Major Changes in Glucose Metabolism, Including New-Onset Diabetes, Within 3 Months After Initiation of or Switch to Atypical Antipsychotic Medication in Patients With Schizophrenia and Schizoaffective Disorder

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Objective: To investigate 3-month changes in glucose metabolism in a naturalistic sample of patients with schizophrenia newly started on or switched to specific atypical antipsychotic medication therapy.

Method: One hundred eighty-three patients were evaluated before initiation and 3 months after with a 75-g glucose load oral glucose tolerance test (OGTT). Data were collected between November 2003 and January 2007.

Results: Eight patients (4.4%) developed new-onset diabetes within 3 months. Initiation of clozapine resulted in a significantly higher risk for new-onset glucose abnormalities than initiation of aripiprazole (odds ratio = 67.29, 95% CI = 5.23 to 866.49). Significant drug × time interactions were found for all OGTT glucose assessments (fasting: $F = 6.79$, $df = 5,177$; $p < .0001$; 30 minutes: $F = 3.89$, $df = 5,177$; $p = .0023$; 60 minutes: $F = 5.03$, $df = 5,177$; $p = .0002$; 120 minutes: $F = 3.78$, $df = 5,177$; $p = .0028$), with the evolution of plasma glucose levels being significantly worse in patients initiated on clozapine therapy (fasting, 30 minutes, and 60 minutes), olanzapine therapy (fasting, 60 minutes, and 120 minutes), and quetiapine therapy (fasting and 60 minutes) than in patients initiated on aripiprazole therapy ($p < .05$). Clozapine was also significantly more deleterious than risperidone and amisulpride for fasting plasma glucose level changes ($p < .05$). Type of initiation (start or switch) did not affect any of the metabolic parameters.

Conclusions: The incidence of new-onset glucose abnormalities, including diabetes, in the first 3 months after newly starting or switching atypical antipsychotic medication is high and may be markedly influenced by type of prescribed antipsychotic. The importance of accurately screening for new-onset glucose abnormalities after initiation of an atypical antipsychotic is emphasized.

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High prevalence rates of diabetes have consistently been reported in patients with schizophrenia,[1,2] with growing evidence suggesting a direct diabetogenic effect of atypical antipsychotic medication.[3–6] Evidence, however, also suggests that a diagnosis of schizophrenia may be a relevant factor for the development of diabetes independently of medication effects. Increased central obesity,[7] decreased insulin sensitivity,[8] impaired fasting glucose,[9] and impaired glucose tolerance[10] were also shown at increased rates in unmedicated subjects presenting with a first episode of psychosis. Furthermore, high prevalence rates of diabetes and cardiovascular morbidity were reported in unaffected relatives.[2,10–12] These findings not only support the high liability for developing diabetes in patients with schizophrenia but also underscore the possible relevance of diagnostic homogeneity. Next to medication effects,[5] shared genetic factors could partly underlie reported associations,[13,14] although not all studies found evidence for insulin resistance in drug-naive patients.[15,16]

In 2 diagnostically mixed samples treated with atypical antipsychotics, annual incidence rates of new-onset diabetes were 4.7%[17] and 6.9%.[18] In a sample consisting only of patients with schizophrenia, Leslie and Rosenheck[19] observed an annual incidence rate of 4.4% in patients on a stable regimen of antipsychotic treatment. Likewise, in a study using the oral glucose tolerance test (OGTT), an annual incidence rate of 4.2% was found in 240 schizophrenia patients who were on stable treatment with OGTT-confirmed nondiabetic status at baseline.[20]

