Prediabetes in Patients Treated With Antipsychotic Drugs

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ABSTRACT

Background: In 2010, the American Diabetes Association (ADA) proposed that individuals with fasting glucose level of 100–125 mg/dL (5.6–6.9 mmol/L) or glucose level of 140–199 mg/dL (7.8–11.0 mmol/L) 2 hours after a 75-g oral glucose tolerance test or hemoglobin A_{1c} 5.7%–6.4% be classified as prediabetic, indicating increased risk for the emergence of diabetes mellitus. At the same time, the ADA formulated guidelines for the use of metformin for the treatment of prediabetes.

Objective: To determine the prevalence of prediabetes in a cohort of psychiatrically ill adults receiving antipsychotics and to compare the clinical and metabolic features of prediabetic patients with those of patients with normal glucose tolerance and those with diabetes mellitus.

Method: The 2010 ADA criteria were applied to a large, consecutive, single-site European cohort of 783 adult psychiatric inpatients (mean age: 37.6 years) without a history of diabetes who were receiving antipsychotics. All patients in this cross-sectional study underwent measurement of body mass index (BMI), waist circumference, oral glucose tolerance test, and fasting insulin and lipids from November 2003 through July 2007.

Results: 413 patients (52.8%) had normal glucose tolerance, 290 (37.0%) had prediabetes, and 80 (10.2%) had diabetes mellitus. The fasting glucose and/or hemoglobin A_{1c} criteria were met by 89.7% of prediabetic patients. A statistically significant intergroup gradient from normal glucose tolerance to prediabetes and from prediabetes to diabetes mellitus was observed for waist circumference, triglycerides, fasting insulin levels, and frequency of metabolic syndrome ($P = .02$ to $P < .0001$). Only 19/290 prediabetic patients (6.6%) met the 2010 ADA criteria for treatment with metformin.

Conclusions: Prediabetes is highly prevalent in adults treated with antipsychotic drugs and correlates with markers of increased intra-abdominal adiposity, enhanced lipolysis, and insulin resistance. Criteria for using metformin to prevent the emergence of diabetes mellitus may need to be revised for this population.

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In January 2010, the American Diabetes Association (ADA) published criteria for the identification of prediabetes, a term that indicates a high risk for the future development of diabetes mellitus.[1] The risk is defined by the results of widely available and highly reliable biochemical assessments, including impaired fasting glucose (fasting plasma glucose level in the range of 100–125 mg/dL) *or* impaired glucose tolerance (plasma glucose level in the range of 140–199 mg/dL 2 hours after the ingestion of 75 g of glucose) *or* a glycosylated hemoglobin (A_{1c}) level in the range of 5.7%–6.4%. Prediabetes is associated with abdominal obesity, hypertension, and dyslipidemia, with decreased levels of high-density lipoprotein (HDL) cholesterol and/or increased triglycerides.[1–3]

The management of prediabetes aims to prevent or delay the emergence of type 2 diabetes through weight loss of 5%–10% of body weight and at least 150 min/wk of physical activity of moderate intensity. In addition to these lifestyle changes, pharmacologic intervention with metformin has been recommended for patients who have both an elevated fasting glucose level *and* abnormal glucose tolerance *plus* at least 1 other significant risk factor, such as hemoglobin A_{1c} level > 6%, family history of diabetes in a first-degree relative, obesity, elevated triglycerides, low levels of HDL cholesterol, hypertension, and age younger than 60 years.[1,4]

The prevalence of prediabetes, as reflected in studies published after the ADA's 2010 statement, is difficult to pinpoint, because the proposed glycosylated hemoglobin (A_{1c}) criterion was not uniformly applied and the oral glucose tolerance test not always performed. The most complete data indicate a prevalence of 29.5% among 2,332 individuals aged 35–74 years from Qingdao, China,[5] and 44.9% in a multiethnic cohort comprising 8,696 individuals aged 40–75 years from Leicestershire, United Kingdom.[6] In the United States, data collected for the National Health and Nutrition Examination Survey from 2005 to 2006 indicated a prevalence of prediabetes of 34.6% among 1,547 nondiabetic adults (age > 18 years) without a history of myocardial infarction,[7] but the hemoglobin A_{1c} criterion was not used. This omission may have significance, because prediabetes diagnosed by hemoglobin A_{1c} level > 5.6% appears to be more prevalent in the United States than prediabetes diagnosed by fasting glucose, at least among older adults.[8]

