Risk of Extrapyramidal Syndrome in Schizophrenic Patients Treated with Antipsychotics: A Population-based Study

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To compare the prevalence of extrapyramidal syndrome (EPS) between the first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs), the co-prescribing rate of anti-Parkinson drugs (APDs) of each antipsychotic drug was analyzed using population database. Fourteen antipsychotics had been prescribed during the 5-year study period. Among the SGAs, quetiapine had the lowest crude co-prescribing rate of APDs (27.09%), whereas risperidone had the highest rate (66.50%). Among the FGAs, thioridazine and loxapine had the lowest (60.99%) and highest rates (96.35%), respectively. The rankings of the co-prescribing rate of APDs among antipsychotics, in increasing order, were quetiapine, clozapine, olanzapine, thioridazine, zotepine, chlorpromazine, risperidone, sulpiride, clotiapine, flupentixol, haloperidol, zuclopentixol, trifluoperazine, and loxapine. The results indicate that the risk of EPS appears to be lower in SGAs than in FGAs; however, the considerably high rate of EPS in some of the newer generation of antipsychotics warrants clinical attention.

Antipsychotic drugs (antipsychotics) are the primary treatment for several mental health problems, including schizophrenia. The mechanism of action is believed to be through blocking the activities of dopamine.[1] However, the blocking of dopamine in the cortex could lead to extrapyramidal syndromes (EPS) and movement disorders, including acute dystonias, parkinsonism, akathisia, dyskinesia, choreiform or dystonic-form movements, and tremor.[2,3] It has been suggested that the risk of EPS and tardive dyskinesia was associated with the degree of binding between antipsychotics and dopamine D2 receptors.[4,5] Unlike the first-generation antipsychotics (FGAs; or typical, conventional antipsychotics) that have a strong bond to D2 receptors, the second-generation antipsychotics (SGAs; or atypical, novel antipsychotics) can rapidly dissociate from the D2 receptors and therefore are generally considered as a safer choice with fewer EPS. SGAs also have a high affinity for 5-HT_{2A} receptors, which might attenuate the dopamine activity in the striatum and thus reduce the potential for EPS and tardive dyskinesia.[6–8] Other than the pharmacological properties of individual antipsychotics, the dosage used also affects the risk of EPS. For example, risperidone (SGA generally considered as having low EPS side effect) at a higher than recommended dose could have an EPS risk that is higher than olanzapine or ziprasidone at an average dose.[9,10]

Although FGAs and SGAs were hypothesized to have different risk of EPS, the available studies to compare the two generations have been limited in number and scope.[11] Most studies that examined the relationship were based on clinical trials with selective subjects treated in highly controlled environments. To provide estimates in a "real world" scenario, we used the claims data from the National Health Insurance (NHI) in Taiwan to evaluate the EPS risk associated with FGAs, SGAs, and dosage in hospitalized patients with a diagnosis of schizophrenia.

RESULTS

A total of 98,320 hospitalizations from 40,561 patients with a schizophrenia diagnosis were identified. Among the hospitalizations, 59% were male patients and over 60% were between

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25 and 44 years old (mean: 36.14; SD: 10.29). More than half of the subjects (54.2%) had multiple hospitalizations during the study period.

Most of the hospitalizations (97.8%) were prescribed with at least one antipsychotic, and 58.8% were prescribed with multiple antipsychotics (**Table 1**). Overall, the 5-year data showed that about half of the hospitalizations were prescribed with FGAs only (54.1%), about one-fourth (26.5%) used both FGAs and SGAs, whereas a small portion used only the SGAs (17.2%). However, the longitudinal trend during the study period indicated that the prescribing of FGAs was decreasing although both the SGAs alone and combinational use of FGAs and SGAs were increasing.

