PRESCRIBING PATTERNS OF PHARMACOTHERAPY FOR PEDIATRIC ATTENTION-DEFICIT/HYPERACTIVITY DISORDER UNDER THE ADHD APPROPRIATE DISTRIBUTION MANAGEMENT SYSTEM IN JAPAN: A NATIONWIDE CROSS-SECTIONAL STUDY

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Abstract

This study aimed to clarify the prescribing patterns of pharmacotherapy for pediatric attention-deficit/hyperactivity disorder (ADHD) in Japan after the implementation of the ADHD Appropriate Distribution Management System. We conducted a cross-sectional analysis of children aged 6–17 years who were diagnosed with ADHD in March 2021 using a nationwide administrative claims database. Among the 12,679 children diagnosed with ADHD, 7,976 (62.9%) received at least one ADHD medication and were included in the analysis. Methylphenidate (MPH) was prescribed to 4,403 patients (55.2%). Its use increased with age, and high-dose MPH was more prevalent in late adolescence. Multivariate logistic regression analyses demonstrated that older age was significantly associated with MPH prescriptions. High-dose MPH was independently associated with high-dose atomoxetine and guanfacine and concomitant antipsychotics. The results of this study suggest the presence of a subgroup of patients who require intensive pharmacotherapy under the current regulatory system. This nationwide study visualized the real-world prescribing patterns in pediatric ADHD and highlighted the need for longitudinal investigations to evaluate the appropriateness and long-term safety of high-intensity treatment.

Key words: ADHD; Methylphenidate; Pharmacoepidemiology

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by core symptoms of inattention, hyperactivity, and impulsivity and is typically diagnosed during childhood. The global prevalence of ADHD in children is approximately 5%[1], and the disorder substantially impairs academic performance and interpersonal functioning[2]. In a proportion of individuals, symptoms persist into adulthood, with the prevalence of adult ADHD estimated at 2–3%[3-5]. Consequently, pharmacotherapy is often continued for extended periods. Although stimulant medications such as methylphenidate (MPH) have demonstrated efficacy in reducing core symptoms, their long-term safety, particularly with respect to growth and physical health, remains under investigation[6, 7].

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The ADHD Appropriate Distribution Management System was introduced in Japan in December 2019 to ensure the appropriate use of stimulant medications. Under this system, both physicians and patients are required to register prior to the prescription of osmotic-release oral system methylphenidate (OROS-MPH; Concerta) and lisdexamfetamine (LDX), with the aim of preventing misuse and promoting appropriate clinical practice. Although several studies have reported changes in prescription trends before and after the implementation of this system[8], nationwide studies of prescribing patterns and dose distributions among pediatric patients with ADHD following its establishment remain limited. MPH, one of the most widely used stimulant medications for pediatric patients with ADHD, therefore represents an important target for evaluating prescribing practices under the current regulatory system.

Therefore, this study aimed to provide a cross-sectional overview of prescribing patterns in pharmacotherapy for pediatric ADHD after the implementation of the ADHD Appropriate Distribution Management System, using MPH as a key indicator of prescribing practices in a nationwide administrative claims database. We analyzed children aged 6–17 years with a diagno-

sis of ADHD as of March 2021 and examined factors associated with the use of MPH. Among patients receiving MPH, we further analyzed factors associated with high-dose MPH use, which may reflect intensified pharmacotherapy in clinical practice. Furthermore, by evaluating the use and treatment intensity of other medications for ADHD, we sought to clarify the prescription practice for pediatric ADHD treatment under the current regulatory framework.

2. Materials and Methods

2.1 Study Design and Data Source

This was a retrospective cross-sectional analysis of the JMDC database. We analyzed health insurance claims data for JMDC enrollees as of March 2021. The JMDC database contains anonymized administrative claims data, primarily from employees and their dependents, covered by employer-sponsored health insurance societies in Japan. This database includes information on diagnoses, prescriptions, and medical procedures based on reimbursement claims. As of March 2021, the database included 1,192,155 enrollees aged 6–17 years.

2.2 Study Population

As of March 2021, we identified enrollees aged 6–17 years in the JMDC database who had been diagnosed with ADHD based on the International Classification of Diseases, Tenth Revision (ICD-10) code F90.x. Among these patients, those who received at least one prescription for an ADHD medication—OROS-MPH, atomoxetine (ATX), extended-release guanfacine (GXR), or LDX—during the same month were included in the analysis. March 2021 was selected as the index month because more than one year had elapsed since the implementation of the ADHD Appropriate Distribution Management System in December 2019, which allowed the system to be established in clinical practice. Additionally, March corresponds to the final month of the end of the Japanese school year, when prescribing patterns are presumed to be relatively stable. We did not distinguish between primary and secondary diagnoses and included all cases in which an ADHD diagnosis was recorded. No exclusion criteria were applied.

