ORIGINAL RESEARCH ARTICLE

Drug Safety 2007; 30 (7): 589-599
0114-5916/07/0007-0589/$44.95/0

Risk of Diabetic Ketoacidosis after Exposure to Risperidone or Olanzapine

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Abstract

Background: Atypical antipsychotics have been associated with metabolic abnormalities including impaired glucose metabolism, exacerbation of existing diabetes mellitus and new-onset type 2 diabetes. Not all atypical antipsychotic agents appear to have the same propensity to cause these complications.

Objective: To assess diabetic ketoacidosis risk in patients receiving risperidone or olanzapine.

Methods: California Medicaid data were evaluated for the presence of a diabetic ketoacidosis hospital claim (9th Edition of the *International Classification of Diseases* code 2501x) for patients receiving an atypical antipsychotic agent between July 1997 and September 2000. Initial prescription claims were identified for risperidone, olanzapine, clozapine, quetiapine and multiple atypical medications; however, the final analysis was restricted to risperidone and olanzapine owing to sample size challenges in the clozapine and quetiapine groups. Cases were specified if a claim occurred within 45 days after antipsychotic dispensation. Potential confounding variables and duration of antipsychotic exposure were included.

Results: Initial users of risperidone (n = 51 330; 31 diabetic ketoacidosis) and olanzapine (n = 51 302; 55 diabetic ketoacidosis) were identified between July 1997 and September 2000. The adjusted risk of diabetic ketoacidosis for olanzapine versus risperidone was 1.62 (p = 0.033). The risk of diabetic ketoacidosis was associated with a longer duration of drug exposure. A progressive and statistically significant divergence in risk was observed between the two treatment groups after the first 30 days of therapy. For risperidone patients, diabetic ketoacidosis risk stabilised after the first 90 days; for olanzapine patients, diabetic ketoacidosis risk continued to increase until 360 days (study duration). For exposures of >30 days, >90 days and >180 days, diabetic ketoacidosis risk was 1.7 (p = 0.026), 2.4 (p = 0.004) and 3.5 (p = 0.001) times greater for olanzapine than risperidone.

Treatment group, age, African American race and the presence of schizophrenia or diabetes were significant predictors of diabetic ketoacidosis.
Conclusion: The risk of diabetic ketoacidosis appears to be greater for patients exposed to olanzapine compared with risperidone after adjusting for confounding factors. This risk appears to increase with longer duration of exposure to olanzapine.

Background

Atypical antipsychotics have been associated with metabolic abnormalities including impaired glucose metabolism, exacerbation of existing diabetes mellitus and new-onset type 2 diabetes.[1] It has been suggested that atypical antipsychotic agents may precipitate the onset of hyperglycaemia.[2,3] Case severity has ranged from mild glucose intolerance to hyperosmolar coma or diabetic ketoacidosis, a rare but potentially fatal metabolic complication.[2,4] For some patients, diabetic ketoacidosis is the first presentation of any metabolic disturbance after initiating therapy with an atypical antipsychotic agent.[5,6] Jin et al.[5] propose that the absence of significant physical illness among patients with diabetic ketoacidosis who have taken an atypical antipsychotic suggests that the atypical agent itself, by some unknown mechanism, may be a metabolic stressor that precipitates the diabetic ketoacidosis.

The association between atypical antipsychotic agents and glycaemic abnormalities has been documented in a large number of case reports,[5,7-9] retrospective studies,[10-12] database cohort studies,[3,13-17] pharmacovigilance studies[2,4,18-20] and case-control studies.[21,22] This evidence, considered in conjunction with evidence of a temporal association between initiation of therapy and onset of diabetes and its reversal after drug withdrawal in some cases, supports glycaemic abnormalities being a drug-related effect.[5,8,19]

Although the use of antipsychotic medications has been associated with an increased risk of the metabolic syndrome, baseline data from the CATIE (Clinical Antipsychotic Trials on Intervention Effectiveness) study suggest that patients with schizophrenia may also have an inherent predisposition for the syndrome: the metabolic syndrome was identified in 35.8% of the patients in the CATIE trial at baseline.[23] The metabolic syndrome is an important risk factor for cardiovascular disease.