A vast body of literature has identified patients treated with second-generation antipsychotics as a group at high risk for the emergence of type 2 diabetes mellitus.[9–12] This assessment is based on data demonstrating considerable weight accrual during treatment with these drugs, which is the main reason for the increased prevalence of glucose intolerance,[13–15] atherogenic dyslipidemia,[16–19] and metabolic syndrome[20–23] in this population. From this vantage point, the presence of prediabetes has enormous significance because its identification and proper management could mitigate the adverse metabolic effects of medications used to treat the vast number of patients with schizophrenia, bipolar disorder, major depression, and other severe mental illnesses. Simply put, the antipsychotic-related diabetes mellitus generally is an irreversible condition, while the medical treatment of a prediabetic state offers the chance of avoiding a disease that leads to multiorgan dysfunction, shortens life, and contributes greatly to the cost of medical care worldwide.

To our knowledge, this study is the first application of the 2010 ADA criteria for the definition of prediabetes[1] to a psychiatric population treated

with antipsychotic drugs. Our primary goal was to establish the prevalence of prediabetes and to compare the psychiatric and metabolic characteristics of patients with this entity with antipsychotic-treated patients who have normal glucose tolerance. We further aimed to compare patients who have prediabetes with those who have diabetes. We hypothesized the presence of a biological gradient for markers of intraabdominal adiposity and insulin resistance from normal glucose tolerance to prediabetes and then to diabetes and thought that prediabetes would be more common in patients treated with second-generation antipsychotics with high metabolic liability, such as clozapine and olanzapine, as compared with those treated with antipsychotics with low to medium metabolic liability, such as aripiprazole, amisulpride, and risperidone.

Clinical Points

- In 2010 the American Diabetes Association (ADA) published criteria for the identification of prediabetes, a term that indicates a high risk for the future development of diabetes mellitus: fasting plasma glucose level in the range of 100–125 mg/dL *or* a glycosylated hemoglobin (A_{1c}) level in the range of 5.7%–6.4% *or* plasma glucose level in the range of 140–199 mg/dL 2 hours after the ingestion of 75 g of glucose.
- Prediabetes was identified in 37% of psychiatric inpatients who were receiving antipsychotics.
- Weight reduction through decreased caloric intake and increased physical activity is the keystone of the management of prediabetic state in this population.

METHOD

Setting

From November 2003 through July 2007, consecutively admitted patients without a history of diabetes, hospitalized at the University Psychiatric Center, Catholic University Leuven in Kortenberg, Belgium, were asked by their treating psychiatrist to agree to a routine metabolic screening. Psychiatric diagnoses were established according to *DSM-IV* by experienced psychiatrists affiliated with the University Psychiatric Center and responsible for the patient's treatment. Symptom severity was assessed by the treating psychiatrist using the Global Assessment of Functioning (GAF)[24] from 0 (worst) to 100 (best) and the Clinical Global Impressions Severity of Illness scale (CGI-S) from 1 (normal) to 7 (extremely ill).[25]

Selection of Subjects

The study cohort comprised 820 nondiabetic patients. Fifteen patients (1.8%) declined to consent to metabolic screening, and 22 (2.7%) were not treated with antipsychotic drugs. Therefore, the data used in this cross-sectional study were obtained from 783 patients (95.5%) who met the following inclusion criteria: current treatment with antipsychotic drugs; not known prior to admission, including the period during which they had received outpatient treatment at our institution, to have diabetes mellitus; and not currently receiving oral hypoglycemic drugs or insulin. All subjects gave written informed consent, and the study was approved by the University Psychiatric Center's Ethics committee.

Metabolic Screening

The metabolic screening included measurements of height, weight, body mass index (BMI), waist circumference, arterial blood pressure, glycosylated hemoglobin (A_{1c}), and fasting blood glucose, insulin, and lipids and a 2-hour oral glucose tolerance test performed after the ingestion of 75 g of glucose. All laboratory tests were performed in the same laboratory using the same methods throughout the study period as described previously.[13]

