Treatment Duration is Associated with Functioning and Prognosis in Children with Attention Deficit Hyperactivity Disorder

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ÖZET:
Dikkat eksikliği ve hiperaktivite bozukluğu olan çocukların tedavi süresi işlevsellik ve prognoz ile ilişkilidir

Giriş: Dikkat Eksikliği ve Hiperaktivite Bozukluğu'nun (DEHB) ergenlik ve erişkinliğe dek sürdüğü ve DEHB tanılı çocukların %15-80 oranında erişkinlikte de DEHB tanısı almaya devam ettikleri bilinmektedir. Bununla birlikte, bu bulgular çoğunlukla Kuzey Amerika'da yapılan izlem çalışmalarının sonuçlarıdır. Batılı ülkeler dışındaki ülkelerdeki DEHB'li çocukların uzun dönem izlemi ve DEHB+ Karşıt Olma Karşı Gelme Bozukluğu (KOB) ve DEHB+ Davranım Bozukluğu (DB) olguları arasındaki prognostik farklılıklar ile ilgili çalışmalar faydalı olacaktır. Bu çalışmada, 2000 - 2002 yılları arasında gerçekleştirilen 18 aylık izlem çalışmamızda yer alan 120 DEHB ve eşlik eden KOB veya DB tanılı olguyu ilk başlangıç çalışmamızdan 6 yıl sonra tekrar değerlendirmeyi amaçladık.

Yöntem: Başlangıç çalışmamızın örneklem grubu 2000-2002 yılları arasında 18 ay süre ile izlenmiş olan DEHB + KOB/DB olan çocuklardan oluşmaktadır. Altı yıl önce değerlendirmiş olduğumuz olgulardan ulaşabildiğimiz altmışının şu anki psikiyatrik durumları, akademik başarıları, madde kullanımları ve sosyal işlevsellikleri değerlendirilmiştir. Tedaviye devam süresi 15 ay ve altı, 15-45 ay arası ve 45 ay ve üstü olarak belirlenmiştir.

Bulgular: Başlangıç çalışmamızda hem kombine tedavinin (ilaç tedavisi + ebeveyn eğitimi) hem de sadece ilaç tedavisinin DEHB, KOB ve DB belirtilerini azaltmada etkili olduğu saptanmıştır. Altı yıl sonra yapılan değerlendirmede DEHB ve eşlik eden KOB veya DB tanılı çocukların tedaviye devam süresinin akademik başarı, sınıf tekrarı, okuldan atılma/okuldan uzaklaştırılma, kaza geçirme veya alçı tedavisi uygulanması ve sigara kullanımı alanlarında istatistiksel olarak anlamlı düzeyde etkili olduğu görülmüştür.

Sonuç: DEHB ve eşlik eden KOB/DB semptomları işlevselliğin bir çok alanında bozulmaya neden olabilmektedir. DEHB olguları uygun sürede tedavi edildiğinde ise bu çocukların yaşamlarının bir çok alanında olumlu etkiler olduğu görülmektedir. Sonuç olarak tedaviye devam süresine göre oluşturulan gruplar arasında tedavi başarısı ve prognoz açısından istatistiksel olarak anlamlı farklılık saptanmıştır.

Anahtar sözcükler: Dikkat eksikliği hiperaktivite bozukluğu, tedavi süresi, prognoz, işlevsellik

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ABSTRACT:
Treatment duration is associated with functioning and prognosis in children with attention deficit hyperactivity disorder

Objective: Attention Deficit Hyperactivity Disorder (ADHD) persists through adolescence and adulthood, and 15-80% of the children diagnosed with ADHD continue to have the disorder into adulthood, depending on the diagnostic criteria used; however, these findings have mostly been derived from follow-up studies in North America. The longitudinal outcomes of ADHD children from non-Western countries, such as Turkey, and the prognostic differences between ADHD+Oppositional Defiant Disorder (ODD) and ADHD+Conduct Disorder (CD) cases require further exploration. Six years after an initial study of 18 months conducted between 2000 and 2002, we sought to evaluate 120 cases of ADHD with comorbid ODD or CD.

Methods: The original sample included 120 ADHD + ODD/CD children, followed for 18 months during 2000-2002. We evaluated the last-known psychiatric status, academic achievement, substance use, and social functionality of 60 children who were interviewed six years earlier. The treatment duration was divided into three groups: less than 15 months, 15-45 months, and greater than 45 months.

Results: In the initial study, we found that both combined treatment (parent training and stimulant treatment) and only stimulant treatment were effective in reducing ADHD, ODD, and CD symptoms. Six years after the initial study, the ADHD treatment was found to be effective in many areas, including academic success (p<0.001), grade retention (p=0.026), expulsion or suspension from school (p=0.009), rate of accidents and broken bones requiring reduction (p=0.001), and cigarette smoking (p=0.018).

Conclusions: ADHD symptoms are associated with impairments in multiple functional domains, and ADHD treatment is effective for Turkish children in many of these domains. There is a statistically significant difference in treatment success between groups created according to the treatment duration.

Key words: Attention deficit/hyperactivity disorder, treatment duration, prognostic outcomes, functionality

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INTRODUCTION

Attention Deficit Hyperactivity Disorder (ADHD) is an early onset neurodevelopmental disorder that affects 3-5% of school-age children (1). Attention deficit, hyperactivity, and impulsivity symptoms encompass and impair functionality across multiple functional domains. ADHD persists through adolescence and adulthood, and 15-80% of children diagnosed with ADHD continue to have the disorder into adulthood, depending on the diagnostic criteria used (2,3). Although these findings have mainly been derived from North American follow-up studies, the persistence of the disorder into adulthood is clear. In addition to the effects of core ADHD symptoms on social and academic functioning, the high comorbidity rates indicate the importance of treatment and follow-up in these children.

