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국내 주의력결핍 과잉행동 장애 아동 및 청소년의 약물요법 패턴 및 지속성

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Patterns and Persistence of Pharmacotherapy for Children and Adolescents with Attention Deficit Hyperactivity Disorder in South Korea

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ABSTRACT

Objective: This study aimed to assess treatment persistence in Korean children and adolescents with attention deficit hyperactivity disorder (ADHD) and the factors influencing their adherence to ADHD pharmacotherapy. **Methods:** The study included patients between 6 and 18 years of age with ADHD who were taking various formulations of methylphenidate and atomoxetine on June 1, 2014. Patients were dichotomized as "persistent" or "non-persistent", depending on whether they continued ADHD therapy for 6 months (therapy persistence). We also investigated if the patients were taking the same medication(s) as before and also classified the patients as "medication persistent" or "non-persistent". Patient' characteristics were correlated with therapy persistence and medication persistence. Multiple logistic regression analyses were performed to assess potential risk factors for treatment persistence. **Results:** Overall, 3,317 patients were included in the analysis. A majority of patients were taking stimulants (82.0%), 16.2% were taking non-stimulants and 1.8% were taking a combination therapy of stimulants and non-stimulants. After 6 months, 2,290 patients (69.0%) continued to take medication for ADHD with 1,953 patients taking the same medication(s) as 6 months previously. Common positive factors for therapy persistence and medication persistence were identified as younger age, retardation, and developmental delay, and long-acting formulations of methylphenidate as either monotherapy or in a combination therapy may be used. **Conclusion:** ADHD medications were proven to improve academic performance and social skills of children. Collaboration between patients, parents, school staffs, and prescribers is required to improve the persistent use of ADHD medications.

KEY WORDS: Attention deficit hyperactivity disorder, therapy-persistence, medication-persistence, methylphenidate, atomoxetine

Attention deficit hyperactivity disorder (ADHD) is one of the most common chronic psychiatric disorders in children and adolescents.[1] It is characterized by prevailing symptoms of attention deficit, hyperactivity, and impulsivity.[2] The prevalence of ADHD among children and adolescents worldwide was estimated to be 3%–8%.[3-6] In Korea, the prevalence of ADHD in individuals aged 6–18 years was estimated to be between 1.99% and 13.25%.[7-10]

ADHD may affect many aspects of an individual's life, including functioning in the school environment, academic achievement, and peer and family relationships throughout a lifetime.

The neuropsychiatric comorbidities commonly observed in children and adolescents with ADHD include conduct disorder, oppositional defiant disorder, anxiety disorders, and mood disorders.[11-15] Approximately, 20–46% of children and adolescents with ADHD are estimated to have a learning disability.[15-17] Regarding the nature of ADHD, earlier detec-

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tion, and continuous treatment appear to be important throughout the treatment period.

The two major evidence-based treatments of ADHD are behavioral therapies and pharmacotherapy.[2,16,18,19] The first choice of ADHD pharmacotherapy is stimulants such as methylphenidate and amphetamines. Alternative treatments are non-stimulants such as atomoxetine, guanfacine extended release, and clonidine hydrochloride extended release.[19] ADHD medications have been proven to improve abnormal behaviors associated with ADHD and improve academic achievement, cognition, and social and family relationships.[20,21] Among these, immediate-released methylphenidate (IR-MPH), extended-released MPH (ER-MPH), osmotic-controlled release oral delivery system MPH (OROS-MPH), and atomoxetine (ATX) are the medications approved for reimbursement by the Health Insurance Review and Assessment Service (HIRA) in Korea during the study period.

Due to the chronic nature of ADHD, patients with ADHD require long-term pharmacotherapy.[22] However, substantial portion of children and adolescents with ADHD do not continue pharmacological treatment despite benefits of persistent medication adherence.[23-25] There have been limited data available regarding treatment pattern of patients with ADHD, especially in non-Western countries like Korea.

