

Sociodemographic and Clinical Factors Affecting Treatment Adherence in Adults with Attention Deficit and Hyperactivity Disorder

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ABSTRACT

Background: This study aims to explore sociodemographic and clinical factors affecting medication adherence in adults with attention deficit and hyperactivity disorder and elicit dysfunctional domains and comorbidities with a focus on gender differences.

Methods: Patients were recruited from 2 specialty clinics using chart records in a natural treatment design. Adult attention deficit and hyperactivity disorder self-report scale, Diagnostic Interview for attention deficit and hyperactivity disorder in adults, was applied. Adherence is defined if the patient declared $\geq 80\%$ adherence to medication throughout the last 8-12 weeks.

Results: From 205 attention deficit and hyperactivity disorder patients (male=112 female=93 (age (median) min-max=29 (18-56)), 29% were non-adherent to attention deficit and hyperactivity disorder medication. In the multivariate analysis, having 2 or more comorbid disorders ($P = .009$), dysfunctions in academic/work ($P = .049$), and dysfunctions in family and other relationships ($P = .047$) increased the likelihood of adherence. Adherence rates did not significantly differ between methylphenidate and atomoxetine ($P = .405$). Women were more likely to have 2 or more comorbid psychiatric disorders ($P = .004$) and dysfunctions in social relationships ($P = .001$), free time activities, hobbies ($P < .001$), self-confidence, and self-image ($P < .001$).

Results: Nearly one-third of adult patients with attention deficit and hyperactivity disorder did not adhere to medication treatment. Comorbid psychiatric disorders and dysfunctions in life domains appear to increase the likelihood of adherence to attention deficit and hyperactivity disorder medications, possibly through increasing motivation for treatment. The effect of cognitive-behavioral therapy on compliance with attention deficit and hyperactivity disorder medication should further be explored with prospective controlled studies.

Conclusion: We suggest that future longitudinal studies use objective measures of adherence and confirm the role of dysfunctional life domains and comorbid psychiatric disorders as correlates of medication adherence.

ARTICLE HISTORY

Received: June 30, 2021

Accepted: May 26, 2022

KEYWORDS: Attention deficit hyperactivity disorder, cognitive behavioral therapy, drugs/medication, pharmacology, treatment compliance

INTRODUCTION

Decades of research have revealed attention deficit hyperactivity disorder (ADHD) as a lifelong neurodevelopmental disorder with defined genetic bases, neurochemical and structural brain abnormalities, and common symptom presentations.¹ It is considered a significant public health issue that affects millions of lives.² Attention deficit and hyperactivity disorder is presented by inattention, impulsivity, and hyperactivity³ along with deficits in executive function, emotional regulation, and motivation⁴ with onset in childhood that persists into adulthood in almost half of all diagnosed cases.⁵ Clinic presentation of ADHD is classified as combined type, predominantly inattentive type and predominantly hyper

active-impulsive type.³ Attention deficit and hyperactivity disorder affects approximately 6.8% of children, 2.8% of adolescents, and 2.5% of adults worldwide;⁶ symptoms are more debilitating in adulthood.⁷ This multifactorial disorder presents with high rates of comorbid psychiatric disorders, along with problems and complications in different domains of individual functioning.^{7,8} Academic or occupational underachievement, prolonged duration of education, financial difficulties, legal issues, increased risk of mortality due to accident or suicide, relationship or marriage problems, unplanned or teenage pregnancies, sexual dysfunctions, and sexually transmitted diseases, early onset of addiction, increased risk of health problems,

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Cite this article as: Erkan A, Kılıç Ö, Semerci B. Sociodemographic and clinical factors affecting treatment adherence in adults with attention deficit and hyperactivity disorder. *Psychiatry Clin Psychopharmacol.* 2022;32(2):107-117.



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violent behavior and exposure to violence, unemployment, inadequate parenting and difficulties in taking responsibility are more prevalent in ADHD than non-ADHD people.^{5,7}

The National Institute for Health and Clinical Excellence (NICE) Guidelines⁹ recommend a pharmacological treatment as a first-line treatment in adults if ADHD symptoms still cause a significant deterioration in at least one area of daily life despite environmental changes. The efficacy of stimulants and atomoxetine in reducing the ADHD severity symptoms in adults was demonstrated by meta-analyses of randomized-controlled trials.¹⁰⁻¹² Previous studies have indicated that the management of medication adherence is as important as the efficacy of treatment, and overall improvement can be achieved by both parameters together. Despite pharmacological treatment, some residual symptoms may be due to poor adherence to the medical regimens, which were shown to be valid for ADHD in particular, considering the nature of its core symptoms.¹³⁻¹⁵ O’Callaghan et al¹⁵ (2014) reported that the adherence rate for adults prescribed medication for ADHD is less than 12% after 3 months following an initial prescription. Compared to the other psychiatric disorders, this may be especially valid for ADHD because of the core symptoms of ADHD (e.g., inattention, disorganization, impulsivity, and forgetfulness),¹³ and this could interfere with the possible beneficial effects of pharmacological treatments.¹⁶ Drug treatment for adults with ADHD should always form part of a comprehensive treatment program that addresses psychological, behavioral, educational, or occupational needs.⁹ Psychological interventions for ADHD include a range of cognitive and behavioral approaches, psychoeducation, family/partner training, supportive approaches such as coaching, and social skills training.⁹

