Risk of Developing Diabetes Mellitus from Antipsychotic Exposure in the United States

4/18/2001ABSTRACT

Objective: To determine the risk of developing diabetes mellitus (DM) associated with antipsychotics

Background:

Treatment-emergent diabetes mellitus has been reported for both conventional and atypical antipsychotics in case reports and small case series. In the present study, a large prescription claim database was used to determine the risk of developing diabetes during treatment with antipsychotics.

Method:

Antipsychotic prescription claims in the AdvancePCS' database were used to identify patients starting antipsychotic therapy. The incidence of DM was determined using prescription claims for antidiabetic agents in the general patient population cohort, and the following monotherapy cohorts: conventional antipsychotics combined (N= 19,782), haloperidol (N= 8,476), thioridazine (3,133), atypical antipsychotics combined (N= 38,969), olanzapine (N=13,863) and risperidone (N=20,633). Cox regression was used to estimate the risk of diabetes after adjusting for difference in age and sex between cohorts. Hazard ratios (HRs) of DM of antipsychotic cohorts, relative to the general PCS patient population, were determined.

Results: The HRs of DM during treatment with conventional and atypical antipsychotics cohorts were 3.5 (95% CI: 3.1-3.9) and 3.1 (CI: 2.9-3.4), respectively. The corresponding HRs after discontinuing antipsychotics were 2.5 and 1.4. The HRs and 95% confidence intervals of individual antipsychotics were quetiapine (1.7; CI: 1.2-2.4), olanzapine (3.0; CL: 2.6-3.5), haloperidol (3.1; CI: 2.6-3.7), clozapine (3.3; 1.4-8.0), risperidone (3.4; CI: 3.1-3.8) and thioridazine (4.2; CI: 3.2-5.5). The risk of the fourth dose quartile of both the conventional and atypical cohorts (all agents combined) was significantly different from that of the first dose quartile.

Conclusions: Treatment with either conventional or atypical antipsychotics was associated with an increase in the risk of developing diabetes. Dose dependent increase in risk of developing diabetes was suggested by this study.

INTRODUCTION

Studies over several decades suggest that diabetes mellitus (DM), impaired glucose tolerance (IGT), and insulin resistance were more common in patients with psychiatric disorders, including major mood disorders and schizophrenia, than in the general population[1,2, 3,4,5,6]. The role of the underlying mental disorders and antipsychotic agents remain to be determined. Treatment-emergent glucose intolerance was suggested for both conventional antipsychotics[7, 8, 9, 10, 11, 12,13, 14, 15] and atypical antipsychotics[16, 17, 18, 19, 20, 21,22, 23] in humans. This possibility was supported also by animal studies, where chlorpromazine was shown to cause hyperglycemia in normal animals[24,25]. However, a role of neuroleptics in development of diabetes was not supported by all investigations[26, 27] as higher rates of insulin resistance and impaired glucose tolerance than expected had been reported in schizophrenic patients prior to the introduction of neuroleptics [28, 29, 30, 31, 32].

Studies in literature are limited to small case series and prevalence determination. Epidemiology studies are needed to determine the potential of antipsychotics in inducing glucose intolerance. Using the General Practice Research (GPRD) database, we have recently showed that treatment with conventional and atypical classes of antipsychotics was associated with an increase in the frequency of treatment-emergent diabetes in UK. However, the number of patients who took atypical antipsychotics in that database was small. Consequently, we were able to demonstrate a higher risk of developing diabetes only in patients who took risperidone. In the present retrospective cohort study, the AdvancePCS (PCS) prescription claim database, with a much larger number of patients who took atypical antipsychotics, enabled us to estimate the risk of developing diabetes in patients who received antipsychotic monotherapy in the United States. This database enabled us to compare their diabetogenic potential of antipsychotics, and to assess the effect of antipsychotic doses. To our knowledge, this is the only large scale epidemiology study as of this date that assesses the incidence and hazard ratio of diabetes of patients who received antipsychotic as a single agent.

