



Comparison of Persistence and Adherence Between Adults Diagnosed with Attention Deficit/Hyperactivity Disorder in Childhood and Adulthood

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Purpose: Long-term treatment of attention deficit/hyperactivity disorder (ADHD) is important, but adherence and persistence in practice are still suboptimal. To better understand medication compliance for ADHD, we divided adults with ADHD into groups based on their history of childhood and adolescent ADHD, and compared their characteristics, medication adherence and persistence, and associated factors.

Patients and Methods: This study included participants aged 18–23 years with claims related to ADHD (International Classifications of Diseases 10th edition, F90.0x) and anti-ADHD medication from July 1, 2017 to December 31, 2018, and with a history of any F90.0x claim(s) from January 1, 2007 to June 30, 2017 in the Korean National Health Insurance System Claims database. Participants were divided into those diagnosed with ADHD in childhood and adulthood. Persistence with or without a 30-day gap and adherence according to a medication possession ratio (MPR) >80% were calculated.

Results: There were 10,604 patients included in the study. Adults with a childhood diagnosis of ADHD showed significant male predominance, more use of National Health Insurance, and were more often treated by psychiatrists and in hospitals than those with an adulthood diagnosis. Combination therapy was the most common initial treatment in those with an adulthood diagnosis, while monotherapy with Concerta was most common in those with a childhood diagnosis. Both groups had over 60% of participants with an MPR >80% and over 50% with persistence without a 30-day gap. Treatment in a private clinic and initial monotherapy with bupropion were found to be significantly associated with adherence in both groups.

Conclusion: The significant differences found between these groups add evidence to suggest that adult with ADHD diagnosed in adulthood may be a separate entity from those in childhood. A thorough evaluation at diagnosis and treatment in private clinics may improve medication compliance in this population.

Keywords: adult ADHD, persistence, adherence, compliance

Introduction

Attention deficit/hyperactivity disorder (ADHD) is a prevalent psychiatric disorder among children and adolescents and often continues to adulthood with symptoms. Polanczyk et al reported the global prevalence of ADHD as about 5%,¹ and as 1.2% to 7.3% in adults specifically.² Pharmacotherapy in adults with ADHD is cost-effective and is often recommended as a first-line treatment.³ It is a robust and safe method for the management of ADHD.⁴ In addition, long-term treatment of ADHD with medication results in better outcomes in academic and social function.^{5,6} For children and adolescents, Hong et al reported that medication compliance up to 36 months was only

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approximately 20%.^{7,8} Medication compliance is suboptimal in adults, although it is higher than that in children and adolescents. Because of its chronic nature, long-term pharmacotherapy is needed, but compliance is low.

The Diagnostic and Statistical Manual of Mental Disorders (DSM) and the 10th edition of the International Classification of Diseases (ICD-10) differ in how they define ADHD. The ICD-10 system classifies ADHD as a category of “behavioral and emotional disorders with onset usually occurring in childhood and adolescence” rather than a category of neurodevelopmental disorder, usually diagnosed within the first five years of life.⁹ In addition, the same criteria are required in adults, such as children and adolescents. Meanwhile, the DSM diagnostic criteria for ADHD in adults require a history of childhood (before 12 years of age) symptoms. However, adult-onset ADHD without a childhood history has been reported. Moffitt et al¹⁰ and Agnew-Blais et al¹¹ suggested the possibility of adult-onset ADHD. Cooper et al also found a case of adult-onset ADHD with typical childhood development and suggested that an unidentified form of ADHD might arise during adulthood.¹² It is noteworthy that the parents of 78% of subjects with childhood ADHD had forgotten the age of ADHD onset before age 12 (even though they reported the symptoms at ages 5, 7, 9, and 11 years), and 4% of parents of 35 comparison subjects falsely recalled their child as having ADHD.¹⁰ Although ADHD is a neurodevelopmental disorder, there is still some debate over whether adult ADHD is childhood ADHD diagnosed later in life or is a type of ADHD that simply has a late onset. Considering the chronic condition of ADHD, it will be helpful to compare and analyze adults with ADHD with and without childhood history to further accumulate and improve the knowledge of compliance.

The aim of this study was to investigate and characterize compliance in adults with ADHD who were diagnosed in childhood and diagnosed in adulthood using national health insurance claims data.