Not all atypical antipsychotic agents appear to have the same propensity to cause glycaemic complications. Published case reports indicate a marked difference between agents that could not be explained by the number of prescriptions or the length of time on the market.[1] Olanzapine and clozapine have been represented in a disproportionately large number of case reports of glycaemic complications[1,6,8,9] and seem to be associated with a greater number of reports than either risperidone or quetiapine.[2,3,5,8] More recently, in a case study, diabetic ketoacidosis has been associated with aripiprazole treatment.[24]

Published studies indicate an elevated risk of diabetes onset with olanzapine and clozapine therapy.[8] Leslie and Rosenheck[25] followed 56 849 stable, monotherapy-treated schizophrenic patients without diabetes for 1 year to determine the risk of diabetes onset and diabetic ketoacidosis hospitalisation attributable to specific atypical antipsychotics. A small percentage developed diabetes (7.3%) and fewer experienced a hospitalisation for diabetic ketoacidosis (0.2%). The risk of diabetes onset was highest for patients receiving clozapine and lowest for those receiving risperidone (2.03% and 0.05%,

respectively).[25] Although diabetic ketoacidosis might result from poor diabetes management, the rate of diabetic ketoacidosis in patients receiving atypical antipsychotics appears to be greater than that seen in the general population of patients with diabetes.[26]

Even though the occurrence of diabetic ketoacidosis is relatively rare, understanding the risk is important because of the potential seriousness of an event. This paper describes a retrospective analysis of California Medicaid data, conducted to assess the risk of diabetic ketoacidosis associated with the use of atypical antipsychotics in that population. Since there is evidence that the incidence of diabetes may increase with the duration of exposure to atypical antipsychotic agents,[10,27] we also sought to assess the relationship between the development of diabetic ketoacidosis and the duration of drug exposure.

Methods

California Medicaid data for patients receiving an atypical antipsychotic agent between July 1997 and September 2000 were evaluated (n = 141 286). Diabetic ketoacidosis cases were identified as potentially attributable to atypical antipsychotic agent use if they met two conditions:

1. A diabetic ketoacidosis-related claim (9th Edition of the *International Classification of Diseases* [ICD-9] code 2501x) appeared after the initial prescription claim for an antipsychotic agent; and
2. At least one atypical antipsychotic prescription claim within 45 days before the diabetic ketoacidosis event.

These cases were then grouped according to the initial atypical antipsychotic agent appearing in the claims file. The requirement for an antipsychotic prescription within 45 days of the diabetic ketoacidosis diagnosis was developed *a priori* to ensure a temporal relationship between antipsychotic and diabetic ketoacidosis diagnosis. A 45-day prior period was selected because most antipsychotic prescriptions are dispensed in 30-day increments. Fifteen days were added to account for potential noncompliance, while maintaining a reasonable expectation of drug use in the same time period as the diabetic ketoacidosis diagnosis.

Initial prescription claims were identified for risperidone, olanzapine, clozapine, quetiapine and multiple atypical medications. An initial antipsychotic prescription was defined as the first prescription for an antipsychotic agent after a 6-month period during which there were no claims for antipsychotic medications. The final analyses were restricted to risperidone and olanzapine cases owing to sample size challenges in the clozapine and quetiapine groups (reliable estimation could be compromised). Cases that displayed treatment with multiple antipsychotic agents were excluded since potential attribution to a specific agent became problematic.

Patients were also categorised according to their duration of exposure to risperidone or olanzapine. Duration of drug exposure was calculated as the number of days between initiation of therapy and first diagnosis of diabetic ketoacidosis. For patients who did not develop diabetic ketoacidosis, exposure was calculated as the number of days between initiation of therapy (first dose) and the end of the index period (September 2000). Patients were grouped by duration of drug exposure: ≤30 days; >30 and ≤90 days; >90 and ≤180 days; >180 and ≤360 days; and >360 days.

