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Association Between Antipsychotic Treatment and Advanced Diabetes Complications Among Schizophrenia Patients With Type 2 Diabetes Mellitus

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Objective: **Antipsychotic drug use is an established risk factor for the development of type 2 diabetes mellitus. However, the effect of antipsychotic drug on the progression of diabetes complications remains unclear. This study aimed to explore the association between antipsychotic treatment and advanced diabetes outcome among schizophrenia patients with type 2 diabetes.** ***Methods:*** **The authors conducted a retrospective cohort study using Taiwan's universal health insurance database. A total of 17 629 schizophrenia patients with newly-diagnosed diabetes were enrolled. The mean duration of follow-up, after excluding the first 6-month observation period, was 4.8 years, ranged from 1 month to 11.5 years. Antipsychotic treatment patterns within a 6-month time window were classified into none, irregular use, and regular use. Antipsychotics were further categorized into the high, intermediate, and low metabolic risks. The status of exposure was treated as time-dependent variables. The outcomes measures included any advanced diabetes complications, macrovascular and microvascular complications, and all-cause mortality.** ***Results:*** **Compared to no antipsychotic treatment in the past 6 months, regular antipsychotic use was associated with a lower risk of any advanced diabetes complications (adjusted hazard ratio, aHR = 0.81, 95% CI = 0.69–0.95), macrovascular complications (aHR = 0.80, 95% CI = 0.66–0.97), and all-cause mortality (aHR = 0.73, 95% CI = 0.62–0.85). The hazard ratios for advanced diabetes complications with regular use of antipsychotics with a high, intermediate, and low metabolic risk were 0.69 (95% CI = 0.53–0.91), 0.82 (95% CI = 0.68–0.99), and 0.85 (95% CI = 0.70–1.02), respectively.** ***Conclusions:*** **Regular antipsychotic treatment in the past 6 months was associated with reduced risks of any diabetes complications, compared to no antipsychotic treatment.**

Key words: antipsychotics/metabolic risk/schizophrenia/type 2 diabetes mellitus/complications

Introduction

Schizophrenia patients are often comorbid with diabetes mellitus.[1,2] Lack of physical activity, poor dietary habits, heritability, and antipsychotic treatment are associated with an increased diabetes risk in patients with schizophrenia.[3] Diabetes mellitus is associated with an increased mortality rate and macrovascular (acute myocardial infarction, cerebrovascular accident, and peripheral vascular disease) and microvascular (nephropathy, retinopathy, and diabetes foot) complications.[4,5] The relationship between diabetes and vascular complications begins in the early stage of glucose dysregulation.[6] Studies showed diabetes patients with schizophrenia have higher risk for diabetes complications than those without schizophrenia.[7,8] Intensive glycemic control, active anti-diabetes treatments, and lifestyle modification are recommended for diabetes management.[9]

Antipsychotic drug use is an established risk factor for the development of type 2 diabetes mellitus.[10,11] However, the metabolic adverse effects vary across different antipsychotics. For example, clozapine and olanzapine carry the highest metabolic risk for body weight gain, dyslipidemia, and hyperglycemia,[12] and aripiprazole, ziprasidone, and high-potency first-generation antipsychotics are associated with low or no metabolic disturbance.[13–15] A growing body of evidence has shown that switching to antipsychotics with a low metabolic risk is a potential strategy to improve metabolic parameters and reverse weight gain induced by antipsychotics with a high metabolic risk.[16,17] However, switching antipsychotics could increase the risk of treatment discontinuation.[18] Furthermore, the benefit

of improving metabolic parameters on diabetes outcome is inconclusive.[19,20] The effect of switching antipsychotics on the clinical outcome of diabetes has yet to be investigated.

We conducted a national cohort study of schizophrenia patients with newly-diagnosed diabetes to explore the associations between antipsychotic treatment and the clinical outcome of diabetes, including advanced diabetes complications, such as macrovascular and microvascular complications, and all-cause mortality. In addition, the beneficial effects of switching antipsychotics on reducing advanced diabetes complications were also investigated.