Materials and Methods

Data Source and Study Population

This was a retrospective study using data from the Korean National Health Insurance Service (NHIS) claims database. The diagnosis of ADHD was determined based on the presence of claims registered by the physician. An enrolment flowchart is shown in Figure 1. Cases aged 18–23 years with any ICD-10 F90.0x code and any anti-ADHD medication (Table 1) claim(s) between July 1, 2017 and December 31, 2018 were divided into groups according to the history of any F90.0x ICD-10 code claim(s) between January 1, 2007 to June 30, 2017 (Figure 1). Adults with a previous history of ICD-10 F90.0x claim(s) were considered to have been diagnosed with ADHD in childhood or adolescence (childhood group), while those without a previous history were considered to be newly diagnosed in adulthood (adulthood group). Medication use in adults with ADHD has been approved in Korea since June 2016. Data from the NHIS are available from January 1, 2007. Considering the period during which medication use in this population became popular for about one year, cases with the F90.0x code were targeted from July 1, 2017 to December 31, 2018. In particular, the age was confined to 18–23 years to define and compare the childhood and adulthood groups based on available data. This study was approved by the institutional review board of Myongji Hospital (MJH 2019-05-014).

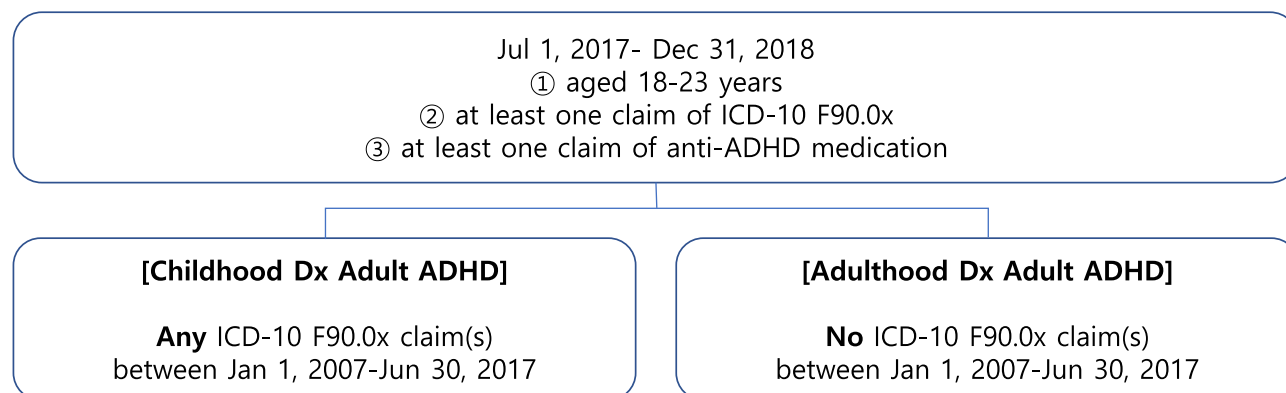


Figure 1 Flow of sample grouping.

Abbreviations: ADHD, attention deficit/hyperactivity disorder; Dx, diagnosis; ICD-10, International Classification of Diseases, 10th edition.

Table I Characteristics of Adult Patients Diagnosed with Attention Deficit/Hyperactivity Disorder in Adulthood and Those Diagnosed in Childhood

			Adulthood Diagnosis				Childhood Diagnosis				Total	p-value
			n	%	n	%	n	%	n	%		
Sex			Male		Female		Male		Female			
			1328	54.61%	1104	45.39%	6228	76.21%	1944	23.79%	M 7556	<0.0001
											F 3048	
Age	18		345	48.3%	370	51.7%	2043	75.3%	671	24.7%	3429	<0.0001
	19		235	62.5%	141	37.5%	1419	77.5%	411	22.5%	2206	
	20		205	59.4%	140	40.6%	1023	79.7%	260	20.3%	1628	
	21		209	59.9%	140	40.1%	703	75.8%	225	24.2%	1277	
	22		164	51.6%	154	48.4%	575	73.6%	206	26.4%	1099	
	23		170	51.7%	159	48.3%	465	73.1%	171	26.9%	965	
	Mean (standard deviation)		20.07(1.79)				19.65(1.62)					<0.0001
			n		%		n		%			
Region												
	Others		1161		47.74%		3688		45.13%		4849	0.0234
	Urban		1271		52.26%		4484		54.87%		5755	
Insurance												
	National Health Insurance		2301		94.61%		7509		91.89%		9810	<0.0001
	Medical Aid		131		5.39%		663		8.11%		794	
Clinician's specialty												
	Psychiatry		2281		93.79%		7891		96.56%		10,172	<0.0001
	Others		151		6.21%		281		3.44%		432	
Treatment facility												
	Hospital		630		25.90%		2767		33.86%		3397	<0.0001
	Private clinic		1802		74.10%		5405		66.14%		7207	
Medication at initiation												
	Monotherapy	Penid	245		10.07%		498		6.09%		743	<0.0001
		Medikinet	25		1.03%		100		1.22%		125	
		Bisphentin	2		0.08%		60		0.73%		62	
		Concerta	689		28.33%		3283		40.17%		3972	
		Atomoxetine	269		11.06%		913		11.17%		1182	
		Bupropion	76		3.13%		172		2.10%		248	
		Clonidine	12		0.49%		39		0.48%		51	
	Combination or augmentation		1114		45.81%		3107		38.02%		4221	
Total			2432		22.93%		8172		77.07%		10,604	