Logistic regression was used to predict the relative risk of diabetic ketoacidosis while controlling for potential confounding factors. Covariates were treatment group (olanzapine or risperidone); age; months of Medicaid eligibility; sex; race; history of diabetes prior to atypical antipsychotic agent use; mental health diagnosis; and dispensation of a conventional antipsychotic or diabetogenic agent within 45 days of the diabetic ketoacidosis event. Diabetogenic agents included α- and β-adrenoceptor antagonists (α- and β-blockers), thiazide-

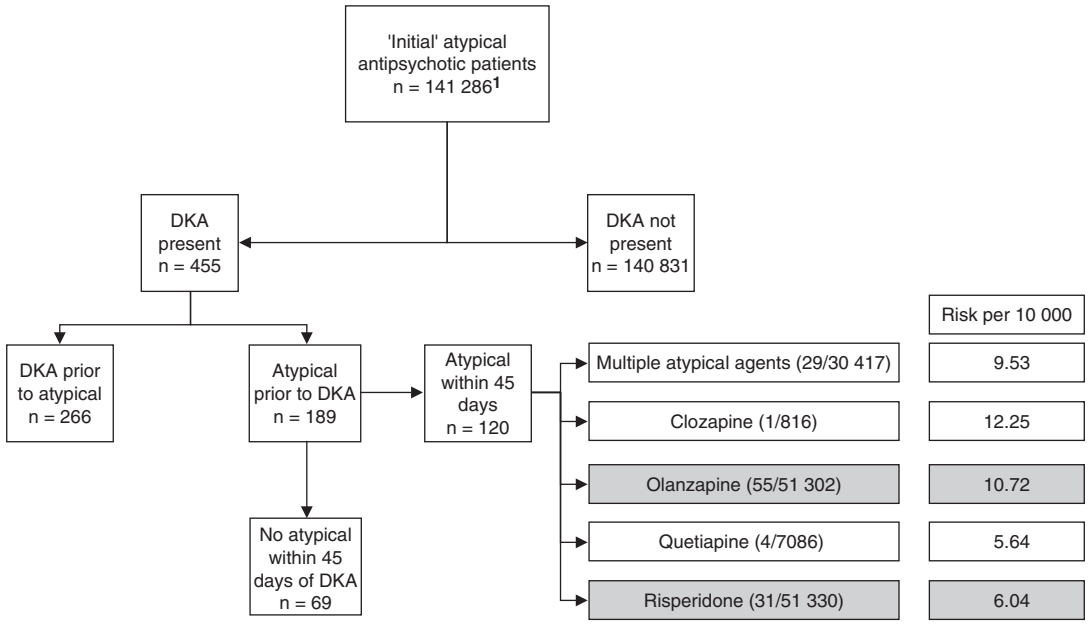

Fig. 1. Diagram of potentially attributable cases of diabetic ketoacidosis (DKA) in the 100% dataset and unadjusted risk per 10 000 patients. **1** Initial atypical antipsychotic patients were defined as those with ≥6 months of no use prior to their first prescription in the index period.

containing diuretics, glucocorticoids, phenytoin, valproic acid and oral contraceptives. A history of diabetes prior to the use of an atypical antipsychotic agent was determined on the basis of a claim for diabetes care. The presence of a claim with a 3-digit ICD-9-Clinical Modification code of 250 in any diagnosis field (i.e. hospital, physician) was indicative of a history of diabetes. Although the use of claims data to identify diabetes is subject to underestimation, it is the only clinically logical approach to diagnosis identification in this analysis. Such underestimation occurs because of the number of undiagnosed diabetic patients in the population and because the claims data do not typically reflect all diagnoses at any given resource visit.

