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A retrospective cohort study of diabetes mellitus and antipsychotic treatment in the United States

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Abstract

Treatment-emergent diabetes mellitus (DM) has been described for conventional and atypical antipsychotics. In our study, antipsychotic prescription claims from AdvancePCS's database were used to identify patients starting antipsychotic monotherapy. The relative risk of developing DM was determined using prescription claims for antidiabetic agents in the following cohorts: AdvancePCS general patient population, combined conventional antipsychotics, and combined atypical antipsychotics. Cox proportional hazards regression was used to adjust for differences in age, gender, and duration of antipsychotic exposure between cohorts in the estimation of risk of developing diabetes. Hazard ratios for developing DM in the combined conventional, combined atypical, and individual conventional and atypical antipsychotic treatment cohorts were greater than the AdvancePCS general patient population cohort. An increased risk of developing diabetes compared with the AdvancePCS general patient population was observed during treatment with conventional or atypical antipsychotics.

*Keywords: A*ntipsychotics; Diabetes; Epidemiologic study

1. Introduction

Studies over several decades have suggested that diabetes mellitus (DM), impaired glucose tolerance, and insulin resistance are more common in patients with psychiatric disorders, including major mood disorders and schizophrenia, than in the general population [1–6]. Literature reports have associated treatment-emergent glucose intolerance with conventional antipsychotics [7–15] and atypical antipsychotics [16–23] in humans. This possibility has been supported also by animal studies, where chlorpromazine was shown to cause hyperglycemia in normal animals [24,25]. However, a role of neuroleptics in the development of DM has not been supported by all investigations [26,27] because higher than expected rates of insulin resistance and impaired glucose tolerance had been reported in patients with schizophrenia before the introduction of neuroleptics [28–32].

A number of recent studies have attempted to clarify whether the rate of diabetes is elevated in patients treated with antipsychotics. However, reports in the literature have consisted primarily of small case series and prevalence studies in relatively small population samples [33–36]. These studies have been marked by significant methodologic limitations, and the results have been largely inconclusive. Questions regarding the frequency of DM in patients treated with antipsychotics are most effectively answered in epidemiologic studies. Due to their large sample size and less rigorous exclusion criteria compared with prospective clinical trials, epidemiologic studies can accurately assess the frequency of relatively rare events and provide results that are more representative of the general population.

Recently, there has been increasing interest in the pharmacoepidemiology of antipsychotics and DM. Mahmoud et al [37] examined prescription claims data from two large mixed indemnity and managed health care plans in the United States and determined the hazard ratios (HR) for developing DM during exposure to antipsychotic medications. They identified treatment-emergent diabetes by prescription claims and ICD-CM-9 diagnostic criteria over a 2-year period, with 4- and 8-month prescreening periods before the initiation of antipsychotic therapy. They reported an increased risk of developing DM in patients exposed to high- and low-potency

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conventional antipsychotics, clozapine, and olanzapine. Another recent epidemiologic study by Caro et al retrospectively examined treatment-emergent diabetes during exposure to risperidone or olanzapine from prescription claims and physician diagnoses from the Régie de l'Assurance Maladie du Québec (RAMQ) [38]. The results of this study showed a greater incidence of DM for the olanzapine cohort (1.7%) as compared with the risperidone (1.5%) cohort. On the basis of a crude relative risk of 1.08 (95% confidence interval [CI] 0.89–1.31) and HR of 1.2 (95% CI 1.0–1.43), the authors concluded that the risk of developing diabetes was higher for patients treated with olanzapine than for those who had been treated with risperidone. The Mahmoud [37] and RAMQ [38] studies included patients in their cohorts who were taking more than one antipsychotic medication concurrently. To our knowledge, no large-scale, peer-reviewed epidemiologic study evaluating the potential association of diabetes with antipsychotic treatment has been published.

In the present retrospective cohort study, the AdvancePCS (Scottsdale, AZ) prescription claim database was used to identify large cohorts of patients treated with a single antipsychotic during a defined period of observation. The purpose of this study was to estimate the incidence and risk of developing DM among patients in the United States who received a single antipsychotic drug, irrespective of indication. Individual antipsychotic cohorts were compared with each other and with the AdvancePCS general patient population.

