REVIEWS OF THERAPEUTICS

Olanzapine-Associated Diabetes Mellitus

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Study Objective. To explore the clinical characteristics of hyperglycemia in patients treated with olanzapine.

Design. Retrospective, epidemiologic survey of spontaneously reported adverse events related to olanzapine therapy.

Setting. Government-affiliated drug evaluation center.

Patients. Two hundred thirty-seven patients with olanzapine-associated diabetes or hyperglycemia.

Intervention. One hundred ninety-six cases from January 1994–May 15, 2001, were identified with the United States Food and Drug Administration's MedWatch Drug Surveillance System, and 41 cases published through May 15, 2001, were identified with MEDLINE or through meeting abstracts.

Measurements and Main Results. Of the 237 cases, 188 were new-onset diabetes, 44 were exacerbations of preexistent disease, and 5 could not be classified. Mean patient age for newly diagnosed cases was 40.7 ± 12.9 years and male:female ratio was 1.8. Seventy-three percent of all cases of hyperglycemia appeared within 6 months of start of olanzapine therapy. Eighty patients had metabolic acidosis or ketosis, 41 had glucose levels of 1000 mg/dl or greater, and 15 patients died. When olanzapine was discontinued or the dosage decreased, 78% of patients had improved glycemic control. Hyperglycemia recurred in 8 of 10 cases with rechallenge.

Conclusions. Number of reports, temporal relationship to start of olanzapine therapy, relatively young age, and improvement on drug withdrawal suggest that olanzapine may precipitate or unmask diabetes in susceptible patients.

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OUTLINE

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Results
   Nature of Hyperglycemia Reports

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Olanzapine (Zyprexa; Eli Lilly and Company, Indianapolis, IN), marketed in the United States since 1996, is a psychotropic agent indicated for the management of schizophrenia[1, 2] and short-term treatment of acute manic episodes in bipolar disorder in adults.[1] In addition to approved indications, it has been administered for the treatment of a variety of other conditions including psychosis in dementia and Parkinson's disease, delusional or resistant depression, conduct disorders, aggression, agitation, resistant anxiety disorders, and delirium.[3–6] Known adverse reactions to olanzapine include orthostatic hypotension, weight gain, akathisia, increased salivation, and somnolence.[1] Published reports of hyperglycemia occurring in association with olanzapine began occurring in 1998.[7–28] The spectrum of reported illness ranged from mild glucose intolerance to diabetic ketoacidosis and nonketotic hyperosmolar coma. To gain further insight into the clinical characteristics of diabetes reported in association with olanzapine, we attempted to identify all such cases that had been submitted to the Food and Drug Administration's (FDA) MedWatch surveillance program.

Methods

We identified cases by querying the FDA MedWatch Drug Surveillance System (January 1994–May 15, 2001). Published cases were identified by means of MEDLINE (through May 15, 2001). Selected abstracts from national psychiatry meetings also were reviewed. We combined reports occurring in multiple identification systems. Drug utilization data were obtained from the National Prescription Audit Plus (IMS Health, Inc., Plymouth Meeting, PA) and the National Disease and Therapeutic Index (IMS Health, Inc.) databases.

We assessed documentation of diabetes, severity of hyperglycemia, whether the hyperglycemia was newly diagnosed, demographic features, time to onset of hyperglycemia, and effect of drug discontinuation. We defined "documentation" of newly diagnosed diabetes on the basis of a fasting glucose level of 126 mg/dl (7 mmol/L) or greater, a random glucose level of 200 mg/dl (11 mmol/L) or greater, or elevated glycohemoglobin values; and/or presence of metabolic acidosis or ketosis; and/or physician institution of an antidiabetic drug. Patients without definitive documentation were classified separately. Because individual MedWatch reports

and published cases vary in the completeness of the demographic and clinical information provided, we have specified where such data were missing. Hence, this is a descriptive report based primarily on summary statistics.

We used correlation coefficients, χ^2 tests, and unpaired t tests (all two-tailed) to assess the relationship between certain variables or groups; p values of 0.05 or less were viewed as significant.

Results

We identified 237 distinct cases of olanzapine-associated diabetes or hyperglycemia, including 41 cases in 22 publications.[7–28] Of these reports, 215 originated in the United States and 22 were from international sources.

Nature of Hyperglycemia Reports

Among the 237 reports, there were 188 (79%) cases of newly diagnosed hyperglycemia, 44 (19%) cases of exacerbation of established preexistent diabetes, and 5 (2%) cases that could not be classified. Of the 188 cases of newly diagnosed hyperglycemia, 153 cases fit the serum glucose or glycohemoglobin criteria for the diagnosis of diabetes. Of the patients whose diabetes was determined by fasting blood glucose level, all but two had fasting glucose levels of 140 mg/dl or greater. Of the 35 patients with new-onset hyperglycemia whose reports did not include sufficient glucose data for the diagnosis of diabetes, 19 received antidiabetic drug therapy. Five of the 19 patients were also reported to be acidotic or ketotic. Another three patients were acidotic or ketotic at the time of hyperglycemia, but lacked additional diagnostic data. In addition to these 188 newly diagnosed cases, there were 44 reports of patients with established diabetes in whom metabolic status worsened after starting olanzapine. As stated previously, there were five additional cases in which it was unclear whether the diabetes was newly diagnosed or preexistent.

