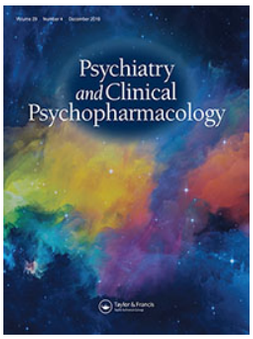

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Parent-reported social problems and clinician-evaluated adverse effects may be differentially affected by differing extended release methylphenidate formulations: a prospective, naturalistic study from Turkey

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ABSTRACT

OBJECTIVE: Medikinet retard® is a nonosmotic, extended-release formulation of Methylphenidate (MPH) and has been used in Turkey for the last 4–5 years. The aim of our study is to compare the efficacy on functionality of Medikinet retard® and Concerta® and their adverse events.

METHODS: Participants were referred to the Kayseri Training and Research Hospital and followed up there between August 2016 and June 2018. This study design is a 16-week prospective trial, each child received 16 weeks of OROS-MPH or MPH-ER. A total of 103 children were enrolled in the study, but only 70 children ($n = 35$ concerta, $n = 35$ medikinet retard) completed the study. Weiss Functional Impairment Rating Scale-Parent Report Form (WFIRS-P) and Barkley Side Effect Rating Scale (BSERS) were used for assessment.

RESULTS: In both treatment groups, children improved significantly over time, both in intensity and in the number of problems. Regarding the social problems, Medikinet retard® was superior to the Concerta in terms of effects. The side effects of insomnia and euphoria were seen more common in the Concerta® group than the Medikinet retard®. Additionally, the mean severity scores of euphoria were shown higher in the Concerta® group than the Medikinet retard.

CONCLUSION: From this study, we concluded that Medikinet retard® is also an effective and safety MPH formulation.

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KEYWORDS
Methylphenidate; Concerta; Medikinet retard; ADHD; social; functionality

Introduction

Attention deficit/hyperactivity disorder (ADHD) is one of the most common childhood psychiatric disorders with a worldwide prevalence rate of 5.3% and a persistent condition with inattention and/or hyperactivity-impulsivity that interferes with the functioning or development of children and adolescents. Patients with ADHD exhibit functional impairments across multiple settings, especially at school and home and so on [1,2]. These impairments may affect teacher, family, and peer relationships, and cause both academic and social difficulties [3,4]. Treatment of children and adolescents with ADHD usually focuses on symptom control during the school day in order to improve academic performance but, as emphasized in previous studies, therapeutic targets should be extended in scope to include social difficulties and improvements in the functionality of individuals and their families [5].

Methylphenidate (MPH) is recognized the first-line stimulant treatment and the most widely used psychostimulant for children and adolescents with ADHD [6], it decreases symptom frequency and/or severity and improves functionality [7,8]. MPH has various release formulations (immediate [MPH-I], extended release [MPH-ER], or osmotic release [OROS-MPH]) [9], and the effects of different preparations of MPH have been shown in meta-analyses [6,10].

Previously, the most commonly prescribed medication for ADHD in Turkey was OROS MPH [11] – amphetamine derivatives are not available in our country-, they were produced to maintain efficacy through 12 h with once-daily dosing. The tablet of Concerta® dissolves within 1–2 h and releases 22% of the total dose of MPH and 78% of the dose is osmotically controlled and released over 10 h. It is known that Concerta® has a safety profile and efficacy for ADHD treatment [12–15]. In previous two studies, it was shown that OROS-MPH was effective in Turkish children with ADHD and OROS-MPH significantly decreased the symptoms of attention deficit, hyperactivity/impulsivity, oppositional defiance, and conduct disorders [16,17].

MPH-ER (Medikinet®; Flynn Pharma, Dublin, Ireland) is a nonosmotic, extended-release formulation of MPH and has been used in our country for the last 4–5 years. Each capsule contains two different types of MPH pellets; white pellets are immediate-release formulation and the blue pellets are extended-

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release formulation. The different size of capsules makes them easier to swallow, also different from the OROS-MPH, it is possible to empty their content into any soft food without significantly shortening the duration of effect [18]. This once-daily drug has the duration of action for about 8 h [19].