ADHD, one of the most frequent childhood disorders, can cause important psychiatric, academic, and social problems unless treated (1). The natural course and treatment efficacy of ADHD in children is well-known. The relationship between ADHD and academic and school life problems is detailed in the literature (4,5,6). Core ADHD symptoms and their related executive dysfunction are linked to academic underachievement (7). In addition to academic difficulties, additional problem areas include frequent accidents, early onset and higher rate of substance use, trouble with rules/laws and higher delinquency rates. Treatment has been shown to clearly ameliorate these problems. Satterfield et al. (1981) followed 100 individuals with ADHD who received various treatment modalities according to their individual features; those with longer treatment duration had significantly improved academic outcomes and social functioning (8).

Furthermore, additional psychiatric disorders frequently accompany ADHD, and the comorbidity rates are high. The most frequent comorbid diagnosis is Oppositional Defiant Disorder (ODD). ODD is a disruptive behavior disorder characterized by negative, hostile, rebellious, provocative, and disruptive behaviors without an attack on social norms or the fundamental rights of others. ODD is also one of the most frequent disorders seen in clinical referrals and epidemiological studies (9,10). In a recent systematic review and meta-analysis, Canino et al. (2010) have suggested that the prevalence of ODD is 3.3% (11). ODD, which frequently accompanies

other psychiatric disorders, can lead to multiple life impairments and ultimately to Conduct Disorder (CD) and substance use disorders (SUD) (10,11,12). The comorbidity of ADHD and ODD has been found to be 40% by August et al. (1999) and 65% by Biederman et al. (1996) (13,14). The comorbidity of ODD/CD is high; some ODD children are ultimately diagnosed with CD upon further evaluation, and ODD is well-accepted as a mild form of CD (15,16).

Comorbidity is also frequently seen in CD. CD is characterized by the persistent and repetitive violation of the fundamental rights of others in addition to age-appropriate social norms and rules. The prevalence of CD is reported to range from 1-16% in community samples, with a mean prevalence of 5% (17). CD co-occurs in 30-50% of ADHD children (18). Hyperactivity, impulsive and explosive behaviors, cognitive and academic problems, learning disorders, and social skills deficits usually accompany this disorder (19). These children are at high risk for future legal problems, substance use, and physical injuries and early interventions have demonstrated positive effects on their prognosis. Hence early diagnosis and treatment is important in CD cases.

Despite the high comorbidity of CD and ODD with ADHD, long-term follow-up studies and data concerning the level of functioning in these comorbid cases are scarce. Moffit (1990) has reported that ADHD+CD cases have more antisocial features, verbal IQ deficits, and familial disturbances than other children (20). Furthermore, CD comorbidity is related to higher levels of academic problems, higher rates of early departure or expulsion from school, and earlier-onset and higher rate of substance use. Comorbid ADHD and ODD/CD diminish the functioning of children and adolescents and enhance their vulnerability to the above risks. As stated, however, these results are mostly derived from follow-up studies conducted in North America. Data regarding the longitudinal outcomes in comorbid ADHD and ODD/CD children from non-Western countries, such as Turkey, would be a useful addition to the current knowledge in the field. The effects of treatment duration and utilization on functionality are also important. The effects of stimulants on ADHD core symptoms are well-known, and strong evidence suggests that stimulants improve short-term academic productivity and accuracy in classroom analogue settings (21,22). Although the short-term efficacy of methylphenidate and other stimulant medications is well-

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documented, relatively less is known about their long-term efficacy (23). Several authors have pointed out that no evidence is currently available to suggest that stimulant medication has an effect on long-term academic achievement (7,21). Stimulant treatments are thought to reduce the development of additional psychiatric diagnoses, the risk of academic underachievement, and the risk of future SUD (24,25). All of these findings highlight the importance of the long-term treatment and follow-up of ADHD+CD/ODD cases.

We sought to evaluate 120 cases of ADHD with comorbid ODD or CD 6 years after an initial 18-month follow-up study conducted between 2000-2002. In the present study, we evaluated the last-known psychiatric status, academic achievement, substance use, and social functioning of the available children.

METHODS

All of the study procedures were completed in the Child and Adolescent Psychiatry Department of the Ege University School of Medicine. The study was conducted in accordance with the principles of the Declaration of Helsinki. The parents of all the participants gave informed consent prior to the study.

Participants and Procedure

This study is a continuation of our initial 18-month follow-up study conducted with 120 ADHD and ODD/CD cases. The initial study started in 2000, and the results from 83 children were published as a preliminary report after the first 6 months (23). We then increased the study

group to 120 children and continued the follow-up. In the initial study (Table 1), the mean (SD) age was 9.07 years (1.92), 82 (68.3%) were males and 38 (31.7%) were females, and this study has also been published (26).

The detailed inclusion criteria and diagnostic standards of the initial study have been described in prior publications (23,26). To summarize, a structured interview based on the DSM-IV criteria was used in the initial study to assess the presence or probable presence of ADHD, ODD, and CD (1). A second child psychiatrist who knew that the child was a candidate for the study but was blind to the initial diagnosis of comorbid disorders conducted the second diagnostic interview. As in the first interview, a structured interview based on the DSM-IV criteria was used to assess the presence of ADHD and ODD/CD. After these two evaluations, the final diagnosis was confirmed. Stimulant treatment was started and the participants were invited to attend parent-training groups. One-hundred and twenty ADHD and ODD/CD cases were assessed by their parents and teachers across multiple domains using multiple sources of information at baseline and at the end of the 1st, 3rd, 6th, 12th and 18th months. The assessments included the Conners Parent Rating Scale (CPRS), the Conners Teacher Rating Scale (CTRS), and the Turgay Diagnostic and Statistical Manual of Mental Disorders, the 4th edition (DSM-IV)-Based Child and Adolescent Behavior Disorders Screening and Rating Scale (T-DSM-IV-S) (27,28,29,30). The results of the initial study are summarized in Tables 1, 2, and 3 (for detailed information see Ercan et al. 2011) (26).

