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Effects of Maternal Symptom Ratings and Other Clinical Features on Short-Term Treatment Response to OROS Methylphenidate in Children and Adolescents with ADHD in a Naturalistic Clinical Setting

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ABSTRACT:

Effects of maternal symptom ratings and other clinical features on short-term treatment response to OROS methylphenidate in children and adolescents with ADHD in a naturalistic clinical setting

Objective: To investigate the effect of Attention Deficit Hyperactivity Disorder (ADHD), antisocial behavior and anxiety/depression ratings of mothers, and child and adolescents' age, gender, ADHD subtype, and comorbidity on one-month drug treatment response to OROS methylphenidate in ADHD in a naturalistic setting.

Methods: The analyses included 223 subjects (191 boys, 32 girls; age 6-15 years, mean: 9.4) treated with OROS methylphenidate (18-72 mg/day, mean: 31 mg/d; 0.4-1.4 mg/kg/d) for one-month. Treatment response was defined as larger than 25% or more decrease in pre-treatment the Conners Parent Rating Scale (CPRS) or the Conners Teacher Rating Scale (CTRS) total scores and the Clinical Global Impression improvement with drug treatment 3 (minimally improved) or higher. Maternal ADHD, antisocial behavior and anxiety/depression ratings were obtained by the Adult Self Rating (ASR). Logistic regression analyses were computed in order to calculate the effects of gender; age; ADHD subtype; comorbid anxiety disorder, learning disorder, oppositional defiant/conduct disorder; maternal ASR Anxiety/Depression, ADHD and Antisocial scores.

Results: 35.2% of subjects had statistically significant 25% or more decrease in pretreatment CPRS total scores and 38.6% of subjects had statistically significant 25% or more decrease in pretreatment CTRS total scores. The subjects with comorbid anxiety disorder had the poorest drug response. Maternal self-reported antisocial and anxiety/depressive symptomatology were statistically significantly associated with worse response to treatment in terms of CPRS (respectively, OR=0.83, 95% CI: 0.75-0.92, p<0.01; OR=0.95, 95% CI: 0.9-0.99, p<0.05) and CTRS total scores (OR=0.9, 95% CI: 0.82-0.99, OR=0.95, 95% CI: 0.91-1, p<0.05). Baseline rating scores were also important predictors of drug treatment response. Effects of age, gender and maternal ADHD were not statistically significant.

Conclusion: ADHD children and adolescents with comorbid anxiety disorders and those whose mothers have more self-reports of antisocial and depressive symptoms showed less favorable short-term response to OROS-MPH. These subjects may require further attention and additional interventions to augment treatment with OROS methylphenidate.

Keywords: attention deficit hyperactivity disorder, OROS methylphenidate, short-term treatment, moderators

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INTRODUCTION

Attention Deficit Hyperactivity Disorder (ADHD) is one of the most common and persistent psychiatric disorders involving school age children and adolescents. Stimulants are the first-line of ADHD treatment. Although immediate release (IR) methylphenidate (MPH) preparations have been shown to be very effective, due to their short half-life, they need to be administered two or three times a day. The administration of IR MPH during school hours often compromise children's privacy and may further contribute to stigmatization. Furthermore, fluctuation of drug blood concentration during that time may cause behavioral and cognitive problems. To overcome these difficulties, long-acting MPH preparations have been manufactured worldwide. Among these OROS MPH has a unique design that provides longer lasting effectiveness[1]. Several studies have shown that treatment with OROS MPH is as effective[2,3], and more efficient[4,5], compared to the IR MPH.

However, the predictors of short-term response to OROS MPH treatment have not been examined as extensively as that for IR-MPH. The National Institute of Mental Health-funded Multimodal Treatment Study of ADHD (MTA) has shown that comorbidity with an anxiety disorder, parental depressive symptomatology, baseline poverty, child IQ, and severity of ADHD are important moderators of overall treatment response in children with ADHD[6,7]. While other studies[8] showed that ADHD subtype may be an important factor in treatment response, this has not been a consistent finding[9,10].

It has been reported that parents of children with ADHD have increased risk of both internalization (e.g., anxiety/depression), and externalization (e.g., antisocial behaviors, adult ADHD) problems. Almost 20% of the mothers of children with ADHD themselves had ADHD with almost five times increased risk compared to parents of the control group[11]. The same authors reported that major depressive disorder was found in more than a third of the mothers of children with ADHD, consistent with reports from other studies[12]. In addition, antisocial behavior symptoms are more commonly reported among parents of ADHD children and adolescent with comorbid ODD/CD[11,13]. Furthermore, maternal psychopathology has been shown to be associated with a worse overall treatment response in ADHD, particularly for psychosocial interventions[6,14,15].