The fasting glucose level, 2-hour postprandial glucose level during an oral glucose tolerance test, and hemoglobin A_{1c} data were used to define normal glucose tolerance (fasting glucose level less than 100 mg/dL, 2-hour postprandial glucose level less than 140 mg/dL, and hemoglobin A_{1c} level less than 5.7%), prediabetes (fasting glucose level 100–125 mg/dL, 2-hour postprandial glucose level 140–199 mg/dL, or hemoglobin A_{1c} level 5.7%–6.4%), and diabetes mellitus (fasting glucose level greater than 125 mg/dL, 2-hour postprandial glucose level greater than 199 mg/dL, or hemoglobin A_{1c} level greater than 6.4%).[1] The fasting glucose and insulin data were used for the homeostatic model assessment of insulin resistance (HOMA-IR).[24] The weight and height were used to calculate the BMI and classify patients as underweight (BMI less than 18.5), normal weight (BMI, 18.5–24.9), overweight (BMI, 25.0–29.9), and obese (BMI, 30 or greater). The waist circumference, arterial blood pressure, and fasting glucose, triglycerides, and HDL cholesterol levels were used to determine whether the patient met criteria for metabolic syndrome, which was defined by the presence of at least 3 of the following 5 items: waist circumference > 88 cm in women and > 102 cm in men, fasting blood glucose level ≥ 100 mg/dL, serum triglycerides ≥ 150 mg/dL, HDL cholesterol < 40 mg/dL in men and < 50 mg/dL in women, and arterial blood pressure ≥ 130/85 mm Hg or current treatment with antihypertensive agents.[26]

Statistical Analyses

Analyses of variance and χ^2 tests were used to compare continuous and categorical variables, respectively, in patients with normal glucose tolerance, prediabetes, and diabetes mellitus. The Bonferroni correction was applied to clusters of dependent variables. Analyses were 2-sided, with α of $P < .05$, using JMP 5.0.1, 1989–2003 (SAS Institute Inc, Cary, North Carolina).

RESULTS

The 783 patients participating in this study had a mean ± SD age of 37.6 ± 11.7 years, and the gender distribution within the

Table 1. Demographic and Clinical Features of Patients With Normal Glucose Tolerance, Prediabetes, and Newly Discovered Diabetes

Feature	Total (N = 783)	Normal Glucose Tolerance (n = 413)	Normal Glucose Tolerance vs Prediabetes, *P* Value[a]	Prediabetes (n = 290)	Prediabetes vs Diabetes Mellitus, *P* Value[a]	Diabetes Mellitus (n = 80)
Age, mean ± SD, y	37.6 ± 11.7	33.7 ± 10.7	**< .0001**	40.6 ± 13.0	**.0001**	46.9 ± 11.7
Male gender, n (%)	478 (61.1)	275 (66.5)	**.007**	164 (56.6)	.22	39 (48.8)
Smoking, n (%)	485 (61.9)	256 (62.0)	.73	176 (60.7)	.36	53 (66.2)
Psychiatric diagnosis, n (%)						
Schizophrenia	524 (66.9)	287 (70.0)	.25	191 (65.9)	.08	36 (45.0)
Schizoaffective disorder	99 (12.6)	40 (9.7)	**.03**	44 (15.2)	.45	15 (18.8)
Bipolar disorder	114 (14.6)	63 (15.3)	.35	37 (12.8)	.29	14 (7.5)
Major depression	19 (2.4)	5 (1.2)	.14	8 (2.7)	.07	6 (7.5)
Personality disorder	27 (3.5)	16 (3.9)	.77	10 (3.5)	.26	1 (1.3)
GAF score, mean ± SD	55.8 ± 12.5	55.3 ± 12.9	.30	56.3 ± 12.4	.67	56.9 ± 10.5
CGI-S score, mean ± SD	4.3 ± 0.9	4.4 ± 0.9	.19	4.3 ± 0.9	.60	4.2 ± 0.9
Antipsychotic drug, n (%)						
Olanzapine	236 (30.1)	130 (31.5)	.27	80 (27.6)	.39	26 (32.5)
Risperidone	195 (24.9)	108 (26.2)	.48	69 (23.8)	.81	18 (22.5)
Quetiapine	111 (14.2)	58 (14.0)	.72	38 (13.1)	.21	15 (18.8)
Clozapine	104 (13.3)	40 (9.7)	**.001**	53 (13.3)	.33	11 (13.8)
Amisulpride	53 (6.8)	33 (8.0)	.37	18 (6.2)	.16	2 (2.5)
Aripiprazole	41 (5.2)	25 (6.1)	.48	14 (4.8)	.34	2 (2.5)
First-generation	43 (5.5)	19 (4.6)	.35	18 (6.2)	.68	6 (7.5)

[a]Boldface values reflect differences statistically significant after Bonferroni correction.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness, GAF = Global Assessment of Functioning.