Demographic Features

At the time of the adverse event, those with newly diagnosed hyperglycemia were younger than those with an exacerbation of preexistent diabetes (Table 1). Among the 153 cases (151 with age data) of newly diagnosed diabetes that were diagnosed by serum glucose or glycohemoglobin levels, the mean ± SD age was

Table 1. Age Distribution of 226 Patients with Olanzapine-Associated Hyperglycemia

Nature of Hyperglycemia Report	Age (yrs)[a]	Distribution by Age Cohort (yrs), no.						
		11–20	21–30	31–40	41–50	51–60	61–70	≥ 70
Newly diagnosed hyperglycemia (n=184)	40.7 ± 12.9	12	23	60	55	20	10	4
Glucose or glycohemoglobin level (n=151)	39.8 ± 12.4	9	20	55	45	11	8	3
Drug therapy ± acidosis or ketosis (n=20)	47.4 ± 12.4	0	2	3	8	5	1	1
Less well documented (n=13)	41.3 ± 17.0	3	1	2	2	4	1	0
Exacerbation of preexistent diabetes (n=38)	51.7 ± 15.4	2	0	7	11	8	4	6
Unknown if new onset or exacerbation (n=4)	38.8 ± 5.4	0	0	3	1	0	0	0
Totals	42.6 ± 13.8	14	23	70	67	28	14	10

[a]Data are mean ± SD.

Age was unknown for 11 patients. Age range of the 226 patients was 13–79 years. Hyperglycemic events were categorized by type of documentation available and patient's age in years at the time of the event.

39.8 ± 12.4 years (range 13–75 yrs), and 68% of these cases occurred before the age of 45 years. Fifty percent of these cases occurred in the third and fourth decades of life. There were twice as many men as women in this subgroup. Twelve cases of newly diagnosed hyperglycemia occurred in the 11–20-year age group, and six of these cases were pediatric patients younger than 18 years. Of the 44 patients (38 with age data) with exacerbation of preexistent diabetes, mean age was 51.7 ± 15.4 years (range 17–79 years), with a male:female ratio of 1.5.

Information on race was available for 150 patients, and of these, 84 (56%) were Caucasian, 58 (39%) were of African descent, 5 (3%) were Hispanic, and 3 (2%) were Asian.
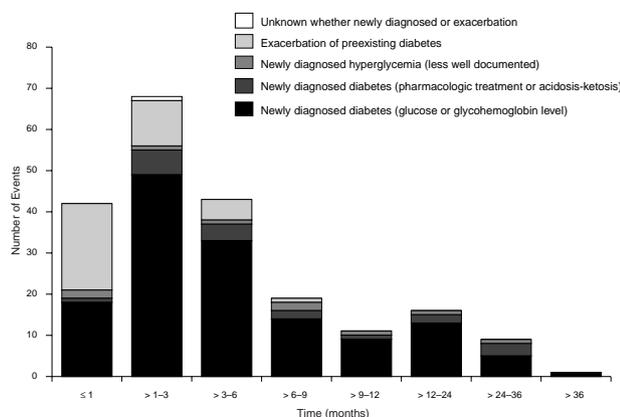

Figure 1. Time to hyperglycemic event. Hyperglycemic events were categorized by the time to occurrence after start of olanzapine therapy. Data were available for 209 (88%) of the 237 patients. Among these, hyperglycemia was identified within the first 6 months of olanzapine therapy in 153 patients (73%). A notable number of cases had delayed onset up to 45 months.

Time to Onset

The time to diagnosis of hyperglycemia for all subjects for whom these data were available (209 patients) ranged from 2 days to 45 months, but for 73% (153 patients), it was 6 months or less from the time olanzapine therapy was started (Figure 1). Among those with newly diagnosed diabetes documented by glucose or glycohemoglobin levels and for whom adequate time-to-onset information was available (142 patients), the onset of diabetes occurred within the first month of olanzapine therapy in 18 patients (13%). Forty-seven percent of such cases occurred within the first 3 months, and 70% of such cases occurred within 6 months of drug exposure. Time-to-onset information was available for 38 of 44 patients with exacerbation of preexistent diabetes. In these patients, the glycemic exacerbation was observed within the first month of olanzapine therapy in 55% of cases, within the first 3 months in 84%, and within the first 6 months in 97%.

Olanzapine Dosages

Dosage information was available for 202 (85%) of the 237 cases. In these patients, the mean ± SD olanzapine dosage was 15.6 ± 7.0 mg/day (range 2.5–40 mg/day). Mean daily doses did not differ by sex (male patients 15.3 ± 6.8 mg, female patients 15.6 ± 7.2 mg). Mean daily doses were lower for patients with preexistent diabetes (13.2 ± 6.2 mg) versus those with new-onset hyperglycemia (16.1 ± 7.0 mg) (p=0.02) and tended to be higher in those with ketosis or acidosis (16.6 ± 6.8 mg) than in those without (15.0 ± 7.0 mg) (p=0.12). There was no significant correlation between dose and the reported glucose level or between dose and time

to onset. Drug levels, which may be more predictive of clinical effects, typically were not available.