Study Variables

Medication

Methylphenidate (Penid, Medikinet, Concerta, Metadate CD, Bisphentin), atomoxetine, bupropion, and clonidine are used to treat ADHD. While these 8 types of anti-ADHD medications are all available in Korea, Metadate CD, Bisphentin, and clonidine are not approved for adults with ADHD in Korea.

Persistence and Adherence

Persistence was defined as the number of days of continuous therapy (without a 30-day gap) during the post-index period (from the index date to the last date of medication prescription). Adherence was calculated using the medication possession ratio (MPR). The MPR reflects the number of days for which patients were in possession of their prescribed medication. In this study, the MPR was calculated by summing the daily supply and dividing by the treatment period.

Covariates

Information regarding sociodemographic factors, such as age, sex, type of insurance, region of residence, and medical factors (including hospital level and clinician specialty), were obtained from the Health Insurance and Review Assessment (HIRA) database. The insurance types were classified into two categories: National Health Insurance (NHI) and Medical Aid. Clinicians' specialties were categorized as psychiatry and others (non-psychiatry). Hospitals were classified as either hospitals or clinics.

Statistical Analysis

Descriptive statistics and chi-squared tests were used to assess medication use and clinical and demographic variables. Student's *t*-tests were used to compare the adulthood

and childhood groups. The chi-squared test and Cochran-Mantel-Haenszel tests were used to assess persistence and adherence. To investigate the factors associated with adherence and persistence, multivariate logistic regression analysis was employed. SAS 9.3 (SAS Institute, Cary, NC) was used to analyze the data. An a priori significance level of $p < 0.05$ was used for all statistical analyses.

Results

Group Characteristics

Table 1 shows the demographic characteristics of the 10,604 study participants. After stratification, 8172 (77.06%) were assigned to the childhood group and 2432 (22.94%) to the adulthood group. The childhood group showed significant male predominance compared to the adulthood group ($p < 0.0001$). Most participants in both groups lived in urban areas, with significantly more living in urban in the childhood group ($p = 0.0234$). Most participants in both groups used NHI for insurance, with significantly more using NHI in the adulthood group ($p < 0.0001$). Most adult ADHD cases were diagnosed by psychiatrists (95.92%). The proportion of patients diagnosed by non-psychiatrists was significantly higher in the adulthood group than in the childhood group (6.21% vs 3.44%; $p < 0.0001$). Most adult ADHD patients were treated in private clinics (67.96%), with significantly more patients in the adulthood group than in the childhood group ($p < 0.0001$). There were significant differences between groups in first prescribed anti-ADHD medications ($p < 0.0001$). Most participants in the childhood group were initially prescribed Concerta (40.17%), followed by combination therapy (38.02%), atomoxetine (11.17%), Penid (6.09%), bupropion (2.10%), and

