Retrospective Cohort Study of Diabetes Mellitus and Antipsychotic Treatment in a Geriatric Population in the United States

Peter D. Feldman, PhD, Linda K. Hay, PhD,† Walter Deberdt, MD, John S. Kennedy, MD, David S. Hutchins, MHSA, Donald P. Hay, MD, Thomas A. Hardy, MD, Vicki P. Hoffmann, PharmD, Kenneth Hornbuckle, DVM, PhD, MPH, and Alan Breier, MD

Objectives: The objective of this study was to investigate risk of diabetes among elderly patients during treatment with antipsychotic medications.

Design: We conducted a longitudinal, retrospective study assessing the incidence of new prescription claims for antihyperglycemic agents during antipsychotic therapy.

Setting: Prescription claims from the AdvancePCS claim database were followed for 6 to 9 months.

Participants: Study participants consisted of patients in the United States aged 60+ and receiving antipsychotic monotherapy. The following cohorts were studied: an elderly reference population (no antipsychotics: n = 1,836,799), those receiving haloperidol (n = 6481) or thioridazine (n = 1658); all patients receiving any conventional antipsychotic monotherapy (n = 11,546), clozapine (n = 117), olanzapine (n = 5382), quetiapine (n = 1664), and risperidone (n = 12,244), and all patients receiving any atypical antipsychotic monotherapy (n = 19,407).

Measurements: We used Cox proportional hazards regression to determine the risk ratio of diabetes for antipsychotic cohorts relative to the reference population. Covariates included sex and exposure duration.

Results: New antihyperglycemic prescription rates were higher in each antipsychotic cohort than in the reference population. Overall rates were no different between atypical and conventional antipsychotic cohorts. Among individual antipsychotic cohorts, rates were highest among patients treated with thioridazine (95% confidence interval [CI], 3.1– 5.7), lowest with quetiapine (95% CI, 1.3–2.9), and intermediate with haloperidol, olanzapine, and risperidone. Among atypical cohorts, only risperidone users had a significantly higher risk (95% CI, 1.05–1.60; $P = 0.016$) than for haloperidol. Conclusions about clozapine were hampered by the low number of patients.

Conclusion: These data suggest that diabetes risk is elevated among elderly patients receiving antipsychotic treatment. However, causality remains to be demonstrated. As a group, the risk for atypical antipsychotic users was not significantly different than for users of conventional antipsychotics. **(J Am Med Dir Assoc 2004; 5: 38–46)**

Keywords: Antipsychotics; diabetes mellitus; geriatrics; prescriptions; drug

Use of antipsychotic medications among the elderly is substantial, with as much as half of all repeat prescriptions for antipsychotics being accounted for by patients over age 65.[1] It has been estimated that 38% to 43% of all elderly patients residing in skilled care facilities receive antipsychotic medication,[2,3] although as many as 60% to 80% of elderly patients at facilities for the mentally ill could be receiving such treatment.[4,5] Fully 20% of the population aged 80 and older are affected by dementia,[6] and approximately one fourth to one half of these develop psychotic features that require the use of an antipsychotic agent.[7,8] In addition to being prescribed for this condition, however, a considerable proportion of antipsychotic prescriptions for the elderly are for use as a tranquilizer or anxiolytic.[9,10]

Use of conventional high-potency antipsychotics such as

†Deceased.
Lilly Research Laboratories, Indianapolis, IN (P.D.F., L.K.H., W.D., D.P.H., T.A.H., V.P.H.; K.H., A.B.); Indiana University School of Medicine, Indianapolis, IN (J.S.K.); and AdvancePCS, Inc., Scottsdale, AZ (D.S.H.).

Address correspondence to Peter D. Feldman, PhD, Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, IN 46285. E-mail: pdfeldman@lilly.com.

DOI: 10.1097/01.JAM.0000102962.50469.1F

haloperidol is associated with high levels of extrapyramidal symptoms,[11,12] to which elderly patients are particularly vulnerable.[13,14] In contrast, extrapyramidal symptoms in patients treated with atypical antipsychotics are less common.[15] Nevertheless, an issue has been raised recently regarding the safety of both conventional and atypical antipsychotics, as it has been suggested that their use could be associated with induction of insulin resistance and an increased risk of type 2 diabetes mellitus.[16–18] For example, one study[19] reports that 12% of patients treated with clozapine developed type 2 diabetes compared with a prevalence in the general population of 5.1%.[20] Some studies appear to associate the use of specific antipsychotic medications with a higher rate of new-onset hyperglycemia or type 2 diabetes.[16,17,19] This is still a point of controversy, however, because such studies have largely relied on case reports and chart reviews and might not accurately reflect the actual incidence of hyperglycemia among antipsychotic users relative to the general population, let alone the population of patients with mental illness. Moreover, the contribution of undiagnosed diabetes or impaired glucose tolerance among patients before their use of antipsychotics is unknown.[21] By contrast, other studies have concluded that antipsychotic use is merely coincidental to an underlying predisposition to diabetes among patients with schizophrenia.[22]

Many attempts to investigate the potential link between antipsychotic use and an increased risk of diabetes have been hampered by limited sample size, and studies have yielded largely inconclusive results. However, a recent analysis[21] has been conducted using a drug prescription claim database maintained by AdvancePCS (Scottsdale, AZ), the United States' largest health plan provider, with more than 75 million members linked to 58,000 pharmacies throughout the country. The analysis suggested that there is a statistically significant increase in the risk of diabetes during treatment with either conventional or atypical antipsychotics. However, large-scale studies of this sort that focus on an elderly population have received little attention. Accordingly, the current analysis was undertaken, using the AdvancePCS prescription claim database, to investigate the risk of diabetes among patients aged 60 and older who had been receiving either conventional or atypical antipsychotic medications.

