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Naturalistic Pharmacotherapy Compliance among Pediatric Patients with Attention Deficit/Hyperactivity Disorder: a Study Based on Three-Year Nationwide Data

Minha Hong,[1] Bongseog Kim,[2] Jun-Won Hwang,[3] Soo-Young Bhang,[4] Hyung Yun Choi,[5] In-Hwan Oh,[6] Yeon Jung Lee,[7] and Geon Ho Bahn[8]

[1]Department of Psychiatry, Myongji Hospital, Seonam University College of Medicine, Goyang, Korea; [2]Department of Psychiatry, Sanggyepaik Hospital School of Medicine, Inje University, Seoul, Korea; [3]Department of Psychiatry, Kangwon National University School of Medicine, Chuncheon, Korea; [4]Department of Psychiatry, Eulji University, College of Medicine, Seoul, Korea; [5]Department of Biostatistics, Graduate School of Public Health, Seoul National University, Seoul, Korea; [6]Department of Preventive Medicine, Kyung Hee University, School of Medicine, Seoul, Korea; [7]Department of Psychiatry, Soonchunhyang University, School of Medicine, Seoul, Korea; [8]Department of Psychiatry, Kyung Hee University, School of Medicine, Seoul, Korea

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Address for Correspondence:
Geon Ho Bahn, MD
Department of Psychiatry, Kyung Hee University Hospital, 23 Kyungheedae-ro, Dongdaemun-gu, Seoul 02447, Korea
E-mail: mompeian@khu.ac.kr

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We examined short- and long-term medication compliance among youth with attention-deficit hyperactivity disorder (ADHD), using data from the National Health Insurance database in Korea. Of the 5,699,202 6-14-year-old youth in 2008, we chose those with at least 1 medical claim containing an ICD-10 code for diagnosis of ADHD (F90.0) and no prescription for ADHD within the previous 365 days. We tracked the data every 6 months between 2008 and 2011, to determine treatment compliance among newly diagnosed, medicated patients. Further, we checked every 1 month of the 6 months after treatment commencement. Treatment continuity for each patient was calculated by sequentially counting the continuous prescriptions. For measuring compliance, we applied the medication possession ratio (MPR) as 0.6, 0.7, and 0.8, and the gap method as 15- and 30-days' intervals. There were 15,133 subjects; 11,934 (78.86%) were boys. Overall 6-month treatment compliance was 59.0%, 47.3%, 39.9%, 34.1%, 28.6%, and 23.1%. Monthly drop-out rates within the first 6 months were 20.6%, 6.5%, 4.7%, 3.7%, 3.0%, and 2.5%, respectively. When applying MPR more strictly or shorter gap days, treatment compliance lessened. This is the first nationwide report on 36-month treatment compliance of the whole population of 6-14-year-olds with ADHD. We found the beginning of the treatment, especially the first month, to be a critical period in pharmacotherapy. These results also suggest the importance of setting appropriate treatment adherence standards for patients with ADHD, considering the chronic course of ADHD.

Keywords: Attention Deficit Disorder with Hyperactivity; Medication Adherence; National Health Programs; Compliance

INTRODUCTION

In the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5), attention-deficit/hyperactivity disorder (ADHD) is included in the category of neurodevelopmental disorders (1). This seemingly supports previous studies' reports that ADHD shows chronic progression and that symptoms persist into adulthood in approximately 50% of individuals (2-7). Compared to typical adults, those with ADHD have a higher rate of substance abuse, lower education levels, and lower occupational ability (8-10). In this regard, considering the chronic progression of ADHD and the socioeconomic costs of the disease itself, long-term continued treatment is essential. However, administration of long-term treatment is difficult in practice. Of the various treatment methods that might be applicable in the long term, drug treatment is the main choice, although compliance thereto is low. Although the results of previous studies differ, due to methodological differences, 3-year long-term drug compliance for pediatric ADHD patients is approximately 30% (11-16). In particular, there are large differences in the 6-month drop-out rate, at 20% (17), 42.4% (18), and more than 80% (19), depending on the drop-out criteria. Although the treatment discontinuance rate is high, it is also not true that all pediatric patients receive medicinal treatment after diagnosis of ADHD. In a previous study (20), the proportion of patients starting drug treatment after ADHD diagnosis was 69%, and studies in the United States using a birth cohort or a local community sample have found drug treatment rates of 59%-73% (21-23).