Methods and Materials

Data Source

This cohort study utilized Taiwan's National Health Insurance Research Database (NHIRD) derived from Taiwan's single-payer compulsory National Health Insurance program, which covers up to 99% of the 23 million Taiwanese population.[21] The NHIRD includes patients' demographic characteristics, clinical diagnoses, medical procedures, and prescription records. The validation of major clinical diagnoses in the NHIRD, such as diabetes, stroke, and acute coronary syndrome, has been well-established.[22–25]

Study Population

To explore association between advanced diabetes complications and antipsychotic exposure after diabetes onset, we assembled a cohort of schizophrenia patients with newly-diagnosed diabetes between 2001 and 2012 (n = 24 827). The date of first diagnosis of diabetes was the cohort entry date. Schizophrenia patients with newly-diagnosed diabetes included in this study must have had (1) at least 2 ambulatory claims or 1 inpatient discharge diagnosis of diabetes (ICD9-CM code: 250.x); (2) at least 2 ambulatory claims or 1 inpatient discharge diagnosis of schizophrenia-spectrum disorder (ICD9-CM code: 295.x); (3) a diagnosis of schizophrenia prior to that of diabetes; and (4) an absence of any diagnosis of diabetes in the 1 year before the cohort entry date. The validation of diagnosis of type 2 diabetes and schizophrenia in Taiwan's NHIRD were documented in previous studies.[22,25,26] The concordance of type 2 diabetes between self-report and claims record was substantial (κ = 0.76).[25] In terms of schizophrenia, 89% were diagnosed by psychiatrists.[26] The positive predictive value of diagnosis would be further improved by increasing number of claims; however, the sensitivity would be decreased.[22] To trade off positive predictive value and sensitivity, we chose 2 ambulatory claims or 1 inpatient discharge diagnosis as the definition of study populations.

Schizophrenia patients with type 1 diabetes mellitus (n = 440) or age < 18 years (n = 44) on the cohort entry date were excluded. It should be noted that a significant proportion of newly diagnosed diabetic patients have diabetes complications.[27] Therefore, we excluded patients who had any advanced diabetes complication before the cohort entry date (n = 5069) in order to have a clear temporal relationship between exposure and outcome. Furthermore, to have at least a 6-month observation period to quantify the association between antipsychotic treatment pattern and diabetes outcome, we further excluded those who had diabetes complications or who were censored within 6 months after the onset of diabetes (n = 1260). At last, a total of 17 629 schizophrenia patients with newly-diagnosed diabetes were included in this study.

Main Outcome Measures

The primary outcome measures were the combined endpoints of macrovascular and microvascular complications. Macrovascular and microvascular complications of diabetes were identified using the ICD-9-CM diagnostic and procedure codes and NHI procedure codes. Macrovascular complications included hospitalization for ischemic heart diseases, hospitalization for stroke, and ambulatory or inpatient claims for peripheral vascular diseases with stent insertion, vascular shunt or bypass, or vessel repair procedure. Microvascular complications included ambulatory or inpatient claims of diabetic retinopathy with laser photocoagulation or vitrectomy, blindness, end-stage renal disease with dialysis, vessel operations for hemodialysis, or kidney transplantation, hospitalization for diabetic foot infection, and lower extremity amputations (supplementary table 1).

Secondary outcomes were macrovascular complications, microvascular complications, and all-cause mortality. The date of death was identified using the date of inpatient death or the Registry for Catastrophic Illness Patients, which is established by the Bureau of National Health Insurance and contains information for the date of death.[21] Given that the cause of death was not available in the NHIRD or the Registry for Catastrophic Illness Patients, we assessed all-cause mortality only in this study. Study cohorts were followed up until the date of occurrence of a given study outcome, death, or the end of 2012. For analyses for macrovascular complications, patients would be followed up even microvascular complication occurred (vise versa).

