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전국 자료를 이용한
국내 소아청소년 우울장애에서의
비정형 항정신병 약물의 사용경향

Trends in the Use of Atypical Antipsychotics
among Children and Adolescents
with Depressive Disorders in Korea

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박 기 정

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이 논문을 의학박사 학위논문으로 제출함

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Abstract

Objective: Atypical antipsychotics (AAPs) are increasingly being prescribed in children and adolescents. Most AAPs are prescribed off-label in children and adolescents with depressive disorders. We aimed to investigate the prevalence and trends of AAP prescribing in Korean children and adolescents with depressive disorders.

Methods: We analyzed data from the Korean National Health Insurance Review and Assessment Service (HIRA) to assess AAP prescription among Koreans aged 0-18 years with depressive disorders between 2010 and 2022. This population-based study used an annual cross-sectional assessment to evaluate trends in AAP prescription.

Results: The average annual proportion of AAP prescriptions was 20.30% in children and adolescents with depressive disorders, which increased from 8.11% in 2010 up to 40.95% in 2022 (AAPC, 14.4; 95% CI, 13.8 to 15.9). This rapidly rising trend was pronounced in depressive disorders with psychiatric comorbidities compared to those without. From recent data (2022), the most prescribed AAP for children and adolescents with depressive disorders was aripiprazole, followed by risperidone, quetiapine, and olanzapine. Children and adolescents with depressive disorders and psychiatric comorbidities, particularly ADHD, were prescribed AAPs more frequently ($p<.001$). The dominant AAP has shifted from risperidone to aripiprazole over the last 13 years.

Conclusion: The use of AAPs in children and adolescents with depressive disorders has been increasing over the last decade in Korea. The lack of evidence of off-label AAP use in children and adolescents raises concerns with this finding. Future studies are needed to establish safer and more evidence-based treatments for depressive disorders in children and adolescents.

Keywords: children, adolescents, depression, atypical antipsychotics, comorbidities, longitudinal trends

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Introduction

The worldwide prevalence of depressive disorders is known to be 4-8% in children and adolescents [1]. Depressive disorders are one of the most common leading causes of impairment such as school adaptation problems, interpersonal relationship problems, and educational and occupational underachievement for children and adolescents [2, 3]. However, it is not easy to treat depressive disorders in children and adolescents. Depressive disorders have a high treatment resistance rate of 30-40% despite appropriate first-line antidepressant therapy in children and adolescents [4, 5].

Several studies evaluating the effectiveness of atypical antipsychotics (AAPs) augmentation for depressive disorders suggested that AAPs were effective in treating treatment-resistant depression in adults [6-10]. In this context, AAP prescriptions have been increasing in adults with depressive disorders [11, 12]. U.S. Food and Drug Administration (FDA) approved the use of aripiprazole, brexpiprazole, cariprazine, olanzapine, and quetiapine for major depressive disorder [13]. However, those AAPs use was extended exclusively to individuals above 18. In Korea, aripiprazole (2008) and quetiapine (2010) were approved by the Ministry of Food and Drug Safety only in adults with major depressive disorder.

In children and adolescents, there is no clear consensus on the use of AAP in depressive disorders. To date, there are no randomized controlled trials that examined AAP treatment in unipolar depression. A secondary analysis of TORDIA outcomes at 24 weeks suggests a potential advantage from early augmentation with atypical antipsychotics [14]. On the other hand, augmentation strategies with antipsychotics could be considered to have insufficient evidence in the pediatric population [15, 16]. Treatment guidelines for depression in children and adolescents are also inconsistent with the use of AAPs. Canadian Network for Mood and Anxiety Treatments (CANMAT) recommends psychotherapy as first-line treatment and antidepressant monotherapy as second-line treatment for depressive disorders in children and adolescents [17]. This aligns with the American Academy of Child and Adolescent Psychiatry (AACAP) guidelines [18, 19]. In the AACAP guidelines, the combination of antidepressants with antipsychotics is recommended only for patients with psychotic depression [18]. In Korea, the Korean Medication Algorithm Project for Depressive Disorder (KMAP-DD) recommends first-line therapy in children and adolescents with depressive disorders as antidepressant monotherapy [20]. KMAP-DD also recommends the combination of antidepressants and AAPs as the first-line strategy for severe depression with or without psychotic features [20].

Nevertheless, AAPs are already increasingly being prescribed to children and adolescents including those with depressive disorders [21-25]. Today, most AAPs are used off-label in children

and adolescents with depressive disorders. However, only a few studies have shown the use of AAPs in Korean children and adolescents even that represents overall mental illness, not depressive disorders [24, 26]. Therefore, we aim to provide prescription trends of AAPs in Korean children and adolescents with depressive disorders using nationwide data. We evaluated 1) prevalence and longitudinal trends of depressive disorders and AAP prescription, 2) current prescription patterns of AAP and concomitant medications according to psychiatric comorbidities, and 3) factors associated with AAP prescription in children and adolescents with depressive disorders. Without Korean population data, this study could provide epidemiological data based on real-world evidence. It could contribute to establishing optimal and safe treatment approaches for children and adolescents with depressive disorders.

Materials and Methods

We conducted a population-based study with an annual cross-sectional assessment of AAP prescription between 2010 and 2022 for all Korean residents aged 0-18 years with depressive disorders using the Korean National Health Insurance Review and Assessment Service (HIRA).

The research protocol was approved by the Institutional Review Board of Asan Medical Center (IRB no.2023-0265). The requirement of informed consent was waived by the board.

Data source

Korea has maintained a government-run health insurance system managed by the Korean National Health Insurance Service (NHIS) for over 40 years. NHIS database covers about 97% of the Korean population and contains medical information that is highly representative of the entire Korean population [27]. All claims from NHIS and the medical aid program (the other 3%) have been covered by the Health Insurance Review and Assessment Service (HIRA). We used the HIRA database between 2010 and 2022, the maximum amount of data allowed from HIRA (HIRA research data, M20230626014).

The HIRA database provides claim records including each patient's demographic, diagnostic, and prescription information. Diagnoses are coded according to the International Classification of Disease, 10th revision (ICD-10). Prescription data contains the drug's Anatomical Therapeutic

Chemical (ATC) code, the date of prescription, the number of prescription days, and information on the prescribing physician's specialty.

Study population

The study population was defined as individuals aged 0-18 years who had at least one claim for depressive disorders from January 1, 2010, to November 30, 2022 (This was the most recent data available at the time of the study). Using data on the primary diagnosis and first sub-diagnosis in each calendar year, we identified patients with depressive disorders (ICD-10: F32, F33, F34.1, F34.8, F34.9, F38.1, F38.8, F39). Individuals who had been diagnosed with both depressive disorders and bipolar disorders in that calendar year were excluded. We exclude those who were diagnosed with organic mental disorders; mental and behavioral disorders due to psychoactive substance use; schizophrenia; intellectual disability; autism spectrum disorder; and disorders of the nervous system.

According to the previous literature [28, 29] and clinical experts' advice, ten drugs among the antipsychotics were considered atypical antipsychotics: amisulpride, aripiprazole, blonanserin, clozapine, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone, and zotepine. Atypical antipsychotic prescription in calendar year was defined as having at least one claim record for an atypical antipsychotic prescription with a diagnosis code for depressive disorder, either as the primary diagnosis or the first sub-diagnosis.

Study design

Analysis for longitudinal trends

We estimated the annual prevalence rates of depressive disorders and prescriptions of AAP from 2010 to 2022 based on number of patients. Those prevalence rates were adjusted for age groups with the 2005 Korean census and world standard populations as references [30].

1) Depressive disorders prevalence rate: number of children and adolescents aged 0-18 years with depressive disorders per 1,000 pediatric population

2) The proportion of AAP prescriptions: number of children and adolescents aged 0-18 years with depressive disorders and AAP prescription per children and adolescents aged 0-18 years with depressive disorders

We estimated changes in the prevalence of the annual period using joinpoint analysis. Joinpoint analysis was used to identify the best-fitting point, where a statistically significant change (called the joinpoint) had occurred, and to determine the trends between joinpoints. Trends were assessed by calculating Annual Percent Change (APC) and its corresponding 95% confidence interval (CI) between consecutive change points. With this approach, the prevalence rates are assumed to change at a constant percentage of the previous year's rate. Rates at a constant percentage every year change linearly on a log scale. In addition, Average Annual Percent Change (AAPC) was calculated as a summary measure of the trend. It allows us to use a single number to describe the average APCs over multiple years. It is valid even if the joinpoint model indicates that there were changes in trends during those years. It is computed as a weighted average of the APCs from the joinpoint model, with the weights equal to the length of the APC interval [31].

Annual prescription trends of each AAP were analyzed based on number of claims. We defined one case as one claim with 28 days of prescription. The number of cases was counted proportional to the number of prescription days. Claim with more than one antipsychotic prescription was counted as separate cases for each AAP.

Analysis for current trends

To evaluate characteristics and detail prescription patterns of AAPs and concomitant medication, we only used data from 2022. All characteristics and detailed prescription patterns of AAPs and concomitant medication were analyzed based on number of patients.

We evaluated the characteristics of children and adolescents with depressive disorders prescribed with AAPs including variables as follows: age, sex, types of health security programs, types of healthcare services received, types of healthcare institution, physician specialty, and psychiatric comorbidities. The types of health security programs were exclusively divided into NHIS and medical aid program. Patients enrolled in the medical aid program were defined as those with at least one experience in the medical aid program during the calendar year. Patients enrolled in the NHIS were defined as those continuously enrolled in the NHI program during the calendar year. The types of healthcare services received were divided into inpatient and outpatient services. The study population was defined as inpatients who had experienced hospital admission at least once and outpatients if who had only outpatient visits during the calendar year. The types of healthcare institutions were divided into two groups: clinics (<30 beds and primarily for outpatients) and hospitals (>= 30 beds) [32]. The types of healthcare institutions were determined based on those that

provided the first services to the patients during the calendar year.

A logistic regression analysis was performed to identify the patient's characteristics associated with AAP prescribing. The dependent variables of patients who received at least one AAP prescription during a calendar year were denoted as 1 and 0 if otherwise in the logistic regression model. The initial analysis was adjusted for age and comorbid disorder with a significant level of $p < 0.1$ in subsequent analysis.

For the AAP prescription pattern by comorbid psychiatric disorders in 2022, we subdivided depressive disorders patients into those without any psychiatric comorbidities, those with comorbid ADHD, and those with psychiatric comorbidities other than ADHD. The concomitant medication of those prescribed AAP was also investigated according to comorbidities. Previous studies reported that ADHD was the most prevalent diagnosis in children and adolescents who used antipsychotics [15, 33]. We assumed that ADHD could influence on AAP prescription of depressive disorders in children and adolescents.

The analyses were performed using SAS Enterprise Guide software (version 7.1; SAS Institute, Inc., Cary, NC). The joinpoint regression analyses for identifying changes in trend were performed using the Joinpoint Regression Program (version 5.0.2, May 2023; Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute). All the significance level was set at $p < .05$.

Results

Overall, the data comprised information from more than 7.5 million children and adolescents in each calendar year (2010: 10,979,932, 2022:7,851,681)

Prevalence of depressive disorders and AAP prescription

The annual prevalence of depressive disorders among children and adolescents increased over the 13-year study period from 2.85 in 2010 up to 7.10 per 1,000 population in 2022, which is a 2.49-fold increase (Figure 1). Over the whole period from 2010 to 2022, the prevalence increased by an average of 1.074-fold per year (AAPC, 7.4; 95% CI, 5.9 to 9.7). The change in prevalence was not

significant until mid-2010, but it has increased after mid-2010: 2010-2016 (APC, -0.9; 95% CI, -12.7 to 5.3) and 2016-2022 (APC 16.3; 95% CI, 13.5 to 22.8) (Figure 2A).