Serious Outcomes

Metabolic abnormalities ranged from mild glucose intolerance to diabetic ketoacidosis and hyperosmolar coma. In 69 cases, the blood glucose level was 700 mg/dl or greater. Of these, at least 65 (94%) had newly diagnosed diabetes and 2 (3%) had exacerbation of preexistent diabetes. Two other cases could not be classified because of incomplete information. (In two additional cases, the patients progressed to hyperosmolar coma with glucose values of 1676 mg/dl and 800 mg/dl, respectively. Eight months earlier, the first patient had a fasting glucose of 131 mg/dl and a hemoglobin A_{1c} of 6.4%. The second patient developed hyperglycemia again with rechallenge.) Of these 69 patients, 41 (59%) had blood glucose levels of 1000 mg/dl or greater. Thirty-eight (93%) of the 41 cases were newly diagnosed diabetes. At least 43 (62%) of the cases with high glucose levels occurred within 6 months of the start of olanzapine therapy. (Hyperglycemia [800 mg/dl] occurred within 3.5 months of rechallenge in an additional patient.) The mean age of these patients was 42.4 ± 12.7 years (if glucose ≥ 700 mg/dl but < 1000 mg/dl) or 41.4 ± 9.4 years (if glucose ≥ 1000 mg/dl). Information on ethnic background was available for 50 of those with high glucose levels (≥ 700 mg/dl). Forty-two percent (21 patients) were African-American, whereas 54% (27 patients) were Caucasian.

Metabolic Acidosis

There were 80 cases of ketosis or metabolic acidosis; 92% (74 patients) of these cases were newly diagnosed diabetes. In three patients, whether the diabetes was newly diagnosed or preexistent was unclear. Although the degree of acidosis was generally mild, the presenting glucose value was 500 mg/dl or greater in 57 patients. In 41 patients, the acidosis or ketosis was accompanied by glucose values of 700 mg/dl or greater.

Mental Status Changes

In 43 patients, mental status changes (obtundation or confusion) occurred in conjunction with the hyperglycemia. Of these, 42 patients had newly diagnosed diabetes and 1 had exacerbation of preexistent diabetes.

Table 2. Characteristics of the 15 Patients Who Died

Characteristic	Data
Age, mean ± SD (yrs)	43.1 ± 16.3
M/F (no.)	8/7
Ethnic background (no.)	
Caucasian	6
African-American	1
Asian	1
Unknown	7
Hyperglycemia presentation (no.)	
Newly diagnosed	14
Exacerbation	1
Time to onset < 3 mo. (no.)	8
Olanzapine dose, mean ± SD (mg)	17.9 ± 10.3
Glucose level ≥ 700 mg/dl (no.)	3
Acidotic (no.)	9

Setting

Most cases occurred in the community setting. In four patients, hyperglycemia was identified during incarceration in a prison. In two of these patients, glucose levels were 1622 and 1299 mg/dl, respectively. In a third patient, the glycohemoglobin was 13%, and the patient subsequently died. The fourth patient, with a history of diabetes, had a glucose level of 800 mg/dl and was reported to be "unresponsive to high insulin doses." Whether the mental status changes that can occur with hyperglycemia were the reason for incarceration was not known.

Pancreatitis or Hyperamylasemia

Pancreatitis or hyperamylasemia in association with hyperglycemia was reported in 17 patients. Of the 10 patients with concomitant acidosis or ketosis, 7 had elevated lipase levels, diagnostic computed tomographic findings, and/or treatment with pancreatic enzymes. Six patients with reported pancreatitis or hyperamylasemia had glucose values of 700 mg/dl or greater, and four of these patients had elevated lipase levels or confirmatory imaging studies. One case occurred in a 15-year-old boy who died of necrotizing pancreatitis 1 month after diabetes mellitus was diagnosed.

Deaths

Fifteen patients (8 male and 7 female patients, 6 Caucasian) died, including the 15-year-old boy (Table 2). Fourteen of these deaths occurred in patients with newly diagnosed diabetes. For eight of these patients, the time to onset was less

than 3 months. The mean daily dose of olanzapine was 17.9 ± 10.3 mg. Of the 15 deaths, 13 occurred during or shortly after a hyperglycemic episode, with acidosis or ketosis reported in 9 of the 13 cases. In the other two cases, the patients died a month after the hyperglycemia was identified, one with necrotizing pancreatitis and the other of unknown causes. Often, these patients had many medical problems at the time of death, making it difficult to assign a primary role for the hyperglycemia in their deterioration. One of the patients, a 39-year-old woman with symptoms of polydipsia and blurred vision, died after 8 months of olanzapine therapy. At autopsy, the vitreal glucose level was 867 mg/dl, and the patient was acidotic.

Additional Risk Factors

The reports did not uniformly provide systematic information on risk factors for diabetes. Limited body weight data were available for 169 patients. Approximately 24% of these patients did not appear either to be overweight or to have had sustained weight gain. Of the 80 patients with newly diagnosed hyperglycemia for whom family history information was provided, 43 (54%) had a positive family history (in 2 cases, it was remote), and 37 (46%) had a negative family history for diabetes. Hepatitis, a putative risk factor,[29, 30] was reported in six patients (five with hepatitis C and one with hepatitis B). There was also no systematic pattern of concomitant drug therapy, as reported below.