Antipsychotic Exposure

Using the Anatomical Therapeutic Chemical Classification System, we identified antipsychotics (N05A) except lithium (N05AN01), which was generally categorized as a mood stabilizer. The primary exposure in our analysis was overall antipsychotic treatment pattern. Medication possession ratio (MPR), a quantitative index for assessing medication adherence, is calculated by the ratio of the

sum of the number of days with supply of dispensed drug to a given observational period. The overall antipsychotic treatment pattern was classified into no use (MPR = 0), irregular use (0 < MPR < 0.8), and regular use (MPR ≧ 0.8).[28] Second, we further classified regular use of antipsychotics based on their metabolic risks. The metabolic risk varied markedly across antipsychotics. We classified second-generation antipsychotics (SGAs) into high (clozapine and olanzapine), intermediate (paliperidone, quetiapine, risperidone, and zotepine) and low metabolic risk categories (amisulpride, aripiprazole, sulpiride, and ziprasidone).[13,15] The metabolic risk of high-potency first-generation antipsychotics (FGAs) (flupentixol, fluphenazine, haloperidol, pimozide, thiothixene, trifluoperazine) was categorized as low, but that of low- and mid-potency FGAs (chlorpromazine, chlorprothixene, clopentixol, clothiapine, loxapine, methotrimeprazine, perphenazine, pipotiazine, prochlorperazine, thioridazine, and zuclopentixol) was categorized as intermediate.[13–15]

Covariates Assessment

Patients' demographic variables included age at diagnosis of type 2 diabetes, sex, and calendar year of diabetes diagnosis. In addition, potential confounders that might be associated with both diabetes complications and antipsychotic exposure included comorbid medical and psychiatric conditions, concomitant use of medications, and health system utilization. Comorbid medical and psychiatric conditions included hypertension, dyslipidemia, chronic pulmonary disease, chronic liver disease, malignancy, depressive disorder, dementia, anxiety disorder, alcohol-related disorder, and substance use disorder. Concomitant use of medications included angiotensin converting-enzyme inhibitor/angiotensin II receptor blocker (ACEI/ARB), beta blockers, calcium channel blockers, diuretics, lipid-lowering agents, antithrombotics, nonsteroidal anti-inflammatory drugs (NSAID), anticonvulsants, lithium, antidepressants, and benzodiazepine. In addition, we assessed the proxy measures for glycemic status and quality of diabetes care, including number of oral anti-diabetes drugs, adherence to anti-diabetes medications, use of insulin, examination for Hb_{A1c} and lipid profile, and emergency room visits or hospitalizations for hyperglycemic crisis. To control for medical accessibility, we assessed health system utilization, including the number of outpatient visits and hospitalizations.

Statistical Analysis

To explore the effect of the antipsychotic treatment pattern on advanced diabetes complications and all-cause mortality in schizophrenia patients with type 2 diabetes, we conducted time-dependent covariates Cox proportional hazards regression. The overall period of follow-up was prospectively divided into 30-day intervals, beginning at 6 months after the cohort entry date (figure 1). At the start of each interval, the antipsychotics exposure status and above-mentioned confounding factors were assessed over a 6-month observation period prior to each interval. Given the prevalence of nonadherence, switching, and combination use in the whole treatment course, the status of antipsychotic use was accounted for with time-dependent variables. The overall antipsychotic treatment pattern in a 6-month time window was classified into no use, irregular use, and regular use. "No use" was used as a reference group. Second, we further classified regular use of antipsychotics, based on metabolic risks, into high, intermediate, and low risk, and combination use of antipsychotics as different levels of metabolic risks. The potential confounders included above-mentioned comorbid medical and psychiatric conditions, concomitant use of medications, and levels of health system utilization, and were treated as time-dependent covariates. In terms of comorbid conditions, once a patient had been diagnosed, he/she would be categorized as having these diseases in further follow-up periods. Benzodiazepines were chosen as a negative comparator drug because they have not been associated with hyperglycemia or hypoglycemia. To test the robustness of our results, we also conducted propensity score analyses. Propensity score analysis is a statistical approach to mimic randomization study by creating groups that received the specific treatment that is comparable on all observed covariates to a reference group. The propensity scores, a patient's probability of receiving antipsychotic treatment in a specific time period, were estimated using multinomial logistic regression which including above-mentioned covariates. For each patient, the propensity score could change over study period. Inverse probability weighing approaches, based on estimated propensity scores, were used to balance confounding covariates between treatment groups. In brief, patients with a high probability (propensity score) of a given treatment pattern would receive a lower weight (inverse propensity score), compared with those with a low probability. Thus, the differences in covariates between patients with different treatment patterns would be corrected. The balance was assessed using standardized difference.[29]