This trend was similar between boys and girls, although there was a one-year difference in the year the increase began. Girls started showing a significant increase from 2015 (Figure 2C). A year later than that, boys showed a significant increase starting from 2016 same as the overall children and adolescents with depressive disorders (Figure 2B). In addition, depressive disorders have increased more rapidly in girls (2016-2022 APC, 16.6; 95% CI, 13.9 to 22.5) than in boys (2015-2022 APC 14.8; 95% CI, 12.3 to 20.3) after mid-2010 (Figure 1, 2). As a result, the gap between boys and girls has become wider after mid-2010. The estimated gap in prevalence between boys and girls was 0.18 per 1,000 population in 2010 and 1.53 per 1,000 population in 2022, respectively.

It was also observed that the prevalence of depressive disorders increased with age. The estimated average prevalence of depressive disorders was 0.18, 2.50, and 8.49 per 1,000 population among younger children (aged 0–5 years), older children (aged 6–12 years), and adolescents (aged 13–18 years), respectively.

Figure 3 shows the proportion of AAP prescriptions among children and adolescents with depressive disorders from 2010 to 2022. The annual proportion of AAP prescriptions among children and adolescents with depressive disorders rapidly increased from 7.84% in 2010 to 41.17% in 2022, which is a 5.25-fold increase. Over the whole period from 2010 to 2022, the proportion increased by an average of 1.144-fold per year (AAPC, 14.4; 95% CI, 13.8 to 15.9). Based on joinpoint analysis, the increase in proportion was steady in overall children and adolescents with depressive disorders (Figure 4A). The overall trend was the same in boys (Figure 4B), but three periods with distinct trends were observed in girls (Figure 4C): 2010-2015 (APC, 9.9; 95% CI, -6.8 to 16.3), 2015-2018 (APC, 25.4; 95% CI, 20.1 to 31.3) and 2018-2022 (APC 12.9; 95% CI, 11.2 to 14.4). The rise in the proportion of AAP prescriptions coincides with the rise in the prevalence of depressive disorders in girls. The proportion of AAP prescriptions was similar in boys and girls at the beginning of the study period, but the gap gradually widened during the study period (3.57% in 2010 vs 14.37% in 2022). Contrary to the prevalence of depressive disorders, the proportion of AAP prescriptions was steadily higher in boys.

Regardless of age group, the proportion of AAP prescriptions has steadily increased (Figure 5A). Among age groups, older children showed the highest proportion. The average annual proportion of AAP prescriptions was 12.75%, 26.89%, and 20.39% among younger children, older children, and adolescents with depressive disorders, respectively. The proportion of AAP prescriptions most

increased over the 13 years in younger children (increased by 38.13%, from 1.13% to 39.26%), followed by older children (increased by 38.06%, from 10.74% to 48.80%), and adolescents (26.61%, from 10.45% to 37.06%). However, the prevalence of AAP prescriptions with depressive disorders increased with age (Figure 5B). The prevalence of AAP prescription with depressive disorders was highest in adolescents (from 0.617/1,000 person to 5.813/1,000 person), followed by older children (from 0.230/1,000 persons to 2.283/1,000 person), and younger children (from 0.002/1,000 person to 0.120/1,000 person). This trend has been maintained over the 13 years.

We also estimated the proportion of AAP prescriptions in depressive disorders by psychiatric comorbidities. The increasing trend observed in overall depressive disorders was more pronounced and evident in depressive disorders with psychiatric comorbidities (Figure 6A). The proportion of AAP prescriptions with psychiatric comorbidities (increased by 39.42%, from 11.68% to 51.10%) rapidly increased than those without psychiatric comorbidities (increased by 17.2%, from 3.91 % to 21.11%). With psychiatric comorbidities, younger children showed the most rapid increase (increased by 51.27%), followed by older children (increased by 41.78%), and adolescents (increased by 26.87%). Without psychiatric comorbidities, the proportion increased slowly across all age groups (younger children, increased by 14.87%; older children, increased by 16.88%; adolescents, increased by 19.48%). The trend of higher prevalence with increasing age remained over the whole period (Figure 6B).

Longitudinal prescription trend of AAPs with depressive disorders

The dominantly prescribed AAPs with depressive disorders were aripiprazole, risperidone, quetiapine, and olanzapine (Figure 7A). Risperidone was the most commonly prescribed AAP drug, followed by quetiapine, aripiprazole, and olanzapine in 2010. Over the 13 years, the proportion of risperidone prescriptions decreased (from 76.10% in 2010 to 14.91% in 2022), whereas that of aripiprazole prescriptions increased (from 15.97% in 2010 to 87.77% in 2022). The proportion of aripiprazole prescriptions in 2022 was more than five times that in 2010. The proportion of quetiapine (from 11.47% in 2010 to 10.47% in 2022) and olanzapine (from 1.53% in 2010 to 1.46% in 2022) relatively remained over the whole period. The proportion of the other AAPs, which was 3.99% in 2010, gradually decreased to only 0.61% in 2022.

Current prescription pattern of AAPs with depressive disorders

Among children and adolescents with depressive disorders, the proportion of AAP prescriptions was 41.17% in 2022. The proportion of AAP prescriptions was 47.98% in boys and 33.68% in girls, respectively.

In the multivariable logistic regression analysis, elementary school student (6-12 years) (Adjusted Odds Ratio, AOR 1.32; 95% CI 1.27-1.38), boys (AOR 1.24; 95% CI 1.20-1.28), hospitalization in calendar year (AOR 5.39; 95% CI 4.54-6.38), visit at clinic (AOR 1.08; 95% CI 1.03–1.13), visit a psychiatrist (AOR 1.91; 95% CI 1.74-2.09), having comorbid ADHD (AOR 2.63; 95% CI 2.51-2.76), and the other comorbid mental disorders (AOR 2.18; 95% CI 2.09-2.27) significantly increased the odds of having an AAP prescription in depressive disorders (Table 2).

In this study, the most frequently prescribed AAPs in children and adolescents with depressive disorders were aripiprazole (87.77%), followed by risperidone (14.91%), quetiapine (10.47%), and olanzapine (1.46%) in 2022 (Table 3).

In Table 4, the proportion of AAP prescriptions was highest in the group with comorbid ADHD (51.25%), followed by the group with the other comorbidities (43.20%) and without comorbidities (25.25%) ($p < .001$). Aripiprazole was the most commonly prescribed AAP in groups without comorbidities and with other comorbidities, followed by quetiapine, risperidone, and olanzapine. However, the prescription pattern differed in the comorbid ADHD group, where aripiprazole became the preferred AAP, followed by risperidone, quetiapine, and olanzapine. Notably, quetiapine emerged as the second most common AAP in the other groups, while risperidone took that position in the comorbid ADHD group.

Current prescription pattern of concomitant medications among children and adolescents with depressive disorders who were prescribed AAP

Concomitant medications among children and adolescents with depressive disorders who were prescribed AAP were evaluated (Table 5). Typical antipsychotics were prescribed most frequently in the other comorbidities group, followed by the comorbid ADHD group and without comorbidities group ($p < .001$). Mood stabilizers were showed the same pattern ($p<.001$).

On the other hand, antidepressants and anti-anxiety drugs were prescribed less frequently in children and adolescents with comorbid ADHD, than followed by the without comorbidities group and with the other comorbidities group (both $p < .001$).

Differences among groups are observed with the prescription trend of specific drugs by category.

In mood stabilizers, the most commonly prescribed drug was lithium in the other two groups, but valproate in the comorbid ADHD group. The comorbid ADHD group was prescribed significantly less lithium ($p<.001$) and more valproate ($p<.001$) than the other two groups. In anti-anxiety drugs, the most commonly prescribed drug was alprazolam in all three groups, respectively. The secondary most common prescribed drug was lorazepam in the other two groups, but clonazepam in the other comorbidities group. Clonazepam was significantly more prescribed in the other comorbidities group than in the other two groups ($p<.001$).

In Table 5, only the top three drugs are listed for each drug class. The other drugs prescribed in each group can be found in Table 6.

Discussion

Several studies have shown the prevalence of depressive disorders in the general pediatric population as 1-8% [1, 34, 35]. The prevalence (range: 0.285-0.710%) was lower in this study. Another study using sample data of HIRA that includes 3% of the total population reported the prevalence of depressive disorders among Korean children and adolescents as 0.364% [36]. We assumed that the following several factors may have had an impact. First, the HIRA database only contains information on the population who used medical services. The 2022 national mental health survey found that only 6.6% of children and adolescents with a lifetime history of psychiatric disorders ever received mental health services in Korea [37]. Second, we used only the primary diagnosis and first sub-diagnosis data of clinic patients to increase diagnostic accuracy.

In this study, depressive disorders have increased significantly in children and adolescents. This result is consistent with that of other studies conducted in various countries including Asia, Europe, and North America [1, 38-41]. In Korea, we only found the prevalence of major depressive disorder (MDD) in diagnostic epidemiologic studies conducted on children and adolescents [37, 42]. The one-year prevalence rate of MDD was 0.52% in 2005 [42]. A recent study conducted in 2022 reported a current prevalence rate of 0.5% and a lifetime prevalence rate of 1.0% for MDD [37]. However, this study showed a sharp increase in depressive disorders since mid-2010. The rise in depressive disorders among Korean children and adolescents could be related to several factors. Firstly, mental health awareness for children and adolescents has increased. Since the early 2010s, parenting-focused reality TV shows, media appearances, and book publications of child & adolescent psychiatrists have

become more frequent, and some have even grown into celebrities. Those phenomena could have an impact on destigmatizing mental health treatment for children and adolescents and promoting the role of child & adolescent psychiatrists. Secondly, school-based mental health services have been gradually expanding since the late 2000s, making it easier for children and adolescents to access psychiatric intervention. As part of that, the Korean government began to promote Emotional and Behavioral Screening Questionnaires (EBSQ, 2007) [43] and the Wee project (2008) [44]. EBSQ, which is a self-report scale for screening mental health problems has been performed for all children and adolescents nationwide since 2012. The Wee project, which was started as a crisis support system now offers school counseling for all students [44]. Thirdly, adolescents in South Korea face intense competition for college entrance. This academic stress, often called "education fever," significantly burdens them. Based on the Comprehensive Survey of Children (2013), Korean children and adolescents reported the highest levels of academic stress among the 30 OECD member countries [45]. This pressure is further amplified by the rising number of students repeating college entrance exams each year [46]. Fourthly, the rapid increase in depression since mid-2010 coincides with the explosive increase in smartphone penetration and Social Network Service (SNS) use starting in the early 2010s. Smartphone penetration among children and adolescents under 18 increased from 8% in 2011 to 64% in 2015 in Korea [47]. Previous studies reported the association between social media use and depressive symptoms [48, 49].

Additionally, several studies suggest that exposure to self-harm contents on social media could evoke copycat behavior in adolescents [50, 51]. This aligns with the rise in the number of self-harm behaviors among Korean adolescents over the past decade [51, 52]. One possible explanation for the rise of depressive disorders could be that an initial self-harm episode triggers the development of depressive symptoms through a cycle of repeated self-harm behavior [53].

The prevalence of depressive disorders steadily increased among both boys and girls, but gender disparity has widened over time in the current study. The results of this study are consistent with Daly's report [38]. Daly found that the gender disparity in depression more than doubled, driven by a substantial rise in the prevalence of depressive episodes among girls in the 2010s. The author suggests that potential reasons for this increase include increases in bullying and use of social media and technology which may have been more impactful for girls than boys [38, 48].

