

Incidence of New-Onset Diabetes Mellitus Among Patients Receiving Atypical Neuroleptics in the Treatment of Mental Illness

Evidence From a Privately Insured Population

Edward Alan Miller, PhD, MPA,* Douglas L. Leslie, PhD,†‡ and Robert A. Rosenheck, MD†‡

Abstract: The purpose of this study is to determine sociodemographic, clinical, and pharmacotherapeutic characteristics, especially use of atypical antipsychotics, associated with incident diabetes mellitus in a population of privately insured patients with mental health diagnoses. Patients with a mental health diagnosis stably medicated for a 3-month period during January 1999 through October 2000 and having no diabetes were followed through December 2000. Cox proportional hazards models were developed to identify antipsychotic medications associated with newly diagnosed diabetes. Of the 7381 patients identified, 339 developed diabetes, representing an annual incidence rate of 4.7%. Diabetes risk among the entire sample was lowest for risperidone (hazard ratio [HR] = 0.69; $p < 0.05$), while quetiapine (HR = 0.74), olanzapine (HR = 0.95), and clozapine (HR = 1.22) were not significantly different from first-generation antipsychotics. Diabetes risk was significantly lower among males receiving risperidone (HR = 0.49; $p < 0.01$) or quetiapine (HR = 0.50; $p < 0.10$), while diabetes risk among females did not differ significantly from first-generation antipsychotics for any atypical examined. These findings are substantially different from other reports.

Key Words: Antipsychotic agents, psychopharmacology, diabetes mellitus, risk factors, comparative study.

(*J Nerv Ment Dis* 2005;193: 387–395)

*A. Alfred Taubman Center for Public Policy and American Institutions, Brown University, Providence, Rhode Island; †VA-Connecticut Mental Illness Research, Education and Clinical Center, West Haven, Connecticut; and the ‡Departments of Psychiatry and Epidemiology and Public Health, Yale University School of Medicine, New Haven, Connecticut. Supported in part by the Department of Veterans Affairs and the National Institute of Mental Health Training Program.

Send reprint requests to Edward Alan Miller, PhD, MPA, Taubman Center for Public Policy, Brown University, 67 George Street, Providence, RI 02912.

Copyright © 2005 by Lippincott Williams & Wilkins
ISSN: 0022-3018/05/19306-0387
DOI: 10.1097/01.nmd.0000165292.11527.16

Pharmacotherapy is the foundation of effective treatment of schizophrenia. Atypical antipsychotic medications, including clozapine (Kane et al., 1988), olanzapine (Tollefson et al., 1997), quetiapine (Small et al., 1997), risperidone (Marder and Meibach, 1994), ziprasidone (Goff et al., 1998), and aripiprazole (Kane et al., 2002) have been found to be as effective as first-generation antipsychotics, with substantially fewer extrapyramidal side effects (Stahl, 1999). However, there is some evidence to suggest that these medications have other side effects, such as weight gain and increased risk of diabetes mellitus (DM), which have been associated with the use of clozapine (Bustillo et al., 1996; Cohen et al., 1990; Gianfrancesco et al., 2002; Henderson et al., 2000; Lamberti et al., 1992), olanzapine (Allison et al., 1999; Fertig et al., 1998; Koro et al., 2002; Ober et al., 1999; Wirshing et al., 1998), and quetiapine (Sobel et al., 1999). Other studies suggest that there might be a link between atypical antipsychotics and diabetic ketoacidosis (Jin et al., 2002; Lafayette et al., 2003; Ragucci and Wells, 2001; Straker et al., 2002; Tavakoli and Arguisola, 2003; Wheeler, 2003; Wilson et al., 2003). There is also some concern that weight gain and increased risk of DM may be a class effect of all atypical antipsychotics (Burton, 2003; Goode, 2003), which led the Food and Drug Administration to update the labeling requirements for these medications to include information about the potential for hyperglycemia and its related symptoms (Rosack, 2003). However, there is little evidence to link risperidone with DM (Feldman, 2003; Fuller et al., 2004; Gianfrancesco et al., 2002; Koro et al., 2002), and the newer atypical drugs, ziprasidone and aripiprazole, appear not to cause significant weight gain (Keck and McElroy, 2003; Marder et al., 2003; Potkin et al., 2003; Taylor and McAskill, 2000). Much of the evidence linking clozapine, olanzapine, and quetiapine to weight gain and DM consists of case reports and studies involving relatively small samples (Allison et al., 1999; Bustillo et al., 1996; Cohen et al., 1990; Fertig et al., 1998; Gianfrancesco et al., 2002; Henderson et al., 2000;

Koro et al., 2002; Lamberti et al., 1992; Ober et al., 1999; Sobel et al., 1999; Wirshing et al., 1998), although a few studies using large sample sizes have recently been published (Leslie and Rosenheck, 2004; Sernyak et al., 2002).

While few published studies have examined DM prevalence among patients with schizophrenia (Wheeler, 2003) or risk of new-onset DM or DKA (Gianfrancesco et al., 2003; Wilson et al., 2003), only one study has reported the DM incidence rates in this population (Leslie and Rosenheck, 2004). Using administrative data from the Department of Veterans Affairs (VA), in particular, this recent study found that 7.3% of patients with schizophrenia initially stable on an antipsychotic medication were diagnosed with DM during follow-up, for an annual incidence rate of 4.4%. Whereas patients on clozapine (hazard ratio [HR] = 1.57) and olanzapine (HR = 1.15; $p < 0.05$ for both) exhibited significantly higher risk of developing diabetes than patients on first-generation antipsychotics, patients on quetiapine (HR = 1.20) and risperidone (HR = 1.01) were not significantly different. The attributable risk of DM associated with atypicals was small, however, ranging from 0.05% (risperidone) to 2.03% (clozapine).

