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Examining the Use of Oral Aripiprazole in Patients With Autism Spectrum Disorder: A Study of Retrospective Chart Review at a University Medical Center

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Objectives: The purpose of this study was to examine the patterns of use of oral aripiprazole treatment in children and adolescents diagnosed with autism spectrum disorder (ASD) at a university medical center in Korea.
Methods: We retrospectively reviewed the medical records of 164 outpatient children and adolescents diagnosed with ASD by child and adolescent psychiatrists. Patient demographic characteristics, clinical features, age and dose of aripiprazole treatment, associated adverse events, and concomitant medications, etc. were evaluated.
Results: Aripiprazole treatment was initiated at a mean age of 7.64 years, at a mean initial dose of 1.15 mg. Methylphenidate was often co-administered with aripiprazole. The most commonly reported adverse effects were increased appetite and weight gain, which in some cases led to discontinuation of medication.
Conclusion: A follow-up study is warranted to evaluate the efficacy and safety of aripiprazole treatment in Korean children and adolescents diagnosed with ASD, and it is crucial to consider their clinical characteristics and response to treatment in the evaluation.

Keywords: Autism spectrum disorder; Aripiprazole; Children; Adolescents.

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INTRODUCTION

Autism spectrum disorder (ASD) is defined as persistent impairment in social interaction, communication, and restricted interests and behavior [1]. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) defines ASD as the core features of "persistent impairments in social communication and social interaction" (criterion A) and "restricted, repetitive patterns of behavior, interests, or activities" (criterion B). These symptoms manifest in early childhood and result in daily functional limitations (criterion C, D).

In addition to the core symptoms mentioned above, individuals with ASD typically exhibit additional symptoms such as obsessive-compulsive behaviors, self-injurious behaviors, attention deficits, atypical emotional responses, and tics [2]. In order to provide appropriate treatment, it is essential to identify and address the behavioral problems associated with these symptoms. Behavioral symptoms of ASD can impede the educational and developmental progress of affected individuals, thereby causing considerable challenges for their primary caregivers [3]. Although behavioral therapy is used to manage the symptoms, complete control of all of the symptoms might not be achieved with these treatments alone [4]. Therefore, complementary measures such as pharmacological treatments are necessary in many cases.

Both first-generation typical antipsychotics and second-generation atypical antipsychotics have been used to manage the behavioral symptoms of ASD [5]. Randomized controlled trials have demonstrated that haloperidol administration improves specific behavioral symptoms in individuals with ASD [6]. However, typical antipsychotic medications have limited use because of the associated side effects, including drug-induced movement disorders such as tardive dyskinesia and acute dystonia [5]. This has resulted in an increased use of atypical antipsychotics, since these medications can effectively address challenging behaviors such as repetitive movements, self-injurious behaviors, and aggression in individuals diagnosed with ASD [7]. Atypical antipsychotics

are effective for the management of behavioral problems associated with ASD. Risperidone and aripiprazole have been approved by the United States Food and Drug Administration (FDA) and are widely used in the treatment of ASD [8,9].

Aripiprazole is an atypical antipsychotic medication commonly prescribed to alleviate symptoms in individuals with ASD. It is also widely used to treat serious mental illnesses such as schizophrenia and bipolar disorder [10]. The partial agonist activity of the drug at the D2 receptors reduces the possibility of extrapyramidal symptoms, including involuntary movements [11]. Aripiprazole demonstrates a greater propensity for inhibiting 5-HT2 receptors when compared to other atypical antipsychotic drugs [12]. Aripiprazole is a safe and effective treatment for behavioral problems in people with ASD [10]. In a double-blind, randomized controlled trial involving 218 individuals with ASD, aripiprazole was found to be effective in improving irritability and hyperactivity [13]. Another randomized, double-blind study of 98 individuals with ASD showed a significant improvement in problem behaviors with aripiprazole after 8 weeks compared to placebo [14]. That study also showed that aripiprazole had excellent tolerability. Aripiprazole is approved for the treatment of irritability in children and adolescents aged between 6 to 17 years with ASD [15], and is currently widely used in clinical practice for this purpose. However, aripiprazole use in children and adolescents is associated with certain side effects such as increased appetite, weight gain, elevated fasting blood glucose, dyslipidemia, and increased insulin resistance [16]. These effects on the metabolism increase the risk of developing diabetes and cardiovascular diseases [17]. When administering aripiprazole to individuals with ASD, it is important to understand the common dosing patterns, reported adverse drug reactions, and common side effects.

