ORIGINAL ARTICLE

Oman Medical Journal [2025], Vol. 40, No. 3: e752

Clinical Features and Comparative Treatment Outcomes of Atomoxetine and Methylphenidate in Omani Adults with ADHD

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ARTICLE INFO

Article history:
Received: 12 January 2025
Accepted: 20 May 2025

Online:
DOI 10.5001/omj.2025.73

Keywords:
Attention Deficit Hyperactivity Disorder; Adult; Treatment Outcome; Atomoxetine; Methylphenidate; Outcome Assessment; Oman.

ABSTRACT

Objectives: To investigate the clinical presentation and treatment outcomes in Omani adults diagnosed with attention-deficit hyperactivity disorder (ADHD), with a focus on the efficacy of atomoxetine and methylphenidate in reducing symptoms, and identify clinical predictors of treatment response. ***Methods***: This prospective study enrolled Omani adults with ADHD receiving treatment at Sultan Qaboos University Hospital, Oman. Data on sociodemographic and clinical history were collected. Treatment response was quantified using the Clinical Global Impressions-Improvement (CGI-I) scale, after three months of initiating treatment. Statistical analysis used independent chi-square tests and *t*-tests, with a significance threshold set at $p < 0.05$. ***Results:*** Among 171 participants, 60.8% were male. The majority (80.7%) received methylphenidate, while the others (19.3%) received atomoxetine. Inattentive subtype of ADHD (66.1%) was the most common, followed by combined hyperactivity and inattention (24.0%). Most (72.5%) patients had at least one comorbidity. After three months, 83.6% of the patients showed significant improvement on the Clinical Global Impressions-Improvement scale. Response rate for methylphenidate (84.8%) was higher than for atomoxetine (78.8%). Significant predictors of treatment response were male sex (odds ratio = 2.42, 95% CI: 1.00–5.71; $p = 0.044$) and absence of a family history of ADHD (odds ratio = 2.93, 95% CI: 1.18–7.28; $p = 0.020$). ***Conclusions:*** Both atomoxetine and methylphenidate were effective in treating adult ADHD, but methylphenidate showed a higher response rate. Male sex and the absence of a family history of ADHD were associated with greater response to treatment. These factors may serve as clinical indicators for tailoring pharmacological treatment decisions for individual adult ADHD patients in Oman.

Attention-deficit hyperactivity disorder (ADHD) is a widespread neurodevelopmental condition that persists into adulthood, correcting the traditional perception of it as solely a childhood disorder.[1] Adult ADHD presents unique challenges due to its varied clinical presentations, coexisting psychiatric comorbidities, and impact on daily functioning.[1]

A systematic review and meta-analysis from 2001 to 2019 covering 40 studies from 30 countries, estimated an adult ADHD prevalence of approximately 6.8%, representing 366.3 million adults globally.[2] Another study based on the World Health Organization's World Mental Health Survey reported a prevalence of 2.8% in a sample of 26744 adults.[3]

In the Middle East and North Africa (MENA), a systematic review and meta-analysis by Al-Wardat et al,[4] found a surprisingly high adult ADHD prevalence of 13.5%— even higher than the 10.1% in children and adolescents in the region. The authors suggested that this may be due to methodological differences, but such an unusual finding underlines the need for further research on adult ADHD in the MENA region.

Oman, a Gulf Cooperation Council member state in the MENA region, has a population of about 5 million, of whom roughly 2.2 million are Omani nationals. Bedawi et al,[5] recently analyzed

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39 881 adult outpatients visiting a major referral hospital in Musat over five years, and found an ADHD prevalence of 1.8%, significantly lower than reported by Al-Wardat et al,[4] for the MENA region. This suggests that more detailed research is required to establish the prevalence of adult ADHD in the region, including Oman.

This typically involves pharmacological interventions, usually central nervous system stimulants (methylphenidate, amphetamines) or non-stimulant selective norepinephrine reuptake inhibitors such as atomoxetine. Response to these medications varies significantly across individuals, further complicating management. Mészáros et al,[6] conducted a meta-analysis of 11 double-blind clinical trials with parallel-group designs (n = 1991). They found that active medications significantly improved ADHD symptoms compared to placebo, with a standardized mean difference of 0.43 and a 95% CI of 0.24–0.62. A recent meta-analysis from Radonjic et al,[7] revealed that non-stimulant drugs such as atomoxetine were more effective in treating ADHD in adults than placebo. However, the placebo had better acceptability and tolerability. Cortese et al,[8] in a systematic review and network meta-analysis, found the most recommended ADHD medications to be methylphenidate for children and adolescents, and amphetamines for adults.