The average length of stay was 90.71 days (SD: 161.86; median: 42) for all hospitalizations. Hospitalizations prescribed with both FGAs and SGAs (combinational use hospitalizations) had the longest length of stay (mean, 120.38 days), followed by FGAs alone (82.46 days) and SGAs alone (77.74 days). Among the hospitalizations prescribed with FGAs alone, the mean of prescribed daily dose/defied daily dose (PDD/DDD) ratios was 2.14, with 78% higher than one. On the other hand, in the hospitalizations with SGAs alone, the PDD/DDD ratios had a mean of 1.15 and about half (48%) of these hospitalizations had a ratio higher than one. (**Table 1**).

The co-prescribing of anti-Parkinson drugs (APDs), an indicator of presence of EPS, was frequent among the hospitalizations. Nearly 90% of the FGA hospitalizations were prescribed an APD. The rates were lower in hospitalizations with concurrent use of FGAs and SGAs (77.6%) and SGAs alone (49.4%).

A subset of 37,483 hospitalizations using only one of the 14 antipsychotics was extracted to estimate the prevalence of EPS of individual antipsychotics. There are no significant differences between the larger population and the subset in age and gender distribution. Over the years, co-prescribing of APDs has decreased, and a 15% reduction was observed between 1999 and 2003. Longer length of stay appears to increase the co-prescribing of APDs. In terms of antipsychotics, it was found that 84.6% FGA hospitalizations had co-prescribing of APD as compared to 47.8% in the SGA group (**Table 2**). The relative risk of APD prescribing in the FGA hospitalization was approximately 1.8 times greater than in the SGA hospitalizations (relative risk: 1.77; 95% CI: 1.74–1.80; $P<0.0001$). Hospitalizations that used a higher than recommended dose of antipsychotics (*i.e.*, PDD/DDD>1) also had a greater risk of APD prescribing as compared to those using recommended or lower dose of antipsychotics (relative risk: 1.83; 95% CI: 1.78–1.89; $P<0.0001$). The concurrent use of psychotropic medications, including hypnotics and sedatives, anxiolytics, antidepressant, and mood stabilizers, also increased the risk of APDs prescribing (**Table 2**).

Among the SGAs, the one with the lowest APD co-prescribing rate was quetiapine (27.1%) and the highest was risperidone (66.5%). Among the FGAs, the rate ranged from 61.0% in thioridazine to 96.4% in loxapine. Five antipsychotics were found to have a significant dose–response relationship with the rate of co-prescribing APD ($P<0.0001$). The odds ratio per one increment in PDD/DDD ratio was 2.52 for thioridazine (95% CI: 1.83–3.47), 1.39 for chlorpromazine (95% CI: 1.20–1.61), 1.82 for sulpiride (95% CI: 1.69–1.97), 1.96 for haloperidol (95% CI: 1.75–2.18), and 1.32 for risperidone (95% CI: 1.21–1.44) (**Table 3**).

The rankings of the crude co-prescribing rate of APDs among antipsychotics, in increasing order were quetiapine, clozapine, olanzapine, thioridazine, zotepine, chlorpromazine, risperidone, sulpiride, clotiapine, flupentixol, haloperidol, zuclopentixol, trifluoperazine, and loxapine. The rankings were similar after being adjusted for covariates. (**Table 3**) Both the crude and adjusted figures indicate that some SGAs had higher APD co-prescription rates (*e.g.*, 71.8% adjusted rate in zotepine and 74.6% adjusted rate in risperidone) than the conventional antipsychotics (*e.g.*, 66.4% adjusted rate in thioridazine and 69.2% adjusted rate in chlorpromazine).