The fundamental objective of this research is to investigate the factors affecting medication adherence in adult ADHD patients. The secondary aim is to elicit the domains of dysfunction and comorbidities and examine whether gender differences exist regarding these characteristics.

METHODS

Design

Chart records and natural treatment of adult ADHD patients who have been followed up at 2 private clinics within a year were reviewed retrospectively.

MAIN POINTS

- Nearly one-third of adult patients with ADHD did not adhere to medication treatment.
- Having two or more comorbid psychiatric disorders and dysfunctions in the academic-work and family and other relationships domains positively affected adherence to treatment.
- The adherence to methylphenidate did not differ from adherence to atomoxetine.

Participants

Adult patients diagnosed with ADHD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 criteria and who have been followed up within the last year and at least for 12 weeks constituted the study population. Exclusion criteria were bipolar disorder, schizophrenia, and autism spectrum disorder comorbidities that may confound the diagnosis. Medical records of 213 adults with ADHD who meet the criteria mentioned above were reviewed. Five patients diagnosed with comorbid bipolar disorder were excluded. Three patients refused to participate in the study. Data of 205 patients were included in the study. The study population from the 2 clinics was similar in terms of sociodemographics and resided in the urban sites of 2 metropolitan cities of the country. In both clinics, the psychiatrists were experts in the field of ADHD, provided pharmacological and psychotherapeutic treatment where appropriate, and performed chart reviews. Data on sociodemographic and clinical characteristics, comorbidities, medications, psychosocial interventions, adherence to treatment, and domains of functional impairment were recorded.

Measures

Eligible subjects were adults with an ADHD diagnosis according to the DSM-5.³ The diagnoses were confirmed using Diagnostic Interview for ADHD in Adults Diagnostic Interview for ADHD (DIVA) 2.0¹⁷ (which was the latest Turkish version of DIVA available in Turkey in that period). The comorbidities were assessed by DSM-5, and functional impairments were assessed by comprehensive psychiatric interview and DIVA 2.0 and DSM-5.

Diagnostic Interview for ADHD in Adults

Diagnostic Interview for ADHD in Adults 2.0 (DIVA 2.0) is a semi-structured interview that consists of 2 sections: first, to assess the presence of all 18 criteria in the DSM-IV during both childhood and in the present; second, to evaluate deterioration in 5 domains of functioning (i.e., education, work, family, social/relationships, and self-confidence).¹⁷

Adult ADHD Self-Report Scale

The Adult ADHD Self-Report Scale (ASRS)¹⁸ is a self-report symptom checklist consisting of 18 items developed based on DSM-IV criteria. Six of the 18 items determined to be the most predictive of ADHD constituted part A, and at least 4 of the 6 responses that exceeded the threshold were considered positive for ASRS. Both the patient- and rater-administered versions of the scale had high internal consistency, with Cronbach’s alpha coefficients of 0.88 and 0.89, respectively. The agreement of raters as assessed by intra-class correlation coefficients between scales for total scores was (0.84). Intra-class correlation coefficients for subset symptom scores were both 0.83. The reliability of the individual symptoms was evaluated

by Kappa coefficients. Individual item agreement was acceptable (percent agreement: 43%-72%), and all items had significant kappa coefficients.¹⁹

The validity and reliability studies of the latest Turkish version of ASRS-v1.1 up to date were performed by Doğan and colleagues.²⁰ The Turkish version of ASRS has a good level of internal consistency (Cronbach's alpha=0.88), according to reliability studies. The Cronbach's alpha values for the subscales "inattention" and "hyperactivity/impulsivity" were likewise high (0.82 and 0.78). These findings imply that the Turkish ASRS is a reliable and valid tool for adult ADHD screening.²⁰

Treatment Adherence

Treatment adherence is defined as the extent to which patients take medication, as prescribed by their healthcare provider, over the period when they are persistent with medication. A patient was deemed adherent if he/she declared at least 80% adherence to the prescribed regimen during the last 3 months based on the patient's self-report.¹³ This information was collected from patients' last medical records as this was routinely questioned at every session by the attending psychiatrist.