METHODS

Study Design and Patient Sample

This longitudinal study was conducted retrospectively to compare the risk of new development of diabetes mellitus among selected antipsychotic cohorts drawn from the AdvancePCS prescription claim database. The validity and reliability of their prescription database has been verified independently. Over 300 million prescription claims per year are processed in this database for more than 50 million members covered by over 2000 managed care plans and employers. Most claims were submitted by pharmacies handling the outpatient prescription needs for these patients, although some prescriptions were filled in long-term care settings. Only patients who maintained coverage with AdvancePCS were followed; if patients discontinued their coverage, they were censored from the analysis. This analysis examines the data from patients aged 60 and older, amounting to a total patient sample of nearly two million patients. Because this was an examination of only the potential effects of exposure to antipsychotic medications, diagnostic information was not captured. Information regarding patients' ethnicity was also not available. For the purposes of this analysis, patients were examined both together as a single geriatric population (all patients aged ≥60 years) and stratified as two separate subgroups, a younger one consisting of patients aged 60 to 74 and an older one of patients aged 75 and older.

Inclusion/Exclusion Criteria

Patients who were qualified for prescription claims through AdvancePCS for the entire 12 months before enrollment were eligible for inclusion in the analysis. No obvious differences were seen in the number of patients using a diabetes medication when comparing a 12-month preenrollment period versus a 24-month preenrollment period; thus, the 12-month preenrollment period was used.[21] The exclusion criteria applicable to all cohorts included (1) a preexisting history of diabetes mellitus, as evidenced by a prescription claim for any antihyperglycemic medication during the 12-month period before enrollment; (2) a prescription claim for any antipsychotics within the 6-month period before the enrollment date; and (3) absence of information on sex or year of birth.

Cohort Studies

A "general patient population" cohort, consisting of all subjects who had made any AdvancePCS-covered prescription claim during a 2-month enrollment window (January 1 to February 29, 2000), was used as a standard reference population. Patients in the general population cohort must not have made a claim for any diabetes drug for at least 12 months before enrollment. In addition, they must not have received a prescription for an antipsychotic for at least 6 months before and 6 months after enrollment.

Only patients who were prescribed a single antipsychotic were included in the antipsychotic cohorts for this study, regardless of indication for antipsychotic therapy. The antipsychotic cohorts studied consisted of the following: (1) patients receiving haloperidol monotherapy; (2) patients receiving thioridazine monotherapy; (3) all patients receiving monotherapy with any single conventional antipsychotic, referred to as the "combined conventional antipsychotic" cohort; (4) patients receiving clozapine monotherapy; (5) patients receiving olanzapine monotherapy; (6) patients receiving quetiapine monotherapy; (7) patients receiving quetiapine monotherapy; (8) patients receiving risperidone monotherapy; and (9) all patients receiving monotherapy with any single atypical antipsychotic, referred to as the "combined atypical antipsychotic" cohort. Antipsychotic agents included both conventional antipsychotics (chlorpromazine, chlorprothixene, fluphenazine, haloperidol, loxapine, mesoridazine, molindone, perphenazine, pimozide, prochlorperazine, promazine, thioridazine, thiothixene, trifluoperazine, and triflupromazine) and atypical antipsychot-

ics (clozapine, olanzapine, quetiapine, and risperidone). Haloperidol and thioridazine were chosen as separate cohorts from among the conventional antipsychotics as a result of their sufficient numbers, whereas the remaining conventional antipsychotics individually formed less than 10% of the total prescriptions for typical antipsychotics, yielding cohorts that were too small for analysis. Clozapine was included as a separate cohort from among the atypical antipsychotics as a result of the intense focus it has received for a possible association with diabetes risk.

The enrollment window for subjects in the antipsychotic cohorts was December 1, 1998, through February 29, 2000. Subjects who started therapy during this period and continued treatment with the same single antipsychotic were included in the antipsychotic cohorts. Patients receiving antipsychotics were studied for as long as they had continuous therapy and did not terminate AdvancePCS coverage. The data cutoff point for this study was August 31, 2000. For all antipsychotic cohorts, patients who received more than one antipsychotic during the enrollment window were excluded. The earliest date during the enrollment window that any patient filed a prescription claim, either an antipsychotic agent in the case of the antipsychotic cohorts or a nonantipsychotic agent in the case of the general patient population, was considered the enrollment date for that subject.

Incidence of Diabetes Mellitus

New onset of diabetes mellitus during antipsychotic exposure was identified by claims for any medication indicated for the treatment of diabetes regardless of the route of administration. For the purposes of this analysis and of the language in this report, the incidence of new prescriptions for antihyperglycemic medications is equated with the incidence of new-onset diabetes without regard to clinicians' standards for diagnosis or choices of treatment. To identify the timing of onset of new cases of diabetes, the date of the first antihyperglycemic agent prescribed after the enrollment date was considered the start of antidiabetic therapy. Each patient in the antipsychotic cohort was tracked for new onset of diabetes from the enrollment date to the time that the antipsychotic was discontinued for more than 15 days, or until the data cutoff point, whichever came first.