In this current study (study II), sixty of the 120 ADHD children with comorbid ODD or CD in the initial study were evaluated by telephone interview 6 years after the

Table 1: The demographic and clinical characteristics of the children in study I							
	All cases	Comorbidity groups			Treatment Groups		
		ADHD+ODD (n=67)	ADHD+CD (n=53)	p	Med. + PT (n=83)	Med. Only (n=37)	p
Age							
Mean (SD)	9.07 (1.92)	9.28 (1.77)	8.79 (2.09)	0.16[†] (F: 1.95)	9.23 (2.00)	8.70 (1.70)	0.17[†] (F: 1.93)
Gender							
Male (%)	82 (68.3%)	52 (77.6%)	30 (56.6%)	0.01[‡] (x²: 6.03)	53 (63.9%)	29 (78.4%)	0.11[‡] (x²: 2,5)
Female (%)	38 (31.7%)	15 (22.4%)	23 (43.4 %)		30 (36.1%)	8 (21.6%)	
MPH Dose[¶]							
Mean (SD)	24.79 (8.10)	22.88 (9.19)	27.33 (5.71)	0.11[§] (t:-1,652)	24.8 (7.9)	24.2 (11.8)	0.89[§] (t:0.136)

†: ANOVA, ‡: Pearson Chi-squared test, §: Independent samples t test, p<0,05 was significant, ¶: Because the dose adjustments continued throughout the study, the mean MPH doses reported here were calculated using both the dose and the duration of use. MPH: Methylphenidate, ADHD: Attention Deficit / Hyperactivity Disorder, ODD: Oppositional Defiant Disorder, CD: Conduct Disorder, Med. + PT: Medication and parent training, Med.Only: Medication only

Table 2: Comparisons of baseline, 6th month and 18th month mean (SD) scores using within-subjects ANOVA models for the fifteen dependent measures

Scale	Subscale	Rater	Baseline mean (SD)	6th month mean (SD)	18th month mean (SD)	F*	Pairwise comparisons**
T-DSM-IV-S	HI	Parent	20.36(4.89)	10.29(5.13)	11.93(7.50)	21.284	6.mo, 18.mo (p<.0001) < Baseline
T-DSM-IV-S		Teacher	16.77(8.05)	9.41(7.35)	10.59(7.05)	7.790	6. mo (p<.002), 18.mo (p<.035) < Baseline
CPRS		Parent	9.53(1.87)	7.25(2.70)	7.22(2.89)	6.878	6.mo (p<.0001), 18.mo (p<.004) < Baseline
T-DSM-IV-S	AD	Parent	18.55(5.58)	10.09(4.47)	12.33(5.67)	19.201	6.mo, 18.mo (p<.0001) < Baseline
T-DSM-IV-S		Teacher	15.79(5.73)	11.46(6.37)	11.17(6.23)	4.775	non significant
CPRS		Parent	7.03(3.02)	5.10(2.34)	5.97(2.87)	4.683	6.mo (p<.001) < Baseline
T-DSM-IV-S	ODD	Parent	13.94(6.12)	8.00(3.92)	8.67(5.30)	11.793	6.mo (p<.0001), 18.mo (p<.004) < Baseline
T-DSM-IV-S		Teacher	11.74(7.05)	7.35(6.06)	7.43(5.54)	4.880	18.mo (p<.032) < Baseline
CPRS		Parent	8.13(4.16)	4.56(2.59)	4.94(3.08)	10.209	6.mo (p<.0001), 18.mo (.006) < Baseline
T-DSM-IV-S	CD	Parent	5.61(3.93)	1.10(1.37)	1.74(1.80)	22.788	6.mo, 18.mo (p<.0001) < Baseline
T-DSM-IV-S		Teacher	5.83(4.81)	1.87(2.97)	1.91(2.87)	6.543	6.mo (p<.013), 18.mo (p<.024) < Baseline
CPRS		Parent	15.91(7.83)	7.53(5.38)	7.97(5.50)	22.006	6.mo, 18.mo (p<.0001) < Baseline
CTRS	Total score	Teacher	38.29(13.24)	31.79(15.59)	28.13(13.58)	4.555	18.mo (p<.003) < Baseline
T-DSM-IV-S	Total score	Parent	59.22(16.72)	30.52(12.55)	36.74(16.77)	21.815	6.mo (p<.0001) < Baseline 18.mo (p<.001)< Baseline
T-DSM-IV-S	Total score	Teacher	50.62(21.17)	29.71(19.09)	32.38(18.79)	7.605	6.mo (p<.007), 18.mo (p<.025)< Baseline

*All the main effects were significant at p<.001; the degrees of freedom was 80.

** Multiple within-subject pairwise comparisons were performed using the Bonferroni adjustment for multiple comparisons. All the pairwise comparisons are significant at p<.001 unless otherwise specified in parenthesis.