Although the "gold standard" for treatment efficacy is double-blind placebo-controlled randomized clinical trials, there are few controlled effectiveness studies given the significant logistical difficulties to conduct such studies in naturalistic settings. Daily clinical practice takes place in a different context than controlled clinical trials; for example, controlled trials usually exclude patients with intellectual disability, although it is very common to treat patients with ADHD, learning problems, as well as a range of other co-occurring mental disorders in the same setting, especially in poor-resource areas.

In the present systematic analysis of our clinical experience we evaluated a number of factors associated with one-month short term drug response to OROS MHP (defined as 25% or more decrease in pre-treatment parents and teacher ratings) among a relatively large sample of children and adolescents with ADHD. We examined the effects of co-occurring anxiety disorders (AD), oppositional defiant disorder/conduct disorder (ODD/CD), and learning disabilities (LD); DSM-IV subtype of ADHD combined (C), predominantly hyperactive impulsive (PHI), predominantly inattentive (PI)); age, gender; and maternal Anxiety/ Depression, antisocial, and ADHD self-report ratings.

METHODS

The children and adolescents, aged 6-15 years, attending an outpatient clinic of a general public hospital and who met the ADHD diagnostic criteria were included in the analysis. The Institutional Ethics Review Committee approved the study, participation was voluntary and families could opt out at any time. All drug treatments did not entail

additional cost to families they are entitled to health benefits under social security. All relevant baseline and follow-up data were obtained as part of the routine clinical evaluation and treatment process. Follow-up data were collected one month after in order to measure early onset treatment response with OROS MPH. There were a total of 642 children and adolescents enrolled consecutively; all assessments were standardized at the outset. The children and adolescent who were not drug-free at least for 15 days at the time of their intake were excluded from the analyses: there were 345 were already on stimulant treatment other than OROS MPH. Of the remaining 297 subjects, 74 were excluded as they did not either return to the clinic, the rating scales were incomplete, or the children and adolescents were on other psychotropic medications. The remaining 223 children and adolescents with ADHD with complete assessments were included in the final analyses.

Child Diagnostic Assessments. The Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime Version (K-SADS-PL), Turkish version[16]. All the DSM-IV diagnoses were based on the K-SADS-PL semi-structured interview administered by experienced child and adolescent psychiatrists (EC, OO, PO) trained for the use of the instrument. The children and adolescents meeting DSM-IV ADHD criteria were screened for co-occurring anxiety (AD), mood, oppositional defiant/conduct (ODD/CD), tic and elimination disorders as assessed by respective modules.

Learning Disabilities (LD). Co-occurrence of intellectual and learning disabilities was assessed by means of the Weschler Intelligence Scale For Children- Revised (WISC-R) and by reading, writing and mathematics tasks.

OROS MPH Treatment: The dose of OROS MPH was between 18-72 mg/day with a mean of 30.1 mg and SD of 9.0 mg. The protocol for OROS MPH administration was as follows: all subjects had an initial dose of 0.5 to 1 mg/kg/d OROS MPH (18 to 36 mg/d); if treatment response was judged to be inadequate (CGI=3, or worse) during the first control visit, and if significant side effects did not emerge, the drug dose was increased to a maximum of 2 mg/kg/day or 72 mg/day. If no treatment response was achieved at the highest dose, treatment was switched from OROS MPH to an alternate medication. At each control visit, clinical examination and Conners Parent and Teacher Ratings were obtained and emerging side effects systematically reviewed. All treatment protocols were reviewed by EC and OO: the response ratings reflect the subject's best CGI score.

Child ADHD Symptom Severity Ratings: We evaluated ADHD symptom severity by means of the Conners Parent and Teacher Rating Scales.

Conners Parent Rating Scale (CPRS): This form includes 48 items, which aims to evaluate behavior of children assessed by their parents[17]. The scale includes oppositional behavior, inattentiveness, hyperactivity, psychosomatic, and irritability domains. Turkish translation has good validity and reliability[18].

Conners Teacher Rating Form (CTRS). This form includes 28 items, which aim to rate classroom behavior of children assessed by teachers[19]. There are three subscales of the form: 8 items for inattentiveness, 7 items for hyperactivity, and 8 items for conduct problems. CTRS is translated to Turkish by Şener[20], and the Turkish form showed adequate validity and reliability (Cronbach's alpha 0.95).