Comparison of Risk Between Cohorts

To compare the risk of developing diabetes among cohorts, both incidence density and risk ratios were determined. Incidence of diabetes for antipsychotic cohorts might not be linearly related to time, with more cases being experienced earlier during treatment exposure. Annualization of incidence density might therefore be likely to inflate the true incidence. Also, differences in incidence between cohorts could be partially accounted for by differences in mean age, sex, and the amount of exposure to antipsychotics among cohorts. To control for these variables in the estimation of the risk of diabetes, the Cox proportional hazards regression was used to determine the risk ratio of diabetes for antipsychotic cohorts relative to the general AdvancePCS population, matching the antipsychotic cohort with the reference population by age ($\geq$60 years, 60–74 years, or $\geq$75 years). Several Cox proportional hazard models were analyzed with the "PHREG" (proportional hazards regression) procedure in SAS (Statistical Analysis Systems, SAS Institute, Cary, NC) using covariates for sex and duration of exposure. For comparisons of diabetic risk among the atypical antipsychotic treatment groups, the haloperidol cohort was used as a reference standard because of its status as the most widely used conventional antipsychotic agent. The alpha level for statistical significance was 0.05.

RESULTS

Observational Results

A total of 30,953 elderly outpatients who had received prescriptions for antipsychotic treatment were included in this analysis (Tables 1 and 2), and an additional 1,836,799 outpatients from the general population who had received prescriptions for other, nonantipsychotic medications were used as the standard for comparison. Prescriptions for atypical antipsychotic medications (Table 2) outnumbered those for conventional antipsychotics (Table 1) by nearly 70%. In terms of raw numbers of patients, relative rates of prescribing for the atypical agents were as follows: risperidone > olanzapine > quetiapine > clozapine. For conventional antipsychotic agents, prescription rates were highest for haloperidol, followed by thioridazine, and finally by all other conventional agents. It was noted that, in terms of chlorpromazine equivalents (doses converted to an equivalent daily dose of chlorpromazine, based on minimum effective doses[23]) and relative to dose recommendations for older patients with schizophrenia, the mean administered doses were low for thioridazine (36.1 mg chlorpromazine equivalents), risperidone (75.0 mg), quetiapine (87.2 mg), haloperidol (90.0 mg), and clozapine (90.3 mg), but moderate to high for olanzapine (165.0 mg). Mean durations of treatment were, for the most part, in the vicinity of 70 to 100 days. The one exception was clozapine, which was administered for a mean duration of over 140 days.

As shown in Tables 1 and 2, a higher proportion of patients in the older group of patients had prescriptions for antipsychotics compared with the younger group ($\geq$75 years: 21,742 patients compared with a corresponding general population of 690,545 patients, or an equivalent frequency of 32 per thousand; 60–74 years: 9211 of 1,146,254 patients, or an equivalent frequency of 8 per thousand). The older group of patients had a higher proportion of females relative to the younger subgroup, both overall and within each drug cohort, presumably reflecting age-related changes in demographics. Mean doses of each drug were lower among the older patients relative to their corresponding drug-matched younger counterparts. Mean treatment durations were much longer among the clozapine-treated patients relative to the other drug cohorts, both overall and within each of the two age subgroups.

Comparison of Antipsychotic Users and Nonusers

Compared with the general patient population of patients aged 60+ who received only nonantipsychotic prescriptions, an increased risk of development of diabetes was seen in every antipsychotic cohort (Table 3). The risk was lowest for the

Table 1. *Characteristics of Patients Receiving Conventional Antipsychotics versus the General Patient Population*

Characteristic	General Patient Population	Conventional Antipsychotics		
		All Agents	Haloperidol	Thioridazine
All patients, aged ≥60				
No. of subjects	1,836,799	11,546	6481	1658
Age, mean (SD)	72.1(8.3)	78.4(9.1)	80.8(8.4)	77.8(9.1)
Percent males	39.2	43.1	39.8	35.3
Treatment duration days (SD)		70.2(75.9)	68.5(69.8)	84.7(87.2)
Dose (mg/day)				
mean (SD)			1.8(3.4)	36.1(43.4)
CPZ equivalents			90.0	36.1
Patients aged 60–74				
No. of subjects	1,146,254	3778	1389	564
Age mean (SD)	66.7(4.4)	67.8(4.4)	68.6(4.4)	67.4(4.4)
Percent males	41.1	47.6	46.2	34.0
Treatment duration days (SD)		69.7(80.0)	67.4(71.4)	83.9(88.5)
Dose (mg/day)				
mean (SD)			2.7(6.0)	48.7(58.7)
CPZ equivalents			135.0	48.7
Patients aged ≥75				
No. of subjects	690,545	7768	5092	1094
Age mean (SD)	81.0(5.0)	83.5(5.7)	84.2(5.7)	83.1(5.6)
Percent Males	36.1	40.9	38.0	35.9
Treatment duration days (SD)		70.4(73.8)	68.8(69.4)	85.1(86.5)
Dose (mg/day)				
mean (SD)			1.5(2.3)	29.6(30.9)
CPZ equivalents			75.0	29.6

SD, standard deviation; CPZ, chlorpromazine.

quetiapine cohort, with patients nevertheless being approximately twice as likely to have received a new prescription for antihyperglycemic medication as patients in the general patient population, whereas patients receiving thioridazine had the greatest risk, being four times as likely to have received new antidiabetic treatment. Risk did not appear to be related to dose, however, because the two groups with the highest risk ratios, thioridazine and risperidone, were also associated with the lowest relative doses.