These incidence studies included only patients on a stable antipsychotic regimen for at least 3 months,[19,20] and information on the exact timing of the development of diabetes after initiation of an atypical antipsychotic is scarce. So far, only one study has addressed this issue[21] by identifying all new antipsychotic users with schizophrenia in the database of the U.S. Veterans Health Administration and prospectively following up any diagnosis of diabetes or antidiabetic treatment as recorded in the database. In this study, which examined only patients newly initiated on haloperidol, risperidone, olanzapine, and quetiapine therapies, 1-year incidence rates of a database diagnosis of diabetes or treatment with antidiabetic medication were 2% in patients started on haloperidol therapy, 3.2% in patients with risperidone, 3.3% in patients with olanzapine, and 3.6% in patients with quetiapine. The available data thus confirm that the development of new-onset diabetes represents a major health problem in patients with schizophrenia and suggest that the development of new-onset diabetes may occur rather quickly after initiation of an atypical antipsychotic. However, there have been no studies that have assessed the early changes in glucose metabolism following initiation of atypical antipsychotics in detail by using the OGTT.

The aim of the current study was to investigate the early changes in glucose metabolism, including the 3-month incidence of new-onset diabetes, in a naturalistic sample of patients with schizophrenia with OGTT-confirmed nondiabetic status who were initiated on a specific atypical antipsychotic therapy. Furthermore, we were interested in differential effects of antipsychotic medication on the evolution of glucose metabolism, given the evidence that some antipsychotics, especially clozapine and olanzapine, could be more deleterious than others.[5] We hypothesized that substantial changes in glucose metabolism would occur within 3 months after initiation of an atypical antipsychotic and that these changes would be most severe in patients initiated on clozapine and olanzapine therapies.

METHOD

Study Cohort

At our hospital and affiliate services, all patients treated with antipsychotic medication are screened and monitored prospectively for metabolic abnormalities. The vast majority of patients are part of an extensive clinical metabolic screening and monitoring protocol, which was started in November 2003.[2,20,22,23] The study population is a dynamic, naturalistic cohort. Decisions regarding antipsychotic medication, including dose reduction, dose augmentation, and switch strategies, are made by the treating psychiatrist and the patient. These changes are recorded, and patients are monitored for metabolic abnormalities by means of laboratory tests, OGTTs, and clinical examinations. The baseline characteristics of the first 415 included patients of this dynamic cohort who were screened with an OGTT are described in detail elsewhere.[2,20] The sample of the current study was derived from this large, dynamic cohort. Patients were included if (1) they had a DSM-IV diagnosis of schizophrenia or schizoaffective disorder as established by their treating psychiatrist; (2) they were newly initiated on a specific atypical antipsychotic therapy, meaning that they had not taken any antipsychotic medication and were then newly started on a specific atypical antipsychotic (*starters*) or were switched from another antipsychotic and newly initiated on a specific atypical antipsychotic with complete discontinuation of the previous antipsychotic within 3 weeks (*switchers*); and (3) they did not have diabetes before initiation of the specific atypical antipsychotic as confirmed with an OGTT. As one of the aims of the study was to assess differential medication effects on glucose metabolism, patients for whom the initiated atypical antipsychotic was added to an existing antipsychotic medication (*add-on* or *antipsychotic polypharmacy*) were excluded from the analyses. The study was approved by an ethical committee, and all patients gave written informed consent. Data were collected between November 2003 and January 2007 at the University Psychiatric Center of the Katholieke Universiteit Leuven in Kortenberg, Belgium.

Metabolic Screening

Patients were evaluated 2 times with a full metabolic screening, which included a 75-g glucose load OGTT after an overnight fast, at baseline before the initiation of the atypical antipsychotic and 3 months after initiation of the new antipsychotic drug. Insulin resistance was determined using the homeostasis model assessment of insulin resistance (HOMA-IR) with fasting plasma glucose and insulin levels.[24]

For the diagnosis of diabetes and prediabetic abnormalities, the American Diabetes Association criteria were used: diabetes (fasting plasma glucose level > 125 mg/dL and/or plasma glucose level > 199 mg/dL at 2 hours into the OGTT), impaired fasting glucose ([IFG]; plasma glucose level 100–125 mg/dL), and impaired glucose tolerance ([IGT], plasma glucose level 140–199 mg/dL at 2 hours into the OGTT).[25]