Table 2. Frequency of Normal Glucose Tolerance, Prediabetes, and Newly Discovered Diabetes by Antipsychotic Used

Variable, n (%)	Olanzapine (n = 236)	Risperidone (n = 195)	Quetiapine (n = 111)	Clozapine (n = 104)	Amisulpride (n = 53)	Aripiprazole (n = 41)	First-Generation Antipsychotic (n = 43)
Normal glucose tolerance	130 (55.1)	108 (55.4)	58 (52.8)	40 (38.4)	33 (62.2)	25 (60.9)	19 (44.1)
Prediabetes[a]	80 (33.9)	69 (35.4)	38 (34.2)	53 (51.0)	18 (34.0)	14 (34.2)	18 (41.9)
Diabetes mellitus[b]	26 (11.0)	18 (9.2)	15 (13.5)	11 (10.6)	2 (3.8)	2 (4.9)	6 (14.0)

[a]*P* = .097 across the row.
[b]*P* = .340 across the row.

sample indicated a moderate male predominance (61.1%). A substantial majority of the patients had been admitted for the treatment of schizophrenia (66.9%) or schizoaffective disorder (12.6%). Overall, the severity of functional impairment was moderate, as reflected by a mean CGI-S score of 4.3 and GAF score of 55.8. Most patients (94.5%) were treated with second-generation antipsychotics (Table 1).

The proportions of patients treated with the same antipsychotic drug for more than 3 months were 81.4% for those receiving first-generation antipsychotics, 76.0% for clozapine, 56.6% for amisulpride, 46.2% for risperidone, 46.2% for olanzapine, 38.7% for quetiapine, and 12.2% for aripiprazole. In addition to antipsychotics, 337 patients (43%) were receiving benzodiazepines, 255 (32.6%) were treated with antidepressants, and 210 (26.8%) were receiving mood stabilizers. Anticholinergic drugs had been prescribed to 102 patients (13.0%) for prevention of extrapyramidal symptoms.

More than half of the patients were overweight (37.2%) or obese (20.7%), and close to one-third (30.8%) had metabolic syndrome.

Prevalence of Prediabetes

The 2010 ADA criteria[1] identified normal glucose tolerance in 413 subjects (52.8%), prediabetes in 290 subjects (37.0%), and newly diagnosed diabetes mellitus in 80 subjects (10.2%).

The diagnosis of prediabetes was established by the presence of 1 criterion in 209 patients (72.1%). Seventy-one patients (24.5%) had 2 positive criteria, and 10 patients (3.4%) fulfilled all 3 criteria. An abnormal hemoglobin A_{1c} level was the sole defining abnormality in 120 of the 290 prediabetic patients (41.4%). The fasting glucose and/or hemoglobin A_{1c} criteria were present in 89.7% of prediabetic patients.

Demographic and Psychiatric Features of Prediabetic Patients

Compared with patients with normal glucose tolerance, the prediabetic group was older (mean age, 40.6 vs 33.7 years, *P* < .0001) and had fewer male patients (56.6% vs 66.5%, *P* = .007). The distribution of psychiatric diagnoses was essentially similar, the exception being a greater frequency of schizoaffective disorder in prediabetic patients compared with subjects with normal glucose tolerance (15.2% vs 9.7%, *P* = .03). The groups did not differ significantly in terms of smoking status, functional impairment, or clinical assessment of the severity of psychiatric illness (Table 1).

Antipsychotic Drug Treatment and Prediabetes

Patients with prediabetes were almost twice as likely to be treated with clozapine than patients with normal glucose tolerance (13.3% vs 9.7%, *P* = .001). The groups were similar with regard to the utilization of all other second-generation

Table 3. Anthropometric and Metabolic Features of Patients With Normal Glucose Tolerance, Prediabetes, and Newly Discovered Diabetes