Medikinet retard® and Concerta® have different release profiles and their efficacy on ADHD symptoms and co-morbid conditions have been proved [20]. Although there are many studies on MPH for the treatment of ADHD, there are a few comparison studies of long-acting drugs [10]. In a study, Döpfner et al. compared the Medikinet Retard® and Concerta® and they concluded that an equivalent daily dose of medikinet retard was superior to Concerta and children and adolescents may also be treated with a lower daily dose of Medikinet retard without resulting in a clinically relevant worse effect [20].

Therefore, there is still a need for the studies comparing ER-MPH and OROS-MPH which are two agents frequently used in the treatment of ADHD. Due to this lack of comparison of these formulations, in the current study, we aimed to evaluate the functional improvement on ADHD of ER-MPH according to families, and compare it with OROS-MPH, additionally to evaluate its adverse effects compared with OROS-MPH in a population of Turkish children with ADHD.

Materials and methods

Participants

Participants were admitted to the Kayseri Training and Research Hospital, Department of Child and Adolescent Psychiatry and were followed there between August 2016 and June 2018. The diagnosis was made by a child and adolescent psychiatrist. All children met diagnostic criteria of ADHD according to the Diagnostic and Statistical Manual of Mental Disorders, 5th ed. (DSM-5) [1]. Inclusion criteria for enrolment in the trial were: (1) age between 6 and 16 years; (2) no mental retardation as clinically assessed; (3) children living in their own family house and attending a normal school; (4) absence of any psychiatric disorder except for oppositional defiant disorder (ODD); (5) no neurological or other serious medical diseases and no constant use of any prescribed medications for medical conditions; (6) no constant use of any prescribed medications for ADHD (stimulants, atomoxetine, etc.) Children were excluded if they had a contraindication to MPH, treatment with psychostimulants other than OROS-MPH or MPH-ER (e.g. immediate release MPH), or needed another ADHD treatment (e.g. behavioural therapy or additional antipsychotic treatment). A total of 103 children were enrolled in the study, but 70 children ($n = 35$ Concerta®, $n = 35$ Medikinet Retard®) completed the study. Thirty-three patients were excluded from the study because they did not continue to follow up in our department. After we reached the 65 patients ($n = 35$ Concerta®, $n = 30$ Medikinet Retard®) we only enrolled the 5 patients that we have started Medikinet Retard® to equalize the number of patients in both groups.

Study design

This study design is a 16-week prospective trial, each child received 16 weeks of OROS-MPH or MPH-ER, in order to allow a head-to-head comparison of the two stimulants. Participants were randomly assigned to one of two medication conditions. Subjects assigned to OROS-MPH on 18 mg and ER-MPH on 10 mg were initiated once daily. Over 4 weeks, the subjects were titrated by weekly or monthly increases, to a maximum of 1.2 mg/kg/day. Drug doses were arranged according to the manufacturers' directions. At the beginning of the study, we aimed to increase the dose of MPH in all patients to the optimal dose of 1.2 mg/kg/day. However, drug doses of some patients were not increased to this recommend dosage because their parents reported complete treatment response and increased functionality was enough with lower doses during the study. In this using lower dose group, we followed the stability of treatment response during least 8 weeks, and then we included in the study.

First, to determine psychiatric disorders of children and adolescents, Kiddie-Schedule for Affective Disorders and Schizophrenia, present and life time version (K-SADS-PL) was applied to parents by a specialist of child psychiatry. Clinical evaluations were conducted at baseline and week 4, week 8, week 12 or week 16. The ADHD symptoms and side effect scales were collected systematically by an interview with the same child and adolescent psychiatrist. Parents' ratings were obtained on Weiss Functional Impairment Rating Scale-Parent Report Form (WFIRS-P) twice. WFIRS-P ratings from parents were obtained at the baseline and at the first control after reaching the optimal drug dosage. In the case of patients who did not achieve optimal drug dosage and who were using lower doses of medication, WFIRS-P scale was filled at the end of the 16-week follow-up. Also Barkley Side Effects Rating Scale (BSERS) ratings were used and they were completed at week 4 after the drug started of each medication condition. The patients were evaluated different times during the study (some of the patients in three times and some of the patients in four times); therefore, scales for assessment were not used for each session.

