

# Antipsychotic Prescription Trends, Patterns and Associated Factors in Taiwanese Children and Adolescents

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## Abstract

This study evaluated the prescription trends, patterns and associated factors of antipsychotic medication in children and adolescents. We conducted a retrospective study by using the database of outpatient health insurance files of a psychiatric center in Northern Taiwan from 2004 to 2013. A total of 173,209 outpatient health insurance files were included. The average age of the study patients was 11.3 ( $\pm 3.9$ ) years. Of all visits of the patients, 13.4% were prescribed antipsychotics. The prescription rate of all antipsychotic medication types in all the outpatients aged  $\leq 18$  years increased yearly by 0.6%. The prescription rate of first-generation antipsychotics decreased with an estimated average annual percent change of 5.6% ( $p < .001$ ). By contrast, the prescription rate of second-generation antipsychotics increased with an estimated average annual percent change of 3.4% ( $p < .001$ ). Multiple logistic regression analysis was performed to examine clinical factors (age, sex and diagnosis) associated with antipsychotic prescription. After adjusting for other variables, antipsychotic prescription was found to be increased by 1.31 times every year with age and by 1.06 times in the male patients. The patients with diagnoses other than schizophrenia appeared less likely to be prescribed antipsychotics. Antipsychotic medications are being increasingly prescribed to children and adolescents in recent years. The efficacy and safety of antipsychotics in children and adolescents warrant clinical attention.

**Keywords:** Children and adolescents, Antipsychotics, Trends, Taiwan

## Introduction

Recently, antipsychotic medications have been increasingly prescribed to children and adolescents in Western Europe, the United States, the Asia-Pacific region, and Taiwan (Bachmann, Lempp, Glaeske, & Hoffmann, 2014; Cooper et al., 2006; Harrison, Cluxton-Keller, & Gross, 2012; Hsu et al., 2013; López-Muñoz et al., 2014; Lao et al., 2017; Olfson, Blanco, Liu, Moreno, & Laje, 2006). Zito et al. (2003) reported that the use of

antipsychotic drugs among children and adolescents in the United States increased by approximately 1.6–5.5 times between 1987 and 1996. Subsequently, the use of antipsychotic drugs among mental health users aged  $\leq 17$  years in the United States increased from 3.2% in 1997 to 5.0% in 2000 (Martin & Leslie, 2003). On the basis of the United States' Medicare data, Patel et al. (2005) indicated that the use of antipsychotics increased by approximately 1.5 to 3-fold from 1966

to 2001; this trend was mainly associated with the increased use of second-generation (atypical) antipsychotics (SGAs). In Germany, the use of antipsychotics in children and adolescents increased from 0.23% in 2005 to 0.32% in 2012 (Bachmann et al., 2014). Maršanić, Dodig-Čurković, & Juretić (2011) analyzed the use of antipsychotics in patients younger than 18 years in Croatia; they found that 1.3% of participants with an average age of 13.87 years had used antipsychotics, and the usage was more common in boys and adolescents. The use of SGAs was significantly higher (80.1%) than that of first-generation antipsychotics (19.9%, FGAs), and the off-label use of SGAs was as high as 52.9%. Kalverdijk (2008) examined antipsychotic drug use among youth in the northern and western parts of the Netherlands between 1997 and 2005 and found that the prevalence rate of antipsychotic drug use increased from 3.0 to 6.8 per 1,000 person-years. Prevalence was highest in the age group of 10–14 years and was more common in boys. The increase in the prevalence rate is mainly attributable to the increase in the use of SGAs. Therefore, the use of antipsychotics among children and adolescents, and the evidence of their efficacy and safety, have caused widespread concern. All these aforementioned increases are mainly linked to the considerable increase in the prescription of SGAs, probably due to the low occurrence of extrapyramidal syndrome (Vitiello et al., 2009) and approval for behavioral indication, which have resulted in doctors feeling more at ease while prescribing these drugs (Cohen et al., 2013; Hurley, Folstein, & Lam, 2003). SGAs were introduced into Taiwan in 1990 (López-Muñoz et al., 2012). Since 2010, there has been approval by the US Food and Drug Administration (FDA) and other international regulatory agencies to use SGAs for manic episodes, for bipolar mania and behavioral disturbances (irritability and aggression) in children and adolescents, and for behavioral problems associated with autism and intellectual