Feature	Total (N = 783)	Normal Glucose Tolerance (n = 413)	Normal Glucose Tolerance vs Prediabetes, *P* Value[a]	Prediabetes (n = 290)	Prediabetes vs Diabetes Mellitus, *P* Value[a]	Diabetes Mellitus (n = 80)
BMI, mean ± SD	26.4 ± 4.9	25.7 ± 4.3	**.005**	26.7 ± 5.4	**.0001**	29.4 ± 5.8
BMI, n (%)						
< 18.5	19 (2.4)	8 (1.9)	.14	11 (3.8)	**.02**	0 (0)
18.5–24.9	311 (39.7)	181 (43.8)	.12	110 (37.9)	**.03**	20 (25.0)
25.0–29.9	291 (37.2)	168 (40.7)	**< .05**	96 (33.1)	.91	27 (33.8)
> 29.9	162 (20.7)	56 (13.6)	**.0001**	73 (25.2)	**.006**	33 (41.3)
Waist circumference, mean ± SD, cm						
Male	96.3 ± 12.3	94.4 ± 11.0	**.02**	97.2 ± 13.1	**.0003**	105.7 ± 12.9
Female	92.4 ± 15.5	88.5 ± 13.8	**.004**	93.7 ± 15.1	**.005**	101.8 ± 17.7
Fasting glucose level, mean ± SD, mg/dL	91.7 ± 12.2	85.4 ± 6.4	**< .0001**	93.4 ± 10.9	**< .0001**	117.9 ± 28.6
2-h Postprandial glucose level, mean ± SD[b]	104.4 ± 26.2	84.4 ± 21.5	**< .0001**	108.5 ± 37.6	**< .0001**	192.7 ± 73.5
Hemoglobin A_{1c}, %	5.5 ± 0.4	5.2 ± 0.3	**< .0001**	5.7 ± 0.4	**< .0001**	6.3 ± 0.7
Fasting insulin, mean ± SD, μU/mL	11.7 ± 9.2	9.9 ± 7.2	**.0007**	11.9 ± 8.2	**< .0001**	20.2 ± 17.9
HOMA-IR, mean ± SD	2.8 ± 2.9	2.1 ± 1.6	**< .0001**	2.8 ± 2.1	**< .0001**	6.3 ± 7.1
Total cholesterol, mean ± SD, mg/dL	202 ± 78.3	197.7 ± 97.8	.21	205.4 ± 43.2	.19	213.4 ± 62.2
Triglycerides, mean ± SD, mg/dL	153.7 ± 108.5	138.5 ± 81.2	**.002**	159.2 ± 95.5	**.002**	212.0 ± 220.2
Cholesterol, mean ± SD, mg/dL						
LDL	118.5 ± 38.5	114.2 ± 35.9	**.003**	122.8 ± 40.6	.75	124.5 ± 43.3
HDL						
Males	46.7 ± 13.0	47.2 ± 13.3	.77	46.8 ± 12.4	.16	43.6 ± 13.5
Females	60.0 ± 17.7	63.1 ± 18.1	**< .05**	58.8 ± 16.0	.06	53.4 ± 15.2
Metabolic syndrome, n (%)	241 (30.8)	67 (16.2)	**< .0001**	119 (41.0)	**< .0001**	55 (68.8)
No. of metabolic syndrome criteria, mean ± SD	1.8 ± 1.2	1.3 ± 1.1	**< .0001**	2.1 ± 1.3	**< .0001**	3.3 ± 1.4

[a]Boldface values reflect differences statistically significant after Bonferroni correction.
[b]Glucose level taken during an oral glucose tolerance test.
Abbreviations: BMI = body mass index, HDL = high-density lipoprotein, HOMA-IR = homeostatic model assessment of insulin resistance, LDL = low-density lipoprotein, OGTT = oral glucose tolerance test.

antipsychotics and of first-generation antipsychotics. The prevalence of prediabetes was highest in patients treated with clozapine (51.0%) and lowest among those receiving olanzapine (33.9%), but across all antipsychotics used, the *P* value was not significant (Table 2). The proportion of patients comedicated with mood-stabilizing drugs was similar in the groups with normal glucose tolerance and prediabetes (25.9% vs 25.5%, $P = .91$), and there were no differences in the frequency of utilization of lithium (5.3% vs 3.8%, $P = .34$) and valproic acid (18.4% vs 17.6%, $P = .78$).

Markers of Metabolic Abnormalities in Prediabetes

The 2010 ADA criteria separated well patients with prediabetes from those with normal glucose tolerance and those with diabetes, as demonstrated by the strong statistical significance ($P < .0001$) of the comparisons of fasting glucose, 2-hour postprandial glucose, and hemoglobin A_{1c} levels. Fasting insulin levels and HOMA-IR were also clearly different in the 3 groups (Table 3).

