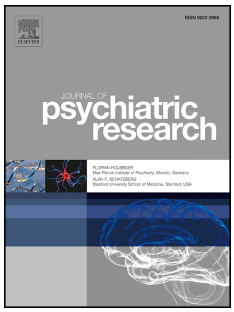

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Author statement

Conflicts of interest

The authors declare that they have no conflicts of interests.

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Incidence, Prevalence and Prescription Patterns of Antipsychotic Medications Use in Asia and US: A Cross-Nation Comparison with Common Data Model

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Abstract

The use of antipsychotic medications (APMs) could be different among countries due to availability, approved indications, characteristics and clinical practice. However, there is limited literature providing comparisons of APMs use among countries. To examine trends in antipsychotic prescribing in Taiwan, Hong Kong, Japan, and the United States, we conducted a cross-national study from 2002 to 2014 by using the distributed network approach with common data model. We included all patients who had at least a record of antipsychotic prescription in this study, and defined patients without previous exposure of antipsychotics for 6 months before the index date as new users for incidence estimation. We calculated the incidence, prevalence, and prescription rate of each medication by calendar year. Among older patients, sulpiride was the most incident [incidence rate (IR) 11.0-23.3) and prevalent [prevalence rate (PR) 11.9-14.3) APM in Taiwan, and most prevalent (PR 2.5-3.9) in Japan. Quetiapine and haloperidol were most common in the United States (IR 8.1-9.5; PR 18.0-18.4) and Hong Kong (PR 8.8-13.7; PR 10.6-12.7), respectively. The trend of quetiapine use was increasing in Taiwan, Hong Kong and the United States. As compared to older patients, the younger patients had more propensity to be prescribed second-generation APM for treatment in four countries. Trends in antipsychotic prescribing varied among countries. Quetiapine use was most prevalent in the United States and increasing in Taiwan and Hong Kong. The increasing use of quetiapine in the elderly patients might be due to its safety profile compared to other APMs.

Key Words: Antipsychotic agents, pharmacoepidemiology.

1. Introduction

Antipsychotic medications (APMs) are mainly indicated for severe mental illnesses, including schizophrenia and bipolar disorder (Association, 2006). Meanwhile, APMs may also be prescribed off-label for treatment of psychosis and behavioral disturbance of dementia, major depression and other cognitive dysfunction in the elderly patients although the evidences for effectiveness and safety remained inconclusive (Cerejeira et al., 2012). Therefore, the range of mental disorders treated with APMs in clinical practice is broad.

Recently, an increased prescribing rate of APMs have been observed in several studies (Ilyas and Moncrieff, 2012; Olfson et al., 2012; Patel et al., 2005; Verdoux et al., 2010), especially the off-label antipsychotic prescription (Kales et al., 2011; Park et al., 2016; Schulze et al., 2013; Weintraub et al., 2011) This has raised concerns about possible increased serious adverse events in patients treated with APMs (Douglas and Smeeth, 2008; Gerhard et al., 2014). In this context, the US Food and Drug Administration (FDA) has issued a “black-box warning”, suggesting to reduce use of APMs in those with dementia and elderly patients (Kuehn, 2005; Setoguchi et al., 2008). Additionally, use of APMs in clinical practice are highly variable and depends on a wide range of different factors. This is especially true for antipsychotic treatment strategies in different countries, where physicians’ choices could be affected by specific economic, cultural and demographic issues. Therefore, the differences of trend in APM prescriptions among different countries might reflect underlying differences in availability, approved indications, patients’ characteristics and clinical practice. Thus, we aimed to investigate the trends of prescription patterns of APMs use among different countries.

The Surveillance of Health Care in Asian Network (SCAN) Project was carried out to gain a better understanding of the health care and drug utilization of the population covered in each participating site database in the Asian pharmacoepidemiology Network (AsPEN) (2012; Pratt et al., 2013). The SCAN project was a collaboration between five countries (the United States (US), Taiwan, Hong Kong, Japan, and South Korea) using electronic health care record databases. It

employs the Observational Medical Outcomes Partnership (OMOP) common data model (CDM) with the corresponding OMOP vocabulary to perform standardized analysis among participating sites (Voss et al., 2015). In this study, we used the OMOP CDM and a common standardized analysis program to investigate the trend of incidence, prevalence and prescribing rate of APMs use over time among participating sites.

2. Methods

2.1. Data Sources

All source data have been converted to the Observational Medical Outcomes Partnership (OMOP) common data model (CDM) with the corresponding OMOP vocabulary to perform standardized analysis among participating sites (Voss et al., 2015). The databases used in this study include (1) a 5% random sample from the United States Medicare database; (2) a 4% random sample of Taiwan's National Health Insurance Research Database (NHIRD); (3) a 1% random sample of the Hong Kong's Clinical Data Analysis and Reporting System (CDARS); (4) The full Japan Medical Data Center database. (Lai et al., 2015) The Medicare provides health insurance coverage approximately 42 million people aged ≥65 years and nearly 9 million people aged <65 years with certain disabilities or end-stage renal disease. The Medicare database consists of Part A (hospitalization), Part B (office based medical care), and Part D (prescription drugs). (Kales et al., 2007) The 4% random sample of NHIRD is a sub-dataset of NHIRD which contains a randomly-selected cohort of one million people from all insured beneficiaries in 2005. The 1% random sample of CDARS includes inpatient and outpatient data of all public hospitals in Hong Kong. The representative of NHIRD and CDARS are described in other published papers (Lai et al., 2015; Lai et al., 2018). The JMDC consists of individuals at working age (age<65) and their family members belonging to the same household (Kimura et al., 2010). The detailed information of the databases and the conversions of CDM are described elsewhere (Lai et al., 2018).

