Screening for Diabetes and Other Metabolic Abnormalities in Patients With Schizophrenia and Schizoaffective Disorder: Evaluation of Incidence and Screening Methods

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Objective: To assess the diagnostic properties of 2 different screening guidelines for the detection of diabetes in patients diagnosed with schizophrenia.

Method: Over a 2-year period (November 2003–November 2005), 415 patients with schizophrenia were screened with a full laboratory screening and a 75-g oral glucose tolerance test (OGTT). The sensitivity of 2 screening strategies was compared with the "gold standard": the OGTT. The 2 strategies were (1) assessing fasting glucose in all patients, as suggested by the American Psychiatric Association/American Diabetes Association (APA/ADA), and (2) a screening strategy derived from the guidelines of the World Health Organization of assessing fasting glucose in all patients (step 1) and subsequently performing an OGTT in patients with impaired fasting glucose (step 2).

Results: Of the total sample, 6.3% (N = 26) met criteria for diabetes, resulting in a mean annual incidence of diabetes of 3.15% (6.3% incident cases/2 years). A screening based on the APA/ADA guidelines detected diabetes in 12 (46.2%) of the 26 cases identified by the OGTT. The proposed 2-step strategy detected 25 (96.2%) of 26 cases.

Conclusion: The data suggest a high incidence of diabetes in patients diagnosed with schizophrenia. However, the guidelines to detect diabetes as proposed by the APA/ADA did not sufficiently detect diabetes in this specific high-risk group. The alternative 2-step strategy was able to detect the vast majority of diabetes cases and should therefore be considered in the clinical routine of screening and monitoring patients with schizophrenia.

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In recent years, there has been a growing interest in the occurrence of medical comorbidity in patients diagnosed with schizophrenia.[1–4] This is certainly the case for diabetes, as numerous case reports and some retrospective cohort studies provided evidence for an increased risk of diabetes in patients diagnosed with schizophrenia or, more broadly, in patients treated with atypical antipsychotics.[5–14] Given this amount of evidence, there is a wide consensus that patients treated with atypical antipsychotics are at high risk of developing diabetes, specifically type 2 diabetes.[15] Schizophrenic patients treated with antipsychotics indeed display many risk factors for type 2 diabetes, such as a sedentary lifestyle, overweight, and unhealthy dietary habits. In addition to these risk factors, all atypical antipsychotics are to some degree associated with weight gain, although their liability to induce weight gain varies from relatively low to relatively high, depending on the individual drug. Furthermore, antipsychotic drugs may even induce insulin resistance,[16,17] although insulin resistance was also found in drug-naive patients with schizophrenia.[18] Another major health concern in patients with schizophrenia is the metabolic syndrome, which comprises abnormalities in glucose metabolism, lipid metabolism, body weight/fat distribution, and blood pressure. The metabolic syndrome is present in as much as 40% of patients diagnosed with schizophrenia, and its presence significantly increases the risk for diabetes and other glucose abnormalities.[19–24]

A recent American consensus conference proposed much-awaited guidelines to screen and monitor patients

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treated with an atypical antipsychotic.[25] Importantly, the consensus conference also acknowledged the need to acquire additional data in order to further improve screening and treatment guidelines. This is especially relevant for 2 reasons. First, preliminary evidence suggests that the use of the proposed guidelines may result in an underdiagnosis of diabetes and other glucose abnormalities in high-risk groups, when compared to the "gold standard" of the oral glucose tolerance test (OGTT).[19,26,27] Second, early detection of glucose abnormalities in patients diagnosed with schizophrenia could well be of eminent importance, as prediabetic abnormalities and even frank diabetes are shown to be potentially reversible in this specific population, at least in cases in which the onset of diabetes was most likely related to antipsychotic treatment.[28–31]

However, the standard use of an OGTT as a screening instrument in all patients treated with antipsychotics may not be an achievable goal in all treatment settings. Therefore, a 2-step strategy derived from the guidelines of the World Health Organization (WHO)[32] was developed that could serve as an alternative for the standard use of an OGTT in patients treated with antipsychotics.