This study aimed to analyze trends in the use of oral aripiprazole by retrospectively reviewing the medical records of children and adolescents with ASD who were outpatients at a university hospital. This study specifically focused on examining aripiprazole dosage, side effects, reasons for discontinuation, and common concomitant medications.

METHODS

Participants

This study was conducted by reviewing the medical records of children and adolescents with ASD who attended the Seoul National University Bundang Hospital Department of Psychiatry outpatient clinics. The study data was collected between November 1, 2020 and October 31, 2021. Patients with a primary or secondary diagnosis of one of the following DSM-IV-TR diagnostic codes: F840 (autistic disorder, childhood autism), F841 (atypical autism), F842 (Rett syndrome), F843 (childhood disintegrative disorder), F845 (Asperger syndrome), and F849 (pervasive developmental disorder) were included. Further, patients who had been prescribed oral aripiprazole by their treating physician and were still taking or had discontinued the medication before the age of 19 years were included. The study excluded patients ≥19 years old, for whom the date of initiation of oral aripiprazole treatment could not be determined from the medical records, those with other medical or psychiatric conditions that could cause significant weight changes or rapid cognitive or mood changes, and those taking medications for the aforementioned conditions.

Measurements

To identify patients who met the criteria for receiving oral aripiprazole treatment, only one child and adolescent psychiatrist reviewed the medical records. The demographic and clinical characteristics of each participant were identified and assessed using chart review. For each patient, information was collected on gender, age, diagnosis, comorbid conditions, concomitant medications, age at start of medication, duration of medication, target symptoms, weight at start of treatment, initial dosage, dosage maintained without change for at least 3 months (fixed dose), dosage maintained without change for at least 3 months after symptom improvement (stabilized dose), side effects experienced during medication, reasons for discontinuation, other prescribed concomitant medications, and any other relevant information regarding medication trends. Other data collected for each patient included age (at the time of data collection), Vineland Adaptive Behavior Scale or Wechsler Intelligence Scale scores, Social Maturity Scale (SMS) scores (SA, SQ), Korean Version of the Childhood Autism Rating Scale (K-CARS-2) scores, Korean Version of the Autism Diagnostic Observation Schedule (K-ADOS-2) comparative scores, and other clinical characteristics. Participants were divided into three groups based on age at the start of the medication: Group 1: early childhood (up to 6 years and 12 months); Group 2: childhood (7 to 12 years and 12 months); and Group 3: adolescence (13 to 18 years and 12 months). This study was approved by the Institutional Review Board (IRB) of Seoul National University Bundang Hospital (IRB approval number: B-2201-731-103). In this retrospective medical records study, informed consent was not required.

Data analysis

Means and standard deviations (SD) were calculated for continuous variables, and frequency analysis was performed for categorical variables. Independent samples t-test and one-

way analysis of variance were used to determine differences between the groups, with an additional post hoc Bonferroni test. All statistical calculations were performed using Statistical Package for the Social Sciences (SPSS) version 26.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Demographic variables

