Atomoxetine Versus Oros Methylphenidate in Attention Deficit Hyperactivity Disorder: A Six-Month Follow Up Study for Efficacy and Adverse Effects

Dikkat Eksikliği Hiperaktivite Bozukluğu Tedavisinde Atomoksetin ve Osmotik Salınımlı Metilfenidat: Etkinlik ve Yan Etki Profilinin Değerlendirildiği Altı Aylık İzlem Çalışması

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ABSTRACT Objective: Attention deficit hyperactivity disorder (ADHD) is one of the most frequently seen neuropsychiatric disorders in childhood. The aim of this study is to compare the efficacy and the adverse effects of two FDA-approved agents, atomoxetine (ATX) and osmotic release oral system methylphenidate (OROS-MPH), in the treatment of ADHD. **Material and Methods:** This research was designed as a randomized, open label, prospective and follow-up study. The study was performed by 120 cases between ages 7-16 years who were diagnosed as ADHD for the first time and given prescription. The cases were divided into two by randomization. One group was given ATX (n=59) while the other was given OROS-MPH (n=61) were evaluated prospectively by clinical examination and Conner's Comprehensive Behavior Rating Scale-Teacher (CRS-T) at the 2nd, 4th, and 6th months. Efficacy of treatment was regarded as a 40% reduction in CRS-T scores when compared to baseline values, and the adverse effects were questioned in every follow up visit. **Results:** The efficacy was 55.7% in CRS-T hyperactivity score, 63.9% in the attention deficit score, and 55.7% in the behavior problems score in OROS-MPH group. Those values were 47.5%, 69.5% and 57.6% respectively in ATX group. Adverse effects were seen in 27.1% (n=16) of the patients in the ATX group, and in 31.1% (n=19) of the patients in the OROS-MPH group. Two groups were not found significantly different for the frequency of adverse effects as well as the efficacy of the medication, at the follow-up evaluations which were performed at 2nd, 4th and 6th months. **Conclusion:** In this study, ATX and OROS-MPH were compared for their efficacy and adverse effects for the treatment of ADHD, and two agents were found similar for their efficacies and adverse effect profiles. ATX and OROS-MPH have similar efficacies in the treatment of ADHD and adverse effect profiles are similar.

Key Words: Attention deficit disorder with hyperactivity; atomoxetine; methylphenidate; adverse effects; efficiency

ÖZET Amaç: Dikkat eksikliği hiperaktivite bozukluğu (DEHB), çocukluk çağında en sık görülen nöropsikiyatrik hastalıklardan biridir. Bu çalışmada, DEHB tedavisinde kullanılan FDA onaylı iki ajan olan atomoksetin (ATX) ile osmotik salınımlı metilfenidat (OROS-MPH)'ın etkinlik ve yan etki profillerinin karşılaştırılması amaçlanmıştır. **Gereç ve Yöntemler:** Bu araştırma randomize, açık uçlu ve prospektif bir izlem çalışması olarak dizayn edildi. Çalışma, DEHB tanısı konulan ve ilk kez ilaç tedavisi başlanan, yaşları 7-16 yıl arasındaki 120 hasta ile yapıldı. Hastalar, randomizasyonla ikiye ayrıldı. ATX (n=59) ve OROS-MPH (n=61) kullanan hastalar 2., 4. ve 6.aylarda Conner's Öğretmen Derecelendirme Ölçeği (CÖDÖ) ve klinik muayene ile değerlendirildi. Başlangıca göre 6. ayda CÖDÖ puanlarında %40 azalma etkinlik olarak kabul edildi ve her görüşmede yan etkiler sorgulandı. **Bulgular:** Etkinlik OROS-MPH grubunda CÖDÖ hiperaktivite puanında %55,7; dikkat eksikliği puanında %63,9; davranım problemleri puanında %55,7 iken bu oranlar ATX grubunda sırasıyla %47,5; %69,5 ve %57,6 olarak saptandı. Yan etki ATX grubunda %27,1 (n=16) iken, OROS-MPH grubunda %31,1 (n=19) olarak belirlendi. İkinci, 4. ve 6. aylarda yapılan değerlendirmede, her iki tedavi grubu arasında etkinlik ve yan etki sıklığı açısından anlamlı farklılık saptanmadı. **Sonuç**: Bu çalışmada, ATX ve OROS-MPH, DEHB tedavisinde etkinlik ve yan etki sıklığı açısından karşılaştırılmış, etkinlik ve yan etki profili açısından iki ajan arasında anlamlı farklılık bulunmamıştır. ATX ve OROS-MPH, DEHB tedavisinde benzer etkinlik profiline sahiptir ve yan etki profilleri benzerdir.