Interactions were tested between the group variable and selected predictors (i.e. those variables where significant differences between risperidone and olanzapine were observed). The logistic regression model was also applied while restricting the sample based on exposure category. The goodness-of-fit statistic was assessed using the Hosmer and Lemeshow test.[28] The presence of linear dependence among the explanatory variables (multicolinearity) could lead to decreased accuracy in risk estimation and was assessed through evaluation of variance inflation factors.[29] All statistical tests were two-tailed and analyses were conducted using SAS/STAT software, Version 8 (SAS System for Windows).

Results

Between July 1997 and September 2000, 141 286 patients were identified as users of atypical antipsychotics. Of the 455 patients with a diabetic ketoacidosis event, 335 did not meet the potentially attributable case specification criteria and were excluded from the analyses (diabetic ketoacidosis diagnosis before the start of the atypical antipsychotic n = 266; or no atypical antipsychotic use within 45 days before the diabetic ketoacidosis event n = 69). Of the 140 951 remaining patients, 51 330 patients re-

Table I. Demographic and clinical characteristics of patients without potentially attributable diabetic ketoacidosis (DKA) who received olanzapine or risperidone

Variable	Olanzapine (n = 51 247)	Risperidone (n = 51 299)	p-Value[a]
Sex [n (%)][b]			0.0001
male	24 358 (47.6)	23 772 (46.4)	
female	26 854 (52.4)	27 482 (53.6)	
Race/ethnicity [n (%)]			<0.0001
White	25 834 (50.4)	28 276 (55.1)	
African American	7 858 (15.3)	7 541 (14.7)	
other	4 147 (8.1)	4 752 (9.3)	
missing data	13 408 (26.2)	10 730 (20.9)	
Diagnosis [n (%)][c]			
schizophrenia	12 454 (24.3)	7 722 (15.1)	<0.0001
bipolar disorder	5 621 (11.0)	3 655 (7.1)	<0.0001
depression	14 159 (27.6)	11 585 (22.6)	<0.0001
anxiety	6 728 (13.1)	5 654 (11.0)	<0.0001
dementia	2 807 (5.5)	5 813 (11.3)	<0.0001
none reported	23 299 (45.5)	26 762 (52.2)	<0.0001
Age [mean (SD) years]	48.5 (19.2)	50.3 (26.1)	<0.0001
Diabetes diagnosis during study [n (%)]			0.1175
yes	6 767 (13.2)	6 605 (12.9)	
no	44 480 (86.8)	44 694 (87.1)	
Diabetes diagnosis after start of atypical antipsychotic use [n (%)]			<0.0001
yes	2 121 (4.1)	1 620 (3.2)	
no	49 126 (95.9)	49 679 (96.8)	
Prescription for a conventional antipsychotic during the study [n (%)]			<0.0001
yes	22 968 (44.8)	18 211 (35.5)	
no	28 279 (55.2)	33 088 (64.5)	
Prescription for a diabetogenic agent during study period [n (%)]			<0.0001
yes	19 790 (38.6)	19 213 (37.5)	
no	31 457 (61.4)	32 086 (62.5)	

a Two-tailed test for categorical variables with chi-squared and t-tests for continuous variables.

b Data on the patients' sex were not available in a few cases.

c Numbers do not sum to 100% since patients may be in more than one diagnosis category.

ceived risperidone, 51 302 received olanzapine, 7086 received quetiapine, 816 received clozapine and 30 417 were on multiple antipsychotics (see figure 1). In all, 31 cases of diabetic ketoacidosis occurred with risperidone (6.04 cases per 10 000 patients); 55 cases with olanzapine (10.72 per 10 000); 1 case with clozapine (12.25 per 10 000); and 4 cases with quetiapine (5.64 per 10 000). Even though the rate per 10 000 patients was found to be high within the clozapine group, the number of cases in both the clozapine and quetiapine cohorts (1 and 4, respectively) was deemed too small for an expectation of reliable estimation.