A total of 164 medical records of child and adolescent patients with ASD who received aripiprazole during the specified period were analyzed (Table 1). Of the total 164 patients, 20 (12.2%) were female. The mean age of the patients was 10.21±3.52 years (mean±SD), ranging from 5 to 18 years. The mean age at the initiation of aripiprazole treatment was 7.64 years with a standard deviation of 2.67 years. The minimum age at treatment initiation was 3 years and the maximum age was 15 years. Of the total 164 patients, 135 (17 females, 12.59%) had a primary diagnosis of F840 (autistic disorder, childhood autism), and 29 (3 females, 10.34%) had a primary diagnosis of F845 (Asperger's syndrome). There were no cases of primary diagnosis of F841 (atypical autism), F842 (Rett's syndrome), F843 (childhood disintegrative disorder), or F849 (pervasive developmental disorder). Out of the total 164 patients, 29 (17.2%) patients were categorized as Group 1 (ages 0 to 6 years 12 months) and included 5 females; 90 (54.9%) patients were categorized as Group 2 (ages 7 to 12 years 12 months) and included 10 females; 45 patients (27.4%) were categorized as Group 3 (ages 13 to 18 years 12 months) and had 5 females. The intelligence quotient of the study patients was 69.44±23.01, ranging from a minimum of 39 and a maximum of 138. The SMS was 65.63±24.96, ranging from a minimum of 16 and a maximum of 137. The K-CARS-2 score was 35.68±5.94, ranging from a minimum score of 22.0 and a maximum score of 50.5. The K-ADOS-2 comparison score was 7.09±1.68, ranging from a minimum of 2 and a maximum of 10. The average initial dose of aripiprazole among all patients was 1.15±1.07 mg, ranging from a minimum dose of 0.25 mg and a maximum dose of 10 mg.

Table 1. Demographic and clinical characteristics of the child and adolescent patients with ASD

Characteristics	Value (n=164)
Sex	
Male	144 (87.8)
Female	20 (12.2)
Age at starting drug (yr)	7.64±2.67 (3–15)
Main diagnosis	
F840 (autistic disorder, childhood autism)	135 (82.3)
F841 (atypical autism)	0 (0)
F842 (Rett's syndrome)	0 (0)
F843 (childhood disintegrative disorder)	0 (0)
F845 (Asperger's syndrome)	29 (17.7)
F849 (pervasive developmental disorder)	0 (0)
Classification	
Group 1 (≤6 yr 12 month)	29 (17.2)
Male	24 (82.8)
Female	5 (17.2)
Group 2 (7 yr–12 yr 12 month)	90 (54.9)
Male	80 (88.9)
Female	10 (11.1)
Group 3 (13 yr–18 yr 12 month)	45 (27.4)
Male	40 (88.9)
Female	5 (11.1)
Full Scale Intelligence Quotient	69.44±23.01 (39–138)
Social Maturity Scale-SQ	65.63±24.96 (16.0–137.0)
K-CARS-2	35.68±5.94 (22.0–50.5)
K-ADOS-2 Comparison score	7.09±1.68 (2–10)

Values are presented as mean±standard deviation (range) or number (%). ADS, autism spectrum disorder; K-ADOS-2, Korean Version of the Autism Diagnostic Observation Schedule; K-CARS-2, Korean Version of the Childhood Autism Rating Scale

Usage patterns of aripiprazole

The time to reach the fixed dose (i.e., the time from starting medication to the time the dose remained unchanged for at least 3 months despite previous dose adjustments) was 35.74±161.09 months (Table 2). The dose at that time was 4.02±3.66 mg, and the minimum dose was 0.5 mg and maximum dose was 20 mg. The stabilized dose (the dose that remained unchanged for at least 3 months after target symptom relief) was 3.67±3.08 mg, and the minimum dose was 0.5 mg and the maximum dose was 15 mg. Of the 164 patients, 162 (99.8%) were prescribed a combination of aripiprazole and other medications.

Among the combination medications, methylphenidate had the highest prescription frequency, accounting for 24.1% of cases (Table 3). The second highest frequency was observed for selective serotonin reuptake inhibitors (SSRIs), at a rate of 15.4%. After SSRIs, the next highest frequency of combination medications were risperidone (13.0%), propranolol (11.1%), atomoxetine (9.3%), and valproate (6.2%).