Anahtar Kelimeler: Hiperaktivite ile birlikte dikkat eksikliği bozukluğu; atomoksetin; metilfenidat; istenmeyen etkiler; etkinlik

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Attention deficit hyperactivity disorder (ADHD) has a prevalence of 5-14% in children worldwide, and it is one of the most frequently diagnosed neuropsychiatric diseases in childhood.[1] ADHD presents with a clinically heterogeneous picture, and it can be accompanied by important psychopathologies including oppositional defiant disorder, conduct disorder, mood disorders, anxiety disorders, and alcohol and substance use disorders.[1] Problems arising out of ADHD such as poor school success, social rejection, accident-related injuries and drug abuse pave the way for important problems both for the individual and the family.[1-5] Therefore, early diagnosis and treatment of this disorder is important.

Although ADHD is a multifactorial disorder in which genetic and environmental factors play part, the imbalance and dysfunction of the dopaminergic and noradrenergic systems is the basic pathophysiological mechanism in its etiology. In the light of this data regarding etiology, it is not surprising that the agents used in the treatment of ADHD show their effects via dopaminergic and noradrenergic transmission.[6] Methylphenidate (MPH), which is a DAT inhibitor, is one of those agents, and it is the most frequently used stimulant in ADHD treatment[7]. The only FDA approved non-stimulant treatment option for ADHD is atomoxetine (ATX), which is a selective NET inhibitor.[8] The efficacy and safety of both drugs have been shown in a large number of studies.[9-13] Some of the randomized controlled comparison studies for efficacy and safety of these two agents found MPH was superior while some others did not find any difference between two agents.[9,10,12,14,15] The meta-analyses of those studies also show similar contradictions.[16-19] Therefore, there is still a need for the studies comparing MPH and ATX which are two agents frequently used in the treatment of ADHD. In addition, there is only one randomized comparison study performed on Turkish population on this topic.[20] In the light of these data, we aimed to compare the efficacy and adverse effect profiles of ATX and oral system methylphenidate (OROS-MPH).

MATERIAL AND METHODS

SUBJECTS AND STUDY DESIGN

This prospective observational study was performed in Gazi University, Child and Adolescent Psychiatry Department between 2012 and 2013. The ADHD patients between the ages of 7-16 years without any comorbid psychopathologies were included in the study. The patients were first evaluated by the residents of Child Psychiatry Department according to DSM-IV-TR diagnostic criteria. After the clinical interviews Schedule for Affective Disorders and Schizophrenia for School Age Children-Present and Lifetime Version-Turkish Version (K-SADS-PL-T) which is a semi-structured interview were performed. The teachers were given Conners Comprehensive Behavior Rating Scale-Teacher (CRS-T). Then, the patients who were diagnosed with ADHD for the first time and who did not have any comorbidities were assessed by the relevant professor, written oral consents of the patients and their parents were obtained, and they were included in the study. A total intelligence quotient <90, presence of a central nervous system disease, organic problems, comorbid psychopathologies or a previous treatment with the diagnosis of ADHD were determined as the exclusion criteria.

A total of 145 patients who met the inclusion criteria and then were administered drugs were included in the study. The sample population were randomized into two groups, and the ones numbered with odd numbers were administered OROS- MPH while the ones numbered with even numbers were given ATX. The patients were called for follow up visits at 2nd, 4th, and 6th months, they were assessed by the same physician in every follow up visit, and their CRS-T scores were noted. The adverse effects and tolerability of medications were evaluated using a questionnaire including 12 questions about anorexia, insomnia, stomachache, nervousness, headache, weight loss, rash, obsessions, sedation, epistaxis, tics and others, in addition to open ended questions which were determined in the light of previous studies.

The study was designed in accordance with Good Clinical Practice Guideline and Helsinki Declaration. The study protocol was approved by local Ethics Committee.

