Title

Prescribing trends and indications of antipsychotic medication in Hong Kong from 2004 to 2014: general and vulnerable patient groups

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Registration

The study protocol was not registered before the commencement of the study.

Author Contributions

KSJL, ICKW and EWC had the original idea for the study and contributed to the development of the idea and study design. KSJL wrote the first draft of the study protocol. KSJL retrieved data and undertook the analysis. AWYT and KKCM independently cross-checked all the analyses and results. KSJL, AWYT, ICKW, KKCM, CSLC and EWC contributed to interpretation of the analyses. KSJL wrote the first draft of the paper. KSJL, AWYT, ICKW, KKCM, CSLC, and EWC critically reviewed the results and the manuscript. FMCB reviewed the data, the presentation of the paper and provided clinical input. ICKW and EWC provided oversight to all aspects of this project. KSJL and EWC are the guarantors. All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of data analysis.

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Abstract (250 words)

Purpose Antipsychotic prescribing patterns remain unclear in Asia. The aims of our study were to investigate prescribing trends of antipsychotic medication in the general population, children, and older patients by drug generation (first or second), the prescribing trend in pregnant women, the probable indication for antipsychotic prescription, and the prescribing trend by dosage form.

Methods This descriptive study identified and included all patients prescribed antipsychotic in Hong Kong from 2004 to 2014 using the Clinical Data Analysis and Report System. This study calculated and reported the prevalence of antipsychotic prescribing in patient groups of interest, the percentage with diagnoses of mental disorders were derived, and the prevalence of antipsychotic by dosage forms.

Results The study included 10,109,206 prescriptions of any antipsychotics to 256,903 patients. Over the study period, the prevalence of antipsychotic prescribing increased from 1.06% to 1.54% in the general population, from 0.10% to 0.23% in children (3-17 years old), and from 2.61% to 3.26% in older patients (≥65 years old). The prevalence of second-generation antipsychotics increased but the prevalence of first-generation antipsychotics did not. Prevalence of antipsychotic prescribing in pre-pregnancy, pregnancy, and postpartum timeframes varied from 0.18% to 0.38%. The percentage of incident prescriptions with a diagnosis of psychosis decreased from 54.1% to 47.5%.

Conclusions Antipsychotics have been increasingly prescribed in the general population, children, and older patients. There is an increase in second-generation antipsychotic prescribing. Over half of incident users had a recent diagnosis of a non-psychotic mental disorder in 2014, suggesting that off-label prescribing of antipsychotics might be common.

1. Introduction

Antipsychotic drugs (APDs) have been commonly prescribed for the management of schizophrenia, bipolar disorder, and major depressive disorder[1]. Safety concerns about APDs use in specific patient groups including older patients, children, and pregnant women, has been raised in past decades. Increased risk of mortality with the use of first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs) in older patients with dementia has been reported[2-6]. SGAs were approved for some indications in children and adolescents recently[7]. However, concerns regarding the safety of SGAs use in children (mostly focusing on metabolic syndrome and cardiovascular effects) have been raised[8 9]. Although APDs have been increasingly prescribed during pregnancy, safety evidence is limited[10 11].

The prescribing prevalence of APDs in general practice (GP) settings in the United Kingdom (UK) and Italy have been reported as 1% to 1.6% between 2000 and 2011[12-16]. In Asia, APDs prescribing was only investigated in patients with psychotic disorders through a survey[15-17], and their use in the general population of patients and in vulnerable patient groups (children, older patients, and pregnant women) remains unclear.

Concerns with respect to off-label use of APDs have also been reported. APDs, especially SGAs, have been widely used off-label for the management of mental disorders including but not limited to anxiety, attention deficit hyperactivity disorder, dementia, and severe agitation in older adults[18 19]. From 2007 to 2011 in UK primary care settings, over half of patients prescribed FGAs had diagnoses of non-psychotic mental disorders, and a similar proportion was reported in patients receiving SGAs[13]. Information regarding off-label use of APDs has not been studied in Asia.