Maternal Adult Self Report (ASR) Ratings. The ASR is a self report scale[21] designed to follow the Child Behavior Checklist (CBCL) and measures social competencies and problem behaviors in subjects age 18-59 years. The ASR yields scale scores such as Anxiety/Depression, ADHD and Antisocial Behaviors as well as broadband Internalization and Externalization scores. ASR scales have good internal consistency and test-retest reliability.

Treatment Response: The response to OROS MPH drug treatment was defined as: (i) 25% or more decrease in pre-treatment the CPRS and CTRS total scores; and (ii) the Clinical Global Impression [CGI, 20] Global Improvement rating change with treatment: 3 (minimally improved) or better. Change in CGI score was determined by a combination of teacher and parent reports and current psychiatric examination. We took both teacher and parent ratings into account for two reasons: first, they measure different behaviors, and second, it is important to test whether parental psychopathology affects both teacher and parent reported outcome measures.

Data Analysis

Baseline and one-month parent and teacher ratings were compared with paired-samples t-test. Multivariate logistic regression analyses were computed in order to calculate the effects of gender, age, ADHD subtype (C, PI, PHI), comorbid AD, LD, ODD/CD; maternal ASR Anxiety/ Depression, ADHD and Antisocial scores, separately; and corresponding baseline CPRS and CTRS scores on treatment response (CPRS and CTRS total scores and CGI improvement). $p<0.05$ was reported as statistically significant.

RESULTS

Of the two hundred and twenty-three subjects 85.7% were males and 14.3% females; age range was 6 to 15 (mean, 9.4 years, SD, 2.2). The distribution by DSM-IV ADHD subtype was: 72.2% (C), 12.1% PI, and 15.7% PHI. The distribution by co-occurrence of mental disorder was: 18.7%, none; 40.8%, one; 29.3%, two; and 11.2%, three or more. The most frequent co-occurring mental disorder was ODD/CD, 48.4%, followed by LD, 38.1%, AD, 13.9%; and 21.3%, other (including mood, tic, and elimination) (Table 1).

Baseline and post-treatment rating scores summarized in Table 2. All rating scores decreased statistically significant with treatment. Percentage of subjects who had 25% or more reduction in pretreatment scores was as follows: CPRS total, 35.2%; CTRS total, 38.6%. The subjects showing at least some CGI improvement with treatment represented 83.4%.

Logistic regression analysis (Table 3) indicated that subjects with PI subtype (OR=0.6, 95% CI: 0.4-0.98, $p<0.05$) were significantly less likely to have a "minimal" or better improvement in CGI scores. Subjects with AD had statistically significant less 25% or more reduction in CTRS total scores (OR=0.32, 95% CI: 0.11-0.99, $p<0.05$).

Maternal ASR Anxiety/ Depression, Antisocial and ADHD scores showed a normal distribution.

Table 1: Demographic characteristics (n=223)

	N/mean(%/±sd)
Male	191 (85.7)
Female	32 (14.3)
Age	9.4±2.2
ADHD subtype	
C	161(72.2)
PI	27(12.1)
PHI	35(15.7)
Comorbidity	
No	42(18.7)
Yes	
1	91(40.8)
2	65(29.3)
≥3	25(11.2)
Comorbidity	
ODD/CD	108(48.4)
LD	85(38.1)
AD	31(13.9)
Other	47(21.3)

ADHD: attention deficit hyperactivity disorder; C: combined; PI: predominantly inattentive; PHI: predominantly hyperactive impulsive; ODD/CD: oppositional defiant disorder/conduct disorder; LD: learning disabilities; AD: anxiety disorders.

Table 2: Baseline and post-treatment rating scores and paired-samples t-test scores

	Baseline	Post-treatment	t	p
CTRS Total (n=208)	32.8±9.4	26.3±10.1	9.3	p<0.001
CPRS Total (n=218)	31.1±11.6	26.6±11.5	6.1	p<0.001

Values are mean±standard deviation.
CTRS, Conners Teacher Rating Scale; CPRS, Conners Parent Rating Scale

