa socială la aceşti pacienţi.

Keywords: attention deficit-hyperactivity disorder (ADHD), methylphenidate, atomoxetine, Child Symptom Inventory-4 scale (CSI-4).

Introduction

Attention deficit-hyperactivity disorder (ADHD) is a chronic disorder characterized by either significant difficulties of inattention or hyperactivity and impulsiveness or a combination of the two. According to the *Diagnostic and Statistical Manual of Mental Disorders* fourth edition (DSM-IV-TR), symptoms emerge before the age of seven. ADHD has its onset during childhood and is estimated to affect 3% to 7% of school-aged children [1]. A high rate is of neurologic etiology, determined by factors which occurred in different stages of the development process.

The consequences of ADHD cause social problems. ADHD behavior contributes to significant problems in relationships, behavior and learning, which may damage their quality of life (QoL) [3]. It requires long-term, ongoing monitoring of symptoms and adjustments of medications and other treatment programs.

Although ADHD can't be cured, it can be successfully managed and some symptoms may improve as the child ages. Treating ADHD in children requires medical, educational, behavioral and psychological interventions. For most children with ADHD, medication is an integral part of the treatment. Medication therapy is an important component of the ADHD treatment.

There are many types of drugs that can be used to control the symptoms of ADHD. One of them is called psychostimulants or stimulants and has been used to effectively treat ADHD for several decades. These medicines help those patients with ADHD to focus on their thoughts and ignore distractions. Stimulant medication is effective in 70% to 80% of the patients. Although these drugs stimulate the central nervous system, they have a calming effect on people with ADHD [10, 19].

Methylphenidate (MPH) is a benzylpiperidine derivative - methyl phenyl (piperidin-2-yl) acetate (IUPAC) (Figure 1).

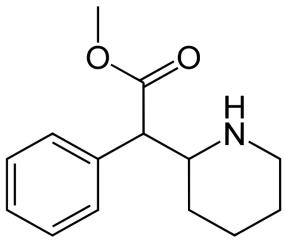

Figure 1
Methylphenidate (MPH)

MPH is a stimulant of the central nervous system (CNS). Its proposed mechanism of action is the release and increase of dopamine in the CNS. This release is secondary to its effect on the dopamine transport mechanism, which results in an increased amount of postsynaptic dopamine. Higher levels of dopamine provide the needed stimulation and proposed activation of the motor inhibitory system in the orbital-frontal-limbic axis. This activation leads to increased inhibition of impulsiveness. Therefore, this medication assists children with ADHD by helping them to focus.

The exact mechanism of action of methylphenidate is dissimilar to that of the amphetamines and cocaine, yet the net effect is an increase in synaptic dopamine [2, 7, 16, 17, 18, 19].

In cases where stimulants don't work or cause unpleasant side effects**,** non-stimulants drugs might help. The first non-stimulant approved by the Food and Drug Administration (FDA) was atomoxetine (ATX) [10]. ATX - (3*R*)-*N*-methyl-3-(2-methylphenoxy)-3-phenylpropan-1-amine; (*R*)-*N*-methyl-3-phenyl-3-(*o*-tolyloxy)propan-1-amine (IUPAC) (Figure 2). The mechanism of action of ATX consists in a highly selective and potent inhibition of the pre-synaptic noradrenaline transporter, without directly affecting the serotonin or dopamine transporters. ATX has minimal affinity for other noradrenergic receptors or for other neurotransmitter transporters or receptors [11].

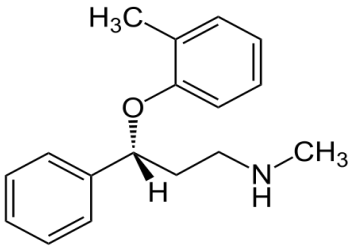

Figure 2
Atomoxetine (ATX)

Materials and Methods

In the Pediatrics and Pediatric Neurology Department of „Victor Gomoiu" Children Clinical Hospital Bucharest, Romania there have been studied 48 pediatric ADHD patients: 16 patients received pharmacologic treatment with ATX (group 1), 16 patients underwent pharmacologic treatment with MPH (group 2) and 16 patients did not receive pharmacological treatment (group 3 = control group), but individual psychotherapy and specific guidance on patient and family. The study was approved by the Ethics Committee of „Victor Gomoiu" Children Clinical Hospital. For all the children in the study, the written consent was obtained from children' s parent for using the medical data, ensuring also privacy and identity protection of the subjects.

