

Article

# Psychotropic medications prescribing trends in adolescents: A nationwide population-based study in Taiwan

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## Abstract

**Objective:** To describe psychotropic medications prescription patterns among adolescents in Taiwan; focusing on age, gender, duration of treatments and various classes of psychotropic medications.

**Design:** A retrospective description analysis.

**Setting:** Taiwan National Health Insurance Database.

**Participants:** Twelve to seventeen years' patients treated with psychotropic medications.

**Intervention:** None.

**Main Outcome Measure(s):** Percentage and duration of treatment with psychotropic medications during the study periods by medication classes and age groups were calculated. In addition, top three prescribed psychotropic medications were also determined.

**Results:** A total of 3,120 patients were prescribed psychotropic drugs. The percentage of adolescent patients that received anxiolytics and antidepressants in 2002–2012 were 2.89% and 2.15%, respectively. Also, 851 patients (1.21%) were prescribed hypnotics and 638 (0.91%) were given sedatives. The prevalence rate of the prescription of psychotropic drugs increased steadily with age and females were more treated than males except antipsychotic. Among psychotropic drugs, antidepressants (mean: 8.6 times) were refilled more but antipsychotics (mean 188 days) were the long-term treatment drugs. Additionally, the trend of hospital visits fluctuated over the year while May and December showed a higher rate of visits.

**Conclusions:** These findings show that the prevalence of psychotropic drug prescriptions in Taiwanese adolescents is even low but increasing trends in the prescription of these medications

raises some concern. As the evidence of psychotropic drug safety and effectiveness in adolescents is still inadequate; we recommend that healthcare providers should consider psychotropic drugs therapy, continuously monitor for outcomes and empower their patients to improve their knowledge, therapeutic outcomes and quality of life.

**Key words:** Adolescent, psychotropic medications, epidemiology, national health insurance

## Introduction

A depressive disorder is a common mental health problem in adolescents, and a total of 13–20% of children living in the USA experience a mental disorder [1]. Depression is also a major risk factor for suicide; the second leading cause of death among adolescents in the USA in 2010 [2]. However, over the past decade, psychotropic medication has gained popularity as treatment for psychiatric disorders in adults [3]. Recently, the rate of psychotropic medications prescribed to adolescents has significantly increased. Although several studies support the efficiency of psychotropic drugs for alleviating symptoms in some disorders such as adolescents insomnia, anxiety and depression [4] schizophrenia [5], adolescent bipolar mania [6] but other effectiveness is still questionable.

The overuse of psychotropic medications have become worrisome and concerns have been raised as to the safety of psychotropic treatment of adolescents. However, few studies focused on the adverse effect of psychotropic treatment of children and adolescents. Large-scale epidemiological studies have established that second generation of antipsychotic medications are linked to a greater risk of weight gain, drowsiness, dyslipidemia, hyperprolactinemia and diabetes in adolescents than adults [7, 8]. It is recommended that patient behavior, the options available for treatment, and comprehensive psychotropic assessment is required pertaining to the nature of the adolescent's illness and whether psychotropic medication is an appropriate course of action before initiating psychiatric treatment [9, 10]. As there has been an increase in the off-label use of psychotropic medications in adolescents; clinicians need to be vigilant about the emergence of adverse effects and a proper guideline is needed for both physicians and pharmacists to ensure safe prescribing practice.

Despite concerns about the rise in the treatment of adolescents with psychotropic medications, till now, the prevalence of psychotropic medications used by adolescents is unknown. The extent to which adolescents who are treated with antipsychotics also receive other classes of psychotropic medication is also unclear. To the best of our knowledge, this is the first study describing the patterns and trends in psychotropic use by adolescents in Asia. We focused on age, gender, the number of prescriptions, treatment duration and class related variation in the use of psychotropic medications that will help to find possible reasons for the increase, and recommendations for pediatric primary care providers who care for adolescents with emotional and behavioral disorders.

## Methods

### Data Source

This population-based retrospective study was conducted within a cohort of patients registered with the National Health Insurance Bureau that contributed to the National Health Insurance Research Database (NHIRD). The database included information on patient

demographics (with encrypted patient identification numbers, birth-dates and sex), inpatient or outpatient claim data and pharmacy records, and represented over 99% of the 23 million inhabitants of Taiwan that are registered with the National Health Insurance program. The database also included specific data on the medications prescribed, laboratory and diagnostic test data, dates of visits, lengths of hospitalization and diagnoses based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). The NHIRD has been widely used for studying drug safety. This study retrieved and analyzed an 11-year dataset from the NHIRD that included all patients that filled prescriptions for statins between 1 January 2002 and 31 December 2012.

