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Is Functional Improvement Always Correlated with Symptomatic Improvement in Children with Attention-Deficit/Hyperactivity Disorder Managed with Oros Methylphenidate? A Prospective Open-Label Naturalistic Follow-Up Study

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Abstract

Background: To investigate the relationship between symptomatic improvement and functional improvement in children with attention deficit hyperactivity disorder (ADHD) who were being treated with OROS methylphenidate.

Methods: Parents evaluated the severity of ADHD symptoms on the Turgay-DSM-IV ADHD/Disruptive Behavior Disorders Scale (T-DSM-IV). They assessed functioning on the Weiss Functional Impairment Rating Scale – Parent Form (WFIRS-P), and the Pediatric Quality of Life Inventory (PedsQL) was used to assess quality of life. Clinicians rated global outcome on the Clinical Global Impressions Scale (CGI). Response was measured in terms of the following criteria: a 20% change in symptoms, a CGI-I score that was much improved (2) or very much improved (1), or an improvement of 0.25 (the minimally important difference) on the WFIRS. Improvement in quality of life was defined as ≥ 20% change in PedsQL score.

Results: Sixty-three children completed the study. After 12 weeks, 77.7% of patients met the a priori criteria for treatment response rate. Among patients who exhibited improvement in symptoms, 42.9% also showed improved functioning. Among those who showed improved functioning, 95.5% showed improvement in symptoms. Of patients who showed improvement in symptoms, 34.6% percent also showed improvement in quality of life. Of those who showed improvement in quality of life, 94.4% also showed improvement in symptoms.

Conclusions: Evaluation of changes in functional improvement, quality of life improvement, and symptom improvement during ADHD treatment enables clinicians to identify individuals whose functional impairment/quality of life persists despite symptom improvement. On that basis, additional treatment interventions can be organized for those individuals.

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INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is among the most common neurodevelopmental disorders, with a global prevalence of 3.4–5.3 % [1, 2]. The disorder is characterized by age-inappropriate and impairing symptoms of inattention and hyperactivity [3]. The symptoms interfere with young people's social, emotional, and academic skills and may lead to further comorbidities [3].

Stimulants (e.g., methylphenidate, amphetamine) are recommended as first-line drugs in the treatment of ADHD [4, 5]. OROS methylphenidate (mph) is a long-acting stimulant designed for controlled release over 10–12 hours [6]. In clinical studies evaluating the use of OROS methylphenidate in the treatment of children with ADHD, the drug was found to cause significant improvement in ADHD symptoms [7, 8].

A *symptom* can be described as a physical or mental complaint of disease that is apparent to the patient. *Functional impairment* refers to consequent social and professional limitations [9], including an inability to organize homework and other tasks at home or in school,

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with negative effects on family and peer relationships [10].

According to the World Health Organization (WHO) *quality of life* can be defined as how an individual experiences and perceives their situation in the context of culture, value judgments, goals, expectations, standards, and interests [11]. ADHD has a significant impact on the child and their family, including daily activities such as school work and family and peer relationships [12]. The quality of life of children and adolescents with ADHD is reported to be significantly lower than for community samples [13].

Although functional impairment and symptoms are moderately correlated [14], a significant number of ADHD patients experience improvement in symptoms with residual functional impairment. For that reason, assessment of real-life change in function is critical in determining overall outcome. While functional impairment is only one diagnostic criterion of ADHD [15, 16], it is an important factor for patients seeking treatment because of its impact on everyday life [17].

Follow-up studies have reported that ADHD is not confined to childhood and may persist into adolescence and adulthood [18]. In about two-thirds of cases, symptoms may continue unchanged or with partial remission [19]. Those results suggest that symptomatic remission does not equate with functional recovery, and that even sub-threshold symptoms may affect personal functioning [20]. However, current clinical practice focuses on symptom control in children with ADHD. This means that high-functioning symptomatic patients may receive intensive treatment while mildly symptomatic patients who are severely impaired receive less treatment than they need. [17]. Treatment of ADHD should therefore aim not only to reduce symptoms but to alleviate functional impairment and to improve quality of life [21].

The present study analyzed change in symptom, functional impairment, and quality of life scores in children receiving OROS methylphenidate treatment for ADHD to address the following research question: *Based on a naturalistic follow-up study, what is the correlation between ADHD symptoms, functional impairment, and quality of life?*

METHODS

Participants

The study was conducted at the outpatient units of the Departments of Child and Adolescent Psychiatry at Kocaeli University Medical Faculty and Kanuni Sultan Suleyman Hospital for Training and Research during the period 01.04.2016–01.04.217. IRB approval was granted by the Ethics Committee of Kocaeli University (approval number 2016/113). All study procedures complied with the WMA Declaration of Helsinki and local laws and regulations.