2.2. Study Design and Population Cohort Identification

We conducted a cross-sectional study using population-based databases from four countries. The study population of APM users were identified from databases of Taiwan (2002-2010), Hong Kong (2009-2013), Japan (2007-2014) and US (2007-2011) respectively. We included all patients who had at least a record of antipsychotic prescription in this study. The first date of antipsychotic prescription in the database was defined as index date. To ensure we have sufficient data for

patients' baseline characteristics, we included patients with more than 12 months eligibility of inpatient, or outpatient services and with more than 6 months eligibility of prescription benefit before the index date. We defined patients without previous exposure of antipsychotics for 6 months before the index date as new users. In addition, because age-related pharmacokinetic, pharmacodynamics and comorbidities changes results in increased risk for adverse events (Jeste and Maglione, 2013) which may affects a physician's prescribing behavior, we categorized the study population into two broad age groups: those aged 65 and above (elderly) and non-elderly (under 65 years old) groups for all analyses.

2.3. Antipsychotic medications exposure

We analyzed APMs that are frequently used included paliperidone, amisulpride, aripiprazole, chlorpromazine, clozapine, haloperidol, olanzapine, quetiapine, risperidone and sulpiride. Among these APMs, the first-generation APMs (FGAs) included chlorpromazine, haloperidol and sulpiride, and the remaining were second-generation APMs (SGAs). The amisulpride and sulpiride were not approved in the US. Paliperidone (which is the primary active metabolite of the risperidone) is the newest APM and which is the primary active metabolite of the risperidone, has become available in the Taiwan in 2008, Hong Kong in 2007, Japan in 2010 and US in 2009. We plotted APM exposure by number of incident and prevalent users across years to review possible secular trends.

2.4. Patient characteristics

Patient characteristics including age, gender, years of index date, neuropsychiatric diseases for possible antipsychotic treatment, other comorbidities and concomitant medications were identified. The neuropsychiatric diseases, comorbidities and medications were analyzed based on the patients' diagnosis and prescription history during the 6 months before the index date. We were interested in characterizing the populations based on neuropsychiatric diseases, including schizophrenia, depression, mood disorders, dementia, Parkinson's disease, and a set of particular comorbidities as asthma, atrial fibrillation, congestive cardiac failure, chronic obstructive pulmonary disease

(COPD), epilepsy, hyperlipidaemia, hypertension, myocardial infarction, Parkinson's disease, pneumonia, renal failure, and rheumatoid arthritis. Regarding the medications of interest, the neuropsychiatric agents included anti-dementia agents, antidepressants, anti-Parkinson drugs, benzodiazepines (BZD), and the other concomitant medications included antiarrhythmic agents, antihypertensive agents, beta-blockers, calcium channel blockers, antidiabetic agents, COPD medications, diuretics, NSAIDs, statin and non-statin lipid lowing drugs and renin-angiotensin system (RAS) inhibitors, etc. The details of information was showed in Table1.

2.5. Statistical Analysis

Descriptive statistics were used to summarize baseline characteristics (in the 6 months prior to initiation of the APM) of the study population by each country (US, Taiwan, Hong Kong and Japan) and proportions for discrete variables and means with standard deviations (SD) and/or medians with quartiles for continuous variables. We also described patient characteristics by different APM types and countries. We calculated the prevalence and prescribing rate of APMs as the number of APMs users and prescriptions divided by the total number of patients alive on December 31st per 1,000 subjects, respectively. Moreover, we calculated the incidence rate as the number of new APMs users during the year divided by the total of person-years (per 1,000 patient-years) in the current year. The rates were adjusted by age and gender under a Poisson assumption. The trend of APMs use over time were tested by Poisson regression model. The directions of coefficients ($\pm\beta$) were estimated to represent the increased or decreased of APMs use over time. We performed all statistical analyses using SAS (version 9.3 for Windows; SAS Institute Inc., Cary, NC, USA).

Results

2.6. Patients 65 Years and Older

Table 1 and the supplementary material shows the characteristics of the study population. In the older cohort, we identified 28,070 new users of antipsychotic medications in Taiwan, 1267 in Hong Kong, 2481 in Japan, and 82,641 in the United States during the study period. Among new users, 27.3% to 46.7% were men, and the mean age in the United States was higher than in the other countries. Dementia, mood disorders, and depression were the most common in neuropsychiatric diseases. Concurrent medications at baseline varied widely across the four countries. Among neuropsychiatric medications, benzodiazepines were the most prescribed in Taiwan (38.1%), Hong Kong (23.4%), and Japan (55.3%) and the third most common in the United States (13.0%). Antidepressants were the most prescribed neuropsychiatric medication in the United States (58.9%) and the second most prescribed in Taiwan (26.0%), Hong Kong (20.7%), and Japan (16.5%). Antidementia drugs were the second most prescribed neuropsychiatric medications in the United States (35.6%) but not in other countries (Table 1).

Figures 1 and 2 show trends in the adjusted incidence (IR) and prevalence rate (PR) of the use of 10 antipsychotic medications in each country. Sulpiride had the highest rate of new users in Taiwan over the study period (IR: 11.0-23.3 per 1,000 patient-years from 2002-2010). Haloperidol had the highest rate of new users in Hong Kong (IR: 9.2-14.2 per 1,000 patient-years from 2009-2013) and Japan (IR: 1.6-4.7 per 1,000 patient-years from 2007-2014), and quetiapine had the highest rate of new users in the United States (IR: 8.0-9.5 per 1,000 patient-years from 2007-2011). Quetiapine was ranked the second prevalent antipsychotic in Taiwan and Hong Kong. The incidence (β=0.16; p-value<.0001) and prevalence (β=0.24; p-value<.0001) of quetiapine use increased in Taiwan, while only prevalent use increased in Hong Kong (β=0.14; p-value<.0001) over the study period. The trends in prescription rates was similar to the trends in prevalence in each country (Appendix Figure 1).