Table I compares the demographic and clinical characteristics of patients without diabetic ketoacidosis who were treated with olanzapine or risperidone. The olanzapine group had a higher proportion of all mental illness prescriptions than the risperidone group. A comparison of patients with a diabetic ketoacidosis diagnosis and treated with olanzapine or risperidone is presented in table II. Schizophrenia was more common among those receiving

Table II. Demographic and clinical characteristics of patients with potentially attributable diabetic ketoacidosis (DKA) who received olanzapine or risperidone

Variable	Olanzapine (n = 55)	Risperidone (n = 31)	p-Value[a]
Sex [n (%)]			0.2389
male	23 (41.8)	9 (29.0)	
female	32 (58.2)	22 (71.0)	
Race/ethnicity [n (%)]			0.5812
White	22 (40.0)	16 (51.6)	
African American	18 (32.7)	6 (19.4)	
other	4 (7.3)	2 (6.5)	
missing data	11 (20.0)	7 (22.6)	
Diagnosis [n (%)][b]			
schizophrenia	26 (47.3)	8 (25.8)	0.0506
bipolar disorder	8 (14.5)	4 (12.9)	1.0000
depression	24 (43.6)	8 (25.8)	0.1005
anxiety	9 (16.4)	1 (3.2)	0.0870
dementia	1 (1.8)	2 (6.5)	0.2938
none reported	17 (30.9)	15 (48.4)	0.1074
Age [mean (SD) years]	45.5 (14.2)	55.0 (21.5)	0.0322
Time between drug use and DKA [mean (SD) days]	306.7 (240.6)	158.3 (180.8)	0.0037
Diabetes diagnosis prior to DKA [n (%)]			0.2461
yes	36 (65.5)	24 (77.4)	
no	19 (34.5)	7 (22.6)	
Diabetes diagnosis prior to atypical antipsychotic use [n (%)]			0.1475
yes	23 (41.8)	18 (58.1)	
no	32 (58.2)	13 (41.9)	
Prescription for a conventional antipsychotic within 45 days prior to DKA [n (%)]			1.0000
yes	8 (14.5)	4 (12.9)	
no	47 (85.5)	27 (87.1)	
Prescription for a diabetogenic agent within 45 days prior to DKA [n (%)]			0.3198
yes	18 (32.7)	7 (22.6)	
no	37 (67.3)	24 (77.4)	

a Two-tailed test for categorical variables with chi-squared or Fisher's Exact test for variables with cell sizes <5 and t-tests for continuous variables.

b Numbers do not sum to 100% since patients may be in more than one diagnosis category.

olanzapine, while the risperidone recipients tended to be older. The unadjusted risk of diabetic ketoacidosis was 1.8 times greater with olanzapine than risperidone (p = 0.0096).

Logistic regression analysis identified treatment group, age, African American race and the presence of schizophrenia and diabetes as significant predictors of diabetic ketoacidosis (table III). The findings indicated that the relative risk of diabetic ketoacidosis was 1.62 times greater for patients treated with olanzapine than risperidone (p = 0.033; table III). Tests for interactions between treatment group and selected predictors were conducted to determine whether the relationship between diabetic ketoacidosis and the group variable was moderated by specific variables. The interaction terms were not significant in each instance (presence of schizophrenia p = 0.3648; presence of diabetes p = 0.1600; age p = 0.0588).

Diagnostics indicated that the logistic model was an appropriate specification. The Hosmer and Lemeshow test[28] indicated an adequate fit (p =

Table III. Risk of developing diabetic ketoacidosis: logistic model results[a]

Model term (reference group)	p-Value	Odds ratio (95% CI)
Olanzapine monotherapy (risperidone)	0.033	1.623 (1.047, 2.560)
Age (years)[b]	0.036	0.987 (0.975, 0.999)
Male (female)	0.116	0.695 (0.438, 1.087)
Hispanic race (White)	0.615	1.274 (0.435, 2.989)
African American race (White)	0.032	1.764 (1.037, 2.944)
Missing race (White)	0.549	0.841 (0.467, 1.460)
Other race (White)	0.461	0.473 (0.027, 2.197)
Schizophrenia (no schizophrenia)	0.001	2.216 (1.400, 3.467)
Bipolar disorder (no bipolar disorder)	0.696	1.135 (0.574, 2.064)
Depression (no depression)	0.338	1.248 (0.785, 1.954)
Diabetes mellitus prior to atypical use (no diabetes prior to atypical use)	<0.0001	9.643 (6.066, 15.341)
Medicaid eligibility (months)[b]	0.640	1.006 (0.982, 1.033)

a Eighty observations were not included because of missing demographic variables.

b Continuous variable.