To make the comparisons for the risk of diabetes complication between staying with and switching antipsychotics during the follow-up period, we performed subgroup analyses by stratifying the baseline antipsychotic treatment pattern, which was assessed during a 6-month period before the cohort entry date. Staying with the baseline antipsychotic treatment, which was defined as using the same antipsychotic class during the follow-up period as that used during the baseline period, was used as a reference group. Given that the case number was small in subgroup analyses, no use and irregular use were collapsed into a group; the use of antipsychotics with intermediate and high metabolic risk was also combined.

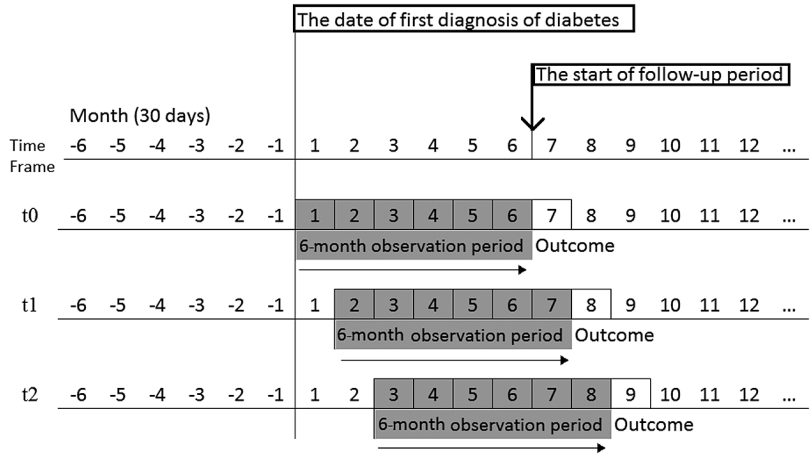

Fig. 1. Study design.

All statistical analyses were conducted with SAS version 9.4 (SAS Institute Inc). The statistical significance of relationships was assessed using 95% CI excluding 1 or P values < .05.

Results

The mean age of the new-onset diabetes patients with schizophrenia at the diagnosis of diabetes was 47.0 years (SD = 12.3); 51.2% were female; 19.2% had hypertension; 11.8% had dyslipidemia; 14.5% were comorbid with depressive disorder. In terms of baseline antipsychotic treatment pattern, 18.3%, 33.3%, and 48.4% of patients had no, irregular, and regular use of antipsychotics over a 6-month period prior to the cohort entry date, respectively (table 1). Mean duration of follow-up, after excluding the first 6-month observation period, was 4.8 years (SD = 3.2), ranged from 1 month to 11.5 years. Supplementary figure 1 presents the distributions of antipsychotic treatment patterns during the study period. In brief, the percentage of regular antipsychotic use increased during the follow-up period; however, the proportion of no use decreased. Among those person-months with regular use, there were 17 109 times of switching between antipsychotics with different metabolic risks. The proportion of switching from lower metabolic risks to higher risks (50.1%) was similar to that from higher risks to lower risks (49.9%). In terms of diabetes treatment, there was no significant difference between none, irregular, and regular antipsychotic treatment except that the medication adherence of oral anti-diabetes drug in none antipsychotic treatment person-months (MPR = 62.5%) was better than that in irregular antipsychotics treatment (MPR = 54.9%) or regular antipsychotic treatment (MPR = 51.8%; supplementary table 2).

Overall, the incidence rate per 1000 person-years was 21.0 for any advanced diabetes complications, 13.7 for macrovascular complications, 9.2 for microvascular complications, and 20.1 for all-cause mortality of schizophrenia patients with newly-diagnosed diabetes (table 2). Stratified by antipsychotics treatment pattern during the follow-up period, we found the crude incidence rate of any advanced diabetes complications per 1000 person-years was 22.2 for no use; 24.0 for irregular use, and 17.9 for regular treatment.