2. Methods

This is a retrospective cohort study that determined the risk of developing DM during antipsychotic treatment using prescription claim data from AdvancePCS, Inc. AdvancePCS processes over 300 million prescription claims per year for the over 50 million members covered by the over 2000 nationwide employers and managed care plans represented in this database. Most of these claims are submitted by pharmacies handling the outpatient prescription needs for this membership; however, some prescriptions are filled in long-term care settings. There was no difference among study groups in terms of how patients received their prescriptions. In this study, we followed patients who maintained coverage with AdvancePCS. Once a patient discontinued their coverage, they were censored in the data analyses. Approximately 15% of the AdvancePCS members are over 65, and the >65 group represents over 24% of AdvancePCS's patient population. As of 1997, 42% of the patients starting an antipsychotic prescription were covered by Medicaid. The data cut-off point for this study was August 31, 2000.

2.1. Study cohorts

Only subjects who were prescribed a single antipsychotic were included in the antipsychotic cohorts for this study, regardless of indication for antipsychotic therapy. For the purpose of this study, monotherapy refers only to antipsychotics and not to any other medications. The cohorts studied (1) a combined conventional antipsychotic cohort (comprised of subjects treated with all agents in this class), (2) a combined atypical antipsychotic cohort, (3) cohorts of individual antipsychotics (comprised of subjects treated with a particular agent [eg, the haloperidol cohort]), and (4) the AdvancePCS general patient population cohort. The general patient population cohort included all subjects who had made a prescription claim for any AdvancePCS-covered benefit during a 2-month enrollment window (1 January 2000 to 29 February 2000). They must not have made a claim for diabetes drug(s) for at least 12 months before enrollment. In addition, they must not have been dispensed an antipsychotic for at least 6 months before and 6 months after enrollment.

Antipsychotic agents included conventional antipsychotics (chlorpromazine, chlorprothixene, fluphenazine, haloperidol, loxapine, mesoridazine, perphenazine, pimozide, prochlorperazine, thioridazine, thiothixene, trifluoperazine, and triflupromazine) and atypical antipsychotics (clozapine, olanzapine, quetiapine, and risperidone).

The enrollment window for subjects in the antipsychotic cohorts was 1 December 1998 through 29 February 2000. Subjects who started therapy during this period and continued to be treated with the same single antipsychotic during this period were included in the antipsychotic cohorts. Only subjects who were eligible for prescription claims through the AdvancePCS system for at least 12 months before enrollment were included in any of the cohorts. There were no significant differences among the number of patients using a diabetes medication when comparing a 12-month pre-enrollment period versus a 24-month pre-enrollment period. Thus, for this study, the 12-month pre-enrollment period was used. The exclusion criteria applicable to all cohorts were (1) a pre-existing history of DM as evidenced by a prescription claim for any anti-diabetic medication during the 12-month period before enrollment, (2) a prescription claim for any antipsychotics within the 6-month period before enrollment date, (3) the absence of information on sex or the year of birth, and (4) being <18 years of age. For all antipsychotic cohorts, patients who received more than one antipsychotic during the evaluation period were excluded. Although the enrollment windows differ between the general patient population and the antipsychotic groups, age at the point of entry into the study was used as the reference age for each study subject for the data analysis. In addition, adjustments for age differences were addressed by including an age variable in the regression analyses.

2.2. Identification of incident cases of DM

New onset of DM during antipsychotic exposure was identified by claim(s) for any medication(s) indicated for the treatment of diabetes, regardless of the route of administration. For subjects in any cohort, the earliest date during the enrollment window that any given subject received an antipsychotic agent (in the case of antipsychotic cohorts) or a nonantipsychotic agent (in the case of the AdvancePCS gen-

eral patient population) was considered the enrollment date for that subject. To identify the timing of onset of new cases of DM, the date of the first antidiabetic agent prescribed after the enrollment date was considered the start of antidiabetic therapy. Each patient in the antipsychotic cohort was tracked for a new onset of DM from the enrollment date (ie, the start of antipsychotic therapy for the antipsychotic cohorts) to the time that the antipsychotic was discontinued for more than 15 days or until 31 August 2000 (the data set cut-off point), whichever came first. Thus, length of therapy was used as the dependent variable in the proportional hazards model.