Statement of Ethics

The study was approved by the research Ethics Committee of Hasan Kalyoncu University (804.01-E.2006220012). Our study confirms the requirements of the 1964 Declaration of Helsinki. Written informed consent was obtained from all participants. No incentives were offered.

Statistical Analysis

The data were analyzed with Statistical Package for the Social Sciences Version 26.0 software (IBM SPSS Corp.; Armonk, NY, USA). The distribution of the data has been tested with the normality test, Kolmogorov-Smirnov. Descriptive statistics were presented with n (%) for categorical variables and were shown as "median (min-max)" for non-normalized variables. Missing data were omitted on an analysis-by-analysis basis, and valid percentages were reported. Non-normalized variables were compared with the non-parametric Mann-Whitney *U* test. Categorical variables were compared with the chi-square test, Fisher's exact test, and Fisher-Freeman Halton Exact Test. In pairwise comparisons with categorical variables, Bonferroni corrected the significance level of 0.017 for 3 comparisons was used. Demographics, disorder variables, and comorbidities were subjected to binary logistic regression.

In the univariable model, associations between treatment adherence and independent variables were assessed with univariable logistic regression, and those variables that impacted treatment adherence with a *p* level of 0.10 were included in the final logistic regression model, and backward method was conducted. Odds ratios and

Table 1. Clinical Characteristics of Patients with ADHD (n=205)

	Median	Min.-Max.
Age	29	18-56
Inattention	20	7-36
Hyperactivity-impulsivity	24	9-54
Total ADHD scores	44	32-71
Pharmacotherapy	n	(%)
Methylphenidate	108	52.68
Atomoxetine	64	31.22
Methylphenidate + atomoxetine	16	7.80
No pharmacotherapy	17	8.30
Presentation type of ADHD		
Inattention	32	15.61
Hyperactivity	9	4.39
Combined	164	80.00
ADHD diagnosis during childhood	30	14.63
Family history of ADHD diagnosis	68	33.17
Referral type		
Self-referral	79	38.54
Referral from the college	3	1.46
From another doctor	75	36.59
Other	48	23.41

ADHD, attention deficit and hyperactivity disorder; min, minimum; max, maximum.

CIs were reported. In all other analyses, a *P*-value of less than .05 (2-tailed) is considered to show a statistically significant result.

RESULTS

Totally 205 patients entered the study at 2 private treatment centers. The general and clinical characteristics of patients are summarized in Table 1. The ADHD treatment in the majority of the participants was methylphenidate (MTX) (108 (52.68%)), followed by atomoxetine (ATX) (64(31.22%)) and MTX+ATX (16(7.80%)) (Table 1). Comparison of characteristics, comorbid psychiatric disorders, and adherence rates among males and females were summarized in Table 2. Mann-Whitney *U* test was used to compare age between genders. Males did not differ in age 27.5 (18-54) from females 30 (18-56) (*P*= .213). A chi-square test showed no statistically significant difference between males and females in education (*P*= .463), marital status (*P*= .474), obsessive-compulsive disorder (*P*= .171), alcohol use disorder (*P*= .054), tobacco use disorder (*P*= .608), and non-adherence to treatment (*P*= .702). The frequency of unemployment was higher in women compared to men (*P* < .001) (Table 2). The most prominent type among males, 95 (84.2), and females, 69 (74.19), was the combined presentation (*P*= .058) Table 2. The presentation type of ADHD significantly differs between

Table 2. Sociodemographic and Clinical Characteristics, Comorbid Disorders, and Adherence Rates by Gender in Patients with ADHD

	Males (n = 112)	Females (n = 93)	Total (n = 205)	P
Age (median, min-max)	27.5 (18-54)	30 (18-56)	29 (18-56)	.213
Inattention (median, min-max)	19 (7-34)	22 (8-36)	20 (7-36)	.001
Hyperactivity-impulsivity (median, min-max)	25 (11-54)	24 (9-40)	24 (9-54)	.011
	n (%)	n (%)	n (%)	P
Marital status				.474
Single	73 (65.18)	65 (69.89)	138 (67.32)	
Married	39 (34.80)	28 (30.11)	67 (32.68)	
Educational status				.463
Elementary and high school	29 (25.89)	20 (21.51)	49 (23.99)	
Bachelor and graduate school	83 (74.11)	73 (78.50)	156 (76.01)	
Vocational status¹				.002
Unemployed	5 (4.46)	19 (20.43)	24 (11.70)	
Employed	68 (60.71)	49 (52.69)	117 (57.07)	
Student	39 (34.82)	25 (26.88)	64 (31.22)	
Presentation type of ADHD²				.039
Combined	95 (84.82)	69 (74.19)	164 (79.81)	
Hyperactive/impulsive	6 (5.36)	3 (3.23)	9 (4.39)	
Inattentive	11 (9.82)	21 (22.58)	32 (15.61)	
Comorbid disorders				
Any psychiatric disorder	51 (45.54)	74 (79.57)	125 (60.98)	<.001
Depressive disorders	17 (15.18)	39 (41.94)	56 (27.32)	<.001
Anxiety disorders	29 (25.89)	47 (50.54)	76 (37.07)	<.001
Obsessive compulsive disorders	9 (8.04)	13 (13.98)	22 (10.73)	.171
Two or more psychiatric disorders	22 (19.64)	35 (37.63)	57 (27.80)	.004
Alcohol use disorders	23 (20.54)	10 (10.75)	33 (16.10)	.054
Tobacco use disorder	30 (26.79)	22 (23.66)	52 (25.37)	.608
Substance use disorders	17 (15.18)	2 (2.15)	19 (9.27)	.001
Non-adherent to treatment	31 (27.68)	28 (30.11)	59 (28.78)	.702