The current study reports on the baseline data of a cohort of 415 prospectively monitored schizophrenic patients treated with antipsychotics. The aim of the current study was 2-fold: first, to assess metabolic abnormalities in a large sample of patients diagnosed with schizophrenia, and second, to assess the sensitivity of 2 different screening guidelines for the detection of diabetes. These 2 strategies were (1) assessing fasting glucose in all patients, as suggested by the American Psychiatric Association/American Diabetes Association (APA/ADA) consensus guidelines, and (2) the screening strategy derived from the guidelines of the WHO of assessing fasting glucose in all patients (step 1) and subsequently performing an OGTT in patients with impaired fasting glucose (step 2).

In line with the previous literature on screening for diabetes in the general population,[26,27,33–35] it was hypothesized that the use of the consensus screening guidelines, but not the use of the 2-step strategy, would result in a large underdiagnosis of diabetes and other glucose abnormalities in the present sample of patients diagnosed with schizophrenia.

METHOD

Over a 2-year period, both inpatients (73.7%) and outpatients (26.3%) with a diagnosis of schizophrenia or schizoaffective disorder who were in contact with the services of the University Psychiatric Center, Katholieke Universiteit Leuven (Kortenberg, Belgium), were asked to participate in the present study. All included patients were on stable medication treatment for at least 3 months and were not diagnosed with diabetes mellitus prior to the baseline screening. All patients were informed about the purpose of the study and provided written informed consent. The study was approved by an ethical committee. The study began in November 2003, and this article includes data available until November 2005.

The baseline screening consisted of a full laboratory screening including fasting insulin and a 75-g OGTT. For the OGTT, patients were instructed to fast overnight and were observed by a nurse during the OGTT, in order to ensure the reliability of the test results. All laboratory analyses were performed in the same laboratory.

For the diagnosis of diabetes and impaired glucose tolerance, the ADA criteria were used,[36] meaning that diabetes was defined as a fasting glucose level > 125 mg/dL and/or a 2-hour post-glucose load > 199 mg/dL. Prediabetes was defined as impaired fasting glucose (fasting glucose level of 100–125 mg/dL) and/or impaired glucose tolerance (IGT: 2-hour post-glucose load 140–199 mg/dL). Insulin resistance was assessed using fasting plasma glucose and insulin levels and a homeostatic model (HOMA-IR). Glycosylated hemoglobin (HbA_{1c}) levels were assessed in diabetic patients. For all patients who were identified with a glucose level that met the criteria for diabetes, a new OGTT was performed within 2 weeks to confirm the diagnosis. To assess the diagnostic properties of 2 different screening strategies, the diabetes cases identified by means of the OGTT were used as the "gold standard" for comparison. The 2 strategies were (1) assessing fasting glucose in all patients, as suggested by the APA/ADA, and (2) a screening strategy derived from the guidelines of the WHO.[32] The WHO guidelines suggest the use of an OGTT in patients presenting with fasting glucose above 109 mg/dL. Following the lower diagnostic fasting glucose levels recommended by the ADA,[36] we modified this WHO strategy to the use of an OGTT in patients presenting with a fasting glucose level above 100 mg/dL (further referred to as impaired fasting glucose [IFG]).

The presence of the metabolic syndrome was assessed using the adapted National Cholesterol Education Program–Adult Treatment Panel III (ATP-III) criteria.[37,38] This is a recent commentary on the original ATP-III criteria that proposes to use a fasting glucose limit of 100 instead of 110 mg/dL and to include drug treatment for hypertension, hyperlipidemia, and hyperglycemia as criteria for the metabolic syndrome. Descriptive statistics were applied for basic demographic and clinical characteristics. An analysis of variance was done to evaluate the influence of the metabolic syndrome on measures of the OGTT.