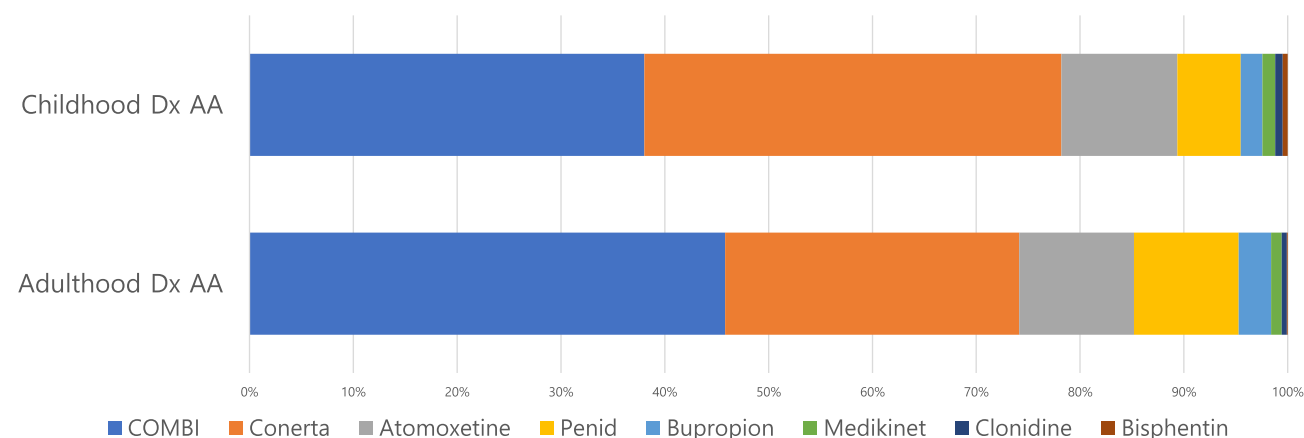


Figure 2 Anti-attention deficit/hyperactivity disorder medication at treatment initiation.

Table 2 Medication Persistence in Adult Patients Diagnosed with Attention Deficit/Hyperactivity Disorder in Adulthood and Those Diagnosed in Childhood

			Age						
			18	19	20	21	22	23	
Adulthood diagnosis	Total	N	251	133	131	136	126	124	901
		Mean	135.43	132.96	142.66	138.82	147.58	125.4	136.95
		(SD)	121.92	114.77	131.99	130.17	125.38	128.57	124.91
		Median	129	109	120	117	134	87.5	118
		(IQR)	0–220	50–217	0–209	0–196	46–231	0–202.5	0–219
	Male	N	123	73	70	81	59	58	464
		Mean	138.95	141.64	138.76	142.15	150.73	111.72	138
		(SD)	126.91	121.77	141.22	135.19	125.82	120.94	128.75
		Median	133	109	117	110	136	75.5	112
		(IQR)	0–224	49–238	0–204	0–189	50–248	0–175	0–219
	Female	N	128	60	61	55	67	66	437
		Mean	132.05	122.4	147.13	133.93	144.81	137.41	135.83
		(SD)	117.32	105.66	121.56	123.46	125.88	134.69	120.85
		Median	119	110.5	129	121	131	110.5	119
		(IQR)	0–210.5	53–179.5	51–241	0–251	0–225	0–246	0–212
Childhood diagnosis	Total	N	1055	797	579	411	347	262	3451
		Mean	201.53	219.75	209.93	202.07	200.25	193.49	206.47
		(SD)	124.96	121.21	126.78	135.27	131.87	127.1	126.74
		Median	188	219	196	184	189	187	196
		(IQR)	105–273	136–293	112–287	104–275	99–286	96–282	110–283
	Male	N	773	601	448	298	250	177	2547
		Mean	200.69	219.25	213.07	203.6	205.57	194.68	207.65
		(SD)	125.07	122.42	124.52	139.22	130	127.37	126.88
		Median	182	217	198.5	183.5	194	186	195
		(IQR)	105–272	133–299	120.5–292.5	101–286	109–290	98–280	111–286
	Female	N	282	196	131	113	97	85	904
		Mean	203.8	221.29	199.18	198.02	186.55	191	203.15
		(SD)	124.88	117.72	134.13	124.75	136.31	127.26	126.37
		Median	197	223.5	191	184	174	193	196
		(IQR)	112–278	147–284	91–275	115–259	88–265	93–283	104.5–275.5
p-value	Total		Adulthood diagnosis			Childhood diagnosis			<0.0001

Abbreviations: SD, standard deviation; IQR, interquartile range.