Inclusion criteria: diagnostic of ADHD (neurologic etiology) according to DSM-IV-TR criteria, age 5 – 12 years, males and females.

Exclusion criteria: patients with a medical history of cardiovascular disease and narrow angle glaucoma, patients whose parents don't understand the items from The Child Symptom Inventories – 4 (CSI-4) scale.

Age descriptive statistics for each of the three groups are presented in Table I.

Table I

Age descriptive statistics for each group of patients

Group	No. of subjects	Age (mean)	Standard Deviation	Standard Error	95% Confidence Interval for Mean		Min age	Max age
					Lower limit	Upper limit		
1	16	8.25	1.915	0.479	7.23	9.27	5	12
2	16	7.88	2.062	0.515	6.78	8.97	5	12
3	16	6.94	2.048	0.512	5.85	8.03	5	12
Total	48	7.69	2.044	0.295	7.09	8.28	5	12

The paper presents the assessment of the ADHD symptoms in patients with treatment *versus* control group (without pharmacological treatment).

The initial dose of MPH was 10 mg/kg bodyweight/day (bw) and could be increased to 40 mg/kg bw per day depending on the intensity of the symptoms. ATX was gradually titrated from 0.5 mg/kg bw to a maximum dose of 1.2 mg/kg bw per day over a dose titration period of 4 weeks.

The severity of ADHD symptoms was screened with parent-rated CSI-4 scale at baseline (when the pharmacological treatment was initiated) and 3 months after.

All the patients were followed-up over a 3 months observation period.

Results and Discussion

In the absence of national guidelines, the pharmacological treatment was the doctor's option depending on each patient's individual particularities, taking also into consideration that neither MPH, nor ATX are indicated in all children with this syndrome and treatment plans are adaptive.

The CSI-4 scale parent-rating scores measured at two time points were statistically analyzed (Table II).

Table II

Descriptive Statistics of the scores measured at two time points

CSI-4 scale score	Group	Mean	Standard Deviation	No of subjects
Baseline score	1	43.56	4.993	16
	2	43.94	4.464	16
	3	41.13	6.344	16
	Total	42.88	5.362	48
3 months score	1	36.69	5.375	16
	2	36.31	4.029	16
	3	38.81	6.316	16
	Total	37.27	5.327	48

Significance of differences between CSI-4 scale scores measured at baseline and 3 months after was tested using Analysis of Variance (ANOVA) for Repeated Measures. ANOVA for Repeated Measures calculates an overall statistic having an F distribution which is determined also by the associated degrees of freedom (df). The number of df is calculated as the number of repeated measures minus 1. The results of ANOVA for Repeated Measures obtained for the scores rated by parent (mother) at baseline and 3 months after are presented below.

Within-subjects analysis taking into consideration the CSI-4 scale score at baseline which was compared with CSI-4 scale score after 3 months for the whole sample established a statistic test $F=745.990$ with $df=1$. Based on these results, it can be concluded that there is a statistical significant difference ($p<0.001$) between the two time points (baseline and 3 months after) which corresponds to an improvement of the disease symptoms.

An ANOVA analysis was performed also for the mean difference of the score between the two time points (baseline and 3 months after), for the three groups. The results revealed a statistical significant difference ($p<0.001$) between the three groups with an overall $F=65.454$ with $df=2$, which confirmed the above ANOVA for repeated measures within-subjects results.

We have also performed a *post hoc* multiple comparisons analysis, that emphasized a statistical significant difference ($p<0.001$) between each of the two treatment groups (group 1 and group 2) on one side and the control group on the other side (Table III). Thus it can be concluded that the pharmacological treatment influenced the within-subject variation of the scores.

Table III

Pairwise comparison

Treatment/ Control Group (I)	Treatment/ Control Group (J)	Mean Difference (I - J)	Standard Error	p	95% Confidence Interval for Difference	
					Lower limit	Upper limit
1	2	-0.750	0.503	0.337	-2.02	0.52
	3	4.563*	0.503	<0.001	3.29	5.83
2	1	0.750	0.503	0.337	-0.52	2.02
	3	5.313*	0.503	<0.001	4.04	6.58
3	1	-4.563*	0.503	<0.001	-5.83	-3.29
	2	-5.313*	0.503	<0.001	-6.85	-4.04

I, J = letters that designate the first (I) and the second (J) members of all the possible pairs formed with the three measurements (group 1, 2, 3)
Standard error = standard deviation of the sample-mean's estimate of the population mean
p = probability of error in considering statistical significant difference.
Between the means of the two compared score measurements there is a statistically significant difference if the probability p is less than 0.05
*The mean difference is significant at the 0.05 level

However, between-subjects analysis taking as factor the treatment group could not highlight a statistical significant difference ($p>0.05$) between the two treatment groups and the control group.