RESULTS

Subjects

The mean age of the patients was 34.7 years (SD = 11.3), and they had been ill for a mean of 10.8 years

Table 1. Antipsychotic Treatment

Treatment	% (N)
Only first-generation antipsychotic[a]	8.4 (35)
Only second-generation antipsychotic[a]	80.2 (333)
Combination of first-generation antipsychotic and second-generation antipsychotic	10.8 (45)
Only 1 antipsychotic	84.1 (349)
First-generation	10.0 (35)
Second-generation	90.0 (314)
Second-generation antipsychotic	91.1 (378)
Second-generation antipsychotic (400 prescriptions)	
Amisulpride	7.7 (32)
Aripiprazole	1.0 (4)
Clozapine	17.8 (74)
Risperidone	23.6 (98)
Quetiapine	12.8 (53)
Olanzapine	33.5 (139)

[a]Within-class combinations included.

(SD = 10.2). The majority of the sample was male (67%), and 99% were Belgian natives and of Caucasian descent. The mean Global Assessment of Functioning[39] score was 60.6 (SD = 9.1). Patients had been admitted a mean of 5.1 times (SD = 4.5), with the mean age at first admission being 23.9 years (SD = 6.6). Of all patients, 68% were smokers, and many patients had a family history of diabetes (31.1%), dyslipidemia (34.7%), or cardiovascular disorders (47.5%).

All but 2 patients were treated with antipsychotic medication at the time of assessment. First-generation antipsychotics were used by 19.3% (N = 80) of patients, and second-generation antipsychotics were used by 91.1% (N = 378). The majority of patients were on monotherapy (84.1%, N = 349), with 90.0% of this group receiving a second-generation antipsychotic and 10.0% a first-generation antipsychotic (Table 1). Patients received a mean of 3.2 (SD = 2.0) different medications. Antipsychotics were combined with anticholinergics (16.1%), antidepressants (38.3%), benzodiazepines (35.7%), mood stabilizers (21.2%), and non-psychoactive medications (40.9%). Of the non-psychoactive medications, 24.4% were related to metabolic disturbances, with 7 patients (1.7%) taking a statin (3.5% of all non-psychoactive medications) and 42 patients (10.1%) taking antihypertensive medication (20.9% of all non-psychoactive medications).

Metabolic Abnormalities

Only a minority of patients had a normal body mass index (BMI) (47.2%). Overweight (BMI of 25–30) was present in 34.2% of patients, and an additional 18.6% even had a BMI of more than 30. The mean BMI was 25.8 (SD = 5.0). An increased waist circumference (> 102 cm for men, > 88 cm for women) was present in 36.1% of patients. Female patients were more likely than male patients to be overweight or obese and to have an increased waist circumference ($\chi^2 = 30.6$, $p < .0001$). Lipid abnormalities were also highly prevalent: 47.9% of patients had elevated total cholesterol (> 190 mg/dL), 41.2% had elevated triglycerides (> 150 mg/dL), 28.9% had low high-density lipoprotein (HDL; men: < 40 mg/dL; women: < 50 mg/dL), and 45.1% had elevated low-density lipoprotein (LDL; > 115 mg/dL).

In the total sample, 6.3% (N = 26) met criteria for diabetes. Since the inclusion and screening of patients were performed over a period of 2 years, this results in a mean annual incidence of diabetes of 3.15% (6.3% incident cases/2 years). Of the patients meeting criteria for diabetes, 12 (46.2%) met the criterion of fasting glucose > 125 mg/dL, 18 (69.2%) met the criterion of glucose > 199 mg/dL at 120 minutes in the OGTT, and 4 (15.4%) met both of these criteria. All 26 diabetes cases had another OGTT within 2 weeks that confirmed the diagnosis in all patients. IFG was present in another 79 patients (19.0%). IGT was present in 53 patients (12.8%), of whom 31 (58.5% of all IGT cases) had a normal fasting glucose level. Prediabetic abnormalities, defined as IFG and/or IGT, were present in 97 patients in total (Table 2). The prevalence of diabetes and prediabetic abnormalities was significantly higher in the patients treated with clozapine ($\chi^2 = 23.87$, df = 4, $p < .0001$) (Table 3), and the use of clozapine was significantly associated with the presence of glucose abnormalities ($\chi^2 = 13.15$, df = 1, $p < .001$; controlled for the possible confounders age, gender, and BMI).