Table 3 Medication Adherence of Adult Patients Diagnosed with Attention Deficit/Hyperactivity Disorder in Adulthood and Those Diagnosed in Childhood

Sex	Adulthood Diagnosis														Subtotal	TOTAL
	F															
	M						F									
Age	18	19	20	21	22	23	Subtotal		18	19	20	21	22	23		
MPR >70%	258 74.8%	179 76.2%	152 74.1%	145 69.4%	121 73.8%	132 77.6%	987 74.3%	275 74.3%	97 68.8%	93 66.4%	95 67.9%	99 64.3%	116 73.0%	775 70.2%	1762 72.5%	
MPR >80%	223 64.6%	159 67.7%	138 67.3%	125 59.8%	103 62.8%	115 67.6%	863 65.0%	239 64.6%	86 61.0%	76 54.3%	86 61.4%	87 56.5%	103 64.8%	677 61.3%	1540 63.3%	
MPR >90%	178 51.6%	119 50.6%	119 58.0%	98 46.9%	84 51.2%	91 53.5%	689 51.9%	190 51.4%	65 46.1%	67 47.9%	66 47.1%	70 45.5%	78 49.1%	536 48.6%	1225 50.4%	
TOTAL	345	235	205	209	164	170	1328	370	141	140	140	154	159	1104	2432	
Sex	Childhood Diagnosis														Subtotal	TOTAL
	F															
	M						F									
Age	18	19	20	21	22	23	Subtotal		18	19	20	21	22	23		
MPR >70%	1575 77.1%	1086 76.5%	759 74.2%	513 73.0%	419 72.9%	354 76.1%	4706 75.6%	485 72.3%	297 72.3%	188 72.3%	155 68.9%	137 66.5%	119 69.6%	1381 71.0%	6087 74.5%	
MPR >80%	1351 66.1%	920 64.8%	649 63.4%	436 62.0%	367 63.8%	315 67.7%	4038 64.8%	417 62.1%	261 63.5%	157 60.4%	131 58.2%	112 54.4%	98 57.3%	1176 60.5%	5214 63.8%	
MPR >90%	1038 50.8%	688 48.5%	483 47.2%	356 50.6%	302 52.5%	240 51.6%	3107 49.9%	332 49.5%	204 49.6%	116 44.6%	93 41.3%	86 41.7%	78 45.6%	909 46.8%	4016 49.1%	
TOTAL	2043	1419	1023	703	575	465	6228	671	411	260	225	206	171	1944	8172	

Abbreviation: MPR, medication possession ratio.

Medikinet (1.22%). Most participants in the adulthood group were initially prescribed combination therapy (45.81%), followed by Concerta (28.33%), atomoxetine (11.06%), Penid (10.07%), bupropion (3.13%), and Medikinet (1.03%) (Figure 2).

Persistence and Adherence

The first 30-day gap occurred 136.95 ± 124.91 days and 206.47 ± 126.74 days after treatment initiation in the adulthood and childhood groups, respectively (Table 2). The timing of this gap was significantly different between groups ($p < 0.0001$) (Table 2). The proportions of medication persistence without a 30-day gap were 62.95% and 57.77% in the adulthood and childhood groups, respectively. An MPR of 80% was achieved in 63.3% and 63.8% of the adulthood and childhood groups, respectively (Table 3 and Figure 3).

Associated Factors Affecting Adherence

The results of the multivariate logistic regression analysis of adherence (MPR >80%) are presented in Table 4. Treatment in a private clinic and initiation with combination medication were significantly associated with an MPR >80% (odds ratios, 1.37 and 1.710, respectively) in the adulthood group. In the regression analysis excluding non-persistent participants, treatment in a private clinic and initial treatment with bupropion were significantly associated with an MPR >80% in both groups (Table 4).

Discussion

This is the first study to compare the characteristics of adults with ADHD diagnosed in childhood or adolescence and those diagnosed in adulthood. Specifically, pharmacotherapy compliance was identified using NHIS claims data in terms of both persistence and adherence. This study

