Undiagnosed Hyperglycemia in Patients Treated With Atypical Antipsychotics

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This work was supported by the Department of Veterans Affairs VISN 1 Mental Illness Research, Education, and Clinical Center.

Dr. Sernyak has received grant/research support from AstraZeneca; Dr. Rosenheck has received grant/research support from Lilly and AstraZeneca and has been a consultant for Janssen and Bristol-Myers Squibb; and Dr. Gulanski reports no financial or other relationships relevant to the subject of this article.

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Background: The use of atypical antipsychotics has been associated with abnormalities of glucose metabolism in patients with schizophrenia. This study was designed to determine the proportion of undiagnosed hyperglycemia in patients receiving a broad range of atypical antipsychotics.

Method: All outpatients treated at an urban Veterans Affairs medical center who received a prescription for clozapine, risperidone, olanzapine, quetiapine, or ziprasidone were identified, and an attempt was made to obtain a fasting plasma glucose (FPG) test. Testing took place October 2000 to November 2002. Patients previously diagnosed as diabetic were excluded.

Results: Of the 647 patients who received antipsychotic prescriptions and were not diagnosed as diabetic, 494 (76.4%) had a random glucose result, while 153 (23.6%) had an FPG result. Within the FPG group, 107 (69.9%) had a normal FPG level, while 46 (30.1%) had an abnormally elevated FPG. There were no differences between these 2 groups in terms of race/ethnicity, age, body mass index, or comorbid diagnoses. However, significantly more patients receiving clozapine were found to have occult hyperglycemia ($p = .001$); no significant differences in the percentage of patients with FPG levels ≥ 100 mg/dL and those with FPG levels < 100 mg/dL were observed for any of the other medications.

Conclusion: Hyperglycemia is common in patients treated with atypical antipsychotics and thought to be euglycemic. Screening for elevated FPG is indicated for patients receiving atypical antipsychotics.

(J Clin Psychiatry 2005;66:1463–1467)

For nearly a decade, published reports have suggested an association between the receipt of atypical antipsychotics and the development of diabetes mellitus. These reports have taken the form of case reports,[1,2] pharmacovigilance studies,[3–6] and secondary analyses of administrative databases.[7–9] Not only has a significantly increased rate of diagnosed diabetes mellitus been observed in many of these studies, but it is also likely that available studies underestimate the risk of diabetes attributable to atypical antipsychotic usage since the American Diabetes Association estimates that almost 50% of patients with type 2 diabetes are undiagnosed.[10] A previous screening effort[11] showed that 23% of patients receiving clozapine and thought to be euglycemic by their clinician either had an abnormal fasting plasma glucose level or met criteria for diabetes mellitus.

This article reports on a similar effort designed to determine the proportion of undiagnosed hyperglycemia in patients receiving a broader range of atypical antipsychotics including clozapine, olanzapine, risperidone, quetiapine, or ziprasidone at an urban Veterans Affairs (VA) medical center.

METHOD

Sample

Data were obtained in a quality-of-care initiative performed at the VA Connecticut Healthcare System (VACT). All patients treated at VACT who were documented as

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having received a prescription for clozapine, risperidone, olanzapine, quetiapine, or ziprasidone in fiscal year 2001 (October 1, 2000, to September 30, 2001) were identified using VA administrative data. Providers were then contacted and asked to document (1) the type and dosage of antipsychotic that the patient was currently receiving (if any), (2) the patient's height and weight, and (3) whether the patient was currently diagnosed with diabetes. For patients not known to be diabetic, a fasting plasma glucose test was requested. If a fasting plasma glucose test could not be obtained, results of a random glucose test were accepted. Testing took place October 2000 to November 2002.

Method

Data describing patient characteristics such as principal psychiatric diagnosis, age, income, gender, race and ethnicity, receipt of VA compensation or pension, comorbid medical and psychiatric diagnoses, and the number and type of outpatient clinic visits were obtained from VA administrative workload databases. Since half of the patients receiving atypical antipsychotics[12] do not have the diagnosis of schizophrenia, this study was broadened to include all psychiatric diagnoses in order to investigate the independent effects of these diagnoses on the risk of undiagnosed hyperglycemia.