136 *2.7. Patients Younger Than 65 Years*

137 In the younger cohort, we identified 91,801 news users of antipsychotics in Taiwan, 1,743 in
138 Hong Kong, 59,945 in Japan, and 61,841 in the United States, and 44.7% to 51.4% were men.
139 Depression and schizophrenia was also among the most common mental disorders in four countries
140 (Table 1). Among neuropsychiatric medications, benzodiazepines were the most prescribed in
141 Taiwan (31.3%), Hong Kong (30.9%), and Japan (41.0%) and ranked third in the United States
142 (17.0%). Antidepressants were the most common neuropsychiatric medications in the United States
143 and second most common in Taiwan (20.6%), Hong Kong (30.5%), and Japan (31.1%).

144 Sulpiride was the most incident and prevalent antipsychotic medication in Taiwan (IR range:
145 4.3-8.6 per 1,000 patient-years from 2001-2010; PR: 3.1-4.1 per 1,000 subjects from 2001-2010)
146 and Japan (IR: 2.1-2.8 per 1,000 patient-years from 2007-2014; PR: 1.8-2.4 per 1,000 subjects from
147 2007-2014). However, incident use of sulpiride declined in Taiwan (β=-0.02; p-value<.0001) and
148 Japan (β=-0.03; p-value<.0001). Risperidone was the second most common antipsychotic in Taiwan
149 (IR: 0.6-0.7 per 1,000 patient-years from 2001-2010; PR range, 0.5-1.3 per 1,000 subjects from
150 2001-2010), Japan (IR: 0.8-1.0 per 1,000 patient-years from 2007-2014; PR: 1.7-1.8 per 1,000
151 subjects from 2007-2014), and the United States (IR: 14.2-18.2 per 1,000 patient-years from
152 2007-2011; PR: 55.7-56.0 per 1,000 subjects from 2007-2011). In addition, risperidone had the
153 highest incidence in Hong Kong between 2009 and 2011 (PR: 2.6-3.0 per 1,000 patient-years), and
154 prevalence increased over the study period (β=0.10; p-value<.0001). Trends in prescription rates
155 were similar to trends in prevalence in each country (Appendix Figure 2).

156

3. Discussion

In this cross-national observational study, we found that the trends of clozapine prescriptions were consistent across the four countries, though the most prevalent antipsychotics differed. Such variation may be attributable to differences in availability, labeled indications and patients' demographic issues in each country.

Taking older and younger patients together, the results revealed that the proportion of patients diagnosed with schizophrenia was decreased with age, and the proportion of patients diagnosed with dementia was increased with age in elderly patients as compared to the younger group. Not surprisingly, because schizophrenia is known to develop in early adulthood and rare in persons older than 40 years (Loranger, 1984), while the incidence of dementia increases after age 65 years (Prince et al., 2013; Ruitenberg et al., 2001).

According to literatures, the indications of clozapine is specific to schizophrenia or schizophrenia with resistance to other antipsychotics (Association, 2006). In both the elderly and younger study groups, we found that trend of clozapine use was stable over time compared to other APMs, that might imply clozapine prescriptions compliant with guideline were not changed over time. Therefore, the changes of APMs use could be attributable to off-label antipsychotic prescriptions, especially use of APMs in elderly patients such as dementia, Parkinson's disease, depressive disorder, anxiety or sleep disorders. Increased proportions of those diseases in older patients were also observed in our results. The use of quetiapine in older patients was significantly increased over time in Taiwan and Hong Kong. This change might also reflect the increased trend of off-label antipsychotic prescriptions. In Taiwan and Hong Kong, the elderly quetiapine users had higher proportions of dementia and Parkinson's disease compared to other APMs users (Appendix), which might be associated with its better safety profile as suggested in the literature (Kales et al., 2012; Kales et al., 2011).

It is worth noting that prescribing antipsychotic medications to elderly patients is challenging because the patients often have concomitant medical illnesses, such as cardiovascular disease,

diabetes mellitus, Parkinson's disease, or dementia and receive multiple medications. Thus, the potential effects of polypharmacy must be carefully considered by physicians. In our study, a higher proportion of the elderly patients received concurrently antidepressant, BZDs and anticholinergic drugs for COPD, which could result in drug-drug interaction with selected second-generation APMs (Kennedy et al., 2013).

On the other hand, among patients younger than 65 years in our study, although the most antipsychotic prescription in Taiwan and Japan was sulpiride, and quetiapine in the United States, risperidone was second common use in these countries. Risperidone was approved for treatment in adults with schizophrenia by the US Food and Drug Administration in 1994 (Carter et al., 1995), and its oral form was later approved for use in children and adolescents with schizophrenia. In 2003, long-acting injection was approved for schizophrenia, and both oral and long-acting risperidone were extended for bipolar disorder (Sajatovic et al., 2005) and agitation in autism spectrum disorder (Scahill et al., 2007). Risperidone has been associated with lower rates of akathisia, rigidity, tremor and extrapyramidal symptoms (Carter et al., 1995) but seems to be associated with an increased risk of hyperglycemia (Koller et al., 2003). These different dosage forms and well-documented side effect profiles might support the prevalent use of second-generation agents in these countries.