This investigation was approved by the Ethical Committee of Erciyes University (Date: 15.07.2016, Approval Number: 2016/421). Written consent was

obtained from parents and verbal assent was requested from children and adolescents to participate.

Measures

Kiddie-Schedule for Affective Disorders and Schizophrenia, present and life-time version (K-SADS-PL)

K-SADS-PL is a semi-structured interview that was applied to parents for screening psychiatric disorders and determining comorbidities. Gokler et al. performed the Turkish reliability and validity study of K-SADS-PL [21].

Weiss Functional Impairment Rating Scale-Parent Report Form (WFIRS-P)

The WFIRS-P evaluates ADHD-related functional impairment. This scale consists of 50 questions with which parents rate their child's functional impairment over the past month. The items of the WFIRS-P are scored on a four-point Likert-type rating scale: 0 (never or not at all), 1 (sometimes or somewhat), 2 (often or much) or 3 (very often or very much) and have six domain scores. The subdomains include Family, Learning and School, Life Skills, Child's Self-Concept, Social Activities and Risky Activities. Response options are assigned values from 0 to 3. According to the instructions, scores can be calculated as the number of items scored as a 2 (often or much) or 3 (very often or very much), and overall score (summary index) is also computed from all of the WFIRS-P items. Lower scores on each WFIRS-P domain and sum scores indicate better functioning [22]. The validity and reliability of scale was conducted by Tarakcıoglu et al. in Turkish population [23].

Barkley Side Effect Rating Scale (BSERS)

The BSERS is a 17-item, parent-rated scale of potential stimulant side effects, where each item is rated from 0 "absent" to 9 "serious." It addresses side effects about sleep, appetite, emotional symptoms, energy level, physical complaints, and social engagement [24].

Statistical analyses

We used Shapiro–Wilk test to analyse homogeneity of variables. Wilcoxon Signed Rank test was used for the analysis of functionality differences before and after treatment for each group. Among-group differences on non-homogenous variables were analysed using Mann–Whitney U test. Independent samples *t*-test was used for homogenous variables. Chi-square test was used for categorical variables. ANCOVA was used for comparison of the WFISP-R between two groups. Pearson correlation analysis was used to assess the correlations. Data analysis was performed using SPSS 22.0 and *p*-values < 0.05 were considered statistically significant.

Results

Of the 70 patients, 35 patients were using OROS-MPH, 35 patients were using extended-release MPH. Sociodemographic characteristics are shown in Table 1.

At the endpoint, the mean daily dose of OROS-MPH was 32.4 ± 9.81 (1 ± 0.21 mg/kg; range 18–54 mg), the mean daily dose of extended release MPH was 20 ± 5.94 mg (0.84 ± 0.23 mg/kg; range 10–40 mg). The drug dosage/weight (mg/kg) was found significantly lower in the MPH-ER group than in the OROS-MPH group (t(df) = 2.91(68), $p = 0.005$*).

Differences of WFIRS-P between before and after treatment for each group were analysed with Wilcoxon Signed Rank test. Significant differences between baseline and post-treatment scores of WFIRS-P are shown in Table 2.

Both OROS-MPH and MPH-ER have significant improving effects on all domains of WFIRS-P ($p < 0.001$).

Our ANCOVA model revealed no statistically significant effect of treatment option reducing the WFIRS-P subdomains except for social activities domain. We found statistically significant effect of treatment option reducing on WFIRS-P social activities domain [$F(1,70)$, $r = 128$, $p = 0.01$]. The mean of reducing on WFISP-R domains is shown in Table 3.