METHODS

This is a retrospective cohort study that determined the risk of developing diabetes during antipsychotic treatment using the prescription claim data of PCS, Inc (PCS). PCS processed over 300 million prescription claims per year for over 50 million members covered by over 2,000 employers and managed care plans.

Study Cohorts

Only subjects who were prescribed antipsychotics as monotherapy were included for this study. Cohorts studied were 1). conventional antipsychotic combined cohort (comprised of all agents in this class) , 2) atypical antipsychotic combined cohort, 3) cohorts of individual antipsychotics (e.g. olanzapine monotherapy cohort), 4) general PCS patient population cohort. The general PCS patient population included all subjects who had made a claim for any PCS-covered benefit (e.g. drug) during a 2-month enrollment window (January 1, 2000 to February 29, 2000). They must not have made a claim for diabetes drug(s) for at least 12 months prior to enrollment. In addition, they must not have made a claim for antipsychotics for at least 6 months prior to enrollment, and for 6 months after enrollment.

Conventional antipsychotics included in the present study were chlorpromazine, chlorprothixene, fluphenazine, haloperidol, loxapine, mesoridazine, molindone, perphenazine, pimozide, prochlorperazine, promazine, thioridazine, thiothixene, trifluoperazine, and triflupromazine. Atypical antipsychotics studied were clozapine, olanzapine, quetiapine and risperidone.

The "enrollment window" for subjects in the antipsychotic cohorts was December 1, 1998, through February 29, 2000. Only subjects who had started antipsychotics as monotherapy during this period were included. "Continuation cohort" is defined as cohort with patients who were receiving an antipsychotic. When antipsychotic was discontinued, the patient was automatically enrolled into the "discontinued cohort".

Only subjects who were eligible for prescription claims through the PCS system for at least 12 months prior to enrollment were included in any of the cohorts. The exclusion criteria applicable to all cohorts, were 1) a pre-existing history of diabetes, as evidenced by the dispensing of any

diabetes medication during the 12-month period before enrollment; 2) the dispensing of any antipsychotics within the six month-period before enrollment date; 3) absence of information on either sex or the year of birth; 4) less than 18 years of age. For antipsychotic cohorts, patients who received more than one antipsychotic during the evaluation period were excluded.

Identification of Incident cases of Diabetes Mellitus

New onset of diabetes mellitus during antipsychotic exposure was identified by claim(s) for any medication(s) indicated for the treatment of diabetes, regardless of the route of administration during the evaluation period. For subjects in any antipsychotic cohort, the earliest date during enrollment window that any given subject received an antipsychotic agent is the enrollment date for that subject. For identifying incident cases of diabetes during antipsychotic treatment episode, each subject was followed from the enrollment date (when antipsychotic was started) to the time when his or her antipsychotic was discontinued (including 15 days of wash out period), or when he or she left the benefit plans processed by PCS, but no later than August 31, 2000. Antipsychotic exposure periods separated by 15 days or less were considered as one antipsychotic treatment episode. For identifying incident cases of diabetes for the discontinued cohort, each patient was followed until antipsychotic was resumed, or when the patient were no longer eligible for benefit claim through the PCS system, or till August 31, 2000, whichever came first. Thus the following up period for both the continuation or discontinued cohorts were variable. The following up period for the general member or patient population was 6 months that immediately followed the enrollment date.

Comparison of the risk of developing diabetes between cohorts

The PHREG procedure in SAS was used for fitting the proportional hazard models. Two models were used. Regression model A had age and sex as covariates, and regression model B had age, sex and dose quartiles as covariates. The daily dose of antipsychotic was calculated by dividing the total amount of antipsychotic prescribed (in mg) divided by the total number of days that the medication was prescribed. The three age categories in this model were 18-44, 45-64 and 65 years of age and older. The dummy variables were 18-44 year old, females and first dose quartile. Unless otherwise specified, model A was used to estimate hazard ratios. The hazard ratios between antipsychotic cohorts, and between a given antipsychotic cohort and general PCS

patient population were estimated with model A. Unless otherwise stated, this is the model used for all regression analysis in this study. Model B was used to estimate the risk of developing diabetes of various antipsychotic dose quartiles relative to the general patient population.