Statistical Analyses

Descriptive statistics were computed for the basic demographic and clinical variables as well as for the variables relevant to the evaluation of metabolic abnormalities. Differences between treatment groups at baseline were evaluated through 1-way analysis of variance (ANOVA). The influence of known diabetes risk factors and type of medication on the occurrence of glucose abnormalities (diabetes + prediabetes) was modeled through logistic regression in patients without glucose abnormalities at baseline (N = 153). Known risk factors for diabetes, as measured at baseline, were included in the model (fasting plasma glucose level, plasma glucose level at 120 minutes in the OGTT, body mass index [BMI], a family history of diabetes, high-density lipoprotein [HDL] cholesterol blood level, low-density lipoprotein [LDL] cholesterol blood level, HDL/LDL ratio, and triglycerides blood level).[25] Drug (6) × time (2) repeated-measures ANOVAs were performed to evaluate changes in plasma glucose and insulin levels and in HOMA-IR as a function of antipsychotic medication over the follow-up period. Pairwise comparisons between antipsychotic treatment groups were evaluated through Tukey's studentized range test at an α level of .05.

RESULTS

Subjects

In 220 patients, a specific atypical antipsychotic was newly initiated. Of these, 12 were diagnosed with diabetes at the OGTT that was performed before initiation. As one of the aims of the current study was to examine the incidence of new-onset diabetes, these patients were excluded from the analyses. Of the remaining 208 subjects, the initiated atypical antipsychotic was added to existing antipsychotic medication in 25 patients (add-on or antipsychotic polypharmacy). The 25 patients with polypharmacy were also excluded in order to be able to reliably assess differential medication effects, resulting in a final sample of 183 patients. Of these 183, 126 had not been treated with antipsychotic medication before study entry because they were drug-naive first-episode patients (N = 22) or because of noncompliance with their previous treatment (N = 104). Duration of noncompliance was not recorded. The remaining 57 patients had been treated with antipsychotic medication (20 with risperidone, 18 with olanzapine, 6 with amisulpride, 5 with a typical antipsychotic, 4 with quetiapine, 3 with clozapine, and 1 with bifeprunox) and were switched to the specific atypical medication under study. No significant differences in age, sex, Clinical Global Impressions scale score, Global Assessment of Functioning score, and number of different medications were found between starters and switchers, but starters did have a significantly shorter duration of illness ($F = 4.51$, $df = 1,181$; $p = .0350$) and a significantly lower mean BMI ($F = 16.42$, $df = 1,181$; $p < .0001$).

Olanzapine was initiated in 50 patients (27.3%), risperidone in 48 patients (26.2%), quetiapine in 24 patients (13.1%), aripiprazole in 22 patients (12.0%), clozapine in 21 patients (11.5%), and amisulpride in 18 patients (9.8%). Anticholinergic medication was prescribed in 13.7% of patients, antidepressants in 32.8%, benzodiazepines in 33.9%, mood stabilizers in 23.0%, antihypertensive medication in 10.4%, and statins in 1.1%. No significant differences in age, duration of illness, GAF score, or CGI score were found for the different antipsychotic treatment groups, but there was a significant main effect of BMI ($F = 3.28$, $df = 5,147$; $p = .0078$), although only the contrast between patients initiated on aripiprazole and olanzapine therapies reached significance, with patients initiated on aripiprazole therapy having a significantly higher baseline BMI than patients treated with olanzapine ($p < .05$).

Patients had DSM-IV diagnoses of schizophrenia (76.0%) or schizoaffective disorder (24.0%). Their mean age was 33.7 years (SD = 11.6), and they had been ill for a mean of 7.5 years (SD = 9.4). The majority of the sample was male (60.7%). Many patients had a family history of diabetes (31.2%), dyslipidemia (37.7%), or cardiovascular disorders (50.8%).

