A Survey of Reports of Quetiapine-Associated Hyperglycemia and Diabetes Mellitus

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Objective: To explore the clinical characteristics of hyperglycemia in patients treated with quetiapine.

Method: A pharmacovigilance survey of spontaneously reported adverse events in quetiapine-treated patients was conducted using reports from the U.S. Food and Drug Administration MedWatch program (January 1, 1997, through July 31, 2002) and published cases using the search terms hyperglycemia, diabetes, acidosis, ketosis, and ketoacidosis.

Results: We identified 46 reports of quetiapine-associated hyperglycemia or diabetes and 9 additional reports of acidosis that occurred in the absence of hyperglycemia and were excluded from the immediate analyses. Of the reports of quetiapine-associated hyperglycemia, 34 patients had newly diagnosed hyperglycemia, 8 had exacerbation of preexisting diabetes mellitus, and 4 could not be classified. The mean ± SD age was 35.3 ± 16.2 years (range, 5–76 years). New-onset patients (aged 31.2 ± 14.8 years) tended to be younger than those with preexisting diabetes (43.5 ± 16.4 years, p = .08). The overall male:female ratio was 1.9. Most cases appeared within 6 months of quetiapine initiation. The severity of cases ranged from mild glucose intolerance to diabetic ketoacidosis or hyperosmolar coma. There were 21 cases of ketoacidosis or ketosis. There were 11 deaths.

Conclusion: Atypical antipsychotic use may unmask or precipitate hyperglycemia.

Update: An additional 23 cases were identified since August 1, 2002, the end of the first survey, by extending the search through November 30, 2003, bringing the total to 69.

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Quetiapine fumarate is a psychotropic agent that was approved in the United States in 1997 for the treatment of schizophrenia.[1] In addition to the approved indication, quetiapine has been administered for the treatment of a variety of other conditions including dementia-related behavioral disorders, delusional disorder, Parkinson's-related psychosis, acute mania, bipolar disorder, and obsessive-compulsive disorder.[2–9] Quetiapine, like clozapine and olanzapine, has antiserotonergic ($5\text{-}HT_2$) and antidopaminergic (D_2) activity.[1] It is a dibenzothiazepine with a chemical structure distinct from the dibenzodiazepines. Eleven metabolites are formed by hepatic oxidation,[10] which includes sulfoxidation by the cytochrome P450 isoenzyme 3A4 to an inactive metabolite.[1] There are 2 active metabolites present at low levels (≤ 12% circulating parent drug).[10] Drug levels are increased by hepatic impairment.[1] Drug clearance is decreased by coadministration of cytochrome P450 3A4 inhibitors, e.g., erythromycin, fluconazole, itraconazole, and ketoconazole.[1,10] Clearance is accelerated by carbamazepine, phenytoin, and thioridazine.[1,11,12] Quetiapine's use is accompanied by less weight gain than observed with other atypical antipsychotics but more than that observed with many conventional antipsychotics.[13–17]

Sporadic reports of diabetes have occurred in the last 5 years, but the risk and characteristics of quetiapine-associated hyperglycemia remain unclear.[18–22] To gain further insight into this potential problem, we attempted to identify all such cases that had been submitted to the U.S. Food and Drug Administration's (FDA) MedWatch Safety Information and Adverse Event Reporting Program and MEDLINE.

METHOD

We identified cases by querying the FDA MedWatch Safety Information and Adverse Event Reporting Program (January 1, 1997, through July 31, 2002). Published cases were identified by using MEDLINE (January 1, 1997, through July 31, 2002). We combined duplicate reports. Drug utilization data were obtained from the National Prescription Audit *Plus*™ (IMS HEALTH, Inc., Plymouth Meeting, Pa.) and the National Disease and Therapeutic Index Audit™ (IMS HEALTH) databases.

We assessed the documentation of diabetes, the severity of hyperglycemia, whether the hyperglycemia was newly diagnosed, demographic characteristics, time to onset of hyperglycemia, dosages, and effect of drug discontinuation. We defined 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 the presence of frank ketoacidosis or ketosis; and/or physician institution of an antidiabetic drug. Cases in which the acidosis was not related to or did not occur in the setting of hyperglycemia were excluded. Patients without definitive documentation were classified separately. In cases in which the dose was changed, the maximal daily dose was utilized.