In an effort to understand better the risks of new-onset DM among patients prescribed antipsychotic medications, we sought to replicate this VA study in a privately insured population. Comparing the results of similar studies across public sector and privately insured populations is instructive given differences in financing, service delivery, and the populations served (Leslie and Rosenheck, 2000). To examine whether the use of atypical antipsychotics increases the risk of new-onset DM among privately insured patients as they did with VA patients, the goals of the present study were (1) to determine the proportion of privately insured patients with a mental health diagnosis initially stable on an antipsychotic medication who developed DM, and (2) to identify patient demographic, clinical, and pharmacological characteristics associated with these adverse events. In light of considerable off-label use of antipsychotic medications for psychiatric illnesses other than schizophrenia (Rosenheck et al., 2001), we expand the sample in this study to include any mental health patient receiving an antipsychotic.

METHODS

Data for this study come from MEDSTAT's Market-Scan database, which compiles claims information for individuals nationwide who are privately-insured through the benefit plans of large employers. The covered individuals include employees, their dependents, and early retirees of companies who participate in the database. MEDSTAT collects the claims data, standardizes and combines them, and then reports back to the firms who participate. The database contains information for over 2.5 million covered lives between 1999 and 2000. These claims data are collected from

over 200 different insurance companies, including Blue Cross and Blue Shield plans and third-party administrators.

We identified patients with a mental health diagnosis who were stable on an antipsychotic regimen for any 3-month period between January 1999 and October 2000 following the first prescription for an antipsychotic medication. Patients were identified as stable on an antipsychotic regimen if they received at least 30 days' worth of prescriptions for the same agent during the 3-month period, although the dose could change. Patients could be stable in any 3-month interval during January 1999 to October 2000.

Patients were defined as having a mental health diagnosis if they had any claims with an ICD-9 code in the range of 290.00 to 312.99 or 331.00 to 331.99, excluding 305.1 (tobacco use disorder). Any claim with a diagnosis within this range of ICD-9 values was considered a mental health claim, regardless of whether care was received in an inpatient or outpatient setting. Like the VA study, we had initially considered focusing exclusively on patients diagnosed with schizophrenia. Because we could identify fewer than 1000 individuals with schizophrenia who were stable on an antipsychotic regimen, we chose to expand our criteria to include individuals with other mental health diagnoses. If we had limited our study to patients with schizophrenia, we would have excluded most individuals receiving antipsychotic medications during the period studied.

We defined five groups of antipsychotic medications: clozapine, risperidone, olanzapine, quetiapine, and all first-generation antipsychotics. Ziprasidone and aripiprazole were not included in the study because they were only recently approved for use, and very few patients received these drugs during the study period. First-generation antipsychotics were lumped together as a group because years of experience with these medications have shown that they are not significantly different from each other in their risk of DM, and to be consistent with the VA study (Leslie and Rosenheck, 2004). Although some patients in the sample received prescriptions for multiple antipsychotic medications in the 3 months following first prescription of an antipsychotic (polypharmacy), they were not considered to be stable on a medication regimen and were excluded from the analysis.

Outpatient and inpatient claims were checked for existing DM in all visits back to January 1, 1999, preceding the 3-month stable period. Patients with any claims for DM (ICD-9 codes 250.00–250.99) were also excluded from the sample. Stable patients with no history of DM were followed through December 31, 2000. Patients with a diagnosis of DM during the follow-up period were identified, along with the date of the first diagnosis of DM.

Cox proportional hazards models were used to model the time to DM diagnosis. Independent variables included in the models were antipsychotic agent prescribed during the stable period, age, gender, mental health diagnoses, and

clinical comorbidity. Mental health diagnoses were based on ICD-9 diagnostic codes and included the following: adjustment reaction, anxiety disorder, dementia or Alzheimer disease, bipolar disorder, dysthymia, major depression, psychosis other than schizophrenia, posttraumatic stress disorder, personality disorder, schizophrenia, substance abuse, and other mental health disorders. Clinical comorbidity is measured using a weighted index developed by Charlson et al. (1987) and adapted for use with ICD-9 administrative databases by Deyo et al. (1992).

RESULTS

We identified 7381 patients who were stable on an antipsychotic medication. Characteristics of these patients are presented in Table 1. The average age of patients in the sample was 40.4 years, and 43% were male. The most common medication on which patients were stable was risperidone (35%), followed by first-generation antipsychotics and olanzapine (27% each), quetiapine (10%), and clozapine

(1%). Particular agents received by patients on first-generation antipsychotics were perphenazine (25.6%), haloperidol (15.5%), thioridazine (14.2%), prochlorperazine (12.6%), thiothixene (9.4%), trifluoperazine (7.5%), chlorpromazine (6.4%), fluphenazine (3.7%), loxapine (2.5%), mesoridazine (1.3%), and molindone (1.1%). The most common mental health diagnoses were major depression (47%), dysthymia (36%), bipolar disorder (28%), and anxiety disorder (25%). Only 17% were diagnosed with schizophrenia. Patients exhibited little clinical comorbidity, as indicated by an average score of 0.5 on the index used.