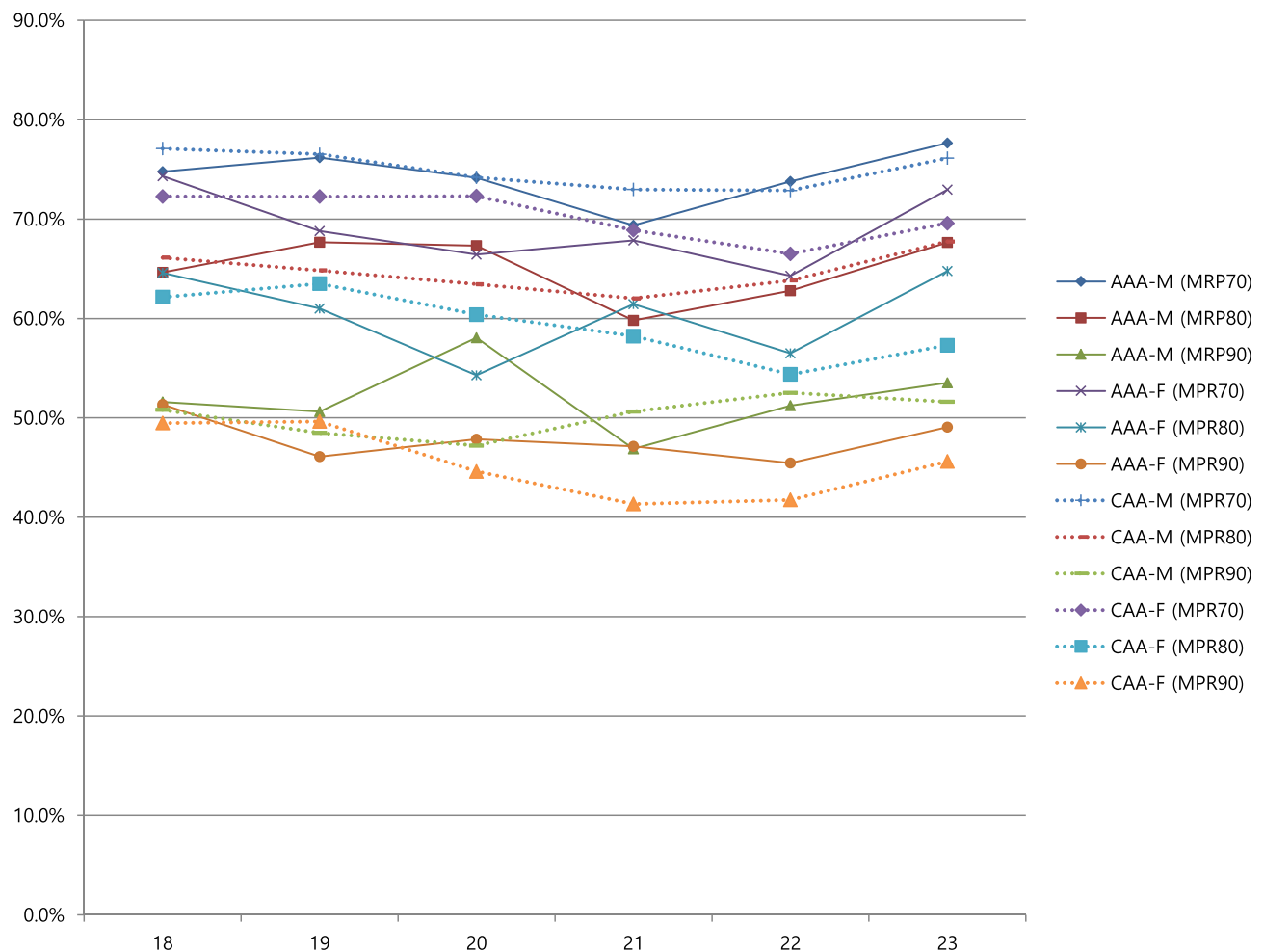


Figure 3 Medication adherence of adult patients diagnosed with ADHD in adulthood and those diagnosed in childhood.

Abbreviations: ADHD, attention deficit/hyperactivity disorder; AAA, Adulthood diagnosis of ADHD; CAA, Childhood or adolescent diagnosis of ADHD; M, male; F, female; MPR, medication possession ratio.

Table 4 Multivariate Logistic Regression Analysis of Factors Associated with Medication Possession Ratio of at Least 80%