Concomitant Drugs

There was no consistent pattern of concomitant drug therapy that emerged from the data reported for these patients. Only a limited number of patients were receiving drugs known to induce hyperglycemia. One patient received systemic steroids for sinusitis, two others received nonsystemic steroids as a cream or inhaler, one had been taking niacin, and nine had been taking thiazide diuretics. Of note, eight patients had been taking another atypical antipsychotic (risperidone [three patients], clozapine [four], or quetiapine [one]). Treatment with valproate, a controversial putative risk factor for hyperglycemia,[31–34] was reported for 59 of the 190 patients with some information on serial or concomitant drug therapy. The frequency of known valproate therapy in those

with glucose levels of 700 mg/dl or greater (35%), however, did not differ from that in patients with glucose levels less than 700 mg/dl (33%) (χ^2=0.1, degrees of freedom [df]=1, p=0.75). Valproate therapy was reported in seven cases (41%) of pancreatitis or hyperamylasemia. The other most frequently reported concurrent drugs were lithium, benztropine, conventional antipsychotics, thyroid hormone, antidepressants (fluoxetine, paroxetine, sertraline, venlafaxine), and clonazepam. A trend for a higher frequency of lithium therapy in those with glucose levels of 700 mg/dl or greater (20%) than that in patients with lower glucose levels (9%) failed to reach significance (χ^2=3.4, df=1, p=0.06).

Olanzapine Withdrawal and Rechallenge

Complete data on the course of diabetes were lacking in many cases. Olanzapine was discontinued for various reasons in 105 cases, but follow-up data were available only for 76 of these cases. Of the 76 cases, 60 patients (79%) were reported to have improved, and 16 (21%) did not improve. Complete follow-up information was not available to determine how many of the patients who improved had glucose levels that returned to normal or how many of these patients required continuing therapy. Nonetheless, some of the cases with more complete information were compelling. A thin, otherwise healthy, 72-year-old man with a negative family history of diabetes was hospitalized for psychiatric decompensation after self-discontinuation of drug therapy. His glucose levels were normal, and he was started on olanzapine 10 mg/day. Approximately 2 months later, for behavioral changes, his dosage was decreased to 5 mg/day. Shortly thereafter, the patient became polydipsic and somnolent. He was hospitalized with a glucose level of 1600 mg/dl. Olanzapine was discontinued. The patient was treated initially with insulin and later with oral antidiabetic agents. Subsequently, these also were discontinued. The patient remained normoglycemic without antidiabetic agents for 8 months after the hyperglycemic episode—although subsequently a low dosage of an oral antidiabetic was required.

Of the nine patients switched from olanzapine to another identified atypical antipsychotic, glucose control improved in five of seven patients switched to risperidone and in one of two patients switched to quetiapine. Two patients who developed diabetes while taking olanzapine also had a history of hyperglycemia with

clozapine.

The olanzapine dosage was reduced in at least six patients. Follow-up data were available only for five patients because one patient died of complications before a response to the lower dosage could be assessed. Of the five patients, three improved and two had no change. For patients in whom olanzapine was not discontinued, insufficient data were available to determine the course of their diabetes.

Ten patients were rechallenged with olanzapine. Of these, eight (80%) experienced deterioration in glycemic control. This occurred within 3 days of rechallenge for two patients. In two others patients, deterioration in glycemic control occurred 7 and 8 days after rechallenge. Approximately 5–6 months after reinstitution of olanzapine, another patient developed diabetic ketoacidosis and hyperamylasemia complicated by diffuse clotting and death. Among the 10 patients, outcome was unknown for one patient. The one other patient who did not have a recurrence of hyperglycemia had an interval weight loss of at least 24 pounds. Glycemic control again improved after olanzapine discontinuation in three patients.

Discussion

We identified 237 cases of newly diagnosed hyperglycemia or diabetes mellitus, or diabetic exacerbation, associated with olanzapine. These reports are most notable for the number of patient in whom glucose levels equaled or exceeded 700 mg/dl and for the relatively young age of these patients. In contrast to our findings, the hyperosmolar diabetic state typically is found in elderly patients, often living alone, who decompensate because of a stroke, infection, or drug therapy and who are unable to ingest sufficient fluid.[35, 36] We also identified other significant outcomes, including metabolic acidosis or ketosis in 80 patients, obtundation or confusion in 43, pancreatitis or hyperamylasemia in 17, and death in close temporal proximity to the hyperglycemic episode in 13. The gravity of these outcomes highlights the need to further examine this potential association.

Several of our findings suggest a relationship between olanzapine therapy and diabetes. These include the number of cases reported, the temporal relationship to the start of olanzapine therapy, and the prompt reversibility of hyperglycemia with drug withdrawal in some cases. Furthermore, the mean age in the newly