A comparison of patients within each of the stratified age groups (Table 3) showed the risk ratio (RR) among younger patients (60–74 years of age) to be highest for the risperidone (RR = 5.1) and haloperidol (RR = 5.0) cohorts. It should be pointed out, however, that the number of younger patients in the clozapine cohort was too low to permit a meaningful statistical analysis, and therefore no comparisons could be made regarding the risk ratio in patients treated with clozapine compared with the other antipsychotics. Among older patients (75+), diabetes risk was highest for the clozapine and thioridazine cohorts. In fact, older patients receiving clozapine had the highest risk of any subgroup, being 5.8 times as likely as older patients in the reference population to have received new antidiabetic treatment. This figure takes into account the longer duration of exposure in the clozapine cohort, because the Cox proportional hazards regression analysis was adjusted for duration of exposure as well as sex. However, this figure must nevertheless be regarded as tentative, again as a result of the large confidence interval associated with this small group of patients. Younger patients receiving quetiapine were unique in being the only subgroup not to have a significantly higher risk of diabetes (95% confidence interval [CI], 0.5–2.7; $P = 0.794$) than their age-matched general reference population; similarly, among older patients, quetiapine use was temporally associated with the lowest risk of any cohort compared with their age-matched general patient population.

Comparison of Atypical Antipsychotic Users and Conventional Antipsychotic Users

The risk for patients receiving prescriptions for atypical antipsychotics was not significantly different from that for patients taking conventional antipsychotics (Table 4). This was true for the overall patient sample (95% CI, 0.92–1.25; $P = 0.382$) and within each age-stratified group (aged 60–74: 95% CI, 0.74–1.22; $P = 0.686$; aged ≥75: 95% CI, 0.97–1.44; $P = 0.104$). For a comparison of diabetes risk among the different drug cohorts, risk ratios were calculated using the haloperidol drug cohort as the reference population (Table 4). Of the atypical antipsychotics, only the risperidone cohort had a significantly higher diabetes risk relative to haloperidol. This was seen both overall (95% CI, 1.05–1.60; $P = 0.016$) and among the older patients (95% CI, 1.05–1.75; $P = 0.019$). Among younger patients (60–74 years of age), the quetiapine cohort was again seen to have the lowest risk of diabetes, with an incidence rate

TABLE 2. *Characteristics of Patients Receiving Atypical Antipsychotics versus the General Patient Population*

Characteristic	General Patient Population	Atypical Antipsychotics				
		All Agents	Clozapine	Olanzapine	Quetiapine	Risperidone
All Patients aged ≥60						
No. of subjects	1,836,799	19,407	117	5382	1664	12,244
Age mean (SD)	72.1 (8.3)	79.2 (8.8)	75.2 (7.2)	77.4 (9.1)	76.9 (8.5)	80.4 (8.4)
Percent males	39.2	35.2	45.3	34.2	40.4	34.8
Treatment duration days (SD)		97.6 (89.8)	141.2 (124.3)	102.0 (96.1)	99.2 (86.9)	95.1 (86.6)
Dose (mg/day)						
mean (SD)			77.9 (120.9)	4.4 (3.8)	64.6 (83.5)	1.0 (0.8)
CPZ equivalents			90.3	165.0	87.2	75.0
Patients aged 60–74						
No. of subjects	1,146,254	5433	52	1961	619	2801
Age mean (SD)	66.7 (4.4)	68.1 (4.4)	68.6 (4.3)	67.7 (4.5)	68.0 (4.4)	68.5 (4.4)
Percent Males	41.1	38.7	48.1	38.0	42.2	38.2
Treatment duration days (SD)		91.4 (86.9)	149.0 (131.7)	93.9 (91.2)	95.9 (83.4)	87.7 (83.1)
Dose (mg/day)						
mean (SD)			114.0 (160.1)	5.1 (4.3)	75.8 (86.9)	1.2 (1.0)
CPZ equivalents			132.2	191.3	102.3	90.0
Patients aged ≥75						
No. of subjects	690,545	13,974	65	3421	1045	9443
Age mean (SD)	81.0 (5.0)	83.6 (5.7)	80.5 (3.9)	83.0 (5.7)	82.3 (5.3)	83.9 (5.7)
Percent males	36.1	33.8	43.1	32.1	39.4	33.8
Treatment duration days (SD)		100.0 (90.7)	135.0 (118.8)	106.6 (98.5)	101.1 (88.8)	97.3 (87.6)
Dose (mg/day)						
mean (SD)			49.1 (64.4)	4.0 (3.4)	58.0 (80.7)	0.9 (0.7)
CPZ equivalents			57.0	150.0	78.3	67.5

SD, standard deviation; CPZ, chlorpromazine.

in this younger subgroup of 0.97% and a risk ratio significantly lower than that of haloperidol. The older subgroup of quetiapine users, however, showed no significant difference from haloperidol. The risk ratio for the olanzapine group was not significantly different from that of the haloperidol reference group, either overall or in either age subgroup. Relative to the risperidone cohort, the olanzapine group had a risk ratio of 0.97 (95% CI, 0.76–1.24; $P = 0.814$). The risk for clozapine also was not different overall from that of the haloperidol reference group. In terms of incidence rates, however, clozapine had the highest percentage of new cases of diabetes, both overall (5 of 117 [4.27%]) and in the older subgroup (4 of 65 [6.15%]), but this must again be taken in the context of the low overall numbers of patients in the clozapine cohort.