ADHD, attention deficit and hyperactivity disorder; min, minimum; max, maximum; IN, Inattention; HI, Hyperactivity-impulsivity; CO, Combined. "<" shows there is a significant difference between groups, "=", shows there is no significant difference between groups. For the statistical analysis:

¹The Chi-Square test, was used. Vocational status (unemployed<employed ($P = .001$), (employed, student) ($P = .712$), (unemployed<student) ($P = .001$))

²Chi-Square test, and the Fisher's Exact Test were used. Presentation type of ADHD: (IN, HI) ($P = .128$), (IN<CO) ($P = .014$), (HI, CO) ($P = .737$).

genders ($P = .039$) (Table 2). When inattention type was excluded from the comparison, there was no longer a significant difference in presentation type between genders (Fisher's Exact test, $P = .737$). A significantly higher proportion of women (21 (22.58%)) were likely to present with inattention compared to the proportion of men (11 (9.82%)) who presented with inattention ($P = .012$) (Table 2).

In data analyses, it was determined that the patients received other psychosocial interventions consisting of supportive approaches such as cognitive-behavioral approaches, psychoeducation, family/partner education, and coaching, in addition to drug therapy. Participants

undergoing Cognitive Behavioral Therapy (CBT) (103(50.24%)) received standardized CBT sessions based on the 3+3 modules model of Safren et al.²¹ In this group, after 10 weekly sessions lasting 45 minutes each, followed by 2-4 sessions every 2 weeks, the patients continued their standard ADHD medical and psychosocial follow-up procedures.

Almost one-third of all patients were found non-adherent to medication. Patients who are adherent (146(71.22%)) and non-adherent (59(28.78%)) to medication did not differ in terms of age ($P = .396$), gender ($P = .702$), marital ($P = .060$), vocational ($P = .627$), or educational status ($P = .745$) (Table 3). Presentation type of ADHD did not

Table 3. Sociodemographic and Clinical Characteristics of Adherent and Non-adherent Patients with ADHD

	Non-adherent	Adherent	P
	(n = 59)	(n = 146)	
	Median (min-max)	Median (min-max)	
Age	32 (18-54)	28 (18-56)	.396
Inattention	19 (8-28)	21 (7-36)	.010
Hyperactivity-impulsivity	24 (11-40)	25 (9-54)	.187
	n (%)	n (%)	P
Gender			.702
Male	31 (52.54)	81(55.48)	
Female	28 (47.46)	65(44.52)	
Educational status			.745
Elementary and high school	15 (25.42)	34 (23.29)	
Bachelor and graduate school	44 (74.58)	112 (28.77)	
Vocational status			.627
Unemployed	5 (8.48)	19 (13.01)	
Employed	34 (57.63)	83 (56.85)	
Student	20 (33.90)	44 (30.14)	
Marital status			.060
Single	34 (57.63)	104 (71.23)	
Married	25 (42.37)	42 (28.77)	
Cognitive behavioral therapy	23 (38.98)	80 (54.80)	.040
Presentation type of ADHD			.696
Combined	45 (76.27)	119 (81.51)	
Hyperactive/impulsive	3 (5.08)	6 (4.11)	
Inattentive	11 (18.64)	21 (14.38)	
Medication type ¹			.029
Methylphenidate	29 (26.85)	79 (73.15)	
Atomoxetine	21 (32.81)	43 (67.19)	
Methylphenidate + atomoxetine	0 (0.0)	16 (100)	
Comorbid disorders			
Any psychiatric disorder	30 (50.85)	95 (65.07)	.059
Depressive disorders	8 (13.56)	48 (32.88)	.005
Anxiety disorders	16 (27.12)	60 (41.10)	.061
Obsessive compulsive disorders	6 (10.17)	16 (10.96)	.869
Two or more psychiatric disorders	7 (11.86)	50 (34.25)	.001
Alcohol use disorders	7 (11.86)	26 (17.81)	.294
Tobacco use disorder	16 (27.12)	36 (24.66)	.714
Substance use disorder	6 (10.17)	13 (8.90)	.777

ADHD, attention deficit and hyperactivity disorder; MTX, Methylphenidate; ATX, Atomoxetine.