In addition, although there is limited evidence suggesting superior efficacy and safety of APDs depot injections compared to oral dosage[20], depot injections were prescribed for one quarter to one third of patients with schizophrenia in western countries[21]. However, we could find no previous published studies of the utilization of APDs in depot injections or other dosage forms in an Asian population.

There were four specific objectives of our study to investigate prescribing of APDs in Hong Kong (HK), namely to determine the following.

1) The prescribing trend over time of APDs in the general patient population, children, and older patients by drug generation (FGAs/SGAs).

2) The prescribing trend over time of APDs in pre-pregnancy, pregnancy, and postpartum timeframes.

3) The probable indication of incident APDs prescriptions.

4) The prescribing trend over time of APDs by dosage forms.

2. Method

2.1. Data source

We retrieved prescription and diagnosis data from the Clinical Data Analysis and Report System (CDARS), the clinical database developed by the Hospital Authority, HK, which is a statutory body managing public hospitals, specialist outpatient clinics, and general outpatient clinics. The Hospital Authority provides a full range of healthcare services, including primary, secondary, and tertiary services to all HK residents (>7,300,000 population). Since 1995, patient data

including demographic information, diagnosis, payment method, prescription information, admission/discharge information and laboratory test results have been made available on CDARS for research and audit purposes[22 23]. Prescription records are categorised using the British National Formulary (BNF) classification in CDARS. Diseases are coded using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) in CDARS. The validity and accuracy of the CDARS database have been reported in several earlier studies[24-27].

2.2. Antipsychotic drugs

With reference to the BNF, this study included all medications under categories 4.2.1 and 4.2.2 and classified them as either FGAs or SGAs. The APDs not included in the BNF but prescribed during the study period were classified as either FGAs or SGAs based on chemical structure or according to registration information (Supplementary table 1). APDs prescriptions were further categorized according to dosage form (Supplementary table 2).

2.3. Study population

We retrieved all prescription records of APDs from CDARS. Age was defined using mid-year age, which is age on 1st July in the year of date of prescription and used to group individuals as children (3-17 years old) and older patients (≥65 years old).

2.4. Prevalence in the general population and by age group and dosage form

The annual prevalence calculation was adapted from Man *et al.*[25]; it was defined as the number of patients prescribed at least one APDs per calendar year divided by the mid-year population of

HK. The number of patients with at least one APDs prescription during the study period of 1st January 2004 to 31st December 2014 was used as the numerator in the calculation of prevalence. Population statistics were requested from the Census and Statistics Department, HK. This study calculated the prevalence for the general patient population, by drug generation (FGAs/SGAs), age group and dosage form.

2.5. Prevalence in pregnancy

We identified pregnant women with records of delivery episodes from 1st January 2004 to 31st December 2014 in the CDARS database and calculated prevalence of APDs use by calendar year for three timeframes: pre-pregnancy (180 days before conception to conception), pregnancy (from date of conception to date of delivery), and postpartum (from delivery to 180 days after delivery). Delivery episodes in calendar year 2003 and 2015 were also included to investigate their postpartum and pre-pregnancy timeframes overlapping with the study period (2004-2014). This analysis calculated the annual prevalence of APDs by using the number of women prescribed APDs during pregnancy in the respective timeframe divided by the total number of women who were recorded as having been in that pregnancy timeframe during the particular calendar year. Details of the pregnancy timeframes are included in supplementary material.

2.6. Indication analysis

Using the ICD-9-CM, mental illnesses were categorized as organic psychotic conditions (290-294), other psychoses (295-299), neurotic disorders, personality disorders and other nonpsychotic mental disorders (300-316), and intellectual disabilities (317-319). Since diagnosis records of chronic mental disorders are more likely to be omitted in non-incident prescriptions,

this analysis only included new users of APDs. As indication information is not available in CDARS, all mental illnesses diagnosed within 180 days before or after incident prescriptions (the first prescription during the study period) were retrieved and considered as probable indications. As such, it is possible that one APDs prescription could have been mapped to multiple mental illness categories as probable indications. This analysis calculated the percentages of patients with probable indications by category. Since a APDs prescription can belong to multiple mental illness categories, the percentage of patients with probable indications may sums up exceeding 1.