T-DSM-IV-S: Turgay DSM-IV Based Child and Adolescent Behavior Disorders Screening and Rating Scale, CPRS: Conners Parent Rating Scale, CTRS: Conners Teacher Rating Scale, HI: Hyperactivity/Impulsivity, AD: Attention Deficit, ODD: Oppositional Defiant Disorder, CD: Conduct Disorder, mo: month
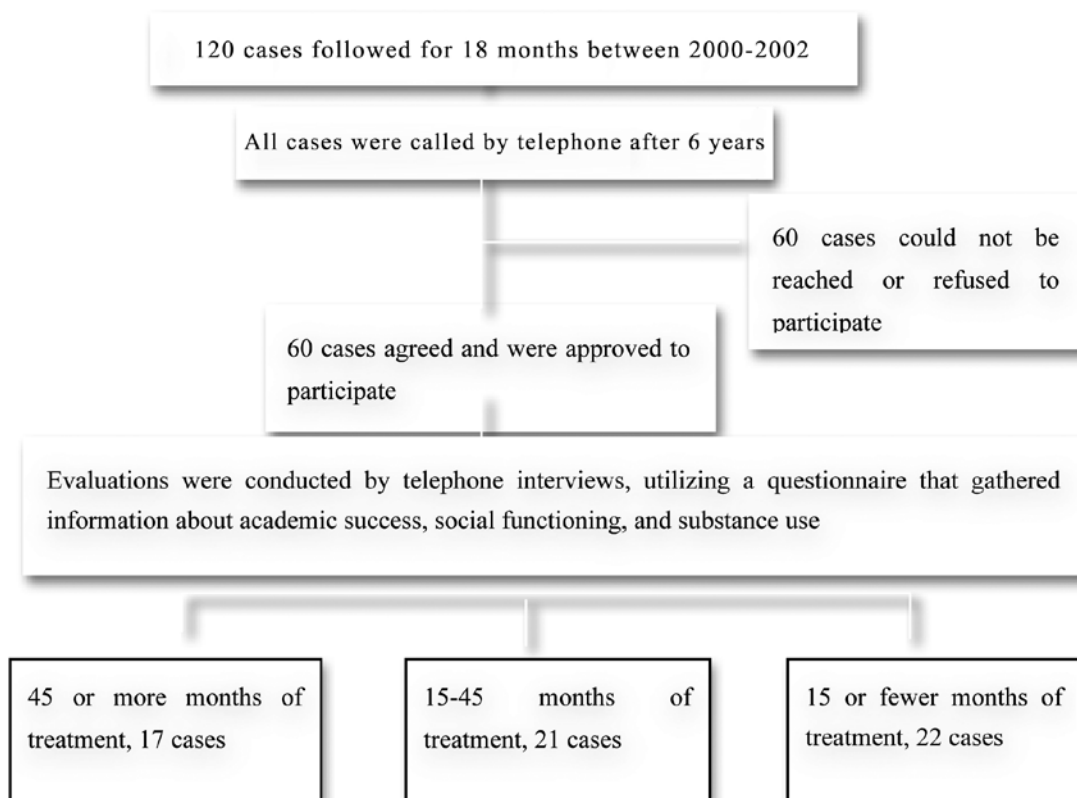

120 cases followed for 18 months between 2000-2002

All cases were called by telephone after 6 years

60 cases could not be reached or refused to participate

60 cases agreed and were approved to participate

Evaluations were conducted by telephone interviews, utilizing a questionnaire that gathered information about academic success, social functioning, and substance use

45 or more months of treatment, 17 cases

15-45 months of treatment, 21 cases

15 or fewer months of treatment, 22 cases

Figure 1: The implementation scheme of the study

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Table 3: Mean (SD) scores of the medication + parent training and the medication only treatment groups at baseline and at the end of the 6th and 18th months

Scale	Subscales	Rater	Baseline mean (SD)		1st month mean (SD)		6th month mean (SD)		12th month mean (SD)		18th month mean (SD)	
			Med.+PT	Med. Only	Med.+PT	Med. Only	Med.+PT	Med. Only	Med.+PT	Med. Only	Med.+PT	Med. Only
T-DSM-IV-S	HI	Parent	19.70(4.65)	19.54(5.18)	14.15(6.07)	14.42(6.81)	11.85(5.58)	12.84(6.16)	13.25(6.70)	12.71(5.90)	12.00(7.21)	13.33(8.08)
T-DSM-IV-S		Teacher	16.67(7.41)	16.49(7.85)	13.37(7.17)	12.09(7.50)	11.07(7.17)	10.86(7.24)	11.04(8.52)	11.00(6.36)	11.13(7.37)	8.00(1.00)
CPRS		Parent	9.67(2.07)	9.57(2.36)	8.39(2.67)	7.22(3.31)*	7.56(2.88)	7.44(2.80)	7.12(3.19)	8.07(3.10)	7.26(2.63)	5.67(5.03)
T-DSM-IV-S	AD	Parent	18.28(5.26)	17.78(4.82)	14.67(5.38)	13.46(6.51)	11.29(5.20)	11.52(5.87)	13.00(6.17)	14.00(7.01)	12.52(5.80)	9.33(1.53)
T-DSM-IV-S		Teacher	16.49(5.89)	16.81(6.43)	13.96(6.00)	13.38(7.16)	11.99(6.29)	12.00(5.89)	12.04(6.73)	14.29(6.34)	12.16(6.75)	8.33(3.51)
CPRS		Parent	7.48(2.69)	7.38(2.94)	6.59(2.64)	5.59(2.47)**	5.58(2.39)	5.25(3.04)	6.00(2.72)	5.80(2.51)	6.32(3.08)	4.67(1.15)
T-DSM-IV-S	ODD	Parent	13.76(5.36)	14.00(4.84)	10.32(4.65)	9.08(5.32)	8.18(4.34)	9.00(5.61)	8.83(5.36)	9.93(6.18)	8.61(5.46)	8.00(3.00)
T-DSM-IV-S		Teacher	11.61(6.30)	10.32(6.71)	9.59(5.84)	6.47(4.63) ***	7.37(5.72)	7.09(5.49)	7.55(5.75)	9.20(4.28)	7.92(6.05)	4.33(2.52)
CPRS		Parent	8.20(3.59)	7.51(3.47)	6.84(2.93)	5.92(3.07)	5.13(2.85)	5.60(3.37)	4.96(3.20)	6.33(3.33)	4.97(3.19)	5.00(2.65)
T-DSM-IV-S	CD	Parent	5.52(4.41)	6.11(5.92)	2.49(2.99)	2.11(2.30)	1.63(2.19)	2.28(1.79)	1.86(2.63)	2.13(1.88)	1.87(2.03)	1.67(2.08)
T-DSM-IV-S		Teacher	5.84(5.54)	4.61(4.36)	3.07(3.51)	2.64(3.31)	2.16(3.11)	2.32(4.69)	2.45(3.39)	2.64(2.13)	2.52(3.81)	1.00(1.41)
CPRS		Parent	16.18(7.32)	14.35(7.28)	12.81(6.77)	10.89(6.38)	8.62(6.05)	8.96(6.23)	7.91(6.90)	10.07(5.74)	7.97(5.61)	7.33(4.73)