DISCUSSION

We found that the APD co-prescribing rate in FGA hospitalizations was almost twice that of the SGAs. The 48% APD co-prescribing rate among SGAs in this study was similar to the 42% reported by Porcyshyn *et al.*[12] According to a survey on the safety of psychiatric medicine in Germany, the incidence rate of involuntary movement disorders was lower in clozapine and higher in risperidone among SGAs, and lower for perazine and higher for haloperidol among FGAs.[13] In our study, when the co-prescribing of APDs was used to indicate the occurrence of EPS, a similar pattern was found for clozapine and risperidone. The two studies seem to support the use of APD co-prescribing as an indicator for EPS. Evidence from clinical trials had indicated that SGAs were more effective against negative symptoms and had a lower risk of causing EPS than FGAs.[14] The better safety profile of SGAs could have led to the increased prescribing of these drugs to substitute the FGAs in our study duration, which in turn could have decreased EPS and the need of APDs over the years.

We also sought to understand the timing of EPS side effect after the use of antipsychotics. Keepers had found that EPS declined from peak incidence after the start of treatment.[15] Miller[16] also reported that the incidence and severity of EPS are higher in acute therapy than in maintenance therapy. However, we did not observe a decline in APD prescribing for patients who had a longer length of stay. We found that the rate of prescribing APDs was slightly increased as the length of stay exceeds one week and remained constant afterward. Such discrepancy may result from the differences in patient characteristics, severity of the illness, or the prescribing patterns, which awaits further investigations.

Previous literature suggests that extrapyramidal adverse effects are more frequent when a higher than recommended dose of antipsychotics was used, especially in FGAs.[17–19] In

Table 1 Prescribing patterns of antipsychotics among hospitalizations of patients with schizophrenia, 1999–2003, Taiwan

	Total	FGAs only	SGAs only	FGAs and SGAs	No antipsychotics
No. of admissions (% of total)	98320 (100.00)	53170 (54.08)	16934 (17.22)	26065 (26.51)	2151 (2.19)
Admission year N (row %)					
1999	17216 (100.00)	11566 (67.18)	1780 (10.34)	3591 (20.86)	279 (1.62)
2000	19657 (100.00)	12359 (62.87)	2282 (11.61)	4123 (20.97)	893 (4.54)
2001	22156 (100.00)	12911 (58.27)	3392 (15.31)	5484 (24.75)	369 (1.67)
2002	20727 (100.00)	9418 (45.44)	4617 (22.28)	6420 (30.97)	272 (1.31)
2003	18564 (100.00)	6916 (37.25)	4863 (26.20)	6447 (34.73)	338 (1.82)
Age (year)					
Mean (SD)	36.14 (10.29)	36.35 (10.14)	36.01 (10.70)	35.82 (10.25)	35.87 (11.09)
Gender					
Male (%)	58439 (59.44)	32681 (61.47)	9593 (56.65)	14956 (57.38)	1209 (56.21)
Length of stay (day)					
Mean (SD)	90.71 (161.86)	82.46 (150.05)	77.74 (136.21)	120.38 (197.39)	37.25 (79.00)
Median	42	40	37	55	17
No. of antipsychotics, N (column %)					
0	2151 (2.19)	0 (0.00)	0 (0.00)	0 (0.00)	2151 (100.00)
1	38355 (39.01)	23042 (43.34)	15313 (90.43)	0 (0.00)	0 (0.00)
2	29536 (30.04)	17357 (32.64)	1473 (8.70)	10706 (41.07)	0 (0.00)
3	16428 (16.71)	8499 (15.98)	141 (0.83)	7788 (29.88)	0 (0.00)
4	7370 (7.50)	3074 (5.78)	7 (0.04)	4289 (16.46)	0 (0.00)
5	2895 (2.94)	914 (1.72)	0 (0.00)	1981 (7.60)	0 (0.00)
$\geqslant 6$	1585 (1.61)	284 (0.53)	0 (0.00)	1301 (5.00)	0 (0.00)
Doses by PDD/DDD ratio[a]					
Antipsychotics					
Mean (SD)	1.84 (1.81)	2.14 (2.10)	1.15 (0.95)	1.65 (1.40)	
Median	1.45	1.73	0.99	1.37	
>1 PDD/DDD ratio *N* (%)	68875 (70.05)	41695 (78.42)	8187 (48.35)	18993 (72.87)	0 (0.00)
Anti-Parkinson drugs					
Mean (SD)	0.64 (0.60)	0.71 (0.64)	0.53 (0.57)	0.50 (0.44)	0.67 (0.72)
Median	0.53	0.60	0.43	0.44	0.48
Concurrent medications N (%)					
Anti-Parkinson drugs	76169 (77.47)	47251 (88.87)	8361 (49.37)	20238 (77.64)	319 (14.83)
Sedatives and hypnotics	77389 (78.71)	42958 (80.79)	11292 (66.68)	22485 (86.27)	654 (30.40)
Anxiolytics	65908 (67.03)	35673 (67.09)	8990 (53.09)	20610 (79.07)	635 (29.52)
Antidepressants	15267 (15.53)	6992 (13.15)	2879 (17.00)	5063 (19.42)	333 (15.48)
Mood stabilizers	33966 (34.55)	16598 (31.22)	4764 (28.13)	12328 (47.30)	276 (12.83)

