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Effect of Backward Medication Switching on the Risks of Adverse Events of Schizophrenia Patients Using Atypical Antipsychotics

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ABSTRACT

Many studies explore the effects of medication switching from second generation antipsychotic (SGA) to first generation antipsychotic (FGA), yet few exam the health effect of backward medication switching. This study investigated whether backward medication switching (from SGA to FGA) and reduced dosages on SGA increased adverse events in outpatient schizophrenia patients treated by SGA in Taiwan. This study applied a three-year historical cohort design and compared the risks of adverse events (outcome) in 2004, measured by emergency room and hospital admissions, of patients experienced backward medication switching or dosage reduction on SGA (exposure status) in 2003 with those who did not (control group). This study was based on a national fixed cohort (census) of 12,107 patients who have ever received SGA during the study period and used hospitals as regular source of care during 2002-2004. Most data were drawn from National Health Insurance claims provided by Department of Health. Cox proportional hazards model for recurrent events using Prentice, Williams and Peterson total-time approach was applied to estimate the hazard ratio (HR) of adverse events by exposure status of the patients while controlling the covariates. The results showed that backward medication switching in 2003 significantly increased the risk of emergency room or hospital admissions (HR=1.15, 1.00-1.31) in 2004. Backward medication switching and reduced dosages on SGA might increase the risk of adverse events of the schizophrenia patients treated by SGA in Taiwan.

Key words: medication switching, antipsychotic, atypical antipsychotic, schizophrenia

INTRODUCTION

Antipsychotic medications are typically prescribed by physicians to treat the symptoms of the schizophrenia patients. Many recent studies have shown that atypical antipsychotics, or the second generation antipsychotics (SGA), were more effective in treating positive symptoms, reducing extra pyramidal symptoms, improving social functioning and health-related quality of life[1-5], and reducing hospital costs[6-8] than first generation antiphychotics (FGA). Although other studies found the opposite results and some even found SGA increased the risk of diabetes and abnormal weight gains[2], SGA still gradually replaced FGA as predominated regimes after mid-1990s[9-11]. However, most SGA are expensive, up to several times more than FGA[12-14], and may not pay for themselves (off-set other treatment costs)[8,13-16]. As the result, in facing with cost containment policy, physicians might decide to replace expensive SGA with less expensive FGA. We were thus curious whether medication switching might have negative impact on patients' health.

In 2004, the National Health Insurance (NHI) in Taiwan, a mandatory social insurance scheme covering almost 99% of the population, introduced a series of major payment system reforms. A previous study[17] found that the cut on the outpatient hospital global budget (expenditure cap) of the NHI in 2004 in Taiwan was significantly associated with the increased risk of medication switching from SGA to FGA or reduced dosages on SGA in schizophrenia patients (Odds ratio = 4.01). However, only few studies, to our knowledge, have investigated the effect of backward medication switching on the health of the schizophrenia patients. Therefore, the objective of this study was to explore the effect of backward medication switching on patients' risk of adverse effects of schizophrenia patients treated by SGA.

Hospitals in Taiwan traditionally were paid by fee-for-services without limits. Since a national hospital expenditure cap has been imposed on all hospitals on July 2002, hospitals have been rapidly expanding their outpa-

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tient sector to increase profit from outpatient services[18]. To control costs and to improve the allocation efficiency of the NHI, the Department of Health (DOH) has changed the allocation of hospital global budgets (expenditure cap) between outpatient and inpatient sector from 52%:48% in 2002 to 50%:50% in 2003 and further to 45%:55% in 2004[19]. This policy gradually reduced outpatient budgets, including costs of medications. Meanwhile, NHI has also introduced other reform strategies such as hospital self-management, which allows hospitals to be waived from claim review if hospitals could control their expenditures within a limited range, or Hospital Center of Excellence Initiative (HCEI), which grants each voluntarily participated hospital pre-determined budgets to facilitate hospital to cope with budget reallocation and to improve quality of care[20]. Both strategies could lead hospitals to switch expensive medications to control costs. Regarding the impact of HCEI, we have found in the same study mentioned above[17] that HCEI mediated the effect of increased medication switching associated with budget reduction. Therefore, this study also controlled HCEI status in addition to patients' and hospitals' characteristics. Although outpatient budget reduction in 2004 had more impact on the increased medication switching than that in 2003, we could only evaluate the risk of adverse events in 2004 following medication switching in 2003, because we were unable to obtain 2005 data at the present time.