2.3 Medication and Dose Definitions

The following medications were considered for ADHD treatment: OROS-MPH, ATX, GXR, and LDX. The daily dose of each medication was calculated by dividing the total prescribed dose in March 2021 by 30 days, and the resulting value was considered as the average daily dose.

The use of ADHD medication was categorized into no use, maintenance-dose, high-dose. For OROS-MPH, dose categories were defined based on the conventional upper limit of maintenance dosing in pediatric patients. Doses of ≤ 45 and ≥ 46 mg/day were classified as maintenance and high doses, respectively. These thresholds were determined based on the approved dosing limits described in the Japanese package inserts. For ATX and GXR, the high-dose categories were defined according to the maximum approved doses per unit body weight as stated in the Japanese package inserts. The corresponding dose thresholds were estimated using age-specific average body weights reported in the 2021 School Health Statistics Survey conducted by the Ministry of Education, Culture, Sports, Science, and Technology of Japan. Doses equivalent to or exceeding the estimated maximum approved dose were classified as high-dose. For LDX, doses ≥ 70 mg/day, corresponding to the maximum approved dose in Japan, were defined as high-dose.

2.4 Definitions of Covariates

Sex and age (6–8, 9–11, 12–14, and 15–17 years) were included as covariates. Comorbid conditions were identified based on ICD-10 codes and included autism spectrum disorder (F84.x) and intellectual disability (F70–F79). Each comorbidity was entered into the regression model as a binary variable (presence/absence). Concomitant psychotropic medications, including antipsychotics, hypnotics, antidepressants, and mood stabilizers, were also assessed. These variables were similarly treated as binary indicators (use/no use). The drug classes were defined according to the Anatomical Therapeutic Chemical (ATC) Classification System, and the corresponding codes are provided in Supplementary Material 1. In addition, the use of other ADHD medications was categorized into no use, maintenance-dose, and high-dose, and was incorporated into the analytical models.

2.5 Statistical Analysis

Continuous variables are summarized as means and standard deviations, and categorical variables are presented as counts and percentages. To examine the factors associated with MPH prescriptions, binary logistic regression analyses were conducted among pediatric patients with ADHD receiving pharmacotherapy. MPH use (use/no use) was treated as the dependent variable. The use of other ADHD medications was included as a binary variable (use/no use) in Model 1. Other ADHD medications were categorized into no use and maintenance- and high-dose groups to account for the treatment intensity in Model 2. To identify the factors associated with high-dose MPH prescriptions, additional binary logistic regression analyses were performed among patients receiving MPH with high-dose use (≥ 46 mg/day) as the dependent variable. Similar Models 1 and 2 specifications were applied to other ADHD medications.

Statistical significance was defined as a two-sided p-value <0.05. No adjustments were made for multiple comparisons. All statistical analyses were performed using SPSS version 28 (IBM Corp., Armonk, NY, USA). There were no missing data.

2.6 Ethical Considerations

This study was approved by the Ethics Committee of the Akita University Graduate School of Medicine and conducted in accordance with the principles of the Declaration of Helsinki.

Table 1. Baseline Characteristics of Pediatric Patients Diagnosed with ADHD (Aged 6–17 Years) in March 2021

	Pediatric Patients Diagnosed with ADHD N=12,679
Sex	
Male	10,236 (80.7%)
Female	2,443 (19.3%)
Age	11.36 (3.1)
Age groups	
6-8y	2,654 (20.9%)
9–11y	4,064 (32.1%)
12–14y	3,529 (27.8%)
15–17y	2,432 (19.2%)
ADHD medication treatment status	
Received any ADHD medication	7,976 (62.9%)
MPH	4,403 (34.7%)
ATX	2,019 (15.9%)
GXR	2,953 (23.3%)
LDX	109 (0.9%)
No ADHD medication	4,703 (37.1%)

Note: Values are presented as number (%) or mean (standard deviation). Some patients received combination therapy; therefore, the numbers for individual medications are not mutually exclusive and may exceed the total number of treated patients.
Abbreviations: ADHD, attention-deficit/hyperactivity disorder; MPH, methylphenidate; ATX, atomoxetine; GXR, guanfacine extended-release; LDX, lisdexamfetamine.

As this study used anonymized administrative claims data for secondary analysis, the requirement for individual informed consent was waived by the ethics committee. This study was conducted in accordance with Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

3. Results

3.1 Study Population and Prescribing Patterns

As of March 2021, there were 7,468,386 enrollees in the JMDC database, of whom 1,192,155 were aged 6–17 years. Among individuals aged 6–17 years, 12,679 were diagnosed with ADHD based on ICD-10 code F90.x, and 10,236 were male. The baseline characteristics of the patients diagnosed with ADHD are presented in Table 1.

Among the 12,679 patients with ADHD, 7,976 (62.9%) received at least one ADHD medication in March 2021 and were included in the analytical cohort. The distribution of ADHD medication uses and prescribing patterns among the analytical cohort is summarized in Table 2. The combinations of the prescribed ADHD medications are illustrated in the UpSet plot in Figure 1.