Trends in side effects of aripiprazole

Of the 164 patients, 106 had adverse effects to aripiprazole use which were reported by their caregivers (Table 4). Weight gain (17.9%) was the most frequently reported adverse ef-

Table 2. Oral aripiprazole dosing profile in child and adolescent patients with ASD

	Dosage	Range (min–max)	Missing value*
Start dose (mg)	1.15±1.07	0.75 (0.25–10)	5
Period until dose fixation (month)	35.74±161.09	1451 (0.1–1451)	84
Fixed dose (mg)	4.02±3.66	19.5 (0.5–20)	62
Stabilized dose (mg)	3.67±3.08	14.5 (0.5–15)	109

Values are presented as mean±standard deviation. *the number of individuals with no information found during chart review out of 164 individuals. ADS, autism spectrum disorder

Table 3. Types and frequency of concomitant medications used with aripiprazole in child and adolescent patients with ASD

Drug	Value (n=162)
Methylphenidate	39 (24.1)
SSRI	25 (15.4)
Risperidone	21 (13.0)
Propranolol	18 (11.1)
Atomoxetine	15 (9.3)
Valproate	10 (6.2)
Trihexine	8 (4.9)
Benzodiazepine	7 (4.3)
Quetiapine	4 (2.5)
Trazodone	3 (1.9)
Lithium	3 (1.9)
Benztropine	3 (1.9)
Clonidine	2 (1.2)
Olanzapine	2 (1.2)
TCA	1 (0.6)
Pocral	1 (0.6)

Values are presented as number (%). ADS, autism spectrum disorder; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant

Table 4. Side effect profile of aripiprazole

Side effect	Value (n=106)
Weight gain*	19 (17.9)
Appetite ↑*	18 (17.0)
Irritability ↑*	13 (12.3)
Somnolence	12 (11.3)
Insomnia *	7 (6.6)
Crying ↑*	5 (4.7)
Impulsivity ↑	3 (2.8)
Agility ↓	2 (1.9)
Stereotyped behavior	2 (1.9)
Emotional expression ↑	2 (1.9)
Headache	2 (1.9)
Nausea/vomitting	2 (1.9)
EPS (extrapyramidal symptoms)	2 (1.9)
Constipation	2 (1.9)
Hyperactivity	2 (1.9)
Rash*	2 (1.9)
Sensitivity	2 (1.9)
Abnormal liver lab*	1 (0.9)
Nail biting	1 (0.9)
Diarrhea	1 (0.9)
Appetite ↓	1 (0.9)
Obsession	1 (0.9)
Penile erection	1 (0.9)
Night terror	1 (0.9)
Gynecomastia	1 (0.9)
Nasal bleeding	1 (0.9)

Values are presented as number (%). An upward-pointing arrow indicates an increase in frequency, while a downward-pointing arrow indicates a decrease in frequency. *side effects that led to medication discontinuation

fect, followed by increased appetite (17.0%), hypersensitivity (12.3%), and drowsiness (11.3%). Furthermore, numerous other unfavorable responses were recorded, including an increase in frequency of crying, heightened impulsiveness, dullness, stereotyped behavior, increased emotional expression, headache, vomiting, extrapyramidal symptoms, constipation, hyperactivity, rash, increased sensitivity, abnormal liver function, increased nail biting frequency, diarrhea, decreased appetite, compulsions, priapism, nocturnal awakening, gynecomastia, and epistaxis, among others. The medication was stopped due to adverse reactions such as weight gain, increased appetite, hypersensitivity, insomnia, increased crying frequency, rash, and abnormal liver function.