¹For the statistical analyses, the Chi-Square test was used. “<” shows that there is a significant difference. “,” shows there is no significant difference between groups. Adherence rates (MTX, ATX ($P = .405$), MTX < MTX + ATX ($P = .022$) ATX < MTX + ATX ($P = .008$).

differ between patients who were adherent and non-adherent ($P = .696$) (Table 3). Patients who had depressive disorders (48(32.88%)) ($P = .005$), who were diagnosed with 2 or more comorbidities (50(34.25%)) ($P = .001$), and who received standardized CBT (80(54.80%)) ($P = .040$) were more likely to be in the treatment-adherent group. The comparison of patients who received pharmacotherapy and

other psychosocial interventions' combination (consisting of psychoeducation, family/partner training, supportive approaches such as coaching) with patients who received the combination of pharmacotherapy and standardized CBT yielded the findings as shown in Table 4. Males were more likely to receive the first group of treatment (74(72.54%)), whereas women were more likely to receive

Table 4. Comparison of Patients Who Received Pharmacotherapy and Other Psychosocial Treatment to Patients Who Received Pharmacotherapy and Cognitive-Behavioral Therapy

	Pharmacotherapy and Other Psychosocial Treatments (n = 102)	Pharmacotherapy and Cognitive-Behavioral Therapy (n = 103)	P
	Median (min-max)	Median (min-max)	
Age	29 (18-56)	31 (18-52)	.002
ASRS inattention scores	18 (11-29)	23 (7-36)	<.001
ASRS hyperactivity/impulsivity scores	27 (11-54)	23 (9-38)	<.001
	n (%)	n (%)	
Gender			<.001
Male	74 (72.54)	38 (36.9)	
Female	28 (27.46)	65 (63.31)	
Adherence to medication treatment			
Yes	66 (64.71)	80 (77.67)	.040
No	36 (35.29)	23 (22.23)	
Educational status			.745
Education- high school or lower	27 (26.47)	22 (21.36)	.391
Education- university and higher	75 (73.53)	81 (78.64)	
Vocational status¹			<.001
Unemployed	8 (7.84)	16 (15.53)	.087
Employed	49 (48.04)	68 (66.02)	.009
Student	45 (44.12)	19 (18.45)	<.001
Marital status			
Single	73 (71.57)	63 (53.11)	.197
Married	29 (28.43)	38 (36.89)	
Presentation type of ADHD			.751
Combined	84 (82.4)	80 (77.67)	.402
Hyperactive/impulsive	4 (3.9)	5 (4.85)	1.000
Inattentive	14 (13.7)	18 (17.48)	.459
Comorbid disorders			
Tobacco use disorder	24 (23.53)	28 (27.18)	.548
Alcohol use disorders	16 (15.69)	17 (16.50)	.873
Substance use disorders	13 (12.75)	6 (5.83)	.088
Two or more comorbid psychiatric disorders	6 (5.88)	51 (49.51)	<.001

ADHD, attention deficit and hyperactivity disorder; min, minimum; max, maximum; ASRS, adult attention deficit and hyperactivity syndrome self-report scale.

¹For the statistical analyses, the Chi-Square test was used. “<” shows that there is a significant difference between the groups. “,” shows there is no significant difference between groups. Vocational status: (unemployed, employed) ($P = .437$), (unemployed < student) ($P < .0001$) (employed, student) ($P < .0001$).

the latter group of treatment ($P < .001$) that included standardized CBT (65(63.31%). Education status, the rates of tobacco, alcohol, and substance use disorders, and combined ADHD presentation did not differ between the 2 treatment groups (Table 4). A chi-square test that was conducted to investigate the group differences showed that adherence rates differ between the 3 medication groups MTX 79(73.15%), ATX 43(67.19%), and MTX+ATX 16(100%) ($P = .029$) Table 3. However, when MTX+ATX treatment was removed, there was no longer a difference between adherence rates to MTX and ATX ($P = .405$) (Table 3). Among

patients who were on stimulants ($n = 108$), 11 (10.19%) had substance use disorder and 21 (19.44%) had alcohol use disorder. The comorbid alcohol/substance use disorder did not lead to physical health problems; nonetheless, patients were warned to avoid simultaneous consumption of alcohol and stimulants and limit alcohol use. A total of 204 were included in the logistic regression model. In the univariable model, the associations between treatment adherence and the presence of dysfunctions in the academic-work domain and family and other relationship domains, having 2 or more psychiatric disorders, the type of the medication