We analyzed the NHI claim data on a fixed historical cohort of schizophrenia patients who have ever been treated by SGA during the study period, and compared the risk of emergency room and hospital admissions of those who have experienced backward medication switching/reduced dosages on SGA with those who have not. The results of our study might fill the knowledge gap on the health impact of medication switching from SGA to FGA for schizophrenia patients.

METERIALS AND METHODS

I. *Study Design*

This study is a three-year national population-based historical cohort study which estimated one-year risk of recurrent adverse events (outcome) in 2004 following medicaiton switching (from SGA to FGA) or dosage reduction on SGA (exposure status) in 2003, and compared that with the control group who have no exposure at all. Prescription data in 2002-2003 were used to determine patients' exposure status.

II. *Study Population and Settings*

Out study population were outpatient schizophrenia patients (ICD-9-CM codes 295.xx) treated with SGA medicaiotn during the study period and regularly used outpatient services during 2002-2004. Our samples contained a fixed cohort (national census) of 12,107 patients, drawn from NHI claim data, who fulfilled the above criteria and also had at least 3 outpatient visits with schizophrenia as primary diagnosis in 2003 and 2004. The latter criteria allowed us to rule out patients who were either short term schizophrenia patients[21] or did not need continuous care to increase the validity of the diagnosis. To reduce bias, patients in hospitals which temporarily participated in HCEI (11 hospitals) were eliminated.

III. *Data Source and Measurement*

Our analyses were based on nation-wide population-based NHI Research Database provided by DOH in Taiwan. The database included complete outpatient, inpatient and medication claim databases, enrollment database for more than 22 millions population, and registry of contracted medical facilities. Patient information, such as diagnoses, physicians' orders including prescriptions, diagnosis tests, medical and surgical procedures, medical devices and medical expenditures, are submitted monthly to Bureau of National Health Insurance (BNHI) by contracted clinics and hospitals. Each database contains an unique identifier (identification number of a citizen, passport number or alien resident certificate number) to represent data of different individuals. To protect patient's confidentiality, DOH encoded ID using a mathematic formula that can link utilization information of all subjects.

The exposure status (medication switching) was defined as change in the prescription patterns from SGA to FGA or reduced dosages on SGA in 2003 (compared with 2002), including prescriptions which met any one of the following criteria: (1) used only SGA (monopharmacy) and switched to FGA or reduced dosages on SGA; (2) constantly used polypharmacy (SGA+FGA), but percent of reduced dosages on SGA was greater than percent of reduced dosage on FGA; (3) used a mixed type pharmacy and either changed from monopharmacy (SGA) to polypharmacy with reduced dosages on SGA; or change from polypharmacy to monopharmacy with either reduced dosage on SGA or replace SGA with FGA. When applicable, prescribed daily dose (PDD) was used to measure the average daily dosage regimen treated with antipsychotics (mg/day/person) in a specific year. Due to the difficulty to compare PDD across medications with different ingredients, patients who have received polypharmacy and different SGA ingredients during the study period (about 3%) were eliminated entirely from the study.

Outcome variables (adverse events) included the occurrence of either emergency room or hospital admissions in 2004. Other covariates included HCEI status (participated in HCEI or not), patients' characteristics (age, gender, and history of adverse events at last year) as well as hospitals' characteristics (ownership, types, and regions of NHI branch).