Although sulpiride was not available in Hong Kong and United States, it was the most frequently used antipsychotic in both age groups in Taiwan and Japan. According to the labeled indications, sulpiride 150 mg/d was commonly indicated for gastrointestinal upset, whereas doses of 150 to 300 mg/d and 300 to 600 mg/d were indicated for depressive disorders and schizophrenia, respectively. However, sulpiride sometime was prescribed for minor psychiatric symptoms with less 150 mg/d in elderly patients, especially in Taiwan. That might be attributed to physicians' prescribing choice based on the perceived patient benefit. Sulpiride has been reported to be more effective in controlling negative symptoms (Azorin et al., 1992; Gerlach, 1991), had lower rates of extrapyramidal symptoms than other first-generation agents (Gerlach, 1991; Leucht et al., 2009) and better adherence (Lai et al., 2013) than risperidone, olanzapine and haloperidol, which might

explain why sulpiride was most frequently used in Taiwan and Japan.

Some limitations of this study should be noted. First, the diagnoses were based on a vocabulary mapped to ICD-9 and ICD-10 codes in the participating sites' health care claims databases. The accuracy of medical coding is a concern; in particular, dementia is likely to be underdiagnosed and undercoded in clinical practice. (Gerhard et al., 2015) Therefore, underestimate of disease could not be completely ruled out. Second, the integrity of database. The participating site's health care databases were mapped to the OMOP CDM and its vocabularies which may result in some terms not mapping effectively. Therefore, we performed a validation study to ensure the integrity of CDM. The findings indicated that participating data well accommodated the structure of the CDM with mapping rates for diagnosis and medication at 100% and over 90%, respectively (data not shown). The unmapped drug codes were mainly the medications for common cold and cough and would not influence our study substantially (Lai et al., 2018). Third, health care claims databases are less representative in younger patients in the United States and older patients in Japan. Fourth, because of the available data were not the same in calendar years among countries, it was hard to compare the changes of prescribing trends directly. Nevertheless, we observed the rates of off-label use of antipsychotics were increased and stable rate of clozapine use consistently in all countries. Fifth, because indications of using antipsychotics could be multiple and sometimes might not well recorded, for example sulpiride for gastrointestinal disorders as aforementioned, we were not be able to distinguish between indications for APMs or other conditions. The estimation of actual incidence and prevalence of antipsychotic use in mental health care were not precisely. Although the reason for antipsychotic use could not be verified in the study, we believed the safety issues raised by the increased rate of APMs could be common in whatever indications.

Despite the marked differences in prescribing patterns of antipsychotics, we found the rate of APMs were increased except clozapine, which might imply the rate of off-label use of APMs were increased consistently in all countries. The findings warrant future investigations because the effectiveness and safety of antipsychotics for those purpose have not been well determined. Specifically, we found quetiapine was the most prevalent antipsychotic in the United States, and its

use was increasing in Taiwan and Hong Kong. The increasing use of quetiapine had complied with the suggestion from literature that quetiapine has a better safety profile than other antipsychotics in older patients. Our study provided fundamental grounds for future study to evaluate the safety and effectiveness of quetiapine in a real-world scenario.

Conflicts of interest

The authors declare that they have no conflicts of interests.

Acknowledgments

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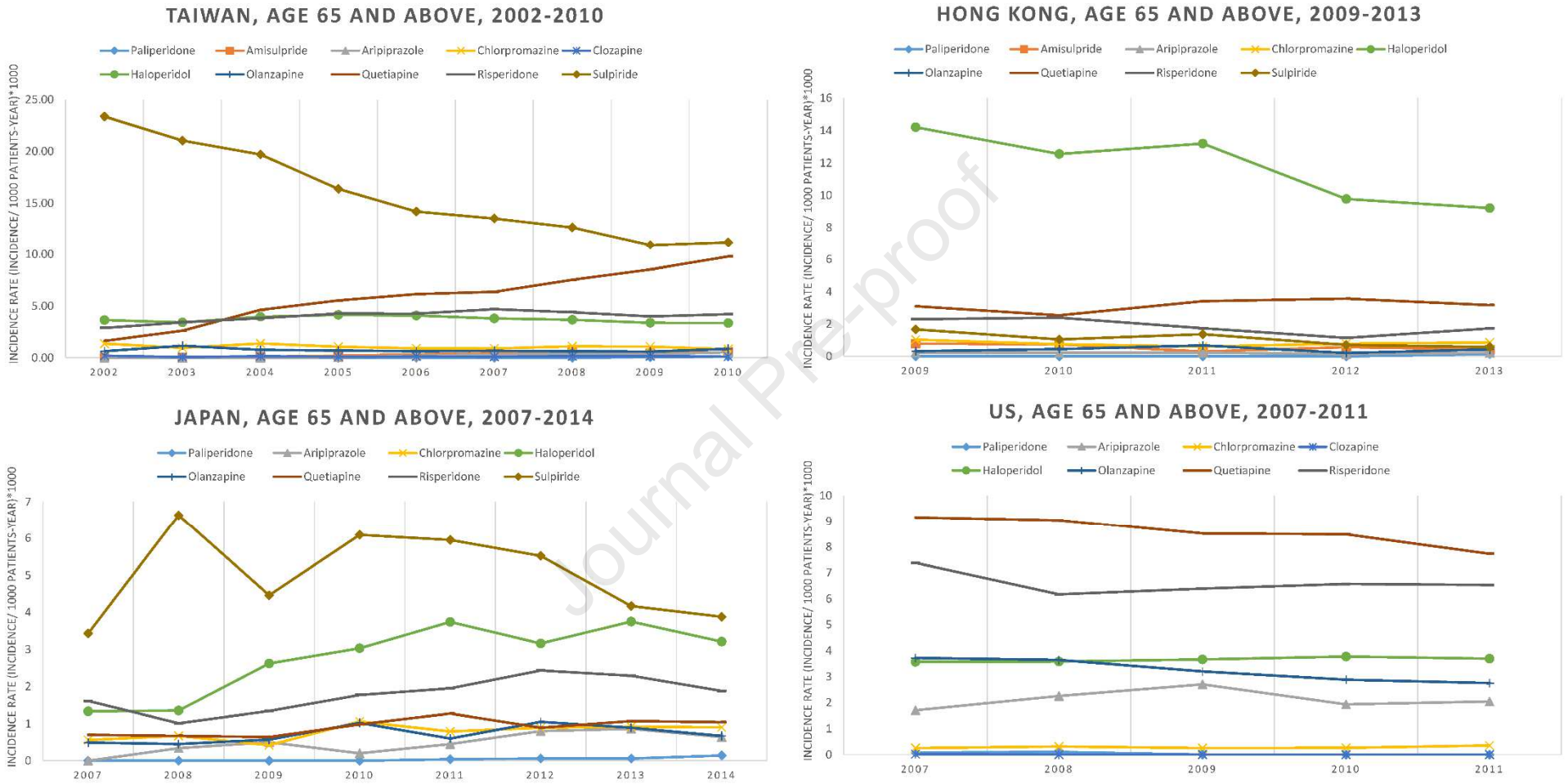
Table 1 Characteristics of Antipsychotic Medications User by Age and Country.