disabilities (Cohen et al., 2013). Indications for antipsychotics include psychotic disorders, bipolar disorders (mania), hyperactivity, severe behavioral problems, and Tourette's syndrome exerted a considerable effect on the psychiatric treatment of children and adolescents (Christian et al., 2012). Common off-label indications for antipsychotics include drug abuse, refractory depression, and anxiety disorders (Fountoulakis, Nimatoudis, Iacovides, & Kaprinis, 2004; Warren, Serrato, & Maguire, 2012).

Currently, the clinical trials and studies of antipsychotic drugs have prominently focused on their efficacy and safety in adults. The information and pharmacoepidemiology for the use of antipsychotic drugs in children and adolescents are still insufficient. The trends, prescribing pattern, and associated factors of antipsychotic medication remain unclear in Asia, as well as in Taiwan.

## Objectives

The objects of this study were to explore the trends, associated factors and prescription patterns of antipsychotic medication in Taiwanese children and adolescents.

## Methods

This retrospective study was based on the database of outpatient health insurance files of a psychiatric center in Northern Taiwan collected from 2004 to 2013. Patients aged 18 years or younger were included. All patients were assessed, diagnosed, followed up, or supervised by certified child and adolescent psychiatry subspecialists at our outpatient clinics of the department of child and adolescent psychiatry.

The variables of the study sample, including age, sex, diagnosis, and medication dosages, were extracted from the electronic medical record system, to explore the trends, prescription patterns, and associated factors of antipsychotic

medication among children and adolescents. Statistical analysis was performed using SPSS (SPSS 20.0 for Windows, SPSS Inc., Chicago, IL, USA) and NCI's Join point Regression Program (version 4.5.0.1). We calculated the prescription rate of antipsychotic drugs and the prescribed daily dosages per year. We compared the prescribed daily dose (PDD), which was the PDD at our outpatient department every year from 2004 to 2013 with the defined daily dose (DDD) from the DDD data established by the World Health Organization (WHO) as the standard. Polypharmacy, which is defined as the use of two or more types of antipsychotic drugs, was also calculated for every year. Categorical variables were compared between groups by using the chi-square test, and trend analysis was performed using the Joinpoint Regression Program. The association of clinical factors with antipsychotic medication prescription was evaluated using multiple logistic regression analysis. All statistical tests were two-tailed and a  $p$  value of  $<.05$  was considered significant.

## Results

A total of 173,209 outpatient health insurance files were included in this study. The average age of the study patients was 11.3 ( $\pm 3.9$ ) years. Antipsychotic medication was prescribed in all visits of 13.4% of the patients; their average age was 14.8 ( $\pm 2.6$ ) years, which was significantly higher than that of the patients who were not prescribed antipsychotic medication ( $p < .001$ ). The use of antipsychotic drugs was significantly higher in the male patients than in the female patients, and significantly increased with age after stratification by age. Risperidone was the most commonly used antipsychotics for each age group. Autism spectrum disorder (28.1%) was the most common diagnosis associated with children and adolescents receiving antipsychotic medication, followed by schizophrenia. Among the visits in which antipsychotic medication was prescribed, FGAs

and SGAs accounted for 36.8% and 63.2% of the total prescriptions, respectively (Table 1). The most commonly used FGA drug classes were sulpiride (24.7%) followed by haloperidol (4.72%); whereas the most commonly used SGA drug classes were risperidone (39.45%), followed by aripiprazole (13.43%).