Various methods are used to assess continuation of drug treatment, including the medication possession ratio or "MPR" (24-

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26) and gap days (27). In a previous study on a small sample (18), authors suggested that it was not appropriate to apply the same criteria for drug treatment in psychiatry, particularly pediatric ADHD, as those applied to other chronic diseases, such as hypertension. At the same time, authors proposed the need for verification in a larger sample.

Hence, following from the previous study, in this study, we analyzed 3-year treatment continuation rates in a large group, using data from the Health Insurance Review and Assessment Service (HIRA), and identified differences in compliance, based on the conventional criteria for treatment compliance.

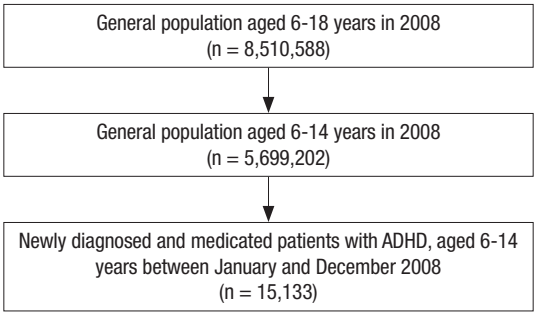

Fig. 1. Flowchart of analysis of treatment continuity among pediatric patients with attention deficit/hyperactivity disorder (ADHD), based on the general population.

MATERIALS AND METHODS

Study subjects

The recruitment group for the present study consisted of a population aged less than 19 years, accessible in the medical claims data for the South Korean National Health Insurance Service (NHIS), obtained from January 1, 2007 to December 31, 2011. The data spans five years because this is the limit for use of the data for research purposes set by the NHIS in South Korea.

The aim of the study was to investigate 3-year patterns of drug treatment continuation for pediatric ADHD patients; therefore, subjects were selected according to the criteria outlined below. First, we selected individuals diagnosed at least once as ICD-10 F90.0, either as inpatients or outpatients. Second, in order to study drug-naïve patients only, we set the washout period to 365 days, in accordance with Hong et al.'s criteria (20). In other words, we selected individuals who were diagnosed between January, 1 and December, 31, 2008, excluding those with a history of treatment between January, 1 and December 2007, 31. Third, because the drug continuance period under study was at least 3 years, we placed an upper limit on subjects' age, such that they should be < 19 years old on December 2011, 31, which was the end-point of usable data. The upper limit for age was set at 19 years because approval for pharmaceutical treatment for ADHD is limited to individuals aged < 19 years in Korea. Therefore, official NHIS medical claims for ADHD drugs are recorded only for individuals aged < 19 years. Within the recruitment group, individuals from the general population, who fulfilled the above-mentioned criteria, were 5,699,202 individuals aged 6-14 years between January 1 and December 31, 2008 (Fig. 1). Among this group were 15,133 individuals who started drug treatment after being first diagnosed with ADHD in 2008; these individuals made up the final sample for analysis in this study.

Research methods

We analyzed the subjects' age, sex, type of medical benefits program (medical insurance/medical protection), attending physicians' sub-specialty (Psychiatry, Pediatrics, or other), and type of medical institution visited (hospital/clinic). The drug continuance period was confirmed on the basis of drug use, as claimed from HIRA. Various techniques, other than drugs, are implemented in the treatment of ADHD. However, in the South Korean medical insurance system, the majority of non-medicinal treatments, such as play therapy, music therapy, and cognitive therapy, are outside the range of medical benefits; so, the analysis in this study was unavoidably limited to drug treatment. Of the drugs approved for ADHD treatment in South Korea, we analyzed immediate-release methylphenidate (MPH) (Phenid®), extended-release MPH (Metadate®), and osmotic-release oral system-MPH (Concerta® OROS), which are MPH formulations; as well as non-stimulant atomoxetine (Strattera®).