The above reviews have focused mainly on studies in industrialized countries of the Global North. Countries of the Global South—particularly those with different genetic, epigenetic, and cultural backgrounds like Oman—remain underrepresented. With most drugs being developed in the global north and their safety trials conducted in Western populations, there is a limited understanding of accurate pharmacodynamic and pharmacokinetic profiles in non-Western ethnicities and cultures. Sentinel studies are needed to examine outcomes and predictors of adult ADHD treatment with atomoxetine and methylphenidate in countries such as Oman, laying the groundwork for future interventions incorporating genetic and epigenetic factors.

In Oman, the typical first-line pharmacotherapies to treat adult ADHD are methylphenidate and atomoxetine.[5] This study addresses knowledge gaps in clinical presentation, treatment outcomes, and predictors of response of adult Omanis newly diagnosed with ADHD and routinely treated with atomoxetine and methylphenidate, through naturalistic observation.

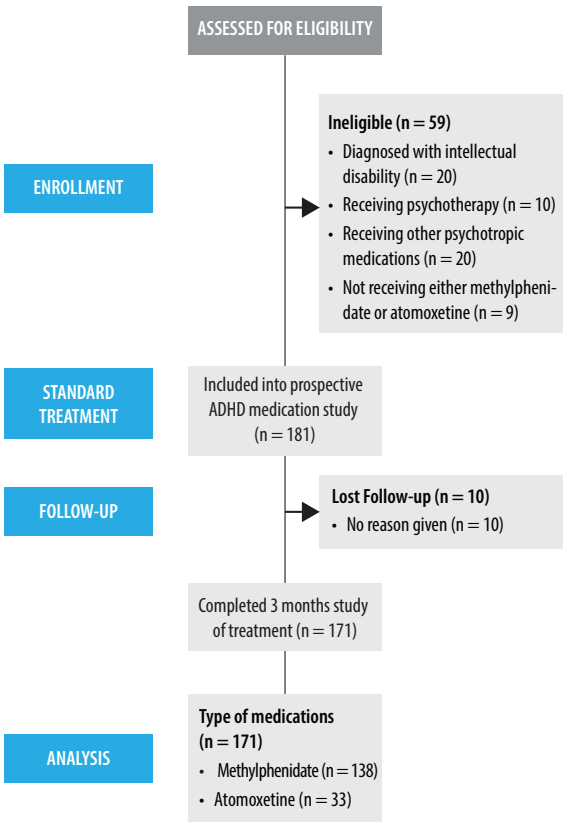
METHODS

This prospective study was conducted among consecutive attendees at the psychiatric clinic of Sultan Qaboos University Hospital, Muscat, Oman, a public sector institution where healthcare services are provided free for Omani citizens. This is also the only adult ADHD clinic in the country; however, due to logistical and travel constraints, most patients come from the urbanized Muscat capital region and its surrounding areas.

The primary outcome measure was improvement in ADHD symptoms following treatment with methylphenidate versus atomoxetine. This was assessed using the Clinical Global Impressions Scale-Improvement (CGI-I) scale, capable of detecting a moderate effect size (Cohen's $d = 0.5$) with a significance level of 0.05 and a power of 80%. Within the SD derived from previous studies,[5] the calculated sample size was approximately 90 participants per group. To account for potential dropouts and exclusions, we planned to enroll at least 120 participants attending from 1 January 2020 to 31 December 2023. This sample size was considered sufficient to detect significant clinical improvements attributable to the given ADHD medication.

All participants in this study were referred from primary or secondary healthcare facilities in Oman. The study included Omani adults (≥ 18 years) diagnosed with ADHD and who had undergone treatment for at least three months. Non-Omani were excluded. To ensure that any observed improvements could be specifically attributed to the ADHD medication used during the study, patients with psychometric evidence of comorbid intellectual disabilities were excluded if they scored below the 25th percentile on Raven's Progressive Matrices. This non-verbal test evaluates current reasoning ability and fluid intelligence.[9] We also excluded patients on other psychotropic medications, those who were not in compliance with their ADHD medications, and those undergoing other psychotherapeutic or alternative and complementary treatments. The flow chart in Figure 1 depicts the process of selection and categorization of participants.