*.008, **.046, *** .002, MANOVA and Pairwise comparisons were performed using the Bonferroni adjustment, T-DSM-IV-S: Turgay DSM-IV Based Child and Adolescent Behavior Disorders Screening and Rating Scale, CPRS: Conners Parent Rating Scale, CTRS: Conners Teacher Rating Scale, HI: Hyperactivity/Impulsivity, AD: Attention Deficit, ODD: Oppositional Defiant Disorder, CD: Conduct Disorder, Med. + PT: Medication and parent training, Med. Only: Medication only

initial study. The last-known psychiatric status, level of academic achievement, substance use, and social functionality were noted on a questionnaire developed by the study authors. The treatment duration was divided into three groups—less than 15 months, 15-45 months, and greater than 45 months—and noted on the questionnaire. The clinician completed both the severity and improvement subscales of the Clinical Global Impression Scale (CGI) (31). The implementation scheme of the study is shown in Figure 1.

We were able to evaluate 60 of the 120 cases from the initial study. Those who failed to participate were unavailable due to address or telephone number changes or refusal to participate. In study II, the mean (SD) age was 16.7 years (1.73), 42 (70%) were males and 18 (30%) were females (Table 4).

MATERIALS

Study I (Initial Study)

Conner's Parent Rating Scale (CPRS): The 48-item Turkish Form of the Conner's Parent Rating Scale (CPRS) was translated and adapted by Dereboy et al. (1998) (27,28). Four indices are obtained by this scale: (1) hyperactivity/impulsivity, (2) inattention, (3) opposition/defiance, and (4) conduct disorder. In rating a child's behavior, a parent responds to each item using a 4-point Likert-type scale: 0 = never, 1 = rarely, 2 = often, and 3 = always.

Conner's Teacher Rating Scale (CTRS): The 28-item Conner's Teacher Rating Scale (CTRS) was developed by Goyette et al. (1978) (27). The teacher ratings are also scored on a 4-point Likert-type scale. The CTRS was translated into Turkish by Şener et al. (1995), and the Turkish form has adequate validity and reliability (a Cronbach's alpha of 0.95). As suggested by the authors, the total score was used instead of the subscale scores (29).

Turgay DSM-IV Based Child and Adolescent Behavior Disorders Screening and Rating Scale, Parent and Teacher Form: The T-DSM-IV-S was developed by Turgay (1994) and was translated/adapted into Turkish by Ercan et al. (2001) (30,32). The T-DSM-IV-S is based on the DSM-IV diagnostic criteria and assesses hyperactivity/

Table 4: The demographic characteristics of the comorbidity and treatment continuity groups (study II)

	All cases	Comorbidity groups			Treatment continuity			
		ADHD+ODD (n=34)	ADHD+CD (n=26)	p	45+months (n=17)	15-45 months (n=21)	15-months (n=22)	p
Age								
Mean (SD)	16,70 (1,73)	16.97 (1.66)	16.35 (1.79)	0.15† (F: 2.14)	16.35 (1,87)	16,48 (1,60)	17,18 (1,71)	0.17† (F:1.8)
Gender								
Male (%)	42 (70%)	22 (64.7%)	20 (76.9%)	0.31‡ (x^2: 1.05)	12 (70.6%)	15 (71.4%)	15 (68.2%)	0.97‡(x^2:0.06)
Female (%)	18 (30%)	12 (35.3%)	6 (23.1%)		5 (29.4%)	6 (28.6%)	7 (31.8%)	

†: ANOVA, ‡: Pearson Chi-squared test, p <0,05 was significant, ADHD: Attention Deficit / Hyperactivity Disorder, ODD: Oppositional Defiant Disorder, CD: Conduct Disorder

Table 5: The effect of the treatment duration on the functionality and problem domains

Problem Domains	Number of cases by treatment duration (n)				p*
	45+ months (n:17)	15 - 45 months (n:21)	15- months (n:22)	total	
Grade retention					
Present	2	6	11	19	0,026
Absent	15	15	10	40	
Total	17	21	21	59	
Academic Success					
Well	6	1	1	8	<0,001
Moderate	9	3	4	16	
Worse	2	17	16	35	
Total	17	21	21	59	
Disciplinary punishment					
None	17	17	14	48	0,163
Once	0	1	4	5	
Twice	0	2	1	3	
Thrice or more	0	1	2	3	
Total	17	21	21	59	
Leaving or being expelled / suspended from school					
Present	17	12	16	45	0,009
Absent	0	9	5	14	
Total	17	21	21	59	
Getting into trouble with law / rules					
None	16	18	17	51	0,606
Once	1	3	3	7	
Twice	0	0	1	1	
Total	17	21	21	59	
Driving without a license					
Present	0	3	3	6	0,259
Absent	17	18	18	53	
Total	17	21	21	59	
Being involved in an accident, broken bones requiring reduction					
Present	0	2	10	12	0,001
Absent	17	19	12	48	
Total	17	21	22	60	
Cigarette smoking					
Present	3	5	12	20	0,018
Absent	14	16	9	39	
Total	17	21	21	59	