3.2 Factors Associated with MPH Prescription

Among the 7,976 patients included in the analytical cohort, 4,403 (55.2%) were administered MPH. The baseline characteristics of patients with and without MPH prescriptions are shown in Table 3. To examine the factors independently associated with MPH prescriptions, we constructed two logistic regression models (Table 4).

Table 2. Distribution of ADHD Medication Uses and Prescribing Patterns Among Treated Pediatric Patients

	Pediatric Patients Prescribed ADHD Medications N=7,976
ADHD medications only	4,938 (61.9%)
One ADHD medication	4,118 (51.6%)
Multiple ADHD medications	820 (10.3%)
ADHD medications plus other psychotropics	3,038 (38.1%)
Antipsychotics	2,469 (31.0%)
Hypnotics	798 (10.0%)
Antidepressants	329 (4.1%)
Mood stabilizers	349 (4.4%)

Note: Values are presented as number (%). Some patients received combination therapy; therefore, the numbers for individual medications are not mutually exclusive and may exceed the total number of treated patients.
Abbreviations: ADHD, attention-deficit/hyperactivity disorder.

In Model 1, female sex was significantly associated with lower odds of MPH prescriptions compared with males (OR: 0.71, 95% CI: 0.59–0.85). With children aged 6–8 years as the reference group, the odds of MPH prescription increased significantly in the 9–11 years (OR: 1.86, 95% CI: 1.52–2.27), 12–14 years (OR: 2.50, 95% CI: 2.03–3.08), and 15–17 years (OR: 2.59, 95% CI: 2.05–3.26) age groups. Intellectual disability was independently associated with lower odds of MPH prescriptions (OR: 0.58, 95% CI: 0.44–0.77). The concomitant use of hypnotics was also associated with reduced odds (OR: 0.70, 95% CI: 0.56–0.87). In contrast, autism spectrum disorder (OR: 0.99, 95% CI: 0.86–1.13), antipsychotics (OR: 0.98, 95% CI: 0.84–1.14), antidepressants (OR: 0.89, 95% CI: 0.64–1.23), and mood stabilizers (OR: 0.78, 95% CI: 0.57–1.07) were not significantly associated with MPH prescriptions. Regarding other ADHD medications, the concomitant use of ATX (OR: 0.003, 95% CI: 0.002–0.004), GXR (OR: 0.007, 95% CI: 0.005–0.010), and LDX (OR: 0.001, 95% CI: 0.000–0.002) was strongly associated with lower odds of MPH prescriptions.

In Model 2, which incorporated the dose levels of other ADHD medications, female sex remained significantly associated with lower odds of MPH prescription than those of male sex (OR: 0.68, 95% CI: 0.56–0.81). Using children aged 6–8 years as the reference group, higher odds of MPH prescription were associated with the 9–11 years (OR: 1.66, 95% CI: 1.35–2.04), 12–14 years (OR: 2.13, 95% CI: 1.72–2.64), and 15–17 years (OR: 2.13, 95% CI: 1.68–2.70) age groups. Intellectual disability was independently associated with lower odds of MPH prescription (OR: 0.59, 95% CI: 0.44–0.78), as well as the concomitant use of hyp-