Because individual MedWatch reports and published cases vary in the completeness of the demographic and clinical information provided, we specify where such data are missing. Hence, this is a descriptive report based primarily on summary statistics to identify trends. We used correlation coefficients, Kruskal-Wallis tests, χ^2 tests, and unpaired t tests to assess the relationship between certain variables or groups; p values of .05 or less were viewed as nominally significant for the purpose of identifying possible associations between variables or groups.

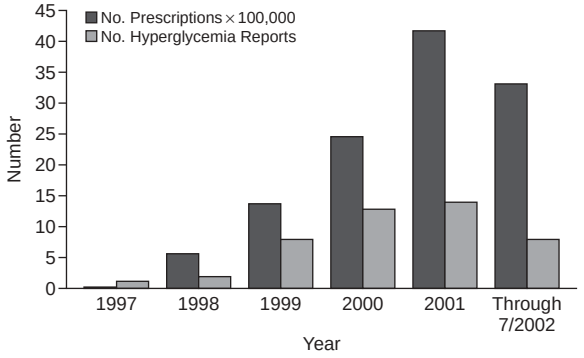
RESULTS

Nature of Hyperglycemia Reports

We identified 46 distinct cases of quetiapine-associated diabetes or hyperglycemia, 5 of which were published.[18–22] The number of reports increased with patient exposure (Figure 1). Patients in these reports suffered from a variety of disorders, including aggression, conduct disorder, bipolar disorder, depression, psychosis, schizoaffective disorder, and schizophrenia. Of the 46 reports, 34 originated in the United States and 12 were from international sources. Of the cases of quetiapine-associated hyperglycemia, 34 had newly diagnosed hyperglycemia, 8 had exacerbation of preexisting diabetes mellitus, and 4 could not be classified. Of the newly diagnosed cases, 23 met the glucose or glycohemoglobin criteria for diagnosis, 5 had antidiabetic therapy instituted, and 6 were reported as being hyperglycemic or diabetic without supportive documentation. One of the patients with preexisting disease was reported to have borderline diabetes and another, impaired fasting glucose levels. In an additional case, a patient who developed hyperglycemia during treatment with olanzapine was switched to quetiapine.[23] Glycemic control did not return until the discontinuation of quetiapine.

There were 9 additional reports of acidosis that did not occur in association with hyperglycemia (4 domestic, 5 international).[24] A variety of causes, including respiratory insufficiency, drug overdose, overdose of a concomitant drug, neuroleptic malignant syndrome, cardiac arrest, and ischemic or hemorrhagic bowel disease, appeared to underlie or contribute to the acidosis.

Figure 1. Changes in Number of Quetiapine Prescriptions and Hyperglycemic Event Reports Over Time[a]

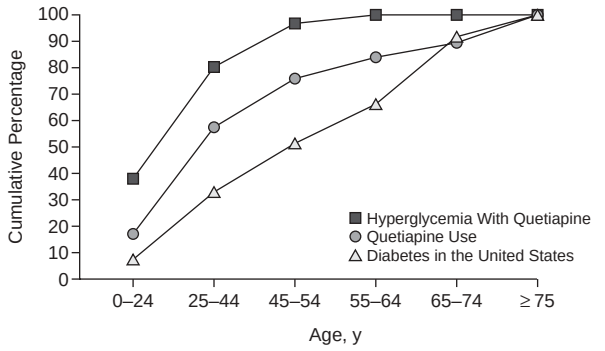


[a]Hyperglycemic events were distributed by the year of their occurrence. If the date of occurrence was unavailable, events were posted to the time of the adverse event report or the time of publication. Prescriptions were similarly distributed by year (IMS HEALTH National Prescription Audit *Plus*). There were approximately 11,932,000 prescriptions dispensed by retail pharmacies (chains, independent, food stores, long-term care sites, and mail-order; data are from 1997 through July 31, 2002). The estimated mean prescription length was 38.2 days (IMS HEALTH National Disease and Therapeutic Index Audit; data from January 1, 1997, through June 30, 2002; duration data available from 49% of survey reports). Reports of hyperglycemia paralleled sales data.