DISCUSSION

This analysis is consistent with earlier reports that patients who receive antipsychotic medications could be at increased

Table 3. *Development of Diabetes Mellitus During Treatment With Antipsychotics, Relative to the General Population of the Same Age Group**

Cohort	All Patients (aged ≥60)			Patients (aged 60–74)			Patients (aged ≥75)		
	Risk Ratio	95% CI	*P* Value	Risk Ratio	95% CI	*P* Value	Risk Ratio	95% CI	*P* Value
Conventional antipsychotics									
All combined	3.6	3.1–4.1	<0.001	4.5	3.7–5.6	<0.001	3.2	2.7–3.8	<0.001
Haloperidol	3.2	2.7–3.9	<0.001	5.0	3.6–6.8	<0.001	2.8	2.2–3.5	<0.001
Thioridazine	4.2	3.1–5.7	<0.001	4.1	2.4–6.9	<0.001	4.3	3.0–6.3	<0.001
Atypical antipsychotics									
All combined	3.5	3.2–3.8	<0.001	4.1	3.5–4.8	<0.001	3.3	3.0–3.7	<0.001
Clozapine	3.1	1.0–9.5	0.051	†	†	†	5.8	1.9–17.8	0.002
Olanzapine	3.6	3.0–4.2	<0.001	3.8	2.9–5.0	<0.001	3.5	2.8–4.3	<0.001
Quetiapine	1.9	1.3–2.9	0.001	1.1	0.5–2.7	0.0794	2.5	1.6–3.9	<0.001
Risperidone	3.7	3.3–4.2	<0.001	5.1	4.2–6.3	<0.001	3.4	2.9–3.9	<0.001

* Cox proportional hazards regression analysis adjusted for sex and duration of exposure.
† Too few patients in cohort to yield meaningful comparison.
CI, confidence interval.

Table 4. *Development of Diabetes Mellitus Among Selected Antipsychotic Cohorts**

Cohort	No. of Patients in Cohort	New Cases No. (%)	Risk Ratio	95% CI	*P* Value
All patients (aged ≥60)					
All conventionals	11,546	238 (2.1)	(1.0)		
Haloperidol	6481	118 (1.8)	(1.0)		
All atypicals†	19,407	515 (2.7)	1.1	0.9–1.3	0.382
Clozapine‡	117	5 (4.3)	1.4	0.6–3.5	0.464
Olanzapine‡	5382	142 (2.6)	1.2	0.9–1.5	0.209
Quetiapine‡	1664	29 (1.7)	0.7	0.5–1.1	0.136
Risperidone‡	12,244	339 (2.8)	1.2	1.1–1.6	0.016
Patients aged 60–74					
All conventionals	3778	100 (2.7)	(1.0)		
Haloperidol	1389	39 (2.8)	(1.0)		
All atypicals†	5433	159 (2.9)	1.0	0.7–1.2	0.686
Clozapine‡	52	1 (1.9)	§	§	§
Olanzapine‡	1961	53 (2.7)	0.8	0.5–1.2	0.297
Quetiapine‡	619	6 (1.0)	0.3	0.1–0.7	0.003
Risperidone‡	2801	99 (3.5)	1.1	0.8–1.7	0.481
Patients aged ≥75					
All conventionals	7768	138 (1.8)	(1.0)		
Haloperidol	5092	79 (1.6)	(1.0)		
All atypicals†	13,974	356 (2.6)	1.2	1.0–1.4	0.104
Clozapine‡	65	4 (6.2)	§	§	§
Olanzapine‡	3421	89 (2.6)	1.3	1.0–1.8	0.065
Quetiapine‡	1045	23 (2.2)	1.1	0.7–1.7	0.807
Risperidone‡	9443	240 (2.5)	1.4	1.1–1.8	0.019

* Cox proportional hazards regression analysis adjusted for sex and duration of exposure.
† Versus all conventional antipsychotics.
‡ Versus haloperidol.
§ Too few patients in cohort to yield a meaningful comparison.
CI, confidence interval.

risk of hyperglycemia or diabetes mellitus. Even among the patients who received quetiapine, the cohort that had the lowest risk ratio of any of the antipsychotic cohorts, the likelihood of receiving a new prescription for antidiabetic treatment was seen to be nearly twice that of the general reference population of geriatric patients, whereas a greater than fourfold risk was seen among patients receiving thioridazine. In the middle of the spectrum of risk in our study were patients who received the remaining antipsychotics, consisting of, in descending order of risk, risperidone, olanzapine, and haloperidol. The results from the clozapine cohorts were inconclusive as a result of the considerably lower numbers of patients involved, which prevented a reliable assessment of clozapine's relative risk.

Further analysis of risk among the atypical antipsychotic cohorts, using the haloperidol cohort as the reference population, appeared to corroborate this relative order of risk, because quetiapine was uniquely found to have a significantly lower risk relative to the haloperidol cohort among younger patients (aged 60–74), whereas the risperidone cohort was uniquely found to have a significantly higher risk both overall and among the older patients (aged 75+). However, it is possible that this latter finding is simply a reflection of the substantially larger size of the patient cohort. In this analysis, the risk of diabetes in the olanzapine cohort was not significantly different from that of patients treated with haloperidol. This, in itself, is a noteworthy finding, because studies have reported an increased risk of diabetes[24,25] or glucose dysregulation[26] in patients treated with olanzapine compared with patients treated with haloperidol or other conventional antipsychotics. Clozapine had the highest risk ratio in the subgroup of patients aged 75 and older, on the order of nearly six times that of the reference population. However, the findings for clozapine throughout the rest of this analysis were inconclusive as a result of the small size of the clozapine cohort and low number of prescriptions for antihyperglycemic medications that were reported.