The inclusion criteria were as follows: application to the participating centers within the specified timeframe; first-time diagnosis of ADHD (any subtype) as per DSM-5 criteria; and provision of informed consent (parents) and verbal/written assent (children) to participation in the study. The following exclusion criteria were applied: a comorbid psychopathology other than ODD; psychotropic medications administered within the previous two months; and chronic medical or neurological disorders requiring treatment. As parents had to be able to complete the psychometric assessments, those with insufficient literacy skills were excluded.

Study Procedure

Patients with a preliminary diagnosis of ADHD (F90.X in ICD-10) were contacted by phone, and an interview to confirm the diagnosis was scheduled with the principal investigators (MCT and NŞ). The Kiddie Schedule for Affective Disorders and Schizophrenia for School-aged Children—Present and Lifetime Version (K-SADS-PL-Turkish) was administered to patients and their primary caregiver. The principal investigators also evaluated clinical severity and functioning at this interview, using the Clinical Global Impressions-Severity Scale (CGI-S).

Parents evaluated the severity of ADHD symptoms in their children on the Turgay-DSM-IV Based ADHD and Disruptive Behavior Disorders Scale (T-DSM-IV). They also assessed functioning on the Weiss Functional Impairment Rating Scale-Parent Form (WFIRS-P), and quality of life was assessed using the Pediatric Quality of Life Inventory (PedsQL).

Participants then entered the open-label dose titration phase. Starting OROS methylphenidate at 0.6 mg/ kg/ day, dose adjustments for each individual were based on clinicians' evaluations at weeks 4 and 8. Due to naturalistic design of the study, evaluations at week 4 and week 8 were made according to clinician's interview with the child, parents and teacher. On the final visit (twelve weeks), T-DSM-IV, CGI-S, WFIRS-P, PedsQL and CGI-Improvement (CGI-I) were again administered. 85 patients were enrolled study and 22 of them failed to finish study.

Response was defined a priori as ≥ 20.0% reduction in T-DSM-IV total score (from baseline) *or* as a CGI-I score of 1 (*very much improved*) or 2 (*much improved*) [22, 23]. Based on previous studies (24), a change of ≥ 0.25 in WFIRS-P-Total mean scores was accepted as a proxy for treatment response. According to Beverung *et al.*, a change of 20% or more in QOL score may indicate significant gains in quality of life [25].

Measures

Turgay DSM-IV-Based Screening Scale for Disruptive Behavior Disorders in Children and Adolescents (T-DSM-IV): This 41-item, 4-point Likert scale is used to evaluate 18 DSM symptoms of ADHD, 8 symptoms of oppositional disorder, and 15 symptoms of conduct disorder as defined in DSM-IV. The Turkish version has previously been found reliable and valid (26).

Weiss Functional Impairment Rating Scale - Parent Version (WFIRS - P): This scale was developed to evaluate functionality in patients with ADHD [24, 27]; the Turkish version has previously been found reliable and valid [28]. The fifty items of the WFIRS-P cover six areas of functional impairment: family, school and learning, life skills, child's

self-concept, social activities, and risky activities. The scale has been deemed internally consistent, with a Cronbach a >0.9 for the total scale [29] and moderate to strong correlations between each subscale and the total scale. A number of studies estimated test-retest reliability as r > 0.7 after 1–4 weeks, based on confirmatory factor analysis of domains [28-36].

Clinical Global Impression-Severity (CGI-S) and Clinical Global Impression – Improvement (CGI-I): Both CGI-S and CGI-I [37] are 7-point Likert-type scales measuring clinician ratings. CGI-S evaluates symptom severity, and CGI-I measures patient improvement since baseline. Turkish versions of CGI-S and CGI-I are known to be valid and reliable and have been used in numerous studies [38].

Pediatric Quality of Life Questionnaire (PedsQL): PedsQL was developed by Varni *et al.* [39] to evaluate health-related quality of life among children and adolescents aged 2–18. This Likert-type scale includes child and parent forms and evaluates physical health and emotional and social functioning. The Turkish versions have previously been reported valid and reliable [40, 41].