Table 3: Results of multivariate logistic regression analysis

	≥25% decrease in pretreatment CTRS total scores			≥25% decrease in pretreatment CPRS total scores			CGI 1 or 2			CGI 1,2, or 3		
	OR	95% CI		OR	95% CI		OR	95% CI		OR	95% CI	
Gender	1.90	0.80	5.00	0.60	0.20	1.70	1.20	0.50	2.80	1.30	0.40	4.40
Age	1.02	0.90	1.20	1.01	0.90	1.18	1.00	0.90	1.20	1.20	0.97	1.40
ADHD subtype	0.80	0.50	1.200	1.10	0.70	1.70	0.80	0.55	1.17	0.60*	0.40	0.98
Comorbidity												
Anxiety Disorders	0.32*	0.11	0.99	0.36	0.12	1.07	1.20	0.48	2.98	1.23	0.34	4.85
Learning Disorder	0.80	0.40	1.60	0.92	0.48	1.77	0.77	0.42	1.40	1.04	0.46	2.31
ODD/CD	0.77	0.42	1.43	0.72	0.37	1.40	1.48	0.80	2.65	1.57	0.72	3.45
Maternal ASR Anxiety/Depression	0.95*	0.91	0.99	0.95*	0.90	0.99	0.97	0.93	1.01	0.92**	0.87	0.97
First CPRS or CTRS score	1.04*	1.01	1.08	1.07**	1.04	1.11						
Gender	1.92	0.76	4.82	0.67	0.26	1.76	1.23	0.53	2.88	1.40	0.44	4.60
Age	1.03	0.90	1.20	1.02	0.90	1.20	1.00	0.87	1.15	1.16	0.96	1.34
Subtype	0.79	0.52	1.19	1.11	0.72	1.70	0.76	0.52	1.10	0.60*	0.40	0.98
Comorbidity												
Anxiety Disorders	0.32*	0.11	0.99	0.34	0.11	1.03	1.20	0.49	3.01	1.33	0.36	4.95
Learning Disorder	0.77	0.41	1.46	0.80	0.41	1.52	0.76	0.42	1.37	0.96	0.44	2.10
ODD/CD	0.71	0.39	1.30	0.71	0.37	1.36	1.34	0.75	2.38	1.20	0.58	2.55
Maternal ASR												
ADHD	0.94	0.87	1.01	0.94	0.88	1.01	0.97	0.91	1.03	0.94	0.87	1.01
First CPRS or CTRS score	1.04*	1.01	1.08	1.07**	1.04	1.11						
Gender	1.90	0.76	4.76	0.59	0.22	1.61	1.20	0.51	2.80	1.30	0.40	4.25
Age	1.01	0.87	1.17	0.99	0.85	1.16	0.99	0.86	1.14	1.14	0.94	1.37
Subtype	0.82	0.54	1.24	1.21	0.77	1.89	0.77	0.53	1.12	0.60*	0.40	0.98
Comorbidity												
Anxiety Disorders	0.32*	0.11	0.99	0.29	0.09	0.92	1.18	0.47	2.93	1.24	0.33	4.65
Learning Disorder	0.81	0.43	1.53	0.86	0.44	1.68	0.77	0.43	1.39	0.97	0.45	2.12
ODD/CD	0.73	0.39	1.35	0.63	0.32	1.26	1.34	0.75	2.37	1.20	0.57	2.56
Maternal ASR												
Antisocial	0.90*	0.82	0.99	0.83**	0.75	0.92	0.95	0.89	1.02	0.90*	0.83	0.98
First CPRS or CTRS score	1.04*	1.01	1.08	1.07**	1.04	1.11						

*: p<0.05; **: p<0.01

ADHD: attention deficit hyperactivity disorder; ODD/CD: oppositional defiant disorder/conduct disorder; CTRS, Conners Teacher Rating Scale; CPRS, Conners Parent Rating Scale; ASR: Adult Self Report; CGI: Clinical Global Impression; OR: odds ratio; CI: confidence interval

High maternal ASR Antisocial score was statistically significantly associated with less likelihood of having 25% or more reduction in both CPRS (OR=0.83, 95% CI: 0.75-0.92, p<0.01) and CTRS (OR=0.9, 95% CI: 0.82-0.99, p<0.05) total scores, and "minimal" or better improvement in CGI scores (OR=0.9, 95% CI: 0.83-0.98, p<0.05). Maternal ASR Anxiety/ Depression scores were statistically significantly associated with lower response to treatment in terms of CPRS (OR=0.95, 95% CI: 0.9-0.99, p<0.05) and CTRS (OR=0.95, 95% CI: 0.91-1, p<0.05) total scores and CGI improvement (OR=0.92, 95% CI: 0.87-0.97, p<0.01). There were no statistically significant association between maternal ASR ADHD scores and CTRS, CPRS and CGI ratings.