AAP prescription in children and adolescents with depressive disorders has been increasing over the last decade in this study. We could only find studies that evaluated AAP trends in the overall pediatric population, not for depressive disorders [23-25]. Although direct comparison is difficult due to differences in subjects, our finding that the prevalence of prescriptions increased with age aligns

with previous studies [21, 22]. Changes in prescribing patterns of antidepressants after black box warning (2004) could be considered one of the causes of the increase. After warning, several studies reported physician reluctance to prescribe antidepressants in children and adolescents [54, 55], accompanied by a decrease in antidepressant use observed [56-58]. This background of concern about the black box warning on antidepressants might have led to an increase in AAP augmentation. Contrary to pharmacological treatment, limited coverage of non-pharmacological treatments by the NHIS could be another reason of an increased use of AAPs in depressive disorders. Also, the increase could be attributed to the expanding indications of AAPs for psychiatric comorbidities in children and adolescents. In Korea, risperidone was the first AAP approved by the Ministry of Food and Drug Safety for its indication as disruptive behavior disorders in children and adolescents (2003). Subsequently, aripiprazole was approved in 2011 for autism spectrum disorder and Tourette's disorder in children and adolescents. Additionally, the launch of a 12.5mg low dose quetiapine (2017) and a 1mg low-dose aripiprazole formulation (2021) could make it easier to prescribe for children and adolescents in Korea.

We found a few studies including data on antipsychotics for depressive disorders in children and adolescents. In the study using nationwide data, the most commonly used antipsychotic was quetiapine, followed by risperidone, olanzapine, and aripiprazole [21]. Since their data spans the past 20 years (2000-2019), our results might differ due to the period discrepancy. Another study using recent data (2018-2021) reported that the most prescribed AAP for children and adolescents with depressive disorders was quetiapine, followed by aripiprazole, olanzapine, risperidone, and lurasidone [59]. Their finding that aripiprazole was used more frequently than risperidone was consistent with this study. In our study, aripiprazole replaced risperidone as the most prescribed atypical antipsychotic drug after 2013. This replacement was also observed in Japan [60]. In the study of Japan (2024), the authors suggested that one of the reasons for replacement was the higher safety and efficacy of aripiprazole than risperidone [60]. This would also apply in Korea. Significantly, fewer side effects such as weight gain, hyperprolactinemia, and over-sedation may contribute to aripiprazole's growing use in Korea. As precocious puberty is on the rise [61], there is a growing emphasis on weight control in Korean children and adolescents. In addition, considering that Korean society values academic achievement, people are susceptible to anything that may disrupt attention, including over-sedation from AAP. This factor may also have contributed to the relatively lower prescription rates of quetiapine, the most common AAP for children and adolescents with depressive disorders in previous studies [21, 59]. From another perspective, Lee and his colleagues explained changes in the use of risperidone and aripiprazole in Korea by the timing of insurance coverage, market adoption process,

and insurance price [24]. Lastly, aripiprazole has been approved for a broader range of indications including Tourette's syndrome in children and adolescents, than risperidone, which is also one of the reasons for the increased prescription rate of aripiprazole.

However, there are several notable findings regarding the proportion of AAP prescriptions among children and adolescents with depressive disorders in this study. Firstly, this study's proportion of AAP prescriptions was highest in older children (aged 6-12 years). This finding was more evidently observed in older children with psychiatric comorbidities than those without psychiatric comorbidities. ADHD and tic disorders are some of the most common psychiatric diseases in children aged 6-12 years old [62, 63]. In particular, hyperactivity is one of the representative symptoms of ADHD, and it increased steadily over the 6-12 years old [62]. Also, the irritability associated with childhood depression and ADHD may manifest as temper tantrum, anger outburst, and hostile behavior [62, 64] and those behaviors can be mistaken as violence. High vigilance to behavior problems in Korean culture can be related to the increased use of AAP in older children with comorbid ADHD.

In Korea, The School Violence Prevention and Countermeasures Act was passed in 2004, which led to the 'Committee for Countermeasures against School Violence' in grade schools nationwide to review bullying. In addition, schools must document bullying incidents in the perpetrator's record according to the law from 2012. After this, students, parents, and teachers became more vigilant to school violence. In the 2023 survey by the Korean Ministry of Education, the highest rate of school violence victims came from elementary schools at 3.9 percent, followed by 1.3 percent in middle schools and 0.4 percent in high schools [65]. This background may have led to more offensive use of AAPs to control behavioral problems in older Korean children with depressive disorders. Also, this may explain the higher proportion of AAP prescriptions in boys, contrary to the prevalence. Secondly, both the prevalence and proportion of AAP prescriptions were increased in younger children over the 13 years. This finding is inconsistent with previous studies in overall children [21, 22, 66]. With studies in other countries with data from a similar period as this, the prevalence of AAP use among children under five years old did not change significantly during the entire study period [21, 22]. Even in the United States, antipsychotic use in young children has been decreasing [66]. In these countries, there are efforts to establish the rational use of antipsychotics for children and adolescents. In England, general practitioners do not initiate antipsychotic medications in patients younger than 18 years old [21]. In the US, over 31 state Medicaid programs have adopted prior authorization policies, requiring peer review before prescribing antipsychotic medications to Medicaid-enrolled children [67]. Those policies have been shown to reduce the prevalence of pediatric antipsychotic use [68-70]. The absence

of monitoring programs or peer review systems for AAP prescriptions in children and adolescents might be a contributing factor to their rise in Korea.

Additionally, in this age group, the difference in the proportion of AAP prescriptions was pronounced regarding psychiatric comorbidities. Psychiatric comorbidities such as ADHD and tic disorder are also common in this age group as well as older children. While ADHD medications are not approved for children under six years old, AAP like risperidone, is approved for disruptive behavior disorders in children five years old and older in Korea. In Korea, methylphenidate and other medical narcotics are subject to very strict regulations, when used outside of approved indications [71]. This background may influence the increased use of atypical antipsychotics to control psychiatric comorbidities in younger children with depressive disorders. Other potential contributors include off-label marketing by pharmaceutical companies [72-75] and the limited coverage of non-pharmacological treatments by the NHIS. However, this finding requires cautious interpretation because of the small number of children in this age group with depressive disorders. The number of patients with depressive disorders in Korea counted in this study is only a few hundred for those of younger children (n, 311-568), and tens of thousands for those of older children (n, 5,677-14,761) and adolescents (n, 20,084-59,270). As the number of patients prescribed AAP increases by one, the proportion of prescriptions inevitably increases more in younger children than older children and adolescents. Nevertheless, further research is needed to identify the specific causes of the increased AAP prescription in younger children. Additionally, specific efforts are necessary to reduce misuse of AAP in this age group.

This study found that AAP prescription was more prevalent in children and adolescents with depressive disorders and psychiatric comorbidities, especially comorbid ADHD, which aligns with previous studies that antipsychotics including AAP are most frequently used for ADHD in children and adolescents [15, 23]. In addition, the prescription patterns of AAP and concomitant medication were different according to psychiatric comorbidities in current study. risperidone was the second most used AAP in the group with comorbid ADHD in this study. In groups without comorbidities or with comorbidities other than ADHD, risperidone was the third drug after quetiapine. We can assume that the choice of risperidone in cases of comorbid ADHD increased risperidone use in children and adolescents with depressive disorders. Risperidone is known as AAP with a relatively well-established basis for controlling behavioral problems in ADHD [76, 77]. Also, the prescription of mood stabilizers was most frequent in children and adolescents with depressive disorders and comorbid ADHD. In children and adolescents, bipolar disorder and ADHD share common symptoms of impulsivity, distractibility, and sleep difficulties that make it difficult to diagnose accurately [78].

In addition, children and adolescents with comorbid diagnoses of major depressive disorder and ADHD had an increased risk of diagnostic conversion to bipolar disorder compared to those who had significant depression alone [79]. Moreover, because this study confirmed the diagnoses with claim data in the year, it is possible that patients who were diagnosed with bipolar disorder before the year were included in the depressive disorders group. Those factors explain some of the reasons for the increased use of mood stabilizers in children with comorbid ADHD. In addition, the reason that valproate was more used than lithium in children with depressive disorders and comorbid ADHD can be appetite loss as a side effect which often occurs with ADHD medication, also occurs with lithium.

In the current study, visiting a clinic was associated with AAP prescriptions. We decided on the types of healthcare institutions based on those that provided the first services to the patients during the calendar year. In 2020, 72.5% of all outpatients used clinics in Korea [80]. Therefore, it is questionable whether this factor is actually associated with AAP prescription.

Some limitations of this study should be noted. Firstly, our findings on the use of AAPs to treat depressive disorders in children and adolescents may be difficult to generalize due to the influence of sociocultural background and circumstances in this specific context. Secondly, the diagnoses were based on ICD-10 codes in the HIRA database. Those diagnoses were not evaluated with structured psychiatric interviews, and we could not determine the intended indication for antipsychotic treatment. We use only the primary diagnosis and first sub-diagnosis data of clinic patients to increase diagnostic accuracy. However, the accuracy of medical coding is still a concern. Thirdly, the results of this study did not include prescription dose and duration data of AAPs. The analysis included cases where only a small dosage of AAP was prescribed, either as a single use or discontinued early before completing the full prescription period. Therefore, the interpretation of results should be done carefully, considering this. Lastly, data to analyze current trends is only covered for part of the year. The most recent data available when the study began was November 2022. Although one-month of data would not change the overall trend, it is necessary to consider this.

Conclusion

To the best of our knowledge, this study is the first to examine the population use of AAP medications among children and adolescents with depressive disorders. Among the use of AAP medication in children and adolescents with mental illness, no study results have shown the specific

use of those drugs. The findings of this study are worthwhile in that they are not only highly representative but also provide valuable data for estimating AAP use in children and adolescents with depressive disorders.

This study showed that the prevalence of AAP prescription progressively increased among Korean children and adolescents with depressive disorders. The major AAP drug of choice among prescribers has shifted from risperidone to aripiprazole over the 13-year study period. This change was observed regardless of the presence or absence of comorbidities.

AAP use increased across all age groups, including younger children aged 0-5 years. The lack of evidence of off-label AAP use in children and adolescents raises concerns with this finding. Future studies are needed to investigate the reasons for the increasing use of AAPs in children and adolescents with depressive disorders.

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국문요약

목적: 소아청소년에서 비정형 항정신병 약물의 처방이 점차 증가하고 있다. 대부분의 비정형 항정신병 약물은 우울장애 소아청소년에서 허가범위 외(off-label)로 사용되고 있다. 본 연구에서는 국내 우울장애 소아청소년에서의 비정형 항정신병 약물의 사용경향과 발생률을 조사하고자 한다.

방법: 건강보험심사평가원 전국민 자료를 기반으로, 2010-2022 년까지 국내 소아청소년 (0-18 세) 우울장애 환자의 비정형 항정신병 약물 처방을 분석했다. 비정형 항정신병 약물의 사용경향을 평가하기 위해 매년 단면적 분석을 시행했다.

결과: 국내 소아청소년 우울장애에서 비정형 항정신병 약물의 처방율은 평균 20.30% 였으며, 2010 년 8.11%에서 2022 년 40.95%로 증가했다 (AAPC, 14.4; 95% CI, 13.8 to 15.9). 비정형 항정신병 약물의 처방율의 급격한 증가는 정신과적 동반이환질환이 있는 소아청소년 우울장애에서 더 유의하게 관찰되었다. 13 년간의 연구기간 동안 가장 많이 처방되는 비정형 항정신병 약물은 리스페리돈에서 아리피프라졸로 바뀌었다. 최신자료(2022)에서는 우울장애 소아청소년에서 아리피프라졸, 리스페리돈, 퀘티아핀, 그리고 올란자핀 순으로 많이 처방되었다. 또한 정신과적 동반이환질환, 특히 ADHD 를 동반한 우울장애 소아청소년에서 비정형 항정신병 약물이 더 빈번하게 처방되었다 ($p<.001$).