DATA TOOLS

Schedule for Affective Disorders and Schizophrenia for School Aged Children, Present and Lifetime Version (K-SADS-PL): K-SADS-PL-T is a semi-structured interview developed by Kauffman et al. to screen psychopathologies in 6-18-year-old children and adolescents.[21] In this scale, psychopathology is studied by combining the data obtained from the child and the parents. The psychopathologies included in the scale are affective disorders, psychotic disorders, anxiety disorders, externalizing disorders, alcohol and substance abuse, and eating and tic disorders. The reliability and validity study of K-SADS-PL-T was performed by Gokler et al. in Turkey.[22]

Conners Comprehensive Behavior Rating Scale-Teacher (CRS-T): CRS-T is composed of 28 questions, and it was developed for the behavioral evaluation of the children on the basis of the observations of the teachers in the classroom. Every question is answered in a 4-point Likert type scale (0: never, 1: rarely, 2: frequently, 3: always). High scores indicate absence of the symptoms specific for the disruptive disorders. In this scale, 3 subscale scores are calculated including hyperactivity, attention deficit, and behavior problems. Its validity study in Turkey was performed by Sener et al.[23]

STATISTICAL ANALYSIS

The data were analyzed using SPSS (Statistical Package for the Social Sciences) 15.0 package program. The descriptive statistics were given with mean, standard deviation and percent, and T test was used to analyze the differences for independent, normally distributed and quantitative data. The qualitative data were compared using Chi-square and Fisher-Exact tests. Per protocol analysis was used for evaluating of results. Two-way ANOVA test was used to determine whether CRS-T scores changed in time in relation with the medication given for treatment. Since similar studies regarded a 40% change in CRS-T scores according to baseline as the reference for efficacy because of the relevance of this criterion was further supported by an analysis by Gao et al., we regarded a 40% decrease in scores as the efficacy of the treatment.[4] In addition, the efficacy was analyzed comparing the CRS-T subscale scores at baseline and at 6th month of treatment. Statistical significance was set at $p<0.05$.

RESULTS

Of 145 patients, nine patients were excluded from the study due to adverse effects requiring discontinuation of the medication, and 16 patients were excluded due to lack of follow up. The reasons for discontinuation of ATX treatment were tachycardia (pulse >120/min) in two patients, allergic reactions (erythema and rash) in one patient, and irritability in one patient. MPH treatment was discontinued due to tachycardia (pulse >120/min) in one patient, allergic reactions (erythema and rash) in one patient, and anorexia (more than 10% weight loss in one month) in 2 patients (Figure 1).

A total of 120 patients, 61 in OROS- MPH group, and 59 in ATX group, were included in the study. The mean doses were determined as 0.73±0.22 mg/kg/day for OROS-MPH, and 1.14±0.13 mg/kg/day for ATX groups. Mean dosage is the arithmetical mean which is found by total drug dosage/day divided by total body mass. The mean age of the study population was 9.47±2.32 years. Girls constituted 13.1% of OROS-MPH group, and 23.7% of ATX group. The diagnosis of ADHD-predominantly inattentive subtype was determined in 8.2% of the patients using OROS-MPH, and 17% of the ones using ATX. Eighty three percent of patients in ATX group and 91.8% of subjects in OROS-MPH group met criteria for ADHD-combined subtype. There were no cases diagnosed with ADHD-predominantly hyperactive subtype. Two groups were not found significantly different for the age, gender, distribution of ADHD subtype, or baseline CRS-T scores (Table 1).

The drug used was considered as efficient in the patients who showed ≥40% decrease in CRS-T