The metabolic syndrome was present in 30.6% of patients. Its prevalence was significantly higher in diabetic subjects (84.6%) compared to patients with prediabetic abnormalities (51.5%) and patients without glucose abnormalities (18.8%). Patients with the metabolic syndrome were more likely to meet criteria for diabetes or prediabetic abnormalities (Table 4).

As expected, all parameters evaluated in the OGTT (glucose and insulin values fasting, at 30 minutes, at 60 minutes, and at 120 minutes) as well as HOMA-IR and HbA_{1c} levels were significantly higher in patients with the metabolic syndrome ($p < .0001$). Similar highly significant differences were found on all fasting serum lipid values and calculated lipid risk factors for cardiovascular disease (cholesterol, triglycerides, HDL, LDL, total cholesterol/HDL, and LDL/HDL) ($p < .0001$). There were no significant differences between antipsychotics for any of the metabolic parameters.

Diagnostic Properties of the Screening Guidelines

In a screening based on the APA/ADA guidelines, 12 (46.2%) of the 26 diabetes cases were identified, as they had a fasting glucose that was higher than 125 mg/dL, and 79 patients (19.0%) showed IFG.

When compared to the consensus screening strategy of fasting glucose alone, the screening according to the WHO-derived guidelines resulted in the detection of an

Table 2. Overlap of Glucose Abnormalities Identified by Means of Fasting Glucose and by Means of 120-Minute Glucose Level in the OGTT in 415 Patients Diagnosed With Schizophrenia[a]

	Fasting Glucose Result			
OGTT Result	Normal Fasting Glucose (< 100 mg/dL)	IFG (≥ 100 < 126 mg/dL)	Diabetes (≥ 126 mg/dL)	All
Normal OGTT (glucose at 120 min < 140 mg/dL)	292 (70.4)	48 (11.6)	4 (1.0)	344 (82.9)
IGT (glucose at 120 min ≥ 140 < 200 mg/dL)	31 (7.5)	18 (4.3)	4 (1.0)	53 (12.8)
Diabetes (glucose at 120 min ≥ 200 mg/dL)	1 (0.2)	13 (3.1)	4 (1.0)	18 (4.3)
All	324 (78.1)	79 (19.0)	12 (2.9)	415 (100)

[a]Data shown as N (%). The table describes the overlap between the fasting glucose results and the OGTT results. For example: 18 subjects met the 120 minutes OGTT criterion for diabetes, and 12 subjects met the fasting glucose criterion for diabetes. Of these 12, 4 also met the 120 minutes OGTT criterion. Thus, the total number of patients with diabetes was 18 (OGTT criterion) + 12 (fasting glucose criterion) – 4 (subjects that met both criteria) = 26.
Abbreviations: IFG = impaired fasting glucose, IGT = impaired glucose tolerance, OGTT = oral glucose tolerance test.

extra 13 diabetes cases (25 of 26, or 96.2% of all diabetes cases).

Thus, the difference between the 2 strategies was most striking with regard to the number of missed diabetes cases or "false-negatives" (3.8% for the WHO-derived guidelines against 53.8% for the APA/ADA guidelines), resulting in a lower sensitivity for the APA/ADA guidelines. The number needed to diagnose (NND), which is the expression of how many tests one has to do in order to get 1 correct test result (either negative or positive), was much higher in the consensus screening. Ideally, NND equals 1, which means that every test gave a correct result. The sensitivity, specificity, percentage of false-negatives, and NND of the 2 strategies compared to the "gold standard" are shown in Table 5.