Therefore, we aimed to assess the treatment persistence of Korean children and adolescents with ADHD and its influencing factors using the real-world data.

Methods

Study Data

We analyzed the Pediatric Patient Sample data from 2014 (Serial No. HIRA-PPS-0066). The HIRA-PPS is a type of Patient Sample Data using stratified and systematic sampling methods, considering sex and age group, for all patients who used medical services in 2014.[26] The representativeness of the Patients Sample Data was verified by the HIRA and five other medical associations in Korea.[26] The HIRA-PPS contains approximately 10% of the Korean population younger than 20 years, which are about 1.1 million patients per year. The following data are available in the HIRA-PPS: diagnosis, age, sex, insurance type, institution, medical expenses, operation name, and prescription drugs.

Study Subjects

We identified patients with ADHD using KCD-6 code (Korean version of ICD-10) of F90.0. Patients aged between 6 and 18 years who were taking ADHD medications, including IR-MPH, ER-MPH, OROS-MPH, and ATX, on June 1, 2014, were included (Fig. 1). The pre-existing neuropsychiatric comorbidities of each patient were also identified using KCD-6 codes.

Treatment persistence

Treatment persistence usually refers to whether a patient continues to receive treatment. Persistence can be measured in either prospective or retrospective manner and reported as dichotomy either persistent or non-persistent at the end of the observation or a continuous variable like a number of days of continuous therapy from the initiation to the end of the study.[27] There are differences in the medication gap length defining discontinuation ranged from 15 to 180 days among studies, which can influence the persistence rate.[28] Currently, there is no general consensus available regarding the best definition or measure for treatment persistence.[29] Treatment persistence can be related to a specific medication (medication persistence) or a set of medications (therapy persistence).[30] We operationally defined “therapy persistence” as there being an ADHD prescription covering the index date of December 1, 2014, in the patient’s claim data. “Medication persistence” was defined as the same medication or regimen were continued up to the index date. Dose and schedule changes were not considered in estimating the medication persistence.

Statistical Analysis

All statistical analyses were performed using the SPSS software programs, version 23 (IBM Corporation, Armonk, NY, USA). Variables were expressed as mean or frequency value. We collected the patients’ characteristics (age, sex, insurance cover, neuropsychiatric comorbidities, and medication use) and correlated these with treatment persistence using Pearson’s chi-square tests. We performed multiple logistic regression analysis to estimate any factors that predicted treatment persistence. All statistical analyses were two-tailed, and a p-value of <0.05 was defined to be statistically significant.

Ethics statement

This study was approved for exemption by the institutional review board of Pusan National University (IRB No. PNU IRB/2018_70_HR) because the data of HIRA-PPS was de-

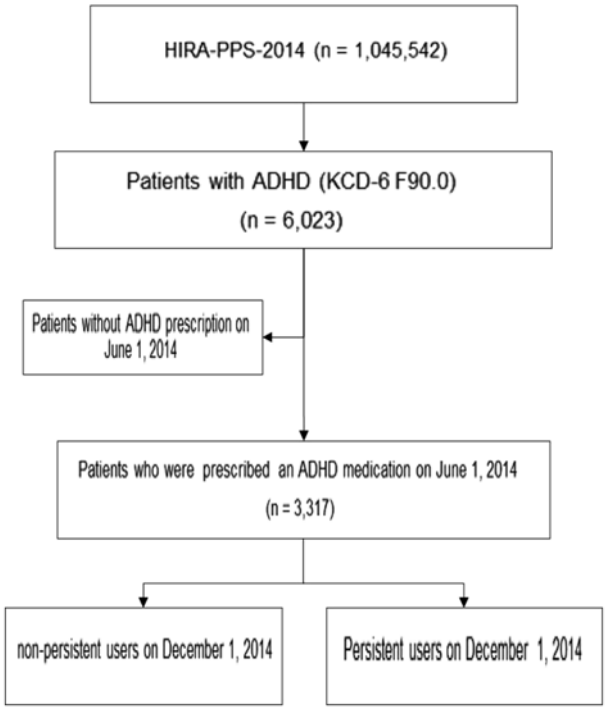

Fig. 1. Case extraction diagram

identified.