결론: 지난 십여 년간 한국 소아청소년 우울장애에서의 비정형 항정신병 약물의 사용은 증가하고 있다. 허가범위 외 사용에 대한 근거가 부족한 현실에서 비정형 항정신병 약물의 사용에 주의가 필요하다. 소아청소년 우울장애에서 보다 안전하고 근거중심의 치료가 이루어지기 위해서는 추가연구가 필요하다.

핵심어: 소아, 청소년, 우울장애, 비정형 항정신병 약물, 동반이환질환

Table 1. Epidemiology of children and adolescents with depressive disorders who were prescribed atypical antipsychotics in Korea (2022)

	Depressive disorders overall		Depressive disorders with AAP prescription		Depressive disorders without AAP prescription	
	n=59,270		n=23,712		n=35,558	
Age, years						
mean (SD)	14.24	(3.36)	13.80	(3.53)	14.54	(3.21)
0-5 years, n(%)	568	(0.96)	223	(0.94)	345	(0.97)
6-12 years, n(%)	14,761	(24.90)	7,204	(30.38)	7,557	(21.25)
13-18 years, n(%)	43,941	(74.14)	16,285	(68.68)	27,656	(77.78)
Sex, boys, n(%)	27,056	(45.65)	12,134	(51.17)	14,922	(41.97)
Types of health security programs, n(%)						
national health insurance	56,155	(94.74)	22,411	(94.51)	33,744	(94.90)
medical aid	3,115	(5.26)	1,301	(5.49)	1,814	(5.10)
Types of healthcare services received, n(%)						
outpatient care	58,522	(98.74)	23,166	(97.70)	35,356	(99.43)
inpatient care	748	(1.26)	546	(2.30)	202	(0.57)
Types of health care institutions, n(%)						
clinics	49,068	(82.79)	19,833	(83.64)	29,235	(82.22)
hospitals	10,202	(17.21)	3,879	(16.36)	6,323	(17.78)
Physician specialty, n(%)						
psychiatry	56,372	(95.11)	23,028	(97.12)	33,344	(93.77)
non-psychiatry	2,898	(4.89)	684	(2.88)	2,214	(6.23)
Psychiatric comorbidities, yes, n(%)	40,511	(68.35)	18,975	(80.02)	21,536	(60.57)
without psychiatric comorbidities	18,759	(31.65)	4,737	(19.98)	14,022	(39.43)
with ADHD	18,293	(30.86)	9,376	(39.54)	8,917	(25.08)
with the other psychiatric comorbidities	22,218	(37.49)	9,599	(40.48)	12,619	(35.49)

Note: Data was analyzed from January 1 to November 30, 2022. AAP, atypical antipsychotic; ADHD, attention deficit hyperactivity disorder; SD, standard deviation

Table 2. Factors associated with atypical antipsychotics prescribing among children and adolescents with depressive disorders in Korea (2022)

		95% CI for OR				95% CI for OR		
	OR	lower	upper	p-value	adjusted OR	lower	upper	p-value
Age								
0-5	1.10	(0.93	, 1.30)	0.281	1.11	(0.93	, 1.32)	0.264
6-12	1.62	(1.56	, 1.68)	<.001*	1.32	(1.27	, 1.38)	<.001*
13-18	1.00				1.00			
Sex								
boys	1.45	(1.40	, 4.50)	<.001*	1.24	(1.20	, 1.28)	<.001*
girls	1.00				1.00			
Types of health security programs								
medical aid	1.08	(1.00	, 1.16)	0.038*	1.06	(0.98	, 1.14)	0.154
national health insurance	1.00				1.00			
Types of healthcare services received								
Inpatient care	4.13	(3.51	, 4.85)	<.001*	5.39	(4.54	, 6.38)	<.001*
outpatient care	1.00				1.00			
Types of health care institutions								
clinics	1.11	(1.06	, 1.16)	<.001*	1.08	(1.03	, 1.13)	<.001*
hospitals	1.00				1.00			
Physician specialty								
psychiatry	2.24	(2.05	, 2.44)	<.001*	1.91	(1.74	, 2.09)	<.001*
non-psychiatry	1.00				1.00			
Psychiatric comorbidities, yes, n(%)								
without psychiatric comorbidities	1.00				1.00			
with ADHD	3.11	(2.98	, 3.25)	<.001*	2.63	(2.51	, 2.76)	<.001*
With the other psychiatric comorbidities	2.25	(2.16	, 2.35)	<.001*	2.18	(2.09	, 2.27)	<.001*

Note: Data was analyzed from January 1 to November 30, 2022. The odds ratio was adjusted for $p < 0.1$ and psychiatric comorbidities groups.*Significant at the $p < .05$ level. AAP, atypical antipsychotic; ADHD, attention deficit hyperactivity disorder; C.I, confidence interval; OR, odds ratio

Table 3. Prescription pattern of atypical antipsychotics among children and adolescents with depressive disorders in Korea (2022)

Atypical antipsychotics	n	(%)
Aripiprazole	20,813	(87.77)
Risperidone	3,535	(14.91)
Quetiapine	2,483	(10.47)
Olanzapine	346	(1.46)
Paliperidone	44	(0.19)
Blonanserin	44	(0.19)
Amisulpride	26	(0.11)
Ziprasidone	18	(0.08)
Zotepine	7	(0.03)
Clozapine	6	(0.03)

Note: Data was analyzed from January 1 to November 30, 2022. The denominator refers to the total number of pediatric patients with depressive disorders and AAP prescription, whereas the numerator pertains to the number of pediatric patients with depressive disorders and a specific AAP prescription. AAP, atypical antipsychotic.

Table 4. Prescription pattern of atypical antipsychotics among children and adolescents with depressive disorders according to psychiatric comorbidities in Korea (2022)

	without comorbidities		with comorbidities				p-value
			ADHD		The others		
	n=18,759		n=18,293		n=22,218		
number of patients	n	(%)	n	(%)	n	(%)	
Aripiprazole	4,276	(22.79)	8,114	(44.36)	8,423	(37.91)	<.001*[a,b,c]
Risperidone	300	(1.60)	2,136	(11.68)	1,099	(4.95)	<.001*[a,b,c]
Quetiapine	494	(2.63)	559	(3.06)	1,430	(6.44)	<.001*[a,b,c]
Olanzapine	50	(0.27)	55	(0.30)	241	(1.08)	<.001*[b,c]
Paliperidone	4	(0.02)	19	(0.10)	21	(0.09)	0.005*[a,b]
Blonanserin	3	(0.02)	7	(0.04)	34	(0.15)	<.001*[b,c]
Amisulpride	3	(0.02)	5	(0.03)	18	(0.08)	0.003*[b]
Ziprasidone	3	(0.02)	6	(0.03)	9	(0.04)	0.356
Zotepine	0	(0.00)	2	(0.01)	5	(0.02)	Not estimated
Clozapine	1	(0.01)	1	(0.01)	4	(0.02)	Not estimated

Note: Data was analyzed from January 1 to November 30, 2022. [a]Significant difference between without comorbidities and with comorbid ADHD. [b]Significant difference between without comorbidities and with the other comorbidities. [c]Significant difference between with comorbid ADHD and with the other comorbidities.*Significant at the $p < .05$ level. AAP, atypical antipsychotic; ADHD, attention-deficit hyperactivity disorder

Table 5. Prescription pattern of concomitant medications among children and adolescents with depressive disorders who were prescribed atypical antipsychotics according to psychiatric comorbidities in Korea (2022)

	without comorbidities		with comorbidities				p-value
			ADHD		The others		
	n=4,737		n=9,376		n=9,599		
number of patients	n	(%)	n	(%)	n	(%)	
Typical antipsychotics							
Perphenazine	17	(0.36)	67	(0.71)	80	(0.83)	0.005*[a,b]
Haloperidol	12	(0.25)	10	(0.11)	60	(0.63)	<.001*[b,c]
Sulpiride	2	(0.04)	5	(0.05)	4	(0.04)	0.923
Mood stabilizers							
Lithium	172	(3.63)	247	(2.63)	436	(4.54)	<.001*[a,b,c]
Valproate	125	(2.64)	392	(4.18)	319	(3.32)	<.001*[a,c]
Lamotrigine	52	(1.10)	71	(0.76)	108	(1.13)	0.023*[c]
Antidepressants							
Escitalopram	2,203	(46.51)	2,978	(31.76)	4,645	(48.39)	<.001*[a,c]
Fluoxetine	1,545	(32.62)	1,932	(20.61)	3,324	(34.63)	<.001*[a,c]
Sertraline	991	(20.92)	1,561	(16.65)	2,480	(25.84)	<.001*[a,b,c]
ADHD medication							
Methylphenidate	26	(0.55)	7,169	(76.46)	97	(1.01)	<.001*[a,b,c]
Atomoxetine	8	(0.17)	2,838	(30.27)	19	(0.20)	<.001*[a,c]
Clonidine	1	(0.02)	264	(2.82)	3	(0.03)	<.001*[a,c]
Anti-anxiety drugs							
Alprazolam	1,217	(25.69)	1,032	(11.01)	3,809	(39.68)	<.001*[a,b,c]
Lorazepam	605	(12.77)	618	(6.59)	1,831	(19.07)	<.001*[a,b,c]
Clonazepam	86	(1.82)	430	(4.59)	1,924	(20.04)	<.001*[a,b,c]

Note: Data was analyzed from January 1 to November 30, 2022. [a]Significant difference between without comorbidities and with comorbid ADHD. [b]Significant difference between without comorbidities and with the other comorbidities. [c]Significant difference between with comorbid ADHD and with the other comorbidities. *Significant at the $p < .05$ level. Only three drugs are listed in the table in the order of the highest number of patients who prescribed the specific drugs for each category. The other drugs are listed in Table 6. AAP, atypical antipsychotic; ADHD, attention-deficit hyperactivity disorder

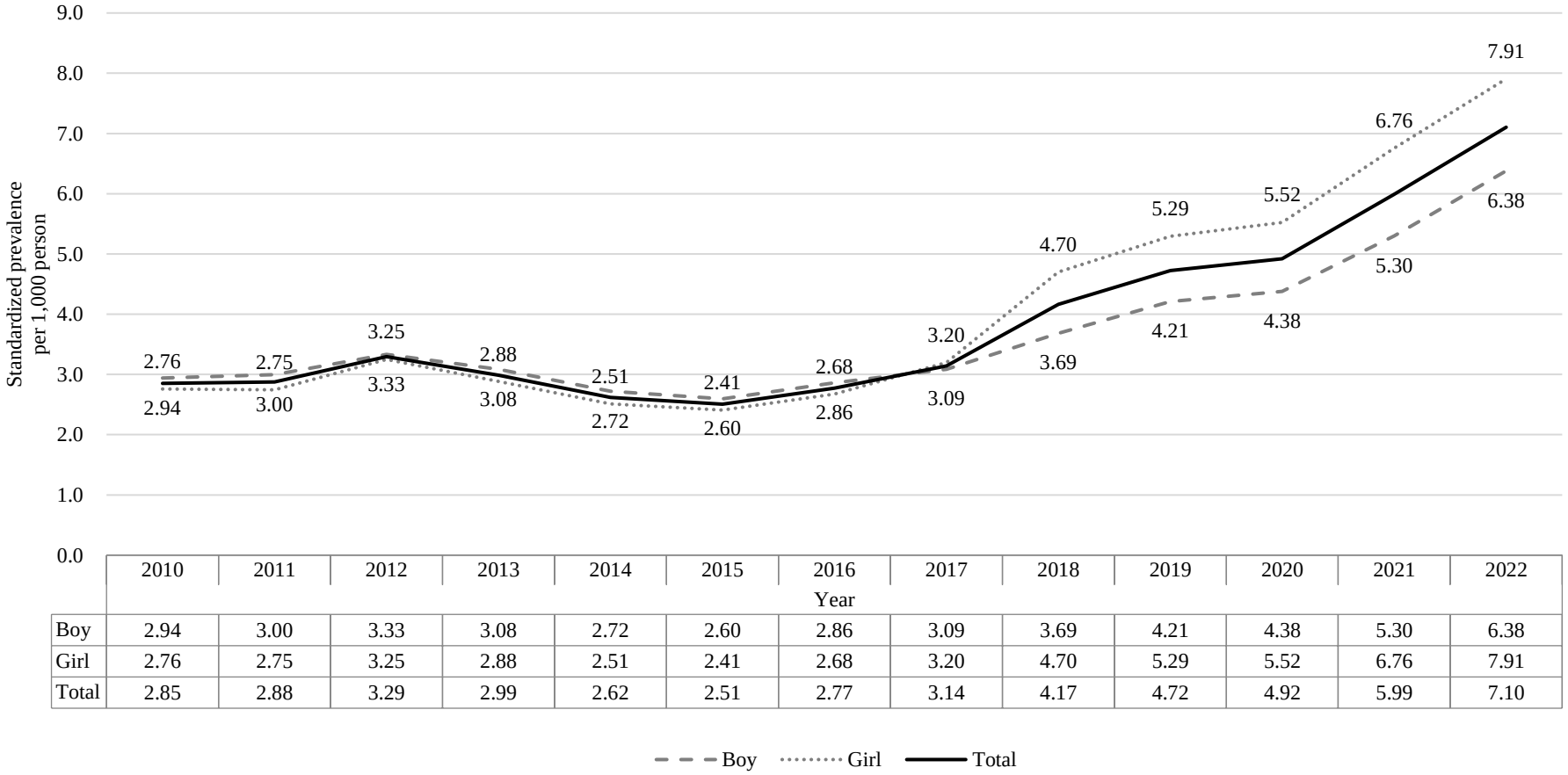
Table 6. Overall concomitant medications among children and adolescents with depressive disorders who were prescribed atypical antipsychotics according to psychiatric comorbidities in Korea (2022)