When we included the drug dosage (mg/kg) in the ANCOVA model, we found that WFIRS-P drug dose was significant in predicting on reducing the school domain total score ($p = 0.009$) and social domain score ($p = 0.02$). The effect of the drug option without the effect of drug dosage was also statistically significant on WFISP-R school domain score ($p = 0.03$, adjusted R squared = 91%) and WFISP-R social domain score ($p = 0.003$, adjusted R squared = 119%).

The percentage for all 17 side effects listed in the Barkley Side Effect Rating Scale (BSERS) was calculated for those who had parent ratings of 1 or higher. The percentage was also calculated for parent ratings of 7 or higher to establish the frequency of severe side effects to the treatments. The results are shown in Table 4. Of the 17 side effects, only insomnia and euphoria were significantly more frequent (respectively, $p = 0.05$, $p = 0.02$), in the 4.weeks of treatment with the OROS-MPH group compared to the ER-MPH group.

The mean severity ratings by parents for each of the 17 side effects were also analysed. The results are shown in Table 5. It was observed that only the euphoria side effect was significantly higher in the OROS-MPH group than the ER-MPH group ($p = 0.05$).

Correlations between drug dosage (mg/kg) and BSERS were analysed and it was found that there was a significant positive correlation between the OROS-MPH dosage and decreased appetite ($r = 0.41$, $p = 0.01$),

Table 1. Demographic characteristics for the both groups.

Group	OROS-MPH group mean ± SD/median (IR)	MPH-ER group mean ± SD/median (IR)	Group differences
Mean of age	8 (3)	7(1)	$p = 0.003$*
Gender [*n* (%)]			
Female	7 (20%)	9 (74.3%)	$p = 0.56$
Male	28 (80%)	26 (25.7%)	
Mean of mother's age	35 (10)	32(10)	$p = 0.32$
Mother's educational status [*n* (%)]			
Primary School	14 (40%)	10 (28.6%)	$p = 0.63$
Secondary school	7 (20%)	12 (34.3%)	
High school	11 (31.4%)	9 (25.7%)	
University	3 (8.6%)	4 (11.4%)	
Mother's profession			
House wife	32 (91.4%)	29 (82.9%)	$p = 0.42$
Public servant	2 (5.8%)	4 (11.5%)	
Worker	–	1 (2.9%)	
Self-employed	1 (2.9%)	1 (2.9%)	
Median of Father's age	39 (10)	36 (8)	$p = 0.21$
Father's educational status			
Primary school	10 (28.6%)	11 (31.4%)	$p = 0.46$
Secondary school	10 (28.6%)	11 (31.4%)	
High school	10 (28.6%)	11 (31.4%)	
University	5 (14.3%)	2 (5.7%)	
Father's profession			
Worker	13 (37.1%)	15 (42.9%)	$p = 0.67$
Public servant	6 (17.2%)	5 (14.4%)	
Self-employed	6 (17.1%)	9 (25.7%)	
No employment	3 (8.6%)	1 (2.9%)	
Other	7 (20%)	5 (14.3%)	
ADHD subtype			
Combined type	33 (94.3%)	30 (85.7%)	$p = 0.23$
Inattentive sub-type	2 (5.7%)	5 (14.3%)	
Hyperactive/ impulsive sub-type;	–	–	
Mean of weight (kg)	32.8 ± 9.82	23.97 ± 4.21	$p < 0.001$*
Mean of drug daily dosage (mg)	32.4 ± 9.81	20 ± 5.94	$p < 0.001$*
Drug dosage/weight (mg/kg)	1.00 ± 0.21	0.84 ± 0.23	$p = 0.005$*
Weight loss			
Yes	15 (42.9%)	8 (22.9%)	$p = 0.07$
No	20 (57.1%)	27 (77.1%)	

Note: SD: Standard deviation; IR: Interquartile range.

Table 2. Differences in WFIRS-*P* scores between baseline and post-treatment for the both groups.