2.7.Statistical analysis

This descriptive study calculated prevalence (%) using the number of patients in the respective category divided by the total general population, and then multiplied by 100%. Annual prevalence of antipsychotic prescribing was calculated and reported with 95% confidence intervals (95% CI), estimated using Poisson regression. We tested trends in prevalence over time using the t-test on the change in annual prevalence, with significance level of 0.05. Statistical power for the trend test was calculated. Considering data included in trend test is limited (11 data points), some of the analyses might be underpowered to detect the trend. Statistical computing software R (version 3.1.2, R Core Team) and SAS software (version 9, SAS Institute Inc.) was used for data manipulation and analysis. Data was analysed by KSJL using R and independently cross-checked by AWYT and KKCM.

This study protocol was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (reference number: UW 15-619).

3. Results

From 2004 to 2014, there were 10,109,206 APDs prescriptions issued to 256,903 patients (Table 1). Haloperidol (20.7%), chlorpromazine (9.5%) and sulpiride (7.6%) were the most frequently prescribed FGAs in HK over this period, while risperidone (12.1%), quetiapine (11.3%) and clozapine (7.1%) were the three most commonly prescribed SGAs (Supplementary table 1).

The prevalence of APDs prescribing in the general population increased 45% from 1.06% (2004) to 1.54% (2014). The prevalence of FGAs prescribing decreased 13% from 0.95% (2004) to 0.83% (2014), while SGAs prescribing increased by 480% from 0.19% (2004) to 0.91% (2014). The trend test for any APDs and SGAs showed statistically significant results (Figure 1 and Supplementary table 3). The statistical power of the trend test of FGAs prescribing prevalence in the general patient population was 0.42. The statistical power of trend tests in this groups was less than 0.8, which indicates that the real trend might be undetectable due to lack of statistical power. Subsequent analyses with statistical power less than 0.8 should be interpreted as underpowered similarly.

In children, there was an increase in the prevalence of APDs prescribing from 0.10% (2004) to 0.23% (2014) by 2.3 times. The prevalence of FGAs prescribing decreased 57% from 0.07% (2004) to 0.03% (2014), while the prevalence of SGAs increased from 0.04% (2004) to 0.21% (2014) by more than 5 times. Changes in the trends of APDs, FGAs, and SGAs prescribing were statistically significant (Figure 2 and Supplementary table 4).

In older patients, the prevalence of APDs prescribing increased 24% from 2.61% (2004) to 3.23% (2010) and was then stable at 3.26% (2014). The prevalence of FGAs was stable from 2004 to

2010, followed by an 18% decrease from 2.45% (2010) to 2.01% (2014). The prevalence of SGAs increased from 0.39% (2004) to 1.52% (2014) by about 4 times. FGAs were more frequently prescribed than SGAs in this age group throughout the study period. The changes in prescribing trends of any APDs and SGAs were statistically significant (Figure 3 and Supplementary table 5). Statistical power of the trend test of FGAs prescribing prevalence in older patients was 0.28.

There were 320,739 delivery episodes from 319,564 pregnant women identified with at least one pregnancy timeframe during the study period. Among these, 1,749 women were prescribed APDs during relevant pregnancy timeframes. From 2004 to 2014, 0.18% to 0.32% of women were prescribed APDs during the pre-pregnancy timeframe, 0.18% to 0.27% during the pregnancy timeframe, and 0.30% to 0.38% during the postpartum timeframe (Figure 4 and Supplementary table 6). There were no statistically significant changes in trends in any annual APDs prescribing in pre-pregnancy, pregnancy, or postpartum timeframes over the study period. The highest statistical power of the trend tests of the three timeframes was 0.21.