Baseline CPRS and CTRS scores were significantly associated with treatment response (OR=1.07, 95% CI: 1.04-1.11, p<0.01 and OR=1.04, 95% CI: 1.01-1.08, p<0.05, respectively) indicating that subjects with higher baseline score were more likely to have a 25% or more reduction in these scores after treatment.

DISCUSSION

In a standardized clinical treatment study of children and adolescents in a naturalistic setting, our results support a number of important observations. First, noted an association between maternal self-report of antisocial behavior and Anxiety/ Depression and lower response to treatment with OROS MPH. This was indeed evident in terms of parent, teacher, and clinician ratings of ADHD, indicating that the effect of maternal antisocial behavior and Anxiety/ Depression on children's treatment efficiency cannot be explained by maternal reporting bias. Second, the teachers reported that children and adolescents with co-occurring AD were less likely to have a OROS MPH treatment response. Third, the child and adolescent age and gender, as also noted in other studies[7], were not important predictors of drug treatment response.

Several prior studies[6,23] 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. It must be kept in mind that 25% decrease in baseline scores does not necessarily mean total improvement, and some members of the responder group might still have high scores. Owens et al. reported that severe cases tend to show a large treatment response although they are less likely to be normalized by treatment[6]. Subjects with the PI subtype of ADHD were less likely to have 25% or greater improvement in the CTRS AP score. This was consistent with some of the previous studies[8], while other studies reported no difference of treatment response among ADHD subtypes[9,10].

Consistent with the previous studies, we found that ADHD subjects with co-occurring AD responded less favorably to pharmacological treatment[6,24-28]. However, we did not observe any differences in children and adolescents with ODD/ CD in terms of response to OROS MPH, which is again consistent with previous studies[7].

We found that maternal self-report of antisocial behaviors and anxiety/ depressive symptoms were associated with several behavioral outcomes derived from both teacher and parent reports and from clinical CGI examination. We did not find any associations between response to treatment with OROS MPH and maternal ADHD symptoms. In the MTA study, parental inattention was noted to be associated with less improvement on ADHD and reading[29]. Additionally,"high" level of parental ADHD ratings was noted to mitigate child improvement following parent training programs[15]. Nonetheless, these former studies did not investigate the possible association of maternal antisocial behavior with child outcome. It is also notable that another recent study has supported worse methylphenidate drug response associated with maternal ADHD and antisocial symptoms[30]. Our results are consistent with this latter observation. It is important to note that we used a single rating (ASR) to obtain anxiety/depression, ADHD and antisocial scores, and we did not make any formal maternal DSM-IV diagnosis. Analyzing

the MTA data Owens and associates reported that maternal depressive symptoms were associated with poorer outcome in the drug treatment group[6]. Our results are consistent with their work.

Worse treatment response in subjects whose mothers have higher antisocial and anxiety/ depressive symptom could be due to several reasons. First, this might be directly due to dysfunctional parenting that itself may reflect role modeling of maternal behavioral problems by the child, inconsistent or negative discipline and structure, or simply by decreasing treatment compliance, e.g., negative response to drug treatment might also imply the interference of maternal depressive symptoms with children and adolescents receiving their medication[6]. Second, there may be attributional differences between mothers with or without antisocial and anxiety/ depressive symptoms. However, the lower treatment response in teacher ratings argues against this explanation. Third, ADHD subjects whose mothers have antisocial and anxiety/ depressive symptoms might be a different subtype with different neurobiological properties.

The present findings need to be viewed in the context of certain limitations. First, this was not a controlled treatment trial. However, as emphasized at the outset the sample is more to everyday clinical practice. In the present study, we evaluated drug treatment response only to one form of psychostimulant agent, it is obvious that children who were not responsive to one form could do better with another, like amphetamines; however, amphetamines are not marketed as available in Turkey. Second, our response thresholds were low: our results showed that maternal antisocial and anxiety/ depressive symptoms were associated with lack of any response to treatment, but results did not indicate that a very good treatment response could not be achieved.

The study has a number of strengths that should be noted. First, we examined a large sample of consecutively recruited clinical population at a single center. The clinic was by no means a tertiary care program but represents a recruitment resource for evaluation of children and adolescents in a public health catchment setting. Second, the children were diagnosed by the use of reliable semi-structured diagnostic interviews administered by trained raters. Third, the children were drug free at inception. Fourth, information was obtained from both parents and teacher informants with the use of reliable scales to measure symptom severity. To our knowledge, this is the first study to provide data on possible moderators of OROS MPH drug treatment response from a country outside North America and Western Europe. It is therefore highly beneficial to compare and contrast findings from future studies in other countries and cultures.

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