DISCUSSION

The present study, which describes the baseline data of 415 patients, is the largest study to date using an OGTT to assess glucose abnormalities in patients treated with antipsychotics. A screening based on the consensus guidelines showed that diabetes was present in 12 patients (2.9%) and impaired fasting glucose in another 79 patients (19.0%). However, in line with our hypothesis, these cases represented only 46.2% of diabetes cases and 69.3% of prediabetes cases (IGT and/or IFG) of the cases identified by means of an OGTT. In total, 6.3% (N = 26) met criteria for diabetes, resulting in a mean annual incidence of diabetes of 3.15% (6.3% incident cases/2 years).

These data confirm that metabolic abnormalities are highly prevalent in a relatively young sample of schizophrenic patients treated with antipsychotics. Compared to the estimated prevalence of diabetes in the Belgian general population, the prevalence in this sample is about double.[40,41] Two large-scale naturalistic studies,[42,43] however, revealed that the screening and diagnosis of these abnormalities in patients treated with antipsychotics still have not become routine practice and that therefore these abnormalities frequently remain untreated.

Table 3. Glucose Abnormalities in Relation to Antipsychotic Treatment, % (N)

Treatment	Diabetes (N = 26)	Prediabetes (N = 97)	Normal Values (N = 292)
Only first-generation antipsychotic (N = 35)[a]	8.6 (3)	25.7 (9)	65.7 (23)
Combination of first-generation antipsychotic and second-generation antipsychotic (N = 45)	2.2 (1)	28.9 (13)	68.9 (31)
Combination of second-generation antipsychotics (N = 19)	5.3 (1)	21.0 (4)	73.7 (14)
Only 1 second-generation antipsychotic (N = 314)	6.7 (21)	22.6 (71)	70.7 (222)
Amisulpride (N = 26)	0 (0)	3.9 (1)	96.1 (25)
Aripiprazole (N = 3)	0 (0)	0 (0)	100 (3)
Clozapine (N = 54)	9.3 (5)	42.6 (23)	48.1 (26)
Risperidone (N = 75)	6.6 (5)	22.7 (17)	70.7 (53)
Quetiapine (N = 44)	11.4 (5)	9.1 (4)	79.5 (35)
Olanzapine (N = 112)	5.4 (6)	23.2 (26)	71.4 (80)

[a]Within-class combinations included.

Moreover, one must take into account that all patients who were screened were not diagnosed with diabetes prior to this baseline screening, so that the diagnosed cases are newly detected or incidence cases. As the screening was performed over the period of 2 years, the current data suggest a mean annual incidence of diabetes of 3.15% (6.3% incident cases/2 years). One could argue that at the start of an extensive screening program there is a possibility that in addition to new cases, already existing but previously undiagnosed cases are detected. However, before the start of the current screening program, subjects were regularly screened with fasting plasma glucose assessments as a part of clinical routine, and none of the included subjects had diabetes according to these assessments. Therefore, the newly detected cases most likely indeed represent incidence cases. This interpretation is strengthened by a sensitivity analysis for the 250 patients for whom data on the first year of follow-up were already available. Of these 250 patients, 10 (4.0%) were diagnosed with diabetes at the baseline screening. Of the remaining 240 patients

Table 4. Relationship of Glucose Abnormalities to the Metabolic Syndrome[a]

Metabolic Syndrome?	Normal Values, % (N)	Prediabetes, % (N)	Diabetes, % (N)	Total, % (N)	p Value[b]
No	82.3 (237)	16.3 (47)	1.4 (4)	69.4 (288)	.0001
Yes	43.3 (55)	39.4 (50)	17.3 (22)	30.6 (127)	

[a]Criteria are (1) waist circumference >102 cm (male subjects)/> 88 cm (female subjects), (2) blood pressure ≥ 130/85 mm Hg or treatment with antihypertensive medication, (3) high-density lipoprotein (HDL) < 40 mg/dL (male subjects)/< 50 mg/dL (female subjects) or treatment with antihyperlipidemic medication, (4) triglycerides ≥ 150 mg/dL or treatment with antihyperlipidemic medication, (5) fasting glucose ≥ 100 mg/dL or treatment with antihyperglycemic medication. The metabolic syndrome is present if at least 3 criteria are met.
[b]Analysis of variance.