DDD, defined daily dose; FGAs, first-generation antipsychotics; PDD, prescribed daily dose; SGAs, second-generation antipsychotics. [a]The DDD assignment was based on dose information obtained from the literature and the PDD was calculated from prescription data of each hospitalization. The PDD/DDD ratio of a drug, thus, indicates the relative dosage of any given drug as compared to what has been recommended. The greater the ratio, the higher the dose is prescribed.

Table 2 Characteristics of hospitalizations with and without APDs, *N*=37,483

	Hospitalizations with APDs	Hospitalizations without APDs	Relative risk	95% CI	*P*-value
Total hospitalizations	26106	11377			
Antipsychotics N (%)					
FGA	18838 (84.60)	3429 (15.40)	1.77	1.74–1.80	<0.0001
SGA (reference)	7268 (47.77)	7948 (52.23)	1		
Admission year N (%)					
1999	4396 (77.30)	1291 (22.70)	1.24	1.21–1.27	<0.0001
2000	5295 (74.92)	1773 (25.08)	1.20	1.17–1.23	<0.0001
2001	6324 (71.30)	2545 (28.70)	1.14	1.12–1.17	<0.0001
2002	5418 (64.73)	2952 (35.27)	1.04	1.01–1.06	0.0023
2003 (reference)	4673 (62.40)	2816 (37.60)	1		
Age, N (%)					
18–24 yrs	3459 (71.53)	1387 (28.62)	1.03	1.01–1.05	0.0146
25–34 yrs	8845 (69.12)	3951 (30.88)	1.00	0.98–1.01	0.5757
35–44 yrs (reference)	7825 (69.46)	3441 (30.54)	1		
45–65 yrs	5977 (69.70)	2598 (30.30)	1.00	0.99–1.02	0.7092
Mean (SD) yrs	36.47 (10.64)	36.62 (10.60)			
Gender N (%)					
Male (reference)	15693 (69.74)	6837 (30.09)	1		
Female	10327 (69.62)	4506 (30.38)	1.00	0.98–1.01	0.8022
Length of stay N (%)					
⩽7 days (reference)	2851 (63.09)	1668 (36.91)	1		
8–30 days	8712 (68.93)	3926 (31.07)	1.09	1.07–1.12	<0.0001
31–60 days	7136 (72.06)	2767 (27.94)	1.14	1.11–1.17	<0.0001
61–90 days	2765 (71.84)	1084 (28.16)	1.14	1.11–1.17	<0.0001
91–120 days	1221 (71.61)	484 (28.39)	1.14	1.10–1.18	<0.0001
121–150 days	646 (71.70)	255 (28.30)	1.14	1.08–1.19	<0.0001
>150 days	2775 (69.93)	1193 (30.07)	1.11	1.08–1.14	<0.0001
Mean (SD) days	74.32 (134.48)	68.74 (126.26)			
Median	35	31			
Antipsychotic doses by PDD/DDD[a] ratio					
Mean (SD)	1.65 (1.84)	1.13 (1.08)			
Median	1.30	0.94			
⩽1, N (%) (reference)	8818 (58.35)	6294 (41.65)	1		
>1	17288 (77.28)	5083 (22.72)	1.83	1.78–1.89	<0.0001
Concurrent medication N (%)					
Hypnotics and sedatives					
Yes	19882 (74.51)	6803 (25.35)	1.66	1.61–1.71	<0.0001
No (reference)	6224 (57.64)	4574 (42.36)	1		