RESULTS

The characteristics of cohorts studied were shown in Table 1. As compared to the general member and patient population, patients in either conventional and atypical antipsychotic cohorts were older. Among the cohort of individual antipsychotics, subjects in the haloperidol cohort was notably older, with almost two-third of patients in this cohort over 64 years of age. With the exception of clozapine cohort, there were more females than males in the cohorts. The average duration of antipsychotic treatment, ranging from 67-137 days, was longer for the atypical antipsychotic cohorts.

Cox regression analyses were performed to evaluate the effect of covariates in the regression model used for estimating the risk of diabetes in various cohorts. Results in Table 2 showed that male gender had a significant effect in the general patient population cohort and atypical antipsychotic cohort but not the conventional antipsychotic cohort. Age and the fourth dose quartile had a significant effect for the general population cohort, the conventional and the atypical antipsychotic cohorts. The age effect shown was consistent with US survey which showed that the incidence of diabetes increases with age[33]. The significant hazard ratios for the fourth dose quartile suggests that the risk of diabetes was dependent on the doses of antipsychotics.

Table 3 showed the incidence per 1000 patient-years and the hazard ratios of various cohorts. As compared to the incidence density of the general PCS patient population, the incidence of diabetes during antipsychotic treatment was 2.5 to 6.1 times higher. The incidence density of the conventional antipsychotic combined cohort was numerically, but not significantly, higher than that of the atypical antipsychotic cohort. As incidence of diabetes for antipsychotics might not be linearly related to time, annualization of incidence density may not be appropriate especially if the mean duration of antipsychotic treatment is short. In this case, annualization of incidence could likely inflat the incidence density as patients who developed diabetes from antipsychotic treatment might have done so within certain period of drug exposure, and those who were not susceptible to this drug effect would not have developed diabetes regardless of how long that they were treated. A better method to compare the risk of diabetes is using regression analysis to

adjust for difference in age, gender and treatment duration between cohorts. Such analysis showed that both conventional and atypical antipsychotic cohorts had significantly higher risk of diabetes than the general patient population. The risk of conventional antipsychotic cohort was numerically, but not significantly, higher than that of atypical antipsychotic cohort. The risks of all individual atypical antipsychotic cohorts (clozapine, olanzapine, risperidone and quetiapine) were significantly higher than the general patient population. The risk of quetiapine was signficantly lower than that of olanzapine or risperidone cohorts. The sample size of clozapine cohort (277) was too small to permit a meaningful comparison with other atypical antipsychotic cohort as reflected by the very large 95% confidence interval for its hazard ratio.

With the exception of the small clozapine cohort, the hazard ratios of diabetes of discontinued cohorts (comprising of patients who had discontinued their antipsychotics) was significant, indicating a higher risk of diabetes for these cohorts as compared to the general patient population. The HRs for the discontinuation cohorts are indicative of the background risk of developing diabetes for these cohorts, and varied widely between cohorts, ranging from 0.6 to 2.5. Similar in concept to the calculation of attributable risk, the difference between the HR during treatment and the HR after antipsychotic discontinuation might be a more accurate comparator between cohorts.

Schizophrenic patients often require higher dose of antipsychotics for the adequate management of the disease, and the doses encompassed by the fourth dose quartile are the most commonly doses used for the management of schizophrenia. Thus the risk associated with the fourth dose quartile is particularly relevant for the schizophrenic population. The hazard ratios of the fourth dose quartile (Table 5) show that the hazard ratio of conventional antipsychotic combined cohort was significantly higher than that of atypical antipsychotic combined cohort during drug treatment. However, if one takes into account the HR of the discontinuation period of these cohorts, then the risk for developing diabetes for atypical antipsychotic combined cohort was higher. Among the conventional antipsychotics evaluated individually, the HR of thioridazine was significantly higher than that of haloperidol. Among the atypical antipsychotic evaluated individually, the HR of clozapine, olanzapine, quetiapine, and risperidone were comparable.