All plasma glucose concentrations were measured using the Olympus AU640 Chemistry Analyzer (Olympus Optical Co., Ltd., Tokyo, Japan) that employs the hexokinase G-6-PDH method to determine the amount of glucose present in the plasma. With this method, a coefficient of variance of < 2% is reported.[13]

A cutoff of 100 mg/dL (5.6 mmol/L) was used for hyperglycemia since in 2004 the American Diabetes Association lowered the upper limit of normal fasting plasma glucose (FPG) from 110 mg/dL (6.1 mmol/L) to 100 mg/dL (5.6 mmol/L).[14] The result of this reclassification is that after an 8-hour fast, plasma glucose levels less than 100 mg/dL (5.6 mmol/L) are considered normal, while the diagnosis of impaired fasting glucose is made if a patient has an FPG level of 100–125 mg/dL (5.6–6.9 mmol/L). This reclassification did not affect the diagnosis of diabetes mellitus, which still requires 2 separate FPG results of at least 126 mg/dL (≥ 7.0 mmol/L).

The collation of the screening information, its merger with other VA databases, a waiver of informed consent, and the preparation of this manuscript were approved by the local institutional review board.

Analysis

Patients were divided into 3 groups: (1) those with random glucose measurements, (2) those with FPG < 100 mg/dL (< 5.6 mmol/L), and (3) those with FPG ≥ 100 mg/dL (≥ 5.6 mmol/L). The initial analysis consisted of t tests and χ^2 tests comparing the random group and the 2 fasting groups with respect to demographic and clinical variables to determine whether there were any significant differences between the fasting and random groups.

The principal analysis compared the 2 fasting groups on those same demographic and clinical variables.

RESULTS

Patient Characteristics

Altogether 647 patients were identified at the West Haven and Newington campuses of the VA Connecticut Healthcare System who (1) had a prescription for an atypical antipsychotic recorded in fiscal year 2001, (2) were identified by their clinician to still be receiving an atypical antipsychotic, and (3) were not currently identified as diabetic.

For 494 patients (76.4%), only a random plasma glucose level was available. Since meaningful interpretation of random plasma glucose results requires clinical correlation, and this information was not routinely available, definitive diagnoses were not made. However, within this group 16 (3.2%) had a random plasma glucose level of 140–199 mg/dL (7.8–11.0 mmol/L) and 5 (1.0%) had a random plasma glucose level of greater than 200 mg/dL (> 11.1 mmol/L). Were these values obtained and confirmed during a glucose tolerance test, they would have been consistent with impaired glucose tolerance and diabetes, respectively. Nonetheless, as a diagnosis could not be definitively made with the available information, the results from the group with random plasma glucose values were only analyzed to determine the degree to which the entire random plasma glucose group reflected the general population.

The only significant differences between the random plasma glucose and the FPG groups were that patients for whom an FPG was available were significantly more likely to be high outpatient service utilizers ($\chi^2 = 15.96$, df = 2, $p < .0001$) and to be diagnosed with schizophrenia ($\chi^2 = 10.22$, df = 2, $p = .01$).

For 153 patients (23.6%), a FPG level was obtained. Within the fasting group, 107 (69.9%) had normal FPG results, 38 patients (24.8%) had a FPG of 100–125 mg/dL (5.6–6.9 mmol/L), while 8 patients (5.2%) had an FPG greater than or equal to 126 mg/dL (≥ 7.0 mmol/L). Within this group of 8 patients, 4 (50%) had either a repeat FPG level greater than 126 mg/dL (> 7.0 mmol/L) or a random glucose level greater than 200 mg/dL (> 11.1 mmol/L), 2 (25%) had a repeat FPG level of 100–125 mg/dL (5.6–6.9 mmol/L), and 2 (25%) had a repeat FPG level of < 100 mg/dL (< 5.6 mmol/L). Due to its relatively small size and our emphasis on screening for any abnormalities of glucose metabolism, this group of 8 patients was combined with the group of 38 patients with FPG levels of 100–125 mg/dL (5.6–6.9 mmol/L) for analysis (Table 1).