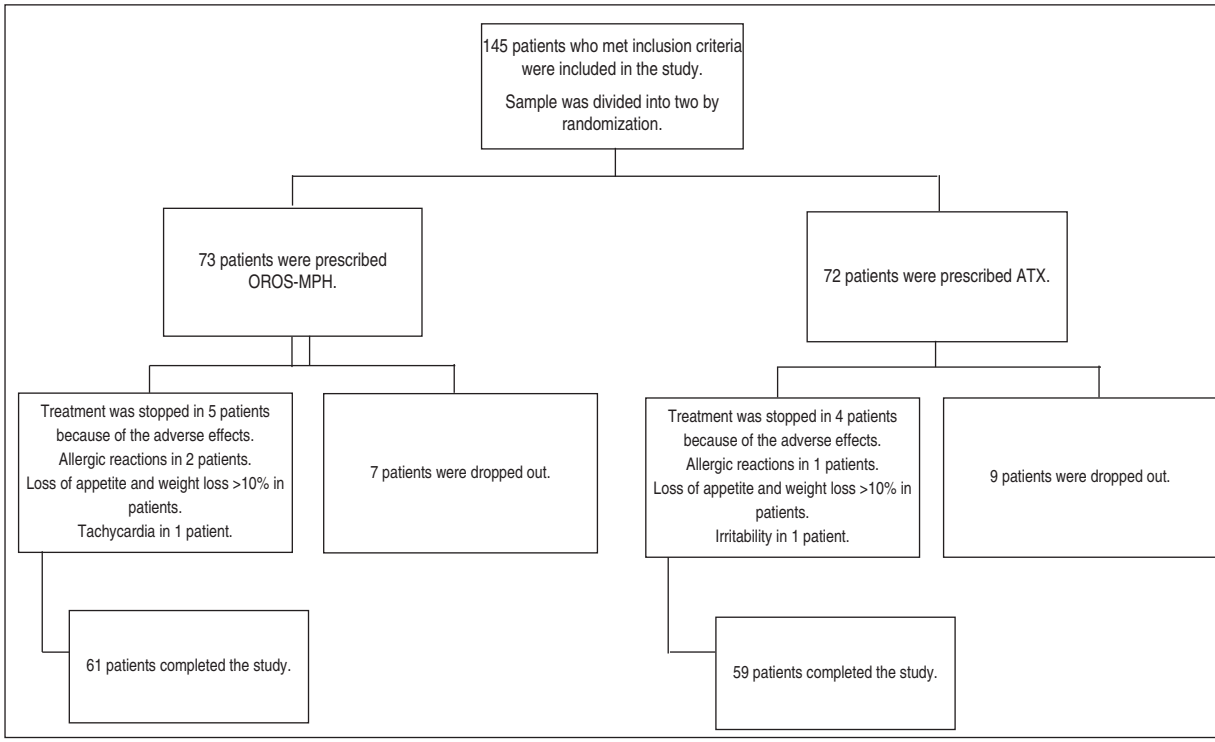

FIGURE 1: Flow chart of the study.
59 patients completed the study.

attention deficit (AT), hyperactivity (HP) and behavior problems (BP) scores at the 6th month follow up visit. Accordingly, the rate of patients in whom efficacy was observed was 55.7% in CRS-T hyperactivity score, 63.9% in attention deficit score, and 55.7% in behavior problems score in OROS-MPH group. These rates were 47.5%, 69.5% and 57.6%, respectively in ATX group. Comparison of the ATX and OROS-MPH groups for the rates of the patients in whom efficacy was observed did not reveal any statistically significant differences (Table 2).

TABLE 1: The sociodemographical characteristics of the patients.

Variables	OROS- MPH (n=61)	ATX (n=59)	TOTAL (n=120)	p
Age, (year) M±SD*	9.95±2.02	9.55±2.71	9.47±2.32	0.371
Gender, n (%)				
Girls	8 (13.1)	14 (23.7)	22 (18.3)	0.133
Boys	53 (86.9)	45 (76.3)	98 (81.7)	
ADHD type				
Combined type	56 (91.8)	49 (83.0)	105 (87.5)	0.147
Predominantly inattentive type	5 (8.2)	10 (17.0)	15 (12.5)	
Baseline CRS-T scores				
Hyperactivity	12.78±3.28	13.03±3.92	12.69±3.75	0.709
Attention deficit	16.14±4.07	17.13±3.15	16.68±3.94	0.141
Behavior problems	8.19±3.40	8.44±4.01	8.20±3.65	0.720

*Mean and standard deviation.
ADHD: Attention deficit hyperactivity disorder; CRS-T: Canners comprehensive behavior rating scale-teacher.

Two agents were also compared for the differences of the mean baseline and the last (ie. at 6th month follow up visit) determined CRS-T subscales scores, in other words, the change of the scores after two medications in the subscales. The changes were as in OROS-MPH group: 5.90±3.13 in CRS-T hyperactivity score, 7.91±3.54 in attention deficit score, 4.00±3.13 in behavior problems score. In ATX group, those values were 5.57±3.52, 8.76±4.06, and 4.08±3.01, respectively. When two agents were compared for the unitary changes in the subscales, no difference was found between the efficacies of two agents (Table 3).