For the indication analysis, 201,371 new APDs users were identified, among which 104,451 had a diagnosis of a mental disorder identified within the period of 180 days before or after the date of the incident prescription (51.9%). The percentage of incident prescriptions associated with the diagnosis of other psychoses decreased from 54.1% (2004) to 47.5% (2014). The percentage of incident prescriptions for organic psychotic conditions increased from 38.5% (2004) to 46.1% (2010), then decreased to 40.4% (2014). For neurotic disorders, personality disorders and other nonpsychotic mental disorders, this percentage increased from 25.4% to 33.9%. The percentage

of incident APDs prescriptions for intellectual disabilities decreased from 2.7% (2004) to 2.0% (2014) (Table 2).

Results of prescribing trend by dosage forms showed that the majority of APDs were administered orally as a tablet or capsule. The annual prevalence increased from 1.00% (2004) to 1.45% (2014) by 45%. The prevalence of depot injection prescribing increased from 0.15% (2004) to 0.18% (2005) by 20% and remained stable through 2005 to 2014. Prescribing prevalence of immediate injection increased from 0.08% (2004) to 0.12% (2014). The prevalence remained stable at 0.02% for oral solutions. Statistically significant change was detected only in the prevalence in the oral tablet/capsule subgroup (Supplementary table 2). The highest statistical power of the trend tests for oral solutions, immediate injection, and depot injection prescribing prevalence was 0.48.

4. Discussion

APDs prescribing is increasing in HK in the general population, children, and older patients. The prevalent usage and increase are particularly notable in older patients. Although an increase in SGAs prescribing was found, SGAs prescribing was less prevalent in HK compared to western countries. During the study period, the percentage of incident prescriptions for organic psychotic conditions increased, as did the prescriptions for nonpsychotic disorders. Finally, the most commonly prescribed dosage form, which was oral tablets/capsules, increased over the study period, while the prevalence of depot injections remained stable.

4.1.Interpretation and comparison with other studies

We found that 1.06% (2004) to 1.54% (2014) of the HK population were prescribed at least one APDs and that there was a statistically significant change in prevalence. In comparison, the annual prevalence of APDs prescribing in patients from GP settings in Italy was reported as having increased from 1.33% (2000) to 1.74% (2005)[14]. Using a community population sample from the Clinical Practice Research Datalink database in the UK, the prescribing prevalence of APDs and medication used for treating mania was reported as 1.0% and 1.4% in males and females, respectively, in 2010[12]. Information from GP settings shows a similar increase in APDs prescribing to the data in our study, which provides a comprehensive view of drug prescribing from outpatient, inpatient, and emergency departments. However, comparison between our results and data from other sources needs to take full account of the differences of data source in the groups studied.

Differences in APDs prescribing were found in specific age groups, including children and older patients, when comparing the results of our study to those from other regions. Results of a survey study conducted in the US showed that 1.83% of children (0-13 years old) and 3.76% of adolescents (14-20 years old) who visited a physician between 2005 and 2009 were prescribed APDs[28], which are higher percentages than the results of our study. The prevalence of APDs prescribing in older adults (65 years old and above) from GP settings was reported as 3.6% in Italy in 2005[14]. APDs were prescribed to 12.7% and 12.8% of the older population (≥65 years old) in Taiwan inpatient and outpatient settings in 2004 and 2005, respectively[29]. Results of our study showed that 2.70% of older patients were prescribed APDs, which was lower than the prevalence reported in Italy and Taiwan. These discrepancies of APDs prescribing in specific age group could be associated with various factors including local practice. Patient care in regions may vary due to different clinical guidelines followed. Clinical practice guidelines of early onset

psychoses (less than 18 years old) in US and UK recommend SGAs as treatment option[30 31], while HK local guideline for children and adolescents has not yet been developed.