### Selection of Study Population

The study cohort comprised all patients aged 12–17 years who were treated with psychotropic medications over an 11-year period from 1 January 2002 to 31 December 2012. If the adolescents were twelve years before entering cohort or eighteen years after ending cohort, they were excluded from this study.

### Psychotropic Medications Exposure

Information regarding adolescents' medications were retrieved from the outpatient prescription database. Psychotropic medications were categorized into four major groups such as Antipsychotics (N05A), Anxiolytics (N05B), Hypnotics and Sedatives (N05C) and Antidepressants (N06A) according to the Anatomical Therapeutic Chemical (ATC) classification system. In this study, we collected information about oral psychotropic medications for adolescents' (12–17 years) which were classified as pseudo-ID, age, gender, dispensing dates, drug names, drug indications and drug days.

Sometimes, psychotropic medications are used for other purposes except for mental disorders. For example, sulpiride is not only an antipsychotic to treat schizophrenia but also could treat peptic ulcers. Chlorpromazine (antipsychotics) is used to relieve from vomiting, and imipramine (antidepressant) is used in the treatment of urinary frequency as well. To avoid over-estimating the usage of psychotropic medications, we only observed psychotropic medications for mental disorders which were identified ICD-9-CM codes 290–319. If there were no diagnosis codes between 290 and 319 of psychotropic medications, the prescriptions were excluded.

### Data Analysis

We observed that the prevalence of psychotropic medications such as antipsychotics, anxiolytics, hypnotics and sedatives, and antidepressants for adolescents. The descriptive statistics were computed for the number of days supplied, the number of psychotropic medications, and *t*-test was used to measure the significant difference of psychotropic medication use between genders. We also categorized psychotropic medication use among age groups such as 12, 13, 14,

15, 16, 17 and the psychotropic medications prescribed among months. The trend of psychotropic medications prescribed among age groups was evaluated with Cochran–Armitage Trend Test. Finally, we calculated the top three prescribed medications for each psychotropic group. We used the SAS statistical software package (version 9.4) to conduct all statistical analyses.

### Results

We identified 203 186 adolescents during the entire study period (2002–2012), of which 133 131 adolescents were excluded based on

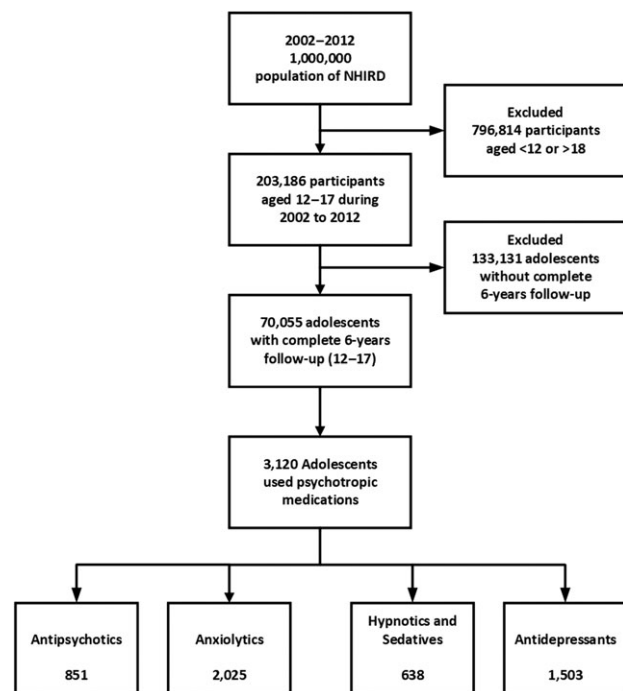


Figure 1 The flowchart of study participants.

Table 1 The use of psychotropic medications

	Combination of medications				Total users	% <sup>a</sup>	P-value
	1	2	3	4			
Female	1046	368	177	105	1696	5.1%	<0.001
Male	862	335	156	71	1424	3.9%	
Total	1908	703	333	176	3120	4.5%	

<sup>a</sup>Total population: 70 055 / Female: 33 416 / Male: 36 639.