Table 5. Diagnostic Properties of the Different Screening Strategies for Diabetes

Screening Strategy	Baseline Assessment	Subsequent OGTT	Sensitivity[a] (%)	Specificity[b,c] (%)	False-Negatives[d] (%)	Number Needed to Diagnose[e]
"Gold standard"[f]	Weight (BMI) Waist circumference Blood pressure Fasting glucose Fasting lipids OGTT	Not applicable	100.0	100.0	0	1
APA/ADA consensus guidelines	Weight (BMI) Waist circumference Blood pressure Fasting glucose Fasting lipids	No	46.2	100.0	53.8	2.16
Two-step strategy	Weight (BMI) Waist circumference Blood pressure Fasting glucose Fasting lipids	In patients with IFG (N = 79)	96.2	100.0	3.8	1.04

[a]Sensitivity: the probability of an individual with the condition having a positive test (true-positives divided by true-positives plus false-negatives).
[b]There were no false-positives, since (1) the diagnosis of diabetes is defined by abnormal glycemic levels (fasting or at 120 minutes in the OGTT) and (2) all values that were above the diabetes diagnosis threshold were double-checked and confirmed in all cases. As there were no false-positives, the specificity by definition is 100% for all strategies.
[c]Specificity: the probability of an individual without the condition having a negative test (true-negatives divided by false-positives plus true-negatives).
[d]False-negatives: undiagnosed or "missed" diabetes cases.
[e]Number needed to diagnose: the expression of how many tests one has to do in order to get 1 correct test result (either negative or positive). Ideally, the number needed to diagnose equals 1, which means that every test gave a correct result.
[f]The "gold standard" is defined as being 100% specific and sensitive.
Abbreviations: ADA = American Diabetes Association, APA = American Psychiatric Association, BMI = body mass index, IFG = impaired fasting glucose, OGTT = oral glucose tolerance test.

(who did not have diabetes at baseline), another 10 developed diabetes during the first year of follow-up (4.17%), indicating that the rate reported for the whole sample (3.15%) is not likely to be an overestimation of the actual incidence rate. Furthermore, the reported incidence rate is in line with other incidence rates in patients treated with antipsychotics that ranged from 4.7% to 7.3%,[44–46] although the methods that were used to derive incidence rates in these studies were less extensive and the screening was performed in other regions, which makes a comparison across studies difficult.

The data of the current study suggest that, even when screened according to the APA/ADA guidelines, 53.8% of patients with diabetes would not have been recognized and thus would not have been adequately treated. This is in line with previous research[26,27,33,34] and underscores the need for more thorough screening in high-risk populations. Clearly, schizophrenic patients treated with antipsychotics should be considered at very high risk of developing diabetes,[15] as was convincingly shown by the current data. The results of the present study also suggest that the use of OGTTs to screen and monitor glucose abnormalities in this high-risk population should be encouraged. This is especially so since it has been shown that patients with postload hyperglycemia are at risk for cardiovascular morbidity, even in the absence of impairments in fasting glucose,[47] which further underscores the usefulness of the OGTT.

However, since the use of OGTTs as the standard screening instrument may not be an achievable practice in all treatment settings due to concerns of inconvenience and high cost,[48,49] the diagnostic properties of an alternative, 2-step strategy were assessed. The WHO-derived 2-step strategy of performing an OGTT in patients with IFG detected 96.2% of diabetes cases. The loss of sensitivity that is inherent to a 2-step strategy, as one tries to identify

a certain risk group within a larger sample, was limited to 3.8%, or 1 diabetes case that had a fasting glucose < 100 mg/dL. This limited loss of sensitivity resulted in a superior sensitivity and NND when compared to the APA/ADA consensus guidelines, suggesting that the 2-step strategy would provide a substantial improvement over the currently used APA/ADA consensus screening guidelines.