Results

A total of 3,317 patients with ADHD were included in the analysis (Fig. 1). The baseline characteristics of the study subjects are shown in Table 1. There were more children (6–12 years of age) than adolescents (13–18 years of age). The mean age (± *SD*) of the patients was 11.61±3.21 years. Males accounted for 82.0% of the study subjects. The mean age of females was slightly higher than that of males (11.96±3.39 vs. 11.54±3.17 years, $p < 0.01$). More than half of the patients (58.6%) had at least one neuropsychiatric comorbidity. The most prevalent neuropsychiatric comorbidity was depression (17.8%), followed by tic disorders (16.2%). Most patients were covered by national health insurance (NHI, 91.3%) and were prescribed stimulants (82.0%). Only 1.8% of patients received a combination therapy of stimulant(s) and ATX. The most utilized MPH formulation was OROS-MPH (37.4%) followed by ER-MPH (30.2%) (Fig. 2).

Treatment persistence

Overall, ADHD therapy persistence and medication persistence were estimated to be 69.0% and 58.9%, respectively.

Table 1. Patient characteristics

Variables	Total patients (n = 3317)	n	%
Age group	6–12	1981	(59.7)
	13–18	1336	(40.3)
Sex	Male	2720	(82.0)
	Female	597	(18.0)
Insurance	NHI	3029	(91.3)
	MedAid	288	(8.7)
Neuropsychiatric comorbidities	Bipolar disorder	215	(6.5)
	Depression	590	(17.8)
	Anxiety	408	(12.3)
	Retardation	253	(7.6)
	Developmental delay	355	(10.7)
	Conduct disorder	400	(12.1)
	Tic disorders	536	(16.2)
	Epilepsy	133	(4.0)
Meds	IR-MPH	174	(5.2)
	ER-MPH	1001	(30.2)
	OROS-MPH	1241	(37.4)
	IR & ER-MPH	101	(3.0)
	IR & OROS-MPH	168	(5.1)
	ER & OROS-MPH	36	(1.1)
	ATX	537	(16.2)
	Combination stimulants and non-stimulants	59	(1.8)

ADHD, attention deficit hyperactivity disorder; NHI, National Health Insurance; MedAid, Medical Aid Plan; IR-MPH, immediate-released methylphenidate; ER-MPH, extended-released methylphenidate; OROS-MPH, osmotic-controlled release oral delivery system methylphenidate; ATX, atomoxetine

Three hundred thirty seven patients (10.2%) continued ADHD therapy but switched their medication to a different drug or regimen. Table 2 describes the association between patient characteristics and therapy persistence and medication persistence. Children had a significantly higher persistence than adolescents in both therapy persistence (73.2% vs 62.9%, $p < 0.001$) and medication persistence (61.2% vs 55.4%, $p = 0.001$). Male patients were more likely to continue ADHD pharmacotherapy than female patients (70.1% vs. 64.7%, $p = 0.01$). Although not statistically significant, they also were more likely to continue the same regimen. Significant differences were not observed in the type of insurance. Therapy persistence was significantly associated with neuropsychiatric comorbidities such as depression (65.2%, $p = 0.025$), retardation (76.2%, $p = 0.011$), and developmental delay (77%, $p = 0.001$). In terms of medication persistence, retardation (66.0%, $p = 0.017$), developmental