Overall, 339 patients (4.6%) contracted diabetes during the follow-up period, representing an annual incidence rate of 4.7%. Table 1 reports comparisons of patient characteristics according to whether the patient eventually contracted DM. Patients who developed new-onset DM were significantly older ($p < 0.0001$) and were more often prescribed a first-generation antipsychotic ($p < 0.0001$) and less often prescribed risperidone ($p < 0.0001$) and quetiapine ($p = 0.04$).

TABLE 1. Characteristics of the Sample

Variable	Overall (N = 7381)		Patients who eventually were diagnosed with diabetes (N = 339)		Patients who did not contract diabetes (N = 7042)		t statistic or χ^2 statistic	df	p
	N	%	N	%	N	%			
Age ^a	40.4	16.8	51.5	10.9	39.9	16.8	-18.54	420	<0.0001
Male gender	3176	43%	130	38.3%	3046	43.3%	3.1764	1	0.0747
Stable medication									
First generation	1981	27%	145	42.8%	1836	26.1%	45.9413	1	<0.0001
Clozapine	84	1%	7	2.1%	77	1.1%	2.7129	1	0.0995
Olanzapine	1986	27%	93	27.4%	1893	26.9%	0.0501	1	0.8229
Quetiapine	775	10%	24	7.1%	751	10.7%	4.4232	1	0.0355
Risperidone	2555	35%	70	20.6%	2485	35.3%	30.6248	1	<0.0001
Mental health diagnoses									
Adjustment reaction	878	12%	38	11.2%	840	11.9%	0.1595	1	0.6896
Anxiety disorder	1836	25%	78	23.0%	1758	25.0%	0.6619	1	0.4159
Alzheimer disease/dementia	568	8%	35	10.3%	533	7.6%	3.4575	1	0.0630
Bipolar disorder	2084	28%	110	32.4%	1974	28.0%	3.1135	1	0.0776
Dysthymia	2623	36%	97	28.6%	2526	35.9%	7.4352	1	0.0064
Major depression	3467	47%	158	46.6%	3309	47.0%	0.0189	1	0.8906
Other psychosis	858	12%	22	6.5%	836	11.9%	9.1192	1	0.0025
PTSD	291	4%	17	5.0%	274	3.9%	1.0786	1	0.2990
Personality disorder	297	4%	13	3.8%	284	4.0%	0.0329	1	0.8561
Substance abuse	613	8%	26	7.7%	587	8.3%	0.1884	1	0.6642
Schizophrenia	954	13%	76	22.4%	878	12.5%	28.4559	1	<0.0001
Other mental health disorders	1253	17%	48	14.2%	1205	17.1%	2.0002	1	0.1573
Clinical comorbidity ^a	0.5	1.3	1.1	1.9	0.5	1.3	-5.83	354	<0.0001

^aStatistics presented for these variables are mean and SD instead of N and %.

Patients who contracted DM were more often diagnosed with schizophrenia ($p = <0.0001$), had more comorbid medical conditions ($p < 0.0001$), and were less often diagnosed with dysthymia ($p = 0.0064$) and psychoses other than schizophrenia ($p = 0.0025$).

Table 2 reports the results from the Cox proportional hazards model predicting time to DM onset. With respect to the effect of antipsychotic medication, the lowest risk of new-onset DM was associated with risperidone (HR = 0.69; CI = 0.51, 0.93). Quetiapine had the second lowest risk (HR = 0.74), although it did not reach statistical significance (CI = 0.48, 1.15). The reduced risk associated with olanzapine was small (HR = 0.95) and not statistically significant (CI = 0.73, 1.24). Though the risk associated with clozapine was greater than first-generation antipsychotics (HR = 1.22), it did not achieve statistical significance either (CI = 0.73, 1.24). Diabetes risk was also higher for individuals diagnosed with schizophrenia (HR = 1.62; CI = 1.23, 2.13), bipolar disorder (HR = 1.36; CI = 1.07, 1.71), and PTSD (HR =

1.69; CI = 1.02, 2.81), and lower for individuals with other psychoses (HR = .60; CI = 0.39, 0.93).

Fitted survival functions associated with each stable medication from the Cox proportional hazards model predicting time to DM onset are illustrated in Figure 1. The survival functions are very close together until approximately 5 months (150 days) past the end of the stable period, when the curve for first-generation antipsychotics starts to fall faster than the others. The olanzapine and quetiapine curves start to fall faster at about 7 months (200 days) and remain close together until about the eighth month (240 days), after which the olanzapine curve begins to fall more quickly. The clozapine curve drops suddenly at 8.5 months (260 days), most likely as a result of the unique characteristics of the small number of patients prescribed that drug. The risperidone curve hovers above the other curves for the duration of the follow-up period.