Table 2 Continued

	Hospitalizations with APDs	Hospitalizations without APDs	Relative risk	95% CI	*P*-value
Anxiolytics					
Yes	14982 (71.95)	5842 (28.05)	1.18	1.15–1.22	<0.0001
No (reference)	11124 (66.77)	5535 (33.23)	1		
Antidepressants					
Yes	3608 (65.17)	1928 (34.83)	0.85	0.82–0.88	<0.0001
No (reference)	22498 (70.42)	9449 (29.58)	1		
Mood stabilizers					
Yes	6431 (68.69)	2932 (31.31)	0.96	0.93–1.00	0.0215
No (reference)	19675 (69.97)	8445 (30.03)	1		

APDs, anti-Parkinson drugs; DDD, defined daily dose; FGAs, first-generation antipsychotics; PDD, prescribed daily dose; SGAs, second-generation antipsychotics. [a]The DDD assignment was based on dose information obtained from the literature, and the PDD was calculated from prescription data of each hospitalization. The PDD/DDD ratio of a drug, thus, indicates the relative dosage of any given drug as compared to what has been recommended. The greater the ratio, the higher the dose prescribed.

Table 3 Antipsychotics dosage associated with APDs: results from simple logistic regression

	DDD of antipsychotics		Co-prescribing of APDs			PDD/DDD ratio of antipsychotics		Odds ratio/PDD/DDD ratio increase		
	N	mg	N	Crude %	Adjusted %	Mean (SD)	Median	Odds ratio	95%CI	*P*-value
FGAs										
Thioridazine	446	300	272	60.99	66.36	1.08 (1.02)	0.86	2.52	1.83–3.47	<0.0001
Chlorpromazine	822	300	517	62.90	69.18	1.61 (1.58)	1.34	1.39	1.20–1.61	<0.0001
Sulpiride	9489	800	7365	77.62	82.52	1.36 (1.92)	1.13	1.82	1.69–1.97	<0.0001
Clotiapine	434	40	347	79.95	81.94	1.35 (1.03)	1.18	1.22	0.92–1.61	0.1619
Flupentixol	2380	6	2167	91.05	91.15	2.07 (2.00)	1.65	1.11	0.99–1.23	0.0653
Haloperidol	7074	8	6617	93.54	94.26	2.25 (2.13)	1.88	1.96	1.75–2.18	<0.0001
Zuclopenthixol	456	30	432	94.74	95.37	1.96 (1.53)	1.61	1.61	1.03–2.51	0.0351
Trifluoperazine	892	20	857	96.08	96.54	1.58 (1.33)	1.27	1.09	0.81–1.48	0.5706
Loxapine	274	100	264	96.35	96.26	1.40 (1.26)	1.13	2.34	0.73–7.50	0.1535
SGAs										
Quetiapine	897	400	243	27.09	32.99	1.13 (1.08)	0.91	0.89	0.76–1.05	0.1597
Clozapine	4769	300	1321	27.70	30.89	0.99 (0.92)	0.88	1.05	0.98–1.12	0.1365
Olanzapine	2065	10	783	37.92	36.42	1.76 (1.25)	1.53	0.96	0.89–1.03	0.2454
Zotepine	1160	200	715	61.64	71.83	1.11 (0.84)	0.99	1.03	0.90–1.19	0.6503
Risperidone	6325	5	4206	66.50	74.59	1.04 (0.79)	0.91	1.32	1.21–1.44	<0.0001