IV. *Data Processing and Statistical Analysis*

After data were screened, cleaned and checked for consistency, all patient data within three year were merged by an encoded patient identifier as above mentioned. Because emergency and hospital admissions are recurrent events among schizophrenia patients, to take the multiple events into account, we applied Cox proportional hazards regression for recurrent events using Prentice, Williams and Peterson's total-time (PWP-CP) model[22] in SAS® statistical software version 9.1 to estimate the hazard ratio (HR) of adverse events of the exposure group versus the control group while controlling the covariates. This model used "total time" to define the risk interval (i.e., the duration of time that the subject is at-risk of having an event) which considers each duration between the commencement of the study to each adverse event (censoring) as a separate risk interval[23].

Table 1. Patients' characteristics, exposure status and outcome (n = 12,107)

Variables	Frequency	%
Age group		
under 25	646	5.34
25~44	6,664	55.04
45~64	3,987	32.93
65 ~	810	6.69
Mean ± SD	42.67 ± 12.75	
Gender		
Female	6,050	50.03
Male	6,057	49.97
Medication switching (2003)		
no	10,948	90.43
yes	1,159	9.57
SGA to FGA	80	6.90
Dosage reduction	1,079	93.10
Total adverse events in 2004	2,062	17.03%

RESULTS

In our results, 12,107 schizophrenia patients from 165 hospitals fulfilled the study criteria (Table 1). Most of the study population were between 25-64 years with a mean age of 42.67±12.75 years. The gender of the patients were about the same for female (50.03%) and male (49.97%). On the other hand, 1159 (9.57%) patients experienced medication switching or dosage reduction in 2003. Among them, only 80 (6.9% or 0.73% of total patients) experienced medication switching from SGA to FGA; the remaining 1,079 patients (93.1% or 9.85%) experience dosage reduction. 2,062 adverse events were repeated in 2004 (17.03% of all subjects).

Table 2 shows hospital characteristics in terms of ownership, types, regions and HCEI status. About the

Table 2. Hospital characteristics

Variables	Hospital (n = 165)		Patient (n = 12,107)	
	N	%	N	%
Ownership				
Public	66	40.00	6,341	52.37
Private	45	27.27	1,034	8.54
Non-profit proprietary	54	32.73	4,732	39.08
Type of hospital				
Medical center	17	10.30	3,952	32.64
Psychiatric center	29	17.58	4,143	34.22
Others	119	72.12	4,012	33.14
Region				
Taipei	54	32.73	4,474	36.95
Northern	24	14.55	1,556	12.85
Southern	22	13.33	1,301	10.75
Center	27	16.36	1,933	15.97
Kao-Ping	29	17.58	2,164	17.87
Eastern	9	5.45	679	5.61
Hospital center of excellence initiative				
Participant	82	49.70	7,048	58.21
Non-participant	83	50.30	5,059	41.79

same proportion of hospitals participated (49.7%) and not participated (50.3%) in HCEI, but more patients (58.21%) were HCEI than non-HCEI. Regarding ownership, more patients used public (52.37%) than non-profit proprietary hospitals (39.08%) as regular source of care than private hospitals (8.54%). About the same proportion of study subject were in medical center (32.64%), psychiatric center (34.22%) and other hospitals (33.14%). As for the distribution of patients, Taipei region ranked highest (36.95%), Kao-Ping region (17.87%) ranked second, whereas the Eastern region ranked lowest (5.61%). The remaining three regions were about the same.

Table 3 shows the results of Cox proportional hazard regression with recurrent events. Hazard ratio of patients with medication switching on risk of adverse events was 1.15 (95% C.I. 1.00-1.31) and was significant (p = 0.04). In another words, those who experienced medication switching had 15% higher risk on the occurrence of adverse events compared with those who did not. HCEI was associated with lower risk (HR = 0.91, 95% C.I. 0.82-1.02) of adverse event, although not significant. For other covariates, patients aged less than 65 years had significant higher risk of adverse event compared with those aged 65 or over (HR 1.53 to 1.98). Males tended to had significantly higher risk (HR = 1.10) of adverse events than females. Those who had adverse events in the previous year (HR = 1.40), and used public (HR = 1.23) or private hospitals (HR = 1.19) as regular sources of care has significantly higher risk of adverse events; whereas those who received care from hospitals at Southern (HR = 0.76) and Central regions (HR = 0.81) had significantly lower risks of adverse events than their reference groups.

