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ATOMOXETINE AND METHYLPHENIDATE TREATMENT IN ADHD

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Abstract

Objective: ADHD (Attention deficit/hyperactivity disorder) is the most common diagnosed neurobehavioral disorder in childhood and adolescence. Core symptoms of ADHD are persistent inattention, hyperactivity and impulsivity. In Slovakia, there are two specific medication choices to treat ADHD - atomoxetine and methylphenidate. Even though methylphenidate is option number one according to guidelines, the highest amount of patients are taking atomoxetine.

Aim: Our aim was to observe atomoxetine and methylphenidate effect in 40 child and adolescent patients with ADHD to compare their efficacy in child and adolescent patients using ADHD-RS-IV scale and CGI scale.

Methods: We included 40- hospitalised patients, 20 patients were taking atomoxetine and 20 patients methylphenidate. Therapeutic effect on symptoms of inattention, hyperactivity/impulsivity and global score was measured by ADHD-rating scale IV. Global clinical condition of patients was evaluated by CGI (Clinical Global Impression Scale). Symptomatology was measured before treatment, and every 2 weeks during 8 weeks of treatment. CGI was administrated before and after treatment.

Results: We found significant therapeutic effect of atomoxetine and methylphenidate on core symptoms of ADHD after 8 weeks of treatment both with atomoxetine and methylphenidate. We found non-significant difference CGI scale scores.

Conclusion: Our study evaluated atomoxetine and methylphenidate treatment effect on ADHD. Atomoxetine and methylphenidate showed significant effect on core symptoms of ADHD, there were no significant between group differences in ADHD-RS-IV. Our study revealed non-significant difference CGI scale scores between medication groups.

Keywords: Attention Deficit Hyperactivity Disorder, atomoxetine, methylphenidate, CGI, ADHD-RS-IV

INTRODUCTION

Attention-deficit hyperactivity disorder (ADHD) has become the most commonly diagnosed neurobehavioral disorder in childhood and adolescence, affecting more than 5% of children all around the world. ADHD is characterized by persistent symptoms of inattention, hyperactivity and impulsivity (1, 2). ADHD belongs to the chronic disorders beginning in childhood with persistent course into the adulthood. ADHD is linked to sub-performance of the dopamine and noradrenaline functions in the brain, primarily in the prefrontal cortex, responsible for self-regulatory and executive functions (3). From this point of view, the medication therapy is essential to reduce ADHD- linked symptomatology.

Worldwide approved effective medications used for ADHD are methylphenidate, as a stimulant, and atomoxetine, as a non-stimulant drug. Mechanism of action in methylphenidate is based on blocking the dopamine and noradrenaline transporter, which leads to increased concentrations of these neurotransmitters within the synaptic cleft. Atomoxetine is a selective inhibitor of the presynaptic noradrenaline transporter (4) with little or no affinity for other noradrenergic receptors, or other neurotransmitter transporters or receptors. Atomoxetine medication leads to increased noradrenergic neurotransmission.

Both, atomoxetine and methylphenidate repeatedly showed comparable efficacy in treating core symptoms of ADHD in several up to date studies (5, 6, 7). There are also studies from country and culturally different backgrounds, finding no differences between atomoxetine and methylphenidate effect on ADHD in their population (8, 9). However, clinical practise in Slovakia shows atomoxetine preference in treating ADHD.

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Aim of our study is to evaluate atomoxetine and methylphenidate effect on ADHD symptoms in child and adolescent patients in Slovakia every second week in 8 weeks of treatment and to compare between the group medication efficacy differences.

METHODS

We recruited 49 patients with the diagnosis of ADHD in the age of 5-16 years. All recruited children were in-patients of the Department of Child and Adolescent Psychiatry, Clinic of Psychiatry, University Hospital in Martin, between January 2012 and June 2013. All patients met diagnostic criteria for attention deficit/hyperactivity disorder – combined type, based on the Diagnostic & Statistical Manual of Mental Disorders DSM-IV-TR (Text Revision). All patients were diagnosed by two independent child psychiatrists using clinical examination, ADHD rating scale IV revision (ADHD-RS-IV) and Clinical Global Impression scale (CGI). Exclusion criteria were other psychiatric and pediatric disorders in need for additional medication, a medical history of cardiovascular abnormalities, previous treatment with atomoxetine and methylphenidate, and use of other psychiatric drugs.