Table 5. Univariable and Multivariable Analysis of Factors Affecting Treatment Adherence

	Univariable Model				Multivariable Model			
	OR	95% CI	CI	P	OR	95% CI	CI	P
Age	0.988	0.957	1.019	.439				
Gender (ref: male)	0.888	0.485	1.629	.702				
Education university and higher	1.123	0.557	2.263	.746				
Hyperactivity/impulsivity score	1.032	0.986	1.08	.179				
Inattention score	1.090	1.027	1.157	.005*	1.054	0.988	1.125	.113
Cognitive behavioral therapy	1.897	1.024	3.514	.042*	0.920	0.381	2.222	.853
Family history of ADHD	1.845	0.926	3.674	.081				
Domains of dysfunction								
Academic-work	2.279	1.067	4.867	.033*	2.256	1.005	5.061	.049
Family and other relationships	3.156	1.345	7.406	.008*	2.451	1.013	5.929	.047
Social relationships	0.720	0.580	0.900	.004*				
Leisure time activities/hobbies	1.415	0.744	2.694	.290				
Self-esteem/self-confidence	1.756	0.933	3.306	.081				
Number of dysfunctional domains	1.399	1.094	1.788	.007*	0.875	0.614	1.245	.875
Comorbidities								
Depressive disorders	3.122	1.373	7.100	.007*	1.555	0.590	4.094	.372
Anxiety disorders	1.875	0.967	3.635	.063				
Obsessive compulsive disorders	1.087	0.404	2.929	.869				
Substance use disorder	0.863	0.312	2.391	.777				
Any psychiatric disorder	1.739	0.938	3.223	.079				
Two or more psychiatric disorders	3.795	1.604	8.974	.002*	3.285	1.353	7.973	.009
Treatment								
Stimulant	1.220	0.666	2.235	.520				
Atomoxetine	0.755	0.398	1.434	.391				

ADHD, attention deficit and hyperactivity disorder; OR, odds ratio.

$R^2 = 0.13$ (Nagelkerke); 0.09 (Cox and Snell)

* = $P < .10$

treatment, inattention score, receiving CBT, number of dysfunctional domains, having a depressive disorder had a significant impact on the treatment adherence. The logistic regression model was significant, $\chi^2_{(3)} = 18.942$, $P < .001$, and it explained 13% (Nagelkerke R^2) of the variance in the whole group. Among the variables tested, dysfunctions in the academic work and family and other related domains and having 2 or more comorbid psychiatric disorders were independent factors that stayed in the subsequent steps and that significantly affected treatment adherence

(odds ratio (OR) = 2.256, 2.451, 3.285), respectively (Table 5) with an effect size of 0.30. Table 6 summarizes the comparison of domains of dysfunction in males and females. Dysfunctions in academic/occupational and family/romantic domains did not differ between females and males with ADHD ($P = .095$, $P = .063$, respectively), whereas a higher number of females had dysfunctions in free time activities/hobbies ($P < .001$) and self-confidence/self-image ($P < .001$) compared to the number of males having these dysfunctions.

Table 6. Domains of Dysfunction by Gender in Adults with ADHD

	Males	Females	Total	P
	(n = 112), %	(n = 93), %	(n = 205), %	
Academic/occupational	89 (79.50)	82 (88.17)	171 (83.41)	.095
Family/romantic relationships	94 (83.92)	86 (92.47)	180 (87.81)	.063
Other social relationships	76 (67.85)	82 (88.17)	158 (77.07)	.001
Free time activities and hobbies	65 (58.04)	78 (83.87)	143 (69.76)	<.001
Self-confidence and self-image	60 (53.57)	80 (86.02)	140 (68.29)	<.001

ADHD, attention deficit and hyperactivity disorder.

DISCUSSION

This study sought to explore factors affecting medication adherence in adult patients with ADHD and inquire into and compare domains of dysfunction and comorbidities between males and females with ADHD. We have found that almost one-third of all patients with ADHD were not adherent to medication treatment for a duration of 8-12 weeks, with no statistically significant difference between the adherent and non-adherent group in terms of age, gender, marital, and educational status. The adherence levels did not differ between MTX and ATX. Having two or more comorbid psychiatric disorders and dysfunctions in the academic-work and family and other relationships domains increase the likelihood of being adherent to treatment. This statistically significant result reflects the clinical importance of the finding, given the OR values and effect size of the relationship. Women were more likely to have two or more comorbid psychiatric disorders, whereas men were more likely to have a substance use disorder. Dysfunctions in social contacts, free time activities and hobbies, self-confidence, and self-image domains pertain to women with ADHD more than men with ADHD.