diagnosed cases in our sample (40.7 yrs) is considerably less than the typical mean age of patients with newly diagnosed type 2 diabetes. Data from the National Health Interview Surveys (NHIS) indicate that the overwhelming majority of newly diagnosed cases of type 2 diabetes occurs in older individuals, with the highest incidence in the 65–74-year age cohort (8.6/1000/yr).[37] In the U.S. population, prevalence also increases with age: 81% of diabetes cases are in people older than 44 years. Indeed, in the 65–74-year and the 75-year and older age groups, 11% and 10%, respectively, have diabetes. In contrast, the incidence of diabetes in people aged 25–45 years is 1.79/1000/year, and only 1% in that age group have the disease.[37] Figure 2 illustrates an indirect comparison of the cumulative relative frequency of new-onset diabetes cases by age in our study with that of the U.S. population. The frequency of newly diagnosed cases in the 0–44-year age group appears to be twice as high among olanzapine-treated patients (66%) than in the U.S. population (33%). When we compared the distribution of olanzapine-associated new-onset cases with that of the NHIS using the same age groups, we determined that the difference was statistically significant ($\chi^2=113.6$, $df=5$, p<0.0001). These data suggest that the onset of diabetes mellitus occurs earlier in life among
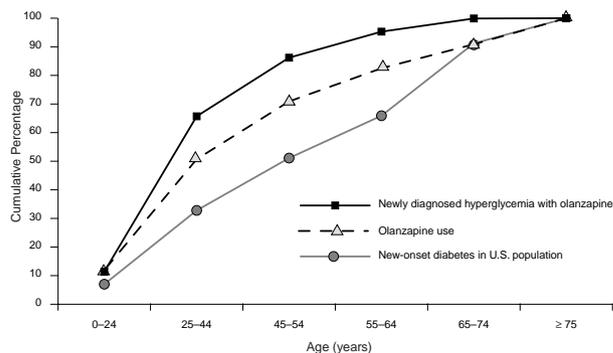
Figure 2. Distribution by age. Age distribution of olanzapine-associated new-onset diabetes was compared with the distribution of new-onset diabetes cases in the U.S. population.[37] The National Disease and Therapeutic Index drug appearance data from office visits for 1996–2000 were used to assess olanzapine treatment by age.[38] Drug appearances include new and refill prescriptions, as well as samples provided to patients by physicians. Patient age was unspecified for 2.8% of drug appearances. There were twice as many cases of diabetes associated with olanzapine in the 0–44-year age range as there were in the U.S. population survey, demonstrating the relatively young age of these cases. The two distributions were different (p<0.0001).

those receiving olanzapine than it does in the general population, with the sharpest rise in those younger than 44 years. The age distribution of patients with olanzapine-associated newly diagnosed hyperglycemia is also to the left of the age distribution for all olanzapine prescription recipients (based on utilization data from IMS Health, Inc.[38]). This suggests that the distribution of cases is unlikely to simply reflect the age distribution of the population that receives the drug. This relatively young age at the time of onset of hyperglycemia also was observed with another atypical antipsychotic, clozapine.[39]

In addition to the relative youth of the olanzapine-associated cases, the observed imbalance between the sexes is atypical of diabetes. The male:female ratio for all cases of newly diagnosed hyperglycemia in our series was 1.8. Data from NHIS indicate a male:female prevalence ratio of 0.8 and a male:female incidence ratio of 0.7.[37] There is no known sex disparity for the prevalence of schizophrenia or bipolar disease.[40–42] The National Disease and Therapeutic Index data indicate that the male:female ratio of olanzapine therapy is 0.8 (Figure 3).[38] This same sex disparity was observed with clozapine-associated hyperglycemia.[39]

No other clear risk factors for olanzapine-associated hyperglycemia emerged from this study other than possibly race and lithium therapy. African-Americans compose about 10% of patients receiving olanzapine (Figure 4) but compose nearly 39% (58 of 150) of cases of diabetes with ethnic heritage information in this report. Although the prevalence of diabetes was higher among African-Americans than among Caucasians for all age groups, the disparity in prevalence increases with age. The prevalence of diabetes is approximately 1.3 times higher in the 25–44-year age group and is only 2-fold higher in older age groups.[37] We did not find a clear dose effect, although there was a trend for newly diagnosed cases and cases with ketosis or acidosis to have higher mean olanzapine daily doses. There was a weak association between concomitant lithium therapy and very high glucose levels. Lithium can cause diabetes insipidus and weight gain[43] and, as such, increase the risk for hyperosmolar states.

There is no obvious mechanism by which olanzapine might impair carbohydrate metabolism. Although weight gain can occur during therapy,[1] the prompt onset of diabetes in many

A

Hyperglycemia Cases by Sex (%)