From 2004 to 2013, the prescription rate of all antipsychotic medication types in all the outpatients increased yearly by 0.6%. The prescription rate of FGAs decreased considerably, with an estimated average annual percent change of 5.6% ( $p < .001$ ). By contrast, the prescription rate of SGAs increased with an estimated average annual percent change of 3.4% ( $p < .001$ , Figure 1). The SGA drug class had the largest increase in aripiprazole and quetiapine, whereas the FGA drug class had the highest decrease in haloperidol and thioridazine. Polypharmacy also increased yearly by 5.2%; however, it was not significant with an alpha level of  $<.05$ . We compared the PDD with the DDD of antipsychotic prescription. The average rate of PDD higher than the DDD, was in all visits of 11.9% of the patients from 2004 to 2013. The rate of PDD higher than the DDD, increased significantly yearly with an estimated average annual percent change of 5.9% ( $p < .001$ , Table 2). In the case of average PDD higher than the standard adult DDD, the most common FGAs prescription was fluphenazine decanoate, and the most common SGAs prescriptions were amisulpride, olanzapine, and ziprasidone.

Multiple logistic regression analysis was performed to evaluate the association of age, sex, and diagnosis with antipsychotic prescription. After adjusting for other variables, antipsychotic prescription was observed to significantly increase by 1.31 times every year with age and by 1.06 times in the male patients. After selecting schizophrenia as the reference group, the patients with other diagnoses appeared less likely to be prescribed antipsychotics (Table 3).

**Table 1:** Demographic data and clinical characteristics of participants (n = 173,209)

	Antipsychotics		
	No, n (%)	Yes, n (%)	
Patients	150,002 (86.6)	23,207 (13.4)	
Age			
Mean ± SD	10.8 ± 3.8	14.8 ± 2.6	
1 - 6 y/o	16,138 (10.8)	110 (0.5)	$\chi^2=24043.91^{***}$ df=4
7 - 9 y/o	36,999 (24.7)	651 (2.8)	
10 - 12 y/o	37,547 (25.0)	2,624 (11.3)	
13 - 15 y/o	36,199 (24.1)	6,975 (30.1)	
16 - 18 y/o	23,119 (15.4)	12,847 (55.4)	
Gender			
Male	113,319 (75.6)	14,293 (61.59)	$\chi^2=2018.22^{***}$ df=1
Female	36,683 (24.5)	8,914 (38.4)	
Diagnosis (ICD-9-CM)			
Autistic spectrum disorder (299)	33,121 (22.1)	6,526 (28.1)	$\chi^2=46952.51^{***}$ df=7
Schizophrenia (295)	705 (0.5)	4,472 (19.3)	
Childhood hyperkinetic syndrome (314)	75,400 (50.3)	3,245 (14.0)	
Affective psychosis (296)	2,539 (1.7)	2,528 (10.9)	
Organic/non-organic psychosis (293, 294, 298)	726 (0.5)	2,341 (10.1)	
Neurotic disorder (300-302, 306-312)	14,071 (9.4)	2,121 (9.1)	
Mental retardation (317-319)	10,957 (7.3)	1,150 (5.0)	
Others	12483 (8.3)	824 (3.6)	
Antipsychotics			
First-generation antipsychotics, FGAs		8850 (36.8%)	
Second-generation antipsychotics, SGAs		15218 (63.2%)	