Compared to no use in the past 6 months, regular antipsychotic use was associated with a lower risk of any advanced diabetes complications (adjusted hazard ratio, aHR = 0.81, 95% CI = 0.69–0.95), macrovascular complications (aHR = 0.80, 95% CI = 0.66–0.97), and all-cause mortality (aHR = 0.73, 95% CI = 0.62–0.85). However, use of antipsychotics in the past 6 months was not associated with the risk of microvascular complications. In the analyses of the effect of the negative control, benzodiazepine use pattern was not associated with the risk of any advanced diabetes complications (table 3).

In terms of the relationship between antipsychotic classes and diabetes outcomes, we found the regular use of antipsychotics with a high or intermediate metabolic risk yielded significantly reduced risks of advanced diabetes complications of 0.69 (95% CI = 0.53–0.91) and 0.82 (95% CI = 0.68–0.99), respectively. In addition, we found antipsychotic treatment was associated with a reduced risk of all-cause mortality, regardless of the level of the metabolic risks of antipsychotics. In sensitivity analysis using inverse probability weighting, the difference in the distribution of covariates between treatment groups were well balanced (supplementary table 2). The results in weighting for propensity score were consistent except that antipsychotic with low metabolic risk yielded significantly reduced risks of any advanced diabetes outcome (supplementary table 3).

In analyses for the effect of antipsychotic switching on the risk of advanced diabetes complications, the results revealed no statistically significant changes among those switching to antipsychotics with different metabolic

Table 1. Baseline Characteristics of Diabetes Patients With Schizophrenia (N = 17 629)

	N (%)
Age, year	
18–44	7913 (44.9)
45–64	8127 (46.1)
≥65	1589 (9.0)
Gender	
Female	9018 (51.2)
Comorbidity	
Hypertension	3378 (19.2)
Dyslipidemia	2088 (11.8)
Chronic liver diseases	497 (2.8)
Chronic pulmonary diseases	910 (5.2)
Malignancy	265 (1.5)
Depressive disorders	2559 (14.5)
Anxiety disorders	1512 (8.6)
Alcohol related disorders	466 (2.6)
Substance related disorders	167 (0.9)
Medication use	
ACEI/ARB	1620 (9.2)
Beta blocker	5218 (29.6)
Calcium channel blocker	2239 (12.7)
Diuretics	1265 (7.2)
Antithrombotic agent	791 (4.5)
Lipid lowering agent	1900 (10.8)
NSAID	7983 (45.3)
Anticonvulsants	2713 (15.4)
Lithium	921 (5.2)
Antidepressants	4382 (24.9)
Antipsychotics	
None	3227 (18.3)
Irregular use	5871 (33.3)
Regular use	8531 (48.4)
Benzodiazepine	
None	5405 (30.7)
Irregular use	5060 (28.7)
Regular use	7164 (40.6)
Healthy system utilization	
Number of outpatient visits	
<10	6301 (35.7)
10–19	6172 (35.0)
≥20	5156 (29.2)
Hospitalization	2658 (15.1)

Note: ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin-receptor blockers; NSAID, Non-steroidal anti-inflammatory drug.

risks, compared to those staying with baseline treatment (table 4).

The aHRs of covariates for any diabetes complications and mortality using Cox-regression model are shown in supplementary table 4. Old age, male gender, comorbid conditions (hypertension, chronic pulmonary disease, alcohol related disorder), drug markers of chronic disease (diuretics, antithrombotic agent, and anticonvulsant), polypharmacy of oral anti-diabetic agent, monopharmacy of oral anti-diabetic agents with poor compliance, and hospitalization in the past 6 months were associated with an increased risk of any diabetes complications. However, use of beta blocker and receiving examination of blood glucose or Hb_{A1C} were related to a reduced risk of diabetes complications.