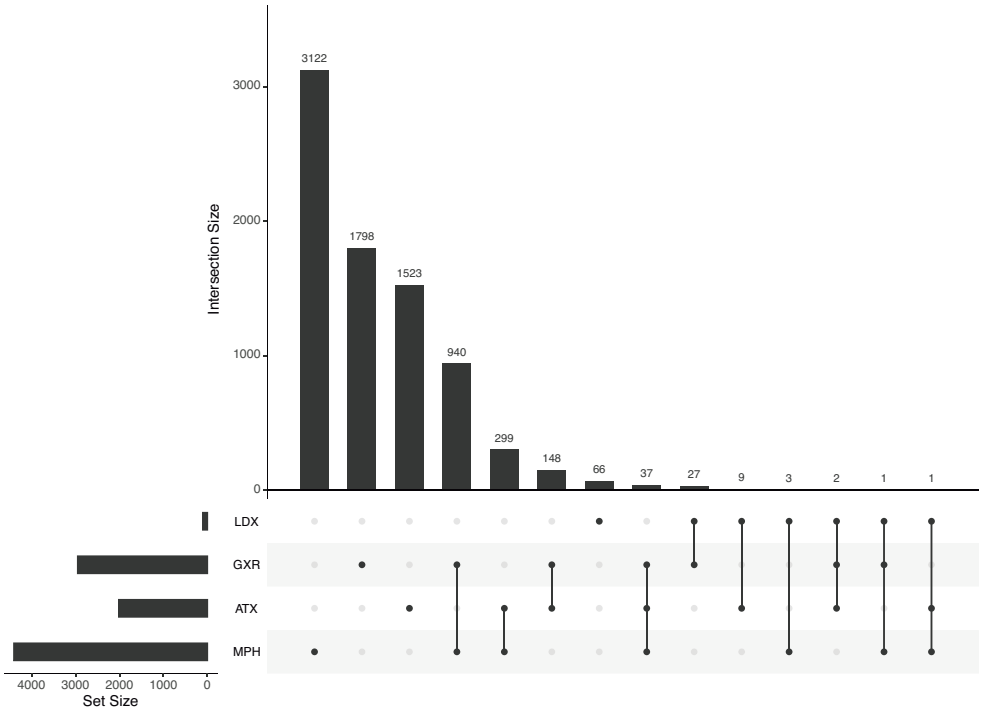

Figure 1. UpSet plot of ADHD medication combinations among pediatric patients.
UpSet plot showing the combination patterns of ADHD medications among pediatric patients (aged 6–17 years) who received at least one ADHD medication in March 2021 (n = 7,976). The horizontal bars indicate the total number of patients receiving each medication, and the vertical bars represent the number of patients corresponding to each specific combination pattern. Medications included osmotic-release oral system methylphenidate (MPH), atomoxetine (ATX), guanfacine extended-release (GXR), and lisdexamfetamine (LDX).

notics (OR: 0.70, 95% CI: 0.56–0.87). Autism spectrum disorder, antipsychotics, antidepressants, and mood stabilizers were not significantly associated with MPH prescriptions. Regarding the dose levels of other ADHD medications, maintenance-dose ATX (OR: 0.004, 95% CI: 0.003–0.005), high-dose ATX (OR: 0.001, 95% CI: 0.001–0.002), maintenance-dose GXR (OR: 0.010, 95% CI: 0.007–0.014), high-dose GXR (OR: 0.005, 95% CI: 0.003–0.006), and maintenance-dose LDX (OR: 0.001, 95% CI: 0.000–0.002) were strongly associated with lower odds of MPH prescription.

3.3 Factors Associated with High-Dose MPH Prescription

Among the 4,403 patients who received MPH, 473 (10.7%) were prescribed a high dose (>45 mg/day; Table 5). To identify factors associated with high-dose MPH prescriptions, we constructed two logistic regression models (Table 6). LDX was not included in the high-dose analyses because the number of cases was small and could have compromised model stability.

In Model 1, female sex was not significantly associated with high-dose MPH prescription compared with male sex (OR: 0.95, 95% CI: 0.72–1.25). Age was a strong independent factor. Using children aged 6–8 years as the reference group, the odds of high-dose prescriptions increased stepwise in the 9–11 years (OR: 2.09, 95% CI: 1.27–3.44), 12–14 years (OR: 3.44, 95% CI: 2.12–5.60) and 15–17 years (OR: 6.63, 95% CI: 4.06–10.82) age groups. Concomitant antipsychotics were significantly associated with high-dose MPH prescriptions (OR: 1.52, 95% CI: 1.21–1.91). Conversely, autism spectrum disorder, intellectual disability, concomitant hypnotics, antidepressants, and mood stabilizers were not significantly associated with high-dose prescriptions.

In Model 2, which incorporated the dose levels of other ADHD medications, the association with age was more pronounced. Using children aged 6–8 years as the reference group, the odds of high-dose MPH prescriptions were 2.37 (95% CI: 1.43–3.92) for those aged 9–11 years, 3.99 (95% CI: 2.43–6.53) for those aged 12–14 years, and 8.00 (95% CI: 4.86–13.17) for those aged 15–17 years, indicating a marked increase in high-dose prescriptions during late adolescence. Concomitant antipsychotics remained significantly associated with high-dose MPH prescriptions (OR: 1.51, 95% CI: 1.20–1.91). Regarding the dose levels of other ADHD medications, high-dose ATX was strongly associated with high-dose MPH prescriptions (OR: 5.55, 95% CI: 2.90–10.61). Likewise, high-dose GXR was significantly associated with high-dose MPH prescriptions (OR: 2.28, 95% CI: 1.64–3.17).

4. Discussion

This nationwide study clarified the prescribing patterns of pharmacotherapy for pediatric ADHD in Japan after the establishment of the ADHD Appropriate Distribution Management System. The principal findings are as follows: First, MPH prescriptions increased with advancing school age. Second, high-

Table 3. Comparison of Baseline Characteristics Between Patients With and Without MPH Prescription