Table 3. Results of Cox Proportional Hazard model for recurrent events-risk of adverse events among patient with schizophrenia

Variable (reference group)	Hazard ratio	95% C.I. for hazard ratio	p-value
Medication switching			
Switch	1.15	1.00–1.31	0.04
Reference: non-switch			
HCEI			
Participant	0.91	0.82–1.02	0.10
Reference: non-HCEI			
Age group			
Under 25	1.98	1.46–2.68	<0.01
25~44	1.83	1.42–2.35	<0.01
45~64	1.53	1.18–1.97	<0.01
Reference: > = 65			
Gender			
Male	1.10	1.01–1.20	0.03
Reference: female			
Adverse Events in last year	1.40	1.37–1.44	<0.01
Region			
Northern	1.03	0.89–1.19	0.70
Southern	0.76	0.64–0.91	<0.01
Central	0.81	0.69–0.94	0.01
Kao-Ping	1.00	0.87–1.15	0.97
Eastern	0.96	0.79–1.17	0.69
Reference: Taipei			
Hospital type			
Medical center	0.86	0.76–0.97	0.01
Psychiatric center	0.96	0.86–1.08	0.53
Reference: others			
Ownership			
Public	1.23	1.10–1.36	<0.01
Private	1.19	0.99–1.43	0.07
Reference: non-profit proprietary			

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DISCUSSION

We investigate in this study whether backward medication switching or reduced SGA dosage might increase the risk of adverse events by historical cohort study on schizophrenia patients who regularly visited hospitals and treated by SGA during 2002-2003 in Taiwan through analysis of NHI claim database. Our result indicates that 9.57% patients had exposure experience, majority of them were rendered dosage reduction. Those who experienced backward medication switching from SGA to FGA or reduce dosages in SGA might increase the risk of adverse events of schizophrenia patients treated by SGA in Taiwan. One might suspect that patients who experienced medication switching or dosage reduction might be patients with more severe condition thus with poor outcome. However, control on the covariates such as age, gender, and adverse events in the previous year might partially rule out this plausible explanation.

Our study might be a good start for this area of study, because few studies have demonstrated the health impact associated with either backward medication switching or dosages reduction on SGA in schizophrenia patients. A study most closed to ours have found that patients with bipolar disorder who experienced multi-class medication switching (anticonvulsants, mood stabilizers, FGA and SGA) and concomitant prescription were more likely to visit emergency department or be hospitalized[24]. Although both studies differed in study subjects and types of medication switching, these similar results raise concerns about the adequacy of care provided to patients.

Our study was in general consistent with previous studies which found SGA reducing hospital costs compared with FGA[6-8], but inconsistent with another randomized controlled trial (RCT) conducted by Rosenheck[8] which found SGA (Zyprexa) did not lower hospitalization rates than FGA (Haloperidol). The discrepancy between ours and Rosenheck's study might be due to differences in design (observational vs. RCT), sample size (large (12,107 patients) vs. small (309 patients)), type of drugs (all SGAs and FGAs available vs. one on each generation of antipsychotics).

Our study indicates that dosage reduction was far more prevalent than medication switching in Taiwan for patients treated by SGA. Rather than presenting the results separately, we decided to combine both exposures into one because of small sample size. Nevertheless, the increased risk of adverse events associated with dosage reduction on SGA in schizophrenia patients was even less addressed than medication switching. We are unable, and have no intention at all, to make judgment on the appropriateness of dosage reduction. However, our results did suggest that physicians should be careful in making the decision to reduce SGA dosages for their patients, particularly when the decision is drawn by financial reasons rather than by clinical reasons.