2.3. Comparison of the risk of developing diabetes among cohorts

To compare the risk of developing DM among cohorts, incidence density and HRs were determined. Because the incidence of DM for antipsychotic cohorts might not be linearly related to time with more cases being experienced early, annualization of incidence density could inflate the true incidence. Also, differences in incidence between cohorts could be partially accounted for by differences in mean age, gender, and the amount of exposure to antipsychotics among cohorts. To control for these variables in the estimation of the risk of DM, the Cox proportional hazard regression was used to determine the HR of DM for antipsychotic cohorts relative to the AdvancePCS general patient population. Using the PHREG procedure in SAS, several proportional hazards models were created using various combinations of the following covariates: age (three categories), gender (two categories), and amount of exposure (five categories). The reference categories for these covariates, represented by zero in the model, were the 18 to 44 group for age and female patients for gender. Amount of exposure was viewed as continuous days of treatment determined from the date of first antipsychotic prescription filled and the last successive prescription(s) that was not separated by more than 15 days. Individual doses were determined for each subject by summing the product(s) of strength and number of tablets for the successive prescriptions and dividing that sum by the number of continuous days of treatment. Because these doses varied widely within and among the antipsychotic cohorts, subjects within a cohort were grouped into dose quartiles. Subjects in the AdvancePCS general patient population were assigned a fifth dose "quartile" with a value of zero. Age was also standardized into the 18 to 44, 45 to 64, and 65 years of age and older categories because these ranges correspond with those cited for the incidence of diabetes in the United States general population [39]. In addition, given the wide doses observed in the antipsychotic cohorts, the HRs of DM were determined for each dose quartile relative to the AdvancePCS general patient population. The HRs of DM between selected antipsychotic cohorts were also determined. The alpha level for staistical significance was 0.05.

3. Results

The characteristics of the antipsychotic cohorts studied are summarized in Table 1. Haloperidol, thioridazine, risperidone, and olanzapine were the most commonly prescribed agents in their respective antipsychotic classes in the AdvancePCS database. Compared with the AdvancePCS general patient population, patients in the combined conventional and combined atypical antipsychotic cohorts were older. Among individual antipsychotic cohorts, the average age of the haloperidol cohort was notably older, with almost two thirds of patients over 64 years of age. There were more women than men in all cohorts, with the exception of the clozapine cohort. The average duration of antipsychotic treatment, ranging from 67 to 137 days, was longer for the atypical antipsychotic cohorts.

Separate regression analyses were performed to determine the association between the covariates and the development of DM (Table 2). A significant HR for age was found for most cohorts (excluding the thioridazine and clozapine cohorts), and a significant HR for gender was found for the AdvancePCS

Table 1
Characteristics of cohorts studied

	AdvancePCS general patient	Conventional antipsychotic			Atypical antipsychotic				
Number of subjects in cohort	population 5,816,473	All agents 19,782	Haloperidol 8476	Thioridazine 3133	All agents 38,969	Clozapine 277	Olanzapine 13,863	Quetiapine 4196	Risperidone 20,633
Age distribution, y									
18–44, %	36.5	20.8	11.9	25.7	30.2	36.8	36.6	35.8	24.6
45–64, %	39.3	26.0	15.3	26.7	23.6	25.3	28.7	28.1	19.2
65 and older, %	24.2	53.2	72.8	47.7	46.3	37.9	34.7	36.0	56.2
Mean age, y	52	64	72	61	60	55	55	55	64
Male, %	37	44	41	38	38	53	39	37	37
Average duration of antipsychotic treatment, d (SD)	NA	67 (74)	68 (70)	76 (81)	90 (83)	137 (125)	89 (85)	89 (79)	90 (82)
Mean dose of antipsychotic, mg (SD)	NA	NA	2.5 (5.2)	43.9 (54.6)	NA	183.1 (198.6)	5.1 (4.2)	79.9 (96.7)	1.2 (1.0)