	With MPH N=4,403	Without MPH N=3,573
Sex		
Male	3,773 (85.7%)	2,885 (80.7%)
Female	630 (14.3%)	688 (19.3%)
Age (year)	11.9 (2.8)	11.2 (3.0)
Age groups		
6-8y	529 (12.0%)	752 (21.0%)
9–11y	1,520 (34.5%)	1,226 (34.3%)
12–14y	1,458 (33.1%)	976 (27.3%)
15–17y	896 (20.3%)	619 (17.3%)
Autism spectrum disorder (F84)	2,373 (53.9%)	2,073 (58.0%)
Intellectual disability (F70-F79)	220 (5.0%)	285 (8.0%)
Concomitant psychotropics		
Antipsychotics	1,213 (27.5%)	1,256 (35.2%)
Hypnotics	341 (7.7%)	457 (12.8%)
Antidepressants	169 (3.8%)	160 (4.5%)
Mood stabilizers	144 (3.3%)	205 (5.7%)
ATX daily dose (mg)	3.9 (16.5)	31.36 (49.1)
ATX dose groups		
No use	4,066 (92.3%)	1,891 (52.9%)
Maintenance-dose	292 (6.6%)	1,093 (30.6%)
High-dose	45 (1.0%)	589 (16.5%)
GXR daily dose (mg)	0.5 (1.3)	1.7 (2.3)
GXR dose groups		
No use	3,425 (77.8%)	1,598 (44.7%)
Maintenance-dose	667 (15.1%)	971 (27.2%)
High-dose	311 (7.1%)	1,004 (28.1%)
LDX daily dose (mg)	0.1 (1.5)	1.1 (7.1)
LDX dose groups		
No use	4,398 (99.9%)	3,469 (97.1%)
Maintenance-dose	5 (0.1%)	98 (2.7%)
High-dose	0 (0.0%)	6 (0.2%)

Note: Values are presented as number (%) or mean (standard deviation).
Abbreviations: ADHD, attention-deficit/hyperactivity disorder; MPH, methylphenidate; ATX, atomoxetine; GXR, guanfacine extended-release; LDX, lisdexamfetamine

dose MPH prescriptions markedly increased in late adolescence. Third, high-dose use of ATX and GXR was strongly associated with high-dose MPH prescriptions. Concomitant antipsychotics were observed in a substantial proportion of patients and were independently associated with high-dose MPH use.

In the present study, among 1,192,155 JMDC enrollees aged 6–17 years, 12,679 were diagnosed with ADHD (ICD-10 code F90.x), corresponding to a diagnostic prevalence of approximately 1.1%. A previous nationwide claim-based study reported a prevalence of approximately 1.5% among children and adolescents in Japan, agreeing with our results[9]. Several database studies have demonstrated that the diagnosis of ADHD in Japan has increased in recent years[10-12], accompanied by a parallel rise in ADHD medication prescribing. For example, an analysis of Japanese administrative data reported an increase in both ADHD diagnoses and medication prescriptions among pediatric outpatients between 2012 and 2018, with changes in medication selection over time[13]. Furthermore, the estimated prescription rate

Table 4. Logistic Regression Analysis of Factors Associated With MPH Prescription

	Model 1 OR (95%CI)	Model 2 OR (95%CI)
Sex		
Male	Reference	Reference
Female	0.71 (0.59-0.85)*	0.68 (0.56-0.81)*
Age groups		
6-8y	Reference	Reference
9–11y	1.86 (1.52-2.27)*	1.66 (1.35-2.04)*
12–14y	2.50 (2.03-3.08)*	2.13 (1.72-2.64)*
15–17y	2.59 (2.05-3.26)*	2.13 (1.68-2.70)*
Autism spectrum disorder (F84)	0.99 (0.86-1.13)	0.99 (0.85-1.14)
Intellectual disability (F70-F79)	0.58 (0.44-0.77)*	0.59 (0.44-0.78)*
Concomitant psychotropics		
Antipsychotics	0.98 (0.84-1.14)	1.00 (0.85-1.14)
Hypnotics	0.70 (0.56-0.87)*	0.70 (0.56-0.87)*
Antidepressants	0.89 (0.64-1.23)	0.87 (0.62-1.22)
Mood stabilizers	0.78 (0.57-1.07)	0.80 (0.58-1.10)
ATX prescription	0.003 (0.002-0.004)*	
GXR prescription	0.007 (0.005-0.010)*	
LDX precription	0.001 (0.000-0.002)*	
ATX dose groups		
No use		Reference
Maintenance-dose		0.004 (0.003-0.005)*
High-dose		0.001 (0.001-0.002)*
GXR dose groups		
No use		Reference
Maintenance-dose		0.010 (0.007-0.014)*
High-dose		0.005 (0.003-0.006)*
LDX dose groups		
No use		Reference
Maintenance-dose		0.001 (0.000-0.002)*
High-dose		Not estimable

Note: Odds ratios (OR) and 95% confidence intervals (CI) were estimated using multivariable logistic regression analysis. Model 1 included other ADHD medications as binary variables (use/no use). Model 2 included other ADHD medications categorized by dose level (no use, maintenance-dose, high-dose).

* $p < 0.05$.

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; MPH, methylphenidate; ATX, atomoxetine; GXR, guanfacine extended-release; LDX, lisdexamfetamine

of MPH among children and adolescents in Japan has increased stepwise from 0.003% in 2007 to 0.23% in 2016[14]. In the present study, 62.9% of the children diagnosed with ADHD received at least one ADHD medication in the index month, indicating that pharmacotherapy constitutes a major component of pediatric ADHD management. Consistent with this, a domestic study of child and adolescent psychiatric outpatients reported the frequent use of MPH among patients receiving pharmacological treatment[15].