Recruited patients were randomised into two groups. The first group consisted of 24 patients (18 boys, 6 girls) treated with atomoxetine. The second group consisted of 25 patients with ADHD (20 boys, 5 girls) treated with methylphenidate, osmotic-controlled release oral delivery system, (OROS). We followed the generally recommended dosage according to the U.S. Food and Drug Administration (FDA). During the 8-week period, 9 patients discontinued the study due to non-compliance to treatment. 40 patients (29 boys, 11 girls; 11 ± 0.3 years) finished the study and were included in the statistical evaluations. 20 patients (14 boys, 6 girls) aged 5-16 years (10.35 ± 0.5yr) were taking atomoxetine and 20 patients (15 boys, 5 girls) aged 5-16 years (10.7 ± 0.5yr) were treated with methylphenidate.

ADHD-RS-IV is an 18 item worldwide reliable and valid scale used for clinical and research purposes, which identifies symptoms of inattention and hyperactivity/impulsivity. The CGI comprises two companion one-item measures evaluating the following: severity (CGI-Severity) of psychopathology from 1 to 7 and change from the initiation of treatment (CGI-Improvement) on a similar seven-point scale. CGI-S is rated on the following seven-point scale: 1 = normal, not at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; 7 = among the most extremely ill patients. CGI-I is rated on the following seven-point scale: 1 = very much improved since the initiation of treatment; 2 = much improved; 3 = minimally improved; 4 = no change from baseline (the initiation of treatment); 5 = minimally worse; 6 = much worse; 7 = very much worse since the initiation of treatment. The scale includes questions revealing the symptoms of hyperactivity, impulsivity and inattention in a four-point scale from 0 to 3 (not at all – very much). ADHD-RS-IV was used to evaluate the treatment effects prior to and every second week for 8 weeks of treatment. CGI was used prior to and after 8 weeks of medication

Statistical analysis

The data were analysed using SYSTAT (©2008, Cranes Software International Ltd, USA). Wilcoxon test was used for the assessment of differences because of nongaussian distribution of the data determined by Lilliefors test. Data are expressed as the mean ± SD. Mann-Whitney test was used to analyses between medication group differences by CGI, and non-paired t-test was used to analyse between medication group differences by ADHD-RS-IV. The significance level was set at $p < 0.05$.

RESULTS

We found statistically significant decrease in ADHD-RS-IV score after 8 weeks of treatment in both medication groups (Table 1, 2). Figures 1, 2 show reduction in symptoms of ADHD by ADHD-RS-IV before and after 8 weeks of atomoxetine and methylphenidate treatment.

Table 1 Mean scores and standard deviation by ADHD-RS-IV prior to and every 2nd week for 8 weeks of atomoxetine treatment

	Week 0	Week 2	Week 4	Week 6	Week 8	p-value
Inattention	21.021 ± 4.556	18.111 ± 4.087	15.231 ± 6.305	12.056 ± 5.038	10.336 ± 5.774	p 0.000
Hyperactivity/ impulsivity	20.236 ± 5.947	16.798 ± 6.327	13.387 ± 5.901	11.602 ± 6.832	9.528 ± 6.043	p 0.000
Global score	41.251 ± 8.882	34.909 ± 10.027	28.618 ± 11.760	23.658 ± 11.874	19.864 ± 11.757	p 0.000

Table 2 Mean scores and standard deviation by ADHD-RS-IV prior to and every 2nd week for 8 weeks of methylphenidate treatment

	Week 0	Week 2	Week 4	Week 6	Week 8	p-value
Inattention	15.636± 5.957	12.212± 4.801	10.758± 4.213	9.909± 4.516	9.909± 4.516	p 0.000
Hyperactivity/ impulsivity	18.121± 6.061	14.636± 5.349	13.455± 5.701	12.212± 5.225	12.212± 5.225	p 0.000
Global score	33.455± 11.051	26.848± 9.378	24.212± 9.242	22.727± 9.796	22.727± 9.796	p 0.000