Incidence of New-Onset Diabetes

Eight patients developed diabetes within 3 months after the start of the atypical antipsychotic, resulting in a 3-month incidence rate of 4.4% (8/183). Patients with new-onset diabetes were initiated on clozapine (2 of the 21 treated patients, 9.5%), olanzapine (4 of the 50 treated patients, 8.0%), quetiapine (1 of the 24 treated patients, 4.2%) and risperidone (1 of the 48 treated patients, 2.1%) therapies, whereas no new cases developed in the groups treated with aripiprazole and amisulpride. Of the 8 new-onset diabetes cases, 2 already had IFG at baseline, 1 had IGT at baseline, and 2 had both IFG and IGT, indicating that 16.7% of patients with prediabetic abnormalities developed diabetes (Table 1). The remaining 3 had no glucose abnormalities at baseline (Table 1). Prediabetic abnormalities regressed in 12 patients (40% of 30 patients with preexisting glucose abnormalities), mainly in patients initiated on aripiprazole therapy, whereas prediabetic abnormalities developed in 29 patients (19.0% of 153 normoglycemic patients), mainly in patients initiated on clozapine and olanzapine therapies (Table 1).

Three-Month Evolution of Glucose, Weight, and Insulin

The repeated-measures drug (6) × time (2) ANOVA on plasma glucose and insulin levels and HOMA-IR revealed significant main effects of time on plasma glucose levels at 120 minutes ($F = 4.76$, $df = 1,177$; $p = .0304$) and insu-

Table 1. Glucose Abnormalities After 3 Months' Exposure to an Atypical Antipsychotic Drug in a Naturalistic Sample of Schizophrenic Patients Who Were Normoglycemic and Prediabetic[a] at Baseline[b]

Antipsychotic Drug	Abnormality	N (%)
Normoglycemic patients (N = 153)		
All	None	121 (79.1)
	IFG and/or IGT	29 (19.0)
	Diabetes	3 (2.0)
Amisulpride (N = 14)	None	12 (85.7)
	IFG and/or IGT	2 (14.3)
	Diabetes	0 (0.0)
Aripiprazole (N = 17)	None	16 (94.1)
	IFG and/or IGT	1 (5.9)
	Diabetes	0 (0.0)
Clozapine (N = 18)	None	8 (44.4)
	IFG and/or IGT	9 (50.0)
	Diabetes	1 (5.6)
Olanzapine (N = 39)	None	31 (79.5)
	IFG and/or IGT	8 (20.5)
	Diabetes	0 (0.0)
Quetiapine (N = 23)	None	17 (73.9)
	IFG and/or IGT	5 (21.7)
	Diabetes	1 (4.4)
Risperidone (N = 42)	None	37 (88.1)
	IFG and/or IGT	4 (9.5)
	Diabetes	1 (2.4)
Prediabetic patients (N = 30)		
All	None	12 (40.0)
	IFG and/or IGT	13 (43.3)
	Diabetes	5 (16.7)
Amisulpride (N = 4)	None	2 (50.0)
	IFG and/or IGT	2 (50.0)
	Diabetes	0 (0.0)
Aripiprazole (N = 5)	None	5 (100.0)
	IFG and/or IGT	0 (0.0)
	Diabetes	0 (0.0)
Clozapine (N = 3)	None	0 (0.0)
	IFG and/or IGT	2 (66.7)
	Diabetes	1 (33.3)
Olanzapine (N = 11)	None	3 (27.3)
	IFG and/or IGT	4 (36.4)
	Diabetes	4 (36.4)
Quetiapine (N = 1)	None	1 (100.0)
	IFG and/or IGT	0 (0.0)
	Diabetes	0 (0.0)
Risperidone (N = 6)	None	1 (16.7)
	IFG and/or IGT	5 (83.3)
	Diabetes	0 (0.0)

[a]IFG (fasting plasma glucose level = 100–125 mg/dL) and/or IGT (plasma glucose level = 40–199 mg/dL at 2 hours into the oral glucose tolerance test).
[b]Percentages may not total 100 because of rounding.
Abbreviations: IFG = impaired fasting glucose, IGT = impaired glucose tolerance.

lin at 60 minutes (F = 4.38, df = 1,177; p = .0378). There were no significant main effects of drug. There were no significant differences in the evolution of any of the metabolic parameters between switchers and starters.

