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Research report

Risk of developing diabetes mellitus and hyperlipidemia among patients with bipolar disorder, major depressive disorder, and schizophrenia: A 10-year nationwide population-based prospective cohort study

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ABSTRACT

Background: The high comorbidity of metabolic side effects with severe mental disorders (SMDs), including bipolar disorder (BD), major depressive disorder (MDD), and schizophrenia, had gained much attention, because the excess mortality of these patients is mainly due to physical illness. However, most of these studies were with cross-sectional study design, the time course of metabolic side effects and SMD cannot be elucidated without a cohort study.

Method: Using a nationwide database with a large sample size and a matched control cohort study design, we enrolled patients with SMDs but without diagnoses of and medications for DM and hyperlipidemia from 1996 to 2000, and followed them to the end of 2010. We compared them with age and gender-matched controls (1:4) for the incidence of DM and hyperlipidemia.

Results: The identified cases were 367 patients with BD, 417 patients with MDD, and 1993 patients with schizophrenia, with average age of 45.3 ± 14.0, 46.5 ± 13.7, and 45.9 ± 12.3, respectively. The patients with BD and schizophrenia had increased risk of initiation of anti-diabetic medications (10.1% vs. 6.3%, $p=0.012$; 13.3% vs. 7.2% $p<0.001$; respectively), and anti-hyperlipidemia medications (15.8% vs.10.5%, $p=0.004$; 14.2% vs.12.1%, $p=0.005$; respectively) than the controls. After controlling age, gender, urbanization, and income, the Cox regression model showed significantly increased risk of initiation of anti-diabetic medications among patients with BD (hazard ratio (HR) of 1.702, 95% confidence interval (CI): 1.155–2.507) and schizophrenia (HR of1.793, 95% CI: 1.532–2.098). Increased risk of initiation of anti-hyperlipidemia medications was also noted among patients with BD (HR of 1.506, 95% CI: 1.107–2.047) and schizophrenia (HR of 1.154, 95% CI: 1.002–1.329). The patients with MDD did not show increased risk of initiation of these medications than the controls.

Conclusions: This first 10-year nationwide population-based prospective matched control cohort study showed increased risks of initiation of anti-diabetic and anti-hyperlipidemia medications among patients with BD and schizophrenia. No significant increased risk was noted among the patients with MDD.

1. Introduction

The increased risk of metabolic side effects with severe mental disorders (SMDs), including bipolar disorder (BD), major depressive disorder (MDD), and schizophrenia, has gained much attention, because the excess mortality of these patients is mainly due to physical illness (DeHert et al., 2011). Compared to the general population, many studies showed that metabolic syndrome is 2–3 times more common in patients with these SMDs (Ohaeri and Akanji, 2011). Patients with BP and schizophrenia have a comparable prevalence of metabolic syndrome, ranging from 32% to 50% (Yumru et al., 2007; Correll et al., 2008; Fiedorowicz et al., 2008; Garcia-Portilla et al., 2009). The possible causes of the increased comorbidity included a sedentary lifestyle, eating behavior, genetic factors, increased nicotine dependency, and psychotropic medications, including antipsychotics and mood stabilizers (Correll et al., 2008). Among the antipsychotics, clozapine and

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olanzapine were associated with the highest risk of weight gain; quetiapine and risperidone with an intermediate risk, and ziprazidone and aripiprazole with the least risk of metabolic side effects (Newcomer, 2007). In general, the rank order of risk observed for these antipsychotic medications suggests that the differing weight gain liability of atypical agents contributes to the differing relative risk of metabolic side effects (Newcomer, 2006, 2007). For the mood stabilizers, approximately 30% of lithium-treated patients gained weight 4–10 kg in 1 year (Sachs et al., 2006; Grandjean and Aubry, 2009). The use of valproic acid increased fast food fats cravings (Martin et al., 2009), and induced similar weight gain (around 6 kg in one year) (Chengappa et al., 2002). Regarding the patients with depression, the research results are inconsistent. Although some evidences showed patients with depression have a twofold risk of obesity (Pine et al., 2001; Goodman and Whitaker, 2002), 1.6–3 times increased risk of diabetes (Arroyo et al., 2004; Golden et al., 2004), and an increased risk of cardiovascular disease (Rudisch and Nemeroff, 2003), a comprehensive meta-analysis showed that amitriptyline, mirtazapine, and paroxetine were associated with a greater risk of weight gain; in contrast, some weight loss occurred with fluoxetine and bupropion. The authors concluded that long-term effect of antidepressants on metabolic side effects may vary greatly depending on the individual's characteristics (Serretti and Mandelli, 2010).

In summary, previous studies showed an increased risk of metabolic syndrome among patients with SMDs, but most had cross-sectional study design. The time course of metabolic side effects and mental disorders cannot be elucidated without a cohort study. In this study, using a nationwide database with a large sample size and a matched control cohort study design, we enrolled patients with SMDs but without diagnoses of and medications for DM and hyperlipidemia from 1996 to 2000, and followed them to the end of 2010. They were compared with age and gender-matched controls (1:4). We attempted to clarify the long-term risk of developing DM and hyperlipidemia among the patients with SMDs.