A second Cox proportional hazards model that included interaction terms between stable atypical regimen and gender

TABLE 2. Results of the Cox Proportional Hazards Model of New-Onset Diabetes (Total Population, Males, and Females)

Variable	Total population (N = 7881)			Males (N = 3176)			Females (N = 4205)		
	Hazard ratio	95% Confidence limits		Hazard ratio	95% Confidence limits		Hazard ratio	95% Confidence limits	
		Lower	Upper		Lower	Upper		Lower	Upper
Age	1.047***	1.037	1.057	1.069***	1.052	1.086	1.030***	1.017	1.042
Male gender	1.194	0.954	1.495	—	—	—	—	—	—
Stable medication ^a									
Clozapine	1.222	0.563	2.652	1.051	0.320	3.453	1.435	0.517	3.983
Olanzapine	0.947	0.726	1.236	0.790	0.516	1.209	1.079	0.766	1.520
Quetiapine	0.740	0.477	1.146	0.499	0.224	1.108	0.929	0.546	1.580
Risperidone	0.690*	0.514	0.925	0.485**	0.298	0.789	0.849	0.587	1.226
Mental health diagnoses									
Adjustment reaction	1.294	0.915	1.830	1.204	0.675	2.149	1.352	0.874	2.092
Anxiety disorder	1.111	0.856	1.443	1.419	0.946	2.129	0.940	0.668	1.324
Alzheimer disease/dementia	0.960	0.664	1.387	0.829	0.478	1.438	1.129	0.689	1.848
Bipolar disorder	1.355*	1.073	1.711	1.474*	1.015	2.141	1.213	0.896	1.643
Dysthymia	0.831	0.651	1.060	0.817	0.546	1.222	0.819	0.602	1.114
Major depression	1.065	0.850	1.335	1.400	0.968	2.025	0.891	0.666	1.192
Other psychosis	0.602*	0.389	0.931	0.587	0.295	1.169	0.585	0.331	1.034
PTSD	1.691*	1.019	2.806	2.012	0.712	5.688	1.591	0.885	2.862
Personality disorder	1.002	0.570	1.762	1.509	0.549	4.148	0.870	0.440	1.718
Substance abuse	1.051	0.696	1.588	0.850	0.456	1.585	1.142	0.651	2.001
Schizophrenia	1.622***	1.233	2.132	1.811**	1.158	2.832	1.541*	1.085	2.189
Other mental health disorders	1.058	0.775	1.445	1.327	0.832	2.115	0.905	0.592	1.385
Clinical comorbidity	1.154***	1.095	1.216	1.164***	1.075	1.260	1.141***	1.063	1.224

* $p < 0.05$. ** $p < 0.01$. *** $p < 0.001$.

^aFirst-generation antipsychotics were the omitted reference group.

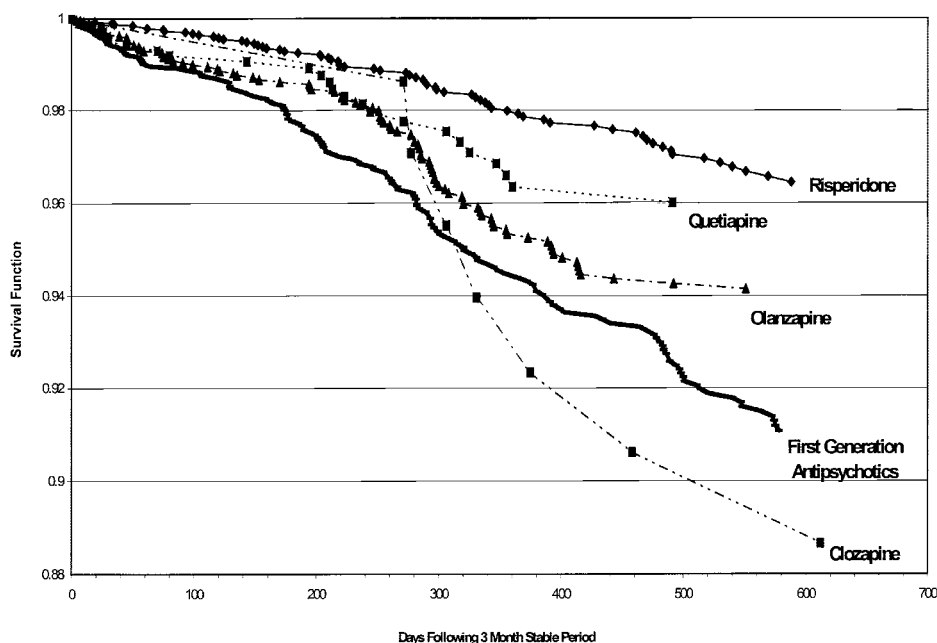


FIGURE 1. Fitted survival functions from the Cox proportional hazards model predicting time to DM onset among privately insured patients with a mental health diagnosis.

revealed a significant interaction between male gender and risperidone (HR = 0.53; $p = 0.0345$; CI = 0.29, 0.95). To further explore the relationship between gender and time to new DM onset, therefore, separate Cox models were estimated for male and female enrollees. The lowest risk of new-onset DM among males was associated with risperidone (HR = 0.49; CI = 0.30, 0.79) and quetiapine (HR = 0.50; CI = 0.22, 1.11), although the latter was only statistically significant at the .01 level. The reduced risk associated with olanzapine was smaller (HR = 0.79) and not statistically significant (CI = 0.52, 1.23), nor was the slightly greater risk associated with clozapine (HR = 1.05; CI = 0.32, 3.45). Though the relative ordering of atypicals with respect to DM risk was the same for females as for males, diabetes risk among females did not differ significantly from first-generation antipsychotics for any of the atypical drugs.

DISCUSSION

This study estimated the annual incidence of new-onset DM between 1999 and 2000 in a sample of privately insured patients with a mental health diagnosis who were stable on an antipsychotic medication. We found that the annual incidence rates in this population were high, averaging 4.7 new cases per 100 patient-years across the entire sample. Patients initially stable on risperidone were at significantly lower risk for DM than patients initially stable on a first-generation antipsychotic; patients initially stable on quetiapine, clozapine, and olanzapine were no more likely to develop new-onset DM than those on first-generation antipsychotics. Gender-specific analyses indicate that while males initially stable on risperidone were significantly less likely to develop diabetes,

females were no more likely to develop diabetes regardless of which atypical antipsychotic they were on.