The CRS-T subscale scores were determined for four times throughout the study, including baseline, and 2nd, 4th, and 6th months follow up visits. The mean baseline and 6th month CRS-T-HP, CRS-T-AD and CRS-T-BP scores of the patients in OROS- MPH and ATX groups have been mentioned in Table 3. In OROS- MPH group, the mean CRS-T-HP scores were 9.24 and 7.02, mean CRS-T-AD scores were 11.53 and 8.38, and the mean CRS-T-BP scores were 6.43 and 5.24, at 2nd and 4th months follow up visits respectively. Those values were determined as 10.68 and 7.81, 12.68 and 9.01, and 5.96 and 4.38, respectively in the ATX group. When the means were transferred into a graph and the changes of HP, AD and BP scores in time were compared for both drugs, no statistically significant differences were determined (p=0.649 for CRS-T-HP, p=0.657 for CRS-T-AD, and p=0.105 for CRS-T-BP) (Figures 2, 3 and 4).

A standard questionnaire developed for the current study was used in every follow up visit in order to find out the adverse effects. The rate of adverse effects observed was 27.1% (n=16) in the ATX group, and 31.1% (n=19) in the OROS- MPH group. There was no difference between the groups for the prevalence of the adverse effects (p=0.627).

The most commonly encountered adverse effect was anorexia in both groups, and it was seen in 19.6% of the patients in the OROS- MPH group and 13.5% of the patients in the ATX group. Insomnia (8.1% vs. 5.0%), headache (3.2% vs. 0%), and obsessions (3.2% vs. 0%) were more common in OROS-MPH group, however nervousness (6.7% vs. 3.2%), stomach ache (6.7% vs. 4.9%), and sedation (3.3% vs. 0%) were more common in the ATX group. The prevalence of the adverse effects was not found statistically significantly different between two groups (Table 4).

TABLE 2: The efficacy rates in OROS-MPH and ATX groups.*

	OROS-MPH (n=61)	ATX (n=59)	p
CRS-T-HP† n, (%)	34 (55.7)	28 (47.5)	0.364
CRS-T-AT† n, (%)	39 (63.9)	41 (69.5)	0.519
CRS-T-BP† n, (%)	34 (55.7)	34 (57.6)	0.835

*The drug was regarded as efficient when there was a ≥ 40% decrease in CRS-T subscale.

†HP: Hyperactivity; AT: Attention deficit; BP: Behavior problems.

TABLE 3: Efficacy in patients using OROS- MPH and ATX: The change in symptom severity.

	Baseline	Posttreatment	Change	Change %	p
CRS-T - HP*					
OROS-MPH	12.78±3.28	6.88±2.80	5.90±3.13	44.83±22.18	0.443
ATX	13.03±3.92	7.45±3.45	5.57±3.52	41.66±23.08	
CRS-T -AT*					
OROS-MPH	16.14±4.07	8.22±3.60	7.91±3.54	49.18±20.22	0.590
ATX	17.13±3.15	8.37±4.07	8.76±4.06	51.23±21.51	
CRS-T - BP*					
OROS-MPH	8.19±3.40	4.19±2.58	4.00±3.13	47.54±32.80	0.814
ATX	8.44±4.01	4.35±2.95	4.08±3.01	46.23±27.68	

*HP: Hyperactivity; AT: Attention deficit; BP: Behavior problems.

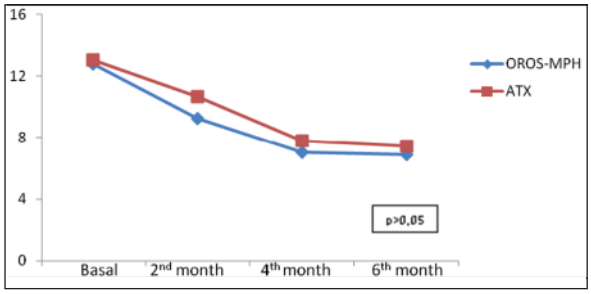

FIGURE 2: The change of CRS-T-HP scores in 6 months with OROS-MPH and ATX.

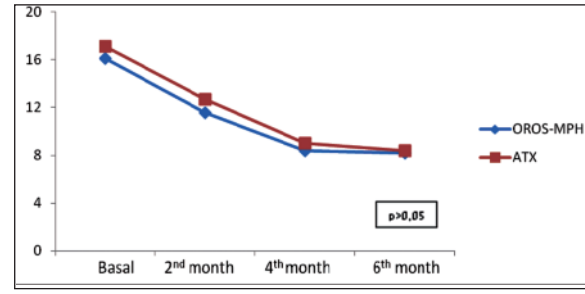

FIGURE 3: The change of CRS-T -AT scores in 6 months with OROS- MPH and ATX.