Kiddie Schedule for Affective Disorders and Schizophrenia for School-age Children – Present and Lifetime Version (K-SADS-PL): K-SADS is a semi-structured interview used to evaluate present and lifetime pediatric psychiatric diagnoses according to DSM-IV-TR criteria [42]. The Turkish version has previously been reported reliable and valid [43].

Data Analysis

A sample size of 186 subjects, each measured for a fixed duration, would achieve 70.0% statistical power to detect a Poisson event-rate difference of 0.40 using a two-sided, large-samples z-test at a significance level of 0.05 [44, 45]. However, we could enroll only 63 patients within the specified duration, yielding a power of 31.0%. The collected information was entered into a database using the Statistical Program for Social Sciences (SPSS), version 20.0. Assumptions of normality were tested using Kolmogorov-Smirnov tests. As age, maternal age, and baseline T-DSM-IV, WFIRS-P, and PedsQL scores were not normally distributed ($p < 0.05$), the analysis was based on non-parametric methods. Quantitative data were summarized as means/standard deviations or medians/inter-quartile ranges according to normality and outliers. Bivariate comparisons were based on t-tests or Mann-Whitney U tests. Correlations were analyzed using Spearman's tests; p was set at 0.05 (two-tailed), and effect sizes were also reported for significant findings.

RESULTS

In total, 63 children were enrolled during the study period, with a median age of 10.2 years (IQR = 8.4-12.2). A majority (63.5%) were male, and the median grade level was 4.0 (IQR = 3.0-7.0). Most of the mothers were housewives (73%) with a primary education or lower (54%). Fathers were mostly menial workers or middle-level managers (88.9%) with a high school education or higher (52.4%). A subset of the patients had siblings who had also been diagnosed with ADHD (n = 10,15.9%), and 17.5% had a family history of psychopathology (Table 1).

Table 1. Sociodemographic variables of Children with ADHD

Age (Median, [IOR])	10,2 (8.4-12.2)
Gender (Male, n[%])	40 (63.5)
Grade Level (Median, [IOR])	4.0 (3.0-7.0)
Mother Occupation (n[%])	
Non-Employee	46 (73.0)
Employee	17 (27.0)
Mother Education Status (n[%])	
≤ 8 years	34 (54.0)
≥ 9 years	29 (46.0)
Father Occupation (n[%])	
Non-Employee	7 (11.1)
Employee	56 (88.9)
Father Education Status (n[%])	
≤ 8 years	30 (47.6)
≥ 9 years	33 (52.4)
Psychopathology of Sibling (n[%])	10 (15.9)
Psychopathology of Parent (n[%])	11 (17.5)

Patients were most commonly diagnosed with ADHD-Combined Type (74.6%, n = 47), followed by Inattentive (17.5%, n = 11) and Hyperactive/Impulsive (7.9%, n = 5) subtypes. ODD comorbidity was present in 19% of participants (n = 12). Median doses of OROS methylphenidate at the study's start and endpoints were 0.5 mg/ kg/day (IQR = 0.22) and 1.1 mg/ kg/ day (IQR = 0.10), respectively. Clinicians' and parents' baseline and end visit ratings are summarized in Table 2.

Table 2. Clinician and parent evaluations of children with ADHD treated with OROS MPH

Measure (Median, IQR 25-75)	Baseline	12th week	p*	Cohen's d
CGI-S	4.00 (4.00-4.00)	-	-	
CGI - I	-	2.00 (2.00-3.00)	-	
T-DSM-IV - Inattentive	18.00 (15.00-22.00)	13.00 (11.00-16.00)	< 0.001	1.09
T-DSM-IV - Hyperactive/ Impulsive	15.00 (9.00-20.00)	11.00 (8.00-15.00)	< 0.001	0.78
T-DSM-IV - ODD	11.00 (6.00-16.00)	7.00 (4.00-12.00)	< 0.001	0.72
T-DSM-IV-CD	2.00 (0.00-4.00)	1.00 (0.00-2.00)	< 0.001	0.43
T-DSM-IV - Total	46.00 (33.00-57.00)	34.00 (26.00-39.00)	< 0.001	1.06

*Wilcoxon signed ranks test, IQR: Inter-quartile Range, CGI: Clinical Global Impressions, S: Severity, I:Improvement, SE: Side Effects, CGAS: Children's Global Assessment Scale, T-DSM-IV: Turgay DSM-IV Based Screening and Diagnostic Scale for Disruptive Behavior Disorders, ODD: Oppositional Defiant Disorder, CD: Conduct Disorder

Clinical severity of ADHD as measured by parents decreased significantly from baseline to week 12, and clinicians' ratings of child functioning increased significantly. As evaluated by parents, treatment with OROS mph led to a significant decrease in all symptom domains. Based on WFIRS-P scores, treatment with OROS mph led to significantly reduced impairment in all domains while PedsQL scores indicated that physical and total quality of life improved significantly with treatment (Table 3). Changes in T-DSM-IV ADHD and total PedsQL scores correlated significantly with changes in WFIRS-P total score (r weaker than ± 0.5).