□ Unspecified   ■ Male   ▨ Female

B

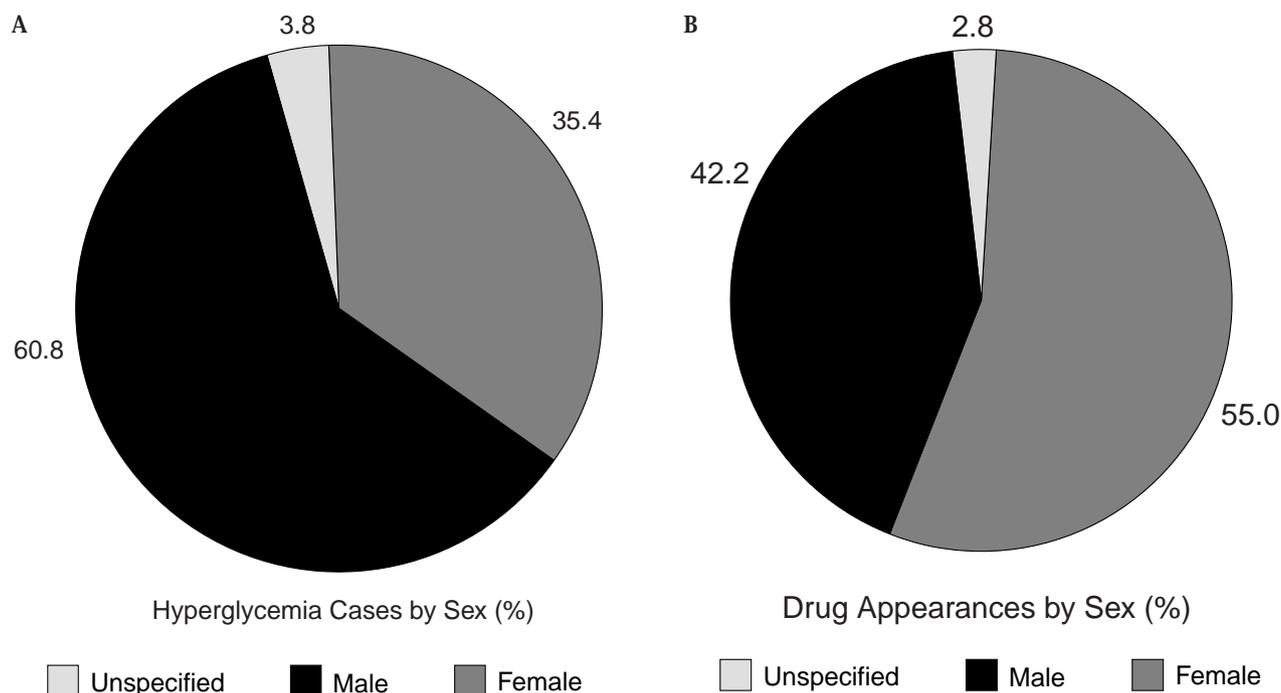Drug Appearances by Sex (%)

□ Unspecified   ■ Male   ▨ Female

Figure 3. Sex of patients with olanzapine-associated hyperglycemia (A) and sex of patients treated with olanzapine (B). National Disease and Therapeutic Index drug appearance data from office visits for 1996–2000 were used.[38] Drug appearances include new and refill prescriptions, as well as samples provided to patients by physicians. The patterns do not explain the sex differences observed in the adverse event reports. Curiously, these data indicate that 58% of the men versus 44% of the women receiving olanzapine were younger than 45 years. Diabetes in this age group is more common in women.[37]

patients (six cases within the first week of treatment) argues against a primary role for weight gain in the development of olanzapine-associated diabetes. Weight gain may contribute to the late-onset hyperglycemia that was observed. The variations in the time to onset of hyperglycemia may reflect several mechanisms of action (e.g., direct islet cell toxic reaction vs interference with non–insulin-mediated glucose utilization vs insulin resistance). There is no overt chemical similarity between olanzapine and other compounds known to be islet cell toxins (Figure 5).[44, 45] Olanzapine also may be unmasking diabetes in genetically vulnerable patients. The metabolism of olanzapine in sensitive individuals may differ from that in unaffected individuals as well.

There are limitations to this report. The MedWatch database relies on spontaneous adverse event reporting. Substantial under-reporting is characteristic of systems such as MedWatch.[46–53] Indeed, olanzapine does not require specific routine laboratory monitoring, and the symptoms of diabetes may be missed in low-functioning patients. Distortions in reporting may occur over time as prescribers become aware of a particular adverse event from experience, literature, and/or changes to product labels. Also, clinicians possibly were more attuned to hyperglycemia because weight gain is a known adverse effect[1] and glucose monitoring may have been more common in such patients. Although we know the total number of prescriptions, approximately 15 million between 1996 and 2000 inclusive, we cannot determine patient-year-exposure (i.e., we have no precise estimates on patient carryover from year to year or the numbers of patients who received olanzapine in the populations who contributed to these reports).[54] Furthermore, control populations were absent, and case descriptions may be incomplete. Even indirect comparisons of age distribution of our cases with population patterns derived from another study can be biased by several factors. Hence, we cannot determine causality or incidence. The possibility that other factors (e.g., detection bias, preexistent risk factors, prior drug therapy, or concomitant drugs) contributed to the hyperglycemia cannot be excluded. Nonetheless, the MedWatch surveillance system can provide signals for adverse events, including those that might not be
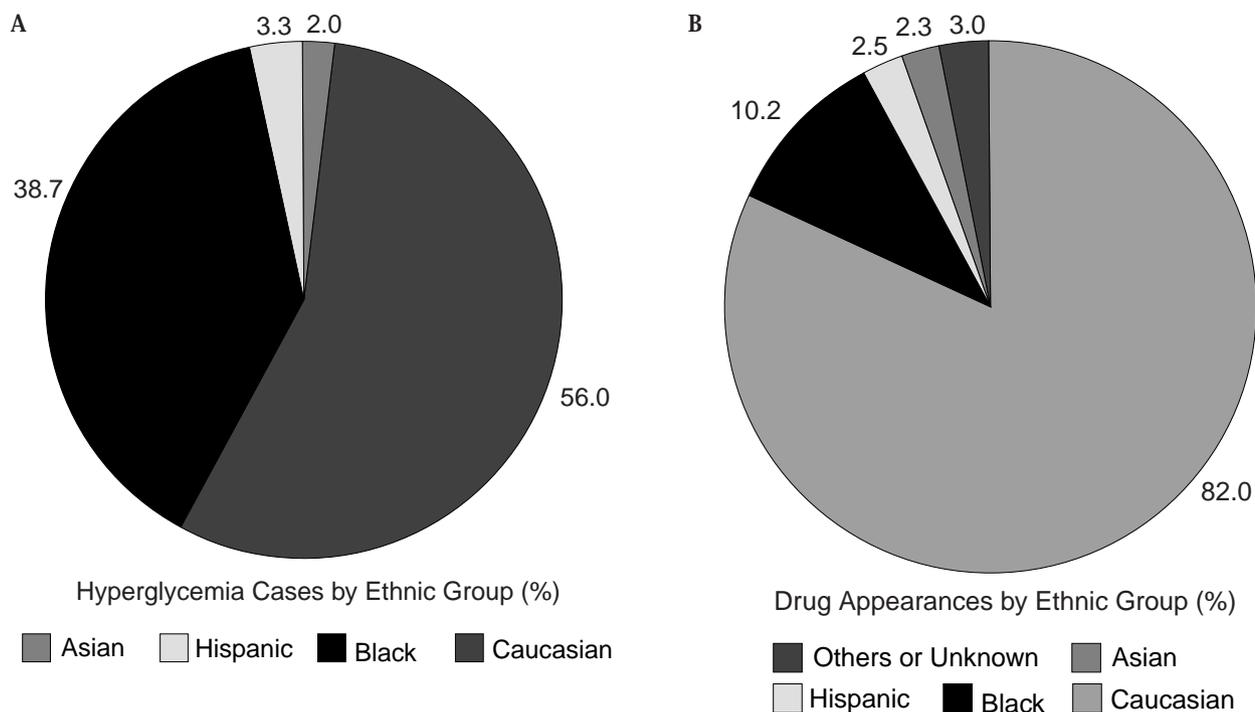