Demographic and clinical data collected included sex, marital status, and level of education.



ADHD: attention-deficit hyperactivity disorder.

Figure 1: Flow diagram for study participants.

Body mass index was recorded in line with World Health Organization guidance, which identifies overweight and obesity as health risks.[10] Participants were also asked to report whether any member of the family had a history suggestive of ADHD or specific developmental disorders. Other background information included any history of suicidal attempts, previous forensic involvement, or prior psychiatric hospital admissions.

Psychiatric comorbidities were assessed via the Arabic version of the Mini International Neuropsychiatric Interview.[11] Specific subscales were used to determine substance dependence (alcohol and non-alcohol), bipolar affective disorder, major depressive episodes, generalized anxiety disorder, obsessive-compulsive disorder, and psychotic disorders. Remaining psychiatric diagnoses were classified collectively as 'any psychiatric comorbidity.' Personality disorders were assessed via protracted interviews and collateral history, which enabled evaluation of maladaptive personality traits, distorted perceptions of reality, abnormal behaviors, and distress across various aspects of life (e.g., work, relationships, and social functioning) where these appeared to deviate from cultural expectations in at least two areas.

The ADHD diagnosis was confirmed through a two-step process. First, a comprehensive retrospective assessment of childhood symptoms was conducted using the Wender Utah Rating Scale, a 25-item self-report checklist designed to evaluate childhood symptoms and behaviors consistent with ADHD that persist into adulthood.[12] Wender Utah Rating Scale is a Likert scale with responses ranging from 'not at all or very slightly' (score 0) to 'very much (score 4). An overall score of ≥ 46 indicates a history of childhood ADHD.[13] Second, the evaluation of current adult ADHD was acquired through the Conners Adult ADHD Diagnostic Interview for DSM-IV.[14] A senior child psychiatrist conducted is semi-structured interview.

The study adopted a naturalistic observation protocol. Our institution follows a flexible patient-centered approach. Methylphenidate, a central nervous system stimulant, is our typical first-line treatment for adult ADHD. However, atomoxetine is used as a first-line option in a minority of cases—usually for patients who do not respond to methylphenidate, have significant comorbid anxiety, or have a history of substance use disorders. Some patients prefer non-stimulants due to their extended duration of action or to avoid stimulant-related side effects. All medications are initiated at low dosages and titrated based on the individual patient's response and tolerability.

Participants were encouraged to refrain from all other treatments for ADHD during the observation period. Before starting pharmacotherapy, all participants were tested for substance misuse. This was repeated at subsequent four-weekly follow-ups to ensure that illicit drugs did not assist any improvement.

In the methylphenidate protocol, the treatment was initiated with either short or extended-release methylphenidate at 20 mg per day, gradually increasing to a maximum of 60 mg in line with the National Institute for Health and Care Excellence guidelines.[15] These recommend starting at 5–10 mg daily and titrating as needed in 5–10 mg weekly increments, up to 60 mg per day. At each four-week follow-up visit, clinicians assessed medication adherence, core ADHD symptoms, blood pressure, heart rate, weight, other mental health symptoms, functional outcomes, and adverse reactions.

In the atomoxetine protocol, the treatment began with an oral dose of 40 mg per day, which could be increased to a maintenance dose of 80 mg per day after three days.

CGI-I scale was used to document the treatment outcome.[16] This 7-point clinician-scored index compares a patient's current symptoms and overall functioning to baseline with ratings as follows: 1 = very much improved; 2 = much improved; 3 = minimally improved; 4 = no change; 5 = minimally worse; 6 = much worse; 7 = very much worse. For the purposes of this study, a positive treatment response was defined as a patient experiencing 'very good' to 'good improvement' in CGI, or a composite score of CGI-I > 2.

Data was analyzed using IBM SPSS Statistics (IBM Corp. Release 2022. IBM SPSS Statistics for Windows, Version 29.0 Armonk, NY: IBM Corp.). Continuous information was presented as mean ± SD, and categorical data as frequency and percentages. Categorical associations were compared using the chi-square test. Continuous data between groups were compared using the independent *t*-test. A *p*-value of < 0.05 was considered statistically significant.

The study was approved by the Medical Research Ethics Committee, College of Medicine and Health Sciences, Sultan Qaboos University, Muscat, Oman (Ref: MREC 2260). All participants provided their written informed consent. The study adhered to the ethical guidelines of the Declaration of Helsinki[17] and the American Psychological Association.