Table 3. Parent reported functioning and quality of life of children with ADHD treatment with OROS MPH

Measure (Median, IQR 25-75)	Baseline	12th week	p*	Cohen's d
WFIRS-P - Family	1.0 (0.7-1.5)	0.8 (0.6-1.2)	< .001	0.69
WFIRS - P - Learning	1.8 (0.75-2.25)	1.3 (1.5)	< .001	0.65
WFIRS-P - Behavior	0.7 (0.5-2.0)	0.5 (0.17-0.83)	< .005	0.40
WFIRS-P - School	1.0 (0.7-1.4)	0.9 (0.6-1.2)	< .001	0.67
WFIRS-P - Life skills	1.2 (0.9-1.6)	1.0 (0.8-1.3)	< .001	0.63
WFIRS-P - Self concept	1.0 (0.33-1.33)	1.0 (0.3-1.0)	< .001	0.48
WFIRS-P - Social	0.9 (0.42-1.57)	0.7 (0.42-1.0)	< .001	0.46
WFIRS-P - Risky behaviors	0.2 (0.1-0.4)	0.1 (0.0-0.3)	< .001	0.52
WFIRS-P - Total	0.8 (0.68-1.3)	0.7 (0.56-.94)	< .001	0.88
PedsQL - Psychosocial	63.3 (50.0-73.33)	71.7 (63.3-78.3)	0.74	-0.83
PedsQL-Physical	75.0 (59.37-87.5)	78.1 (71.87-90.62)	< .001	-0.65
PedsQL-Total	67.4 (54.35-75.0)	73.9 (67.39-78.26)	< .001	-0.89

*Wilcoxon signed ranks test, WFIRS-P: Weiss Functional Impairment Rating Scale – Parent Version, PedsQL:Pediatric Quality of Life Questionnaire

By the end of study, according to a priori criteria, treatment response was recorded in 77.7% of patients (n = 49); improvement in functional impairment was 34.9 % (n = 22); and improvement in quality of life was 28.6 % (n = 18). Among treatment responders, 42.9% (21/49) exhibited functional improvement, and 34.7% (17/49) showed improved quality of life. Based on functional improvement criteria, 95.5% of patients who showed functional improvement (21/22) had treatment response, and 59.1% (13/22) showed quality of life improvement (Table 4).

Table 4. Proportion of children and adolescents with functional improvement by symptom improvement

	Symptom Response	Symptom Non-Response
WFIRS-P Response	21 (%33,3)	1 (%1,5)
WFIRS-P Non-Response	28 (%44,4)	13 (%20,6)
QOL Response	17 (%26,9)	1 (%1,5)
QOL Non-Response	32 (%50,7)	13 (%20,6)
	WFIRS-P Response	WFIRS-P Non-Response
Symptom Response	21 (%33,3)	28 (%44,4)
Symptom Non-Response	1 (%1,5)	13 (%20,6)
QOL Response	13 (%20,6)	5 (%7,9)
QOL Non-Response	9 (%14,2)	36 (%57,1)

Symptom Response was defined a priori as ≥ 20.0 % reduction in Turgay DSM-IV Based Screening and Diagnostic Scale for Disruptive Behavior Disorders total score. from baseline to end of the open-label phase. WFIRS-P Response: defined as ≥0.25 improvement in WFIRS-P total score from baseline to end of the open-label phase. QOL Response defined 20.0 % increase in total domains of . PedsQL. WFIRS-P: Weiss Functional Impairment Rating Scale – Parent Version. PedsQL: Pediatric Quality of Life Questionnaire