Demographic Features

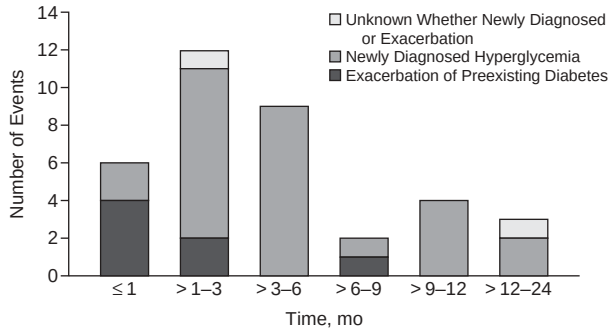
The mean ± SD age of patients with quetiapine-associated hyperglycemia was 35.3 ± 16.2 years (range, 5–76 years; N = 42 of 46 [data unavailable for N = 4]). Nine were under the age of 19 years. Patients with new-

Figure 2. Age Distribution of Quetiapine-Associated New-Onset Hyperglycemia (U.S. cases) Compared With the Distribution of Cases of New-Onset Diabetes in the U.S. Population[a,b]



[a]U.S. general population data from Kenny et al.[25]
[b]IMS HEALTH National Disease and Therapeutic Index Audit drug appearance data from office visits for January 1, 1997, through June 30, 2002, were used to assess quetiapine treatment by age. Drug appearances include new and refill prescriptions as well as samples provided to patients by physicians. Age data were unspecified for only 2.9% of patients using quetiapine. The percentage of cases in which hyperglycemia was associated with quetiapine in the 0- to 44-year-old age group was 2.5 times that in the U.S. population survey, demonstrating the relatively young age of these cases.

Figure 3. Time to Hyperglycemic Event After Initiation of Quetiapine Therapy[a]



[a]Hyperglycemic events were characterized by time to occurrence after initiation of quetiapine therapy. Data were available for 36 (78%) of 46 patients. Among these, hyperglycemia was identified within the first 6 months of quetiapine therapy in 27 patients (75%). A number of cases had delayed onset.

onset hyperglycemia (aged 31.2 ± 14.8 years; N = 30) tended to be younger than those with exacerbated diabetes mellitus (43.5 ± 16.4 years; N = 8; p = .08). When the cumulative distribution of new-onset hyperglycemia cases by age in our series was compared with the age distribution of cases in the U.S. population (National Health Interview Survey data),[25] the relative frequency of diabetes appeared to be higher for quetiapine-treated patients in the younger age cohorts (Kruskal-Wallis test with chi-square statistic: $\chi^2 = 44.1$, df = 5, $p < .001$) (Figure 2). In addition, when the cumulative distribution of new-onset hyperglycemia cases by age in our series was compared with that of the population of patients using quetiapine, the patients who developed diabetes tended to be younger than the general population using quetiapine (Kruskal-Wallis test with chi-square statistic: $\chi^2 = 9.8$, df = 5, p = .08) (Figure 2).

The overall male:female ratio for quetiapine was 1.9 (N = 43). This gender disparity was present in each of the hyperglycemia subgroups: new-onset (1.9, N = 32), exacerbation of preexisting disease (1.7, N = 8), and unclassified (2.0, N = 3). By contrast, the actual use of quetiapine is higher in women; the male:female ratio is 0.7 (IMS HEALTH National Disease and Therapeutic Index Audit; data collected from January 1, 1997, through June 30, 2002; gender unspecified for 2.5% of patients using quetiapine). Information on the ethnic background was available for 19 patients: African American, N = 13, and white, N = 6. Based on the origin of the reports, 3 additional patients most likely were Asian.

Time to Onset

The time to diagnosis of hyperglycemia for all subjects for whom these data were available (N = 36) ranged from several days to 1 year, 9 months, but for 75% (N = 27), it was 6 months or less from the time quetiapine therapy was started (Figure 3). Sometimes the hyperglycemia occurred after a recent dose increase. The time to diagnosis appeared to be shorter in patients with preexisting diabetes; they frequently observed changes in glucose control within days or weeks. Deterioration in glycemic control was noted within the first 3 months for 86% (6 of 7) of such patients, whereas hyperglycemia was identified within the first 6 months for 41% (11 of 27) of new-onset patients.

Drug Dosages

Drug dose data were available for 37 patients, including 1 patient whose hyperglycemia was identified after inadvertent dosing at 1000 mg for a month. Doses ranged from 12.5 to 1000 mg/day. The mean ± SD daily dose was 423.3 ± 250.7 mg and did not differ for new-onset patients (437.5 ± 237.1 mg) and those with preexisting diabetes (423.3 ± 250.7 mg; p = .70). Dose and time-to-onset information was available for 31 patients, including 6 patients receiving combination therapy with risperidone, olanzapine, or chlorpromazine and 1 patient possibly receiving concomitant olanzapine. There was no simple correlation between dose and time to onset or between dose and age. Parent drug and metabolite levels and assessments of compliance were not typically available.