The prevalence of diabetes has been reported to be two to four times greater in patients with schizophrenia than in the general population,[27] and numerous analyses have concluded that patients with schizophrenia who receive antipsychotics, particularly the atypical antipsychotics, could have an increased risk of hyperglycemia.[17,28,29] For example, outpatients with schizophrenia who received atypical antipsychotics were, as a whole, 9% more likely to have an International Classification of Diseases, 9th revision, diagnosis of diabetes than those receiving conventional antipsychotics.[25] Moreover, patients receiving treatment with clozapine, olanzapine, or quetiapine have been reported to have significantly higher prevalences of diabetes relative to those receiving conventional antipsychotics, whereas patients receiving risperidone did not.[25] Glucose tolerance tests, too, have shown that

patients receiving clozapine, olanzapine, or risperidone could have higher plasma glucose levels than patients receiving haloperidol or chlorpromazine.[26] As a consequence, differences in diabetes medication prescription rates in this study could be the result of differences in the characteristics of the populations for which the antipsychotics were prescribed, for example, differences in the percentage of patients with schizophrenia or dementia.

Large-scale studies of the hypothesized link between diabetes and antipsychotic use have until recently been lacking. Many analyses that have been reported have relied on isolated case reports that are lacking matched controls of healthy subjects from the general population.[18,30–33] Such results have been largely inconclusive as a result of various methodologic limitations, and causality remains an issue. Previous analyses of information from claims databases typically have merely examined the overall incidence of diabetes, rather than the onset of new diagnoses of diabetes,[25] or have omitted use of a reference cohort of patients not receiving antipsychotics.[34] For their part, tests of glucose metabolism in patients receiving antipsychotics have typically used healthy, untreated control subjects but no healthy subjects exposed acutely to antipsychotics,[35] which might have provided information regarding the effect of the treatment itself rather than simply about differences between the patients being tested. Some have interpreted these results as indicative that antipsychotics themselves could induce hyperglycemia either through direct effects on pancreatic mechanisms[36] or secondarily through induction of body weight increases.[37] With respect to the latter, nearly all of the atypical antipsychotics have been reported to be associated with increased appetite and weight gain.[38] This appears to be an unlikely explanation of the changes occurring in the present analysis, because the incidence of weight gain in response to antipsychotic treatment among elderly patients, particularly those with dementia, tends to be overshadowed by a greater incidence of weight loss.[39,40] Moreover, weight gain is more highly associated with use of the atypical antipsychotics, whereas increased risk of hyperglycemia was also seen in the current analysis among patients receiving conventional antipsychotics. On the other hand, others have proposed that antipsychotics could merely exacerbate an underlying predisposition to diabetes in patients with schizophrenia[41]; alternatively, the use of antipsychotics could be entirely coincidental to a preexisting comorbidity for diabetes among the schizophrenic population.[22,42] The association between schizophrenia and diabetes was reported as early as the 1920s,[43] well before the development of modern antipsychotic medications, and it has been suggested that schizophrenia is itself the clinical manifestation of a metabolic disorder that can be thought of as "cerebral diabetes."[44] On the other hand, although there could be an association between the clinical condition of schizophrenia and risk of diabetes, the contribution of any schizophrenia-linked predisposition to hyperglycemia in the current analysis was likely to have been minimal, because neuroleptics are more frequently prescribed to the elderly for agitation or psychosis associated with dementia, not for schizophrenia.[9] Unfortunately, important information on patients' baseline glucose levels, underlying comorbidities, and risk factors was not available. As a result, the contribution of patients' preexisting conditions to the observed increases in the incidence of antihyperglycemic prescriptions is not known, and caution should certainly be exercised in equating "new" prescriptions for antihyperglycemic medications with the appearance of new-onset diabetes.

These findings extend the recent work of Buse and coworkers,[21] who reported the results of an analysis from the AdvancePCS database, of which the present results represent a subset. Their analysis involved 58,751 patients aged 18 and older who had received prescriptions for antipsychotics. The results of the present analysis largely reflect their findings in the broader patient population,[21] with higher risks occurring during treatment with all antipsychotics relative to the reference population but no difference in risk between conventional and atypical antipsychotics. Risk ratios for the various cohorts were quite similar between the two analyses, despite the differences in patient ages. Both studies showed the highest risk to be found in the thioridazine cohort and the lowest in the quetiapine cohort. One notable difference, however, was the finding by Buse that patients aged 65+ who received atypical antipsychotics had higher risks of diabetes than did patients aged 45 to 64, implying that, at least among patients receiving atypical agents, increasing age could be a risk factor for diabetes. By contrast, the present analysis showed that, for haloperidol and risperidone, the confidence intervals were in fact lower among patients aged ≥75 years than among those aged 60 to 74 years. It would appear, then, that any age-related increase in risk could have already reached a maximum by the time patients had entered their seventh decade of life. Alternatively, it could be that the older patients, having received considerably lower doses of antipsychotic, could merely have been exposed to a correspondingly lower risk of pharmacologically induced hyperglycemia. Both of these possibilities are, of course, entirely speculative. However, this latter hypothesis seems less likely, because weight increase with olanzapine and risperidone treatment appears uncorrelated with dose.[45] Moreover, hyperglycemic and euglycemic clamp studies failed to show a direct effect of risperidone or olanzapine on insulin production and/or sensitivity. Finally, it is likely that there are differences in the diagnostic mix of the two age groups, with the younger group containing a higher percentage of patients with schizophrenia and the older group containing a higher percentage of patients with dementia. Eventual differences in diabetes risk between these diagnostic groups could explain the differences between the two age groups.