APDs, anti-Parkinson drugs; FGAs, first-generation antipsychotics; DDD, defined daily dose; PDD, prescribed daily dose; SGAs, second-generation antipsychotis.

our study, we found that most of the PDDs of FGA prescriptions were greater than one DDD, which is an indication that they were prescribed in higher than recommended doses and could be responsible, to some degree, for the higher APD rate in FGAs than in SGAs. The finding is consistent with previous studies and further supports a quantitative correlation between the dosage used and the EPS incidence rate. Although SGAs have claimed to have a reduced EPS based on their pharmacological property,[20] current literature does not provide a strong support to the claim.[11,21] It is possible that the more prevailing use of higher than the recommended dosage in FGA prescribing also contributes to the differential EPS side effect between FGAs and SGAs. This dose–response relationship should be considered in clinical decision-making.

The DDD is a recommended dose that reflects the differential potency between various antipsychotics. Presumably, at one unit of DDD, the various antipsychotics should

have similar clinical potency. However, our data indicated that the FGAs were more likely than the SGAs to be prescribed in a higher than recommended dose (*i.e.*, >1 DDD). It is unknown whether this reflects a prescribing pattern specific to the physicians of the patients in our study or it is an indication that the defined DDD does not conform to the clinical response of this specific study population. More evidence is necessary to determine the future approach to address the potential over-prescribing of antipsychotics.

Although APDs are often used with antipsychotics to prevent or treat EPS, there are still uncertainties about their appropriate prescribing. For example, some authors recommended that APDs should not be used for more than 10 days when indicated to prevent EPS;[22] whereas others suggested that the medications could be used as maintenance therapy in the treatment of EPS.[23] As such, the co-prescribing rate with antipsychotics varied significantly (range from 30 to 93%) in the literature.[15,24–28] The safety of APDs has also been questioned. Previous studies, for example, have reported that the anticholinergic toxic effects of APDs can impair memory of schizophrenic patients.[29–31] This memory deficit might damage the cognitive ability of patients, which in turn could negatively impact the psycho-social functioning and rehabilitation of the patients and interfere with their successful return to the community. Our study found the probability of APD co-prescribing to be as high as 80%; it follows that some patients might be suffering from the unwanted effects of APDs. Unfortunately, owing to the limitations of the administrative database, we were unable to evaluate the adverse impacts of APDs on patients with schizophrenia.

SGAs are generally considered to have lower risk of EPS than FGAs; however, in the case of risperidone, both Luo *et al.*[32] and our study did not find a lower EPS risk. Furthermore, we found that not all SGAs have a similar risk. Some SGAs have a higher EPS risk than the others. The finding is compatible with studies that examined the D2 receptor-binding capability of various SGAs.[1,33,34] For example, Tauscher *et al.*[35] found that the D2 receptor occupancy rate of SGAs varied from 30 to 81%, with the lowest in quetiapine and highest in risperidone. Our findings suggest that physicians should be aware of the EPS risk when prescribing FGAs and some high-risk SGAs (*e.g.*, zotepin and risperidone) to schizophrenic patients. We also call for more research on the advantages of SGAs. After all, if SGAs also have considerable risk of EPS or require the use of APDs to prevent or treat EPS, then the major advantage of atypical antipsychotics is lost.[36] Horáèek[37] even suggested that the definition of SGAs must be based on the low or no risk of EPS.