Table 2
Hazard ratio of diabetes mellitus for covariates in the proportional hazard regression model stratified by antipsychotic cohorts

Variable	HR	95% CI	*P* value
Conventional antipsychotic cohort (n = 19,782)			
Age 45–64 y[a]	2.4	1.5–3.9	0.0003
Age ⩾65 y[a]	3.4	2.2–5.3	⩽0.0001
Gender (male)[b]	1.0	0.8–1.2	0.8158
Haloperidol cohort (n = 8476)			
Age 45–64 y	4.5	1.3–15.2	0.0162
Age ⩾65 y	5.9	1.9–18.4	0.0025
Gender (male)	1.3	0.9–1.8	0.1218
Thioridazine cohort (n = 3133)			
Age 45–64 y	1.7	0.7–4.0	0.2061
Age ⩾65 y	2.1	1.0–4.5	0.0610
Gender (male)	0.8	0.5–1.4	0.4729
Atypical antipsychotic cohort (n = 38,969)			
Age 45–64 y	2.8	2.0–4.0	⩽0.0001
Age ⩾65 y	6.1	4.5–8.2	⩽0.0001
Gender (male)	1.3	1.1–1.6	0.0003
Clozapine cohort (n = 277)			
Age 45–64 y	3.0	0.3–33.6	0.3677
Age ⩾65 y	3.4	0.4–31.3	0.2716
Gender (male)	0.7	0.2–3.2	0.6497
Olanzapine cohort (n = 13,863)			
Age 45–64 y	2.6	1.5–4.5	0.0006
Age ⩾65 y	6.5	4.2–10.5	⩽0.0001
Gender (male)	1.3	1.0–1.8	0.0585
Quetiapine cohort (n = 4196)			
Age 45–64 y	1.0	0.3–2.9	0.9670
Age ⩾65 y	3.0	1.3–7.0	0.0095
Gender (male)	1.1	0.6–2.1	0.7649
Risperidone cohort (n = 20,633)			
Age 45–64 y	3.7	2.2–6.2	⩽0.0001
Age ⩾65 y	6.6	4.2–10.3	⩽0.0001
Gender (male)	1.3	1.1–1.7	0.0010
AdvancePCS general patient population cohort (n = 5,816,473)			
Age 45–64 y	3.4	3.3–3.5	⩽0.0001
Age ⩾65 y	4.0	3.9–4.2	⩽0.0001
Gender (males)	1.1	1.1–1.2	⩽0.0001

Abbreviations: HR, hazard ratio; CI, confidence interval.

[a] For all cohorts, age 18–44 used as reference group.

[b] For all cohorts, female gender used as reference group.

HR and 95% CI values were rounded to first decimal place except where such rounding obscured significance cut-off points.

general patient population, combined atypical antipsychotic, and risperidone cohorts. The gender effect was smaller than the age effect. Male gender was associated with a 30% increased risk of DM for the combined atypical antipsychotic cohort (P = 0.0003) and a 10% increased risk for the AdvancePCS general patient population cohort ($P \leqslant 0.0001$).

The incidence of diabetes per 1000 patient-years of antipsychotic treatment and the HR of diabetes of the various cohorts are shown in Table 3. Compared with the incidence density of the AdvancePCS general patient population, the incidences of diabetes during exposure to antipsychotics were several times higher. The Cox proportional hazards regression, adjusting for age, gender, and duration of antipsychotic exposure, showed that the risk of DM for the combined conventional and combined atypical antipsychotic cohorts was significantly higher than in the AdvancePCS general patient population. The HRs for all individual atypical antipsychotic cohorts (clozapine, olanzapine, risperidone, and quetiapine) were significantly higher than those of the AdvancePCS general patient population.