A number of limitations of this analysis warrant mention. For example, no psychiatric diagnostic data were available, and no assessment was possible to determine the confounding effects of other nonantipsychotic drugs that could have hyperglycemic potential such as beta-adrenergic antagonists, thiazide diuretics, corticosteroids, or protease inhibitors.[46] In addition, no data were available on patients' baseline body mass index or family histories of diabetes, which might have provided crucial information regarding preexisting risk, and patients were not systematically randomized to their drug

cohort; rather, assignments were made based on the clinical choices of attending physicians. Finally, treatment exposures were of limited duration, lasting for the most part for just 2½ to 3 months. These relatively short treatment-exposure periods may not have been sufficient to fully evaluate potential treatment effects, although some reports have suggested that the majority of cases of new-onset diabetes incurred during treatment with antipsychotics occur within 3 to 6 months.[32,47,48] The short period in which an acute need for antihyperglycemic medications does appear to increase in the present analysis is therefore somewhat surprising. One explanation could be that the development of hyperglycemia is not entirely the result of the administration of antipsychotic agents, but could in fact be the result of a threshold effect in an already impaired patient population. Possibly ameliorating some of the concerns over the limitations of this analysis is the fact that it involved nearly 31,000 antipsychotic-treated patients and a control population of nearly two million patients, and it might therefore be reasonably expected that, with such a large sample, a fair degree of balancing took place between drug cohorts for such possible risk factors as obesity, family histories of diabetes, and the relative proportions of the different conditions for which these medications were being prescribed.

CONCLUSION

These data indicate that the incidence of new cases of diabetes could be higher among elderly patients who receive prescriptions for antipsychotic medications than among those not receiving antipsychotics. The risk of developing diabetes was highest overall for patients treated with thioridazine. Risk in the overall atypical antipsychotic cohort was not significantly higher than that for the overall conventional antipsychotic cohort. Among the individual atypical antipsychotic cohorts, the risperidone group's risk uniquely was significantly higher than haloperidol's. In conclusion, the risk of diabetes could be higher for patients using any antipsychotic, and clinicians must be cognizant of it, regardless of the antipsychotic selected.

ACKNOWLEDGMENTS

This study was sponsored by Eli Lilly and Company. This article is dedicated to Dr. Linda K. Hay in memory of her many contributions to geriatric psychiatry.

REFERENCES

1. Thacker S, Jones R. Neuroleptic prescribing to the community elderly in Nottingham. Int J Geriatr Psychiatry 1997;12:833–837.
2. Ray WA, Federspiel CF, Schaffner W. A study of antipsychotic drug use in nursing homes: Epidemiological evidence suggesting misuse. Am J Public Health 1980;70:485–491.
3. Svarstad BL, Mount JK. Nursing home resources and tranquilizer use among the institutionalized elderly. J Am Geriatr Soc 1992;39:869–875.
4. Prien RF, Haber PA, Caffey EM Jr. The use of psychoactive drugs in elderly patients with psychiatric disorders: Survey conducted in twelve Veterans Administration hospitals. J Am Geriatr Soc 1975;23:104–112.
5. Segal SP, Cohen D, Marder SR. Neuroleptic medication and prescription practices with sheltered-care residents: A 12-year perspective. Am J Public Health 1992;82:846–852.
6. Gurland BJ, Cross PS. Epidemiology of psychopathology in old age: some implications for clinical services. Psychiatr Clin North Am 1982;5:11–26.
7. Cohen-Mansfield J, Taylor L, Werner P. Delusions and hallucinations in an adult day care population. Am J Geriatr Psychiatry 1998;6:104–121.
8. Drevets WC, Rubin EH. Psychotic symptoms and the longitudinal course of senile dementia of the Alzheimer's type. Biol Psychiatry 1989;25:39–48.
9. Fombonne E, Mousson F, Dassonville B, et al. A study of prescriptions for psychotropic drugs at a French psychiatric hospital [in French]. Rev Epidemiol Sante Publique 1989;37:29–36.
10. Garrard J, Makris L, Dunham T, et al. Evaluation of neuroleptic drug use by nursing home elderly under proposed Medicare and Medicaid regulations. JAMA 1991;265:463–467.
11. Auchus AP, Bissey-Black C. Pilot study of haloperidol, fluoxetine, and placebo in Alzheimer's disease. J Neuropsychiatry Clin Neurosci 1997;9:591–593.
12. Devanand DP, Marder K, Michaels KS, et al. A randomized, placebo-controlled dose-comparison trial of haloperidol for psychoses and disruptive behaviors in Alzheimer's disease. Am J Psychiatry 1998;155:1512–1520.
13. Caligiuri MP, Rockwell E, Jeste DV. Extrapyramidal side effects in patients with Alzheimer's disease treated with low-dose neuroleptic medication. Am J Geriatr Psychiatry 1998;6:75–82.
14. Caligiuri MP, Lacro JP, Jeste DV. Incidence and predictors of drug-induced Parkinsonism in older psychiatric patients treated with very low doses of neuroleptics. J Clin Psychopharmacol 1999;19:322–328.
15. Frenchman IB, Prince T. Clinical experience with risperidone, haloperidol, and thioridazine for dementia-associated behavioral disturbances. Int Psychogeriatr 1997;9:431–435.
16. Lindenmayer JP, Nathan AM, Smith RC. Hyperglycemia associated with the use of atypical antipsychotics. J Clin Psychiatry 2001;62(suppl 23):30–38.
17. Wirshing DA, Spellberg BJ, Erhart SM, et al. Novel antipsychotics and new onset diabetes. Biol Psychiatry 1998;44:778–783.
18. Rigalleau V, Gatta B, Bonnaud S, et al. Diabetes as a result of atypical anti-psychotic drugs—A report of three cases. Diabet Med 2000;17:484–486.
19. Hagg S, Joelsson L, Mjörndal T, et al. Prevalence of diabetes and impaired glucose tolerance in patients treated with clozapine compared with patients treated with conventional depot neuroleptic medications. J Clin Psychiatry 1998;59:294–299.
20. Harris MI, Flegal KM, Cowie KC, et al. Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in US adults. Diabetes Care 1998;21:518–524.
21. Buse J, Cavazzoni P, Hornbuckle K, et al. A retrospective cohort study of diabetes mellitus and antipsychotic treatment in the United States. J Clin Epidemiol 2003;56:164–170.
22. Dvirskii AA. The reciprocally modifying effect of schizophrenia and diabetes mellitus on their phenotypic manifestations [in Russian]. Tsitol Genet 1997;31:67–70.
23. Taylor D, McConnell D, McConnell H, et al. The Bethlem & Maudsley National Health Service Trust Prescribing Guidelines. London: Martin Dunitz; 1999.
24. Koro CE, Fedder DO, L'Italien GJ, et al. Assessment of independent effect of olanzapine and risperidone on risk of diabetes among patients with schizophrenia: Population based nested case-control study. BMJ 2002;325:243–247.
25. Sernyak MJ, Leslie DL, Alarcon RD, et al. Association of diabetes mellitus with use of atypical neuroleptics in the treatment of schizophrenia. Am J Psychiatry 2002;159:561–566.
26. Hedenmalm K, Hägg S, Ståhl M, et al. Glucose intolerance with atypical antipsychotics. Drug Saf 2002;25:1107–1116.
27. Keskiner A, el-Toumi A, Bousquet T. Psychotropic drugs, diabetes, and chronic mental patients. Psychosomatics 1973;14:176–181.
28. Goldstein LE, Sporn J, Brown S, et al. New-onset diabetes mellitus and diabetic ketoacidosis associated with olanzapine treatment. Psychosomatics 1999;40:438–443.