RESULTS

The participants comprised 171 Omani adults with a mean age of 25.8 ± 6.8 years, and a male majority (60.8%). Inattention-type ADHD was the most common clinical presentation (66.1%), followed by combined ADHD with hyperactivity and inattention (24.0%), and hyperactivity (9.9%). Substance use was found in 29.2% of the patients, and 24.0% had a family history of ADHD. Depressive disorders and anxiety disorders were found in 17.5% and 26.3% of patients, respectively, and 72.5% had at least one psychiatric comorbidity. Most patients (80.7%) were treated with methylphenidate, while 19.3% received atomoxetine [Table 1].

Table 1 also presents the treatment results on the CGI-I scale, with a significant improvement

Table 1: Baseline demographic, clinical, and treatment characteristics of Omani adults with ADHD compared with treatment response based on CGI-I (N = 171).

Variables	Total (N = 171)	Improvements		*p*-value
		Minimal/no improvement (n = 28)	Improved/very much improved (n = 143)	
Age	25.8 ± 6.8	25.1 ± 5.4	25.9 ± 7.1	0.586
Sex				
Female	67 (39.2)	16 (57.1)	51 (35.7)	0.055
Male	104 (60.8)	12 (42.9)	92 (64.3)	
BMI (n = 153)				
Underweight	18 (11.8)	3 (12.5)	15 (11.6)	0.429
Normal	71 (46.4)	13 (54.2)	58 (45.0)	
Pre-obesity	32 (20.9)	6 (25.0)	26 (20.2)	
Obesity	32 (20.9)	2 (8.3)	30 (23.3)	
Marital status				
Single	141 (82.5)	22 (78.6)	119 (83.2)	0.589
Married	30 (17.5)	6 (21.4)	24 (16.8)	
Education (n = 165)				
Less than high school	16 (9.7)	3 (11.5)	13 (9.4)	0.806
High school	66 (40.0)	9 (34.6)	57 (41.0)	
Bachelor's degree	40 (24.2)	8 (30.8)	32 (23.0)	
Master's and professionals	43 (26.1)	6 (23.1)	37 (26.6)	
Clinical presentation of ADHD				
Hyperactivity	17 (9.9)	1 (3.6)	16 (11.2)	0.262

Table 1: Baseline demographic, clinical, and treatment characteristics of Omani adults with ADHD compared with treatment response based on CGI-I (N = 171).

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Variables	Total (N = 171)	Improvements		*p*-value
		Minimal/no improvement (n = 28)	Improved/very much improved (n = 143)	
Inattention	113 (66.1)	22 (78.6)	91 (63.6)	
Mixed (hyperactivity and inattention)	41 (24.0)	5 (17.9)	36 (25.2)	
Substance use disorder				
Present	50 (29.2)	8 (28.6)	42 (29.4)	1.000
Absent	121 (70.8)	20 (71.4)	101 (70.6)	
Family history of ADHD				
Present	41 (24.0)	11 (39.3)	30 (21.0)	0.052
Absent	130 (76.0)	17 (60.7)	113 (79.0)	
Psychotic disorders				
Present	2 (1.2)	1 (3.6)	1 (0.7)	0.301
Absent	169 (98.8)	27 (96.4)	142 (99.3)	
Bipolar affective disorder				
Present	24 (14.0)	3 (10.7)	21 (14.7)	0.769
Absent	147 (86.0)	25 (89.3)	122 (85.3)	
Personality disorders				
Present	27 (15.8)	3 (10.7)	24 (16.8)	0.575
Absent	144 (84.2)	25 (89.3)	119 (83.2)	
Depressive disorders				
Present	30 (17.5)	8 (28.6)	22 (15.4)	0.106
Absent	141 (82.5)	20 (71.4)	121 (84.6)	
Anxiety disorders				
Present	45 (26.3)	11 (39.3)	34 (23.8)	0.103
Absent	126 (73.7)	17 (60.7)	109 (76.2)	
OCD				
Present	5 (2.9)	-	5 (3.5)	0.593
Absent	166 (97.1)	28 (100.0)	138 (96.5)	
Any psychiatric comorbidity				
Present	124 (72.5)	22 (78.6)	102 (71.3)	0.496
Absent	47 (27.5)	6 (21.4)	41 (28.7)	
History of scholastic developmental disorders				
Present	13 (7.6)	2 (7.1)	11 (7.7)	1.000
Absent	158 (92.4)	26 (92.9)	132 (92.3)	
Previous suicidal attempt				
Present	10 (5.8)	3 (10.7)	7 (4.9)	0.212
Absent	161 (94.2)	25 (89.3)	136 (95.1)	
Previous forensic history				
Present	1 (0.6)	-	1 (0.7)	1.000
Absent	170 (99.4)	28 (100.0)	142 (99.3)	
Previous hospital admission				
Present	12 (7.0)	3 (10.7)	9 (6.3)	0.418
Absent	159 (93.0)	25 (89.3)	134 (93.7)	
Medication for ADHD				
Atomoxetine (n = 33)	33 (19.3)	7/33 (21.2)	26/33 (78.8)	0.434
Methylphenidate (n = 138)	138 (80.7)	21/138 (15.2)	117/138 (84.8)	