The risk of DM for the combined conventional cohort was not significantly different from that of the combined atypical cohorts (HR 0.97, CI 0.84–1.11; P = 0.626) (Table 4). No significant increase in the risk of DM was observed for the olanzapine (HR 1.09, CI 0.86–1.37; P = 0.479) or the clozapine (HR 1.31, CI 0.60–2.86; P = 0.496) cohort when compared with the haloperidol cohort. The number of patients in the clozapine cohort was small (n = 277) and lacked power to detect a significant difference in the HR ratio within the range of the HRs observed in the other antipsychotic cohorts. The risk of DM for the quetiapine cohort was lower than the risk for the haloperidol cohort (HR 0.67, CI 0.46–0.97; P = 0.033). The risk of DM in the risperidone cohort, relative to the haloperidol cohort, was 1.23 (CI 1.01–1.50; P = 0.040). When comparing the two largest atypical antipsychotic cohorts (olanzapine and risperidone), the HR was 0.90 (CI 0.76–1.07; P = 0.234).

The age- and gender-adjusted HRs for the dose quartiles relative to the AdvancePCS general patient population are displayed in Table 5. A positive dose relationship for the risk of DM was observed for the thioridazine cohort because the 95% CI of the first and fourth dose quartile did not overlap. A significant dose-response relationship was not observed in the atypical antipsychotic cohorts, with the possible exception of quetiapine. Although the HR of the quetiapine cohort was not statistically significant in the first dose quartile relative to the AdvancePCS general patient population (HR 1.8, CI 0.9–3.4; P = 0.096), the HR was statistically significant in the fourth dose quartile (HR 3.1, CI 1.9–5.1; $P \leqslant 0.0001$).

4. Discussion

This large pharmacoepidemiologic study examined at least two important questions: (1) Did patients on atypical agents experience a different risk of treatment-emergent diabetes than those on conventional antipsychotics? and (2) Were there clinically significant differences in the risks of diabetes between antipsychotics? Consistently, the HRs of all antipsychotic treatment cohorts studied were significantly higher than those of the AdvancePCS general patient population. Although the risk of DM was comparable between the combined conventional cohort and the combined atypical cohort, some significant differences were observed when pairwise comparisons were made between individual antipsychotics. Of the atypical antipsychotic cohorts, only the risperidone cohort was associated with a significantly greater risk of diabetes than the haloperidol cohort. Direct comparison of the olanzapine and risperidone cohorts indicated no significant difference in the risk of diabetes during treatment with these agents.

Table 3
Incidence and hazard ratio of diabetes mellitus in patients during treatment with antipsychotics

Cohort	New cases (*n*)	Patients (*n*)	Patient-years	Incidence (per 1000 patient-years)		HR[a]		
				Rate	95% CI	Ratio	95% CI	*P* value
Conventional antipsychotics								
All combined	307	19,782	3645.57	84	75–94	3.5	3.1–3.9	⩽0.0001
Haloperidol	133	8476	1568.39	85	70–100	3.1	2.6–3.7	⩽0.0001
Thioridazine	62	3133	654.28	95	71–119	4.2	3.2–5.5	⩽0.0001
Atypical antipsychotics								
All combined	641	38,969	9571.18	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	0.0070
Olanzapine	194	13,863	3374.57	58	49–66	3.0	2.6–3.5	⩽0.0001
Quetiapine	40	4196	1025.75	39	27–51	1.7	1.2–2.4	0.0020
Risperidone	400	20,633	5066.90	79	71–87	3.4	3.1–3.8	⩽0.0001
General patient population	45,513	5,816,473	2,908,236.5	15.7	15.5–15.8			

Abbreviations: CI, confidence interval; HR, hazard ratio.
[a] Cox proportional hazards regression analysis adjusted for age, gender, and duration of antipsychotic exposure.
HR and 95% CI values were rounded to the first decimal place except where such rounding obscured significance cut-off points.

For all antipsychotic cohorts, increasing age was a significant risk factor for DM. This finding is in keeping with well-established epidemiologic data indicating that the prevalence of diabetes increases with age [40], with an almost two-fold increase past age 49 [39]. Male gender was a significant predictor of increased risk of diabetes only for the combined atypical antipsychotic, the risperidone, and the AdvancePCS general patient population cohorts.