Treatment compliance and attrition

The criteria for treatment compliance in this study were the same as those in Wong et al.'s study (16), with acceptance of cases with at least two rounds of drug prescription coupled with outpatient visits over a 6-month period. We defined at least two claims coupled with outpatient visits as drug continuance because it was not possible to confirm drug continuance from a single visit or prescription. Based on those criteria, we investigated the extent of drug continuance over 6-month intervals from the start of treatment. We determined adherence through MPR, using the following method (27): number of days of medication supplied within the refill interval/number of days in the refill interval. In order to investigate differences according to the extent of MPR, we applied threshold values of 0.6, 0.7, and 0.8. Persistence was defined as the number of days of continuous therapy without a specified gap period during the post-index period (27), and to determine the gap period, we looked at the 15-day and 30-day results. We also investigated drug continuance according to the number of hospital visits. Considering the high treatment drop-out rate by the authors (18), the distribution of drop-out rates over 6 months for the treatment drop-out group was analyzed in 1-month units.

Statistical analysis

The data were processed using SAS 9.3 (SAS Institute Inc., Cary,

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NC, USA), and descriptive statistical analysis was performed for all the data.

Ethics statement

This study was approved by the institutional review board of Kyung Hee University Hospital, Seoul (KMC-IRB 1436-04). Informed consent was waived by the board.

Table 1. Demographic and clinical characteristics of subjects with ADHD

Parameters	No. (%) of children		
	Boys	Girls	Total
Age group, yr			
6	1,449 (81.6)	326 (18.4)	1,775 (100)
7	1,835 (81.1)	427 (18.9)	2,262 (100)
8	1,595 (79.8)	403 (20.2)	1,998 (100)
9	1,419 (78.8)	382 (21.2)	1,801 (100)
10	1,185 (79.7)	301 (20.3)	1,486 (100)
11	1,034 (80.0)	258 (20.0)	1,292 (100)
12	1,181 (76.5)	363 (23.5)	1,544 (100)
13	1,299 (74.8)	438 (25.2)	1,737 (100)
14	937 (75.7)	301 (24.3)	1,238 (100)
	11,934 (78.86)	3,199 (21.14)	15,133 (100)
Mean age (SD), yr		9.66 (2.57)	
Median age (IQR), yr		9.00 (7-12)	
Insurance			
National health insurance		15,010 (99.19)	
Medical aid		123 (0.81)	
Physicians' sub-specialty			
Psychiatry		14,359 (94.89)	
Pediatrics		534 (3.53)	
Others		240 (1.58)	
Treatment facility			
General hospital		4,346 (28.72)	
Private clinic		10,787 (71.28)	

SD, standard deviation; IQR, interquartile range.

RESULTS

Demographic data

The study subjects' mean age was 9.66 years (SD: 2.57), and there were 11,934 male children (78.9%) and 3,199 female children (21.2%) (Table 1). The proportion of individuals covered under the national health insurance was 99.2% (15,010 persons). For 94.9% of the subjects, the specialty of the physician providing initial diagnosis was Psychiatry; for 3.5%, physician specialty was Pediatrics. The proportion of general hospitals and private clinics visited was 28.7% and 71.3%, respectively.