Table 1. Characteristics of Cohorts Studied

	General Patient Population	CONVENTIONAL ANTIPSYCHOTIC			ATYPICAL ANTIPSYCHOTIC				
		All Agents	Haloperidol	Thioridazine	All Agents	Clozapine	Olanzapine	Quetiapine	Risperidone
Number of subjects in cohort	5,816,473	19,782	8,476	3,133	38,969	277	13,863	4,196	20,633
Age Distribution									
18-44	36.4%	20.8%	11.9%	25.7%	30.2%	36.8%	36.6%	35.8%	24.6%
45-64	39.2%	26.0%	15.3%	26.7%	23.6%	25.3%	28.7%	28.1%	19.2%
65 and older	24.5%	53.2%	72.8%	47.7%	46.3%	37.9%	34.7%	36.0%	56.2%
Mean Age (years)	52	64	72	61	60	55	55	55	64
% Male	37%	44%	41%	38%	38%	55%	39%	37%	37%
Average duration of antipsychotic treatment (days)	--	67	68	76	90	137	89	89	90
Mean dose of antipsychotic (mg)	NA	NA	2.5	43.9	NA	183.1	5.1	79.9	1.2

Table 2A. Hazard Ratio of Diabetes Mellitus for Covariates in the Cox Regression Model of General Patient Population and Conventional Antipsychotic Cohorts

VARIABLES	Average dose (mg) for the quartile	Hazard ratio**	95% confidence interval	P value
GENERAL PATIENT POPULATION				
Male	--	1.1*	1.1 - 1.2	0.0001
Age 45-64 years	--	3.4*	3.3 - 3.5	0.0001
Age >=65 years	--	4.0*	3.9 - 4.2	0.0001
CONVENTIONAL ANTIPSYCHOTIC COHORTS				
All Agents				
Male	--	0.9	0.8 - 1.2	0.6408
Age 45-64 years	--	2.5*	1.5 - 4.0	0.0002
Age >=65 years	--	4.1*	2.6 - 6.4	0.0001
2nd dose quartile	--	1.2	0.8 - 1.7	0.3939
3rd dose quartile	--	1.2	0.9 - 1.8	0.2397
4th dose quartile	--	2.4*	1.7 - 3.3	0.0001
Haloperidol				
Male	--	1.3	0.9 - 1.8	0.1363
Age 45-64 years	--	4.7*	1.4 - 16.0	0.0132
Age >=65 years	--	7.1*	2.2 - 22.5	0.0009
2nd dose quartile	0.8	0.9	0.5 - 1.5	0.6124
3rd dose quartile	1.7	0.9	0.6 - 1.5	0.7959
4th dose quartile	8.2	1.5	0.9 - 2.4	0.1071

* Statistically significant with p-value < 0.05.

** The reference groups were the 18-44 year-old group for the age covariate, and the first dose quartile for the dose quartile covariate.

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Table 2B. Hazard Ratio of Diabetes Mellitus for Covariates in the Cox Regression Model of Atypical Antipsychotic Cohorts