Country	Taiwan	Hong Kong	Japan	US	Taiwan	Hong Kong	Japan	US
Characteristics								
Overall, n	28070	1267	2481	82641	91801	1743	59945	61841
Gender, n(%)								
Male	13116 (46.7)	574 (45.3)	1039 (41.9)	22536 (27.3)	41058 (44.7)	857 (49.2)	30812 (51.4)	30408 (49.2)
Age								
Mean(SD)	76 (7.2)	80.5 (8.1)	69.7 (4.3)	81.5 (8.6)	38.7 (14.4)	41.2 (13.9)	36.8 (13.4)	46.2 (10.5)
Age distribution, n(%)[a]								
<18					8268 (9.0)	113 (6.5)	5683 (9.5)	16773 (27.1)
19-39					37586 (40.9)	665 (38.2)	28226 (47.1)	
40-64					45947 (50.1)	965 (55.4)	26036 (43.4)	45068 (72.9)
65-69	6396 (22.8)	125 (9.9)	1237 (49.9)	9359 (11.3)				
70-79	12834 (45.7)	450 (35.5)	1206 (48.6)	23434 (28.4)				
80-89	7641 (27.2)	523 (41.3)	32 (1.3)	49848 (60.3)				
90+	1199 (4.3)	169 (13.3)	6 (0.2)					
Index year, n(%)								
2002	2681 (9.6)				12053 (13.1)			
2003	2821 (10)				11548 (12.6)			
2004	3198 (11.4)				11735 (12.8)			
2005	3171 (11.3)				10322 (11.2)			
2006	3097 (11)				9664 (10.5)			
2007	3195 (11.4)		116 (4.7)	17211 (20.8)	9311 (10.1)		2085 (3.5)	13891 (22.5)
2008	3277 (11.7)		99 (4)	16788 (20.3)	9295 (10.1)		2029 (3.4)	12755 (20.6)
2009	3182 (11.3)	280 (22.1)	149 (6)	16461 (19.9)	9072 (9.9)	340 (19.5)	5071 (8.5)	12296 (19.9)
2010	3448 (12.3)	266 (21)	360 (14.5)	16095 (19.5)	8801 (9.6)	338 (19.4)	9249 (15.4)	11521 (18.6)
2011		269 (21.2)	395 (15.9)	16086 (19.5)		341 (19.6)	11118 (18.5)	11378 (18.4)
2012		230 (18.2)	464 (18.7)			327 (18.8)	11202 (18.7)	
2013		222 (17.5)	471 (19)			397 (22.8)	10018 (16.7)	
2014			427 (17.2)				9173 (15.3)	
History of diseases								
Neuropsychiatric diseases, n(%)								
Dementia	8457 (30.1)	171 (13.5)	271 (10.9)	37770 (45.7)	1159 (1.3)	12 (0.7)	295 (0.5)	2223 (3.6)
Depression	4983 (17.8)	63 (5.0)	871 (35.1)	14950 (18.1)	19049 (20.8)	165 (9.5)	32168 (53.7)	19085 (30.9)
Mood disorder	5528 (19.7)	68 (5.4)	955 (38.5)	17801 (21.5)	22482 (24.5)	227 (13)	34938 (58.3)	30675 (49.6)
Parkinson's disease	1856 (6.6)	21 (1.7)	133 (5.4)	5734 (6.9)	336 (0.4)	4 (0.2)	2323 (3.9)	707 (1.1)
Schizophrenia	862 (3.1)	35 (2.8)	542 (21.8)	4248 (5.1)	11518 (12.5)	296 (17)	17951 (29.9)	18139 (29.3)
Comorbidities, n(%)								
Asthma	2477 (8.8)	21 (1.7)	334 (13.5)	6490 (7.9)	3540 (3.9)	12 (0.7)	7460 (12.4)	10642 (17.2)
Atrial fibrillation	1214 (4.3)	108 (8.5)	139 (5.6)	16864 (20.4)	198 (0.2)	12 (0.7)	347 (0.6)	1468 (2.4)
Cancer	2633 (9.4)	162 (12.8)	1286 (51.8)	11768 (14.2)	2382 (2.6)	117 (6.7)	9529 (15.9)	3088 (5.0)
Congestive cardiac failure	2620 (9.3)	119 (9.4)	595 (24.0)	23071 (27.9)	776 (0.8)	13 (0.7)	2634 (4.4)	4131 (6.7)