Serious Outcomes

Among the quetiapine patients, there were 11 deaths, all in relatively young patients (mean ± SD 37.5 ± 14.2 years; range, 12–47 years). Seven occurred in patients with newly diagnosed hyperglycemia; 1 occurred in a patient with preexisting diabetes after a rechallenge. Five of the

patients who died had glucose levels in excess of 900 mg/dL. Seven were acidotic or ketotic. Three patients were reported to be febrile, and 1 of these had disseminated intravascular coagulation and myoglobinuria. The time to onset of hyperglycemia ranged from 2 weeks in the patient who was rechallenged to over 9 months for 3 patients.

There were 2 reports of pancreatitis, both with confounding concomitant acidosis. For 1 patient, the pancreatitis was diagnosed by lipase levels. Valproate was used by 1 of the 2 patients. There were 2 reports suggestive of neuroleptic malignant syndrome or central serotonin syndrome.

The severity of reported cases ranged from mild glucose intolerance to diabetic ketoacidosis or hyperosmolar coma. There were 21 reports of diabetic acidosis or ketosis. One of these occurred in a patient with preexisting diabetes after rechallenge with quetiapine. Glucose values for 19 patients equaled or exceeded 500 mg/dL.

Drug Withdrawal and Rechallenge

For various reasons, quetiapine was reduced in 1 patient and discontinued in 15 patients. Glycemic control reportedly improved in 7 patients. Antidiabetic medication was known to have been successfully discontinued in 5. One patient had recurrence (glucose level = 1570 mg/dL and ketosis) within 2 weeks of rechallenge. The recurrence was complicated by hypotension, tachycardia, coma, fever, disseminated intravascular coagulation, myoglobinuria, and death. Information on the outcomes in other patients was lacking or confounded by treatment with antidiabetic therapy or the switch to another atypical antipsychotic agent. An additional patient developed hyperglycemia on olanzapine and was switched to quetiapine. The hyperglycemia persisted until the quetiapine was discontinued.[23]

Concomitant Drugs

Thirty-nine reports contained some information on serial or concomitant drug therapy. No consistent pattern of concomitant drug therapy emerged from these data. No patients were reported to be without concomitant medications. Only a limited number of patients were receiving drugs known to induce hyperglycemia. One patient received inhaled and nasal corticosteroids for asthma and nasal polyps. There were no reports of niacin, thiazide diuretics, or protease inhibitor use. There were reports of concomitant use of other atypical antipsychotics: risperidone (N = 6), clozapine (N = 1), and olanzapine (N = 1). (There were 2 additional reports in which olanzapine was used, but the chronology of use was unclear.) Two other patients were being treated with chlorpromazine, which has been postulated to have effects on insulin release.[26] Treatment with valproate, a controversial putative risk factor for diabetes,[27–30] was reported for 11 patients. No patients were reported to be receiving an imidazole that might decrease quetiapine clearance. Concomitant medication data were available for 2 of 2 patients with reported pancreatitis; valproate was used by 1. The other most frequently reported concurrent drugs were lithium, benztropine, antidepressants (paroxetine, sertraline), lorazepam, haloperidol, gabapentin, and clonidine.

Risk Factors

The reports did not uniformly provide systematic information on risk factors for diabetes. Of the 6 patients with newly diagnosed hyperglycemia for whom family history was provided, 3 had a positive family history and 3 had a negative family history for diabetes. One patient whose hyperglycemia could not be classified as new or an exacerbation of preexisting diabetes had a positive family history. Limited body weight data were available for 27 patients. Approximately two thirds of these patients were significantly overweight or sustained a weight gain. Four of 5 additional patients with weight loss had glucose levels (≥ 500 mg/dL) that might be expected to promote diuresis or cachexia. Three patients were reported to have a history of hepatitis, a putative risk factor.[31,32]

DISCUSSION

New-onset hyperglycemia and the exacerbation of previously diagnosed diabetes mellitus have previously been observed after initiation of treatment with clozapine, olanzapine, and risperidone, 3 atypical antipsychotic agents.[33–39] This observation contrasts with the paucity of cases reported with haloperidol (N = 12), except in the setting of combination therapy with atypical antipsychotics despite the long history of haloperidol use.[37,40] Although such a comparison is potentially imperfect because of temporal changes in prescribing and reporting patterns, it should be noted that haloperidol has been marketed in the United States since 1969, with over 67 million prescriptions written since 1981 and over 31 million prescriptions written since 1991.[40]

The data presented here similarly suggest that quetiapine treatment is associated with the development of hyperglycemia. The time to onset of hyperglycemia was 3 months or less for the majority of patients, and prompt reversibility of hyperglycemia followed withdrawal of the drug in some cases. Furthermore, the mean age of newly diagnosed patients in our series (31.2 years) was considerably lower than the typical mean age of patients with type 2 diabetes.