The strengths of this study include its sample being distributed equally across genders and providing sex-segregated data. Our findings on medication adherence rates to ADHD medications in adults (71.22%) were in line with what we expected but higher than the majority of the naturalistic studies in the literature.²²⁻²⁵ Wagoner et al²⁵ (2020) indicated an adherence rate of 56.7% in college students whom 98% were on stimulants. By using data from electronic medical records, Biederman et al²⁴ (2019) reported that 42% of the patients renewed their index prescriptions for a stimulant drug on time as an indication of compliance to treatment. A recent systematic review included 26 studies on treatment adherence, 13 were retrospective data analyses, 10 were patient/parent/caregiver surveys, and 3 were clinician surveys. The reported medication possession ratio – the ratio of the duration of medication supply as days to the total number of days in a determined period – was 49%-59% for stimulants for 12 months. Measurements to assess adherence were not consistent in these studies.²³ Our study considered patients who reported $\geq 80\%$ adherence to drug therapy in the last 8-12 weeks as “adherent,” similar to previous studies.¹³ We found a higher adherence rate compared to the literature. The first reason for this could be using a subjective self-report measure. Self-reports appeared to overestimate adherence rates, and non-compliance was suggested to be higher with objective rather than subjective measures. Still, self-reporting of adherence was suggested as a beneficial and timely way to assess adherence.¹⁶

The second reason could be the other psychosocial interventions, especially CBT sessions combined with medication treatment. Medical treatment for adults with

ADHD should always form part of a comprehensive treatment program that addresses psychological, behavioral, educational, or occupational needs. Psychological interventions for ADHD include psychoeducation, family/partner training, supportive approaches such as coaching, social skills training, and various cognitive-behavioral approaches.⁹ In our setting, all participants received most of the aforementioned psychosocial interventions besides pharmacotherapy. The standardized 10-14 CBT sessions based on Safren et al's²⁰ method include psychoeducation and environmental modification strategies also targeted improving organization, scheduling of activities, problem-solving, dealing with treatment-interfering behavior, social skill training, and cognitive restructuring. CBT was found effective in treating adults with ADHD, especially when combined with pharmacological therapy.^{4,9} The NICE Treatment Guidelines⁹ recommend medication as first-line therapy in adults when ADHD symptoms still cause significant impairment in at least one area of daily life despite environmental changes. For adults who benefit from medications but whose symptoms are still causing a significant deterioration in at least one area, it is recommended that non-drug therapy should be added to drug therapy. It is emphasized that this psychotherapy method should be a standard CBT program or at least include components of CBT, a structured, supportive psychological intervention focused on ADHD, providing regular follow-up and information.²⁶ Several studies have shown the positive effect of CBT on quality of life, attention-deficit symptoms, hyperactivity symptoms, and behavioral outcomes of adult ADHD, especially when combined with pharmacological treatment.⁴ Decreases in core symptoms of ADHD were reasonably consistent: in CBT plus pharmacotherapy versus pharmacotherapy alone, and CBT versus waiting list. Aakil et al²⁷ (2017) proposed an apparent beneficial effect of mindfulness-based cognitive-behavioral therapies, especially when adjunct with stimulant medication, and may increase overall compliance.

Long-term follow-up evidence, replications of the results, and extended study sites are needed to generalize the findings.^{4,28} Patients in our sample were receiving predominantly long-acting MTX (52.7%) followed by ATX (31.2%) (amphetamines are not labeled in Turkey). A few numbers of patients were on the combined treatment of MTX and ATX (7.8%). As this is not a conventional, evidence-based treatment, it was only prescribed when the functionality of the patient was inferior despite adequate therapeutic dose and duration of MTX and when patients gave informed consent after the risks and uncertainties had been explained. No difference in adherence rates was observed between MTX and ATX, which corroborates a study by Semerci et al.¹³ The ATX adherence rate in our study (67.2%) was comparable with the rates in the literature (65.9%) at 3 months post-index date.²⁸ Research has shown that adherence and persistence