There were no significant differences between the patients with normal and elevated FPG results in terms of

Table 1. Characteristics of Atypical Antipsychotic–Treated Patients by Fasting Plasma Glucose Status

Characteristic	FPG < 100 mg/dL (N = 107) N	%	FPG ≥ 100 mg/dL (N = 46) N	%	χ^2 (df = 2)	p
Number psychiatric appointments						
1–3	3	2.8	0	0.0	1.32	.25
4–12	23	21.5	12	26.1	0.38	.54
13–24	14	13.1	4	8.7	0.60	.44
> 24	62	57.9	25	54.4	0.17	.68
Number inpatient psychiatric days						
1–7	7	6.5	2	4.4	0.28	.60
> 7	20	18.7	6	13.0	0.73	.39
Clinical diagnosis						
Organic brain syndrome	2	1.9	4	9.1	3.98	.05
Alcohol abuse/dependence	34	31.8	9	20.5	2.37	.12
Drug abuse/dependence	24	22.4	8	18.2	0.49	.48
Schizophrenia	73	68.2	29	65.9	0.39	.53
Psychosis NOS	11	10.3	3	6.8	0.55	.46
Bipolar disorder	27	25.2	11	25.0	0.03	.86
Major depression	35	32.7	15	34.1	0.00	.99
Dysthymia	43	40.2	16	36.4	0.40	.53
Posttraumatic stress disorder	29	27.1	15	34.1	0.48	.49
Anxiety disorder	22	20.6	9	20.5	0.02	.89
Adjustment disorder	4	3.7	0	0.0	1.77	.18
Personality disorder	6	5.6	2	4.6	0.10	.75
African American	12	11.2	8	17.4	1.08	.30
Hispanic	6	5.6	0	0.0	2.68	.10
Female	6	5.6	5	10.8	1.33	.25
Atypical antipsychotic prescribed						
Olanzapine	53	49.5	18	39.1	1.40	.24
Ziprasidone	5	4.7	5	10.9	2.02	.16
Quetiapine	10	9.4	2	4.3	1.11	.29
Clozapine	9	8.4	13	28.3	10.30	.001
Risperidone	31	29.0	9	19.6	1.63	.20
Polypharmacy	1	0.9	0	0.0	0.43	.51
	Mean	SD	Mean	SD	F (df = 2)	p
Body mass index	29.2	5.1	30.8	5.8	1.58	.21
Age, y	50.0	10.1	50.7	9.7	2.04	.13

Abbreviations: FPG = fasting plasma glucose, NOS = not otherwise specified.

age, ethnic make-up, or service utilization. While there was also no difference between the 2 groups in many of the principal psychiatric diagnoses, a significantly higher percentage of patients in the elevated FPG group had the principal diagnosis of organic brain syndrome. Importantly, there was no difference between the 2 FPG groups in terms of body mass index (BMI), although the mean BMIs of the normal FPG group (29.2 kg/m^2) and the abnormal FPG group (30.8 kg/m^2) were both on the borderline between overweight (25–29.9 kg/m^2) and obese (30 kg/m^2 and above).

When the antipsychotic medications prescribed were analyzed, it was observed that the percentage of patients receiving clozapine was significantly higher in the elevated FPG group than in the normal FPG group (28.3% vs. 8.4%, $\chi^2 = 10.30$, df = 2, p = .001).

DISCUSSION

Within the outpatient clinics of an urban VA medical center, approximately 30% of all patients treated with atypical antipsychotics who were thought to be euglycemic had abnormally high FPG levels. Patients with this abnormality were not differentiable from those with normal FPG levels with regard to ethnicity, gender, age, body mass index, or psychiatric diagnosis.