Discussion

As the first study to explore the effects of antipsychotics on advanced diabetes complications among patients with schizophrenia, we found that regular antipsychotic treatment in the past 6 months was associated with a reduced risk of any advanced diabetes complications, macrovascular complications, and all-cause mortality, compared to no antipsychotic use. In addition, the risk of diabetes complications was the lowest among patients with regular use of antipsychotics with a high metabolic risk. In addition, we found there were no statistically significant differences in the risk of diabetes complications between patients who switched antipsychotics and those who stayed with the same ones.

No previous study has explored the effect of antipsychotic treatment on diabetes outcomes among patients with schizophrenia and diabetes. One population-based cohort study using a database from Finland's nationwide registers showed that long-term cumulative antipsychotic use was associated with lower mortality than no drug use.[30] In addition, a cohort study from Sweden also found the lowest all-cause and cardiovascular mortality rate among patients treated with a low or moderate antipsychotic dose.[31] However, one review article demonstrated that findings for the association between antipsychotics and mortality were inconsistent.[32] In addition, methodological issues for these observational studies were criticized.[33] Our findings are in line with these large scale epidemiological studies, which reported that antipsychotic treatment has a positive effect on health outcome among schizophrenia patients.[30,31,34,35] A possible explanation is that antipsychotic treatment can improve the patient's physical, psychosocial, and self-care functioning[36]; thereby enhancing healthy behaviors and decreasing the risk of diabetes complications. Such benefits would overcome the metabolic adverse effect of antipsychotics.

Furthermore, our findings revealed that regular use of benzodiazepine, a negative control, was not related to diabetes complications. Therefore, our findings could not be explained merely by the "healthy adherer effect," which implies good medication adherence as a surrogate marker for overall healthy behaviors.[37] Of note, we found regular use of benzodiazepine were associated with increased all-cause mortality, which is compatible with the findings by Weich et al.[38] Different pathophysiological pathway, other than glycemic effect, might be responsible for the association between benzodiazepine use and mortality and warrants further investigations.

Despite the higher risks of body weight gain with several antipsychotics, we found that regular use of antipsychotics

Table 2. Crude Incidence Rate of All, Macrovascular-, Microvascular-Diabetes Complications, and All-Cause Mortality Among Patients With Schizophrenia and Diabetes

	All Complications		Macrovascular Complications		Microvascular Complications		All-Cause Mortality	
	Number of Event/ Person-Years	Incidence per 1000 Person-Years	Number of Event/ Person-Years	Incidence per 1000 Person-Years	Number of Event/ Person-Years	Incidence per 1000 Person-Years	Number of Event/ Person-Years	Incidence per 1000 Person-Years
Overall	1745/82 970	21.0	1164/85 201	13.7	791/86 287	9.2	1791/89 013	20.1
Antipsychotic treatment								
No use	411/18 480	22.2	285/18 986	15.0	183/19 434	9.4	491/20 098	24.4
Irregular use	702/29 269	24.0	466/30 114	15.5	328/30 524	10.7	718/31 559	22.8
Regular use, overall	632/35 220	17.9	413/36 100	11.4	280/36 328	7.7	582/37 355	15.6
Low metabolic risk	224/12 500	17.9	148/12 790	11.6	94/12 860	7.3	173/13 215	13.1
Intermediate metabolic risk	245/12 143	20.2	163/12 488	13.1	108/12 635	8.5	253/13 028	19.4
High metabolic risk	71/5588	12.7	49/5723	8.6	28/5718	4.9	62/5864	10.6
Combination use	92/4988	18.4	53/5099	10.4	50/5114	9.8	94/5246	17.9
Benzodiazepine treatment								
No use	554/29 138	19.0	361/29 837	12.1	269/30 227	8.9	575/373 451	18.5
Irregular use	643/25 856	24.9	452/26 648	17.0	279/27 069	10.3	681/336 441	24.3
Regular use	548/27 974	19.6	351/28 715	12.2	243/28 990	8.4	535/358 273	17.9

Table 3. Hazard Ratios for Macrovascular, Microvascular Complications, and Mortality of Schizophrenia by Antipsychotic Use