Treatment compliance patterns

Naturalistic treatment compliance was 59.0% for the first 6 months, 47.4% for 12 months, 39.9% for 18 months, 34.1% for 24 mon-

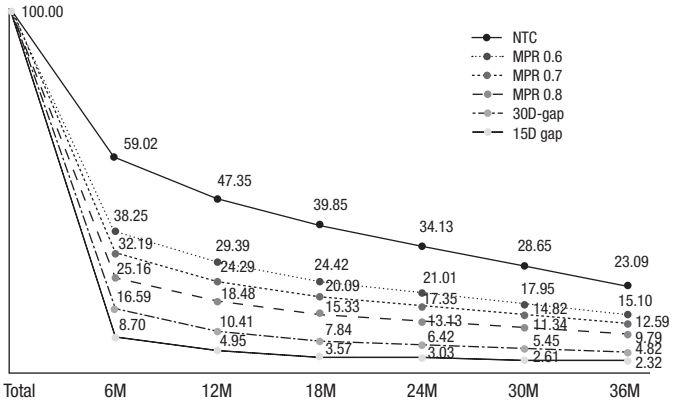
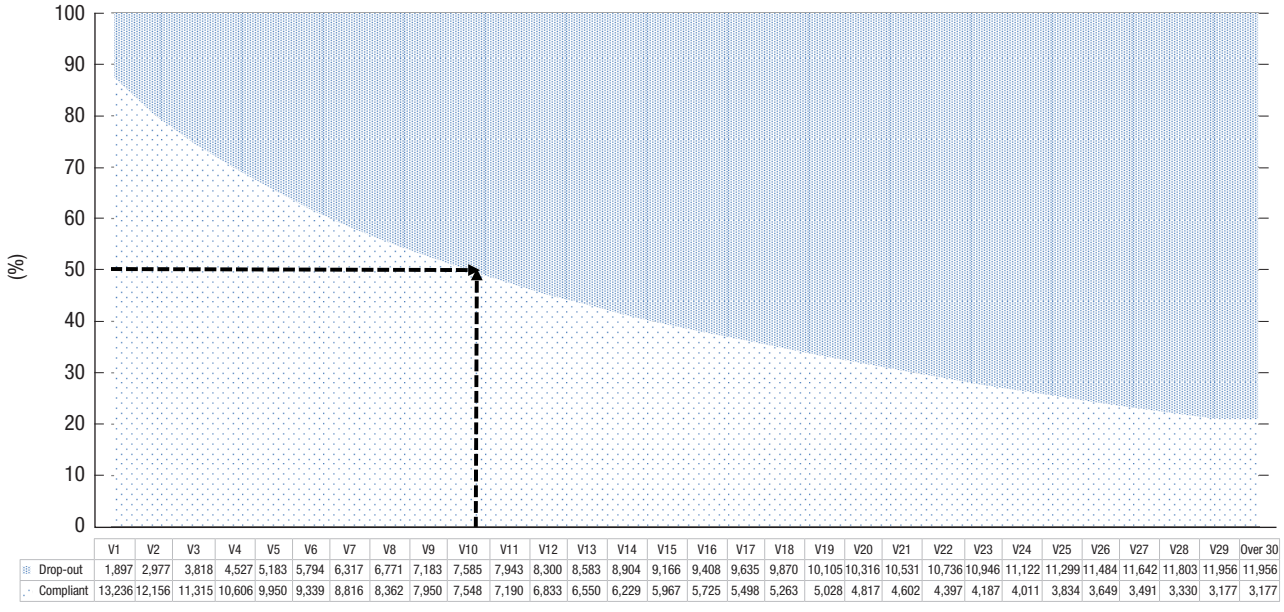


Fig. 2. Adherence/persistence rate (%) every six months according to naturalistic compliance and MPR (Medication Possession Ratio). NTC, naturalistic treatment compliance; MPR, medication possession ratio; D, day(s).



	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20	V21	V22	V23	V24	V25	V26	V27	V28	V29	Over 30
Drop-out	1,897	2,977	3,818	4,527	5,183	5,794	6,317	6,771	7,183	7,585	7,943	8,300	8,583	8,904	9,166	9,408	9,635	9,870	10,105	10,316	10,531	10,736	10,946	11,122	11,299	11,484	11,642	11,803	11,956	11,956
Compliant	13,236	12,156	11,315	10,606	9,950	9,339	8,816	8,362	7,950	7,548	7,190	6,833	6,550	6,229	5,967	5,725	5,498	5,263	5,028	4,817	4,602	4,397	4,187	4,011	3,834	3,649	3,491	3,330	3,177	3,177

Fig. 3. Proportion of compliant/drop-out patients by number of outpatient clinic and hospital visits. V, visit.