0.3457). Variance inflation factors ranged from 1.02 to 1.22, indicating minimal multicolinearity among the variables (data not shown).

The presence of conventional antipsychotics or other diabetogenic therapies did not significantly alter the relative risk of diabetic ketoacidosis for olanzapine. A subsequent logistic model analysis showed that the presence of other diabetogenic drugs did not change the magnitude or significance of the drug effect (olanzapine vs risperidone; data not shown).

The mean duration of follow-up for all patients in the study from initial antipsychotic prescription to end of study period (30 September 2000) was 495.8 days (SD 291.6, median 500). The mean follow-up duration for patients initiating olanzapine was 513.2 days (SD 290.8, median 528), and the mean follow-up duration for patients who initiated risperidone was 478.3 days (SD 291.4, median 471). The unadjusted analysis of diabetic ketoacidosis based on drug exposure is presented in table IV. Statistically significant differences between groups were evident in patients with >180 days of drug exposure.

The logistic regression model restricted for drug-exposure category indicated that the risk of diabetic ketoacidosis associated with olanzapine increased as a function of exposure duration (table V). For an exposure of >30 days, >90 days and >180 days, the relative risk of diabetic ketoacidosis was 1.7 times greater ($p = 0.026$), 2.4 times greater ($p = 0.004$) and

Table IV. Number of cases of diabetic ketoacidosis (DKA) according to exposure category

Exposure category (days)	Olanzapine				Risperidone			
	patients with no DKA[a]	patients with DKA	total	cases per 10 000 patients	patients with no DKA[a]	patients with DKA	total	cases per 10 000 patients
≤30	10 652	7	10 659	6.6	11 045	6	11 051	5.4
>30 to ≤90	10 474	8	10 482	7.6	11 302	10	11 312	8.8
>90 to ≤180	7969	5	7 974	6.3	8836	6	8842	6.8
>180 to ≤360[b]	8859	15	8 874	16.9	8867	4	8871	4.5
>360[b]	11 475	20	11 495	17.4	9311	5	9316	5.4

a Based on patients with 'days supply' data available.

b $p < 0.05$ for olanzapine vs risperidone (chi-squared test).

Table V. Risk of developing diabetic ketoacidosis (DKA) according to duration of drug exposure: logistic model results

Model term[a] (reference group)	p-Value	Odds ratio (95% CI)
Patients with >30 days' exposure		
Olanzapine monotherapy (risperidone)	0.026	1.740 (1.078, 2.886)
Age (years)[b]	0.021	0.985 (0.972, 0.998)
Schizophrenia (no schizophrenia)	0.002	2.191 (1.339, 3.551)
Diabetes prior to treatment (no diabetes)	<0.0001	9.199 (5.540, 15.242)
Patients with >90 days' exposure		
Olanzapine monotherapy (risperidone)	0.004	2.402 (1.345, 4.521)
Age (years)[b]	0.025	0.982 (0.967, 0.998)
Diabetes prior to treatment (no diabetes)	<0.0001	8.951 (4.973, 16.017)
Patients with >180 days' exposure		
Olanzapine monotherapy (risperidone)	0.001	3.515 (1.739, 7.888)
Age (years)[b]	0.001	0.970 (0.952, 0.988)
Diabetes prior to treatment (no diabetes)	<0.0001	8.890 (4.506, 17.212)

a Sex, race/ethnicity (Hispanic, African American, missing or other), bipolar disorder, depression and number of months of Medicaid eligibility were not found to be significant predictors of DKA and the data are not shown. Schizophrenia was a significant predictor of DKA for some exposure categories (data shown where relevant).

b Continuous variable.