COPD	3551 (12.7)	87 (6.9)	588 (23.7)	8250 (10)	1227 (1.3)	1 (0.1)	7665 (12.8)	4021 (6.5)
Epilep				Journal Pre-proof				(9.6)
Diabetes mellitus	6795 (24.2)	134 (10.6)	1268 (51.1)	29333 (35.5)	6101 (6.6)	27 (1.5)	12510 (20.9)	15452 (25)
Hyperlipidemia	5152 (18.4)	70 (5.5)	1180 (47.6)	44366 (53.7)	7973 (8.7)	15 (0.9)	9966 (16.6)	26291 (42.5)
Hypertension	14923 (53.2)	319 (25.2)	1363 (54.9)	67106 (81.2)	10853 (11.8)	54 (3.1)	6354 (10.6)	30004 (48.5)
Myocardial infarction	594 (2.1)	31 (2.4)	247 (10.0)	2668 (3.2)	248 (0.3)	5 (0.3)	1329 (2.2)	635 (1.0)
Pneumonia	3041 (10.8)	157 (12.4)	424 (17.1)	3146 (3.8)	2852 (3.1)	28 (1.6)	4147 (6.9)	1268 (2.1)
Renal Failure	2079 (7.4)	87 (6.9)	119 (4.8)	10848 (13.1)	972 (1.1)	22 (1.3)	629 (1)	3291 (5.3)
Rheumatoid arthritis	447 (1.6)	4 (0.3)	189 (7.6)	3071 (3.7)	654 (0.7)	1 (0.1)	1702 (2.8)	1622 (2.6)
Medications								
Neuropsychiatric medications, n(%)								
Anti-dementia agents	2148 (7.7)	83 (6.6)	123 (5.0)	29443 (35.6)	1111 (1.2)	11 (0.6)	89 (0.1)	1438 (2.3)
Antidepressants	7285 (26)	262 (20.7)	410 (16.5)	48663 (58.9)	18889 (20.6)	531 (30.5)	18636 (31.1)	38069 (61.6)
Anti-Parkinson agents	3895 (13.9)	109 (8.6)	140 (5.6)	8023 (9.7)	10055 (11)	518 (29.7)	3648 (6.1)	11236 (18.2)
BZD	10692 (38.1)	296 (23.4)	1373 (55.3)	10705 (13.0)	28728 (31.3)	538 (30.9)	24597 (41.0)	10537 (17.0)
Other medications, n(%)								
Antiarrhythmic agents	1437 (5.1)	38 (3.0)	1133 (45.7)	6854 (8.3)	1498 (1.6)	9 (0.5)	9797 (16.3)	2399 (3.9)
Antidiabetic agents	5437 (19.4)	253 (20)	261 (10.5)	13887 (16.8)	4211 (4.6)	90 (5.2)	1164 (1.9)	7729 (12.5)
Antihypertensive agents	2211 (7.9)	205 (16.2)	75 (3.0)	6096 (7.4)	1169 (1.3)	33 (1.9)	318 (0.5)	3533 (5.7)
Antiplatelet	9046 (32.2)	514 (40.6)	255 (10.3)	78 (0.1)	7447 (8.1)	84 (4.8)	807 (1.3)	124 (0.2)
Beta-blockers	8599 (30.6)	350 (27.6)	302 (12.2)	34121 (41.3)	15431 (16.8)	276 (15.8)	1637 (2.7)	11734 (19)
CCBs	11599 (41.3)	597 (47.1)	766 (30.9)	21421 (25.9)	7453 (8.1)	149 (8.5)	2885 (4.8)	6026 (9.7)
COPD medications	12514 (44.6)	261 (20.6)	1067 (43)	22226 (26.9)	31834 (34.7)	111 (6.4)	18958 (31.6)	16749 (27.1)
Diuretics	8380 (29.9)	319 (25.2)	394 (15.9)	35284 (42.7)	4868 (5.3)	85 (4.9)	1647 (2.7)	11719 (19)
NSAIDs	18745 (66.8)	158 (12.5)	1355 (54.6)	12886 (15.6)	55547 (60.5)	216 (12.4)	20993 (35.0)	15238 (24.6)
Non statin lipid lowering agents	818 (2.9)	11 (0.9)	60 (2.4)	2191 (2.7)	1394 (1.5)	7 (0.4)	533 (0.9)	2947 (4.8)
RAS inhibitors	4465 (15.9)	317 (25)	105 (4.2)	25302 (30.6)	2868 (3.1)	77 (4.4)	323 (0.5)	10628 (17.2)
Statins	2786 (9.9)	306 (24.2)	537 (21.6)	29473 (35.7)	2545 (2.8)	68 (3.9)	2667 (4.4)	13626 (22)
Vitamin K antagonists	508 (1.8)	29 (2.3)	90 (3.6)	8534 (10.3)	264 (0.3)	10 (0.6)	278 (0.5)	1532 (2.5)