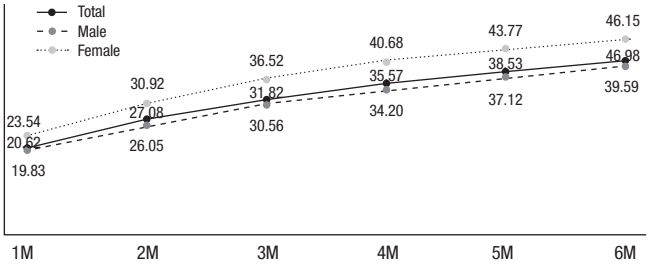


Fig. 4. Drop-out rate (%) of total study population during initial six months. M, month.

ths, 28.6% for 30 months, and 23.1% for 36 months (Fig. 2). There were no differences in treatment compliance patterns according to MPR criteria or gap days, but the drop-out rate for MPR increased from 0.6, to 0.7, to 0.8, and for gap days, it increased from 30-day gaps to 15-day gaps. In terms of drop-out rate according to the number of outpatient visits, 50.1% of the total study subject population (7,585/15,133) had dropped out after the 10th visit (Fig. 3).

Drop-out rate within 6 months

Of the total study population of 15,133 individuals, 6,201 (41.0%) dropped out within 6 months. The drop-out rates at 1-month intervals during the first 6 months were 20.6%, 6.5% 4.7%, 3.7%, 3.0%, and 2.5%. The number of drop-outs within the first month after initiation of treatment made up 50.3% (3,120/6,201) of individuals who dropped out within 6 months (40.98%), and 20.6% (3,120/15,133) of the total study subject population (Fig. 4). The 20.6% who dropped out within 1 month visited the hospital less than 3 times (Fig. 3 and 4).

DISCUSSION

Unlike the present study, there are almost no large-scale, nationwide, long-term drug treatment studies on pediatric ADHD patients. This is because there are not many countries like South Korea or Taiwan that have adopted a single medical insurance system for the whole country, including more than 97% of the total population. Because the medical guarantee system is a product of a country's unique institutional and historical characteristics, one cannot easily compare according to types of medical guarantee system. Therefore, there is a lack of existing data against which the current study results can be compared.

In a study analyzing drug continuance among 40,052 children with ADHD in the southern United States, based on the Medicaid claims database, when applying a 1-month gap, 47.4% of the study population showed drug continuance after 6 months, and 26.9% showed continuance after 12 months (15). When applying a 30-day gap (1-month gap) in the present study, the drug continuance rate after 1 year was 10.4%. In a study by Winterstein et al. (15), when using a 3-month gap, drug continuance was 49.9% after 1 year, 32.8% after 2 years, 17.2% after 5 years, and 15.4% after 9 years. The naturalistic treatment compliance of 47.4% after 1 year in the present study was similar to the result obtained by Winterstein et al. (15) (49.4%), when using a 3-month gap. Although there will be other confounding factors affecting these differences, it should be first be noted that the study subjects in the two studies were recruited from different types of insurance systems. Specifically, Winterstein et al.'s (15) study subjects were drawn from the Medicaid population (low-income group and minorities) in one region in the United States. Our study subjects subscribed to a medical insurance group representing the total population of Korea; in this group, 99.19% of the affiliates of the insurance group are self-funding. A study by Wong et al. (16), using the United Kingdom's General Practice Research Database (GPRD), defined treatment persistence as an interval between claims that spans less than 6 months. The drug continuance rate was 83% after 1 year, 54% after 2 years, 36% after 3 years, 24% after 4 years, 22% after 5 years, and 17% after 6 years. In the present study, we adopted the criteria of Wong et al. (16), but the treatment compliance rate was 47.35% after 1 year, 34.13% after 2 years, and 23.09% after 3 years; these rates were lower than those obtained by Wong et al. (16). These differences could be due to the fact that the United Kingdom's medical system is socialist, whereas in Korea, the insurance system is funded both by individuals and the government. In a retrospective analysis of the medical records of 300 pediatric ADHD patients from a single Korean university hospital (18), naturalistic treatment continuance was found to be 47.3% after 1 year, 29.3% after 2 years, and 20.0% after 3 years. This is similar to the results of the present study, which used data from the whole population. Although there are differences, to some extent, results from international studies and those of the present study show that long-term treatment compliance in pediatric ADHD patients decreases rapidly over time.