The administration of aripiprazole was categorized into two groups: patients who received aripiprazole as monotherapy and those who received aripiprazole in combination with other medications. Dosage and weight changes were analyzed for each group (Table 5). Patients for whom aripiprazole was used as monotherapy, the initial dose was 0.79 mg, the fixed dose was 2.00 mg, and the stabilized dose was 1.89 mg. Patients for whom aripiprazole was used in combination with other medications, the initial dosage was 1.38 mg, the fixed dose was 5.49 mg, and the stabilized dose was 4.27 mg. In patients administered aripiprazole as a monotherapy, it took an average of 15.67 months for dosage fixation. During this time period, the average weight change was 6.94 kg. Conversely, patients who were administered aripiprazole in conjunction with other medications required an average of 44.34 months for dosage fixation. The average weight change during this period was 11.16 kg. During the period leading up to dosage

Table 5. Independent sample t-test comparing in body weight change with aripiprazole usage: categorization based on co-administration of other drugs

	Aripiprazole only (n=64, 39.02%)	Use with other drug (N=100, 60.98%)	t	p
Dosage of aripiprazole (mg)				
Start	0.79±0.38	1.38±1.30	-4.223	<0.001*
Fixed	2.00±1.30	5.49±4.00	-5.476	<0.001*
Stabilized	1.89±1.10	4.27±3.31	-4.005	<0.001*
Weight change (kg)	6.94±6.31	11.16±12.40	-0.952	0.350
Period until dosage fixation (month)	15.67±17.14	44.34±192.09	-0.727	0.469
Weight change per month (kg/month)	0.29±0.30	0.71±0.78	-1.435	0.165

Values are presented as mean±standard deviation. *p<0.05

Table 6. Analysis of variance in body weight change with aripiprazole usage: classification by age group

	Age at start of aripiprazole			F	p	Bonferroni's post-hoc test
	Group 1 (n=64, 39.0%)	Group 2 (n=83, 50.6%)	Group 3 (n=12, 7.3%)			
Dosage of aripiprazole (mg)						
Start	0.74±0.35	1.26±1.19	2.58±1.38	19.727	<0.001*	Group 1<Group 2<Group 3
Fixed	2.34±1.89	4.47±3.93	5.57±1.81	5.672	0.005*	Group 1<Group 2
Stabilized	2.00±0.74	4.10±3.50	4.17±2.32	2.098	0.133	-
Weight change (kg)	5.68±5.37	13.39±12.75	N/A	2.226	0.130	-

Values are presented as mean±standard deviation. Group 1: ages 0 to 6 years 12 months; Group 2: ages 7 to 12 years 12 months; Group 3: ages 13–18 years and 12 months. *p<0.05. N/A, not available

fixation, the average weight change per month was 0.29 kg for those who were administered aripiprazole as monotherapy and 0.71 kg for those were administered aripiprazole in combination with other medications.

Table 6 presents the dosage and weight changes of aripiprazole based on age at medication initiation. For Group 1 (ages 0 to 6 years 12 months), the initial dosage was 0.74 mg, the fixed dose was 2.34 mg, and the stabilized dose was 2.00 mg. For Group 2 (ages 7 to 12 years 12 months), the initial dosage was 1.26 mg, the fixed dose was 4.47 mg, and the stabilized dose was 4.10 mg. For Group 3 (ages 13–18 years and 12 months), the initial dosage was 2.58 mg, the fixed dose was 5.57 mg, and the stabilized dose was 4.17 mg. Weight changes until dosage fixation were as follows: in Group 1 (ages 0–6 years and 12 months) the weight changed by 5.68 kg, and in Group 2 (ages 7–12 years and 12 months) the weight changed by 13.39 kg. There is insufficient data for weight change in Group 3, and hence, it could not be determined.