		OROS-MPH group Mean ± SD			MPH-ER group Mean ± SD		
WFIRS-*P*		Baseline	Post treatment	*P* value	Baseline	Post treatment	*P* value
Family domain		12.08 ± 6.95	4.28 ± 3.07	$p < 0.001$*	12.05 ± 7.80	4.82 ± 3.65	$p < 0.001$*
School	Learning	7.88 ± 3.7	2.25 ± 1.94	$p < 0.001$*	8.48 ± 3.22	1.85 ± 2.43	$p < 0.001$*
	Behaviour	4.68 ± 3.94	0.97 ± 1.27	$p < 0.001$*	6.14 ± 4.78	1.71 ± 2.53	$p < 0.001$*
	Total	12.57 ± 6.43	3.22 ± 2.53	$p < 0.001$*	14.06 ± 5.95	3.57 ± 4.01	$p < 0.001$*
Life skills domain		9.8 ± 5.36	5.74 ± 3.45	$p < 0.001$*	10.68 ± 6.75	6.62 ± 3.54	$p < 0.001$*
Self-Concept		1.25 ± 1.31	7.8 ± 5.27	$p < 0.001$*	3.17 ± 2.47	1.08 ± 1.54	$p < 0.001$*
Social		6.20 ± 4.84	2.82 ± 2.78	$p < 0.001$*	8.22 ± 5.65	2.14 ± 2.13	$p < 0.001$*
Risk		2.2 ± 2.09	0.88 ± 1.23	$p < 0.001$*	3.25 ± 3.48	0.91 ± 0.98	$p < 0.001$*
Number of scoring 2 and 3 item		13.68 ± 8.26	2.42 ± 2.61	$p < 0.001$*	16.08 ± 9.44	2.74 ± 2.90	$p < 0.001$*
Total Score		46.05 ± 19.5	18.22 ± 10.4	$p < 0.001$*	52.02 ± 23.6	19.17 ± 10.32	$p < 0.001$*

Table 3. Reducing of mean ratings by parents for Each of WFIRS-*P* domains and differences between groups.

				ANCOVA *p*-value		
		OROS-MPH group	MPH-ER group		With drug dosage	
WFIRS-*P*		Mean ± SD	Mean ± SD	Without drug dosage	For drug dosage	For group
Family domain		7.8 ± 5.27	7.22 ± 6.88	$p = 0.69$	$p = 0.94$	$p = 0.69$
School	Learning	5.62 ± 3.2	6.62 ± 3.32	$p = 0.2$	$p = 0.42$	$p = 0.14$
	Behaviour	3.71 ± 3.32	4.42 ± 4.76	$p = 0.47$	$p = 0.002$*	$p = 0.07$
	Total	9.34 ± 5.72	11.05 ± 5.87	$p = 0.22$	$p = 0.009$*	$p = 0.03$*
Life skills domain		4.05 ± 3.94	4.05 ± 5.43	$p = 1$	$p = 0.68$	$p = 0.22$
Self-Concept		1.94 ± 2.38	2.08 ± 1.86	$p = 0.78$	$p = 0.96$	$p = 0.8$
Social		3.37 ± 3.54	6.08 ± 5.57	$p = 0.01$*	$p = 0.02$*	$p = 0.003$*
Risk		1.31 ± 1.84	2.34 ± 3.12	$p = 0.09$	$p = 0.45$	$p = 0.07$
Number of scoring 2 and 3 item		11.25 ± 7.25	13.34 ± 9.15	$p = 0.29$	$p = 0.09$	$p = 0.11$
Total Score		27.82 ± 13.6	32.8 ± 21.25	$p = 0.24$	$p = 0.08$	$p = 0.07$

*Reducing of mean rating for these domains in the MPH-ER group higher than the OROS-MPH group.

Table 4. Percentage of subjects displaying each of the 17 side effects during each treatment option.