ADHD: attention-deficit hyperactivity disorder; CGI-I: clinical global impressions-improvement scale; BMI: body mass index; OCD: obsessive compulsive disorder.

Table 2: Predictors of positive treatment response (CGI-I) in Omani adults with ADHD: multivariate logistic regression results (N = 171).

Variables	β	SE	*p*-value	OR	95% CI
Sex, male	0.883	0.439	0.044*	2.42	1.02 – 5.71
Absent family history of ADHD	1.076	0.464	0.020*	2.93	1.18 – 7.28
Absence of depressive disorders	0.693	0.525	0.186	2.00	0.72 – 5.59
Absence of anxiety disorders	0.507	0.475	0.286	1.66	0.65 – 4.21

**Significant; CGI-I: clinical global impressions-improvement scale; ADHD: attention-deficit hyperactivity disorder; β: regression coefficient; SE: standard error; OR: odds ratio.*

shown by 83.6% of participants. Individually, 78.8% of atomoxetine-treated patients and 84.8% of methylphenidate-treated patients improved.

Table 2 presents the multivariate logistic regression model. The overall model was statistically significant ($\chi^2 = 18.73$, df = 4, $p < 0.001$), indicating that the included predictors reliably differentiated between treatment responders and non-responders, with Cox-Snell R^2 explaining 7.0% of the variations. After adjustment, two covariates predicted a statistically significant CGI-I response to treatment: being male ($p = 0.044$) and having no family history of ADHD ($p = 0.020$). The advantages associated with the absence of depressive or anxiety disorders did not reach statistical significance [Table 2].

DISCUSSION

This naturalistic study provides insights into the routine pharmacological treatment and predictors of response among 171 Omani adults with ADHD. To our knowledge, this is the first such study in the Arabian Gulf region.

In this cohort, 60.8% were men and 39.2% were women, consistent with the global trend of higher male prevalence in ADHD in both adults and children.[18] Similarly, in community and healthcare settings, boys and men with ADHD typically display more overt hyperactivity and impulsivity—traits that are more noticed and reported by teachers, parents, and healthcare providers. Girls and women are more likely to have the inattention subtype, which is often overlooked or misdiagnosed as anxiety or depression.[19] In traditional societies such as Oman, cultural and social norms may further accentuate the apparent male predominance, due to their greater public visibility.

Inattentive type ADHD was the most common (66.1%), followed by combined (24.0%) and hyperactive (9.9%) types. Type. Previous research has also found inattentive ADHD-type in most adults.[20] Evidence suggests that these three ADHD subtypes differ in their associated cognitive profiles. For example, LeRoy et al.[21] reported that variation in memory status was the only domain that differentiated ADHD-Inattentive and ADHD-combined subtypes from controls.

Substance use disorder was present in 29.2% of participants. In a large study of 18 167 adult Swedish twins aged 20–45 years, ADHD symptoms were associated with an increased probability of all substance use disorder outcomes, including nicotine, multiple drug use, and alcohol dependence.[22] In our study, all illegal drugs were screened to control for their potential confounding effect, as substance has been hypothesized as a form of self-medication in individuals with ADHD.[23] Some researchers have proposed that the temperament of people with ADHD symptoms leans towards behavioral activation system—linked to impulsivity—rather than the anxiety-driven behavioral inhibition system. In substance abusers with ADHD symptoms, behavioral inhibition system-related traits were positively correlated with a variation in ADHD symptoms. Zayman et al,[24] suggest that substance use in this context may serve to increase pleasure and reduce symptoms of ADHD, rather than being purely impulsive behavior.