A separate analysis was performed for the two groups with pharmacological treatment by the age group. The patients were divided into age groups as follows: 5 – 6 years (before attending public elementary school) and 7 – 12 years (after attending public elementary school). The distribution of the subjects in each age group falling in each treatment group is expressed in observed frequency and percent and it is presented in Table IV.

Table IV

Age group *versus* Treatment group Crosstabulation

			Treatment Group		Total
			1	2	
Age group	5 - 6 years	Count	2	4	6
		% within Age group	33.3%	66.7%	100.0%
	7 - 12 years	Count	14	12	26
		% within Age group	53.9%	46.1%	100.0%
Total		Count	16	16	32
		% within Age group	50.0%	50.0%	100.0%

Descriptive statistics of the CSI-4 scores determined at baseline and 3 months after for the subjects from the two groups (1 and 2) which underwent pharmacological treatment are presented in Table V.

Table V

Descriptive statistics of the scores for cumulative groups 1 and 2 of treatment

CSI-4 scale score	Age group	Mean	Standard Deviation	No of subjects
Baseline score	1	38.33	1.862	6
	2	45.00	4.195	26
	Total	43.75	4.663	32
3 months score	1	32.17	1.835	6
	2	37.50	4.572	26
	Total	36.50	4.677	32

1 = age group 5 – 6 years
2 = age group 7 – 12 years

The results of ANOVA test for Repeated Measures obtained for the CSI-4 scores for group 1 (with ATX) and group 2 (with MPH) are presented below.

Within-subjects analysis confirmed also a statistical significant difference ($p<0.001$) between the two time points for the whole sample, regardless the age group establishing an $F=393.984$ with $df=1$. The interaction between the time points and the age groups (5-6 years and 7-12 years) revealed a threshold approaching, but didn't reach the statistical significance ($p=0.062$).

However, between-subjects analysis considering the age group as between-subjects factor, established a statistics $F=1779.40$ with $df=1$, which

confirms a statistical significant difference ($p<0.01$) between the age groups regarding the evolution of the parent-rating scores.

The Wilcoxon test (a non-parametric test for means comparison between paired samples) was also applied to the treatment groups 1 and 2 in order to confirm the difference between the two time points. Descriptive statistics for scores measured for the two analyzed time points (baseline and 3 months after) are presented in Table VI.

Table VI
Descriptive statistics

CSI-4 scale score	No of subjects	Mean	SD	Minimum	Maximum
Baseline score	32	43.75	4.663	36	54
3 months score	32	36.50	4.677	30	48

Wilcoxon statistic showed $Z = 4.982$ ($p<0.001$), which shows a statistical significant difference between the two time points for the patients who received treatment.

Conclusions

There are no differences between the groups with pharmacologic treatment group 1 and group 2 meaning that both tretaments proved to have similar efficacy in stabilizing the ADHD symptoms. Pharmacologic treatment significantly reduced the ADHD symptoms in children on the basis of parent-rate scoring and although it couldn't be statistically concluded compared to control group this fact was clinically observed. Early identification and diagnosis and initiation of pharmacologic therapy even before attending elementary school can prevent many of the negative consequences regarding social life and the impact on Quality of Life.

The treatment (both ATX and MPH) was generally well tolerated, no patient discontinued administration due to adverse events.

References

1. Adler LA, Sutton VK, Moore RJ, Dietrich AP, Reimherr FW, Sangal RB, Saylor KE, Secnik K, Kelsey DK, Allen AJ.: Quality of life assessment in adult patients with attention-deficit/hyperactivity disorder treated with atomoxetine, J *Clin Psychoparmacol.* 2006 Dec; 26(6):648-52
2. Barkely RA. Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. *Psychol Bull.* 1997;121:65–94
3. Cid Foix A, Proposals for social policies to improve the quality of life in attention deficit/hyperactivity disorder [ADHD], *Cuad Bioet*. 2011 May-Aug;22(75):215-42