Table 2 The number of psychotropic medications prescribed

Drug type	No. patient	% <sup>a</sup>	Prescription						
			Total	Mean	SD <sup>b</sup>	Median (50%)	Q3 (75%)	P90 (90%)	Max
Antipsychotics	851	1.21%	7320	8.6	14.1	3	10	23	118
Anxiolytics	2025	2.89%	5970	2.9	5.5	1	3	6	134
Hypnotics and sedatives	638	0.91%	2954	4.6	7.6	2	5	12	70
Antidepressants	1503	2.15%	9230	6.1	10.2	3	6	14	128

<sup>a</sup>Total patients: 70 055.

<sup>b</sup>SD, standard deviation.

our predetermined eligibility criteria as described above. The remaining 70 055 adolescents completed the 6 years follow-up period but 3120 adolescents used several types of psychotropic medication. Figure 1 summarizes our selection process.

In total, 70 055 adolescents and 25 474 psychotropic medications’ prescription information were included in the study cohort. Table 1 shows an overview of the use of psychotropic medication according to gender basis. Our results show that 4.5% of adolescents were prescribed psychotropic medications whereas, females (5.1%) were prescribed significantly higher than male adolescents (3.9%). Among 3120 adolescents who were treated with psychotropic medications, 1212 adolescents (38.85%) received more than one type of psychotropic medication.

Table 2 provides the prevalence of psychotropic medications prescribed on the basis of the group. It can be seen that the percentages of antidepressants, anxiolytics, antipsychotics, hypnotics and sedatives prescribed were 2.15, 2.89, 1.21 and 0.91%, respectively. The mean prescription for antipsychotics was 8.6 which was higher than the other groups. It is also seen that 50% adolescents were prescribed less than 5 times, and 75% received ≤10 times. The prevalence of psychotropic medications in female was higher than males except for antipsychotics (see Appendix 1). However, there was no significant difference for mean prescription between genders among each psychotropic medication.

Figure 2 presents the trend of psychotropic medications prescribed among age groups. It shows that the prescription of psychotropic medications increased steadily with age. In addition, Appendix 2 provides the trend of prescription over the year and it is shown that psychotropic medication prescription fluctuated over the year while May and December showed higher rates, and February and July showed lower rates.

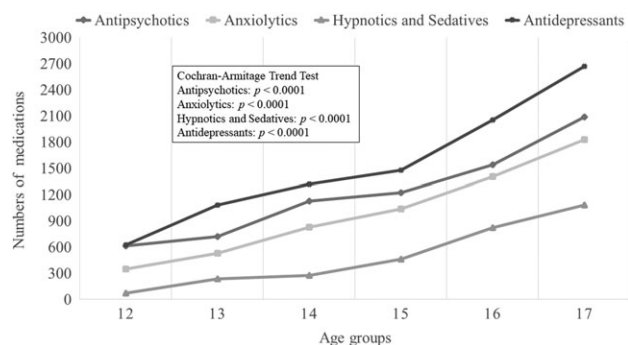
Table 3 provides number of days for each psychotropic medication prescribed. Our results show that the mean drug days of antipsychotics, antidepressants, hypnotics and sedatives, and anxiolytics were 188, 122, 83 and 44 days, respectively. In the case of duration, anxiolytics were used in a shorter period of time and antipsychotics were used in the a period of time. Females used a longer period of time except in the case of antipsychotics in which males used a longer period time than female ( $P = 0.02$ ) (see Appendix 3). Appendix 4 describes top three individual drugs prescribed for each psychotropic medication group. In antipsychotic, anxiolytics, antidepressants, hypnotics and sedatives group, the most frequently prescribed medications were risperidone (32.5%), alprazolam (26.18%), fluoxetine (26.90%) and zolpidem (48.19%).