	All Complications	Macrovascular Complications	Microvascular Complications	All-Cause Mortality
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Antipsychotic use vs no use				
Irregular use	0.90 (0.78–1.03)	0.83 (0.70–0.98)*	0.99 (0.81–1.22)	0.79 (0.69–0.90)*
Regular use, overall	0.81 (0.69–0.95)*	0.80 (0.66–0.97)*	0.83 (0.62–1.11)	0.73 (0.62–0.85)*
Low metabolic risk	0.85 (0.70–1.02)	0.84 (0.67–1.06)	0.83 (0.62–1.11)	0.66 (0.54–0.81)*
Intermediate metabolic risk	0.82 (0.68–0.99)*	0.81 (0.64–1.02)	0.83 (0.62–1.10)	0.78 (0.65–0.94)*
High metabolic risk	0.69 (0.53–0.91)*	0.74 (0.53–1.02)	0.61 (0.40–0.93)*	0.62 (0.47–0.82)*
Combination use	0.84 (0.66–1.08)	0.75 (0.55–1.04)	1.03 (0.72–1.46)	0.82 (0.65–1.05)
Benzodiazepine use vs no use				
Irregular use	0.99 (0.87–1.14)	1.11 (0.95–1.31)	0.82 (0.67–1.00)	1.11 (0.98–1.27)
Regular use	0.96 (0.82–1.12)	0.97 (0.80–1.17)	0.86 (0.68–1.08)	1.25 (1.07–1.47)

Note: HR, hazard ratio.
*P value < .05.

with high or intermediate metabolic risk was associated with a reduced risk of diabetes complications. It should be noted that a risk factor is not necessarily a prognostic factor. For example, obesity is a risk factor for diabetes and cardiovascular diseases; however, a growing body of evidence has shown that overweight or obesity are associated with better clinical outcomes among patients with chronic illnesses, such as diabetes and cardiovascular diseases.[39] A possible explanation is that patients that are overweight or obese have a better nutritional status and cardiorespiratory fitness.[40] In addition, the protective effect of obesity might be mediated by decreasing production of thromboxane (a platelet activator) and increasing sensitivity of ghrelin (a peptide hormone associated with improving left ventricular function).[39] Antipsychotics with a high metabolic risk are associated with overweight or obesity, which might have a protective effect on cardiovascular and diabetes complications.[20] In addition, antipsychotics with high metabolic risk generally have few adverse effects of extrapyramidal syndrome.[41] Therefore, patients treated with those antipsychotics might have little movement impairment and a high level of physical activity, which would decrease the risk of diabetes complications.[42,43] Furthermore, compared with other antipsychotics with a

Table 4. Hazard Ratio for All Diabetes Complications Stratified by Baseline Antipsychotic Treatment Pattern

Baseline / During Follow-up Period	No or Irregular Use	Regular Use of Antipsychotics With Low Metabolic Risk	Regular Use of Antipsychotics With Intermediate or High Metabolic Risk	Regular Use of Combination Antipsychotic Treatment
No or irregular use				
Event/person-year, incidence	735/31 492, 23.3	124/4580, 27.1	157/6873, 22.8	97/4803, 20.2
Adjusted HR, 95% CI	reference	0.89 (0.62–1.28)	1.45 (1.08–1.96)*	0.94 (0.55–1.61)
Regular use of antipsychotics with low metabolic risk				
Event/person-year, incidence	74/3453, 21.4	93/5487, 16.9	29/2099, 13.8	28/1459, 19.2
Adjusted HR, 95% CI	0.96 (0.73–1.27)	reference	0.93 (0.62–1.39)	1.15 (0.67–1.96)
Regular use of antipsychotics with intermediate or high metabolic risk				
Event/person-year, incidence	102/5025, 20.3	36/1568, 22.9	136/8846, 15.4	42/2291, 18.3
Adjusted HR, 95% CI	0.80 (0.63–1.03)	1.04 (0.69–1.56)	reference	1.05 (0.64–1.72)
Regular use of combination antipsychotic treatment				
Event/person-year, incidence	25/1153, 21.7	9/677, 13.3	31/1538, 20.1	27/1617, 16.7
Adjusted HR, 95% CI	0.86 (0.57–1.31)	0.62 (0.31–1.23)	1.42 (0.95–2.10)	reference