The underlying cause of quetiapine-associated hyperglycemia remains elusive and indeed may be multifactorial. Any hypothetical mechanism must explain the relatively rapid onset of hyperglycemia observed in most cases. This mechanism would presumably be independent of weight gain. Of course, any significant weight gain

could be expected to increase insulin resistance and contribute to the later onset of hyperglycemia. Furthermore, patients with underlying beta cell defects, preexisting obesity, poor exercise habits, advanced age, exposure to other diabetogenic drugs, and prior or concomitant exposure to other atypical antipsychotic agents may have risk factors that increase cumulative risk for hyperglycemia.

Direct toxic effects of antipsychotic agents on islet cell function or on glucose transport into the cell would be consistent with rapid onset of action. Ardizzone and colleagues[41] have shown that risperidone and clozapine inhibited the uptake of 3H-2-deoxyglucose in a dose-dependent fashion in rat pheochromocytoma (PC12) cells (dose range, 2–100 μM for both drugs, inhibitory concentration for 50% of glucose uptake [IC_{50}] = 35 μM for risperidone and 20 μM for clozapine; the clozapine metabolite desmethylclozapine was even more potent, with an IC_{50} of 15 μM).[41,42] This inhibition occurred rapidly (within 15 minutes) and was antagonized by addition of increasing doses of nonradioactive 2-deoxyglucose. Schild analysis of the concentration-response curves was consistent with noncompetitive antagonism of the drugs' inhibitory effects by 2-deoxyglucose. These data suggest that some antipsychotic drugs or their metabolites may be capable of inhibiting glucose transport. Dwyer et al.[43] replicated such studies in a dose-dependent manner with quetiapine in PC12 cells and L6 myoblast cells after 30-minute incubations. The IC_{50} was 50 to 60 μM. These data are further supported by in vivo studies in fasted C57BL/6 mice.[44] Hyperglycemia could be induced within 6 hours in animals given intraperitoneal injections (200 μL) of chlorpromazine, clozapine, risperidone, or quetiapine dissolved in either dimethyl sulfoxide (DMSO) or ethanol. Comparable levels of hyperglycemia could be induced with a known glucose transporter, cytochalasin B.

Although we did not observe such a dose effect or a simple correlation between time to onset and dose, this would not be unexpected with a multifactorial disease such as diabetes. Furthermore, dosages do not reflect actual drug exposure when there are compliance issues or interpatient differences in pharmacokinetics.

CONCLUSION

These data, along with similar reports of hyperglycemia with olanzapine, clozapine, and risperidone, suggest that atypical antipsychotic use may unmask or precipitate hyperglycemia. The onset of hyperglycemia may be rapid and severe. Although most cases occurred within 3 months, risk is not eliminated with extended therapy. The most severe hyperglycemia was observed in patients without previously diagnosed diabetes who, as such, were not monitoring glycemic control. The association is not clearly dose-dependent. Definitive conclusions about causality and relative risk cannot be made until controlled, prospective studies are done. Similarly, because prescribing patterns may differ for the various atypical antipsychotics and because adverse reporting patterns are known to change over time, definitive conclusions about the comparative risks for hyperglycemia for the various atypical agents cannot be made until head-to-head, controlled trials using comparable populations for the various indications are conducted.