	without comorbidities		with comorbidities				total N
			ADHD		The others		
	n=4,737		n=9,376		n=9,599		
number of patients	n	(%)	n	(%)	n	(%)	
Typical antipsychotics	31	(0.65)	85	(0.91)	150	(1.56)	266
Perphenazine	17	(0.36)	67	(0.71)	80	(0.83)	164
Haloperidol	12	(0.25)	10	(0.11)	60	(0.63)	82
Sulpiride	2	(0.04)	5	(0.05)	4	(0.04)	11
Chlorpromazine	0	(0.00)	2	(0.02)	7	(0.07)	9
Pimozide	0	(0.00)	2	(0.02)	3	(0.03)	5
Levomepromazine	0	(0.00)	0	(0.00)	2	(0.02)	2
Mood stabilizers	312	(6.59)	656	(7.00)	804	(8.38)	1,772
Lithium	172	(3.63)	247	(2.63)	436	(4.54)	855
Valproate	125	(2.64)	392	(4.18)	319	(3.32)	836
Lamotrigine	52	(1.10)	71	(0.76)	108	(1.13)	231
Carbamazepine	7	(0.15)	12	(0.13)	16	(0.17)	35
Topiramate	3	(0.06)	16	(0.17)	8	(0.08)	27
Gabapentin	1	(0.02)	2	(0.02)	1	(0.01)	4
Oxcarbazepine	0	(0.00)	0	(0.00)	1	(0.01)	1
Antidepressants	4,155	(87.71)	5,728	(61.09)	8,642	(90.03)	18,525
Tricyclic antidepressants	128	(2.70)	308	(3.28)	633	(6.59)	1,069
Imipramine	66	(1.39)	210	(2.24)	241	(2.51)	517
Amitriptyline	59	(1.25)	54	(0.58)	207	(2.16)	320
Doxepin	5	(0.11)	37	(0.39)	176	(1.83)	218
Clomipramine	2	(0.04)	18	(0.19)	42	(0.44)	62
Nortriptyline	0	(0.00)	1	(0.01)	6	(0.06)	7
SSRIs	4,039	(85.26)	5,471	(58.35)	8,376	(87.26)	17,886
Escitalopram	2,203	(46.51)	2,978	(31.76)	4,645	(48.39)	9,826
Fluoxetine	1,545	(32.62)	1,932	(20.61)	3,324	(34.63)	6,801
Sertraline	991	(20.92)	1,561	(16.65)	2,480	(25.84)	5,032
Paroxetine	156	(3.29)	214	(2.28)	661	(6.89)	1,031
Fluvoxamine	15	(0.32)	102	(1.09)	121	(1.26)	238
SNRIs	87	(1.84)	97	(1.03)	359	(3.74)	543

Desvenlafaxine	54	(1.14)	62	(0.66)	202	(2.10)	318
Venlafaxine	29	(0.61)	32	(0.34)	136	(1.42)	197
Duloxetine	4	(0.08)	8	(0.09)	37	(0.39)	49
Milnacipran	5	(0.11)	7	(0.07)	8	(0.08)	20
Atypical antidepressant	812	(17.14)	876	(9.34)	2,168	(22.59)	3,856
Trazodone	416	(8.78)	403	(4.30)	1,299	(13.53)	2,118
Bupropion	312	(6.59)	404	(4.31)	684	(7.13)	1,400
Tianeptine	74	(1.56)	111	(1.18)	223	(2.32)	408
Agomelatin	36	(0.76)	28	(0.30)	145	(1.51)	209
Vortioxetine	38	(0.80)	43	(0.46)	116	(1.21)	197
Mirtazapine	28	(0.59)	28	(0.30)	110	(1.15)	166
ADHD medication	32	(0.68)	8,453	(90.16)	113	(1.18)	8,598
Methylphenidate	26	(0.55)	7,169	(76.46)	97	(1.01)	7,292
Atomoxetine	8	(0.17)	2,838	(30.27)	19	(0.20)	2,865
Clonidine	1	(0.02)	264	(2.82)	3	(0.03)	268
Anti-anxiety drugs	1,909	(40.30)	1,909	(20.36)	6,017	(62.68)	9,835
Alprazolam	1,217	(25.69)	1,032	(11.01)	3,809	(39.68)	6,058
Lorazepam	605	(12.77)	618	(6.59)	1,831	(19.07)	3,054
Clonazepam	86	(1.82)	430	(4.59)	1,924	(20.04)	2,440
Buspirone	238	(5.02)	291	(3.10)	853	(8.89)	1,382
Diazepam	106	(2.24)	234	(2.50)	977	(10.18)	1,317
Etizolam	157	(3.31)	156	(1.66)	452	(4.71)	765
Bromazepam	43	(0.91)	45	(0.48)	195	(2.03)	283
Triazolam	2	(0.04)	30	(0.32)	148	(1.54)	180
Zolpidem	1	(0.02)	29	(0.31)	125	(1.30)	155
Flurazepam	1	(0.02)	4	(0.04)	16	(0.17)	21

Note: Data was analyzed from January 1 to November 30, 2022. AAP, atypical antipsychotic; ADHD, attention-deficit hyperactivity disorder; SNRI, serotonin and norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors

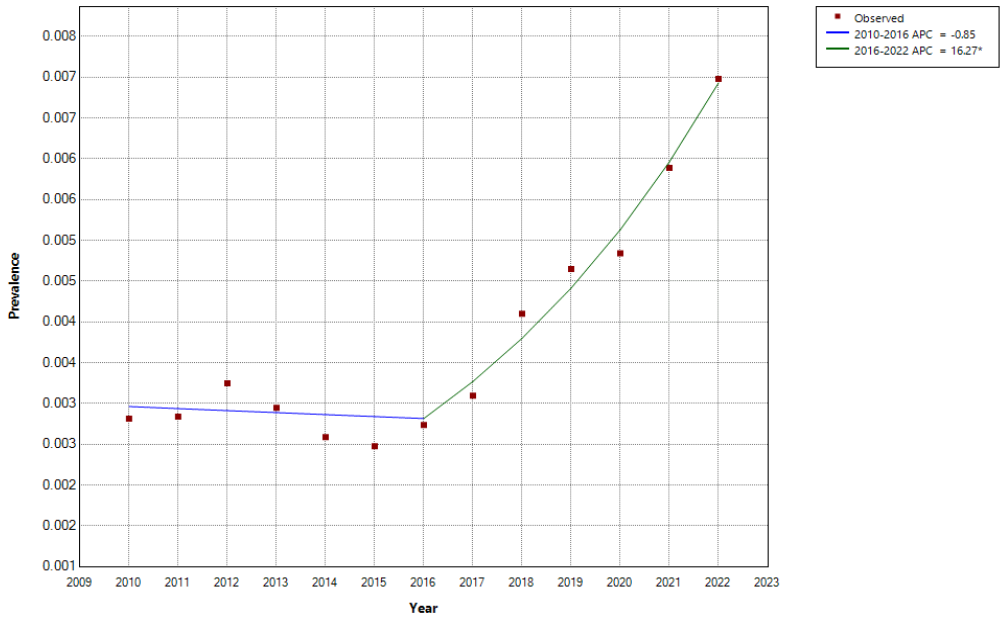
Figure 1. Prevalence of children and adolescents with depressive disorders between 2010 and 2022 in Korea



	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
	Year												
Boy	2.94	3.00	3.33	3.08	2.72	2.60	2.86	3.09	3.69	4.21	4.38	5.30	6.38
Girl	2.76	2.75	3.25	2.88	2.51	2.41	2.68	3.20	4.70	5.29	5.52	6.76	7.91
Total	2.85	2.88	3.29	2.99	2.62	2.51	2.77	3.14	4.17	4.72	4.92	5.99	7.10

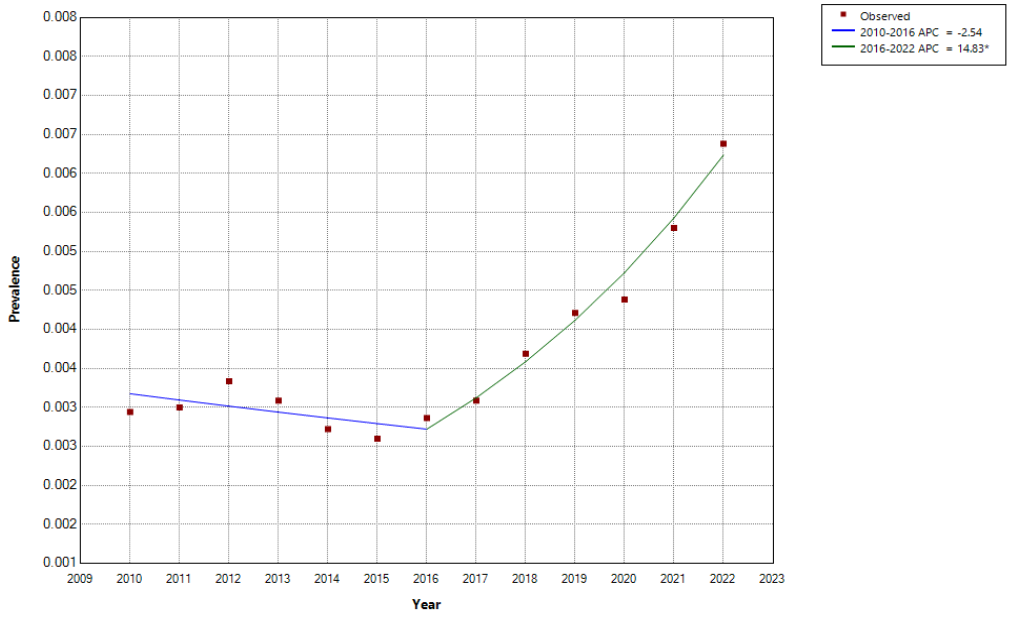
Figure 2. Joinpoint analysis for the prevalence of children and adolescents with depressive disorders between 2010 and 2022 in Korea
Note: *Significant at the $p < .05$ level.