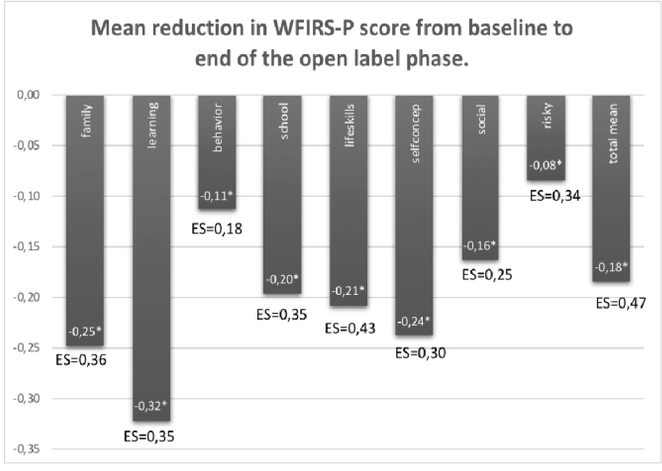

Figure 1. Mean reduction in WFIRS-P score from baseline to end of the open label phase. ES: effect size (defined as mean reduction divided by standard deviation at baseline). WFIRS-P: Weiss Functional Impairment Rating Scale – Parent Version.*p < 0.001.

By the end of week 12, improvement (total and all subscale domains) was found to be statistically significant, with the largest improvement in the Total scale score (Figure 1). Mean (SD) changes from baseline WFIRS-P scores to the end of week 12 were as follows: total 0.18 (0.21); family 0.25 (0.36); learning 0.32 (0.50); behavior 0.11 (0.29); school 0.20 (0.29); life skills 0.21 (0.33); self-concept 0.24 (0.49); social activities 0.16 (0.35); and risky activities 0.08 (0.16).

With the exception of behavior and social activities, effect size for all domains was 0.33–0.47 (Figure 1). Improvement in symptoms was associated with small to medium effect sizes in improvement across all domains. The greatest effect size was for total score, which measures the combined impact of gains in function across all domains.

DISCUSSION

Reporting that functional improvement and quality of life improvement scores showed a significant but moderate correlation with changes in ADHD symptoms [14], Coghill *et al*. suggested that remission of ADHD symptoms may not affect functioning and/or quality of life [14]. In the present naturalistic follow-up study, we examined the association between change in ADHD symptoms, functional impairment, and quality of life in children during 12-week treatment with OROS mph. As assessed by parents, treatment was associated with a significant decrease in all symptom domains. The a priori defined rate for treatment response was 77.7%; treatment response as measured by WFIRS-P was 34.9 %, and 28.6% of the sample reported improvement in total QoL. The vast majority of patients who show improved function also had improved symptoms; in contrast, only slightly more than half of patients who showed symptom improvement also had improved function. Functional improvement is a much more rigorous outcome than symptom improvement, implying that any definition of remission as the highest standard of robust outcome should require functional improvement. An even smaller number of patients with symptom improvement showed changes in quality of life. As quality of life is a very broad concept, it is likely to be determined by many factors beyond symptom severity alone.

Changes in T-DSM-IV ADHD and total PedsQL scores were significantly but at most moderately correlated with changes in WFIRS-P total score (r weaker than ± 0.5). Coghill *et al*. (2017) also reported that ADHD-RS-IV, CHIP-CE:PRF, and WFIRS-P scores were moderately correlated, indicating that symptoms, functional impairment, and quality of life concepts are discrete aspects of treatment response with some overlapping features [14].

Unless clinical evaluation of treatment outcome includes more than symptoms alone, clinicians may assume that treatment response has been achieved without following through on necessary treatment to address residual difficulties. While clinical trials have typically included function and quality of life as secondary outcomes, clinicians tend to monitor response using only a symptom scale. Our data suggest that routine identification of functional impairment is at least as important as symptoms alone. While many aspects of quality of life may not be driven by symptoms, clinicians can and should identify how improved symptoms improve both function and perceived well-being for the patient. This broader outcome evaluation provides a more realistic and accurate view of response and is likely to improve patient engagement and adherence, as patients are more invested in real-life issues than in constructs that seem distant from their primary concerns.

Beverung *et al*. report that a change in QoL of 20% or more may indicate significant gains in quality of life [25]. Based on their definition, we found that 28.6 % (n = 18) of participants showed an increase of 20% or more in total QoL as measured by PedsQL. In an earlier large observation study of individuals with ADHD, methylphenidate therapy was shown to improve quality of life [46]. In another randomized controlled study, Banaschewski *et al*. reported that OROS mph treatment also improved quality of life [47]. In line with those earlier findings, we observed an improvement in the quality of life of ADHD patients following OROS mph treatment.