This overall rate of occult hyperglycemia is higher than the 23% previously observed in patients treated in clozapine clinics at several VA medical centers throughout New England.[11] However, at the time of that report, the upper limit of acceptable FPG was 109 mg/dL (6.0 mmol/L). Recalculating the rate of impaired fasting glucose at the new, lower threshold of 100 mg/dL (5.6 mmol/L) results in an increase from 17% to 44% of patients treated with clozapine meeting criteria for impaired fasting glucose. Remarkably, when the specific percentage of occult hyperglycemia in solely clozapine-treated patients in the current study is calculated, that rate of 59% (13/22 patients) is even higher than the recalculated 44% using the 100-mg/dL (5.6 mmol/L) criterion. Both of these studies emphatically demonstrate the necessity of close monitoring of FPG results in patients receiving clozapine.

Several methodological limitations of this study deserve mentioning. Due to the nature of the available data,

some cases of elevated FPG could not be unequivocally determined to be diabetes mellitus. However, recent studies suggest that even the glucose intolerance associated with "pre-diabetes" (FPG = 110–125 mg/dL [6.1–6.9 mmol/L]) is associated with increased cardiovascular morbidity and mortality even without the onset of frank diabetes.[15,16] These results are especially important since progression from pre-diabetes to the onset of frank diabetes can be prevented by lifestyle changes once the risk is identified.[17]

The reliability of patients' fasting prior to blood being drawn for the FPG test is also unknown. It is possible that some of the high FPG results were the result of the patients' failure to maintain a fasting state prior to the blood draw. However, these patients were assessed by their clinician as to whether they had fasted, and for approximately three quarters of the patients, the test was judged to have been a random glucose screening and excluded from further analysis. While fasting status of some FPG determinations may have been erroneously documented, it is unclear whether the likelihood of false report of fasting in patients with schizophrenia is any greater than in the general population.

It is important to emphasize that this study was not designed to evaluate the increased risk of diabetes or hyperglycemia that is specifically attributable to the atypical antipsychotics or other concomitant medications. Indeed, consistent with our goal, patients receiving atypical antipsychotics already diagnosed with diabetes were excluded. Although we did find that a large fraction of patients receiving clozapine were experiencing previously unknown abnormalities of glucose metabolism, we do not believe that clozapine is in any way unique in its diabetogenicity. Many psychiatric medications such as valproic acid, tricyclic antidepressants, and lithium,[18] along with other medications such as glucocorticoids, hydrochlorothiazide, and β-blockers,[19] have also been implicated in the development of diabetes, and over 60% of patients, regardless of their FPG status, were receiving at least 1 of these concomitant medications. Indeed, these data, along with other recently published findings of a nearly 3 times greater prevalence of diabetes in patients with any severe mental illness when compared with the general population,[20] suggest that attempts such as ours to investigate particular classes of medications might overshadow the more compelling finding that there is an epidemic of diabetes, both diagnosed and undiagnosed, among our patients.

Previous evidence[9] has demonstrated that patients with schizophrenia and treated with typical antipsychotics appear to be more likely to be diagnosed with diabetes than the general population. Since there is no reason to believe that at the time of this study these patients were monitored more carefully for diabetes than those prescribed atypical antipsychotics, it is reasonable to suppose that similar rates of undiagnosed hyperglycemia might also exist in patients treated with typical antipsychotics.

The difficulty in obtaining FPG levels in the majority of patients illustrates the potential utility of other, less favored, measures of screening for abnormalities of glucose metabolism such as hemoglobin A1c determinations and measures of random plasma glucose. While these measures have much less specificity than FPG level determination, in busy and challenging clinical settings these tests may be a reasonable trade-off in an attempt to obtain at least some information about a patient's metabolic status.[21]

The finding that nearly 1 in 3 patients receiving atypical antipsychotics who are thought to be euglycemic actually have demonstrable and clinically significant abnormalities of glucose metabolism argues for periodic screening in even large outpatient populations. It provides empirical support for current recommendations[21–23] that the determination of baseline FPG levels has a role in patients thought to be euglycemic, although the recommended frequency of such screening has yet to be established.

Drug names: clozapine (Clozaril, FazaClo, and others), hydrochlorothiazide (Oretic, Esidrix, and others), lithium (Lithobid, Eskalith, and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), valproic acid (Depakene and others), ziprasidone (Geodon).