3.5 times greater (p = 0.001), respectively, for olanzapine compared with risperidone (table V).

Prior diagnosis of diabetes was a significant predictor of diabetic ketoacidosis (approximately 9-fold greater risk, p <0.0001). Age displayed a slight but statistically significant protective effect (table V). The possible interaction between the group variable (i.e. olanzapine vs risperidone) and the presence of a diabetes diagnosis prior to the diabetic ketoacidosis event was evaluated. The interaction was not significant (p = 0.1600) and therefore was not retained in the analysis. Thus, it appears that olanzapine relative to risperidone is an independent risk factor relative to presence of a prior diabetes diagnosis.

Discussion

Diabetic ketoacidosis is one of a spectrum of metabolic disorders that have been linked to the use of atypical antipsychotic agents. Its occurrence is of interest not only because of its severity – it can progress to coma and death, sometimes within a few hours – but also because it can be the first presenting symptom of metabolic disturbance in patients receiving atypical antipsychotic agents.[5,6] Jin et al.[5] reported that diabetic ketoacidosis was the first manifestation of diabetes in 19 of 45 published cases of new-onset diabetes associated with atypical antipsychotic therapy.

According to the present analysis, there was a significantly greater risk of diabetic ketoacidosis with olanzapine treatment than with risperidone treatment. The differences in background variables are unlikely to explain the magnitude of differential risk observed here. Olanzapine patients with diabetic ketoacidosis had a notably higher incidence of schizophrenia and depression, both of which are associated with a higher prevalence of diabetes.[30] Risperidone patients were significantly older than those in the olanzapine group, and age appears to confer a slightly protective effect. African American race was an important risk factor in our analyses. This patient group is recognised as being particularly susceptible to atypical antipsychotic-induced diabetes.[7] However, olanzapine treatment was a significant risk factor even after adjusting for other confounders. The lack of an interaction between the presence of a schizophrenia diagnosis and treatment

drug provides support for the independent relationship between olanzapine and diabetic ketoacidosis.

Ethnicity may play another role in the incidence of diabetic ketoacidosis in certain patient populations. Ketosis-prone type 2 diabetes (diabetes of the Flatbush type) has been reported in African, African American and Hispanic persons as well as other minority ethnic groups.[31] Patients with ketosis-prone diabetes present initially with impaired insulin secretion and insulin action. With appropriate insulin therapy and aggressive diabetes management, significant improvement in β-cell function and insulin sensitivity is realised and insulin therapy may be discontinued within a few months of follow-up.

The association between schizophrenia and diabetes has been previously documented,[32-34] and predates the introduction of the atypical antipsychotic medications.[8,35] Although this study evaluated the presence of diabetic ketoacidosis relative to specific atypical antipsychotic agents and did not evaluate the onset of diabetes as in Leslie and Rosenheck,[25] our findings are consistent with that recent work. Additionally, we extended our analyses to include the impact of exposure time on the risk of diabetic ketoacidosis. Our findings are consistent with published case reports[1,6,8,9] and a number of studies that suggest a possible elevated risk of diabetes with olanzapine versus risperidone,[2,3,13-17,21] although this has not always been a consistent finding.[20,36]

Lack of consistency among studies of diabetes, diabetic ketoacidosis and atypical antipsychotics use may be explained in part by study limitations.[5] Small sample sizes, retrospective designs and variance in reporting of demographic variables limit the types of analyses than can be conducted. Moreover, how cases are selected and reported and the lack of comparator groups limit the generalisability of findings. When the gold standard (a randomised clinical trial) has not been conducted, one must rely on the preponderance of evidence to understand the association between use of an atypical antipsychotics and the incidence of diabetic ketoacidosis and diabetes.