29. Ober SK, Hudak R, Rusterholtz A. Hyperglycemia and olanzapine. Am J Psychiatry 1999;156:970.
30. Bettinger TL, Mendelson SC, Dorson PG, et al. Olanzapine-induced glucose dysregulation. Ann Pharmacother 2000;34:865–867.
31. Domon SE, Cargile CS. Quetiapine-associated hyperglycemia and hypertriglyceridemia. J Am Acad Child Adolesc Psychiatry 2002;41:495–496.
32. Koller EA, Doraiswamy PM. Olanzapine-associated diabetes mellitus. Pharmacotherapy 2002;22:841–852.
33. Sobel M, Jaggers ED, Franz MA. New-onset diabetes mellitus associated with the initiation of quetiapine treatment. J Clin Psychiatry 1999;60: 556–557.
34. Lund BC, Perry PJ, Brooks JM, et al. Clozapine use in patients with schizophrenia and the risk of diabetes, hyperlipidemia, and hypertension. Arch Gen Psychiatry 2001;58:1172–1176.
35. Newcomer JW, Haupt DW, Fucetola R, et al. Abnormalities in glucose regulation during antipsychotic treatment of schizophrenia. Arch Gen Psychiatry 2002;59:337–345.
36. Melkersson K, Khan A, Hilding A, et al. Different effects of antipsychotic drugs on insulin release in vitro. Eur Neuropsychopharmacol 2001;11:327–332.
37. Wirshing DA, Wirshing WC, Kysar L, et al. Novel antipsychotics: Comparison of weight gain liabilities. J Clin Psychiatry 1999;60:358–363.
38. Allison DB, Mentore JL, Heo M, et al. Antipsychotic-induced weight gain: A comprehensive research synthesis. Am J Psychiatry 1999;156: 1686–1696.
39. Street JS, Clark WS, Gannon KS, et al. Olanzapine treatment of psychotic and behavioral symptoms in patients with Alzheimer's disease in nursing care facilities: A double-blind, randomized, placebo-controlled trial. The HGEU Study Group. Arch Gen Psychiatry 2000;57:968–976.
40. Street JS, Clark WS, Kadam DL, et al. Long-term efficacy of olanzapine in the control of psychotic and behavioral symptoms in nursing home patients with Alzheimer's dementia. Int J Geriatr Psychiatry 2001;16: S62–S70.
41. Mukherjee S, Roth SD, Sandyk R, et al. Persistent tardive dyskinesia and neuroleptic effects on glucose tolerance. Psychiatry Res 1989;29:17–27.
42. Mukherjee S, Decina P, Bocola V, et al. Diabetes mellitus in schizophrenic patients. Compr Psychiatry 1996;37:68–73.
43. Kasanin J. The blood sugar curve in mental disease. Arch Neurol Psychiatry 1926;16:414–419.
44. Holden RJ, Mooney PA. Schizophrenia is a diabetic brain state: An elucidation of impaired neurometabolism. Med Hypotheses 1994;43: 420–435.
45. Basson BR, Kinon BJ, Taylor CC, et al. Factors influencing weight change in patients with schizophrenia treated with olanzapine versus haloperidol or risperidone. J Clin Psychiatry 2001;62:231–238.
46. Luna B, Feinglos MN. Drug-induced hyperglycemia. JAMA 2001;286: 1945–1948.
47. Koller E, Schneider B, Bennett K, et al. Clozapine-associated diabetes. Am J Med 2001;111:716–723.
48. Koller EA, Doraiswamy PM, Cross JT. Risperidone-associated diabetes. Presented at the 84th Annual Meeting of the Endocrine Society; June 19-22, 2002; San Francisco, CA.