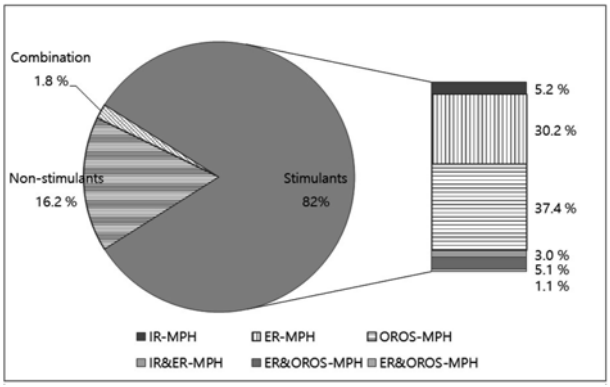

Fig. 2. Utilization of ADHD medications.

delay (67.0%, p = 0.001), tic disorder (63.1%, 0.035), and epilepsy (69.2, 0.015) showed a positive influence. Persistence was also influenced by the type of medications taken. While the user group taking short-acting MPH showed the lowest therapy persistence (58.0%), the user group taking a combination therapy of short-acting and long-acting MPH such as IR-MPH/ER-MPH or IR-MPH/OROS-MPH showed therapy persistence greater than 75%.

Predictors of therapy persistence

According to the results of multiple logistic regression analysis of therapy persistence, less discontinuation was

Table 2. Persistent users of ADHD medications

Variables		Total patients (n = 3317)	Proportion of patients therapy-persistent at 6 month (%)		*p-value*	Proportion of patients medication-persistent at 6 month (%)		*p-value*
Overall			2290	(69.0)		1953	(58.9)	
Age group	6–12		1450	(73.2)	*< 0.001*	1213	(61.2)	*0.001*
	13–18		840	(62.9)		740	(55.4)	
Sex	Male		1905	(70.0)	*0.010*	1621	(59.8)	*0.074*
	Female		385	(64.5)		332	(55.6)	
Insurance	NHI		2091	(69.0)	*1.000*	1784	(58.9)	*0.950*
	MedAid		199	(69.1)		169	(58.7)	
Neuropsychiatric comorbidities	Bipolar disorder		160	(74.4)	*0.080*	133	(61.9)	*0.390*
	Depression		385	(65.3)	*0.031*	329	(55.8)	*0.097*
	Anxiety		290	(71.1)	*0.361*	243	(59.6)	*0.788*
	Retardation		193	(76.3)	*0.009*	167	(66.0)	*0.017*
	Developmental delay		272	(76.6)	*0.001*	238	(67.0)	*0.001*
	Conduct disorder		288	(72.0)	*0.185*	235	(58.8)	*0.957*
	Tic disorders		386	(72.0)	*0.114*	338	(63.1)	*0.035*
	Epilepsy		100	(75.2)	*0.126*	92	(69.2)	*0.015*
Medication	IR-MPH		101	(58.0)	*< 0.001*	76	(43.7)	*< 0.001*
	ER-MPH		710	(70.9)		595	(59.4)	
	OROS-MPH		854	(68.8)		768	(61.9)	
	IR & ER-MPH		80	(79.2)		60	(59.4)	
	IR & OROS-MPH		131	(78.0)		105	(62.5)	
	ER & OROS-MPH		26	(72.2)		14	(38.9)	
	ATX		346	(64.4)		307	(57.2)	
	Combination of stimulants and non-stimulants		42	(71.2)		28	(47.5)	

ADHD, attention deficit hyperactivity disorder; NHI, National Health Insurance; MedAid, Medical Aid Plan; IR-MPH, immediate-released methylphenidate; ER-MPH, extended-released methylphenidate; OROS-MPH, osmotic-controlled release oral delivery system methylphenidate; ATX, atomoxetine

Table 3. Multiple Logistic Regression Analysis of Factors for Therapy- and Medication-persistence.