A) Total



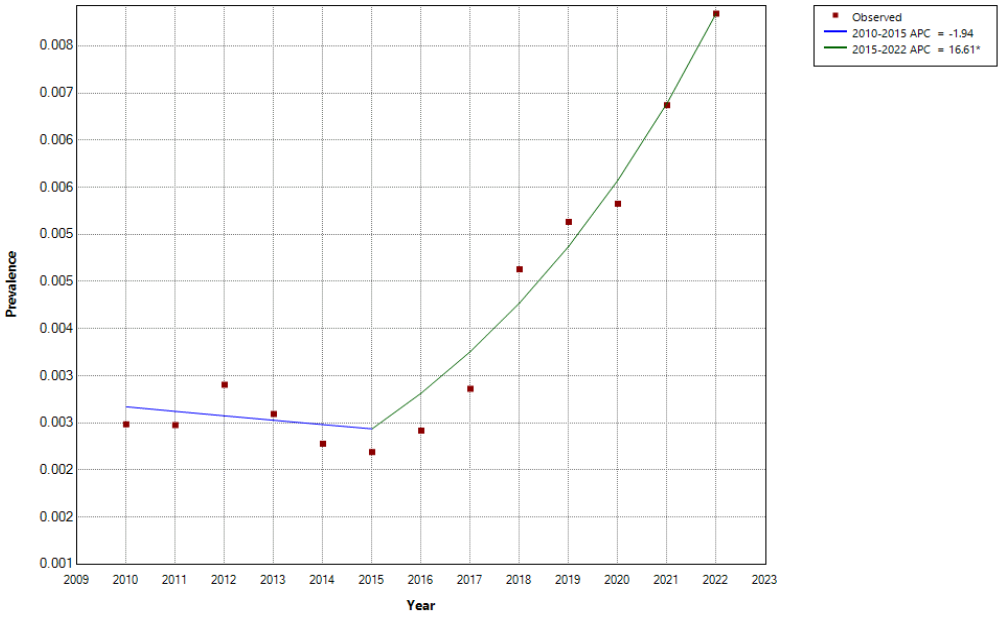
* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.
-- Test Statistic and P-Value not available for the Empirical Quantile method.
Final Selected Model: 1 Joinpoint.

B) Boys



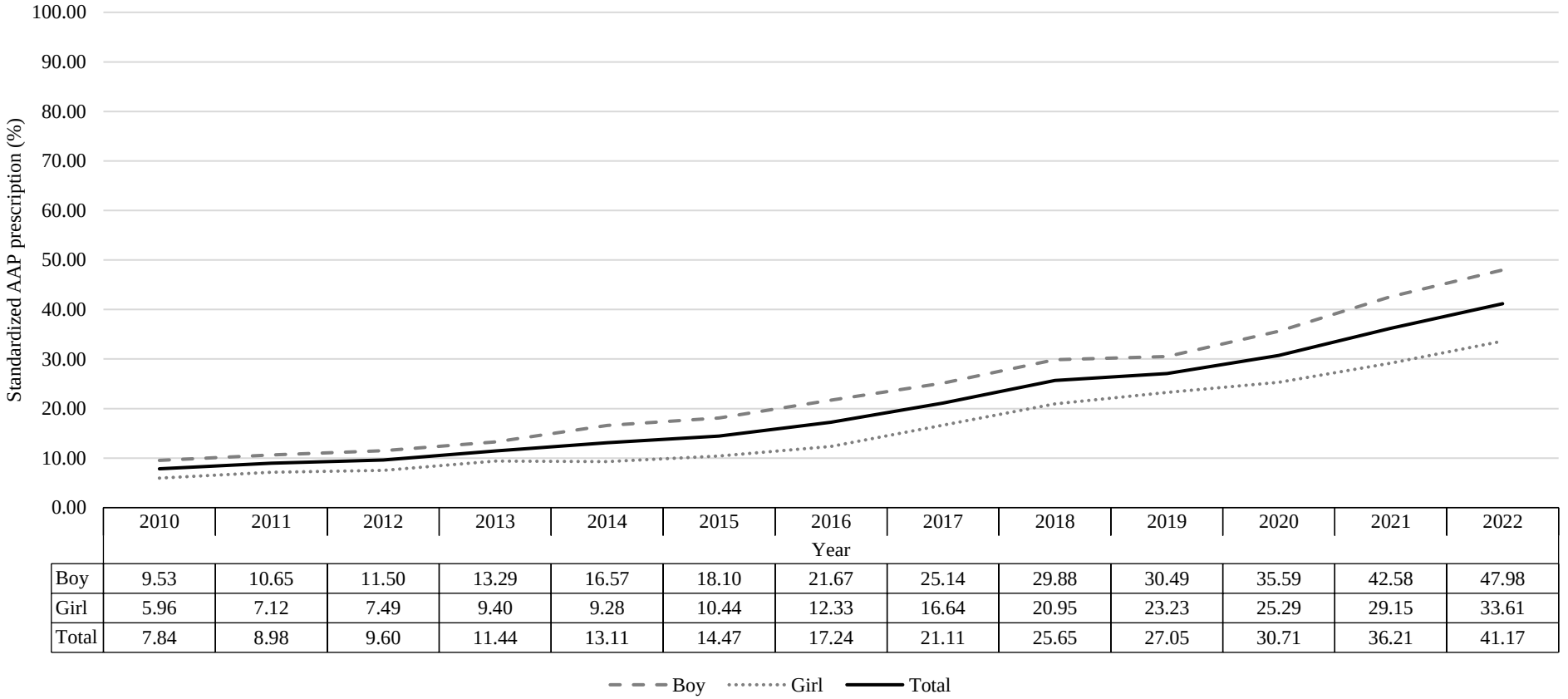
* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.
-- Test Statistic and P-Value not available for the Empirical Quantile method.
Final Selected Model: 1 Joinpoint.

C) Girls



* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.
-- Test Statistic and P-Value not available for the Empirical Quantile method.
Final Selected Model: 1 Joinpoint.

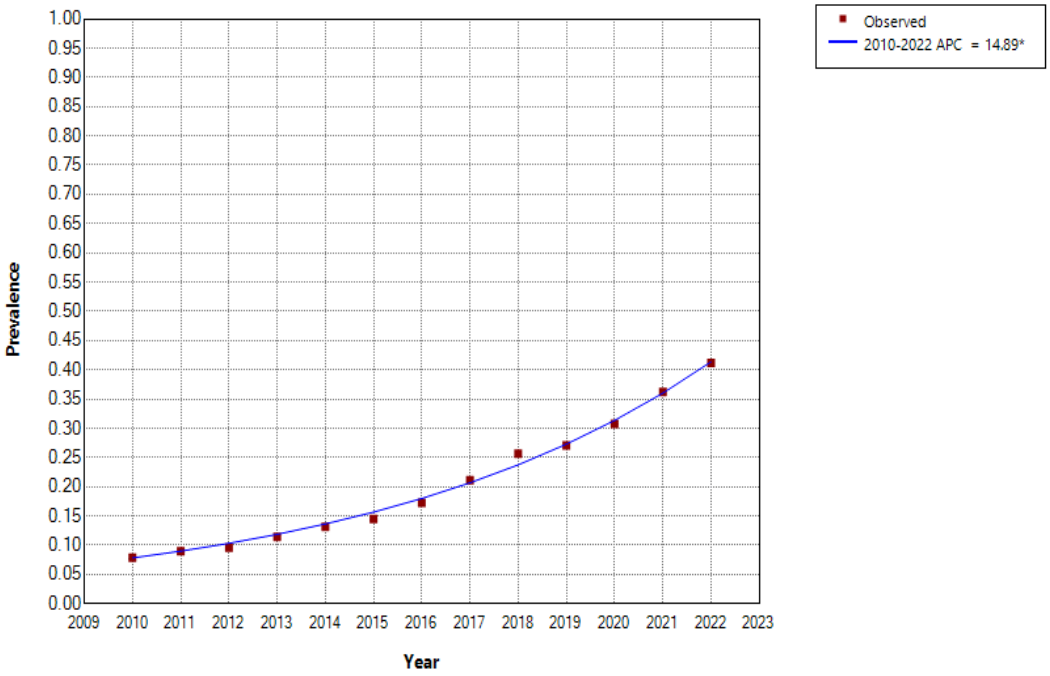
Figure 3. Trends in the atypical antipsychotic prescriptions among children and adolescents with depressive disorders between 2010 and 2022 in Korea
Note: The denominator refers to the number of children and adolescents with depressive disorders, whereas the numerator pertains to the number of children and adolescents with depressive disorder and AAP prescription. AAP, atypical antipsychotic.



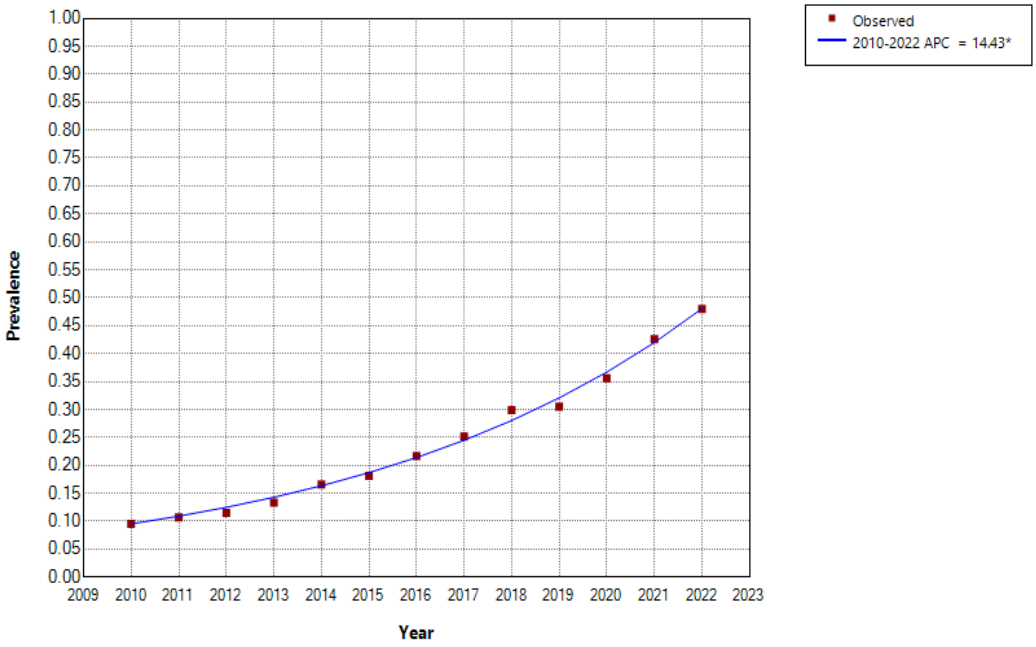
	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
	Year												
Boy	9.53	10.65	11.50	13.29	16.57	18.10	21.67	25.14	29.88	30.49	35.59	42.58	47.98
Girl	5.96	7.12	7.49	9.40	9.28	10.44	12.33	16.64	20.95	23.23	25.29	29.15	33.61
Total	7.84	8.98	9.60	11.44	13.11	14.47	17.24	21.11	25.65	27.05	30.71	36.21	41.17

Figure 4. Joinpoint analysis for the proportion of atypical antipsychotic prescriptions among children and adolescents with depressive disorders between 2010 and 2022 in Korea
Note: *Significant at the p < .05 level.