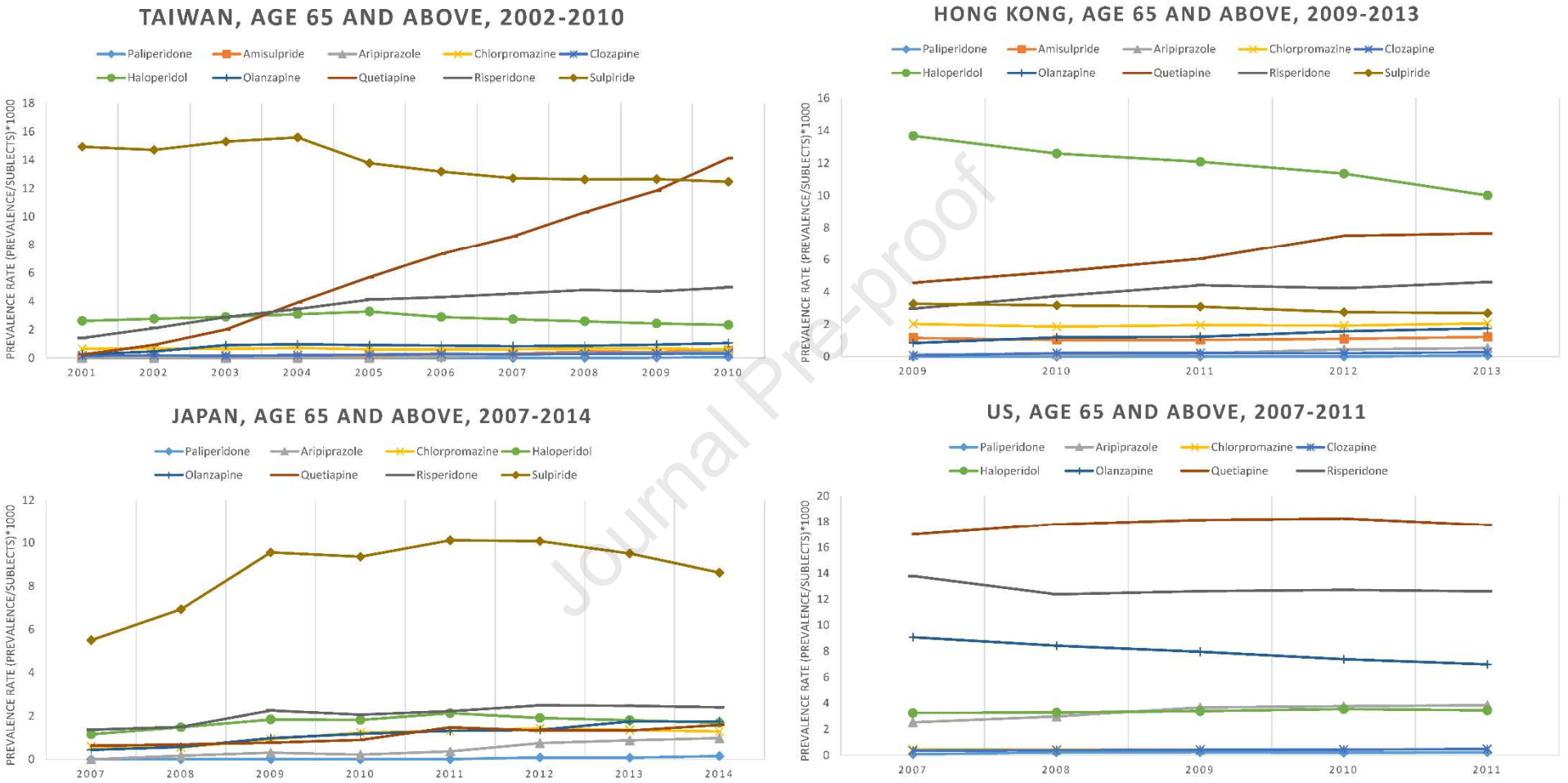
[a] For CMS cell size suppression policy, removing entire age 0-18 subgroup and count numbers appeared less than 11.

Fig. 1. Incidence Rate of Antipsychotic Medications Use Age 65 and Above by Country.



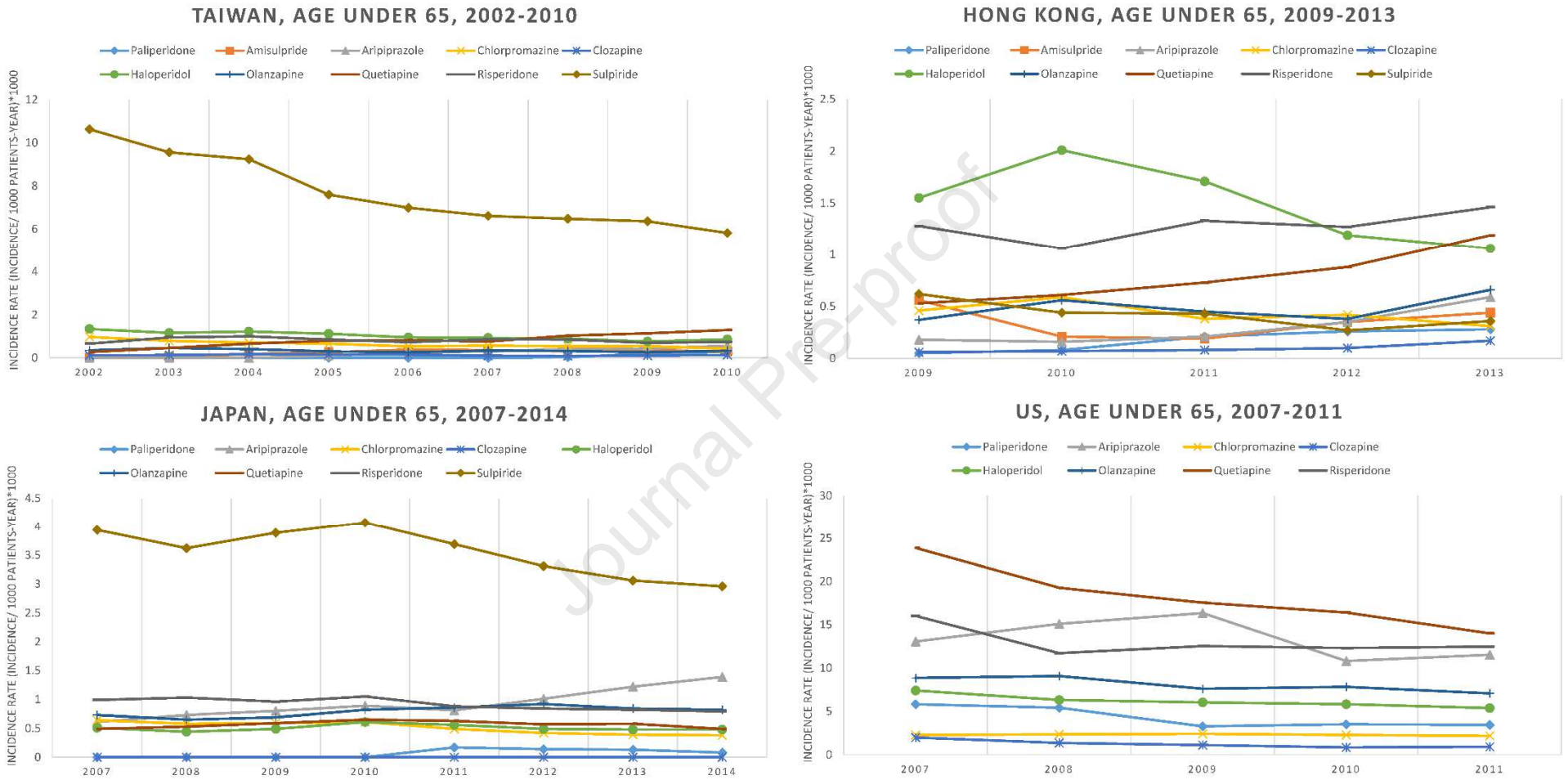
*The rates were adjusted by age and gender under a Poisson assumption.