DISCUSSION

This study is a randomized, open label, prospective and observational study designed to compare the efficacy and tolerability of OROS-MPH and ATX, which are most frequently, used agents in the treatment of ADHD. Kemner et al. followed up 1323 patients in 2005, and found that the ADHD Rating Scale scores decreased 20.24 points with OROS-MPH and 16 points with ATX treatment after 3 weeks when compared to the baseline values and this difference was statistically significant (p<0,00.1).[9] When 25% decrease was regarded as a significant decrease in ADHD Rating Scale, response to treatment was found significantly higher in OROS- MPH group when compared to ATX group.[9] Prasad et al. performed another study on 188 patients in 2007, and compared ATX with other standard treatment options including OROS-MPH.[24] The patients were followed up for 10 weeks, and the change in ADHD Rating Scale scores with ATX was found significantly higher when compared to other agents used (OROS-MPH, short acting MPH, clonidine, and others). In

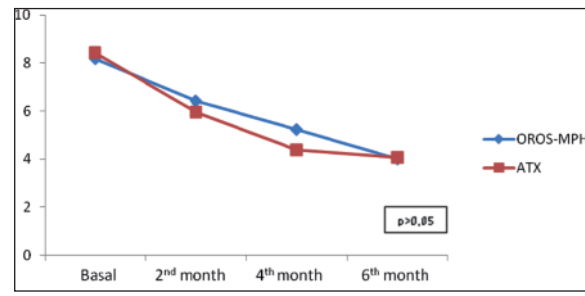

FIGURE 4: The change of CRS-T - BP scores in 6 months with OROS- MPH and ATX.

TABLE 4: The adverse effects seen in OROS- MPH and ATX groups.

Adverse Effect	OROS- MPH n, (%)	ATX n, (%)	TOTAL	p
Anorexia	12 (19.6)	8 (13.5)	20	0.369
Insomnia	5 (8.1)	3 (5.0)	8	0.377
Stomachache	3 (4.9)	4 (6.7)	7	0.481
Nervousness	2 (3.2)	4 (6.7)	6	0.324
Headache	2 (3.2)	0 (0)	2	0.256
Weight loss	1 (1.6)	1 (1.6)	2	1.000
Rash	0 (0)	2 (3.3)	2	0.240
Obsessions	2 (3.2)	0 (0)	2	0.256
Sedation	0 (0)	2 (3.3)	2	0.240
Epistaxis	0 (0)	1 (1.6)	1	0.492
Tic	1 (1.6)	0 (0)	1	0.492

addition, the rate of the patients responding to treatment was significantly higher in ATX group.[24] A double blind placebo controlled study performed by Newcorn et al. in 2008 compared OROS-MPH and ATX.[11] After 10 weeks of treatment, OROS-MPH (n=220) and ATX (n=222) showed efficacy in 56% and 45% of the patients, respectively; both drugs were found superior to placebo, and it was reported that OROS-MPH was significantly more efficient than ATX, and the side effects of these two agents were similar.[11] A cross-change was done between OROS-MPH and ATX in a period of 6 weeks, and it was shown that 43% of the patients who did not respond OROS- MPH responded to ATX while 42% of the patients who did not respond ATX responded to MPH. The effect sizes of ATX and OROS-MPH were 0.6 and 0.8, respectively when compared to placebo, however those values were 0.9 and 1.0 in the ones who had not used any stimulants before.[11] Yildiz et al. performed another study in 2010 on a small series (n=25), followed up the patients for 12 weeks, and found that OROS- MPH provided better improvements both in clinical measures (T-DSM-IV-S, CGI-I) and neuropsychological tests (WCST and Stroop-5) when compared to ATX.[20] The 3-week-follow up period of the first study is not found to be sufficient for ATX to show its effects, and the small sample size of the second study limits generalization of its results.[9,20] The second study which found ATX more efficient emphasized the efficacy concept, the importance of improvement of the symptoms in the morning and in the evening hours, and the absence of on-off effect related with the serum levels of the medication.[24] In our study, we regarded efficacy as a 40% chance in CRS-T subscale scores compared to the baseline scores, and found that the graphical changes in those scores were similar for OROS- MPH and ATX in a follow up period of 6 months. In this respect, our study is the first study which yielded a similar efficacy profile with the studies that compared only OROS-MPH and ATX. In addition, our study has the longest follow up period, which is 6 months.