A) Total



B) Boys



C) Girls

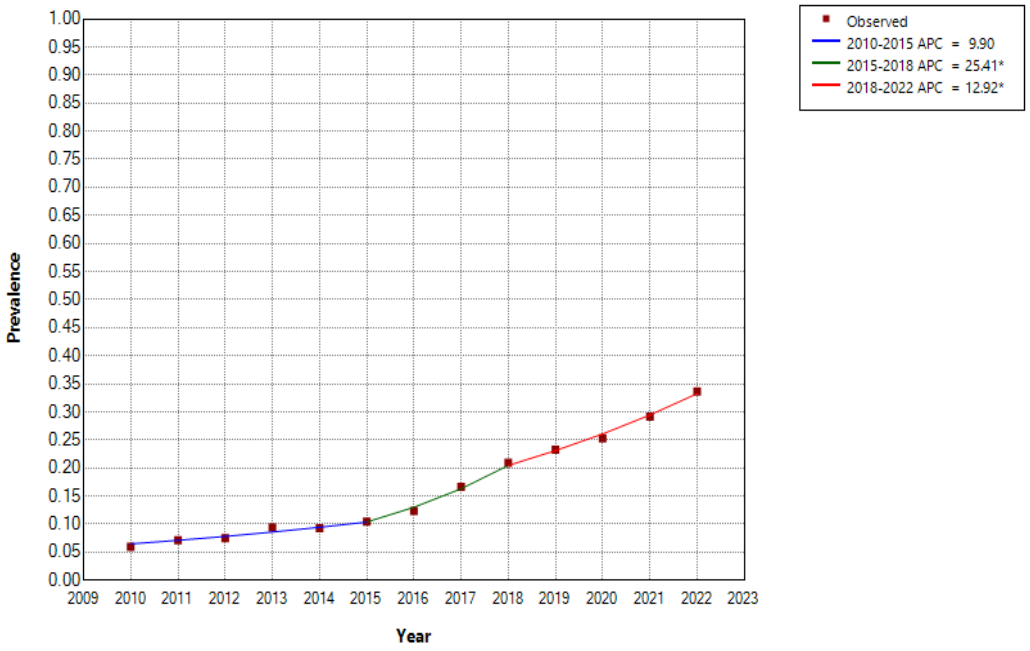
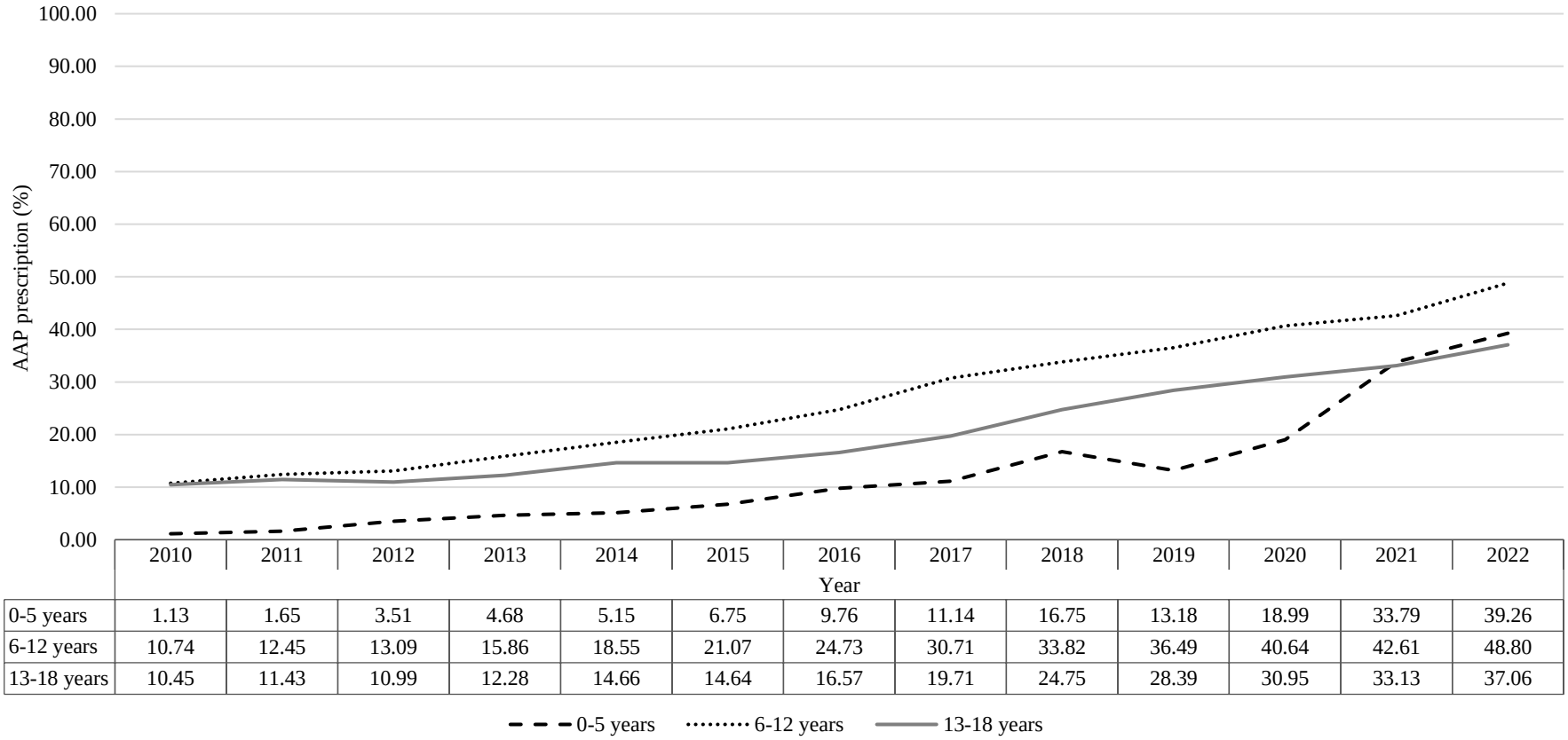


Figure 5. Trends in the atypical antipsychotic prescriptions among children and adolescents with depressive disorders by age group between 2010 and 2022 in Korea

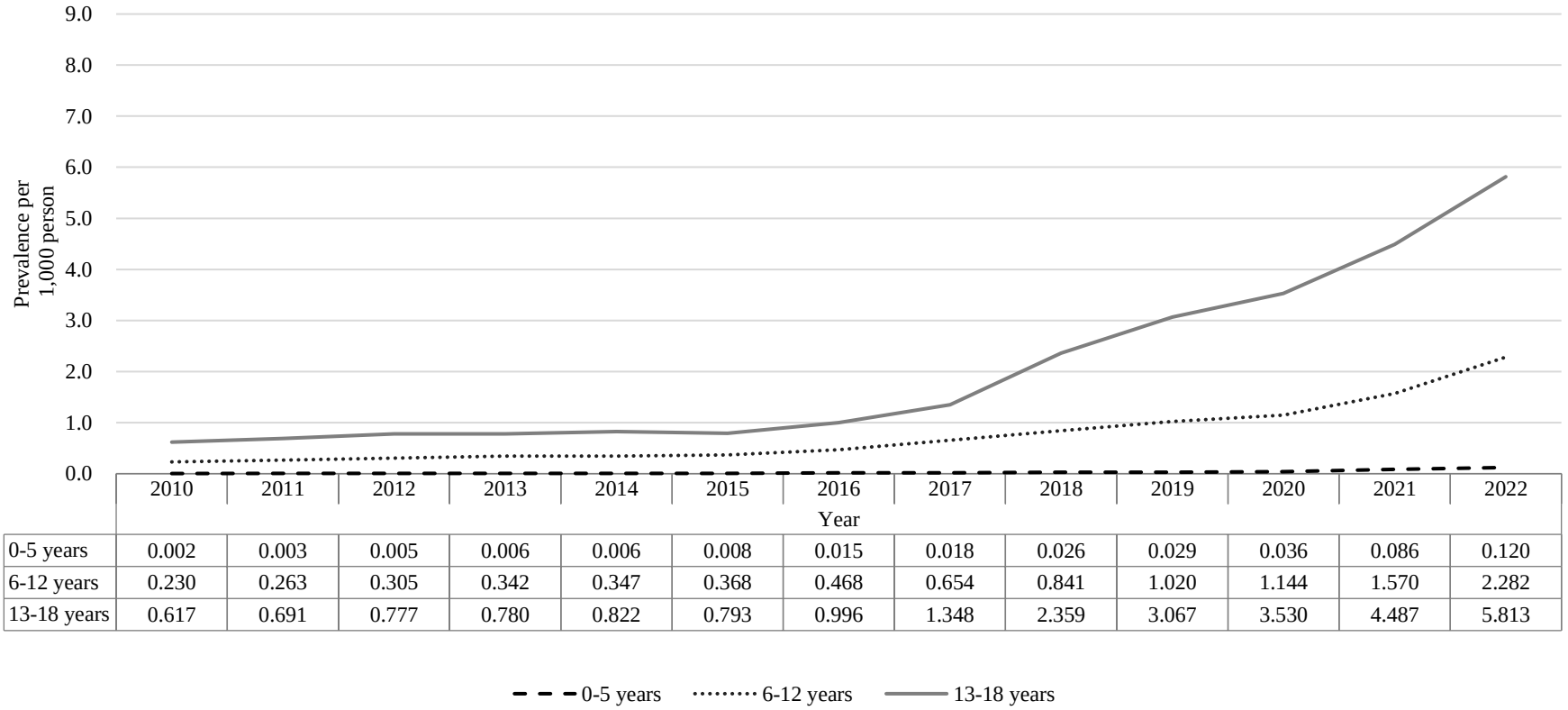
A) Proportion of AAP prescriptions among children and adolescents with depressive disorders

Note: The denominator refers to the number of children and adolescents with depressive disorders, whereas the numerator pertains to the number of children and adolescents with depressive disorders and AAP prescription. AAP, atypical antipsychotic



	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
	Year												
0-5 years	1.13	1.65	3.51	4.68	5.15	6.75	9.76	11.14	16.75	13.18	18.99	33.79	39.26
6-12 years	10.74	12.45	13.09	15.86	18.55	21.07	24.73	30.71	33.82	36.49	40.64	42.61	48.80
13-18 years	10.45	11.43	10.99	12.28	14.66	14.64	16.57	19.71	24.75	28.39	30.95	33.13	37.06

B) Prevalence of children and adolescents with depressive disorders and AAP prescription