Factors related to diagnostic heterogeneity and illness severity may also underlie some of the findings in the dose quartile analysis. The antipsychotic cohorts included all subjects treated with antipsychotics, irrespective of diagnosis and illness severity. The fourth dose quartile in the antipsychotic cohorts contains patients who received the highest doses of antipsychotics that may define a subpopulation of more severely ill, diagnostically homogeneous patients. Compared with other psychiatric disorders commonly treated with antipsychotics, schizophrenic patients often require higher doses of antipsychotics. Thus, the risk of DM associated with the fourth dose quartile may be particularly relevant to patients with schizophrenia.

Recently, there have been a number of reports on the prevalence [36] or the risk [37,38] of DM in subjects treated with antipsychotics. Some of these reports have been limited by relatively small sample sizes, the concurrent use of multiple antipsychotic drugs in the cohorts, or the absence of a reference (control) population. Our study presents a number of strengths: (1) The sample sizes of cohorts were large; (2) only patients who were antipsychotic free for at least 6 months and who received only a single antipsychotic during the evaluation period were included in the antipsychotic cohorts, and thus the study was not confounded by antipsychotics that were recently or concurrently administered; and (3) the use of the AdvancePCS general patient population enabled us to compare the rates of developing DM relative with a reference population that was not exposed to antipsychotic medications.

The major limitation of this study was that psychiatric diagnostic information was not available in the database. Other limitations were that only incident cases of DM that resulted in intervention with antidiabetic medications were identified and that all indications for antipsychotic prescriptions were included, regardless of psychiatric illness spectrum or severity. Furthermore, the selection of a given antipsychotic reflects clinical choices rather than randomized assignment. Potentially, certain patient attributes that influence treatment selection might also affect likelihood of developing DM. While pharmacoepidemiological studies can control for some important factors (e.g., age), others cannot be addressed with available data (e.g., severity of illness); 3) the average duration of antipsychotic treatment was not long, ranging from 68 days to 137 days; 4) the database did not

Table 4
Hazard ratio of developing diabetes comparing other antipsychotic cohorts to the haloperidol cohort

Treatment cohort	New cases (*n*)	Subjects in cohort (*n*)	HR[a]		
			Ratio	95% CI	*P* value
Olanzapine	194	13,863	1.09	0.86–1.37	0.479
Risperidone	400	20,633	1.23	1.01–1.50	0.040
Quetiapine	40	4,196	0.67	0.46–0.97	0.033
Clozapine	7	277	1.31	0.60–2.86	0.496

Abbreviations: HR, hazard ratio; CI, confidence interval.
[a] Cox proportional hazards regression analysis adjusted for age, gender, and duration of antipsychotic exposure.
HR and 95% CI values were rounded to the first decimal place except where such rounding obscured significance cut-off points.
In the haloperidol cohort, there were 133 new cases in a total of 8476 patients.

Table 5
Hazard ratios for antipsychotic cohort dose quartiles relative to the AdvancePCS general patient population