VARIABLES	Average dose	Hazard	95% confidence	P value
ATYPICAL ANTIPSYCHOTICS				
All Agents				
Male	--	1.3*	1.1 - 1.5	0.0005
Age 45-64 years	--	2.8*	2.0 - 4.0	0.0001
Age >=65 years	--	6.6*	4.9 - 8.9	0.0001
2nd dose quartile	--	0.8	0.7 - 1.0	0.1066
3rd dose quartile	--	0.9	0.7 - 1.1	0.1729
4th dose quartile	--	1.3*	1.1 - 1.7	0.0063
Olanzapine				
Male	--	1.3	1.0 - 1.7	0.0736
Age 45-64 years	--	2.6*	1.5 - 4.5	0.0006
Age >=65 years	--	6.9*	4.2 - 11.2	0.0001
2nd dose quartile	3.2	0.8	0.5 - 1.3	0.3412
3rd dose quartile	5.4	0.8	0.6 - 1.2	0.3601
4th dose quartile	11.3	1.3	0.9 - 1.9	0.1950
Risperidone				
Male	--	1.4*	1.1 - 1.7	0.0012
Age 45-64 years	--	3.7*	2.3 - 6.2	0.0001
Age >=65 years	--	7.1*	4.5 - 11.2	0.0001
2nd dose quartile	0.7	0.8	0.6 - 1.1	0.1834
3rd dose quartile	1.2	0.9	0.7 - 1.2	0.5402
4th dose quartile	2.7	1.3	1.0 - 1.7	0.0815

* Statistically significant with p-value < 0.05.

** The reference groups were the 18-44 year-old group for the age covariate, and the first dose quartile for the dose quartile covariate.

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Table 3. Incidence and Hazard Ratio of Diabetes in Adult Patients during treatment with Antipsychotic(s)

COHORT	No. of new cases	No. of patients	No. of patient-years	Incidence (per 1000 patient-years)		Hazard ratio		p-value
				Rate	95% CI	Ratio	95% CI	
TYPICAL								
All combined	307	19,782	3,645.57	84	75-94	3.5	3.1 – 3.9	0.0001
Haloperidol	133	8,476	1,568.39	85	70-100	3.1	2.6 – 3.7	0.0001
Thioridazine	62	3,133	654.28	95	71-119	4.2	3.2 – 5.5	0.0001
ATYPICAL								
All combined	641	38,969	9,571.18	67	62-72	3.1	2.9 – 3.4	0.0001
Clozapine	7	277	103.95	67	16-118	3.3	1.4 – 8.0	0.007
Olanzapine	194	13,863	3,374.57	58	49-66	3.0	2.6 – 3.5	0.0001
Quetiapine	40	4,196	1,025.75	39	27-51	1.7	1.2 – 2.4	0.002
Risperidone	400	20,633	5,066.90	79	71-87	3.4	3.1 – 3.8	0.0001
GENERAL POPULATION								
General Patient Population	45,513	5,816,473	2,908,236.50	15.7	15.6-15.8	--	--	--
General Member Population	31,817	8,224,303	4,112,151.50	7.7	7.6-7.8	--	--	--

Table 4. Incidence and Hazard Ratio of Diabetes of Discontinued Cohort comprising of Patients who had discontinued their Antipsychotic Monotherapy

COHORT	No. of new cases	No. of patients	No. of patient-years	Incidence (per 1000 patient-years)		Hazard ratio*		p-value
				Rate	95% CI	Ratio	95% CI	
CONVENTIONAL								
All combined	212	13,844	6,881	31	27-35	2.5	2.1 - 3.0	0.0001
Haloperidol	97	5,878	2,740	35	28-43	2.2	1.7 - 2.9	0.0001
Thioridazine	27	2,145	1,045	26	16-36	2.0	1.2 - 3.3	0.008
ATYPICAL								
All combined	225	22,289	9,856	23	20-26	1.4	1.2 - 1.7	0.0001
Clozapine	0	967	59	--	--	--	--	0.99
Olanzapine	80	8,049	3,628	22	17-27	1.7	1.3 - 2.3	0.0004
Quetiapine	11	2,208	944	12	5-19	0.6	0.2 - 1.5	0.25
Risperidone	134	11,907	5,225	26	21-30	1.4	1.1 - 1.8	0.004

* Reference cohort for the regression analysis was the general patient population. The covariates for the regression model were age and sex.