### Discussion

This is the first study to evaluate the prevalence of psychotropic medications prescription in the Taiwanese adolescent and, considering the

sample size, it is also the largest epidemiological study ever performed on this topic. This study revealed an overall increase in psychotropic medications used in adolescents (12–17 years) over an 11-year (2002–2012) study period, in which main contributing medications were antipsychotics, anxiolytics, antidepressants, sedatives and hypnotics. We found that psychotropic medication prescription has increased in adolescents over the study period, although the percentage of adolescents treated with psychotropic medications was still lower than in the USA (6%), [11], Italy (2.91%) [12], Netherlands (2.9%) and Germany (2%) [13]. Based on the finding of this study, a higher percentage of Taiwanese adolescents were prescribed with anxiolytics (2.89%) and antidepressants (2.15%) that were followed by antipsychotics (1.21%), sedatives and hypnotics (0.91%). In the case of long-term psychotropic medication use, antipsychotics and antidepressants were in first and second position as well. Finally, prescription rate of psychotropic drugs over the whole year remarkably increased. However, these trends were more noticeable for the antidepressants and also obvious for the antipsychotics and anxiolytics, whereas the prescription rate of sedatives and hypnotics remained stable.

Among the adolescents, however, treatment with psychotropic medications increased gradually with age. Social and biological factors might play a pivotal role in age-related treatment with psychotropic medications because adolescence is a development period characterized by pronounced biological and social changes [14]. Blakemore *et al.* [15] explained that enhanced social understanding and self-awareness might cause changes in brain circuits that are involved in responses to reward and danger, increased stress levels, especially in girls. Several studies also mentioned that before puberty, the prevalence of mood disorders is ~3–5% for both male and female. But in mid-adolescence, females are usually diagnosed with a mood disorders two times than their counterparts. However, the prevalence rate could reach 14–20% in late adolescence [16, 17]. Our study also showed that male adolescents were more likely than



**Figure 2** The trend of psychotropic medications prescribed among age groups.

**Table 3** Drug days of psychotropic medications prescribed

Drug type	No. patient	Drug days					
		Mean	SD <sup>a</sup>	Median (50%)	Q3 (75%)	P90 (90%)	Max.
Antipsychotics	851	188	344	35	196	546	2152
Anxiolytics	2025	44	117	14	30	98	1727
Hypnotics and Sedatives	638	83	166	28	70	234	1740
Antidepressants	1503	122	229	42	116	316	2019

<sup>a</sup>SD, standard deviation.

their female peers to be treated with antipsychotics whereas anxiolytics, antidepressants, sedatives and hypnotics had been prescribed more frequently to females. This gender difference is consistent with the known male predominance of attention deficit hyperactivity disorder (ADHD) and obsessive compulsive disorders as well as mood disorders that tend to have a later age of onset than ADHD [18] and higher prevalence rates of affective disorders could be the main reason of female predominance in prescriptions for these medications.

The rate of adolescents treated with an antidepressant has been steadily increasing from 2002 to 2012, in particularly with selective serotonin reuptake inhibitors (SSRIs). Fluoxetine and sertraline were the most prescribed medications and were being used in 44.2% cases. Although, SSRI medications are the first-line treatment for adolescent anxiety and depression, but it appears to have questionable efficiency and shows an increased risk of unfavorable effects. It is reported that SSRIs (except fluoxetine) are associated with worsening of depression and increased risk of suicidal attempt [19, 20], specifically during the early stage of treatment [21]. Similar associations were found in other developed countries including Sweden, Norway, Finland and Denmark [22]. Contrarily, one study showed that the incidence of suicide among adolescents in the USA decreased as the number of antidepressant prescriptions increased [23]. Another study conducted in Australia noted no decrease in the incidence of suicide despite trends showing increased antidepressant use [24]. In fact, stopping medication is not a good option because it might cause a recurrence of the depression or anxiety [25, 26]. But continuing antidepressants for at least 1 year after successful treatment of a depressive episode may protect against relapse into depression and does not appear in our study to increase the risk for manic relapse [27]. So, it is essential for the healthcare providers to discuss the potential risks and benefits of antidepressants with parents and adolescents.

Furthermore, during the study period, the prescription rate of anxiolytic and sleep medication shown an upward trend. Although a similar trend was found in the USA and it was estimated that ~3% of adolescents have engaged in prescription drug misuse with anxiolytics, sedatives or hypnotics; medication often referred to as 'ASH' medications [28]. The most obvious finding to emerge from the study is that zolpidem was prescribed in about half of adolescents. Obviously, zolpidem has acquired a major role in the treatment of adolescent sleep problems in Taiwan. Treatment of adolescents with zolpidem has been controversial, because it may cause hallucinations, euphoria, declining academic performance and memory problems [29]. However, attention has been drawn to the safety effects of this medication related to age, gender, physical and psychological development.