\*  $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$

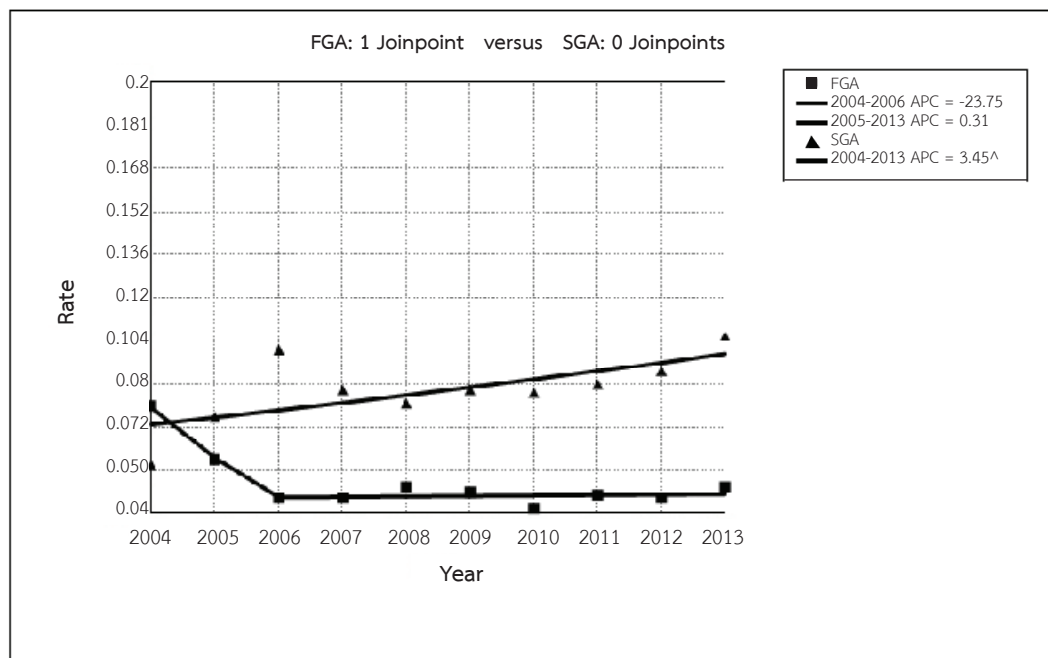
**Table 2:** Rate (%) of prescribing patterns in Taiwan, 2004-2013.

	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	AAPC <sup>1</sup>	95% CI
All Antipsychotic prescribing	13.6	13.3	14.3	13.0	12.8	13.0	12.5	13.1	13.5	15.0	0.6	-1.4,2.6
First-Generation Antipsychotic prescribing***	8.1	6.0	4.6	4.6	5.0	4.8	4.2	4.7	4.6	5.0	-5.6	-10.4,-0.6
Second-Generation Antipsychotic prescribing***	5.8	7.6	10.1	8.6	8.1	8.6	8.5	8.8	9.3	10.6	3.4	0.2,6.8
Polypharmacy	1.9	2.1	1.9	1.7	2.8	2.9	1.6	2.2	2.5	3.6	5.2	-1.4,12.2
Prescribed daily dose> defined daily dose***	11.1	8.7	11.5	9.3	10.5	12	11.6	9.1	17.2	17.8	5.9	0.5,11.6

1. AAPC=Average Annual Percent Change.

2. \*\*\*p < 0.001

FGA Joinpoint: 1\*  
SGA Joinpoint: 0\* \*Not Coincident



^ The Annual Percent Change (APC) is significantly different from zero at alpha = 0.05

**Figure 1:** Prescribing Trends of First-Generation Antipsychotics vs. Second-Generation Antipsychotics in Taiwan, 2004-2013

**Table 3:** Multiple logistic regression analysis for factors associated with antipsychotic medications

	OR (95%CI)
Age***	1.31 (1.30-1.31)
Gender (Female)**	
Male	1.06 (1.02-1.1)
ICD-9-CM Diagnosis (Schizophrenia,295)	
Affective psychosis (296)***	0.18 (0.17-0.2)
Neurotic disorder (300-302, 306-312)***	0.04 (0.04-0.05)
Childhood hyperkinetic syndrome (314)***	0.03 (0.03-0.03)
Organic/non-organic psychosis (293, 294, 298)*	0.86 (0.76=0.97)
Autistic spectrum disorder (299)***	0.08 (0.07-0.08)
Mental retardation (317-319)	0.05 (0.05-0.06)
Others***	0.07 (0.07-0.08)
* $p < 0.05$ , ** $p < 0.01$ , *** $p < 0.001$	

## Discussion

In contrast to psychosocial interpretations that had prevailed until the 1980s, (Drevets, 2000; Egger & Angold, 2006), increasing biological evidence and medical models explaining emotional and behavioral disturbances, and mental health during childhood, have resulted in the increased utilization of medical interventions such as pharmacology.