Cohort	Mean dose/quartile (± SD)	Mean age (± SD)	HR[a]		
			Ratio	95% CI	*P* value
Conventional					
Haloperidol					
Q1	0.5 ± 0.3	77.1 ± 30.6	2.6	1.9–3.7	≤0.0001
Q2	0.9 ± 0.3	75.8 ± 31.5	2.9	2.0–4.2	≤0.0001
Q3	1.7 ± 0.7	72.6 ± 34.1	2.9	2.0–4.1	≤0.0001
Q4	7.0 ± 17.5	61.5 ± 39.5	4.3	3.1–5.9	≤0.0001
Thioridazine					
Q1	9.9 ± 6.3	66.1 ± 39.6	2.1	1.0–4.5	0.0453
Q2	20.1 ± 6.3	63.6 ± 38.8	3.0	1.7–5.4	≤0.0001
Q3	37.3 ± 14.4	60.2 ± 37.9	2.9	1.6–5.2	0.0005
Q4	110.8 ± 151.1	54.9 ± 37.0	8.9	6.2–12.7	≤0.0001
Atypical					
Olanzapine					
Q1	1.7 ± 0.9	60.1 ± 42.2	3.4	2.6–4.5	≤0.0001
Q2	3.1 ± 0.7	55.0 ± 41.0	2.6	1.9–3.6	≤0.0001
Q3	5.3 ± 2.0	53.4 ± 39.6	2.5	1.9–3.3	≤0.0001
Q4	11.3 ± 9.8	50.0 ± 37.1	3.6	2.8–4.7	≤0.0001
Risperidone					
Q1	0.4 ± 0.2	70.9 ± 40.6	3.7	3.0–4.5	≤0.0001
Q2	0.7 ± 0.1	65.1 ± 43.5	3.0	2.4–3.8	≤0.0001
Q3	1.1 ± 0.3	63.6 ± 43.0	3.0	2.5–3.7	≤0.0001
Q4	2.5 ± 2.4	56.0 ± 42.2	4.0	3.3–4.8	≤0.0001
Quetiapine					
Q1	17.0 ± 8.6	60.2 ± 40.7	1.8	0.9–3.4	0.0957
Q2	34.5 ± 11.3	57.1 ± 41.2	1.4	0.7–2.9	0.3347
Q3	64.5 ± 24.4	53.3 ± 37.8	0.6	0.2–1.8	0.3938
Q4	203.7 ± 245.1	49.8 ± 36.4	3.1	1.9–5.1	≤0.0001

Abbreviations: HR, hazard ratio; CI, confidence interval.
[a] Cox proportional hazards regression analysis adjusted for age and gender.
HR and 95% CI values were rounded to first decimal place except where such rounding obscured significance cut-off points.
The sample size of the clozapine cohort (277 subjects with 7 cases of diabetes mellitus) was too small for a meaningful quartile analysis.

contain information on well known risks for DM, including obesity, ethnic origin, or family history. Thus it was not possible to adjust for differences in these risk factors between cohorts; 5) the mean daily doses in antipsychotic cohorts were low. However, the dose quartile analysis showed that relatively higher doses were represented. Thus our findings can only be generalized to populations similar to that represented in the AdvancePCS database; 6) we did not account for exposure to other drugs that may be temporally associated with glucose dysregulation (e.g. protease inhibitors, thiazide diuretics and β-blockers). Therefore, if these drugs were not prescribed uniformly across the cohorts studied, the hazard ratio for developing diabetes may have been overestimated in individual cohorts containing patients prescribed these drugs.

Elevated HR during antipsychotic treatment may reflect a number of factors. While one possibility is an adverse glycemic effect of antipsychotics, other major considerations include (1) a vulnerability for DM which may be genetically or behaviorally linked to the disorder being treated; (2) an indirect medication effect, e.g., via an effect on diet or exercise; and (3) enhanced recognition of DM coinciding with the prescription of antipsychotic medication or illness severity, e.g., increased probability of detecting diabetes for patients who had more frequent contact with medical professionals due to their illness. These additional factors need to be taken into account in determining the risk of developing DM during treatment with antipsychotics. Further, given that differences in background incidence and risk factors for DM might exist between populations commonly treated with antipsychotics and the general population, comparisons between antipsychotic-treated cohorts and a reference population without psychosis may overestimate the potential effect of antipsychotics on the emergence of DM.

In conclusion, our study suggests that patients treated with either conventional or atypical antipsychotics may be at higher risks of developing DM than the AdvancePCS general patient population. The risk of developing diabetes was comparable between conventional and atypical antipsychotic cohorts. What remains unclear is to what extent the observed increases in incidence and risk of DM may be related to factors intrinsic or extrinsic to those psychiatric disorders commonly treated with antipsychotic drugs. Finally, though the potential morbidity and mortality related to DM is serious, it must be evaluated in the context of the significant morbidity and mortality associated with major psychiatric illnesses. Findings from the present study suggest that the decisions regarding the choice of antipsychotic for treat-

ing major psychiatric illness should not be based solely on the relatively modest differences in DM rates observed during treatment with these agents. In patients with schizophrenia as in the general population, consideration should be given to the presence of known risk factors for diabetes [41], including obesity and glucose intolerance and psychotropic therapy should be evaluated in the context of the patient's overall response and tolerability to therapy.

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