Varni *et al*. reported that children with ADHD scored significantly lower in the psychosocial health domain of PedsQL than healthy children [48]. Similarly, Klassen *et al*. reported that children with ADHD showed significantly lower scores than population samples for psychosocial domains of QoL [49]. In their randomized double-blind placebo-controlled study, Greenhill *et al*. reported a significant improvement in the psychosocial summary of Child Health Questionnaire (CHQ) scores among the group receiving dexmethylphenidate treatment as compared to a placebo group [50]. Our findings differ in that we found no significant change in the psychosocial domain of PedsQL. This may be explained by our use of the PedsQL rather than the Child Health Questionnaire, or it may reflect the mild symptom severity and absence of comorbidity, except ODD, in our sample.

Many studies have reported a significant correlation between quality of life and function [51], as replicated here. However, it is important to note that while our measure of function related directly to impairment caused by symptoms, quality of life measures are not illness-specific and are therefore likely to be influenced by many life variables and less closely tied to symptom improvement. Nevertheless, we found that an improvement in ability to function impacted quality of life.

It is interesting that the effect size of improvement in function was small to medium and statistically significant across all domains. By implication, ADHD symptoms impact impairment across the board, and improvement in symptoms therefore leads to improvement in function across all domains. The medium effect size of function improvement suggests that where there is improvement in each domain, any improvement in one area is closely linked to improvement in other areas. For that reason, the most robust and reliable outcome measure is total score.

In a study of stimulant treatment (n = 200), Weiss et al. reported that 94% of patients showed symptom improvement; 56% showed functional improvement. Total scores for all functional areas were statistically and clinically significant, and effect size for all domains was ≥ 0.50 [23]. In the present case, we believe a number of factors contributed to lower effect size and treatment response rates. First, the naturalistic design meant that our participants had been diagnosed with ADHD for the first

time. They were also younger and had less severe symptoms (in the clinician's opinion), with no comorbidity other than ODD. Additional nonpharmacological therapeutic interventions for ADHD, especially with comorbid ODD, were not performed. Finally, while dose titration and follow-up times were weekly in many studies, these were monthly in our study.

Limitations

Our findings must be evaluated in light of the study's limitations. First, the sample size was limited, so reducing explanatory power. Second, excluding patients with comorbidities and enrolling younger patients may have biased our sample toward those with milder ADHD and obscuring treatment effects. Third, monthly visits may not suffice for optimal dose management and evaluation of symptoms; weekly visits may increase sensitivity but at the expense of external validity and naturalistic design. Fourth, the robust improvement in symptoms as compared to function and quality of life may have been strongly influenced by the exclusion of psychosocial treatment. Finally, the a priori definitions of response in terms of symptoms, function, and quality of life may impact our findings. For example, more robust criteria for symptom response and less robust criteria for function or quality of life might impact the percentage of patients showing improvement in each type of outcome. Nevertheless, our key finding that function and quality of life improve in only a subset of patients with symptom response seems unlikely to change. Despite these limitations, the present study is the first to evaluate both general quality of life and ADHD-related functional impairment and their relation to symptom severity and treatment response based on parent and clinician reports within a naturalistic design. Our results should be corroborated in further studies with larger samples.

One strengths of our study is that it is a naturalistic follow-up study in outpatient clinic conditions in Turkey. As this group of children had relatively mild new onset ADHD and had not yet developed secondary psychiatric or other problems that would affect function and quality of life, our key finding is relatively robust. Even in this sample, it proved critical to evaluate secondary outcomes in order to fully understand the impact of treatment. Uniquely, our findings reveal that a significant proportion of children whose symptoms improve with psychostimulant treatment may continue to exhibit functional impairment that requires further clinical intervention.

Compliance with Ethical Standards

Conflicts of interest: M.C.T., Y.Ç., M.T.K., N.O.A., U.M.A., A.E.T., Ö.Y.G. and N.Ç.M declare no conflict of interest. M.D.W. has received travel fees, consultant fees or received honoraria from Purdue Pharma (Canada), Eunethydis, World Federation of ADHD, Mundipharma, Purdue Pharma (US), Akili, Multi – Health Systems, NLS Pharma, Takeda, Rhodes, Huron Consulting, and Global Medical Education.

Ethical approval: All procedures performed in studies involving human participants complied with the ethical standards of Kocaeli University Ethics Committee (approval number: 2016/113) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from the parents of all study participants.

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