However, these trends are not unique to Japan. Population-based studies from multiple countries have consistently demonstrated increasing use of ADHD medications, particularly MPH[16].

Table 5. Comparison of Baseline Characteristics Between High-Dose (>45 mg/day) and Maintenance-Dose (≤ 45 mg/day) MPH groups

	High-Dose N=473	Maintenance-Dose N=3,930
Sex		
Male	401 (84.8%)	3,372 (85.8%)
Female	72 (15.2%)	558 (14.2%)
Age (year)	13.2 (2.6)	11.7 (2.8)
Age groups		
6-8y	19 (4.0%)	510 (13.0%)
9–11y	110 (23.3%)	1,410 (35.9%)
12–14y	166 (35.1%)	1,292 (32.9%)
15–17y	178 (37.6%)	728 (18.5%)
Autism spectrum disorder (F84)	256 (54.1%)	2,117 (53.9%)
Intellectual disability (F70-F79)	25 (5.3%)	195 (5.0%)
Concomitant psychotropics		
Antipsychotics	166 (35.1%)	1,047 (26.6%)
Hypnotics	48 (10.1%)	293 (7.5%)
Antidepressants	26 (5.5%)	143 (3.6%)
Mood stabilizers	24 (5.1%)	120 (3.1%)
MPH daily dose (mg)	60.4 (13.3)	26.2 (8.8)
ATX daily dose (mg)	8.3 (28.8)	3.3 (14.2)
ATX dose groups		
No use	423 (89.4%)	3,643 (92.7%)
Maintenance-dose	33 (7.0%)	259 (6.6%)
High-dose	17 (3.6%)	28 (0.7%)
GXR daily dose (mg)	0.9 (1.9)	0.5 (1.2)
GXR dose groups		
No use	364 (77.0%)	3,061 (77.9%)
Maintenance-dose	53 (11.2%)	614 (15.6%)
High-dose	56 (11.8%)	255 (6.5%)
LDX daily dose (mg)	0.0 (0.0)	0.1 (1.6)
LDX dose groups		
No use	473 (100%)	3,925 (99.9%)
Maintenance-dose	0	5 (0.1%)
High-dose	0	0

Note: Values are presented as number (%) or mean (standard deviation).
Abbreviations: ADHD, attention-deficit/hyperactivity disorder; MPH, methylphenidate; ATX, atomoxetine; GXR, guanfacine extended-release; LDX, lisdexamfetamine

Similar trends have been observed in Asia, including rising diagnostic rates and increased pharmacological treatment among youths in Taiwan[17], and increasing prescription of ADHD medications among children and adolescents in South Korea[18]. Thus, the increase in ADHD diagnosis and treatment appears to reflect international trends. In this context, describing the prescribing patterns of pediatric ADHD pharmacotherapy under the current regulatory framework in Japan and identifying the clinical factors associated with high-dose prescriptions have important clinical and public health implications.

In the present study, the odds of MPH prescription significantly increased with advancing age. Compared with children aged 6–8 years, those aged 15–17 years had more than twice the odds of being administered MPH, and the odds of high-dose prescrip-

Table 6. Logistic Regression Analysis of Factors Associated With High-Dose (>45 mg/day) MPH Prescription

	Model 1 OR (95%CI)	Model 2 OR (95%CI)
Sex		
Male	Reference	Reference
Female	0.95 (0.72-1.25)	0.96 (0.72-1.27)
Age groups		
6-8y	Reference	Reference
9–11y	2.09 (1.27-3.44)*	2.37 (1.43-3.92)*
12–14y	3.44 (2.12-5.60)*	3.99 (2.43-6.53)*
15–17y	6.63 (4.06-10.82)*	8.00 (4.86-13.17)*
Autism spectrum disorder (F84)	0.91 (0.74-1.12)	0.92 (0.74-1.13)
Intellectual disability (F70-F79)	1.03 (0.66-1.59)	1.02 (0.65-1.59)*
Concomitant psychotropics		
Antipsychotics	1.52 (1.20-1.91)*	1.51 (1.20-1.91)*
Hypnotics	1.20 (0.86-1.68)	1.16 (0.83-1.64)
Antidepressants	0.88 (0.56-1.39)	0.87 (0.55-1.38)
Mood stabilizers	1.13 (0.70-1.80)	1.17 (0.73-1.87)
ATX prescription	1.29 (0.93-1.79)	
GXR prescription	1.11 (0.88-1.40)	
ATX dose groups		
No use		Reference
Maintenance-dose		0.92 (0.63-1.36)
High-dose		5.55 (2.90-10.61)*
GXR dose groups		
No use		Reference
Maintenance-dose		0.73 (0.53-0.99)*
High-dose		2.28 (1.64-3.17)*

Note: Odds ratios (OR) and 95% confidence intervals (CI) were estimated using multivariable logistic regression analysis. High-dose MPH was defined as >45 mg/day. Model 1 included other ADHD medications as binary variables (use/no use). Model 2 included other ADHD medications categorized by dose level(no use, maintenance-dose, high-dose). LDX was not included in the high-dose analysis due to the small number of cases.