The incidence of DM in this population was relatively high, even among patients initially stable on first generation antipsychotics. Although the overall DM incidence rate of 4.7% per year is considerably higher than the estimated rate of 2.7 cases per 1000 in the general US population (Kenny et al., 1995), it is nearly identical to the rate of 4.4% found in the VA study, which examined the incidence of diabetes among patients with schizophrenia initially stable on an antipsychotic (Leslie and Rosenheck, 2004). We are not aware of other studies estimating DM incidence rates in VA populations or among patients with schizophrenia or other mental illness; however, DM prevalence rates have been shown to be higher among patients with schizophrenia than among the general population (Dixon et al., 2000; Mukherjee et al., 1996). It is unclear how much of the increased DM incidence rates in the privately insured and VA samples examined here were due to the use of antipsychotic medications (whether first-generation or atypical), to the underlying mental illness, or to other factors such as poorer overall physical health or less healthy lifestyles. However, it is noteworthy that these two very different populations exhibited essentially the same rate of DM incidence. Whereas the entire VA sample population was diagnosed with schizophrenia, only 13% of the privately insured sample was so diagnosed. In addition, the average age of the VA sample was 52.2 years, and it was mostly male (94.3%), while the average age of the privately insured sample was 40.4 years, the majority of whom were female (57%). Because individuals eligible for VA mental health services are poor and frequently homeless (Rosenheck

and Seibyl, 1998) and unemployed (Rosenheck and DiLella, 1999), they are likely to be sicker on average than a group of employed individuals, retirees, and their families with private insurance. That both VA and privately insured populations initially stable on an antipsychotic should exhibit similar rates of DM incidence suggests that the risk of diabetes may extend beyond factors associated with schizophrenia to factors associated with mental illness more generally, possibly including treatment with certain antipsychotic medications.

Independent of how they compare with first-generation antipsychotics, the relative ordering of atypicals with respect to the risk of DM in our study matched that found in the VA study, with risperidone exhibiting the lowest risk of new-onset diabetes, followed by quetiapine, olanzapine, and clozapine. Contrary to the findings of the VA study, however, as well as other prior research and case reports, our results do not support the claim that atypical antipsychotics are associated with elevated risk of DM relative to first-generation antipsychotics. In fact, risperidone was associated with a substantial (HR = 0.69) and statistically significant lower risk of new-onset DM when compared with first generation antipsychotics ($p < 0.05$). The reduced risk of DM associated with quetiapine was also substantial (HR = 0.74), but did not reach the level of statistical significance ($p = 0.18$) in part due to the relatively small number of patients initially stable on this drug (775). This is in contrast to the reduced risk of DM associated with olanzapine, which was small (HR = 0.95) and not statistically significant despite a large number of initially stable patients (1986). However, the protective effects of olanzapine (HR = 0.79) along with risperidone (HR = 0.49) and quetiapine (HR = 0.50) all grew when analyses were limited to male enrollees only. Together with published reports that suggest that the newer atypical drugs (ziprasidone and aripiprazole) do not cause significant weight gain or increase the risk of DM (Keck and McElroy, 2003; Marder et al., 2003; Potkin et al., 2003; Sernyak et al., 2002), results of this study suggest that atypicals fare well where the risk of new-onset diabetes is concerned when compared with first-generation antipsychotics in some populations.

At approximately 5 months, differences in DM risk across antipsychotic medications became apparent, soon after the end of the stable period. As such, the additional DM risk associated with first-generation antipsychotics took less than half a year to develop. In the VA study, differences in DM risk took almost three times as long to become apparent (14 months; Leslie and Rosenheck, 2004). Although elevated DM risk associated with use of certain antipsychotic medications manifested itself more quickly in our study, the 8 months constituted by the stable period and follow-up should still provide clinicians with enough time to identify elevated DM risk and perhaps change antipsychotic regimen accordingly.

The most common medication on which patients were stable was risperidone (35%), followed by first-generation

antipsychotics and olanzapine (27% each), quetiapine (10%), and clozapine (1%). In the VA study, however, the most common medication on which patients were stable was first-generation antipsychotics (41.9%), followed by olanzapine (28.3%), risperidone (24.6%), quetiapine (3.0%), and clozapine (2.2%) (Leslie and Rosenheck, 2004). Focusing on the relatively few patients with schizophrenia in the private sector sample, however, reveals prescription patterns that better approximate what was found in the VA, with the most common medication being first-generation antipsychotics (32.6%), followed by risperidone (27.6%), olanzapine (26.5%), quetiapine (7.1%), and clozapine (6.2%). Thus, although prescription patterns vary between patients diagnosed with mental illness other than schizophrenia, there appears to be a certain degree of uniformity in the patterns of prescriptions provided to both public sector and privately insured populations with schizophrenia (Leslie and Rosenheck, 2000).

The fact that patients with schizophrenia are more likely to develop diabetes than other patients, and are more likely to be prescribed a first-generation antipsychotic, may explain why patients on first-generation antipsychotics were more likely to develop diabetes than patients on three of the four atypicals examined. To assess this possibility, we repeated our analyses for the 954 patients in our sample with a diagnosis of schizophrenia. Although none are significant, coefficients on each of the atypicals—risperidone (HR = 0.89), quetiapine (HR = 0.64), olanzapine (HR = 0.73), and clozapine (HR = 0.82)—still indicate that even among patients with schizophrenia in this sample, atypicals are associated with a lower risk of new-onset diabetes when compared with first-generation antipsychotics, although due to the small sample, these results were not statistically significant.