Compared to HK, SGAs were generally more frequently prescribed in other regions. Our study showed that the SGAs prevalence did not exceed the FGAs prevalence until 2014. With respect to the proportion of prescriptions in other regions, SGAs represented 82% of overall APDs prescriptions in 2002 in Canada[32] and 84% in 2002 in the US[33]. Similar to our findings, and in contrast to the results from North America, SGAs prescribing lagged behind FGAs prescribing in inpatient settings in other Asian countries and regions including China, HK, Japan, Korea, Singapore, and Taiwan[15 16]. However, the prevalence of SGAs prescribing in HK increased, while FGAs prescribing decreased over the study period, in the general patient population, children, and older patient groups. The increase in prescribing SGAs and decrease in FGAs were also reported in Australia from 2000 through 2011[34]. This indicates that the increase in SGAs largely accounted for the overall increase in APDs prescribing. This increase in the prescribing of SGAs could be explained by several factors. In the 2000s, SGAs were recommended as first-line treatment for several mental disorders (e.g. schizophrenia and bipolar disorder) in clinical practice guidelines[20 35-38], including HK local guidelines[39], because of their better tolerability profile and perceived superior efficacy compared to FGAs[40 41]. The better tolerability profile also may have decreased the likelihood of treatment discontinuation, which would have lengthened the duration of prescription and therefore may have increased prevalence, as suggested in a previous study[42]. Other reasons could be an increase in the approved indications of SGAs, which are now approved for the treatment of bipolar mania, adolescent schizophrenia, and behavioural disturbance associated with autism or intellectual disability in children and adolescents[7].

With regard to APDs prescribing in pregnancy, it was expected that the prevalence would take the "U-shape" pattern (statistically significantly higher prevalence in the timeframes of pre-pregnancy and postpartum, compared to the pregnancy timeframe)[43]. However, this was not the case in our study. Although no statistically significant change was detected, our study indicates that APDs prescribing remains common during the pre-pregnancy, pregnancy, and postpartum timeframes.

We found that 45.9% of APDs incident prescriptions in 2004 were associated with a diagnosis of non-psychotic mental disorders, and this number further increased to 52.5% in 2014. These results may suggest that the off-label prescribing of APDs is expanding, since APDs have not received approval for most of the mental disorders under these two categories, including dementia, anxiety disorder, and obsessive compulsive disorder. Since "black-box warnings" have been issued in relation to the increased mortality in older patients with dementia prescribed APDs, these drugs should be used with caution in older patients. Close monitoring and more frequent follow-up should be implemented when APDs are prescribed to patients for unapproved indications, especially in older patients.

Oral capsule/tablet was the most common route of administration of APDs in HK. Audits and surveys from 1996 to 2009 reported that from a quarter to a third of sampled patients were prescribed depot injections in the United States, Europe, Australia, and New Zealand[21]. It is noteworthy that a survey reported that 36.7% of sampled stable patients with schizophrenia from HK outpatient clinics in 2005 and 2006 were prescribed APDs depot injections[44]. As shown in our results, no statistically significant change was detected in the annual prevalence of APDs depot injection prescribing.

4.2. Strength of this study

To our knowledge, this is the first study describing APDs prescribing trends using population-based database in Asia. Apart from providing information on APDs prescribing in the general patient population and patient groups of interest, this study also provides prescribing data by dosage form and on the probable indication of incident APDs prescriptions. Although there are publications on surveys/audits of APDs prescribing/utilization conducted in Asia at local hospitals or certain regional clinics, we could find no previous publications on population-based data. In contrast, data used in this study were derived from CDARS, which consists of medical records from the HK public healthcare sectors, including inpatient, outpatient, and emergency department prescriptions.

4.3.Limitations of this study

Since the database used in this study was derived from the public healthcare system, antipsychotic prescriptions in private clinics were not included, implying that the prevalence of APDs prescribing may have been underestimated. A previous study suggested that public healthcare institutions were the mainstay of the mental health service in HK[45]. As APDs are generally chronic treatment and patients who require long-term follow-up are more likely to use public healthcare due to the lower costs, the CDARS data in this study are likely to have captured most of the APDs prescriptions in HK. In cases where the change in trend over time was not statistically significant, the analyses were underpowered. Results of this study might not be generalizable to healthcare systems of other countries/regions due to different local practice of patient care and age distribution in study population.