Explanatory variable		ADHD therapy-persistence			ADHD medication-persistence		
		adj. OR	95% CI	*p-value*	adj. OR	95% CI	*p-value*
Age group	6–12	1.629	1.393–1.904	*< 0.001*	1.295	1.119-1.500	*0.001*
	13–18 (R)						
Sex	Male	1.242	1.027–1.904	*0.026*			
	Female (R)						
Neuro-psychiatric comorbidities	Depression	0.907	0.747–1.102	*0.325*			
	Retardation	1.540	1.134–2.090	*0.006*	1.455	1.098-1.933	*0.009*
	Developmental delay	1.480	1.139–1.923	*0.003*	1.499	1.183-1.900	*0.001*
	Tic disorders				1.363	1.103-1.684	*0.004*
	Epilepsy				1.567	1.072-2.291	*0.020*
Medication	IR-MPH (R)						
	ER-MPH	1.613	1.153–2.256	*0.005*	1.834	1.320-2.547	*< 0.001*
	OROS-MPH	1.681	1.210–2.336	*0.002*	2.182	1.578-3.016	*< 0.001*
	IR & ER-MPH	2.606	1.469–4.624	*0.001*	1.779	1.076-2.940	*0.025*
	IR & OROS-MPH	3.050	1.887–4.930	*0.000*	2.453	1.583-3.802	*< 0.001*
	ER & OROS-MPH	1.844	0.832–4.088	*0.132*	0.821	0.392-1.720	*0.601*
	ATX	1.277	0.896–1.819	*0.176*	1.534	1.072-2.195	*0.019*
	Combination of stimulants and non-stimulants	1.765	0.924–3.372	*0.085*	1.093	0.600-1.994	*0.771*
c-Statistics		0.836			0.586		
p-value of Hosmer–Lemeshow test				*0.286*			*0.133*

ADHD, attention deficit hyperactivity disorder; IR-MPH, immediate-released methylphenidate; ER-MPH, extended-released methylphenidate; OROS-MPH, osmotic-controlled release oral delivery system methylphenidate; ATX, atomoxetine

observed in children (OR = 1.629; 95% CI, 1.393–1.904). More male patients continued to take medications than female patients (OR = 1.242; 95% CI, 1.027–1.904). Some neuropsychiatric comorbidities, such as retardation and developmental delay, were found to be positive influencing factors for therapy persistence. Long-acting MPH formulations (ER-MPH and OROS-MPH) as either monotherapy or combination therapy were one of the predictors of therapy persistence (Table 3).

Predictors of medication persistence

Like therapy persistence, more children continued to take the same medication than adolescents, but the odds ratio was less (OR = 1.295; 95% CI, 1.119–1.500). We were not able to see any differences in medication persistence between males and females. Four neuropsychiatric comorbidities, including retardation, developmental delay, tic disorder, and epilepsy were positive influencing factors for medication persistence. Long-acting MPH formulations (ER-MPH and OROS-MPH) as either monotherapy or combination therapy were found to be one of the predictors of medication persistence (Table 3).

Discussion

This study explores the patterns and persistence of ADHD pharmacotherapy in Korean children and adolescents and their influencing factors.

We found that stimulants were the most utilized pharmacotherapy, followed by non-stimulants and the combination therapy of MPH and ATX. Among the stimulants, ER-MPH and OROS-MPH were the two most prescribed formulations.

Treatment persistence of children and adolescent with ADHD in Korea was estimated 69% (therapy persistence) and 58.9% (medication persistence) in this study. A systematic review of 67 studies on ADHD medication persistence/discontinuation reported that persistence to ADHD treatment was low although there was variability in participants and definition of persistence/discontinuation across the studies.[22] Ayaz *et al*. indicated that medication persistence of over one year

occurred in only 30.2% of Turkish children and adolescents with ADHD.[31] Winterstein *et al*. reported that 47.4% of Medicaid beneficiaries younger than 20 years persisted at six months when allowing a 1-month gap.[32] A population-based cohort study conducted in Germany reported that approximately 20% of subjects discontinue drug treatment within the first six months of treatment initiation.[33]

According to our results, ADHD medication persistence was significantly lower in adolescents. This result was consistent with previous studies.[34-36] As adolescents develop autonomy, they are more likely to make decisions about their healthcare, with perhaps a concomitant decrease in the parents' or caregiver's management, leading to poorer persistence.[36-38]

Our study indicated that male patients are more likely to continue ADHD treatment than female patients. However, there are conflicting data regarding gender differences in ADHD medication persistence across other studies. While some studies reported that more girls continued ADHD treatment than boys, others reported the opposite pattern like ours.[33,39,40] This might be due to methodological differences among studies.