to ATX treatment were high in general,²⁹ and adult patients with ADHD receiving ATX remained stable for 3 months on the medication after the index treatment.³⁰ Imagawa et al³⁰ (2018) reported a very similar rate of augmentation of ATX with alternative ADHD therapy. Factors found to influence adherence to ATX include age, gender, the description of treatment response, duration of treatment, the initial dose of medication, comorbidity, and refund. Lack of tolerability was indicated as a considerable reason for the discontinuation of the treatment.²⁹ Comorbid psychiatric disorders as factors influencing the likelihood of adherence were not investigated in earlier studies on adherence.¹³ Safren et al¹⁶ neither demonstrate any association either with depression or anxiety nor did they calculate the combined effect of 2 or more comorbid disorders.⁶ However, they demonstrated that ADHD symptoms are correlated with adherence.¹⁶ We found that inattention symptoms did not have a role in adherence. The number of dysfunctional domains and reasons for referral other than ADHD are the factors suggested for predicting adherence in the literature.¹³ Comorbid psychiatric disorders and dysfunctions in essential domains of life may have a role in motivating the patient for medication treatment. Several factors were proposed to be associated with treatment adherence to ADHD medication. Firstly, difficulties in attention, planning, and organization could play a role.²⁴ In young adults, 3 major themes were identified for adherence to ADHD treatment using a focus group and in-depth interview: (1) the patient's option to prefer the drugs, (2) the patient's choice of treatment option with or without medication, and (3) circumstances influencing the patient's preference on taking medication or not. The latter theme includes 15 factors. Dominant factors were enhancing the quality of life and improving oneself, for example, social skills.³¹

We could not demonstrate a difference between males and females regarding treatment adherence in our study, contrary to Kooij et al¹⁴ (2013), who have found that women and newly diagnosed patients seem to have a higher risk of non-adherence.

It is increasingly understood that women who have ADHD display a modified set of behaviors, symptoms, and comorbidities relative to males with ADHD.³² Our findings were in line with previous research that women experience more possibly through dysfunctions in social relationships³² and self-confidence.³¹

The main limitation of our study is that the design is based on retrospective chart records of natural treatment that hampered establishing cause-and-effect relationships. Since no clinicians' note was detected that specially addresses the impact of medication side effects on non-adherence, we could not include the side effect profile of any medications in the analysis. Evaluating adherence to participants' self-report may be subject to recall bias. We did not examine personality psychopathology. We suggest

using a practical self-report tool to screen particularly for borderline personality disorder, given the overlapping symptoms of emotional dysregulation, impulsivity, and internalizing symptoms between ADHD and borderline personality disorder.³³ Our study sample was composed of well-educated patients from high socioeconomic backgrounds from 2 private specialist clinics, which might have impacted the generalizability of the results. Domains of dysfunction would have been preferably explored with a structured method; however, such a reliable and valid measure does not exist in Turkish. Additionally, we do not know the specific reasons why participants did not take their pills. The strengths of this study include its sample being distributed equally across genders and providing sex-segregated data.

Notwithstanding these limitations, these data show that 29% of adult patients with ADHD did not take their medication for more than 20% of the time their prescription. These findings provide further evidence of low treatment adherence to ADHD medications in adults, underlining the need to understand the problem better. Future studies could benefit from examining the reasons for not taking the medications and whether psychoeducation and dialogue with the patient on all factors involved in treatment could promote optimal adherence.¹⁴ To verify our results, future multicenter and multicultural studies using objective adherence measures are needed.¹³ More research is required in order to identify interventions that could improve adherence to treatment at an early stage to ensure a better long-term prognosis.²⁹ Clinicians may help improve treatment adherence by performing psychoeducation of caregivers and patients on treatment goals, prescribing long-acting medications, and follow-up with patients to confirm if medication is still effective and well-tolerated.²³ Besides, cost-effective, accessible options are under investigation to improve adherence as recent studies provide evidence for the efficacy of an innovative text messaging-based intervention.³⁴ Although not available in many countries for adults with ADHD, long-acting transdermal formulations can be other ways of enhancing adherence by minimizing the number of doses necessary compared to conventional formulations.³⁵

CONCLUSION

Nearly one-third of adult patients with ADHD did not adhere to medication treatment. Comorbid psychiatric disorders and dysfunctions in life domains appear to positively impact treatment adherence to ADHD medications, possibly through increasing motivation for treatment. However, the effect of cognitive-behavioral therapy on compliance with ADHD medication should further be explored with prospective controlled studies. We suggest future studies use objective measures of adherence, incorporate assessment of personality psychopathology,

and confirm the importance of dysfunctional life domains and comorbid psychiatric disorders as correlates of medication adherence.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Hasan Kalyoncu University (approval no: 804.01-E.2006220012).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - A.E., O.K., B.S.; Design - A.E., O.K., B.S.; Supervision - B.S.; Resource - A.E., O.K., B.S.; Materials - A.E., O.K., B.S.; Data Collection and/or Processing - A.E., O.K., B.S.; Analysis and/or Interpretation - O.K.; Literature Search - A.E., O.K.; Writing - A.E., O.K., B.S.; Critical Reviews - A.E., O.K., B.S.

Declaration of Interests: The authors have no conflicts of interest to declare.

Funding: The authors declared that this study has received no financial support.

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