* Pearson Chi-squared test, p <0,05 was significant

impulsivity (9 items), inattention (9 items), opposition/ defiance (8 items), and conduct disorder (15 items). The symptoms are scored by assigning a severity estimate for each symptom on a 4-point Likert-type scale: 0 = not at all, 1 = just a little, 2 = quite a bit and 3 = very much.

Study II (Current Study)

Sociodemographic Information and Evaluation Form: The child's age, gender, last-known psychiatric status, academic achievement, substance use, and social functionality were noted on a form developed by the study authors. The treatment duration was also noted.

Clinical Global Impression Scale: The clinician completed both the severity (CGI-S, 1 = not ill and 7 = severely ill) and the improvement subscales (CGI-I, 1 = much improved and 7 = much worse) of the Clinical Global Impression Scale (31). Lower scores reflect a reduced level of psychopathology and greater therapeutic efficacy.

Statistical Analyses

The data were analyzed using the Statistical Package for the Social Sciences-Windows, version 10.0.1. We used the frequency analyses procedure for the demographic variables. Univariate and multivariate analysis of variance (ANOVA and MANOVA) models were used for the continuous variables, and the Pearson Chi-squared test was used for the categorical variables. The Bonferroni correction was used for the pairwise comparisons. Alpha levels of 0.05 or less were considered to be significant.

RESULTS

1. Results of Study I

1.1.- Demographic and Clinical Characteristics: In the initial study (Table 1), the mean (SD) age was 9.07 years (1.92), 82 (68.3%) were males and 38 (31.7%) were females. The diagnosis and treatment groups are shown by age and gender in Table 1.

1.2.- The effects of combined treatment on ADHD, ODD, and CD symptoms: In the initial study, we found that combined treatment (parent training and stimulant treatment) was effective in reducing ADHD, ODD, and CD symptoms (Table 2).

To identify the changes in parent- and teacher-rated hyperactivity-impulsivity, inattention, opposition-defiance, and conduct disorder symptoms, a series of repeated-measures ANOVAs were conducted for each dependent measure. To identify the significant changes between baseline and the 1st, 6th, 12th and 18th month assessments, multiple within-subject pairwise comparisons were performed using the Bonferroni adjustment for multiple comparisons. Table 2 presents the baseline, 6th month, and 18th month means (SD), the results of the repeated measures ANOVAs for the 12 subscale measures and the total scores of the T-DSM-IV-S and CTRS. The results of the repeated measures ANOVAs indicated a significant treatment effect over time for each of the 14 dependent measures. However, the attention deficit (AD) teacher ratings on the T-DSM-IV-S did not show a significant improvement over time. As can be seen from the mean values of the 6th and the 18th month assessments (CTRS total score, T-DSM-IV-S parent and teacher ratings total score), the improvements continued during the ensuing months. When the baseline means were compared with the sixth month means, the effect size for the 15 dependent measures ranged from moderate (0.56) to high (2.27), with an average of 0.90. The mean baseline-to-18th-month effect sizes ranged from low (0.37) to high (1.11), with an average of 0.77.

1.3.- Comparing the effects of medication+parent training to medication only: Table 3 shows the means of the medication + parent training (Med. + PT) and the medication only (Med. Only) groups on 2 subscale measures. The effects of the treatment group (both Med. + PT and Med. Only) were investigated separately for each of the four symptom domains by a mixed-design multivariate repeated measures (three observations) analysis of variance (MANOVA) model with time as the within-group effect and the two treatment conditions as the between-group effect. There was no main effect for the treatment group in any of the four symptom domains ($F_{1.113}=.009$ and $p=.924$ for hyperactivity/impulsivity, $F_{1.113}=.171$ and $p=.680$ for inattention, $F_{1.113}=.121$ and $p=.728$ for opposition/defiance and $F_{1.113}=.537$ and $p=.465$ for conduct disorder). The pairwise comparisons

with the Bonferroni adjustment revealed no significant differences between the Med. + PT and the Med. Only groups. Only at the 1st month, there was a significant difference between the Med. + PT and the Med. Only groups on CPRS inattention and hyperactivity subscales and T-DSM-IV-S-Teacher-completed ratings opposition/defiance subscales scores. There was not any significant difference between the Med. + PT and the Med. Only groups on any subscale scores (Table 3). The effect sizes for the subscale measures ranged from moderate (0.55) to high (1.23) in the Med. + PT group and from low (0.30) to high (1.44) in the Med. Only group. Because the T-DSM-IV-S was completed by both the parents and teachers, it was possible to compare the effect sizes for teacher- and parent-completed ratings. In the Med. + PT group, the average effect size for the parent ratings on the T-DSM-IV-S was 1.08, compared to 0.64 for the teachers. In the Med. Only group, the average effect size was 1.18 for the parents and 0.57 for the teachers. In both groups, therefore, the parent ratings indicated greater improvement at home than did the teacher ratings at school.

2. Results of Study II

2.1. Demographic and Clinical Characteristics: In study II, the mean age (SD) of the 60 participating children was 16.7 years (1.73), 42 (70%) were males and 18 (30%) were females (Table 4). Thirty-four cases were ADHD+ODD, and 26 were ADHD+CD. Seventeen children received treatment for 45 months or longer, 21 children received 15-45 months, and 22 children received less than 15 months (Table 4).