About 10–30% of patients have poor response to antipsychotic medication. Augmenting psychotropic drugs with other medication could allow the use of lower antipsychotic doses, decrease the severity of adverse effects, and improve therapeutic effects in controlling psychotic symptoms.[38,39] However, combining antipsychoitcs and psychotropic drugs could increase the risk of adverse effects and even mortality.[40,41] The concomitant use of psychotropic drugs to treat schizophrenic patients is a common practice. The CATIE trial, which had recruited schizophrenic patients from both academic and community providers, has reported recently that the average number of psychotropics used per patient was 2.03; and among patients taking psychotropic medication, 6% were taking two antipsychotics; 19% also took sedatives or hypnotics; 22% also took anxiolytics; 38% also took antidepressant; and 15% also took other mood stabilizers.[42]

In our study, the average number of psychotropic drugs was five and almost 60% of patients received more than two antipsychotics. Moreover, the concurrent psychotropic medications were more prevalent in our study population except for antidepressants, which was 16% in our survey versus 38% in CATIE trial. In general, the pharmacological treatment of schizophrenia is associated with multiple factors, such as patient characteristics, family and social support, severity of the illness, as well as physician's preference. How and to what extent the high utilization of psychotropic medications may affect the effectiveness and adverse reactions among schizophrenic patients, as revealed by the claims database in Taiwan, require further investigations.

One of our study limitations is that the assessment of EPS was not based on the clinical presentations of the movement symptoms. Because of the limitation in claims database, we had used co-prescribing of APDs as the proxy of EPS. Although previous studies have supported the use of this proxy, the readers are cautioned that the actual EPS rate based on clinical judgment might not be the same as what has been reported in this study. For example, patients with mild EPS might not be treated with APDs; conversely, patients using APDs for prophylaxis would have been included in our analysis. In addition, EPS could happen even without the use of antipsychotics or before an antipsychotic is administered.[43–45] A previous clinical study reported a 20% EPS rate in patients treated with placebo.[46] In our study, there were 2.19% schizophrenic admissions without a prescription of antipsychotics; APDs were nonetheless prescribed for 15% of those hospitalizations. In this case, we could have overestimated the prevalence rate of EPS associated with the use of antipsychotics. However, as this baseline APD rate was considerably smaller than the rates associated with either FGAs or SGAs, we believe the comparisons between the antipsychotics are still valid.

Another limitation is the use of a subset of hospitalizations that included only about 40% of all hospitalizations to derive the EPS rate for individual antipsychotic medication. Although the use of this subset provides cleaner data to delineate the risk for each drug, it might restrict the generalizability of study results. Furthermore, our findings are limited to the Taiwanese population and may not be applicable to the other ethnic groups. It is reported that higher plasma concentrations of haloperidol and clozapine had been demonstrated in the Chinese patients than in the other ethnic groups, such as Latino, Caucasian, and African-American patients.[47–50]

Lastly, we calculated the dose of antipsychotics by averaging the total dose prescribed during hospitalization

over the length of stay. If a patient did not receive the antipsychotics everyday or consistently during the hospital stay, we could have underestimated the daily dose taken by the patient. Therefore, our estimates present a more conservative picture on the dosing of antipsychotics in our patient population.

METHODS

Data source. The NHI was implemented in Taiwan in 1995. Most health services and pharmaceuticals are covered by NHI, with various co-payment rates from the patients. Exemption of co-payments has been granted to certain illnesses, including schizophrenia (ICD-9-CM code 295).[51] All the claims data are routinely compiled by the Bureau of NHI (BNHI) for reimbursement and administrative purposes. A 5-year data set from 1999 to 2003 was obtained from BNHI to carry out this study. All hospitalizations with a diagnosis of schizophrenia were extracted for analysis.