ADDENDUM

Subsequent to submission of our manuscript for publication, we extended our FDA MedWatch inquiry through November 2003, and the findings support our original observations. We identified an additional 23 cases of hyperglycemia (11 domestic and 12 foreign, primarily from Japan and the United Kingdom). (Another case resulting in polydipsia and sudden death in a 30-year-old woman was not included because of insufficient data although the reporter presumed diabetes to be the underlying cause.) Of these, 15 had newly diagnosed hyperglycemia, 6 had exacerbation of preexistent diabetes, and 2 had hyperglycemia that could not be characterized as newly diagnosed or exacerbation of preexisting disease. Of the newly diagnosed cases, 8 met the glucose or glycohemoglobin criteria for diagnosis, 4 had ketoacidosis, 1 had acidosis and antidiabetic therapy instituted, and 2 were reported as being hyperglycemic or diabetic without supportive documentation. Among the cases with age information, the mean ± SD age at the time of diagnosis was 47.3 ± 18.0 years overall (N = 22), 45.3 ± 21.2 years (median = 44 years) for those with newly diagnosed hyperglycemia (N = 15), and 53.0 ± 7.2 years for those with exacerbation of preexisting disease (N = 5). Of the cases of newly diagnosed hyperglycemia, 1 case occurred in a 15-year-old patient, 2 cases in 19-year-old patients, and 1 case in a 91-year-old patient. The male:female ratio was 1.8:1 (N = 23). Most of these reports were in patients with schizophrenia or schizoaffective disorder (N = 13). Other reasons for treatment included unspecified psychosis (N = 2), dementia-related behavior problems (N = 2), bipolar disease (N = 1), depression and obsessive-compulsive disorder or posttraumatic stress disorder (N = 2), and unspecified problems (N = 3).

Metabolic acidosis in the setting of hyperglycemia was reported for 8 patients (7 with newly diagnosed hyperglycemia, 1 with uncharacterized hyperglycemia). Ketosis was the underlying cause for 7 of the cases. In the eighth, renal failure appears to have been the major cause. There were 2 reports of pancreatitis, both in patients with newly diagnosed hyperglycemia. For one of the patients, there was confounding acidosis and no report of the criteria used to make the diagnosis. Neither patient used valproate. One of the patients with pancre-

atitis died. There were 2 reports of neuroleptic malignant syndrome, 1 in a patient with newly diagnosed diabetes and the other in a patient with uncharacterized hyperglycemia. One of these patients died. A third patient with newly diagnosed hyperglycemia presented with hyperosmolar coma and ultimately expired. In addition to the aforementioned case, there were 5 patients (4 with newly diagnosed hyperglycemia, 1 with preexistent diabetes) who presented with glucose values of 500 m/dL or higher.

Hyperglycemia occurred within 6 months for 64% of cases (N = 14). Limited data suggest that hyperglycemia was identified earlier in patients with preexisting disease. Deterioration in glycemic control was identified by 3 months in 75% (3 of 4) of patients with preexisting disease, whereas hyperglycemia was identified by 6 months in 56% (5 of 9) of those with new-onset disease.

The mean ± SD quetiapine dosage in 20 cases was 367.5 ± 282.2 mg/day (range, 50–1000 mg) (using the maximum known therapeutic dose). The mean ± SD daily dosage, 158.3 ± 169.3 mg (N = 6), was lower in patients with preexisting disease than in those with newly diagnosed hyperglycemia, 512.5 ± 245.4 mg (N = 12; p = .02). Although no specific dose appeared problematic, anecdotal evidence suggested that higher doses may precipitate hyperglycemia. For example, a 74-year-old patient taking quetiapine 300 mg/day for 4 months did not experience new-onset hyperglycemia until the dose was increased to 400 mg for 1 week. There was no apparent simple correlation between time to onset of hyperglycemia and quetiapine dose.

Some information on serial or concomitant therapy was available for 19 cases (83%). Four patients received valproate, 3 used olanzapine, 3 used chlorpromazine, 2 used nonsystemic (nasal or inhaled) corticosteroids, and 1 each used lithium, aripiprazole, or risperidone. No patients were reported to have used thiazide diuretics. Of note, one 44-year-old female patient had developed diabetes after approximately 1 year of treatment with clozapine. Discontinuation resulted in markedly improved glycemic control although diabetes persisted. Initiation of therapy with quetiapine resulted in a deterioration in glucose control.

Quetiapine was discontinued for various reasons in 11 patients (5 with preexistent diabetes, 5 with newly diagnosed disease, 1 with uncharacterized hyperglycemia). Outcomes were available for 7. Four patients did not improve although the time for follow-up was limited to 3 weeks for 1 patient. One of these patients did not improve despite concomitant discontinuation of olanzapine. Another developed ketoacidosis on risperidone 2 weeks after quetiapine discontinuation despite prior use of risperidone without hyperglycemia. Three patients were reported to have improved with discontinuation of quetiapine. One of these appears to have experienced another episode of ketoacidosis when rechallenged. Another patient treated with both aripiprazole and quetiapine improved with discontinuation of aripiprazole.