Although there are no meta-analyses in the literature comparing OROS-MPH and ATX, there are important meta-analyses that included the studies comparing ATX and immediate release (IR) MPH. One meta-analysis did not find any difference in terms of efficacy between IR MPH and ATX, but OROS-MPH was found more effective than ATX.[17] ATX and MPH (OROS- MPH and IR MPH) were found to have similar efficacies in another meta-analysis.[18] Another meta-analysis that included only the studies with follow up periods longer than 6 weeks did not find any difference between ATX and MPH (OROS-MPH and IR MPH).[19]

In our study, we found that both agents were tolerated well. The rate of patients in whom side effects were observed was similar in OROS-MPH and ATX groups. Anorexia was the most frequently seen adverse effect in both groups. Insomnia, headache and compulsive behaviors were seen in OROS-MPH group, and sedation, stomachache, and nervousness were seen in ATX group; however the rates of the adverse effects seen in two groups did not show any statistically significant differences which is consistent with the literature.[15] One study reported that ATX and MPH had similar adverse effect profiles, the rates of the patients who had adverse effects were similar, and gastrointestinal side effects and sedation were more common with ATX.[15] Another study from Turkey noted that the most frequent adverse effects due to ATX were anorexia, nausea, nervousness and weight loss while OROS-MPH most frequently led to anorexia, nervousness, insomnia, and headache.[20] A review reported that both agents had the same adverse effect profiles, and noted that the tic disorders frequency increased with MPH, while the tic symptoms improved with ATX.[25] In the light of those data and the findings obtained in our study, we may suggest that the tolerability and the adverse effect profiles of these two agents are similar, anorexia and weight loss are the most frequent side effects observed with both agents, and although insomnia and headache are more frequent with OROS-MPH, somnolence and gastrointestinal symptoms are more frequent with ATX.

Absence of a placebo group is a limitation of our study. This might have prevented us from determining the factors other than the drugs used

played part in the clinical improvement observed during 6-months follow up period. Using per protocol analysis as statistical methods may be another limitation of the study because of dropped out patient's results are not adding to the processing of analysis. Therefore, probably some problems such as adverse effects of the drugs are not evaluated in the processing of analysis. Lastly, the adverse effects were questioned with a questionnaire composed of open ended questions, and determined according to declarations of the patients in our study.

In conclusion, although the efficacy and tolerability of ATX and OROS-MPH in ADHD have been proven in a number of different studies, there are a few conflicting studies in the literature that compared efficacies of these two drugs. Our study showed that OROS- MPH and ATX had similar efficacies and adverse effect profiles in the treatment of ADHD. Therefore, both agents can be used as the first-line therapy in treatment of ADHD. On the other hand, larger, randomized, double blind comparison studies are needed both in our country and in the world, as well as meta-analyses comparing the of efficacy and adverse effects OROS-MPH and ATX.