	Total side effect			Severe side effect (%)*		
Side Effect	(%)OROS-MPH	(%)ER-MPH	*p*-Value	(%)OROS-MPH	(%)ER-MPH	*p*-Value
Insomnia	54.3	31.4	0.05**	14.3	2.9	0.08
Decreased appetite	80	82.9	0.75	25.8	37.1	0.3
Irritable	34.3	31.4	0.79	0	0	–
Prone to crying	22.9	31.4	0.42	0	11.4	0.11
Anxious	25.7	20	0.56	0	2.9	0.5
Sadness	37.1	17.1	0.06	0	0	–
Headaches	25.7	31.4	0.59	0	0	–
Stomach aches	8.6	20	0.17	0	0	–
Nightmares	11.4	8.6	0.69	0	0	–
Stares a lot	17.1	17.1	1	0	0	–
Talks less	28.6	22.9	0.58	0	0	–
Uninterested	22.9	17.1	0.55	0	0	–
Drowsiness	11.4	14.3	0.72	0	0	–
Bites fingernails	14.3	8.6	0.45	0	0	–
Euphoria	25.7	5.7	0.02**	0	0	–
Dizziness	8.6	5.7	0.64	0	0	–
Tics	5.7	2.9	0.55	0	0	–

*% refers to percentage of subjects in whom the side effect was rated 1 or higher on the scale of the severity (1–9); %severe refers to the percentage of subjects in whom the side effect was rated 7 or higher.
**Percentage of insomnia and euphoria in the OROS-MPH group higher than the ER-MPH group.

Table 5. Mean severity ratings by parents for each of 17 side effects for each drug condition.

Side Effect	OROS-MPH Mean ± SD	ER-MPH Mean ± SD	*p*-Value
Insomnia	2.14 ± 2.88	1.42 ± 2.36	0.26
Decreased appetite	4.31 ± 2.91	4.45 ± 2.86	0.83
Irritable	1 ± 1.68	0.85 ± 1.37	0.69
Prone to crying	0.77 ± 1.49	1.42 ± 2.42	0.17
Anxious	0.74 ± 1.35	0.6 ± 1.53	0.68
Sadness	0.82 ± 1.24	0.48 ± 1.17	0.24
Headaches	0.68 ± 0.8	1.32 ± 1.41	0.72
Stomach aches	0.31 ± 1.15	0.51 ± 1.26	0.49
Nightmares	0.17 ± 0.51	0.2 ± 0.67	0.84
Stares a lot	0.45 ± 1.12	0.37 ± 0.97	0.73
Talks less	0.71 ± 1.27	0.85 ± 1.73	0.69
Uninterested	0.71 ± 1.54	0.57 ± 1.39	0.68
Drowsiness	0.2 ± 0.63	0.4 ± 1.06	0.34
Bites fingernails	0.57 ± 1.63	0.28 ± 1.01	0.38
Euphoria	0.57 ± 1.06	0.14 ± 0.69	0.05*
Dizziness	0.22 ± 0.80	0.11 ± 0.47	0.47
Tics	0.22 ± 1.05	0.05 ± 0.33	0.36

*Euphoria scores significantly higher in the OROS-MPH group than the ER-MPH group.

and a negative correlation between the OROS-MPH dosage and euphoria ($r = -0.4$, $p = 0.01$). There was no correlation between the ER-MPH dosage and BSERS.

Correlations between drug dosage (mg/kg) and improvement of WFIRS-P were also analysed and it was found that there was a significant positive correlation between the OROS-MPH dosage and WFIRS-P school domain ($r = 0.34$, $p = 0.04$). In the ER-MPH group, it was found that there were positive correlations between drug dosage and school behaviour subdomain ($r = 0.38$, $p = 0.02$); and between drug dosage and social domain ($r = 0.37$, $p = 0.02$).

Discussion

The aim of our study was to compare between Medikinet retard and Concerta of functional improving effects and adverse effects in children and adolescents with ADHD. Our results support a number of important observations. First, children in both treatment groups improved significantly over time, both in intensity and in the number of problems. Second, regarding the social problems, the effects of Medikinet Retard were superior to those of Concerta. Third, the side effects of insomnia and euphoria have significantly greater prevalence in the Concerta group than the Medikinet retard. Additionally, the mean severity rating of euphoria was shown higher in the Concerta group than the Medikinet retard.