Another possible reason why patients prescribed first-generation antipsychotics were more likely to develop diabetes than patients prescribed risperidone, quetiapine, and olanzapine is that that patients prescribed first-generation antipsychotics may have been on those medications longer. To assess this possibility, we compared average duration between first prescription for a stable medication and last prescription for that medication before diabetes diagnosis across the antipsychotics examined. Although results fail to reveal significant differences in duration before diabetes onset between patients prescribed first-generation antipsychotics (251 days) and patients prescribed olanzapine (235 days; $p = 0.48$) and risperidone (284 days; $p = 0.23$), they indicate that patients prescribed first-generation antipsychotics tended to be on those drugs significantly longer than patients prescribed quetiapine (170 days; $p = 0.04$). We also compared average duration between first prescription for a stable medication and last prescription before the end of our follow-up period for those who did not develop diabetes. Results indicate not only that average duration was significantly longer

for first-generation antipsychotics (321 days) when compared with quetiapine (226 days; $p = <0.0001$) but also that average duration was significantly longer for first-generation antipsychotics when compared with risperidone (247 days; $p < 0.0001$) and olanzapine (242 days; $p < 0.0001$). Consequently, one reason why patients on first-generation antipsychotics may have been more likely to develop diabetes is that they may have had more cumulative exposure to neuroleptic drugs than patients receiving atypical antipsychotics.

Whereas VA patients treated with clozapine and olanzapine exhibited a significantly higher risk of diabetes than patients treated with first-generation antipsychotics, privately insured patients treated with risperidone exhibited a significantly lower risk of diabetes. One possible explanation for the discrepancy in these findings is that VA patients may have been prescribed atypical antipsychotics earlier in the course of the disease than privately insured patients, providing more time for the cumulative effects of these drugs on the likelihood of developing diabetes to build up. Because the VA study focused on patients with schizophrenia, it examined the risk of DM in a sicker population than the present study, which examined the risk of DM in a privately insured population with a variety of mental health diagnoses. Consequently, privately insured patients in our study may have been treated with atypical antipsychotics later in the course of their illness. This may be true because privately insured patients receiving atypical antipsychotics (not all of whom have schizophrenia) may be less seriously ill than VA patients treated primarily for schizophrenia. In addition, privately insured patients may have been treated with atypical antipsychotics later because it takes longer for drugs to diffuse to off-label use (e.g. for major depression rather than schizophrenia as originally intended). Because the VA study did not collect data on when patients initiated treatment, however, we were unable to assess whether patients in our study did in fact initiate treatment later.

Another possible explanation for the discrepancy between the two studies may have been differences in the average daily doses prescribed to VA patients with schizophrenia as compared with privately insured patients with other mental health diagnoses. While patients in the VA study were prescribed daily doses for first-generation antipsychotics that were 80% higher, on average, than those prescribed privately insured patients in our study (628.00 mg vs. 346.44 mg), they were prescribed daily doses that were, on average, only 37% higher for clozapine (583.44 mg vs. 434.47 mg), 31% higher for olanzapine (14.23 mg vs. 10.83 mg), and 56% higher for both quetiapine (330.03 mg vs. 211.93 mg) and risperidone (4.13 mg vs. 2.65 mg). Not surprisingly, VA patients with schizophrenia were prescribed higher doses for each of the antipsychotics examined than privately insured patients with a variety of mental health diagnoses. Greater differences in average daily dose were exhibited with first-

generation antipsychotics than with atypicals, however. Lower doses of atypicals may explain why, in contrast to other studies, we did not find any greater risk of DM with atypical than first-generation antipsychotics, but it does not explain why we found significantly lower risk of DM for males on risperidone or quetiapine relative to first-generation drugs.

There are several limitations that we would like to address. First, we examined the incidence of DM in the private sector among patients with a mental health diagnosis stable on an antipsychotic medication. There may have been cases of DM that were not diagnosed or that were diagnosed outside of the health insurance plans included in the MarketScan database. Because we had access only to claims records and not detailed clinical data, we were unable to identify undiagnosed DM cases. However, we have no reason to believe that there were differences across our medication groups in the number of undiagnosed DM cases, so we suspect any bias resulting from this limitation to be minimal.

More likely is the possibility that all patients with a mental health diagnosis were not identified. Given limited mental health benefits among most private health insurance plans, patients who were more severely ill may have exhausted their plan benefits. Consequently, our claims database may not have captured services used by those patients after their claims were no longer paid. This is a limitation of all analyses that rely on private sector claims. Furthermore, patients in the private sector must follow very specific rules in order for insurance companies to consider their claims valid. Some claims may not be reimbursed and therefore would not have been included in our database (Leslie and Rosenheck, 2000). Because our sample involved only patients with a mental health diagnosis who were covered by health plans participating in MarketScan, our results may not be generalizable to other populations or health care systems.

In addition, our analysis attributed all of the DM risk to the atypical antipsychotic medication on which a patient was stable during a 3-month window. In fact, patients may have been stable on a different medication either before or after the medication identified in our study, and the increased DM risk might be partially attributable to these other medications. Data were not available to identify earlier stable medications, but the proportion of patients who switched drugs during the follow-up period was small (13.3% overall) and was similar across medication groups. Finally, there are limitations associated with all types of administrative data. For example, diagnoses may not be as accurate as in detailed clinical data.