Drug names: aripiprazole (Abilify), benztropine (Cogentin), carbamazepine (Carbatrol, Tegretol, and others), chlorpromazine (Thorazine and others), clonidine (Iopidine, Clorpres, and others), clozapine (Clozaril), erythromycin (Benzamycin, Eryc, and others), fluconazole (Diflucan), gabapentin (Neurontin), haloperidol (Haldol and others), itraconazole (Sporanox), ketoconazole (Nizoral), lithium (Lithobid, Eskalith, and others), lorazepam (Ativan), olanzapine (Zyprexa), paroxetine (Paxil), phenytoin (Cerebyx, Dilantin, and others), quetiapine (Seroquel), risperidone (Risperdal), sertraline (Zoloft).

REFERENCES

1. Seroquel (quetiapine). Physicians' Desk Reference. Montvale, NJ: Medical Economics; 2004: 685-689
2. Atmaca M, Kuloglu M, Tezcan E, et al. Quetiapine augmentation in patients with treatment resistant obsessive-compulsive disorder: a single-blind, placebo-controlled study. Int Clin Psychopharmacol 2002;17:115–119
3. Denys D, Van Megan H, Westenberg H. Quetiapine addition to serotonin reuptake inhibitor treatment in patients with treatment-refractory obsessive compulsive disorder: an open-label study. J Clin Psychiatry 2002;63:700–703
4. Fernandez HH, Trieschmann ME, Burke MA, et al. Quetiapine for psychosis in Parkinson's disease versus dementia with Lewy bodies. J Clin Psychiatry 2002;63:513–515
5. Glick ID, Murray SR, Vasudevan P, et al. Treatment with atypical antipsychotics: new indications and new populations. J Psychiatr Res 2001;35:187–191
6. Molho EA, Factor SA. Parkinson's disease: the treatment of drug-induced hallucinations and psychosis. Curr Neurol Neurosci Rep 2001;1:320–328
7. Scharre DW, Chang SI. Cognitive and behavioral effects of quetiapine in Alzheimer disease patients. Alzheimer Dis Assoc Disord 2002;16: 128–130
8. Tarsy D, Baldessarini RJ, Tarazi FI. Effects of newer antipsychotics on extrapyramidal function. CNS Drugs 2002;16:23–45
9. Weizman R, Weizman A. Use of atypical antipsychotics in mood disorders. Curr Opin Investig Drugs 2001;2:940–945
10. De Vane CL, Nemeroff CB. Clinical pharmacokinetics of quetiapine: an atypical antipsychotic. Clin Pharmacokinet 2001;40:509–522
11. Potkin SG, Thrum PT, Alva G, et al. The safety and pharmacokinetics of quetiapine when co-administered with haloperidol, risperidone, or thioridazine. J Clin Psychopharmacol 2002;22:121–130
12. Wong YW, Yeh C, Thyrum PT. The effects of concomitant phenytoin administration on the steady-state pharmacokinetics of quetiapine. J Clin Psychopharmacol 2001;21:89–93
13. Kelly DL, Conley RR, Love RC, et al. Weight gain in adolescents treated with risperidone and conventional antipsychotics over six months. J Child Adolesc Psychopharmacol 1998;8:151–159
14. Stigler KA, Potenza MN, McDougle CJ. Tolerability profile of atypical antipsychotics in children and adolescents. Paediatr Drugs 2001;3: 927–942
15. Sussman N. Review of atypical antipsychotics and weight gain. J Clin Psychiatry 2001;62(suppl 23):5–12
16. Wetterling T. Bodyweight gain with atypical antipsychotics: a comparative review. Drug Saf 2001;24:59–73
17. Taylor DM, McAskill R. Atypical antipsychotics and weight gain: a systematic review. Acta Pychiatr Scand 2000;101:416–432
18. Domon SE, Cargile CS. Quetiapine-associated hyperglycemia and hypertriglyceridemia [letter]. J Am Acad Child Adolesc Psychiatry 2002;41:495–496
19. Procyshyn RM, Pande S, Tse G. New-onset diabetes associated with quetiapine [letter]. Can J Psychiatry 2000;45:668–669
20. Sneed KB, Gonzalez EC. Type 2 diabetes mellitus induced by an atypical antipsychotic medication. J Am Board Fam Pract 2003;16:251–254
21. Sobel M, Jaggers ED, Franz MA. New-onset diabetes mellitus associated with the initiation of quetiapine treatment [letter]. J Clin Psychiatry 1999;60:556–557