REFERENCES

1. Goldstein LE, Sporn J, Brown S, et al. New-onset diabetes mellitus and ketoacidosis associated with olanzapine treatment. Psychosomatics 1999;40:438–443
2. Wirshing DA, Spellberg BJ, Erhart SM, et al. Novel antipsychotics and new onset diabetes. Biol Psychiatry 1998;44:778–783
3. Koller E, Schneider B, Bennett K, et al. Clozapine-associated diabetes. Am J Med 2001;111:716–723
4. Koller EA, Doraiswamy PM. Olanzapine-associated diabetes mellitus. Pharmacotherapy 2002;22:841–852
5. Koller E, Cross J, Doraiswamy PM, et al. Risperidone-associated diabetes mellitus: a pharmacovigilance study. Pharmacotherapy 2003; 23:735–744
6. Koller EA, Weber J, Doraiswamy PM, et al. A survey of reports of quetiapine-associated hyperglycemia and diabetes mellitus. J Clin Psychiatry 2004;65:857–863
7. Gianfrancesco FD, Grogg AL, Mahmoud RA, et al. Differential effects of risperidone, olanzapine, clozapine, and conventional antipsychotics on type 2 diabetes: findings from a large health plan database. J Clin Psychiatry 2002;63:920–930
8. Wirshing DA, Boyd JR, Meng LS, et al. The effects of novel antipsychotics on glucose and lipid levels. J Clin Psychiatry 2002;63:856–865
9. Sernyak MJ, Leslie DL, Alarcon RD, et al. Association of diabetes mellitus with the use of atypical neuroleptics in the treatment of schizophrenia. Am J Psychiatry 2002;159:561–566
10. Harris MI, Flegal KM, Cowie CC, et al. Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in US adults: the third national health and nutrition examination survey, 1988–1994. Diabetes Care 1998;21:518–524
11. Sernyak MJ, Gulanski B, Leslie DL, et al. Undiagnosed hyperglycemia in clozapine-treated patients with schizophrenia. J Clin Psychiatry 2003; 64:605–608
12. Rosenheck R, Leslie D, Sernyak M. From clinical trials to real-world practice: use of atypical antipsychotic medication nationally in the Department of Veterans Affairs. Med Care 2001;39:302–308

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13. Glucose performed on the Olympus 640, VA Connecticut Healthcare System; 2001. Manual for Olympus AU640 Chemistry Analyzer. Olympus Optical Co., Ltd., Tokyo, Japan
14. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2004;27(suppl 1):S5–10
15. Khaw KT, Wareham N, Luben R, et al. Glycated haemoglobin, diabetes, and mortality in men in Norfolk cohort of European prospective investigation of cancer and nutrition (EPIC-Norfolk). BMJ 2001;322:15–18
16. Fisman EZ, Motro M, Tenenbaum A, et al. Impaired fasting glucose concentrations in nondiabetic patients with ischemic heart disease: a marker for a worse prognosis. Am Heart J 2001;141:485–490
17. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393–403
18. Haupt DW, Newcomer JW. Hyperglycemia and antipsychotic medications. J Clin Psychiatry 2001;62(suppl 27):15–26
19. Luna B, Feinglos M. Drug-induced hyperglycemia. JAMA 2001;286:1945–1948
20. Susce MT, Villanueva N, Diaz FJ, et al. Obesity and associated complications in patients with severe mental illnesses: a cross-sectional survey. J Clin Psychiatry 2005;66:167–173
21. Marder SR, Essock SM, Miller A, et al. Physical health monitoring of patients with schizophrenia. Am J Psychiatry 2004;161:1334–1349
22. American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, et al. Consensus development conference on antipsychotic drugs and obesity and diabetes. Diabetes Care 2004;27:596–601
23. VA Pharmacy Benefits Management Strategic Healthcare Group and Medical Advisory Panel. Antipsychotics and Metabolic Effects: 2002–2003 Update. Available at: http://www.vapbm.org/PBM/treatment.htm. Accessed February 22, 2005