CONCLUSION

Despite limitations posed by our data, results presented here offer important insight into the risk of DM in a privately insured mentally ill population who were prescribed antipsychotics. We found that the risk of diabetes varied across the

atypical antipsychotics examined. **Unlike previous research,** we found that patients treated with certain atypical antipsychotics exhibited a lower risk of new-onset diabetes than patients treated with first-generation antipsychotics. Furthermore, these effects were limited to male enrollees only. This latter finding is reflected in a recent study suggesting that the risk of DM associated with risperidone may be limited to elderly pharmacy plan enrollees 75 and older (Feldman, et al., 2004).

The association between DM and atypical antipsychotics may also be more of a problem for certain subgroups of the population—for example, VA patients with schizophrenia versus privately insured patients with general mental illness.

Although the Food and Drug Administration recently concluded that increased risk of diabetes, hyperglycemia, and related symptoms is an adverse effect associated with atypical antipsychotics as a general class of medications, additional research is needed to determine the true association between the risk of DM and use of atypicals and variation in this risk across subgroups. Health care providers should be aware of this potential association, however, and monitor patients appropriately, in addition to educating them to look for signs and symptoms of DM when using these agents.

REFERENCES

- Allison DB, Mentore JL, Heo M, Chandler LP, Cappelleri JC, Infante MC, Weiden PJ (1999) Antipsychotic-induced weight gain: A comprehensive research synthesis. *Am J Psychiatry*. 156:1686–1696.
- Burton TM (2003) New antipsychotic-drug class is tied to increase in diabetes. *Wall Street J*. August 22, 2003.
- Bustillo JR, Buchanan RW, Irish D, Breier A (1996) Differential effect of clozapine on weight: A controlled study. *Am J Psychiatry*. 153:817–819.
- Charlson ME, Pompei P, Ales KL, MacKenzie CR (1987) A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *J Chron Dis*. 40:373–383.
- Cohen S, Chiles J, MacNaughton A (1990) Weight gain associated with clozapine. *Am J Psychiatry*. 147:503–504.
- Deyo RA, Cherkin D, Ciol MA (1992) Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol*. 45:613–619.
- Dixon L, Weiden P, Delahanty J, Goldberg R, Postrado L, Lucksted A, Lehman A (2000) Prevalence and correlates of diabetes in national schizophrenia samples. *Schizophr Bull*. 26:903–912.
- Feldman PD, Hay LK, Deberdt W, Kennedy JS, Hutchins DS, Hay DP, Hardy TA, Hoffmann VP, Hornbuckle K, Breier A (2004) Retrospective cohort study of diabetes mellitus and antipsychotic treatment in a geriatric population in the United States. *J Am Med Dir*. 5:38–46.
- Fertig MK, Brooks VG, Shelton PS, English CW (1998) Hyperglycemia associated with olanzapine. *J Clin Psychiatry*. 59:687–689.
- Fuller MA, Shermock KM, Secic M, Grogg AL (2003) Comparative study of the development of diabetes mellitus in patients taking risperidone and olanzapine. *Pharmacotherapy*. 23:1037–1043.
- Gianfrancesco FD, Grogg AL, Mahmoud RA, Wang RH, Nasrallah HA (2002) Differential effects of risperidone, olanzapine, clozapine and conventional antipsychotics on type 2 diabetes: Findings from a large health plan database. *J Clin Psychiatry*. 63:920–930.
- Gianfrancesco F, White R, Wang RH, Nasrallah HA (2003) Antipsychotic-induced type 2 diabetes: evidence from a large health plan database. *J Clin Psychopharmacol*. 23:328–335.
- Goff DC, Posever T, Herz L, Simmons J, Kletti N, Lapierre K, Wilner KD, Law CG, Ko GN (1998) An exploratory haloperidol-controlled dose-finding study of ziprasidone in hospitalized patients with schizophrenia or schizoaffective disorder. *J Clin Psychopharmacol*. 18:296–304.
- Goode E (2003) 3 schizophrenia drugs may raise diabetes risk, study says. *New York Times*. (p 8). August 25, 2003.
- Henderson DC, Cagliero E, Gray C, Nasrallah RA, Hayden DL, Schoenfeld DA, Goff DC (2000) Clozapine, diabetes mellitus, weight gain and lipid abnormalities: A five-year naturalistic study. *Am J Psychiatry*. 157:975–981.
- Jin H, Meyer JM, Jeste DV (2002) Phenomenology of and risk factors for new-onset diabetes mellitus and diabetic ketoacidosis associated with atypical antipsychotics: An analysis of 45 published cases. *Ann Clin Psychiatry*. 14:59–64.
- Kane JM, Carson WH, Saha AR, McQuade RD, Ingenito GG, Zimbrow DL, Ali MW (2002) Efficacy and safety of aripiprazole and haloperidol versus placebo in patients with schizophrenia and schizoaffective disorder. *J Clin Psychiatry*. 63:763–771.
- Kane J, Honigfeld G, Singer J, Meltzer H (1988) Clozapine for the treatment-resistant schizophrenic: A double-blind comparison with chlorpromazine. *Arch Gen Psychiatry*. 45:789–796.
- Keck PE Jr, McElroy SL (2003) Aripiprazole: A partial dopamine D2 receptor agonist antipsychotic. *Expert Opin Investig Drugs*. 12:655–662.
- Kenny S, Aubert R, Geiss L (1995) Prevalence and incidence of non-insulin-dependent diabetes. In Harris M, Cowie C, Reiber G, Boyko E, Stern M, Bennett P (Eds), *Diabetes in America* (pp 47–68). Washington DC: US Government Printing Office.
- Koro CE, Fedder DO, L'Italien GJ, Weiss S, Magder LS, Kreyenbuhl J, Revicki D, Buchanan RW (2002) An assessment of the independent effects of olanzapine and risperidone exposure on the risk of hyperlipidemia in schizophrenic patients. *Arch Gen Psychiatry*. 59:1021–1026.
- Lafayette JM, Pirl WF, Henderson DC (2003) Low-dose clozapine and diabetic ketoacidosis. *Psychosomatics*. 44:249–252.
- Lamberti JS, Bellnier T, Schwarzkopf SB (1992) Weight gain among schizophrenic patients treated with clozapine. *Am J Psychiatry*. 149:689–690.
- Marder SR, Meibach RC (1994) Risperidone in the treatment of schizophrenia. *Am J Psychiatry*. 151:825–835.
- Leslie DL, Rosenheck RA (2000) Comparing quality of mental health care for public-sector and privately-insured populations. *Psychiatr Serv*. 51:650–655.
- Leslie DL, Rosenheck RA (2004) Incidence of newly diagnosed diabetes attributable to atypical antipsychotic medications. *Am J Psychiatry*. In press.
- Marder SR, McQuade RD, Stock E, Kaplita S, Marcus R, Safferman AZ, Saha A, Ali M, Iwamoto T (2003) Aripiprazole in the treatment of schizophrenia: safety and tolerability in short-term, placebo-controlled trials. *Schizophr Res*. 61:123–136.
- Mukherjee S, Decina P, Bocola V, Saraceni F, Scapicchio PL (1996) Diabetes mellitus in schizophrenic patients. *Compr Psychiatry*. 37:68–73.
- Ober SK, Hudak R, Rusterholtz A (1999) Hyperglycemia and olanzapine. *Am J Psychiatry*. 156:970.
- Potkin SG, Saha AR, Kujawa MJ, Carson WH, Ali M, Stock E, Stringfellow J, Ingenito G, Marder SR (2003) Aripiprazole, an antipsychotic with a novel mechanism of action and risperidone vs placebo in patients with schizophrenia and schizoaffective disorder. *Arch Gen Psychiatry*. 60:681–691.
- Ragucci KR, Wells BJ (2001) Olanzapine-induced diabetic ketoacidosis. *Ann Pharmacother*. 35:1556–1558.
- Rosack J (2003) FDA to require diabetes warning on antipsychotics. *Psychiatr News*. 38:1.
- Rosenheck RA, DiLella D (1999) Department of veterans affairs national mental health program performance monitoring system: Fiscal year 1998 report. West Haven (CT): Northeast Program Evaluation Center.
- Rosenheck R, Leslie D, Sernyak M (2001) From clinical trials to real-world practice: Use of atypical antipsychotic medication nationally in the department of veterans affairs. *Med Care*. 39:302–308.
- Rosenheck RA, Seibyl CL (1998) Homelessness: Health service use and related costs. *Med Care*. 36:1256–1264.
- Sernyak MJ, Leslie DL, Alarcon RD, Losonczy MF, Rosenheck R (2002) Association of diabetes mellitus with use of atypical neuroleptics in the treatment of schizophrenia. *Am J Psychiatry*. 159:561–566.
- Small JG, Hirsch SR, Arvanitis LA, Miller BG, Link CG (1997) Quetiapine