* $p < 0.05$.

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; MPH, methylphenidate; ATX, atomoxetine; GXR, guanfacine extended-release; LDX, lisdexamfetamine

tions were approximately eightfold higher. These findings may reflect increasing academic demands and social expectations across developmental stages. During late adolescence, functional challenges, such as academic evaluation and career decision-making, become more prominent, and difficulties related to inattention and executive dysfunction may manifest more clearly as clinically significant problems. Therefore, selecting MPH and dose escalation may be an attempt to intensify symptom management in response to functional pressures.

Simultaneously, dose increases during the growth period warrant careful consideration from a long-term safety perspective. Although recent prospective studies have suggested an acceptable safety profile of stimulant treatment[6], a Cochrane review has raised concerns regarding potential growth suppression[7], and observational data have suggested possible associations between long-term MPH exposure and body mass index in adulthood[19]. Although the present study used a cross-sectional design, it provides important evidence regarding the real-world pattern of dose escalation during adolescence.

Another key finding of this study was the strong association between high-dose ATX and GXR and high-dose MPH prescriptions. Importantly, this relationship became more evident in

Supplementary Material. List of psychotropics covered in this study

Antipsychotics

Generic name	ATC code
Aripiprazole	N05AX12
Asenapine	N05AH05
Blonanserin	−
Blonanserin（tape）	−
Brexpiprazole	N05AX16
Bromperidol	N05AD06
Carpipramine	−
Chlorpromazine	N05AA01
Clocapramine	−
Clozapine	N05AH02
Floropipamide	−
Fluphenazine	N05AB02
Haloperidol	N05AD01
Levomepromazine	N05AA02
Lurasidone	N05AE05
Moperone	N05AD04
Mosapramine	N05AX10
Nemonapride	−
Olanzapine	N05AH03
Oxypertine	N05AE01
Paliperidone	N05AX13
Perospirone	−
Perphenazine	N05AB03
Pimozide	N05AG02
Prochlorperazine	N05AB04
Propericyazine	−
Quetiapine	N05AH04
Risperidone	N05AX08
Spiperone	−
Sulpiride	N05AL01
Sultopride	N05AL02
Tiapride	N05AL03
Thioridazine	N05AC02
Timiperone	−
Trifluoperazine	N05AB06
Zotepine	N05AX11

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Hypnotics

Generic name	ATC code
Brotizolam	N05CD09
Estazolam	N05CD04
Etizolam	N05BA19
Flunitrazepam	N05CD03
Flurazepam	N05CD01
Haloxazolam	−
Lormetazepam	N05CD06
Nimetazepam	N05CD15
Nitrazepam	N05CD02
Quazepam	N05CD10
Rilmazafone	−
Triazolam	N05CD05
Zolpidem	N05CF02
Zopiclone	N05CF01
Eszopiclone	N05CF04
Ramelteon	N05CH02
Melatonin	N05CH01
Suvorexant	N05CM19
Lemborexant	N05CJ02

ATC, the Anatomical Therapeutic Chemical classification 2021

Model 2, which incorporated treatment intensity based on the attainment of the maximum approved dose, rather than merely the presence or absence of concomitant medications. This model more clearly demonstrated the association and suggests that a subgroup of patients with difficulty achieving adequate symptom control may have been statistically identified. The approximately 5.5-fold and 2.3-fold increases in the odds of high-dose MPH among patients receiving high-dose ATX and high-dose GXR, respectively, indicate a prescribing structure in which treatment intensification occurs despite the maximal use of alternative agents. Such cases likely involve complex interactions among symptom severity, comorbid conditions, and environmental factors, and may represent a distinct "high-dose, multi-medication cluster" within pediatric ADHD treatment. Previous studies have suggested that polypharmacy in pediatric ADHD is more frequently observed in patients with greater clinical severity and complexity. For example, a clinical study in Japan reported that the use of multiple ADHD medications was associated with higher ADHD symptom severity, increased autistic traits, and behavioral problems such as child-to-parent violence[15]. These findings indicate that polypharmacy may be more likely to occur in patients with not only comorbid conditions but also more severe and behaviorally complex clinical presentations or suboptimal response to standard treatments.

In addition, MPH prescriptions were inversely associated with the use of other ADHD medications in the logistic regression analysis. This finding may reflect not only pharmacological differences but also clinical prescribing strategies. In routine practice, stimulant and non-stimulant medications are often used sequentially rather than concurrently, particularly when treatment response is insufficient or adverse effects occur. For example, patients who do not respond adequately to MPH or experience tolerability issues may be switched to alternative agents such as atomoxetine or guanfacine. This sequential treatment approach is also consistent with clinical guidelines in Japan, which generally recommend monotherapy as the initial treatment strategy[20].