Insulin resistance, as assessed by HOMA-IR values, had a crescendo gradient from normal glucose tolerance to prediabetes to diabetes in patients treated with clozapine ($P < .0001$), olanzapine ($P < .0001$), quetiapine ($P < .0001$), risperidone ($P < .0001$), and amisulpride ($P = .0014$) but not in patients treated with aripiprazole ($P = .246$) and first-generation antipsychotics ($P = .154$).

The proportion of obese individuals (BMI ≥ 30) was almost double in the prediabetes group compared with participants with normal glucose tolerance (25.2% vs 13.6%, $P = .0001$). The waist circumference was significantly larger in prediabetic patients than in subjects with normal glucose tolerance, particularly for female patients (Table 3).

Compared with the normal glucose tolerance group, prediabetic patients had higher mean plasma triglyceride levels (138.5 vs 159.2 mg/dL, $P = .002$) and low-density lipoprotein (LDL) cholesterol levels (114.2 vs 122.8 mg/dL, $P = .003$). The groups were essentially similar with regard to fasting total cholesterol and HDL cholesterol (Table 3).

The prevalence of metabolic syndrome among patients with prediabetes was substantially higher than in patients with normal glucose tolerance (41.0% vs 16.2%, $P < .0001$).

Progression of Anthropometric and Metabolic Abnormalities From Prediabetes to Diabetes

Compared with prediabetic patients, those with newly discovered diabetes mellitus in our cohort were older ($P = .0001$), had a higher BMI ($P = .0001$), a greater prevalence of obesity ($P = .006$), a larger waist circumference ($P = .0003$ for males and $P = .0045$ for females), higher triglycerides levels ($P = .0017$), and a greater prevalence of metabolic syndrome ($P < .0001$).

Prediabetic Patients Eligible for Treatment With Metformin

Twenty-one of the 290 prediabetic patients (7.2%) had a fasting glucose level in the range of 100–125 mg/dL *and* a 2-hour response to the 75-g glucose tolerance test in the range of 140–199 mg/dL. Nineteen of these 21 patients (90.5%) also had at least 1 other notable risk factor, such as hemoglobin A_{1c} level > 6%, family history of diabetes in a

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first-degree relative, obesity, elevated triglycerides, low levels of HDL cholesterol, hypertension, and age younger than 60 years, and were, therefore, eligible for treatment with metformin according to the 2010 guidelines published by the ADA.[4]

The metformin-eligible prediabetic patients were similar with regard to age, gender, psychiatric diagnosis, severity of illness, global assessment of function, and fasting insulin levels compared with the 271 prediabetic patients who did not fulfill the criteria for treatment with metformin, but the metformin-eligible patients had a higher mean ± SD BMI (30.0 ± 7.3 vs 26.5 ± 5.1, $P = .0049$) and larger mean ± SD waist circumference (102.7 ± 14.8 cm vs 95.1 ± 13.9 cm, $P = .0230$) and were more likely to receive clozapine (36.8% vs 17.0%, $P = .03$).

DISCUSSION

In the first application of the 2010 ADA diagnostic guidelines[1] to a European patient population treated with antipsychotic drugs, 37% fulfilled criteria for prediabetes and 10.2% had previously undiagnosed diabetes. Compared with patients with normal glucose tolerance, the prediabetic patients were older and had higher body mass index and prevalence of overweight and obesity, increased abdominal adiposity, higher insulin levels and resistance to insulin, higher levels of atherogenic lipids (ie, LDL cholesterol and triglycerides), and an increased prevalence of metabolic syndrome. The excess in body mass index and abdominal distribution of adiposity found by us confirms the primary role of central obesity in the pathogenesis of insulin resistance in this population.[9–11]

The largest contributor to the identification of prediabetes in this sample of psychiatric patients was the test for hemoglobin A_{1c}, which was the sole defining abnormality in 120 of the 290 prediabetic patients (41.4%). The fasting glucose and/or hemoglobin A_{1c} criteria were present in 89.7% of prediabetic patients. These findings highlight 3 important contributions of our study to clinical practice and research. First is the fact that the addition of hemoglobin A_{1c} to the definition of prediabetes produces a remarkable increase in its prevalence. Second is that reliance on fasting glucose, advocated by the American Psychiatric Association in the widely used guidelines for detection of metabolic abnormalities in patients treated with second-generation antipsychotics,[26,27] is likely to miss a majority of patients with prediabetes. Third is that the more cumbersome test of oral glucose tolerance has only a limited value for the discovery of prediabetes in this population.