5. Conclusion

Our study has confirmed an increasing trend in APDs prescribing to older patients, suggesting that attention should particularly focus on the safety and tolerability profile of APDs in this age group. Further evidence to support the effectiveness and safety of off-label utilization of APDs is required. With the changes in APDs prescribing over time it is important to determine not only the differences in beneficial effects but also differences in adverse effects, particularly for serious, rare, and delayed adverse effects, which may only emerge after considerable clinical experience has been accumulated. Future observational studies using population-based data could be of great value in this regard.

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Table 1. Patient Characteristics

Patients with APDs (%)	
Sex	
Male	123,983 (48.3%)
Female	132,920 (51.7%)
Age (years)	
Median (IQR)	60 (38)
Children (3 to 17 years old)	6,996 (2.7%)
Older patients (65 years old and above)	113,935 (44.3%)
Total patients with APDs	256,903 (100%)
APDs prescriptions (%)	
FGAs	5,706,118 (56.4%)
SGAs	4,403,088 (43.6%)
Total APDs prescriptions	10,109,206 (100%)

Age: age at first prescription during study period; APDs: antipsychotic drugs;

FGAs: first generation antipsychotics; SGAs: second generation antipsychotics.

Table 2. Percentage of incident users by indication category from 2004 to 2014

Year	Other psychoses	Non-psychotic mental disorder	Intellectual disabilities	Organic psychotic conditions
	Percentage, %			
2004	54.14	25.36	2.67	38.47
2005	53.16	26.15	2.35	40.29
2006	52.18	26.05	2.49	40.89
2007	52.83	26.59	2.35	41.79
2008	50.20	25.82	2.00	44.13
2009	49.00	26.79	2.47	44.41
2010	47.66	27.56	2.33	46.10
2011	46.87	29.29	2.50	45.82
2012	48.01	29.98	2.26	43.55
2013	47.98	32.63	2.25	42.11
2014	47.45	33.89	1.95	40.39

Other psychoses (ICD-9-CM 295-299). Nonpsychotic mental disorder (ICD-9-CM 300-316). Intellectual disabilities (ICD-9-CM 317-319). Organic psychoses conditions (ICD-9-CM 290-294). ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification.