2.2. The effect of treatment duration on functionality and problem domains: There was a statistically significant difference on treatment success between the groups created according to the treatment duration. A shorter treatment duration group was found to have significantly higher problems for academic underachievement (p<0.001), grade retention (p=0.026), expulsion or suspension from school (p=0.009), accidents and broken bones requiring reduction (p=0.001) and cigarette smoking (p=0.018) (Table 5). By contrast, longer treatment durations were associated with positive outcomes.

We compared the ADHD+ODD and ADHD+CD groups on all the domains and found no significant differences. We found that the initial diagnosis had no impact on the functionality domains we assessed (p>.05).

Longer treatment showed significant effects on both the symptom severity and improvement subscale scores of CGI (p<0.001).

DISCUSSION

The aim of this study was to replicate previous findings of a positive association between stimulant treatment and improved ADHD+ODD/CD symptoms in children, with subsequent improvements in academic achievement, cigarette smoking, accident rates, and rule-breaking behaviors compared to untreated adolescents.

We sought to replicate and extend these findings in our Turkish sample by using a longitudinal design. We found that ADHD treatment benefits various functional domains in children and adolescents. This study is one of the first such studies in our country. Our initial study, from 2000 to 2002, evaluated ADHD+ODD/CD cases using an 18-month follow-up. The study participants were drawn from the children who were referred to our clinic. After 6 years, we invited them to participate in additional evaluations, although most ultimately were not available or refused.

The efficacy of stimulant and combined treatment on ADHD and ODD/CD cases: In the initial study, we found that both the stimulant and the combined treatments were effective in reducing ADHD, ODD, and CD symptoms. The results of this study, which were consistent with those of the Multimodal Treatment Study of Children with ADHD (MTA), highlighted the role of stimulant medication in ADHD treatment (23,26,32).

The Med. + PT group and the Med. Only group did not differ in treatment efficacy, and this result is consistent with other studies (33,34). As stated in the MTA study and in Abikoff et al. (2004), close and regular monitoring of the treatment regimen with consistent information-gathering from parents and teachers increases treatment success (35). Our results are consistent with these findings. We followed all of the cases and collected the forms diligently, irrespective of the parent training. We think that this close follow-up may have lessened the difference in treatment efficacy between the Med. + PT and Med. Only groups. In both groups, the parent ratings on the T-DSM-

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IV-S showed more improvement at home than the teachers observed in school, indicating that parents may overestimate the improvement in their children. The average effect size for the parent ratings was quite a bit higher than that for the teacher ratings, indicating greater improvement in disruptive behavior at home. This finding may be attributed to the guidance provided to the parents during the evaluations and the training to improve their interactions with their children at home. In this case, it should be noted that the effects of parent training that focused on the parent-child relationship at home were not generalized to the child-teacher relationship at school.

The treatment effect on prognosis: As stated, the main aim of this study was to estimate the importance of treatment continuity in various domains. It is known that ADHD and comorbid CD/ODD symptoms can negatively affect multiple functional domains. We investigated academic success, grade retention, expulsion or suspension from school, disciplinary punishment, accident and plaster treatment, driving without a license, and cigarette smoking. With the exception of the "driving without a license" and "getting into trouble with laws/rules" domains, the treatment duration was significantly related to improvements in all of these areas.

Our study found that the adolescents who discontinued treatment had less improvement in academic achievement, grade retention, expulsion, or suspension from school and disciplinary punishment. The relationship between ADHD and academic failure is well documented in the literature, which emphasizes the impact of the ADHD core symptoms and related executive dysfunction on academic achievement (5,6,7,36).

Children with ADHD have been shown to have poor academic functioning, with poor reading and math scores, learning disabilities, repeated grades, placement in special education, and increased need for academic tutoring (7,37,38). Prospective follow-up studies into adolescence and adulthood have also reported significantly higher rates of grade retention, placement in special education classrooms, and school dropout and expulsion relative to peers, in addition to lower rates of high school graduation and post-secondary education (5,39). In their general population-based longitudinal study, Galera et al. (2009) have recently found that hyperactivity-inattention symptoms independently predicted grade retention, failure to graduate from secondary school, obtaining a lower-level diploma, and lower academic performance (40). They found that negative academic outcomes were also significantly associated with childhood symptoms of conduct disorder, even after accounting for adjustment variables (40). In their study, children with high levels of hyperactivity-inattention symptoms were more than two to three times more likely to display negative academic outcomes than those with fewer symptoms. Interestingly, this association was independent of other predictors (particularly CD symptoms and low socio-economic status) and also remained present after considering school difficulties prior to the baseline (40).

Some researchers have suggested that CD symptoms account for the risk of poor academic achievement and that a link exists between CD and academic underachievement beyond ADHD (6,40). Galera et al. (2009) have suggested that CD core symptoms, such as serious violations of rules, can lead to school failure through noncompliance with basic social and academic rules, truancy from school, and repeated exclusions (40). Below average verbal intelligence, substance use disorders, and environmental risk factors are listed as other probable moderators between CD and poor academic performance (40,41). However, some authors have reported that when ADHD comorbidity is taken into account, the relationship between CD and academic underachievement disappears, and CD is no longer a specific predictor of poor academic outcomes, suggesting that the association with academic problems may be mediated by attention deficits (42,43).