Fig. 2. Prevalence Rate of Antipsychotic Medications Use Age 65 and Above by Country.



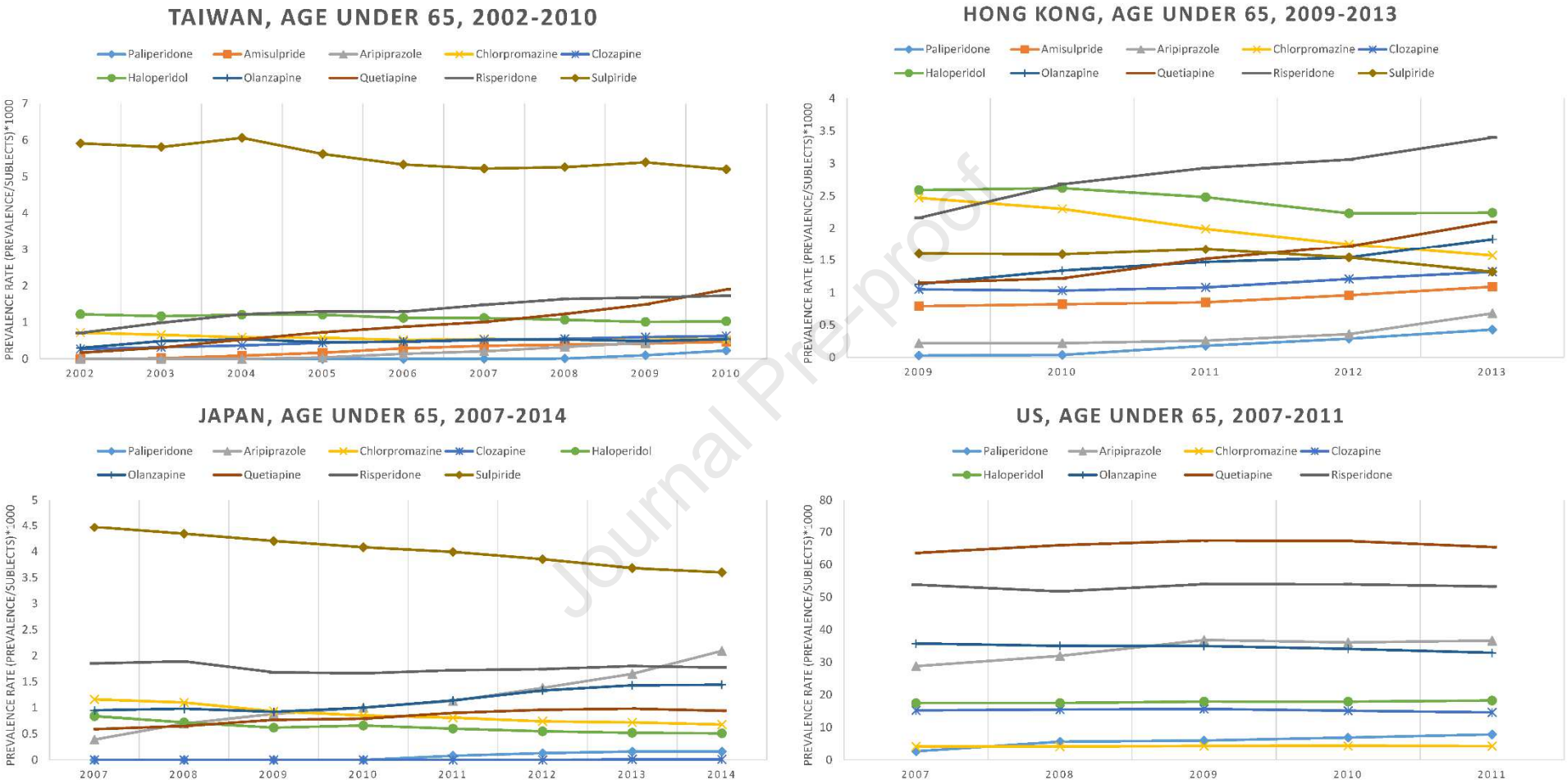
*The rates were adjusted by age and gender under a Poisson assumption.

Fig. 3. Incidence Rate of Antipsychotic Medications Use Age Less than 65 by Country.



*The rates were adjusted by age and gender under a Poisson assumption.

Fig. 4. Prevalence Rate of Antipsychotic Medications Use Age Less than 65 by Country.



*The rates were adjusted by age and gender under a Poisson assumption.