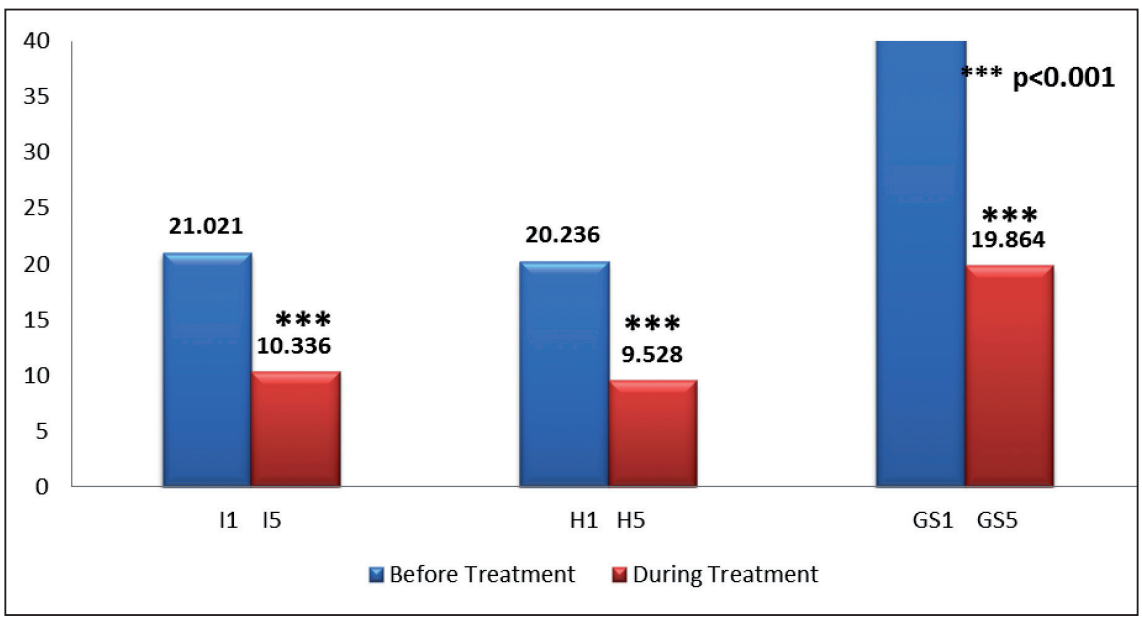

Fig. 1 Changes of mean score in symptoms of hyperactivity/impulsivity, inattention and global score in ADHD-RS-IV in patients treated by atomoxetine in week 0 and 8
Legend: I- inattention, H-hyperactivity, GS- global score, 1- before medication, 5- after 8 weeks of medication

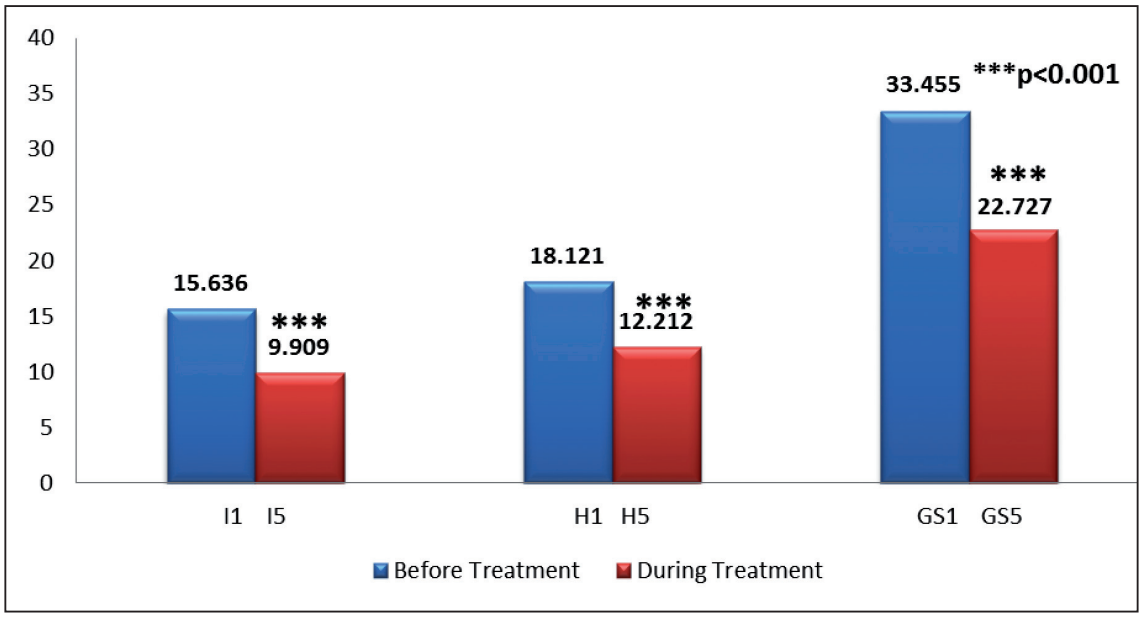

Fig. 2 Changes of mean score in symptoms of hyperactivity/impulsivity, inattention and global score in ADHD-RS-IV in patients treated by methylphenidate in week 0 and 8
Legend: I- inattention, H-hyperactivity, GS- global score, 1- before medication, 5- after 8 weeks of medication