DISCUSSION

This study included children and adolescents with ASD who were prescribed aripiprazole for managing behavioral challenges commonly found in these individuals. Treatment with aripiprazole began at an average age of 7.64 years, with some starting as young as 3 years old. This indicated that patients with severe behavioral issues related to ASD were prescribed a minimum dosage ≥0.25 mg to manage their symptoms even before reaching the previously established FDA-approved age criterion of 6 years old. The study demonstrated that the mean starting dose for all participants was 1.15 mg. Furthermore, patients <7 years old were administered an average of 0.74 mg, between 7–13 years an average of 1.26 mg, and those between 13–19 years an average 2.58 mg . Dosages were higher for older patients due to a correlation between age, weight gain, and the necessary adjustments to medication dosages to accommodate weight-related changes. It is crucial to evaluate disease severity during prescription. However, this retrospective study lacked precise information regarding disease severity. When administering aripiprazole to patients with ASD, higher dosages were prescribed when combined with other medications compared with when administered as monotherapy. Adjunctive medication is often used for individuals with more severe behavioral symptoms, and is considered an adjunctive treatment for patients whose symptoms are not fully resolved by other measures. It is generally believed that adjunctive medication can help improve and stabilize challenging behaviors.

Methylphenidate had the highest co-administration frequency with aripiprazole, which is likely due to the high prevalence of attention deficits or comorbid ADHD diagnoses in individuals with ASD. Additionally, a higher frequen-

cy of co-administration with SSRIs can be attributed to the frequent co-occurrence of anxiety symptoms in autism. The third concurrent medication was risperidone, an atypical antipsychotic often prescribed when monotherapy with aripiprazole failed to adequately manage behavioral symptoms. The fourth commonly utilized medication was propranolol, which is often employed to treat akathisia, a movement disorder that may arise due to aripiprazole treatment. Atomoxetine is frequently considered as a secondary option when the effectiveness of methylphenidate is limited or complications arise due to side effects or other reasons. This decision may result from an inadequate response to methylphenidate treatment, due to an intolerance to its side effects, or other factors. Valproate is likely to be prescribed for individuals with ASD to address simultaneous impulse control and emotional regulation challenges. Valproate, an anticonvulsant and mood stabilizer, is used to modulate excitatory neurotransmission and stabilize mood. Valproate is prescribed to alleviate impulsive behaviors and to enhance emotional regulation in individuals with ASD, and is generally prescribed because of its potential to target and improve these particular symptom domains. A wide range of medications was used to regulate accompanying symptoms specific to each patient. The choice of supplementary prescriptions was based on personalized evaluations of symptom profiles and therapeutic objectives. This illustrates the intricate character of ASD and necessitated individualized treatment to address the difficulties encountered by each individual.

After reviewing the reported side effect profile by caregivers following the administration of aripiprazole, weight gain and increased appetite were the most frequent adverse effects reported. It should be noted that individual experiences may vary and additional side effects were reported, but these occurred at a lesser frequency. In addition to weight gain and elevated appetite, aripiprazole administration commonly leads to increased sensitivity or irritability and heightened drowsiness. Caregivers also reported several side effects because of aripiprazole treatment including insomnia, increased crying, impulsivity, decreased alertness, repetitive behavior, heightened emotional expression, headaches, vomiting, extrapyramidal symptoms, constipation, excessive motor activity, rash, and abnormal liver function, among others. It is noteworthy that the range of reported side effects was extensive, representing a diverse response to the treatment. Among the reported side effects, weight gain, increased appetite, heightened sensitivity or irritability, insomnia, increased frequency of crying, rash, and abnormal liver function led to discontinuation of the medication. These aforementioned side effects were severe enough to preclude any further usage of the medication. Therefore, it is crucial for healthcare providers to remain vigilant and carefully monitor patients for adverse effects.

There were varying degrees of weight gain associated with the use of aripiprazole as a monotherapy versus its concurrent use with other medications. During aripiprazole monotherapy, weight gain was noted to be 0.29 kg per month until the dosage was stabilized, whereas weight gain was higher at 0.71 kg per month when aripiprazole was used in combination with other medications, suggesting a greater propensity for weight gain with concurrent usage. Higher doses of aripiprazole may have been used to manage more severe behavioral symptoms when co-administered with other medications. This is likely the cause of the observed weight gain.