For fasting plasma glucose levels, a significant drug × time interaction was observed (F = 6.79, df = 5,177; p < .0001) (Table 2). Patients initiated on clozapine therapy had a significantly greater increase in fasting plasma glucose levels than patients initiated on risperidone, aripiprazole, or amisulpride therapy (p < .05). Fasting plasma glucose level changes in patients initiated on aripiprazole differed significantly from changes observed in patients on olanzapine or quetiapine therapy (p < .05). The drug × time interaction for plasma glucose levels at 30 minutes also reached significance (F = 3.89, df = 5,177; p = .0023), with decreased levels in patients initiated on aripiprazole therapy significantly different from increased levels in patients on clozapine therapy. There was a significant drug × time interaction for plasma glucose levels at 60 minutes (F = 5.03, df = 5,177; p = .0002), with a decrease in patients on aripiprazole therapy significantly different from increases in patients on clozapine, olanzapine, and quetiapine therapies (p < .05). Finally, we observed a significant drug × time interaction for plasma glucose levels at 120 minutes (F = 3.78, df = 5,177; p = .0028), with decreases in patients on aripiprazole therapy being significantly different from increases in patients treated with olanzapine (p < .05).

A significant drug × time interaction was also found for BMI (F = 43.60, df = 5,177; p < .0001) and waist circumference (F = 26.03, df = 5,177; p < .0001) (Table 2). For waist circumference, the decrease in patients initiated on aripiprazole therapy was significantly different from increases in patients initiated on olanzapine, quetiapine, risperidone, and amisulpride therapies (p < .05) but not from increases in patients initiated on clozapine therapy. For BMI, the decrease in patients initiated on aripiprazole therapy was significantly different from increases in patients treated with any of the other atypicals (p < .05). The increase of both waist circumference and BMI in patients initiated on olanzapine therapy was significantly greater than in patients initiated on risperidone therapy (p < .05). There were no significant drug × time interactions for insulin measures or HOMA-IR (Table 2).

Prediction of New-Onset Glucose Abnormalities

At baseline, 153 patients were normoglycemic, both in the fasting state and after the glucose load. The logistic regression model predicting the incidence of any new-onset glucose abnormality (IFG, IGT, diabetes) based on type of antipsychotic agent and known diabetic risk factors was significant (χ^2 = 42.26, df = 14, p < .0001). Baseline plasma glucose level at 120 minutes (χ^2 = 4.61, df = 1, p = .0318) and type of antipsychotic (χ^2 = 18.40, df = 5, p = .0025) were significantly associated with new-onset glucose abnormalities. None of the known risk factors for diabetes was associated with new-onset glucose abnormalities, although the effect of age just failed to reach significance (χ^2 = 3.79, df = 1, p = .0515). Type of initiation (start or switch) did not significantly predict new-onset glucose abnormalities (χ^2 = 0.32, df = 1, p = .5704). Higher baseline values for plasma glucose levels at 120

Table 2. Evolution of OGTT Measures, BMI, and Waist Circumference per Treatment Group in 183 Patients Initiated on an Atypical Antipsychotic Therapy