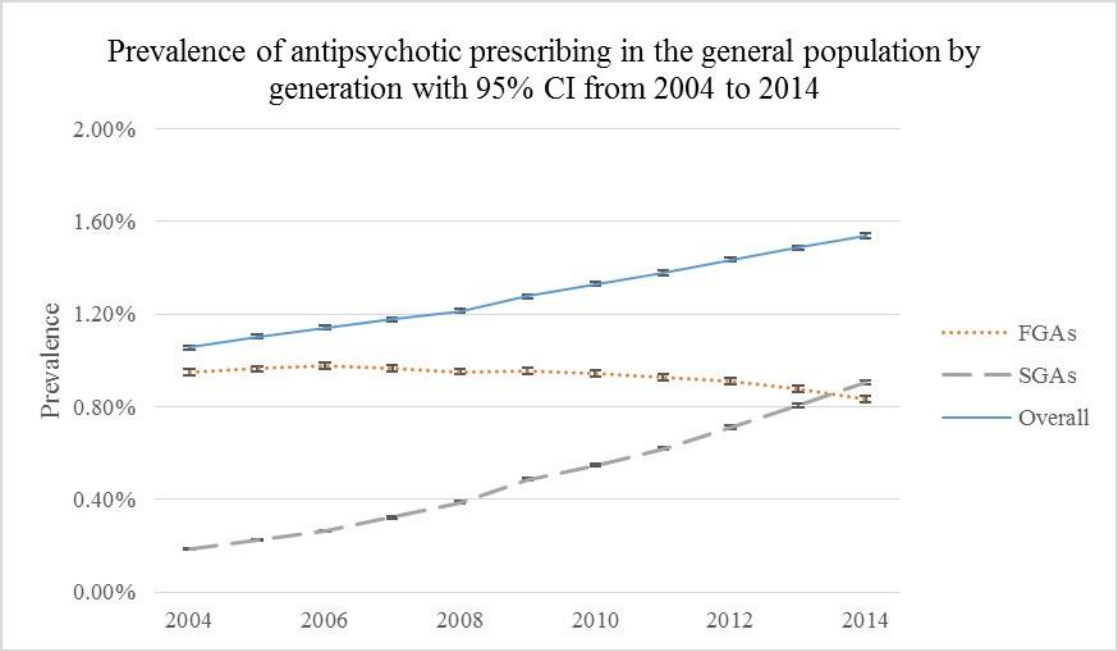

Figure 1. Prevalence of antipsychotic prescribing in the general population by generation with 95% confidence intervals from 2004 to 2014.

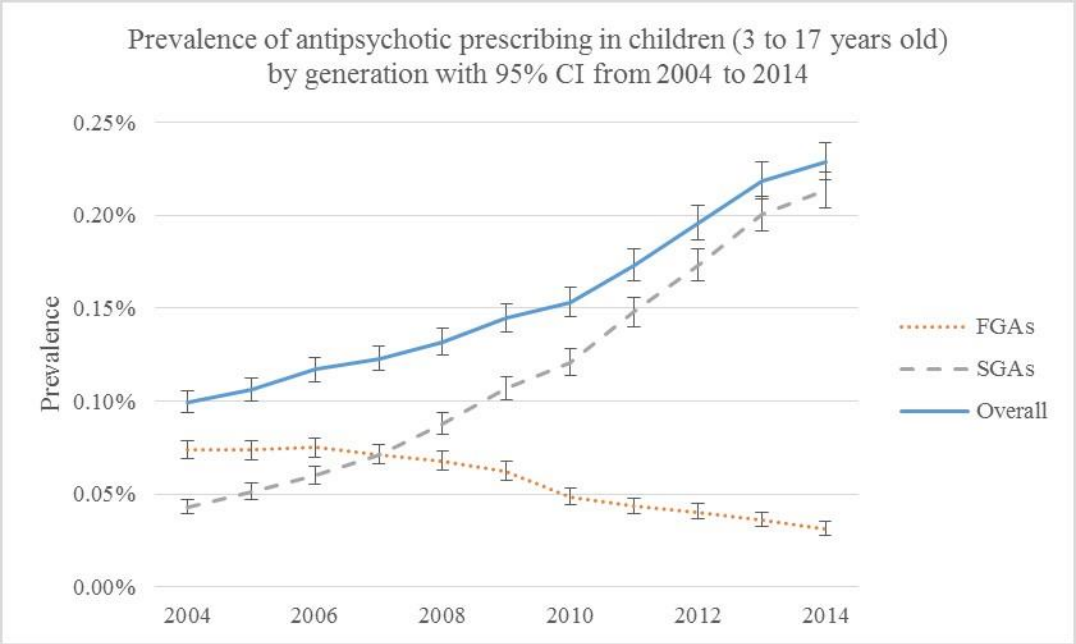

Figure 2. Prevalence of antipsychotics prescribing in children (3 to 17 years old) by generation with 95% confidence intervals from 2004 to 2014.