		MPR 80%							
		Adulthood Diagnosis				Childhood Diagnosis			
		OR	95% CI		p-value	OR	95% CI		p-value
Sex	(ref=male)								
	Female	1.049	0.778	1.414	0.7531	0.907	0.703	1.171	0.4541
Age	(ref=18)								
	19	0.916	0.58	1.448	0.708	0.889	0.668	1.184	0.4227
	20	1.099	0.687	1.757	0.6944	0.839	0.6	1.173	0.3036
	21	1.088	0.686	1.726	0.7199	1.182	0.838	1.667	0.3396
	22	0.992	0.612	1.606	0.9731	1.03	0.7	1.515	0.8816
	23	0.912	0.564	1.473	0.7054	0.912	0.596	1.395	0.6716
Insurance	(ref=Medical Aid)								
	NHI-employee's	0.636	0.35	1.158	0.139	1.217	0.808	1.832	0.3474
	NHI-residence	0.696	0.363	1.336	0.2763	1.545	0.985	2.424	0.0581
Clinician's specialty	(ref=psychiatry)								
	Others	0.802	0.416	1.549	0.512	0.698	0.35	1.389	0.3054
Treatment facility	(ref= hospital)								
	Clinic	1.602	1.1	2.332	0.0139	2.912	2.206	3.845	<0.0001
Region	(ref= others)								
	Urban	0.889	0.664	1.189	0.4263	0.892	0.724	1.101	0.2875
Medication at initiation	(ref=penid)								
	Medikinet	1.142	0.237	5.514	0.8684	0.609	0.203	1.827	0.3765
	Bisphentin	12.02	0.697	207.35	0.087	1.204	0.461	3.144	0.7049
	Concerta	1.684	0.924	3.072	0.0889	0.687	0.436	1.084	0.1066
	Atomoxetine	1.182	0.576	2.424	0.6487	1.081	0.651	1.796	0.7628
	Bupropion	2.513	1.008	6.261	0.048	2.365	1.241	4.508	0.0089
	Clonidine	<0.001	<0.001	>999.999	0.9824	<0.001	<0.001	>999.999	0.9766
	Combination	2.041	1.15	3.622	0.0148	0.96	0.615	1.496	0.8553

Abbreviations: MPR, medication possession ratio; OR, odds ratio; CI, confidence interval; NHI, National Health Insurance.

has great clinical implications in that it presents the results on medication compliance of adult patients with ADHD after medication use was officially approved in Korea.

The main finding of the study is that certain demographic characteristics and the first used anti-ADHD medications for patients diagnosed at childhood or adulthood were identified. Male sex, Medical Aid insurance, and a diagnosis by a psychiatrist were more prominent in the

childhood group than in the adulthood group. While combination or augmentation therapy was the most common initial treatment in the adulthood group, monotherapy with Concerta was the most common at initiation in the childhood group. The adulthood and childhood groups showed different characteristics. Our results may add evidence to suggest that adult-diagnosed ADHD may be a distinct entity from childhood ADHD.^{10,13} The compliance characteristics

of each group were also identified. The childhood group had significantly better medication persistence than the adulthood group, but there was no difference in medication adherence (MPR). Third, the factors associated with adherence (MPR >80%) in each group were identified using multivariate logistic regression analysis.

When the conventional adherence standard of MPR >80% was applied,^{14,15} treatment adherence was over 60% in both groups. In terms of persistence, over half of the participants had no 30-day gap in medications. These figures are similar to or better than previously published results.^{16,17} Zetterqvist et al found that the persistence of medication after 3 years was about 56% with Swedish national registry data.¹⁸

Interestingly, treatment in a private clinic and initial monotherapy with bupropion showed significant positive associations with adherence in our study, as both factors more than doubled the odds ratios. In particular, combination or augmentation therapy increased the odds ratio of adherence by 2.4-fold in the adulthood group. Considering that bupropion is not the first-line treatment option for ADHD and that it is usually indicated for depression, this might suggest that comorbidities coexist in these patients. The association with treatment in a private clinic compared to hospitals can be interpreted as a benefit in accessibility. Based on our findings, it can be inferred that a thorough evaluation at the beginning of treatment and the utilization of private clinics might improve adherence.

There are clear limitations in using secondary databases. As we only used information collected from the NHIS, the effects of potentially significant factors such as educational level, socioeconomic status, intelligence, and disease severity or subtypes could not be determined. This issue can be solved by linking NHIS data with hospital medical records in the future. Second, it is difficult to generalize the results of this study to all adult age groups, as it is limited to only those in early adulthood. Third, unidentified individuals who did not use medical facilities covered by NHI could not be assessed.

Despite these limitations, this study has several strengths. The dataset used in this study is representative of the entirety of Korea and covers almost 97% of the total population. Although the target adult age range was somewhat narrow (18–23 years), each individual's claim data for at least a 10-year period was screened and analyzed by strictly separating those diagnosed in adulthood from those diagnosed in childhood by limiting them to those with or without claims data of ADHD diagnosis and/or drug

claims. In addition, we included almost all types of anti-ADHD medications currently in use in Korea.

A large-scale prospective cohort design that includes non-pharmacological treatment and tracks medical utilization patterns and pathways (dropout, remission, etc) is essential for future research.

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Disclosure

The authors report no conflicts of interest in this work.

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