Weight gain seen in older patient groups administered aripiprazole may occur due to several reasons. First, as people age, their metabolism slows down, making it easier to gain weight. Additionally, adolescent patients are typically exposed to the medication for longer periods compared to pediatric patients, leading to cumulative effects on weight gain. Second, lifestyle factors like decreased physical activity or shifts in dietary habits may lead to weight gain in older adults. Third, the hormonal changes and comorbid conditions often found during adolescence can interact with the impact of the medication on weight regulation. It is also crucial to consider that rapid physical growth during adolescence can result in body composition changes and an increase in weight. Finally, the dosage of the medication prescribed to adolescents is generally higher than that prescribed to pediatric patients, which may increase the occurrence of side effects, such as weight gain. Hence, when examining the age-related patterns of weight gain linked to aripiprazole therapy, it is crucial to bear these factors in mind. Further research and comprehensive analysis are necessary to gain a better understanding of the precise underlying mechanisms responsible for age-related weight gain experienced by individuals administered aripiprazole.

The significance of this study is that it provides insights into the age of treatment initiation, dosage, adverse events commonly reported by caregivers, adverse events leading to treatment discontinuation, types and frequency of concomitant medications, and patterns of weight gain, in pediatric and adolescent patients with ASD treated with aripiprazole. However, this study has several limitations because it is a retrospective chart review study. Another limitation is the reliance on physician interviews or caregiver reports to assess medication side effects and weight changes. This could lead to underreporting and inconsistent results compared with previously established objective assessment methods. In addition, when examining weight gain trends, the correlation between the dose of medication administered and weight gain trends

need to be more closely examined, as well as the dose of medication according to disease severity needs to be evaluated. We were unable to conduct these investigations due to insufficient data in the medical records. Despite these limitations, this study is significant as it is the first report on the pattern of aripiprazole use in 164 child and adolescent patients with ASD in a Korean university hospital. Based on the findings of this study, systematic follow-up studies focusing on patterns of weight gain and other adverse effects of aripiprazole use in Korean children and adolescents should be conducted.

CONCLUSION

This study examined aripiprazole prescribing patterns, associated adverse effects, and concomitant medication trends in 164 child and adolescent patients with ASD using the medical record. Because individuals with ASD often present with significant challenges related to a variety of behavioral issues in addition to core symptoms, it is critical that appropriate medications are used to alleviate symptoms and manage associated adverse effects. To address this, there is a need for future prospective cohort studies and similar follow-up studies to systematically examine comorbid side effects (such as weight changes) associated with medication use.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

Conflicts of Interest

Hee Jeong Yoo, a Editor-in-Chief of the *Journal of the Korean Academy of Child and Adolescent Psychiatry*, was not involved in the editorial evaluation or decision to publish this article. All remaining authors have declared no conflicts of interest.

Author Contributions

Conceptualization: Jae Hyun Han, Hee Jeong Yoo. Data curation: all authors. Formal analysis: Jae Hyun Han. Funding acquisition: Hee Jeong Yoo. Investigation: Jae Hyun Han. Methodology: Jae Hyun Han, Hee Jeong Yoo. Project administration: Hee Jeong Yoo. Resources: all authors. Software: Jae Hyun Han. Supervision: Hee Jeong Yoo. Validation: Jae Hyun Han, Hee Jeong Yoo. Visualization: Jae Hyun Han. Writing—original draft: Jae Hyun Han. Writing—review & editing: Jae Hyun Han, Hee Jeong Yoo.