Definition of drug class and dosage. Drugs that are relevant to this study were identified from the data set. These include FGAs, SGAs, antidepressants, antiepileptics and lithium (or mood stabilizers), anxiolytics, hypnotics and sedatives, and APDs.[52] See Appendix A for a list of drugs included in this study. Two dosage indicators, DDD and PDD, were computed for all antipsychotics and APDs. The DDD assignment was based on dose information obtained from the literature,[53] and the PDD was calculated from prescription data of each hospitalization. The PDD/DDD ratio of a drug, thus, indicates the relative dosage of any given drug as compared to what has been recommended (or standardized, accepted).[54]

Estimate of EPS rate. The most direct way to identify an EPS would be to check the list of diagnosis. However, this is not possible in practice because of the lack of specific ICD-9 coding for EPS. Instead, we used the co-prescribing of APDs as an indicator of probable EPS when antipsychotics were also prescribed. The use of ADPs as an indicator has been supported by the literature.[11,55–59]

Because the switching within and between FGAs and SGAs is common in patients with schizophrenia, some hospitalizations involved the use of both types of medications. To clearly attribute EPS to a specific drug, a subset of hospitalizations using only one oral antipsychotic was extracted to estimate the prevalence of EPS for individual antipsychotics. Hospitalizations with pre-existing Parkinson's disease (ICD-9-CM code 332.0) were also excluded.

Statistical analysis. For describing demographic and medication information, sample mean and SD were calculated. To estimate the association between the antipsychotic dose and APD use, odds ratio and 95% CI were calculated using simple logistic regression. The co-prescription rate of APDs with each antipsychotic drug was adjusted with the year of admission, length of stay, dose of the antipsychotic, hospital type and geographic region, and age and gender of the patient. A *P*-value of less than 0.01 was considered as statistically significant. All the data processing and statistical analyses were performed with SAS software (SAS® version 8.2 for Windows; SAS Institute, Inc., Cary, NC).

CONCLUSION

We found that not all the SGAs are safer compared to FGAs. SGAs such as zotepin and risperidone could have an EPS rate similar to FGAs. It is difficult to have a head-to-head comparison of risk of the adverse reactions among various antipsychotics in clinical trials, not only because of the ethical concern, the limitation of sample size, and homogeneity, but also because of the lack of initiative from the pharmaceutical industry. We used a population-based claims database for this study and found it a valuable source to explore the risk of EPS of antipsychotic use among schizophrenic patients. Using APDs as an indicator of EPS, we found a dose–risk relation of EPS among FGAs and SGAs. The information could be useful for future consideration in the selection of antipsychotics for patients with schizophrenia.

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

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APPENDIX A. LIST OF PSYCHOTROPIC DRUGS INCLUDED IN THIS STUDY

1. *Antipsychotics*

   a. *First-generation (FGAs)*: haloperidol, sulpiride, chlorpromazine, flupentixol, clotiapine, zuclopenthixol, thioridazine, trifluoperazine, loxapine, levomepromazine, chlorprothixene, tiotixene, perphenazine, fluphenazine, pipotiazine, pimozide, clopenthixol, moperone.

   b. *Second-generation (SGAs)*: risperidone, clozapine, olanzapine, zotepine, quetiapine, amisulpride.
2. *Anti-parkinson drugs*: trihexyphenidyl, biperiden, amantadine, benzatropine, piroheptadine.
3. Sedatives and hypnotics: estazolam, flunitrazepam, zolpidem, midazolam, zopiclone, flurazepam, lormetazepam, nitrazepam, triazolam, nimetazepam, brotizolam.
4. *Anxiolytics*: lorazepam, alprazolam, diazepam, fludiazepam, bromazepam, buspirone, nordazepam, potassium clorazepate, oxazepam, oxazolam, mephenoxalone, hydroxyzine, chlordiazepoxide, clobazam, cloxazolam.
5. *Antidepressants*: trazodone, fluoxetine, fluovoxamine, sertraline, paroxetine, imipramine, citalopram, venlafaxine, amitriptyline, clomipramine, moclobemide, doxepin, maprotiline, mirtazepine, dosulepin.
6. *Mood stabilizers*: clonazepam, valproic acid, carbamazepine, topiramate, valpromide, lamotrigine, gabapentin, vigabatrin, lithium.