The point prevalence of prediabetes was similarly high in patients treated with first- and second-generation antipsychotics. This finding might seem surprising, given the widely spread belief in a difference in "metabolic liability" between these 2 classes of drugs, which was considered a reflection of their lower appetite-stimulating effect through central H_1 receptor blockade. In fact, first-generation antipsychotics are part of a heterogeneous group of compounds, and treatment with the so-called low-potency drugs from this class has been recently shown to be associated with an increased risk for diabetes that was similar to those of olanzapine and clozapine.[9,14] Within the second-generation antipsychotic class, clozapine was noted to have the strongest association with prediabetes (point prevalence, 51%), a predictable finding, given its established potential for significant weight gain and alteration in insulin sensitivity and production.[9,14] In contrast stands the fact that the prevalence of prediabetes among patients treated with olanzapine (33.9%) is much lower than in patients receiving clozapine, despite similar central H_1 affinity of these 2 drugs and comparable treatment-emergent weight gain.[9,28]

Our data suggest a potential metabolic advantage of aripiprazole, but the findings must be interpreted very cautiously, given the fact that only a minority of patients had been receiving this drug for more than 3 months. If confirmed in longitudinal research, a possible explanation might be a more frequent progression to diabetes in patients treated with olanzapine, clozapine, and low- and mid-potency first-generation antipsychotics than in those receiving aripiprazole,[14] which is also suggested by the substantial difference in the rate of diabetes among patients treated with these drugs and aripiprazole in our cohort. The findings also indicate that aripiprazole is unique among second-generation antipsychotics used in this clinical sample with regard to the crescendo gradient of insulin resistance from normal glucose tolerance to prediabetes and diabetes, as HOMA-IR was statistically similar in prediabetic and diabetic patients treated with aripiprazole. Of interest is also the fact that prediabetes was not associated with a greater utilization of valproic acid, despite reports indicating that this mood stabilizer contributes to weight gain in pediatric and adult patients.[29] Finally, nonpharmacologic factors, such as unhealthy lifestyle behaviors and genetic/familial risk,[30] might also increase the risk for the emergence of prediabetes.

Of great importance for the management of prediabetes is the identification of patients eligible for treatment with metformin.[4,21] In our cohort, only 21 prediabetic patients (7.2%) had concomitant impaired fasting glucose and glucose tolerance, a frequency that is slightly lower than those observed in surveys of the general population, ranging from 8.2%–9.4%.[4,21] Nineteen of the 21 patients (6.6% of prediabetic patients) had at least 1 additional risk factor for diabetes and were, thus, eligible for a therapeutic trial with metformin. Compared with the other prediabetic patients, those eligible for treatment with metformin were more likely to be treated with clozapine and had larger waist circumferences. The use of metformin for prevention of diabetes is not approved by the US Food and Drug Administration but has been proposed by expert panels convened by the American Diabetes Association[31] and the American College of Endocrinology.[4,32,33] Metformin might be particularly beneficial in psychiatric patients whose prediabetes has been produced by antipsychotic-related weight gain, a population in which the use of this drug has led to significant weight loss and reduced intraabdominal adiposity.[34]

The results of this study need to be interpreted within its limitations. Although relatively large, the study cohort was predominantly white and drawn from a European country with a relatively high standard of living and easy access to high-quality medical care. In addition, the cross-sectional design of the study prevented the assessment of the relationships between the development of glucose intolerance, the duration of the psychiatric illness, and psychotropic drug regimen. Furthermore, the number of measured noncardiometabolic variables was limited and missing regarding lifestyle behaviors. The cohort included patients with a primary diagnosis of schizophrenia, mood disorders, and personality disorder, who may have different lifestyle behaviors and genetic factors that influence cardiometabolic risk prior to the administration of antipsychotic drugs.[35] Nonetheless, while awaiting confirmation in additional, multiethnic samples and from other continents, the finding that more than 1 of 3 antipsychotic-treated mentally ill adults in this study had prediabetes is clearly alarming. These results should further stimulate concerted efforts toward widespread cardiometabolic monitoring, which has remained inadequate,[36] as well as toward more aggressively preserving or restoring glucose tolerance, insulin sensitivity, and overall metabolic health.[30,37]

Drug names: aripiprazole (Abilify), clozapine (Clozaril, FazaClo, and others), lithium (Lithobid and others), metformin (Fortamet, Glucophage, and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal and others), valproic acid (Stavzor, Depakene, and others).

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