In atomoxetine group, score of ADHD-RS-IV- inattention, was 21.021 ± 4.556 prior to and 10.336 ± 5.774 in week 8. Score of ADHD-RS-IV- hyperactivity/impulsivity, was 20.236 ± 5.947 prior to and 9.528 ± 6.043 in week 8 score of ADHD-RS-IV, global score, was 41.251 ± 8.882 prior to and 19.864 ± 11.757 in week 8.

In methylphenidate group, score of ADHD-RS-IV, inattention, was 15.636 ± 5.957 prior to and 9.909 ± 4.516 in week 8, score of ADHD-RS-IV hyperactivity/impulsivity, was 18.121 ± 6.061 prior to and 12.212 ± 5.225 in week 8 and score of ADHD-RS-IV, global score , was 33.455 ± 11.051 prior to and 22.727 ± 9.796 in week 8 .

To evaluate efficacy of medication treatment and improvement of clinical condition of patients CGI scale was used. We found that in atomoxetine group, score of CGI-I after 8 weeks of medication was 1.8 ± 0.797 ($p < 0{,}001$) and in methylphenidate group CGI-I score was 2.3 ± 0.603 ($p < 0{,}001$). Both, atomoxetine and methylphenidate group showed significant improvement in clinical condition measured by score of CGI.

Analysis of between medication group efficacies showed non-significant differences between medication groups after 8 weeks of medication. Table 3 shows atomoxetine superiority in scores of inattention in ADHD-RS scale before medication and in week 2 and 4 and in total score in ADHD-RS scale before medication and in week 2. However, after 8 weeks of medication, there were non-significant findings in scale scores in ADHD-RS-IV. We found non-significant between medication group differences in score of CGI scale after 8 weeks of medication. Figure 3 shows comparison in distribution of mean score of CGI-I after atomoxetine (ATX) and methylphenidate (MPH) treatment in week 8.

Table 4 Between atomoxetine/methylphenidate medication group significance in scores of ADHD-RS-IV scale at the baseline and every second week for 8 weeks of treatment

	Before treatment	2. week	4. week	6. week	8. week
Inattention	<0.001 *	< 0.001 *	<0.01 *	0.061	0.617
Hyperactivity	0.406	0.503	0. 836	0.835	0.187
Total score	<0.010 *	<0.010*	0.170	0.662	0.461