In recent years, the use of antipsychotics in the treatment of depression amongst adolescents has become a topic of considerable debate. This debate is concerned with two issues, namely efficacy

and safety. However, a parallel trend of increasing antipsychotic drug use in adolescents has been observed in Taiwan that is similar to Europe [30], the USA [18], Canada [31] and Australia [32]. Due to the high risk for the onset of psychotic disorders such as autism, bipolar disorder, schizophrenia, ADHD in this development period, antipsychotic use has increased in 2002 and 2012. Risperidone and sulpiride were most commonly prescribed medications among adolescents in Taiwan. A significant amount of studies indicated that risperidone is a most useful treatment for positive and negative symptoms of schizophrenia and bipolar disease but side effects like weight gain, extrapyramidal side effects and prolactin elevation require consideration when evaluating the risk-benefit ratio for individual patients [33].

This paper attempted to show a most comprehensive nationwide analysis of psychotropic medications use among adolescents over time. The main strength of our study is that our analysis was based on complete data on dispense psychotropic medications in both inpatients and outpatients. In addition, all classes of medications included in our analysis were captured by the prescription database as none of the drugs are available over the counter. We have also reported in the percentage of the number of visits and duration of treatments by gender in the study periods, so it is easy to know the precision of the estimate.

However, this study has several limitations. First, this study reported patients prescribed with psychotropic medications from 2002 to 2012 but did not categorize the percentage of populations by each year. Therefore, the data obtained does not allow us to fully ascertain the changes in prescribing practice over this study period. Second, we did not include any information on where the medications were actually taken such as the rural and urban areas. Finally, this study did not reveal any information on the indications of these medications which could have been a valuable information to be addressed.

As psychotic disorders have been rising among the adolescents, the high quality of empirical evidence that supports the efficiency and safety of psychotropic medications treatment in adolescents is scarce. Physicians are facing problems on appropriate drug dosing, efficient treatment and drug safety in this age group. Recently, a question regarding gender difference pharmacotherapy has been raised [34], and Heck *et al.* [35] reported in the gender difference side effects associated with psychotropic treatments induced weight gain, metabolic syndrome and cardiac arrhythmia. In this situation, an effective assessment is essential if depression is suspected in adolescents. It is also important to provide proper guidelines for patients and their families and inform them about the level of severity and options available for treatment; in particularly, alternative therapies such as meditation, exercise and social engagement. If the drug is needed, it should be started at a low dose and the dose increased every two weeks until maximum dose is reached. It is also indispensable to monitor outcomes and patient's condition in a timely basis. The implications of these findings for researchers and policy makers can be gleaned by examining our results in terms of the current level of prescribing and safety/efficacy knowledge [9]. To ensure safety and effective treatment, it will be important that the pharmaceutical industry, NIH institutes, physicians, pharmacists, and families work closely together [36]. Whenever possible, physicians and other healthcare providers should encourage the enrollment of adolescents in responsibly conducted rigorous clinical trials, rather than simply providing the medications in the absence of supporting evidence. If the patients' psychiatric diseases are diagnosed, patients and their families need to be educated about the illness, fully informed about risks and adverse effects of treatments and option available for the

treatments. It is also necessary for clinical policy makers to provide needed resources for education. These might be helpful to mitigate the ongoing prescriptions of psychotropic medications among adolescents and find out safe or effective medications.

## Conclusion

This study showed that psychotropic medication treatment has increased during the study period. Different trends in psychotropic medication use exist in age and gender subgroups. So, close monitoring and frequent systematic reassessment should be used to minimize use and treatment duration. As data showed limited evidence of their long-term effects on the adolescent brain, open communication is needed with patients and their families about potential risks, benefits and adverse effects and safe prescribing practices have to be ensured. In addition, clinical policy makers have opportunities to promote improved quality and safety of antipsychotic medication use in adolescents through the healthcare provider's education programs, proper assessments of disease condition, developed quality measures, internet-based adolescent's psychiatric consultations, and evidence-based psychosocial treatments.

## Supplementary material

Supplementary material are available at *International Journal for Quality in Health Care* online.

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## Conflict of interest statement

None declared.

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