Figure 4. Ethnic background of patients with olanzapine-associated hyperglycemia for whom such information was available (A) and ethnic background of patients treated with olanzapine (B). National Disease and Therapeutic Index drug appearance data from office visits for 1996–2000 were used.[38] Drug appearances include new and refill prescriptions, as well as samples provided to patients by physicians. The patterns do not explain the racial differences observed in the adverse event reports.

identified during relatively short efficacy trials.

Indeed, preliminary findings from a retrospective analysis of a large prescription claims database suggest that the risk for incident diabetes (defined as starting antidiabetic pharmacotherapy) was comparably higher (about 3-fold) in patients receiving a number of antipsychotic agents, including olanzapine, than in those who did not.[55] These findings, in turn, are supported by results of smaller studies suggesting that antipsychotic agents, including some conventional neuroleptics, are associated with altered glucose tolerance and insulin response, especially in the setting of tardive dyskinesia,[56, 57] and that glucose tolerance improves with the discontinuation of antipsychotic agents.[56] Finally, hyperglycemia associated with many of the newer antipsychotics has been reported,[58–61] although the majority of published cases implicate clozapine or olanzapine.

A drug that potentially precipitates diabetes in patients with chronic mental illness has implications for the patients and their families and clinicians.[25, 58] Low-functioning patients may lack sufficient insight to recognize the symptoms of diabetes or may lack access to medical care. Because olanzapine is known to cause weight gain, dry mouth, and sedation,[1] laboratory evaluation of patients with weight loss or polydipsia could be delayed. Mental status changes associated with hyperglycemia or hypoglycemia may be mistaken for psychotic or antisocial behavior and result in improper management or incarceration. The availability of insulin can magnify the lethality of suicide attempts.[25] Further, switching to another antipsychotic agent or noncompliance with the offending agent while a patient is taking antidiabetic pharmacotherapy may result in hypoglycemia.[58]

In patients with olanzapine-associated diabetes, the decision to switch to another antipsychotic versus continuing olanzapine is a difficult one. In the absence of prospective, direct-comparison studies, whether substantive differences exist in the hyperglycemic risk for the various atypical antipsychotic agents is not known. Moreover, changing to another drug carries the risk of a psychotic flare.