Our participants exhibited a high prevalence of comorbid psychiatric disorders (72.5%). Depressive disorders and anxiety disorders were found in 17.5% and 26.3% of the participants, respectively. More than half of a Japanese cohort of adult ADHD patients had a prevalence of at least one comorbid psychiatric condition.[25] A critical review of literature from 1978 to December 2005 found that the comorbidity rate was higher in adult patients with ADHD compared to children, with up to 80% of adults reporting at least one comorbid psychiatric disorder.[26] This could be because of complex inter-

related factors, one of which could be untreated childhood ADHD, generating maladaptive coping behavior, which may increase the chances of comorbidities in adulthood. Another reason could be differences in diagnostic methods and criteria.[27] This suggests that identification and treatment for ADHD should begin in childhood, which could reduce the chances of the development of serious comorbidities.

Regarding treatment, 80.7% of our participants received methylphenidate, and only 19.3% were prescribed atomoxetine. Improvement rates were high, at 84.8% for methylphenidate and 78.8% for atomoxetine ($p = 0.434$). Our improvement rate with methylphenidate exceeded the 76% response in a randomized controlled trial in the USA.[28] Atomoxetine treatment in the current study began with a daily dose of 40 mg, which was titrated according to patient response. A shift of medication between methylphenidate and atomoxetine was considered only after six weeks of non-response or intolerance to either drug. According to the National Institute for Health and Care Excellence guideline,[15] the suggested starting dose for atomoxetine is 0.5mg/kg/day for people under 70 kg, to be gradually increased to a maximum of 120 mg. Above 70 kg, the recommended initial dose is 40 mg daily. We did not find a significant association between the type of medication and the results of treatment, in line with previous studies.[29]

In this study, the absence of a family history of ADHD was a significant predictor of response to medications. This is corroborated by a previous study, which correlated a family history of ADHD with non-adherence.[30] Furthermore, non-adherence was associated with poorer response and lower improvement in the CGI-ADHD scale.[30] This indicates a possible genetic influence on treatment outcomes in the Omani adult ADHD population, and adds valuable data useful for the ongoing research on the interplay between genetic and environmental factors in ADHD.[31]

Our study showed that men had a slightly higher improvement compared to women, which is consistent with previous research that revealed that women feel more impaired than men with similar levels of symptoms.[32] Furthermore, men have a higher density of dopamine receptors,[33] which is the main target of ADHD medications. These biological differences highlight the importance of considering sex-specific factors in ADHD management, for which more research is needed.

Furthermore, our participants without anxiety showed greater improvement, which aligns with previous research suggesting that comorbid anxiety and bipolar disorders are associated with a decreased response to treatment,and a worse clinical presentation.[34,35]

The modest explanatory power of our regression model ($\approx 7.0\%$) highlights the multifactorial nature of treatment outcomes in adult ADHD. Although identified factors provide valuable information, additional unexplored variables can contribute to the remaining variance, including genetic markers, psychosocial factors, and medication adherence. Future research could investigate these aspects to refine predictive models and improve our understanding of the factors that influence response to treatment.

This prospective study had limitations. First of all, it was constrained by its non-interventional design, which precluded the assessment of causal relationships. Ideally, a randomized controlled study would have been more robust, and this would require attention in the future. However, by including all Omani adult patients from the country's only ADHD clinic, this study provides a comprehensive view of routine clinical practice, which could reflect the generalizability of our research results. These findings provide practical guidance to clinicians and increase existing knowledge on the treatment outcomes of ADHD medication regimens.

CONCLUSION

This study found an overall 83.6% improvement rate in adult ADHD in Oman as measured by the CGI-I scale. Methylphenidate showed a higher but non-significant treatment response compared to atomoxetine. There was a high prevalence of comorbid conditions, highlighting the importance of adopting a comprehensive treatment approach that addresses both ADHD symptoms and any concurrent mental health problems. By recognizing and treating comorbidities along with ADHD, clinicians can optimize outcomes and improve overall patient well-being. Furthermore, the absence of a family history of ADHD was associated with improved response to both methylphenidate and

atomoxetine, suggesting its potential as a prognostic indicator in treatment decisions.

Disclosure
The authors declare no conflicts of interest. No funding was received for this study.

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