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REFERENCES

1) **American Psychiatric Association.** Diagnostic and statistical manual of mental disorders, fifth edition, text revision (DSM-5-TR®). Washington, DC: American Psychiatric Association;2022.
2) **Simonoff E, Pickles A, Charman T, Chandler S, Loucas T, Baird G.** Psychiatric disorders in children with autism spectrum disorders: prevalence, comorbidity, and associated factors in a population-derived sample. J Am Acad Child Adolesc Psychiatry 2008;47:921-929.
3) **Yıldız M, Demir Y, Kırcalı A, İncedere A.** Caregiver burden in schizophrenia and autism spectrum disorders: a comparative study. Psychiatry Investig 2021;18:1180-1187.
4) **Breaux R, Baweja R, Eadeh HM, Shroff DM, Cash AR, Swanson CS, et al.** Systematic review and meta-analysis: pharmacological and nonpharmacological interventions for persistent nonepisodic irritability. J Am Acad Child Adolesc Psychiatry 2023;62:318-334.
5) **Posey DJ, Stigler KA, Erickson CA, McDougle CJ.** Antipsychotics in the treatment of autism. J Clin Invest 2008;118:6-14.
6) **Remington G, Sloman L, Konstantareas M, Parker K, Gow R.** Clomipramine versus haloperidol in the treatment of autistic disorder: a double-blind, placebo-controlled, crossover study. J Clin Psychopharmacol 2001;21:440-444.
7) **Doyle CA, McDougle CJ.** Pharmacologic treatments for the behavioral symptoms associated with autism spectrum disorders across the lifespan. Dialogues Clin Neurosci 2012;14:263-279.
8) **Mano-Sousa BJ, Pedrosa AM, Alves BC, Galduróz JCF, Belo VS, Chaves VE, et al.** Effects of risperidone in autistic children and young adults: a systematic review and meta-analysis. Curr Neuropharmacol 2021;19:538-552.
9) **Ghanizadeh A, Tordjman S, Jaafari N.** Aripiprazole for treating irritability in children & adolescents with autism: a systematic review. Indian J Med Res 2015;142:269-275.
10) **Hirsch LE, Pringsheim T.** Aripiprazole for autism spectrum disorders (ASD). Cochrane Database Syst Rev 2016;2016:CD009043.
11) **Ito H, Takano H, Arakawa R, Takahashi H, Kodaka F, Takahata K, et al.** Effects of dopamine D2 receptor partial agonist antipsychotic aripiprazole on dopamine synthesis in human brain measured by PET with L-[β-11C]DOPA. PLoS One 2012;7:e46488.
12) **Sullivan LC, Clarke WP, Berg KA.** Atypical antipsychotics and inverse agonism at 5-HT2 receptors. Curr Pharm Des 2015;21:3732-3738.
13) **Marcus RN, Owen R, Kamen L, Manos G, McQuade RD, Carson WH, et al.** A placebo-controlled, fixed-dose study of aripiprazole in children and adolescents with irritability associated with autistic disorder. J Am Acad Child Adolesc Psychiatry 2009;48:1110-1119.
14) **Owen R, Sikich L, Marcus RN, Corey-Lisle P, Manos G, McQuade RD, et al.** Aripiprazole in the treatment of irritability in children and adolescents with autistic disorder. Pediatrics 2009;124:1533-1540.
15) **Blankenship K, Erickson CA, Stigler KA, Posey DJ, McDougle CJ.** Aripiprazole for irritability associated with autistic disorder in children and adolescents aged 6-17 years. Ped Health 2010;4:375-381.
16) **Teff KL, Rickels MR, Grudziak J, Fuller C, Nguyen HL, Rickels K.** Antipsychotic-induced insulin resistance and postprandial hormonal dysregulation independent of weight gain or psychiatric disease. Diabetes 2013;62:3232-3240.
17) **Blonde L, Kan HJ, Gutterman EM, L'Italien GJ, Kim MS, Hanssens L, et al.** Predicted risk of diabetes and coronary heart disease in patients with schizophrenia: aripiprazole versus standard of care. J Clin Psychiatry 2008;69:741-748.