Hodgkins et al. (28) used data from 4,909 individuals in the Netherlands, who had been newly diagnosed with ADHD and commenced treatment. Defining adherence as MPR > 0.8, they reported an adherence rate of 64% for the first 3 months, and 44% after 1 year. In other words, their drop-out rates of 36% and 56% after 3 months and 1 year, respectively, were similar to the results of the present study, at 34.8% and 53.6%. In addition, there are studies on drop-out rates at around 6 months (3,17, 19), but there are almost no studies on treatment compliance patterns during the first 6 months, even though this is the critical period in which the highest proportion of patients drop out. In the present study, when we performed a detailed analysis of the drop-out rates at 1-month intervals over the first 6 months, known to be the critical period for treatment continuance, we found that approximately one fifth of the total patient group dropped out within 1 month of starting drug treatment. The possible explanation of these high early drop-outs might be lack of enough awareness among parents, children, and physicians.

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Kim et al. (29) suggested parent educational program at or before initiation of pharmacotherapy might increase the long term treatment compliance. There was a positive correlation between the length before pharmacotherapy initiation after diagnosis of ADHD, and treatment compliance at 6-month after initiation of pharmacotherapy. Also recent qualitative study with 25 parents of children with ADHD and 18 practitioners highlighted the importance of parenting programs (30). Considering that ADHD is a condition with a high risk of chronicity, there is a need to provide practice guidelines by performing analysis and establishing measures to account for attrition in the first 6 months, and particularly in the first 4 weeks after commencement of drug treatment.

Although the present study used a large amount of data obtained from the entire national population, this presented some limitations. First, when using data from HIRA, because the necessary consent for use of personal information has not been received, it is impossible to confirm information for several useful parameters, including parents' education, socioeconomic status, and area of residence. Second, because it is not possible to confirm data for non-medicinal treatment due to the nature of the HIRA data, it was not possible to investigate treatment continuance rates for these treatment methods.

In spite of these limitations, the present study is significant, as it is the first to investigate naturalistic pharmacotherapy continuance rates for the first 3 years for ADHD patients, using the entire 6-18-year-old South Korean population.

DISCLOSURE

The authors have no potential conflicts of interest to disclose.

AUTHOR CONTRIBUTION

Conception and design: Bahn GH, Hong M. Acquisition of data: Choi HY. Analysis and interpretation: Oh IH, Choi HY. Writing or revision of the manuscript: Hong M, Bhang SY, Kim B. Technical support: Lee YJ, Hwang JW. Study supervision and others: Bahn GH.

ORCID

Minha Hong http://orcid.org/0000-0003-4924-1107
Bongseog Kim http://orcid.org/0000-0002-2534-6986
Jun-Won Hwang http://orcid.org/0000-0001-5407-8514
Soo-Young Bhang http://orcid.org/0000-0001-5254-0314
Hyung Yun Choi http://orcid.org/0000-0002-6134-3504
In-Hwan Oh http://orcid.org/0000-0002-5450-9887
Yeon Jung Lee http://orcid.org/0000-0002-5624-0447
Geon Ho Bahn http://orcid.org/0000-0002-3550-0422

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