It is known that stimulant treatments ameliorate academic performance, emotional functioning [25], social functioning [26] and improve the Quality of Life in children and adolescents with ADHD [27]. But research studies about comparing stimulant formulations are limited.

Sonuga-Barke et al. report no evidence for differences between the effects of the two formulations on parent ratings of ADHD symptoms at home [28]. This result is in line with our findings. In another study that compared two formulations of MPH, they found that an equivalent daily dose of Medikinet retard with Concerta, it was more effective than Concerta [20]. It is similar to our finding, we also found that although Medikinet Retard had a lower dosage (mg/kg), it showed even a better effect than Concerta. Swanson et al also found better or similar effects of Metadata compared with Concerta during the first 7.5 h after intake [29]. We did not find any study that uses WFISP-R and shows the difference in social functionality between two formulations. But this finding should be considered carefully. Because, several prior studies suggested that baseline rating scores were important predictors of treatment response. This might be due to regression to the mean effect and implies that subjects with highest baseline scores have a higher chance of reduced post-treatment scores [30,31]. Baseline scores were higher in medikinet group and it may

play better a role in improving the symptoms in this group.

Correlations between drug dosage (mg/kg) and improvement of WFIRS-P were also analysed and it was found that there was a significant positive correlation between OROS-MPH dosage and WFIRS-P school domain. In the ER-MPH group, it was found that there were positive correlations between drug dosage and WFIRS-P school behaviour subdomain and between drug dosage and WFIRS-P social domain. In the MTA titration trial, it was demonstrated that there was a strong MPH dose–response relationships at home and in the school [32].

In our study, we found that both agents were tolerated well. Decreased appetite was the most frequently seen adverse effect in both groups. Insomnia and euphoria were seen more common in the OROS-MPH group.

The correlation analyses investigated any relationships between the side effects observed on OROS-MPH and MPH-ER as reported by parents through the BSERS. The analysis yielded significant negative correlations between the dosage of MPH and the side effects of euphoria and significant positive correlations between the dosage of MPH and the side effect of decreased appetite. Rapport and Moffitt found that insomnia and decreased appetite severity were associated with increasing dose [33]. In the present study, mild side effects were common and only decreased appetite in OROS-MPH group increases significantly with the increasing dose. In addition, Steine et al. found that younger children and those who weighed less seemed to be more prone to stimulant side effects [34]. But we did not find any correlation between side effects and weight or age.

Euphoria was found more often than the other stimulant side effect research studies [29,35]. The investigations indicate that stimulants activate brain μ-opioid receptors and this activation is associated with euphoria [36,37]. Clinical studies show that the subjective, positive effects of MPH (feelings of liking or euphoria) are significantly lower when the slow-release formulations are administered compared to the immediate release ones [38]. Different releasing patterns of each formulation might have caused the differences of euphoria between two formulations.

The limitations of study should be noted. First we have not recorded the all patients whom we evaluated and so we did not create a flow chart. Second, both the WFIRS-P and ADHD symptom measures are largely based on parent report. So, the ratings may be subject to parental bias compared with more objective measures. It would be better that a multiple assessment to monitor treatment effects and side effects, such as teachers. Additionally we did not match the group in symptom severity. After we reached the 65 patients we did not enrol the patients that we have started Concerta and this can cause a bias. Symptoms and side effects were evaluated by the treating or other physician in a non-blinded manner. Another limitation is that the absence of placebo group.

Conclusion

From this study, children in both treatment groups improved significantly over time, both in intensity and in the number of problems. Regarding the social problems, the effects of Medikinet Retard were superior to those of the Concerta. The side effects of insomnia and euphoria have significantly greater prevalence in the Concerta group than the Medikinet retard. Additionally, the mean severity rating of euphoria was shown higher in the Concerta group than the Medikinet retard.

Disclosure statement

No potential conflict of interest was reported by the authors.

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