The duration of drug exposure proved to be an important predictor of diabetic ketoacidosis risk. Olanzapine patients faced a higher relative risk as a function of exposure time. The relationship between longer duration of exposure and increased risk of diabetes has been suggested.[10] We found a progressive and statistically significant divergence in risk after 30 days of exposure. The diabetic ketoacidosis risk stabilised within the first 90 days of risperidone treatment, but the risk continued to increase until 360 days (the duration of the study) with olanzapine. This is consistent with an effect mediated by drug-induced weight gain, a sequale associated with increased mortality among patients with schizophrenia.[37] Database constraints prevented the inclusion of body weight in these analyses.

Although there is no shortage of theories to explain the possible mechanism of antipsychotic-associated diabetes, no single mechanism has been clearly identified as the underlying mechanism. Patients can develop diabetes rapidly (often within 3 months) and without significant weight gain, and the diabetes usually improves rapidly after drug withdrawal. Furthermore, the fact that many patients present with diabetic ketoacidosis suggests this may be a function of a more immediate direct metabolic effect rather than one secondary to weight gain. Antagonism of serotonin 5-HT_{2C} or central histamine H_1 receptors or elevation of leptin levels may play a part in the aetiology of atypical-induced diabetes.[9] Although not conclusive, it is interesting to note that for each of these mechanisms, risperidone has a lower propensity than olanzapine to inhibit the relevant receptor,[9] cause weight gain[38,39] or increase leptin levels,[40] providing a possible explanation for the differential effects between the two agents observed in this study.

Although these findings are suggestive of a differential risk between the two agents, the retrospective nature of the study and the limited number of variables available restricts any inference of causality. Additive or synergistic effects on glucose regulation among patients with multiple medications (not captured in these analyses) may exist.[1] There is also an implicit assumption of medication consumption at similar dosages that cannot be verified from the claims record. Additionally, claims screening using specified codes may introduce a possible source of bias. No assessment was made of the impact of dose variation.

Conclusions

In this retrospective study, patients using olanzapine had a greater risk of a diabetic ketoacidosis event than did patients receiving risperidone. The diabetic ketoacidosis rate stabilised within 3 months after the initial prescription for risperidone, while the risk continued to rise for those treated with olanzapine, a notable finding in the extended treatment environment for schizophrenia.

These results underscore the importance of clinical caution as providers decide on the most appropriate treatment course for their patients being treated for schizophrenia. Our findings, coupled with those of previous research, should heighten clinician awareness of the risks of diabetes and metabolic abnormalities in patients using atypical antipsychotics. Not only may the onset of new diabetes develop early in the course of treatment with atypical antipsychotics, but diabetic ketoacidosis may manifest first. Caution is clearly advised in using these agents and it needs to be recognised that the potential for adverse metabolic consequences is not the same across all antipsychotics. Treatment choice should be balanced by the relative benefits and risks of each of the agents.[27]

Clinicians are urged to manage risk by regularly monitoring all patients receiving atypical antipsychotics for the emergence of diabetes. Future research into the relationship of atypical antipsychotic use and diabetes should control for the effects of potentially confounding variables such as age, diagnosis, weight change, activity level, family history and ethnicity.

Acknowledgements

This study was presented at the American College of Neuropsychopharmacology, 42nd Annual Meeting, Puerto Rico, December, 2003 and at the Annual Meeting of the American Psychiatric Association, New York, May, 2004.

This study was supported by funding from Janssen Medical Affairs L.L.C., Titusville, NJ, USA.

Chris Kozma works as a paid consultant for Ortho-McNeil Janssen Scientific Affairs, LLC. Krishnan Ramaswamy is an employee of Janssen Pharmaceutica Products, L.P., Titusville, New Jersey, USA. Henry Nasrallah has received grants/research support from, acted as a consultant to, or served on advisory boards or speakers' bureaus for Abbott Laboratories, AstraZeneca Pharmaceuticals, Janssen L.P., Eli Lilly & Company, Pfizer, Inc. and Shire US, Inc.

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