2. Materials and methods

2.1. Data source

The National Health Insurance (NHI) program, implemented in Taiwan in 1995, offers universal health coverage for all its citizens, including comprehensive medical services and prescription medicines, and covers up to 99% of all 23,000,000 residents of Taiwan. Demographic and medical information on insured residents, including age, gender, residence location, prescription drugs, prescription date, and diagnosis were recorded in the NHI Research Database (NHIRD). The International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) was used for the diagnoses. The completeness and accuracy of the NHIRD has been affirmed by the Taiwan Department of Health and the Bureau of NHI through audit. The National Health Research Institutes has provided a database of medical claims from 1,000,000 random subjects, approximately 4.3% of the population, for use in health service studies. All the registration and claim data of these 1,000,000 individuals collected by the National Health Insurance Program constitute the database in this study, and there were no statistically significant differences in age, sex, and health-care costs between the sample group and the original NHIRD (Pavuluri et al., 2002).The NHIRD has been used extensively in many epidemiologic studies in Taiwan (Huang et al., 2009; Wu et al., 2011; Chen et al., 2012, 2013; Li et al., 2012).

2.2. Study cases

The study cases were patients with a diagnosis of BD (ICD-9-CM code: 296, except 296.2, 296.3), MDD (ICD-9-CM codes: 296.20 and 296.30), and schizophrenia (ICD-9-CM code: 295) given by psychiatrists, and without diagnoses of DM (ICD-9-CM code: 250) or hyperlipidemia (ICD-9-CM code: 401–405), and not receiving any medications for DM (ATC-CODE: A10A or A10B) and hyperlipidemia (ATC-CODE:C10x) between January 1, 1996 and December 31, 2000. The study cohorts were mutually exclusive.

Table 1
Characteristics of patients with bipolar disorder, major depressive disorder, schizophrenia and controls.

	Bipolar ($N=367$)	NC ($N=1468$)	p-value	MDD ($N=417$)	NC ($N=1668$)	p-value	Schizo ($N=1993$)	NC ($N=7972$)	p-value
Age (years)			0.995			> 0.999			0.997
< 20	38 (10.4)	158 (10.8)		33 (7.9)	135 (8.1)		143 (7.2)	572 (7.2)	
20–39	208 (56.7)	833 (56.7)		226 (54.2)	903 (54.1)		1256 (63.0)	5043 (63.3)	
40–59	101 (27.5)	397 (27.0)		141 (33.8)	562 (33.7)		536 (26.9)	2124 (26.6)	
≥ 60	20 (5.4)	80 (5.4)		17 (4.1)	68 (4.1)		58 (2.9)	233 (2.9)	
Mean ± SD	45.28 ± 13.99	45.28 ± 13.98	> 0.999	46.53 ± 13.74	46.53 ± 13.74	> 0.999	45.88 ± 12.30	45.88 ± 12.30	> 0.999
Sex			> 0.999			> 0.999			> 0.999
Male	150 (40.9)	600 (40.9)		144 (34.5)	576 (34.5)		1052 (52.8)	4208 (52.8)	
Female	217 (59.1)	868 (59.1)		273 (65.5)	1092 (65.5)		941 (47.2)	3764 (47.2)	
Cumulative incidence of diabetes mellitus	37(10.1%)	93(6.3%)	**0.012****	36(8.6%)	108(6.5%)	0.118	265(13.3%)	571(7.2%)	< ***0.001****
Cumulative incidence of hyperlipidemia	58(15.8%)	154(10.5%)	**0.004****	62(14.9%)	192(11.5%)	0.056	284(14.2%)	961(12.1%)	**0.005****
Urbanization			0.275			0.059			< **0.001**
1 (most urban)	132 (36.0)	500 (34.1)		161 (38.6)	563 (33.8)		519 (26.0)	2538 (31.8)	
2	124 (33.8)	449 (30.6)		147 (35.3)	542 (32.5)		654 (32.8)	2563 (32.2)	
3	46 (12.5)	247 (16.8)		52 (12.5)	270 (16.2)		298 (15.0)	1307 (16.4)	
4	43 (11.7)	169 (11.5)		34 (8.2)	179 (10.7)		271 (13.6)	927 (11.6)	
5 (most rural)	22 (6.0)	103 (7.0)		23 (5.5)	114 (6.8)		251 (12.6)	637 (8.0)	
Income (NTD)			< ***0.001****			< ***0.001****			< ***0.001****
< 15,000	178 (48.5)	435 (29.6)		178 (42.7)	525 (31.5)		1317 (66.1)	2201 (27.6)	
15,000–29,999	116 (31.6)	621 (42.3)		140 (33.6)	665 (39.9)		574 (28.8)	3125 (39.2)	
≥ 30,000	73 (19.9)	412 (28.1)		99 (23.7)	478 (28.7)		102 (5.1)	2646 (33.2)	

MDD: major depressive disorder; NC: normal control.* $p < 0.05$, ** $p < 0.01$