22. Wilson DR, D'Souza L, Sarkar N, et al. New-onset diabetes and ketoacidosis with atypical antipsychotics. Schizophr Res 2002;59:1–6
23. Bettinger TL, Mendelson SC, Dorson PG, et al. Olanzapine-induced glucose dysregulation. Ann Pharmacother 2000;34:865–867
24. Litovitz TL, Klein-Schwartz W, White S, et al. 1999 annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. Am J Emerg Med 2000;18:517–574
25. Kenny SJ, Aubert RE, Geiss LS. Prevalence and incidence of non-insulin dependent diabetes. In: Harris MI, Cowie CC, Stern MP, eds. Diabetes in America. 2nd ed. Publication no. 95-1468. Bethesda, Md: National Institutes of Health—National Institute of Diabetes, Digestive, and Kidney Diseases; 1995:47–67
26. Ammon HR, Orci L, Steinle J. Effect of chlorpromazine (CPZ) on insulin release in vivo and in vitro in the rat. J Pharmacol Exp Ther 1973;187: 423–429
27. Isojarvi JI, Tauboll E, Pakarinen AJ, et al. Altered ovarian function and cardiovascular risk factors in valproate-treated women. Am J Med 2001; 111:290–296
28. Jallon P, Picard F. Bodyweight gain and anticonvulsants: a comparative review. Drug Saf 2001;24:969–978
29. Odinesen H, Gram L, Andersen T, et al. Weight gain during treatment with valproate. Acta Neurol Scand 1984;70:65–69
30. Turnbull DM, Bone AJ, Tames FJ, et al. The effect of valproate on blood metabolite concentrations in spontaneously diabetic, ketoacidotic, BB/E Wistar rats. Diabetes Res 1985;2:45–48
31. Garrido Serrano A, Guerrero Igea FJ, Lepe Jimenez JA, et al. Hyperinsulinemia in cirrhotic patients infected with hepatitis C [in Spanish]. Gastroenterol Hepatol 2001;24:127–131
32. Piquer S, Hernandez C, Enriquez J, et al. Islet cell and thyroid antibody prevalence in patients with hepatitis C virus infection: effect of treatment with interferon. J Lab Clin Med 2001;137:38–42
33. Brescan DW. Risperidone and glucose intolerance. Presented at the 150th annual meeting of the American Psychiatric Association; May 17–22, 1997; San Diego, Calif. Abstract NR267:137
34. Croarkin PE, Jacobs KM, Bain BK. Diabetic ketoacidosis associated with risperidone treatment? [letter] Psychosomatics 2000;41:369–370
35. Koller EA, Schneider B, Bennett K, et al. Clozapine-associated diabetes mellitus. Am J Med 2001;111:716–723
36. Koller EA, Doraiswamy PM. Olanzapine-associated diabetes mellitus. Pharmacotherapy 2002;22:841–852
37. Koller EA, Cross JT, Doraiswamy PM, et al. Risperidone-associated diabetes mellitus. Pharmacotherapy 2003;23:735–744
38. Wirshing DA, Pierre JM, Eyeler J, et al. Risperidone-associated new-onset diabetes. Biol Psychiatry 2001;50:148–149
39. Wirshing DA, Boyd JA, Meng LR, et al. The effect of novel antipsychotics on glucose and lipid levels. J Clin Psychiatry 2002;63:856–865
40. Koller EA, Cross JT, Doraiswamy PM, et al. Pancreatitis associated with atypical antipsychotics: from the FDA MedWatch surveillance system and published reports. Pharmacotherapy 2003;23:1123–1130
41. Ardizzone TD, Bradley RJ, Freeman AM III, et al. Inhibition of glucose transport in PC12 cells by the atypical antipsychotic drugs risperidone and clozapine, and structural analogues of clozapine. Brain Res 2001; 923:82–90
42. Dwyer DS, Liu Ye, Bradley RJ. Dopamine receptor antagonists modulate glucose uptake in rat pheochromocytoma (PC12) cells. Neurosci Lett 1999;274:151–154
43. Dwyer DS, Lu X-H, Bradley RJ. Cytotoxicity of conventional and atypical antipsychotic drugs in relation to glucose metabolism. Brain Res 2003;971:31–39
44. Dwyer DS, Donohoe D. Induction of hyperglycemia in mice with atypical antipsychotic drugs that inhibit glucose uptake. Pharmacol Biochem Behav 2003;75:255–260