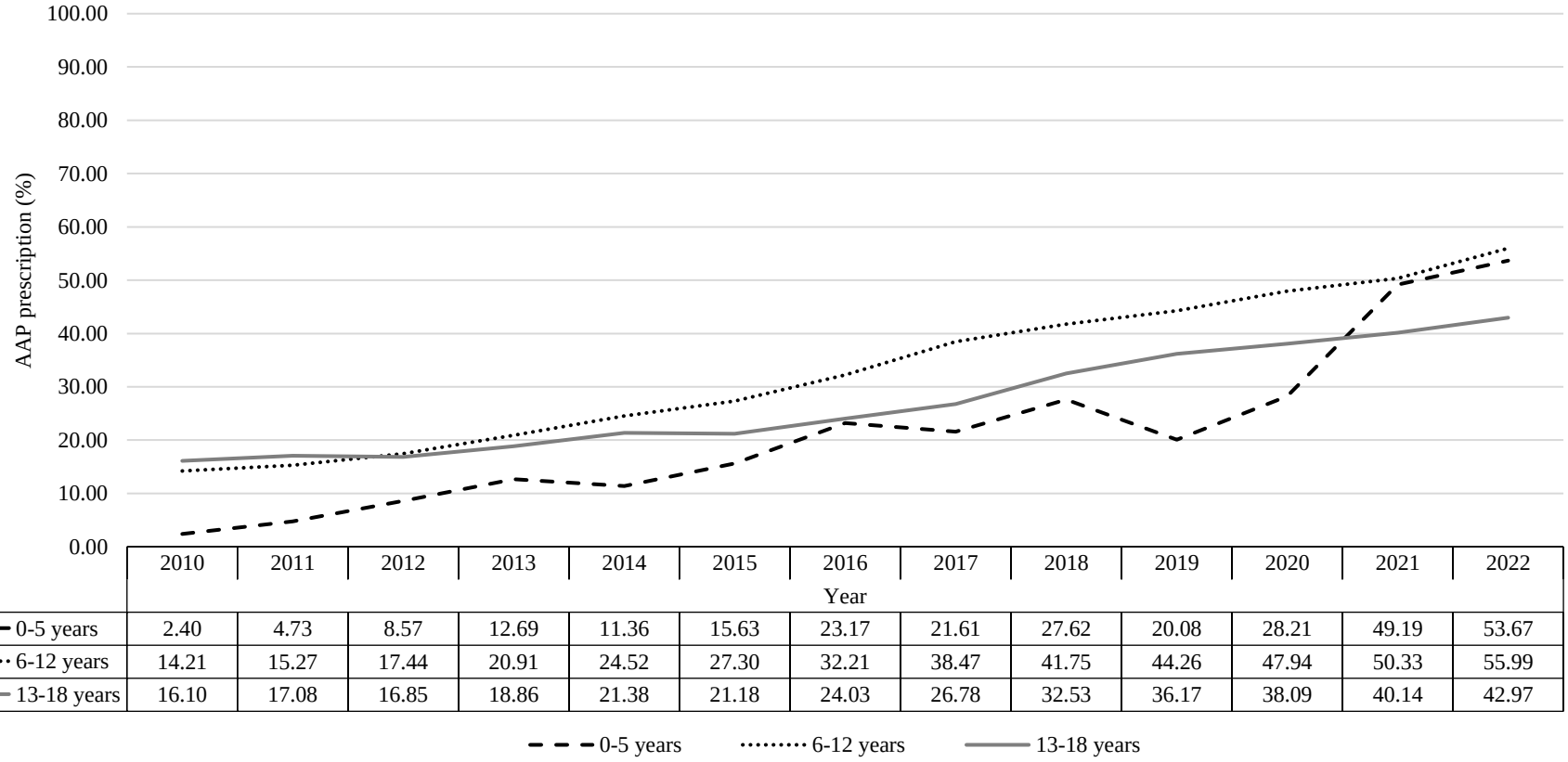


	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
0-5 years	0.002	0.003	0.005	0.006	0.006	0.008	0.015	0.018	0.026	0.029	0.036	0.086	0.120
6-12 years	0.230	0.263	0.305	0.342	0.347	0.368	0.468	0.654	0.841	1.020	1.144	1.570	2.282
13-18 years	0.617	0.691	0.777	0.780	0.822	0.793	0.996	1.348	2.359	3.067	3.530	4.487	5.813

Figure 6. Trends in the atypical antipsychotic prescriptions among children and adolescents with depressive disorders by psychiatric comorbidities and age group between 2010 and 2022 in Korea

A) With psychiatric comorbidities

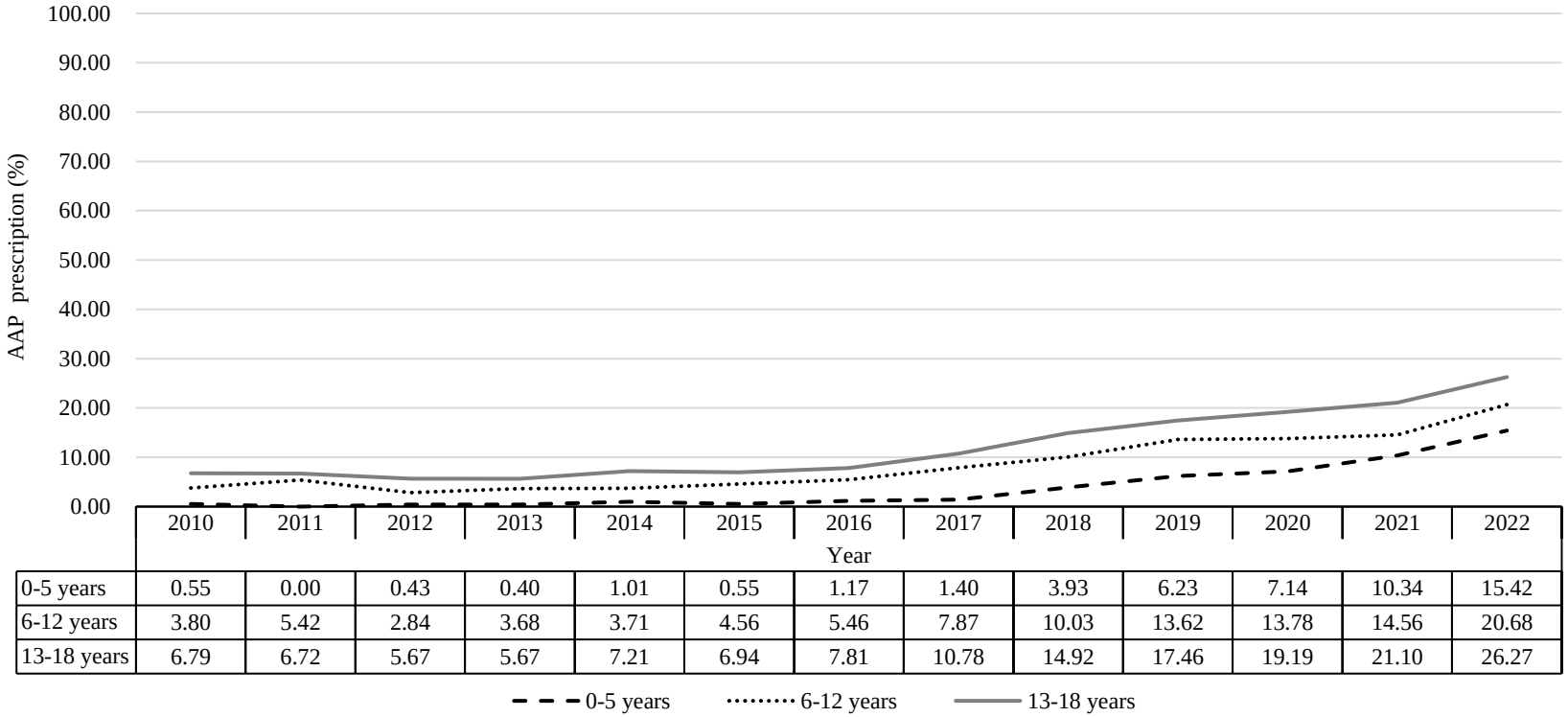
Note: The denominator refers to the number of children and adolescents with depressive disorders who have psychiatric comorbidities, whereas the numerator pertains to the number of children and adolescents with depressive disorders who have psychiatric comorbidities, and AAP prescription. AAP, atypical antipsychotic.



	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
0-5 years	2.40	4.73	8.57	12.69	11.36	15.63	23.17	21.61	27.62	20.08	28.21	49.19	53.67
6-12 years	14.21	15.27	17.44	20.91	24.52	27.30	32.21	38.47	41.75	44.26	47.94	50.33	55.99
13-18 years	16.10	17.08	16.85	18.86	21.38	21.18	24.03	26.78	32.53	36.17	38.09	40.14	42.97

B) Without psychiatric comorbidities

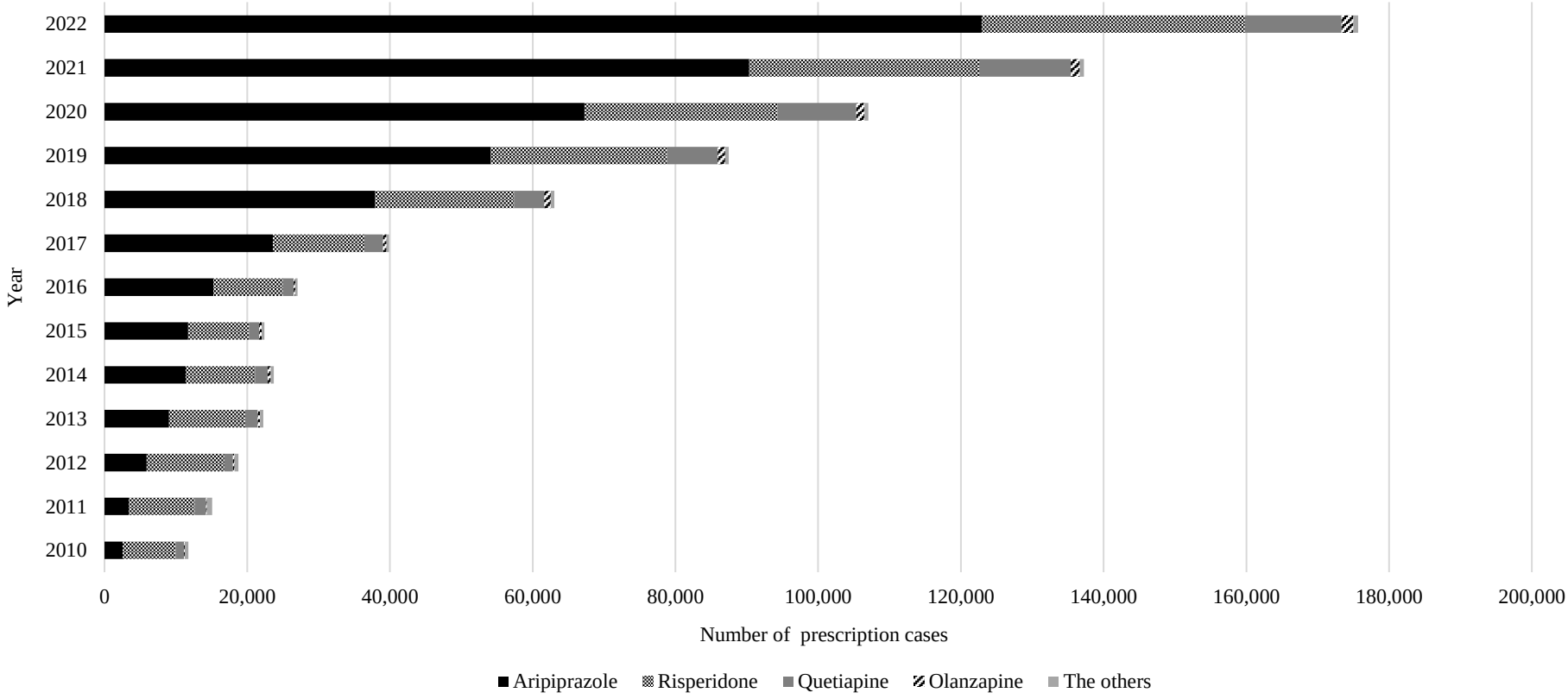
Note: The denominator refers to the number of children and adolescents with depressive disorders who do not have psychiatric comorbidities, whereas the numerator pertains to the number of children and adolescents with depressive disorders who do not have psychiatric comorbidities, and AAP prescription. AAP, atypical antipsychotic.



	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
0-5 years	0.55	0.00	0.43	0.40	1.01	0.55	1.17	1.40	3.93	6.23	7.14	10.34	15.42
6-12 years	3.80	5.42	2.84	3.68	3.71	4.56	5.46	7.87	10.03	13.62	13.78	14.56	20.68
13-18 years	6.79	6.72	5.67	5.67	7.21	6.94	7.81	10.78	14.92	17.46	19.19	21.10	26.27

Figure 7. Prescription trends of atypical antipsychotic among children and adolescents with depressive disorder between 2010 and 2022 in Korea
Note: Annual prescription trends of each AAP were analyzed based on claim-unit. We defined one case as one claim with 28 days of prescription. The number of cases was counted proportional to the number of prescription days. Claim with more than one antipsychotic prescription was counted as separate cases for each AAP. The others include amisulpride, blonanserin, clozapine, paliperidone, ziprasidone, and zotepine. AAP, atypical antipsychotic.

A) Most common four AAPs



B) The other AAPs