	Amisulpride (N = 18)		Aripiprazole (N = 22)		Clozapine (N = 21)		Olanzapine (N = 50)		Quetiapine (N = 24)		Risperidone (N = 48)		
Measure	Baseline, Mean (SD)	3 mo, Mean (SD)	Baseline, Mean (SD)	3 mo, Mean (SD)	Baseline, Mean (SD)	3 mo, Mean (SD)	Baseline, Mean (SD)	3 mo, Mean (SD)	Baseline, Mean (SD)	3 mo, Mean (SD)	Baseline, Mean (SD)	3 mo, Mean (SD)	Drug × Time Interaction[a]
Glucose fasting, mg/dL	88.8 (11.4)	85.5 (6.3)	92.0 (8.1)	86.3 (7.4)	88.4 (9.6)	98.8 (14.1)	88.9 (11.5)	92.1 (15.6)	83.9 (6.7)	88.3 (9.4)	87.8 (7.5)	88.2 (8.1)	p < .0001
Glucose 120min, mg/dL	109.5 (41.0)	107.6 (30.8)	96.3 (35.5)	84.5 (20.8)	95.4 (37.8)	112.2 (43.1)	89.2 (32.7)	111.7 (48.3)	96.0 (28.7)	101.2 (42.7)	93.1 (28.3)	98.9 (40.0)	p = .0028
Insulin fasting, mg/dL	14.5 (9.7)	12.0 (7.1)	12.6 (12.9)	8.4 (4.6)	15.2 (14.1)	17.1 (14.0)	12.4 (16.7)	15.0 (20.1)	13.6 (18.1)	10.7 (4.2)	10.7 (6.9)	11.4 (7.8)	NS
Insulin 120 min, mg/dL	56.6 (48.0)	42.7 (39.4)	42.3 (40.9)	28.0 (20.1)	53.9 (64.0)	78.8 (160.2)	46.1 (55.0)	54.8 (60.0)	44.4 (39.0)	39.5 (37.0)	42.0 (54.5)	55.3 (110.7)	NS
HOMA-IR	3.3 (2.7)	2.6 (1.7)	3.0 (3.3)	1.8 (1.0)	3.4 (3.2)	4.4 (4.3)	3.2 (6.4)	3.6 (5.5)	2.9 (4.3)	2.3 (1.0)	2.4 (1.7)	2.5 (1.9)	NS
BMI, kg/m^2	26.5 (4.3)	27.9 (3.5)	28.4 (5.7)	27.3 (5.2)	24.8 (4.9)	26.5 (5.2)	23.5 (4.9)	25.8 (5.1)	25.2 (6.1)	26.8 (7.2)	24.9 (3.7)	25.8 (4.1)	p < .0001
Waist, cm	95.1 (11.1)	99.1 (10.0)	99.2 (16.0)	96.4 (14.9)	93.6 (13.0)	96.7 (13.0)	87.7 (11.8)	94.6 (11.4)	91.0 (13.3)	97.0 (16.4)	90.5 (11.2)	93.0 (10.7)	p < .0001

[a]Drug × time interaction in the repeated-measures drug (6) × time (2) analysis of variance.
Abbreviations: BMI = body mass index, HOMA-IR = homeostasis model assessment of insulin resistance, NS = not significant, OGTT = oral glucose tolerance test.

minutes slightly increased the risk for the development of glucose abnormalities (odds ratio [OR] = 1.023, 95% CI = 1.003 to 1.044).

Patients treated with clozapine had a significantly higher risk of developing glucose abnormalities at 3 months' follow-up as compared to patients taking aripiprazole (OR = 67.29, 95% CI = 5.23 to 866.49). The risk of developing new-onset glucose abnormalities in patients taking olanzapine, risperidone, amisulpride, and quetiapine did not significantly differ from the risk for patients treated with aripiprazole.

Although thiazides and β-blockers are known to increase the risk for new-onset diabetes in patients with hypertension,[26] treatment with these agents was not associated with the development of new-onset diabetes over the 3-month follow-up period ($\chi^2 = 0.01$, df = 1, p = .9126), and inclusion of treatment with thiazides or β-blockers as a possible confounder did not change any of the other results. None of the 153 patients was taking systemic corticosteroids.