Regarding the covariates, our result indicates that HCEI had slight protection effect over risk of adverse events. This finding is aligned with our previous study[17] which found HCEI significantly mediated the effect of increased medication switching associated with global budget reduction. In addition to HCEI, we have found significantly lower risk of adverse events among hospitals located in southern and central regions compared with Taipei region. These results might reflect variations in case-mix, prescription patterns among hospitals in different regions, and different managerial strategies at different sub-bureaus. In addition, we found significantly lower risk of adverse events in medical center hospitals compared with other hospitals. Medical center hospitals in Taiwan usually provide better and more comprehensive care to their patients than others. This explains why their patients had better outcome in our study. Furthermore, our study indicates that patients in public hospitals had significantly higher risk of adverse events than non-profit proprietary hospitals. The underline reasons might be difference in patient-mix, which we did not control well in our study, or difference in the treatment patterns. There are more chronic schizophrenia patients in public than non-profit proprietary hospitals in Taiwan, some of them are abandoned by their families, are without families and have been in and out of hospitals for many years. Our inability to control the onset of schizophrenia in the present study might partially explain above differences. Lastly we found male and younger patients had significantly higher risk of adverse events. The former on the one way might due to that there were more male veterans than female. The availability of large scale veteran psychiatric hospitals and veterans hospitals might also increase the likelihood of a veteran schizophrenia patient, particular of those without family, to be admitted to the hospital. The finding that the younger patients had higher risk of adverse events might be due to their relative higher severity, which we could not control effectively in our study. In words, the survived old schizophrenia patients might be healthier than those who have already died.

Our study had the following strengths: (1) this is a national population-based study. The large size of study subjects and population-based data had advantages over small RCT on the generalizability and statistical power. (2) Historical cohort design in this study allows us to establish the temporal-sequence, so that the outcome (adverse events in 2004) followed the exposure (medication switching and dosage reduction in 2003) rather than the reverse. (3) Adverse events in schizophrenia patients are very common. The application of Cox proportional hazard regression with recurrent events allows taking the occurrence of multiple events into account[23,25] rather than treating it as dichotomous variable (yes/no). Furthermore, because the occurrence of each adverse event is more likely to be dependent than independent, using total time rather than lag-time (time between two events) to define the risk interval might yield more valid estimation[23].

Our study has the following limitations: (1) this is

an observation study and not a randomized control trial. Although we have controlled the covariates available in the administrative claim data, limited information on patients' function and severity was available. Therefore, we might not rule out all the selection bias. (2) Due to lack of medical record information, we could not determine the clinical reasons, nor could we determine the appropriateness of medication switching or dosage reduction on SGA. Therefore, our results could only be generalized to the schizophrenia patients who use hospital outpatient department as regular source of care and treated by SGA in Taiwan. This study might not be applied to other patients, other countries, nor could it be generalized to any individual patient.

In conclusion, we have found that backward medication switching from SGA to FGA or reduce dosages in SGA might increase the risk of adverse events in schizophrenia patients treated by SGA in Taiwan. This result has the following policy implications: (1) to reduce the risk of the adverse events, NHI may monitor the medication switching and dosage reduction behavior continuously particularly under major cost containment reforms. If patients cared by certain hospitals have unusual high prevalence on medication switching or dosage reduction, BNHI may conduct further investigation or action to assure that patients are receiving appropriate care. (2) Since dosage reduction is common and has been found to increase the risk of adverse events, BNHI may work with Taiwan Society of Psychiatry to develop appropriate guideline on SGA medications. (3) We have found great variations on the risk of adverse events among hospitals in different regions, with different ownership and types. BNHI might conduct further investigation to reduce the variation or to reduce prevalence of adverse events.

This study is the first attempt to investigate health impact of medication switching and dosage reduction. Because our previous study has found significant increase on medication switching associated with payment system reform in 2004[17], we suspect that the prevalence of adverse events associated with medication switching in 2004 might be even greater than that in 2003. BNHI continued to implement hospital self-management in certain sub-bureaus in 2005 and in all sub-bureaus in 2006. It is possible that certain hospitals might still have to cut medication costs under the pressure of cost containment. Therefore, we recommend future studies to evaluate these impacts under the context of payment/utilization management reform in 2004 and thereafter, once data in 2005-2006 are available. In addition, we suggested that clinical data with detailed patients' functional information to be incorporated with NHI data to investigate the actual health impact associated with medication switching as well as dosage reduction on all types of antipsychotics.

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