Some neuropsychiatric comorbidities were an influencing factor in treatment persistence either positive or negative way. While a previous study reported oppositional conduct disorder is the most prevalent comorbidity among Korean children and adolescents with ADHD,[36] we found depression as the most prevalent comorbidity followed by tic disorders. Consistent with previous studies, we found that patients with depression were less likely to continue ADHD pharmacotherapy.[36] Depression influences medication taking for chronic diseases such as asthma and diabetes mellitus, particularly among adolescents; [41] this might be because of the characteristics of depression such as negative expectations of treatment efficacy, reduced ability to remember to take medication, and tendency to shut oneself away.[42,43] These features might diminish the inclination of patients to take their medication.

We also found that among various neuropsychiatric comorbidities, retardation and developmental delay predict better treatment therapy and medication persistence. This finding is in line with a previous study conducted in Taiwan.[28]

Consistent with the recent literature, we found a correlation between the formulations and medication persistence.[28,31,44-51] The long-acting formulations (ER-MPH and OROS-MPH) used as monotherapy or combination therapy increased persistence. A systematic review conducted by Gajria *et al*. also reported higher persistence in patients using long-acting stimulants than short-acting stimulants.[22] Long-acting stimulants require less frequent dosing than short-acting stimulants and this might improve the overall compliance to pharmacotherapy.

Results from the logistic regression analysis of therapy persistence showed that younger age, male sex, the presence of neuropsychiatric comorbidities such as retardation and developmental delay and use of long-acting MPHs (e.g., ER-MPH, OROS-MPH, IR & ER-MPH, and IR & OROS-MPH) predicted higher therapy persistence.

Logistic regression analysis of medication persistence showed the similar results. Younger age, the presence of neuropsychiatric comorbidities (retardation, developmental delay, tic disorder, and epilepsy), and use of long-acting MPHs (e.g., ER-MPH, OROS-MPH, IR & ER-MPH, and IR & OROS-MPH) were identified as a positive predictor of medication persistence. Long-acting formulations

Gajria *et al*. suggested that there were various reasons for discontinuing ADHD medication.[52] The most common reasons for stopping ADHD medications include adverse effects, lack of effectiveness and poor adherence.[52]

There are several limitations to this study. First, we employed claim data, which did not contain certain clinical informations such as the ADHD symptom severity, treatment effects, allergy history, adverse effects, and prognosis. Second, we could not examine other influencing factors known to be related to drug utilization patterns of patients with ADHD (e.g., patient IQ, the role of social stigma, parental education level, and family history).

Conclusion

This cross-sectional study analyzed the utilization of prescription drugs among children and adolescents with ADHD. Age, gender, the presence of neuropsychiatric comorbidities, and formulations showed significant correlations with the utilization patterns and medication persistence. Patient characteristics and formulations are important factors when considering the method of long-term ADHD management to assure continuous symptomatic control. This result may be beneficial to the application of drug therapy to increase the rate of treatment persistence and provide optimum medication usage conditions for Korean children and adolescents with ADHD. Ultimately, patients, parents, school staffs, and clinicians should collaboratively endeavor to improve ADHD treatment persistence.

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We used the Health Insurance Review and Assessment (HIRA) Service's Pediatric Patient Sample 2014 (HIRA-PPS-2014-0066); however, the results are independent of the Ministry of Health and Welfare and the HIRA.

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