- in patients with schizophrenia: A high- and low-dose double-blind comparison with placebo. Seroquel Study Group. *Arch Gen Psychiatry*. 54:549–557.
- Sobel M, Jagers ED, Franz MA (1999) New-onset diabetes mellitus associated with the initiation of quetiapine treatment. *J Clin Psychiatry*. 60:556–557.
- Stahl SM (1999) Selecting an atypical antipsychotic by combining clinical experience with guidelines from clinical trials. *J Clin Psychiatry*. 60(suppl 10):31–41.
- Straker D, Mendelowitz A, Karlin L (2002) Near fatal ketoacidosis with olanzapine treatment. *Psychosomatics*. 43:339–340.
- Tavakoli SA, Arguisola MS (2003) Diabetic ketoacidosis in a patient treated with olanzapine, valproic acid and venlafaxine. *South Med J*. 96:729–730.
- Taylor DM, McAskill R (2000) Atypical antipsychotics and weight gain: A systematic review. *Acta Psychiatr Scand*. 101:416–432.
- Tollefson GD, Beasley CM Jr, Tran PV, Street JS, Krueger JA, Tamura RN, Graffeo KA, Thieme ME (1997) Olanzapine versus haloperidol in the treatment of schizophrenia and schizoaffective and schizophreniform disorders: Results of an international collaborative trial. *Am J Psychiatry*. 154:457–465.
- Wheeler TB (2003) Risks from mental illness drug not adequately noted, some say: Studies link Zyprexa to diabetes death. *Baltimore Sun*. (p 1). March 19, 2003.
- Wilson DR, D'Souza L, Sarkar N, Newton M, Hammond C (2003) New-onset diabetes and ketoacidosis with atypical antipsychotics. *Schizophr Res*. 59:1–6.
- Wirshing DA, Spellberg BJ, Erhart SM, Marder SR, Wirshing WC (1998) Novel antipsychotics and new onset diabetes. *Biol Psychiatry*. 44:778–783.