Table 5. Hazard Ratios for the Fourth Dose Quartile of Antipsychotic Cohorts

COHORT	HR of Continuation Cohort*		HR of Discontinued Cohort*		Increase in risk associated with drug treatment***
	Ratio	95% CI	Ratio	95% CI	
Conventional Antipsychotics					
All agents combined	5.6	4.7-6.7	2.7	1.9-3.7	2.9
Haloperidol	4.3	3.2-5.9	2.5	1.5-4.1	1.8
Thioridazine	8.9	6.2-12.7	1.6	0.5-4.9	7.3
Atypical Antipsychotics					
All agents combined	3.8	3.3-4.4	1.1	0.8-1.6	2.7
Clozapine	4.6	1.1-19.7	--**	--	--
Olanzapine	3.6	2.8-4.7	1.7	1.0-2.9	1.9
Quetiapine	3.1	1.9-5.1	0.3	0.0-1.8	2.8
Risperidone	4.0	3.3-4.8	1.0	0.6-1.5	3.0

* Reference cohort was the general patient population. The covariates for the regression models were age, sex and dose quartiles.

** Not determined as there were no incident diabetes cases for this small cohort.

*** Increase in risk associated with drug treatment = HR during exposure to antipsychotic – HR during discontinuation period

DISCUSSION

In a separate retrospective cohort study with the UK General Practice Research database (GPRD), we found that the risk of developing diabetes for both the conventional and atypical antipsychotic cohorts were significantly higher than that of the general adult population in UK.

In the present study, prescription claims for diabetes medications were used to identify subjects whose diabetes resulted in anti-diabetes medications. As this method would not identify subjects whose diabetes were managed with diet and/or exercise alone, the focus of this study is in determining the relative risk of developing diabetes between cohorts, rather than the incidence of diabetes. Cox proportional hazard model was used to estimate the risk of diabetes for various cohorts after controlling for difference in age, sex and antipsychotic doses.

In another epidemiology study using the General Practice Research database of UK, we identified diabetes by using both physician diagnoses and the dispensing of diabetes medication to identify subjects with diabetes. In both this UK study and the present study, subjects exposed to either atypical or conventional antipsychotics had a higher risk of developing diabetes than the general patient population not exposed to these agents. The risk of diabetes for clozapine, risperidone and olanzapine was significantly higher than the general patient population. was highest for clozapine cohort (N=), and was significantly higher than that of the general patient population inspite of the small sample size. The hazard ratios of olanzapine and risperidone were comparable. The risk of diabetes for atypical antipsychotic cohort was numerically, though not significantly, higher than that of the conventional antipsychotics. Consistent with this, clozapine-treated patients were reported more likely than conventional antipsychotic-treated patients to develop IGT or diabetes[34]. Among conventional antipsychotics, the risk of diabetes of lower potency antipsychotic cohort was significantly higher than that of the high potency cohort. Haloperidol is a high potency antipsychotic. The risk of diabetes for the haloperidol cohort was significantly lower than that of risperidone cohort, but not that of olanzapine or quetiapine cohorts.

The large number of antipsychotic-treated subjects in this database enabled us to estimate the risk of developing diabetes in cohorts comprising only of subjects who received antipsychotic as monotherapy. This avoids the confounding by concomitant antipsychotics.

Several hypotheses have been proposed for hyperglycemia emergent after initiation of antipsychotics. These include inhibition of insulin release by the direct effect of antipsychotics on calcium-dependent potassium channels of pancreatic islet cells[35], and a direct toxic or α_2-adrenergic receptor-mediated inhibition of the pancreatic islet cell receptors[36, 37]. As treatment-emergent weight gain is observed commonly among patients treated with atypical antipsychotic agents[38], increase in insulin resistance from drug-induced weight gain and obesity might account in part in increase in the incidence of type II diabetes. Potency in inducing weight gain, however, does not explain the lack of correlationship between diabetogenic potential of these drugs and their potential for inducing weight gain. Neither did weight gain explains satisfactory treatment-emergent hyperglycemia with markedly elevated plasma glucose levels indicative of insulin deficiency. Other mechanism proposed as cause of glucose dysregulation include a direct effect of serotonin (5-HT1A) receptor antagonism on insulin secretion.

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