Furthermore, a post hoc analysis failed to find an association between weight change over the 3-month period and new-onset glucose abnormalities ($\chi^2 = 0.27$, df = 1, p = .604), and including weight change in the predictive model did not change the significant associations with type of antipsychotic medication ($\chi^2 = 17.31$, df = 5, p = .0039) and baseline plasma glucose levels at 120 minutes into the OGTT ($\chi^2 = 4.81$, df = 1, p = .0284).

CONCLUSIONS

Findings

To our knowledge, this is the first study to examine the incidence of new-onset diabetes and early changes in glucose metabolism by means of the OGTT in patients with schizophrenia who were initiated on a specific atypical antipsychotic therapy. A 3-month incidence rate of new-onset diabetes of 4.4% was found. Most patients with new-onset diabetes already had baseline prediabetic abnormalities (5/8, 62.5%), although a substantial number did not (3/8, 37.5%). Initiation of clozapine resulted in a significantly higher risk of developing glucose abnormalities at 3 months' follow-up as compared to patients taking aripiprazole. There were significant drug × time interactions for all glucose assessments in the OGTT (fasting, 30 minutes, 60 minutes, and 120 minutes), with the evolution of plasma glucose levels being significantly worse in patients treated with clozapine (fasting, 30 minutes, and 60 minutes), olanzapine (fasting, 60 minutes, and 120 minutes), and quetiapine (fasting and 60 minutes) than in patients treated with aripiprazole. Clozapine was also significantly worse than risperidone and amisulpride at the fasting plasma glucose assessment (p < .05). Type of initiation (start or switch) did not affect the evolution of any of the metabolic parameters. Interestingly,

the development of new-onset glucose abnormalities was not associated with BMI or weight change over the 3-month follow-up period.

Incidence

As a 10-year OGTT study[27] in a European general population sample of 837 subjects aged between 40 and 79 years in the village of Bruneck (Italy) revealed a yearly incidence rate of diabetes of only 0.72%, a 3-month incidence of new-onset diabetes of 4.4% in a representative sample of patients with schizophrenia with a mean age of 34 years is disturbingly high. This finding supports the claim that, compared to the general population, patients with schizophrenia treated with atypical antipsychotics are at a considerably increased risk for developing diabetes,[2] although it needs to be noted that the reasons for this increased risk are most likely multifactorial, including differences in known risk factors such as BMI and dietary habits. Compared to the 1-year incidence rate of 4.2% reported in the identically screened sample of 240 patients that was on stable medication therapy,[20] the current 3-month 4.4% incidence rate is strikingly similar, despite a much shorter follow-up period. This finding suggests that the chance of developing diabetes is especially high in the first months after initiation of antipsychotic medication, which underscores the importance of accurately screening for new-onset glucose abnormalities after the initiation of an atypical antipsychotic.[28,29] Indeed, our data convincingly show that even patients without abnormalities at baseline can develop prediabetic abnormalities and even frank diabetes within a 3-month period.

Compared to the only other study so far in patients with schizophrenia who were newly started on a second-generation antipsychotic therapy,[21] the current 3-month incidence rate of 4.4% is higher than the reported 1-year incidence rates of 3.2% in patients started on risperidone therapy, 3.3% in patients started on olanzapine therapy, and 3.6% in patients started on quetiapine therapy. However, this earlier study was an epidemiologic study that used the Veterans Health Administration database to identify new users of atypical antipsychotics and to assess the incidence of new-onset diabetes. This also represents the main limitation of the latter study, as convincing evidence exists that a large proportion of incident diabetes cases remain undiagnosed for years,[30] making it likely that the reported incidence rates are an underestimation of the actual incidence rates. In contrast, the diagnostic accuracy of the current study is very high, as new-onset diabetes was assessed by means of the "gold standard," the OGTT. However, whereas the study by Lambert and colleagues had a sample of 15,767 patients,[21] our study included only 183 patients. Given the low incidence rates typically reported for diabetes, this is a relatively low number.