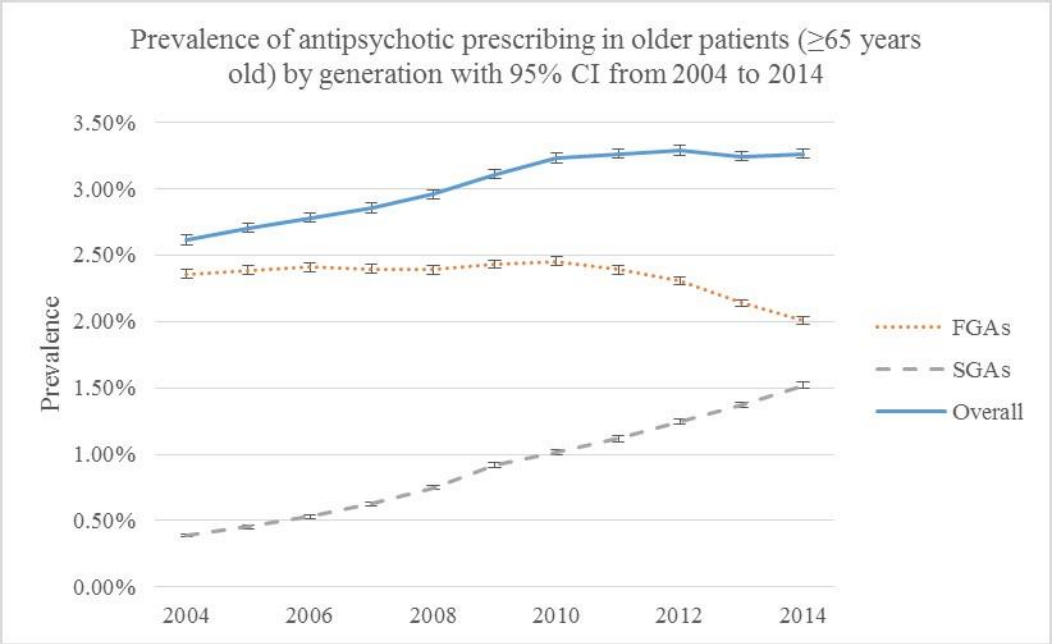

Figure 3. Prevalence of antipsychotic prescribing in older patients (≥65 years old) by generation with 95% confidence interval from 2004 to 2014.

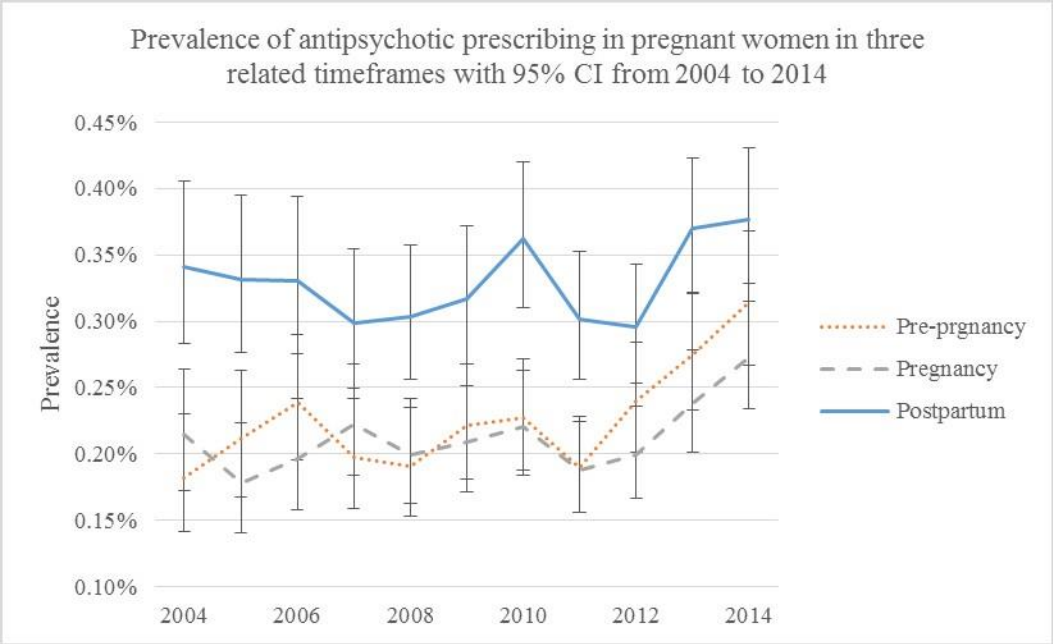

Figure 4. Prevalence of antipsychotic prescribing in pregnant women in pre-pregnancy, pregnancy, and postpartum timeframes with 95% confidence intervals from 2004 to 2014.