Conclusion

These results suggest a causal relationship between olanzapine and development or worsening of diabetes. The onset of hyperglycemia may be rapid and severe, the association is not dose dependent, and the risk does not
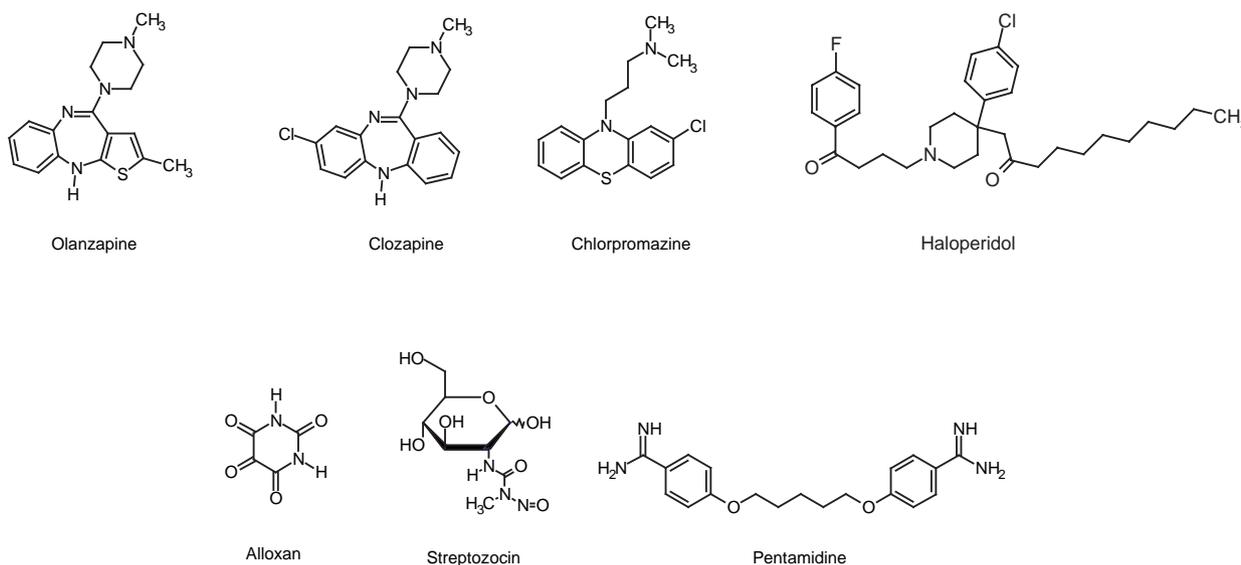

Figure 5. Chemical structures. The physical chemical properties of olanzapine that could contribute to B cell toxic reaction are unknown. Alloxan, streptozocin, and pentamidine are chemical compounds known to induce glucose intolerance through islet cell damage. Chlorpromazine, a classic antipsychotic agent, also has been associated with diabetes,[44] and haloperidol alters the insulin response to a carbohydrate load.[45] Although these compounds all have ring structures, the rings are not uniformly planar nor are any of the side chains common to all.

vanish with extended therapy. Awareness of the potential safety issues will help guide drug selection and direct adverse event monitoring so that patients may more fully benefit from the substantial therapeutic efficacy offered by the atypical antipsychotic agents. Because spontaneous adverse event surveillance can neither establish causality nor determine true incidence and prevalence, further research is indicated.

Addendum

Subsequent to acceptance of our manuscript for publication, we extended our FDA MedWatch inquiry through February 2002, and the findings support our original observations.[62–64] We identified an additional 52 cases of hyperglycemia (42 domestic, 10 foreign). Of these, 37 were newly diagnosed hyperglycemia, 13 were exacerbation of preexistent diabetes, and 2 could not be categorized. Among the cases with age information, the mean ± SD age at the time of diagnosis was 45.1 ± 14.4 years overall (48 patients), 43.4 ± 13.2 years for those with newly diagnosed hyperglycemia (35 patients), and 50.0 ± 17.6 years for those with exacerbation of preexistent disease (12 patients). Two cases occurred in children aged 14 and 16 years, respectively. The male:female ratio was 1.8:1 (51 patients).

Of the 34 patients with ethnic background information, 19 (56%) were Caucasian, 10 (29%) were African-American, 3 (9%) were Asian, and 2 (6%) were Hispanic. Among 38 cases with time-to-onset data, hyperglycemia occurred within 6 months of starting olanzapine in 23 patients (60%). Ketosis and/or acidosis in the setting of hyperglycemia was reported in 20 cases. Of five reports of pancreatitis, four cases were documented by lipase levels or computed tomographic findings; two cases were complicated by death. Eight additional deaths occurred; one of these deaths occurred in a 35-year-old man within 1 month of diagnosis and after olanzapine had been discontinued.

Glucose levels of 700 mg/dl or greater were reported in 14 cases, four of which had levels of 1000 mg/dl or greater. Twelve of these cases occurred in patients with newly diagnosed hyperglycemia, and the other two occurred in patients with exacerbation of preexistent diabetes. Ten of the cases with glucose levels of 700 mg/dl or greater were accompanied by varying degrees of ketosis and/or acidosis. Three of the patients with high glucose levels had

pancreatitis documented by lipase levels and/or computed tomography. Five patients with glucose levels of 700 mg/dl or greater died. One patient had an abnormal fasting glucose level in his record (137 mg/dl) prior to starting olanzapine, but the physicians were unaware of its existence or its significance before the patient progressed to a hyperosmolar state and died.

Mean olanzapine dosage in 43 cases was 14.1 ± 7.3 mg/day (using the maximum known therapeutic dose and excluding an overdose of 1500 mg). No correlation was noted between time to onset and dosage (r=0.37, 36 patients). Some information for concomitant drug therapy was available for 41 cases (79%). Four patients received no concomitant drugs, three were taking a thiazide diuretic, four received nonsystemic corticosteroids (nasal or inhaled), and two were taking systemic corticosteroids (cloprednol 5 mg or prednisone 10 mg). One patient was taking quetiapine; another may have been taking risperidone concurrently. Seven patients received valproate, and six were taking lithium. Olanzapine was discontinued in 27 patients. Although follow-up was incomplete, insulin dosages were decreased successfully in two patients, and antidiabetic drug therapy was discontinued in another two patients. For the latter two patients, oral antidiabetic agents needed to be instituted 8 and 13 months later, respectively.

Acknowledgments

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