In a study conducted by Patel, Crismon, & Shafer (2006), among the diagnoses associated with children and adolescents receiving antipsychotic treatment, disruptive behavioral disorders (35%) ranked the first, followed by depressive disorders (18%). In our study, autistic spectrum disorder was the most common diagnosis (28.1%), followed by schizophrenia (19.3%). Although the most common diagnosis of antipsychotics prescription of the aforementioned two studies was not the same, there were actual similarities in the findings. Regardless of whether the diagnosis was disruptive behavioral disorders

or autistic spectrum disorder, antipsychotics were mainly for the indication of behavioral disturbances (irritability and aggression). Higher prevalence of disruptive behavioral disorders or autistic spectrum disorder in children and adolescents might also be attributed to the ranking of the diagnosis of antipsychotics prescribed in these two studies. Furthermore, after performing multiple logistic regression analysis for adjusting other variables in our study, the patients with schizophrenia appeared more likely to be prescribed antipsychotics.

The increased use of psychotropic medications and psychotropic medication combinations to treat childhood psychiatric disorders reflects a reasonably larger role of the medication treatment of childhood psychiatric disorders (Walkup, 2009). Another major contributor to the wide usage of SGAs among clinicians was the belief that SGAs were safer and more user friendly than other psychotropic medication. Neither a narrow therapeutic window noted, nor repeated blood monitoring required during treatment

(Vitiello et al., 2009). Off-label use is common (Driessen, Baik, & Zhang, 2016), and limited supporting data exists on the efficacy and safety of antipsychotics across the spectrum of neuropsychiatric disorders (Fountoulakis et al., 2004; Patel et al., 2006). For example, in 2009, quetiapine and olanzapine were approved by the US FDA for the short-term treatment of 13–17 year-old adolescents with mental disorders and bipolar disorder manic episodes. However, in January 2010, the US FDA found that olanzapine might cause a higher number of side effects in teens than in adults, such as weight gain and hyperlipidemia. Therefore, the US FDA announced a change in labelling that limits the use of olanzapine as the first-choice drug for teens (Kuehn, 2010).

The dose level of antipsychotic drugs was reported to be related to age and age at illness onset (Uchida et al., 2008). Concerning the prescribed dosage, the DDD established by the WHO is often applied as the standard; however, this DDD is mainly for adults and not specifically for children and adolescents. In addition, although few studies have evaluated the safety profile of antipsychotics during acute and intermediate treatment, the distal benefit-risk ratio during long-term treatment remains to be determined (Vitiello et al., 2009). A study on patient factors that affected the probability of polypharmacy and combined high dose revealed that polypharmacy was the most powerful factor affecting the probability of being prescribed a high dose. Other factors that affected the probability of polypharmacy were younger age, male sex, and being registered under the Mental Health Act (Lelliott et al., 2002). However, no matter what the reason is, the PDD being higher than the DDD, is still an area of clinical focus.

## Limitations

This study had several limitations. First, the diagnoses codes registered in our database, in which were based on the independent judgment of the prescribing physicians rather than on research diagnostic interviews. Second, information was unavailable concerning the severity of symptoms, the function of patients, the weight of patients and other demographic factors. These may have biased the observed patterns of antipsychotic prescribing. Finally, the sample is restricted to a representative psychiatric center, although the distribution of the patient is quite similar to population-based National Health Insurance database. Extended research is required in this area.

### *Clinical implications*

Increased use of antipsychotic drugs in children and adolescents was found in the United States, Europe, Asia and Taiwan. The use of antipsychotic drugs might cause higher side effects in children and adolescents than in adults, including extrapyramidal symptoms and metabolic syndromes such as obesity, glucose intolerance, dyslipidemia, and hypertension. Although these side effects do not have an immediate risk, they may have a long-term effect on health. We should prescribe them effective medications and also ensure that these have the least possible side effects. For that to occur, monitoring and management of these abnormalities are crucial. Evidence of the efficacy and safety of antipsychotic medications prescribed in children and adolescents are clinically worthy of attention.

*Conflicts of Interest: None declared.*



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