* significant between medication group difference

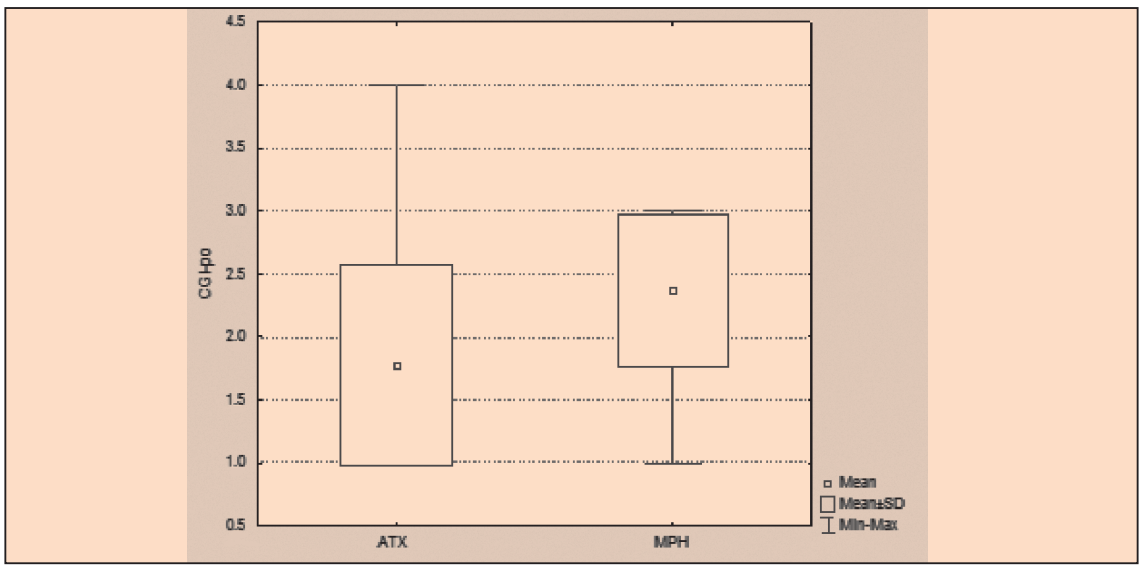

Fig. 3 Comparison of median and interquartile range of CGI-I score after atomoxetine (ATX) and methylphenidate (MPH) treatment in week 8

DISCUSSION

Based on available evidence, psychostimulants are regarded as first-line pharmacologic treatment for children and adolescents with ADHD, as the efficacy and the safety of these agents have been well established based on clinical trials and extensive naturalistic use (10). Even though, Slovak population of child and adolescent patients with ADHD are more frequently treated with atomoxetine.

In our study, we found significant decrease in scores of ADHD-RS-IV and CGI scale, in both medication groups after 8 weeks of treatment, which is corresponding with up to date studies (11, 12). Non-stimulant medication atomoxetine, and stimulant, methylphenidate were significantly efficient in treating symptoms of ADHD using ADHD-RS-IV and CGI scale.

Our findings in between medication group efficacy difference showed non-significant difference in efficacy between medications after 8 weeks of treatment. However, we found significantly higher scores in atomoxetine group in symptoms of inattention in ADHD-RS-IV before medication and in week 2 and 4, and in total score in ADHD-RS before medication and in week 2. Even though scores of symptoms of inattention and total score of ADHD

according to ADHD-RS were higher in atomoxetine patients group, atomoxetine and methylphenidate were comparable efficient after 8 weeks of the study.

Our results have support in several current studies. Hanwella et al. (2011) in the meta-analysis of comparative efficacy of methylphenidate and atomoxetine in treating attention deficit hyperactivity disorder in children and adolescents proved comparable effect of methylphenidate OROS and atomoxetine in treating ADHD. The findings of the meta-analysis have implications for clinical practice. The results from the meta-analysis show that in general atomoxetine and methylphenidate have comparable efficacy and equal acceptability in treatment of ADHD in children and adolescents. It also suggests that OROS methylphenidate is more effective and may be considered as first line treatment in treatment of ADHD in children and adolescents.

In contrast to our results, Newcorn et al. (2008) found significantly greater response with osmotically released methylphenidate than with atomoxetine.

There are several up to date studies aimed on comparison of ADHD linked medication in specific populations of patients. Garg et al. (2014) in their short-term efficacy study of ADHD medication in Indian children found comparable efficacy and tolerability of methylphenidate and atomoxetine treatment. Similarly, Lv et al. (2012) in their systematic review of studies aimed on comparison of efficacy and safety of atomoxetine, methylphenidate-immediate release and OROS methylphenidate in Chinese child and adolescent population with ADHD. There was no difference in the efficacy ratings across different scales and dimensions between OROS-methylphenidate, methylphenidate-immediate release and atomoxetine.

Our results support up to date findings about atomoxetine and methylphenidate equal efficacy also in Slovak child and adolescent patients with ADHD. Even though methylphenidate is suggested as a first choice medication, in majority of studies there is no significant methylphenidate superiority in compare to atomoxetine. Atomoxetine is generally recommended in patients with several comorbidities such as tic disorders and anxiety. Reason for frequent atomoxetine use in Slovak population of patients can be explained by the presence of other mental disorders in these patients at the same time. Another reason can be associated with different medication tolerability, however, we did not analyse tolerability of atomoxetine and methylphenidate in our group of patient.

CONCLUSIONS

Atomoxetine and methylphenidate were significantly efficient in treating ADHD symptoms in Slovak population of child and adolescent patients with ADHD. Using ADHD-RS-iv and CGI scales, scores in symptoms of inattention, hyperactivity and impulsivity decreased. After 8 weeks of medication, we found comparable medication effect with no significant superiority of atomoxetine or methylphenidate.

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