The independent association between concomitant antipsychot-

Antidepressants

Generic name	ATC code
Amitriptyline	N06AA09
Amoxapine	N06AA17
Clomipramine	N06AA04
Desipramine	N06AA01
Dosulepin	N06AA16
Duloxetine	N06AX21
Escitalopram	N06AB10
Fluvoxamine	N06AB08
Imipramine	N06AA02
Lofepramine	N06AA07
Maprotiline	N06AA21
Mianserin	N06AX03
Milnacipran	N06AX17
Mirtazapine	N06AX11
Nortriptyline	N06AA10
Paroxetine	N06AB05
Safrazine	–
Sertraline	N06AB06
Setiptiline	–
Sulpiride	N05AL01
Trazodone	N06AX05
Trimipramine	N06AA06
Venlafaxine	N06AX16
Vortioxetine	N06AX26

ATC, the Anatomical Therapeutic Chemical classification 2021

Mood Stabilizer

Generic name	ATC code
Carbamazepine	N03AF01
Lamotrigine	N03AX09
Sodium Valproate	N03AG01
Lithium carbonate	N05AN01

ATC, the Anatomical Therapeutic Chemical classification 2021

ics and high-dose MPH prescriptions warrants further investigation. Antipsychotics are often prescribed for pediatric ADHD to address aggression, impulsivity, emotional dysregulation, and co-occurring behavioral problems. In the present study, approximately 30% of patients receiving MPH were prescribed concomitant antipsychotics, and this association persisted in the multivariable analyses of high-dose MPH use. These findings suggest that adjunctive pharmacotherapy may be employed in more severe cases, wherein stimulant monotherapy does not achieve sufficient functional improvement. However, antipsychotics are associated with potential adverse effects, including metabolic complications and sedation. Therefore, careful evaluation is required when considering long-term combination therapy for children and adolescents.

This study has several strengths. First, we used a nationwide administrative claims database to provide a detailed analysis of prescribing patterns for pediatric ADHD pharmacotherapy at a single time point after the establishment of the regulatory system. Second, by incorporating the dose levels of other ADHD medications based on the maximum approved doses, rather than simply their use or no-use, we were able to statistically evaluate the differences in treatment intensity. This approach adds novelty to the study by allowing the identification of variations in prescription intensity that may reflect the underlying clinical complexity.

However, this study has limitations. First, this was a cross-sectional analysis conducted at a single time point; therefore, temporal changes in medication dose or treatment modifications could not be evaluated. It remains unclear whether high-dose MPH prescriptions are continuously maintained or represent temporary dose escalations. In addition, the sequence of treatment intensification—whether MPH dose increases occurred after reaching the maximum dose of ATX or GXR or vice versa—could not be determined. Future longitudinal claims-based analyses or cohort studies are required to examine the temporal trajectory of treatment intensity and its association with safety outcomes.

Second, administrative claims data do not contain detailed clinical information, such as symptom severity, psychosocial interventions, school functioning, or family environment. Therefore, it is not possible to determine whether high-dose or multiple-medication prescriptions represent deviations from guideline recommendations or appropriate management of severe or complex cases.

Third, as individual body weight data were not available in the claims database, the maximum approved doses of other ADHD medications were estimated using age-specific average body weights from the 2021 School Health Statistics Survey. As these estimates were not based on each patient's actual body weight, some degree of dose intensity misclassification may have occurred.

Fourth, the JMDC database primarily includes individuals covered by employer-sponsored health insurance, and may not fully represent populations with different socioeconomic backgrounds or healthcare access. Therefore, caution should be exercised when generalizing these findings to the pediatric population in Japan.

5. Conclusion

This nationwide study clarified the prescribing patterns of pharmacotherapy for pediatric ADHD in Japan after the establishment of the ADHD Appropriate Distribution Management System. Both overall MPH and high-dose prescriptions increased with advancing age, with a particularly marked increase during late adolescence. High-dose use of ATX and GXR and concomitant antipsychotics were independently associated with high-dose MPH prescriptions, suggesting the presence of

a subgroup of patients receiving intensified treatment beyond simple multi-medication use.

Although this cross-sectional study did not establish causal relationships, it provides important insights into real-world prescription patterns within the current regulatory framework. Future longitudinal analyses evaluating dose trajectories and long-term safety outcomes are warranted to better define appropriate strategies for high-dose and multi-medication treatments used in pediatric ADHD.

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Conflict of Interest

KY has received speaker honoraria from Janssen Pharmaceutical K.K. KM has received speaker honoraria from Shionogi & Co., Ltd. and Takeda Pharmaceutical Company Limited, and has served as a principal investigator in a specified clinical research supported by Shionogi & Co., Ltd. The other authors declare no conflicts of interest.

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