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REFERENCES

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Washington: The Association; 2013. p.991.
2. Kaya A, Taner Y, Guclu B, Taner E, Kaya Y, Bahcivan H, et al. Trauma and adult attention deficit hyperactivity disorder. J Int Med Res 2008;36(1):9-16.
3. Polderman TJ, Boomsma D, Bartels M, Verhulst F, Huizink A. A systematic review of prospective studies on attention problems and academic achievement. Acta Psychiatr Scand 2010;122(4):271-84.
4. Gao H, Zhao Y, Levine L, Allen A. Determining cut-points for clinically meaningful improvement: a receiver operating characteristic approach. Scientific Proceedings of the 53rd Annual Meeting of the American Academy of Child and Adolescent Psychiatry 2006. p.201.
5. Spencer T, Biederman J, Wilens T. Attention-deficit/hyperactivity disorder and comorbidity. Pediatr Clin North Am 1999;46(5):915-27.
6. Renner TJ, Gerlach M, Romanos M, Herrmann M, Reif A, Fallgatter A, et al. [Neurobiology of attention-deficit hyperactivity disorder]. Der Nervenarzt 2008;79(7):771-81.
7. Biederman J, Monuteaux MC, Doyle AE, Seidman LJ, Wilens TE, Ferrero F, et al. Impact of executive function deficits and attention-deficit/hyperactivity disorder (ADHD) on academic outcomes in children. J Consult Clin Psychol 2004;72(5):757-66.
8. Gau SS, Huang YS, Soong WT, Chou MC, Chou WJ, Shang CY, et al. A randomized, double-blind, placebo-controlled clinical trial on once-daily atomoxetine hydrochloride in Taiwanese children and adolescents with attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol 2007;17(4):447-60.
9. Kemner JE, Starr HL, Ciccone PE, Hooper-Wood CG, Crockett RS. Outcomes of OROS® methylphenidate compared with atomoxetine in children with ADHD: a multicenter, randomized prospective study. Adv Ther 2005;22(5): 498-512.
10. Kratochvil CJ, Heiligenstein JH, Dittmann R, Spencer TJ, Biederman J, Wernicke J, et al. Atomoxetine and methylphenidate treatment in children with ADHD: a prospective, randomized, open-label trial. J Am Acad Child Adolesc Psychiatry J 2002;41(7):776-84.
11. Newcorn JH, Kratochvil CJ, Allen AJ, Casat CD, Ruff DD, Moore RJ, et al; Atomoxetine/Methylphenidate Comparative Study Group. Atomoxetine and osmotically released methylphenidate for the treatment of attention deficit hyperactivity disorder: acute comparison and differential response. Am J Psychiatry 2008;165(6):721-30.
12. Starr HL, Kemner J. Multicenter, randomized, open-label study of OROS methylphenidate versus atomoxetine: treatment outcomes in African-American children with ADHD. J Natl Med Assoc 2005;97(10 Suppl):11S-16S.
13. Wilens TE, Newcorn JH, Kratochvil CJ, Gao H, Thomason CK, Rogers AK, et al. Long-term atomoxetine treatment in adolescents with attention-deficit/hyperactivity disorder. J Pediatr 2006;149(1):112-9.
14. Sangal RB, Owens J, Allen AJ, Sutton V, Schuh K, Kelsey D. Effects of atomoxetine and methylphenidate on sleep in children with ADHD. Sleep 2006;29(12):1573-85.
15. Wang Y, Zheng Y, Du Y, Song DH, Shin YJ, Cho SC, et al. Atomoxetine versus methylphenidate in paediatric outpatients with attention deficit hyperactivity disorder: a randomized, double-blind comparison trial. Aust N Z J Psychiatry 2007;41(3):222-30.
16. Faraone SV, Glatt SJ. A comparison of the efficacy of medications for adult attention-deficit/hyperactivity disorder using meta-analysis of effect sizes. J Clin Psychiatry 2010;71(6):754-63.
17. Hanwella R, Senanayake M, de Silva V. Comparative efficacy and acceptability of methylphenidate and atomoxetine in treatment of attention deficit hyperactivity disorder in children and adolescents: a meta-analysis. BMC Psychiatry 2011;11:176.
18. Hazell PL, Kohn MR, Dickson R, Walton RJ, Granger RE, van Wyk GW. Core ADHD symptom improvement with atomoxetine versus methylphenidate: a direct comparison meta-analysis. J Atten Disord 2011;15(8): 674-83.

19. van Wyk GW, Hazell PL, Kohn MR, Granger RE, Walton RJ. How oppositionality, inattention, and hyperactivity affect response to atomoxetine versus methylphenidate a pooled meta-analysis. J Atten Disord 2012;16(4):314-24.
20. Yildiz O, Sismanlar SG, Memik NC, Karakaya I, Agaoglu B. Atomoxetine and methylphenidate treatment in children with ADHD: the efficacy, tolerability and effects on executive functions. Child Psychiatry Hum Dev 2011;42(3):257-69.
21. Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, et al. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. J Am Acad Child Adolesc Psychiatry 1997;36(7): 980-8.
22. Gökler B, Ünal F, Pehlivantürk B, Kültür EÇ, Akdemir D, Taner Y. [Reliability and validity of schedule for affective disorders and schizophrenia for school age children-present and lifetime version-Turkish version (K-SADS-PL-T)]. Turk J Child Adolesc Ment Health 2004; 11(3):109-16.
23. Sener S, Dereboy Ç, Dereboy F, Sertcan Y. [Conners' Teacher Rating Scale Turkish Version-1]. Turk J Child Adolesc Ment Health 1995;2(3):131-41.
24. Prasad S, Harpin V, Poole L, Zeitlin H, Jamdar S, Puvanendran K; SUNBEAM Study Group. A multi-centre, randomised, open-label study of atomoxetine compared with standard current therapy in UK children and adolescents with attention-deficit/hyperactivity disorder (ADHD). Curr Med Res Opin 2007;23(2):379-94.
25. Lv XZ, Shu Z, Zhang YW, Wu SS, Zhan SY. Effectiveness and safety of methylphenidate and atomoxetine for attention deficit hyperactivity disorder: A systematic review. Translational Pediatrics 2012;1(1):47-53.