4. Childress AC, Berry SA, Pharmacotherapy of attention-deficit hyperactivity disorder in adolescents*, Drugs* 2012 Feb 12;72(3):309-25
5. Cojocaru M, Cojocaru I M, Negres S, Popa F, Purcarea V, Arsene, A L, Intravenous immunoglobulin therapy in neurological diseases, *Farmacia* 2011, 59(6): 737 - 741
6. Fowler JS, Volkow ND. PET imaging studies in drug abuse. *Clin Toxicol.* 1998;36:163–174
7. Gatley SJ, Volkow ND, Gifford AN, et al. Dopamine-transporter occupancy after intravenous doses of cocaine and methylphenidate in mice and humans. *Psychopharmacology (Berl)* 1999;146:93–100
8. Guilherme Polanczyk; Maurício Silva de Lima; Bernardo Lessa Horta; Joseph Biederman; Luis Augusto Rohde, The Worldwide Prevalence of ADHD: A Systematic Review and Metaregression Analysis, *Am J Psychiatry 2007;*164:942-948.
9. Harpin V A, The effect of ADHD on the life of an individual, their family, and community from preschool to adult life*, Arch Dis Child 2005;*90:suppl 1 i2-i7
10. http://www.webmd.com/add-adhd/guide/adhd-medical-treatment
11. http://www.medicines.org.uk/emc/medicine/14482/SPC/strattera
12. Mihai L G, Mitrea N, Papacocea R I, Badarau A I, Dynamic activity of some antioxidant enzymes in primary cultures of neurons under hypoxia and ischemia, *Farmacia* 2012, 60(1): 49 - 57
13. Prince JB, Spencer TJ, Wilens TE, Biederman J. Pharmacotherapy of attention-deficit/hyperactivity disorder across the life span. In: Stern TA, Rosenbaum JF, Fava M, Biederman J, Rauch SL, eds. *Massachusetts General Hospital Comprehensive Clinical Psychiatry*. 1st ed. Philadelphia, Pa: Mosby Elsevier; 2008:chap 49
14. Sprafkin J, Gadow KD, Salisbury H, Schneider J, Loney J, Further evidence of reliability and validity of the Child Symptom Inventory-4: parent checklist in clinically referred boys., *J Clin Child Adolesc Psychol.* 2002 Dec;31(4):513-24
15. The MTA Cooperative Group, A 14-Month Randomized Clinical Trial of Treatment Strategies for Attention-Deficit/Hyperactivity Disorder**,** *Arch Gen Psychiatry.* 1999;56(12):1073-1086
16. Volkow ND, Wang GJ, Fowler JS, Logan J, Gatley SJ, Wong C, Hitzemann R, Pappas NR., Reinforcing effects of psychostimulants in humans are associated with increases in brain dopamine and occupancy of D(2) receptors., *J Pharmacol Exp Ther.* 1999 Oct;291(1):409-15
17. Volkow ND, Ding YS, Fowler JS, et al. Is methylphenidate like cocaine? studies on their pharmacokinetics and distribution in the human brain. *Arch Gen Psychiatry*. 1995;52:456–463
18. Volkow ND, Wang GJ, Fowler JS, et al. Association of methylphenidate-induced craving with changes in right striato-orbitofrontal metabolism in cocaine abusers: implications in addiction. *Am J Psychiatry*. 1999;156:19–26
19. W. Alexander Morton, Pharm.D., B.C.P.P. and Gwendolyn G. Stockton, Pharm.D., Methylphenidate Abuse and Psychiatric Side Effects, *Prim Care Companion J Clin Psychiatry.* 2000 October; 2(5): 159–164
20. DeVincent CJ, Gadow KD., Relative clinical utility of three Child Symptom Inventory-4 scoring algorithms for differentiating children with autism spectrum disorder vs. attention-deficit hyperactivity disorder**.,** *Autism Res.* 2009 Dec;2(6):312-21. doi: 10.1002/aur.106
21. Martényi F, Treuer T, Gau SS, Hong SD, Palaczky M, Suba J, Tiberiu M, Uhlíková P, Xu T, Zoroğlu S, Gadow KD, Walton R, Harrison G., Attention-deficit/hyperactivity disorder diagnosis, co-morbidities, treatment patterns, and quality of life in a pediatric population in central and eastern Europe and Asia, *J Child Adolesc Psychopharmacol.* 2009 Aug;19(4):363-76. doi: 10.1089/cap.2008.0148

Manuscript received: March 18th 2012