Our children had ADHD+ODD or ADHD+CD, and the initial study was a clinical study. We did not observe a diagnosis effect (for ODD or CD) on academic problems, but a longer treatment duration significantly improved the academic performance and related factors. Our participants were clinical cases, and we did not include only ADHD children in our study because of our main aim. Therefore, we cannot say whether CD alone was a risk factor for academic problems, leading to one of the limitations of our study. However, the positive effects of continuing treatment in our group were clear. Although Galera et al. (2009) has emphasized that anxiety/depression and ODD symptoms do not confer a higher risk of negative academic outcomes in adjusted models, internalizing problems such as anxiety and depression should be considered a risk for negative academic outcomes (40,44,45). Another limitation of our

study is that we did not evaluate the comorbid internalizing symptoms of these children using structured interviews.

In addition to its efficacy for the core ADHD symptoms, stimulant treatment has been shown to improve academic productivity and to increase short-term academic success (21,22). Nevertheless, studies of the long-term effects on academic functioning are limited (7). In addition, a new study has found that stimulant treatment can lessen psychiatric comorbidity and the risk of academic underachievement (24). Our findings support these studies and show the importance of regular treatment continuity for academic functioning. This continuity is important because poor academic achievement is a persistent correlate of low self-esteem, interpersonal difficulties and antisocial behaviors, putting individuals on adverse trajectories and leading to lower occupational status, higher use of social welfare, higher rates of incarceration, and a greater burden on society (40,46).

We found higher rates of cigarette smoking in the subjects who discontinued the treatment. This finding is consistent with other reports in the literature indicating that adolescents and adults with ADHD are at higher risk for SUD (25,47,48). Galera et al. (2010) have suggested that children who have significant symptoms of both hyperactivity-inattention and conduct disorder are at increased risk for early substance initiation (18). Adolescents with ADHD use substances more frequently than their peers without ADHD (5,49,50). In adolescent follow-up studies, the absence of consistent stimulant treatment is associated with higher rates of cigarette smoking (51). In their prospective follow-up study, Mannuzza et al. (1989) have suggested that CD comorbidity is a major risk factor for early substance use initiation in ADHD adolescents (52). Comorbid antisocial behaviors, bipolar disorder, eating disorders, severe symptoms of ADHD and/or CD, and quitting school are all related to SUD risk in ADHD children (25).

Some researchers have found that after controlling for CD, only an ADHD diagnosis is significantly related to cigarette smoking or the early onset of tobacco use (47,53). However, others have highlighted the importance of the composite effects of ADHD and CD. For example, the risk of substance use in adolescents with both ADHD and CD is higher than that of individuals who have only one diagnosis or no diagnosis (54). This hypothesis is supported by the notion that individuals with both ADHD and CD

may form a particular subgroup, distinct from ADHD alone or CD alone, with a distinct typology and greater risks for negative outcomes (18). The studies that have examined the ADHD-by-CD interaction have found higher rates of substance use and dependence in ADHD that is comorbid with CD (51,55,56,57). Follow-up studies have reported differing results with respect to the role of ADHD independent of CD (18). In their prospective follow-up study, Mannuzza et al. (1989) have suggested that CD comorbidity is a major risk factor for early substance use initiation in ADHD adolescents (52). Boyle et al. (1992) and Loeber et al. (1999) have reported that an ADHD diagnosis alone is not a relevant factor for substance use (4,58). Significant hyperactivity-inattention, conduct disorder, and disruptive-behavior symptoms have been found to predict early initiation of tobacco and cannabis use (18).

Our sample included adolescents with ADHD and CD/ODD. We did not find differences in smoking behavior between the comorbid diagnoses, but we did note the important role of treatment duration. Some studies have found that treating childhood ADHD with stimulants lessens the risk of later SUD (25,48).

We can say that childhood and adolescent ADHD, when untreated and comorbid with CD, increases the risk of cigarette smoking and early smoking. Given that tobacco initiation is a critical gateway to other substance use, screening disruptive symptoms and first use of substance in order to propose adequate support and management may help reduce the risk that adolescents will become adult substance users (18). Adolescents with CD and/or ADHD may benefit from early medical or psychosocial interventions before or after substance use initiation (18). ADHD pharmacotherapy is a promising means to decrease adolescent cigarette smoking. Also, preventing the development or controlling the symptoms of CD can lessen smoking or relevant results (59).

We also found that those who discontinued the treatment had more accidents and treatments needing casts. ADHD children are known to have more accidents, bicycle injuries, and emergency room visits (60,61,62). Our findings are consistent with the literature and regular stimulant treatment can decrease these problems.

We did not find significant differences in legal problems or driving without a license. This negative finding may be due to the low mean age of the children in our study. We

think that it is important to follow these outcomes through adulthood.

Limitations

The data reported in our study were subject to reporting bias. Our sample size was small because of the high drop-out rates, yielding another limitation. Furthermore, our cases were relatively severe, with both ADHD and comorbid with ODD/CD. As a result, we cannot generalize these findings to ADHD-only groups. It is also possible that those who were benefitting the most remained in treatment. Finally, the use of telephone interviews may have led to an underreporting of problems. Despite these limitations, this is the first Turkish study to report on the long-term functioning and prognosis of ADHD comorbid with ODD/CD.

CONCLUSIONS

ADHD treatment is effective for Turkish children across many domains. We found that close and regular monitoring of treatment, with regular collection of information from parents and teachers, increases the success of treatment. There was a statistically significant difference in treatment success between the groups created according to treatment duration. While we found that treatment positively affected functioning, it could also be that those whose functioning was improved by medications were more likely to remain in treatment. There were no significant differences between the ADHD+ODD and ADHD+CD groups in any of the domains. In other words, we did not find an impact of the initial diagnosis (ODD or CD comorbidity) on functionality after 6 years.

Clinical Significance

Detailed evaluations of the effects of treatment continuity on the clinical course of ADHD and comorbid disorders can be instructive for both clinicians and parents.

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