Risk Factors for New-Onset Glucose Abnormalities and Differential Medication Effects

The finding that clozapine was significantly associated with new-onset glucose abnormalities is in line with earlier evidence, with naturalistic studies finding glucose abnormalities in more than half of patients on stable clozapine treatment for at least 3 months[20] and even frank diabetes in almost half of clozapine-treated patients after 10 years of treatment.[31] The available data also suggest that aripiprazole is safer in this regard,[23] which was confirmed by the finding that the evolution of OGTT plasma glucose levels was significantly better in patients initiated on aripiprazole therapy than in patients initiated on clozapine, olanzapine, or quetiapine therapies.

Interestingly, none of the known risk factors for diabetes was associated with the development of new-onset glucose abnormalities, although the effect of age just failed to reach significance. A post hoc analysis also failed to find an association between weight change and new-onset glucose abnormalities over the 3-month period, and including weight change in the predictive model did not change the significant associations with type of antipsychotic medication and baseline plasma glucose levels at 120 minutes into the OGTT.

The absence of significant associations between known risk factors and glucose abnormalities is in contrast to our research on patients taking stable medication,[20] in whom age and BMI were significantly associated with glucose abnormalities. First, this new finding supports the importance of differential antipsychotic medication effects in the development of new-onset glucose abnormalities in patients with schizophrenia. Second, it may also suggest 2 possible mechanisms, although speculative, for the development of new-onset diabetes in patients treated with antipsychotic medication: a slower onset related to weight gain, leading to insulin resistance and gradual β-cell decompensation,[32] and a quicker onset more directly related to antipsychotic treatment effects, possibly via a specific effect on β-cell function, in which the influence of known risk factors is much less prominent. This claim is supported by the finding that the latter type of diabetes may be reversible following a medication switch to aripiprazole[3] or amisulpride.[33] These findings also suggest that certain antipsychotic medications, especially clozapine, should be considered as medication that can induce diabetes.[25]

Next to type of antipsychotic medication, plasma glucose level at 120 minutes into the OGTT was the only significant predictor of subsequent glucose abnormalities, a finding that further underscores the usefulness of the OGTT in patients treated with atypical antipsychotics, as reported earlier,[1,20,34] certainly when taking into account that IGT,[35] but not IFG,[36] was shown to be associated with increased cardiovascular mortality in the absence of diabetes in the general population.

Limitations

The current study also has some limitations. Although the sample was diagnostically homogeneous, it was heterogeneous in the sense that some patients were not taking antipsychotic medication before start of the study (22 drug-naive and 104 nonadherent patients), whereas the remaining 57 were switched from other antipsychotic drugs. Furthermore, the sample was also relatively small for assessing the low incidence rates typically reported for diabetes. This is especially true for differences between atypical antipsychotics, although the demonstrated differences are in line with previous research.

The current study is also a naturalistic study, meaning that there was no random allocation of antipsychotic medication, which resulted in treatment cohorts that were larger for olanzapine and risperidone than for clozapine, quetiapine, aripiprazole, or amisulpride. It is likely that patients' and caregivers' views of anticipated metabolic side effects have influenced their choice for an antipsychotic. Although we have tried to minimize such influence by controlling for known diabetes risk factors, it is still possible that this disparity in the size of treatment cohorts has biased our results to some extent. Nevertheless, the data provide "real-world" evidence that a significant proportion of a representative, naturalistic sample of patients with schizophrenia will develop new-onset diabetes and prediabetic abnormalities within 3 months after initiation of a second-generation antipsychotic, which is of major clinical significance. The importance of accurately screening for diabetes in patients with schizophrenia, therefore, needs to be emphasized.

Drug names: aripiprazole (Abilify), clozapine (FazaClo, Clozaril, and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

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