To our knowledge, the cost-effectiveness of this 2-step strategy has not been investigated before. Nevertheless, a study by the CDC Diabetes Cost-Effectiveness Study Group[50] revealed that screening for type 2 diabetes is especially cost-effective when done in subgroups at high risk for developing diabetes and in younger patients, resulting in a reduction of lifetime complications such as end-stage renal disease, blindness, and lower extremity amputations. Since the population of patients diagnosed with schizophrenia fits the characteristics of both relatively young age and high risk for diabetes, this suggests that a more extensive screening in this specific population could be cost-effective and would result in a limitation of lifetime major complications and an increase in quality-adjusted life-years (QALYs).[50] Preliminary evidence[28–30] even suggests that in cases in which there is a rapid onset of diabetes following the start of antipsychotic medication, screening for diabetes could possibly result in reversal of diabetes by allowing a rapid switch to another antipsychotic. These findings provide additional arguments emphasizing the importance of adequately screening for and treating diabetes in patients diagnosed with schizophrenia, and underscore the potential relevance of a more thorough screening in this specific population.

Although investigating the prevalence of diabetes and prediabetes per drug treatment was not the primary aim of the study, these data are interesting, since they give "real-world" information on the prevalence of glucose abnormalities in a large sample of patients with schizophrenia. Especially for clozapine, these real-world data support the clinical impression of a higher risk for glucose abnormalities, with not even half of the patients treated with clozapine having a normal glucose metabolism, and are in line with previous naturalistic studies.[5,51] However, one has to be cautious in interpreting the possible causality of the high prevalence of glucose abnormalities, which is especially true for the antipsychotic drugs other than clozapine. Indeed, the explanation for the high prevalence of glucose abnormalities in patients with schizophrenia and schizoaffective disorder is probably multifactorial, since in addition to the possible iatrogenic influence of antipsychotic medication, schizophrenic patients also display many risk factors for diabetes such as bad dietary habits, lack of exercise, and obesity. Furthermore, it is difficult to draw firm conclusions regarding the causality of the reported glucose abnormalities because of the relatively low number of patients per treatment group and the impossibility of controlling for other factors such as dietary habits and exercise.

In addition to diabetes, there was a high prevalence of the metabolic syndrome, which is in line with earlier reports.[20,21,23,24] The high prevalence of diabetes and other metabolic abnormalities including the metabolic syndrome may in part explain the high mortality rates in this population,[52,53] and especially why 50% of the excess mortality in this population is caused by cardiovascular disease.[54]

The current study also has some limitations. First, it is a cross-sectional study, and therefore the adequacy of the current screening guidelines cannot be assessed in a longitudinal fashion. It is possible that some diabetes or prediabetes cases would have been detected with a fasting glucose test in a follow-up screening. Second, this study was restricted to 1 site, meaning that the interpretation of the incidence and prevalence rates of metabolic abnormalities needs to be done with caution, since large regional differences in metabolic parameters have been reported in the literature.[55] Third, although this is the largest study to date that used the OGTT to evaluate the different screening strategies (N = 415), the number of patients with both schizophrenia or schizoaffective disorder and diabetes is relatively low (N = 26), meaning that the interpretation of these results needs to be done with caution. On the other hand, the findings of the current study are in line with previous literature on screening methods for diabetes in the general population. Moreover, the relatively low number of patients with diabetes in the current study is the consequence of the fact that both schizophrenia and diabetes have a relatively low prevalence. In order to collect larger numbers of patients with schizophrenia and diabetes to evaluate these screening guidelines, even larger, multisite studies need to be conducted. As of now, no such studies have been undertaken, probably because of the enormous cost of performing OGTTs in 1000 or more patients.

In conclusion, metabolic abnormalities are highly prevalent in schizophrenic patients treated with antipsychotics. The importance of actively screening for these abnormalities needs to be emphasized, and, by consequence, the widespread use of adequate screening guidelines is crucial. However, the guidelines proposed by the APA/ADA[25] did not sufficiently detect diabetes in this specific high-risk group. In contrast, the alternative 2-step strategy was able to detect the vast majority of diabetes cases and should therefore be considered in the clinical routine of screening and monitoring patients with schizophrenia.

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

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