Note:*P value < .05.

low metabolic risk, olanzapine and clozapine were associated with a lower discontinuation rate and better therapeutic response,[44,45] thereby improving medication adherence and overall health outcome.[46]

We found that switching antipsychotics did not change the risk of diabetes complications, no matter whether the switching was to lower-risk agents from higher-risk agents or to higher-risk agents from lower-risk agents. Switching antipsychotics is a therapeutic strategy to attenuate drug-induced adverse effects. Evidence showed that switching to antipsychotics with a low metabolic risk from those with a high risk would improve metabolic parameters.[47,48] However, the increased risk of treatment discontinuation might attenuate the benefits of switching antipsychotics.[18] Furthermore, improving metabolic parameters might not always lead to a good clinical outcome. One study conducting post hoc analysis of a clinical trial found that weight reduction was associated with an increased risk of diabetes complications and mortality.[20] Our findings did not support the benefit of switching antipsychotics relative to diabetes outcomes.

We found hypertension as well as chronic pulmonary diseases and alcohol related disorder (surrogate indicators of unhealthy life style) were associated with an increased risk of any diabetes complications. Examination for blood glucose or Hb_{A1c}, a proxy measure of quality of diabetes care, was related to a reduced risk of diabetes complications. These findings suggested that treating medical comorbid conditions, life style interventions, and enhancing quality of diabetes care might be a potential strategy for improving diabetes outcome among schizophrenia patients.

Strengths and Limitations

There are several noteworthy strengths of this first study to explore the effects of antipsychotics on advanced diabetes complications among patients with schizophrenia. We utilized a national cohort of schizophrenia patients with newly-diagnosed diabetes. The sample size was large and the length of observation (up to 11.5 years) was long. In addition, we used benzodiazepine as a negative control to assess the "healthy adherer effect." Other strengths included a well-defined method for identifying the complications of diabetes, detailed data on antipsychotic drug treatment, and clear temporal relationships between antipsychotic exposure and diabetes complications.

However, several limitations in this study should be noted. First, the reasons for selecting particular antipsychotics were not available. Antipsychotics with a low metabolic risk might be more likely to be prescribed for patients with poor glycemic control; therefore, our findings might be biased by confounding by indications. Although glycemic status might not be the major consideration for choice of antipsychotic drug,[49] we assessed numerous proxy measures of glycemic status, including the number of using anti-diabetes drugs, hyperglycemic crises, use of insulin, anti-diabetes medication adherence, and examination of Hb_{A1C} and lipid profiles, to reduce the confounding effect from glycemic status. In addition, we also conducted propensity score analyses to minimizing indication bias. However, our findings might be still influenced by residual confounding. Second, several important associated factors, including body weight, the level of glycemic and lipid profiles, smoking, and

psychosocial interventions, such as diet and exercise programs, were unknown. Patients with better antipsychotic adherence might also be more compliant with nonpharmacological diabetes treatment. The impact of these factors on our results warrants further investigation. Third, the accuracy of the diagnosis of microvascular complications and peripheral vascular diseases was not validated in the NHIRD. We used procedure claims to confirm the diagnostic code to minimize the possibility of misclassifications. However, minor diabetes complications that do not require a medical procedure were not included. Fourth, the duration of undiagnosed diabetes and schizophrenia were unknown. Thus, our sample might include a small proportion of patients who might have schizophrenia preceding diabetes. Last, information about the causes of mortality was not available in the NHIRD. Thus, we were not able to specifically explore diabetes-related mortality.

Conclusions

Despite several antipsychotics being associated with metabolic adverse effects, our findings suggested that regular antipsychotic treatment did not increase the risk of diabetes complications and premature mortality. Furthermore, we found switching antipsychotics did not change the risk of diabetes complications. Thus, we suggest switching strategies should be reserved only for those with extremely poor metabolic profiles. However, it should be emphasized that this study was conducted based on naturalistic observational data. Several important unmeasured factors might bias our results. The benefits of switching antipsychotics relative to clinical diabetes outcomes warrants further investigation in large-scale clinical trials.

Supplementary Material

Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

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