Psychiatric Diagnosis as an Independent Risk Factor for Metabolic Disturbances: Results From a Comprehensive, Naturalistic Screening Program

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Objective: Unconfounded differences in inherent vulnerability to metabolic disturbance may be hypothesized for different diagnostic groups with severe mental illness.

Method: A naturalistic cohort of patients diagnosed with DSM-IV bipolar disorder (N = 112), schizophrenia (N = 503), and schizoaffective disorder (N = 92) were assessed for metabolic disturbances. The prospective inclusions started in November 2003 and were concluded in July 2007.

Results: Diagnosis was strongly associated with the metabolic syndrome ($\chi^2 = 14.90$, df = 2, $p < .001$). Compared with bipolar patients, the unadjusted risk for metabolic syndrome was significantly higher for schizoaffective (odds ratio [OR] = 3.51, $p < .0001$) but not for schizophrenia patients (OR = 1.58, p = .094). Differences were not reducible to confounding factors including treatment. Rather, the difference between bipolar and schizophrenia patients also reached significance after adjustment (OR = 1.97, p = .046). Furthermore, the association between diagnosis and glucose dysregulation was significant ($\chi^2 = 6.97$, df = 2, p = .031), with a significantly higher risk in schizoaffective (unadjusted OR = 2.12, p = .022) but not in schizophrenia patients (unadjusted OR = 1.13, p = .640) compared with bipolar patients. Diagnostic differences in glucose dysregulation were in part mediated by body mass index (BMI).

Conclusions: Schizoaffective patients in particular may be at risk for metabolic disturbances compared with bipolar and schizophrenia patients. Differences were not reducible to known metabolic risk factors and could only be explained in part by higher BMI in schizoaffective patients, suggesting an increased inherent vulnerability in this group.

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High prevalence rates of metabolic disturbances have consistently been reported in patients with severe mental illness. Reported rates were especially high in patients with schizophrenia and schizoaffective disorder, reaching as much as 2 to 3 times the prevalence rate of the general population for the metabolic syndrome and diabetes.[1–3] Three retrospective chart reviews of patients with bipolar disorder,[4–6] 1 of which also investigated diabetes prevalence in patients with schizoaffective disorder and schizophrenia,[6] also suggested an increased prevalence of diabetes in bipolar patients when compared with the general population. Using the National Cholesterol Education Program Adult Treatment Panel III (ATP-III) criteria, prevalence rates of the metabolic syndrome were 16.7% in a Belgian sample[7] and 30.0% in a U.S. sample of patients with bipolar disorder.[8] Evidence also suggests an increased prevalence of obesity[9–11] and unhealthy dietary habits in bipolar patients.[12] One study specifically evaluated the presence of the metabolic syndrome in U.S. schizoaffective patients and found a prevalence of 42.2% in a group of 33 subjects according to ATP-III criteria.[13]

Considerable debate exists regarding the causes of the high prevalence rates of metabolic disturbances in patients with severe mental illness, with deleterious effects of atypical antipsychotic medication,[14,15] unhealthy life style,[16] and poor dietary habits[17] as likely contributing factors. In schizophrenia, some authors have pointed to

a possible inherent genetic vulnerability to metabolic disturbances,[18–21] suggesting that metabolic disturbances may even be conceived as intermediary phenotypes associated with genetic risk for schizophrenia,[22] although not all studies in first-episode patients are in line with this suggestion.[23,24]

Patients with bipolar disorder generally have better psychosocial functioning than patients with schizophrenia, may be less likely to take antipsychotic medication, and may therefore be less vulnerable to metabolic disturbances than patients with schizophrenia or schizoaffective disorder, although an increased prevalence of polycystic ovary syndrome may be present in patients with bipolar disorder.[25,26] Polycystic ovary syndrome is an endocrine disorder associated with menstrual disturbances and several possible metabolic disturbances, including an increased risk for type 2 diabetes, insulin resistance, and dyslipidemia, with evidence suggesting an association with valproate treatment,[27,28] although menstrual disturbances in many cases precede the diagnosis and treatment for bipolar disorder.[25]

Therefore, comparisons between diagnostic groups can only be examined meaningfully if the influence of general metabolic risk factors, antipsychotic medication effects, and inherent vulnerability can be disentangled. Thus, the degree to which prevalence rates may differ as a function of inherent vulnerability between diagnostic groups can only be determined if groups are compared adjusting for known risk factors.

The current study therefore aimed to investigate whether psychiatric diagnosis is a relevant risk factor for the presence of metabolic abnormalities by (1) assessing the prevalence of metabolic disturbances in 3 groups with severe mental illness, i.e., schizophrenia, schizoaffective disorder, and bipolar disorder, and (2) examining to what degree possible differences between diagnostic groups were reducible to general metabolic risk factors (age, race, and gender) as well as other possible confounders such as antipsychotic medication, use of classical mood-stabilizing medication (lithium, valproate, lamotrigine, carbamazepine), use of beta-blockers and/or thiazides, current smoking habits, current alcohol use, use of antidepressant medication, familial predisposition, duration of illness, and illness severity.

It was hypothesized that (1) unadjusted odds ratios (ORs) for metabolic disturbances would be higher in schizophrenia and schizoaffective patients than in bipolar patients because of unhealthier lifestyles and possible inherent vulnerability; (2) differences between bipolar patients and schizophrenia and schizoaffective patients would not be reducible to known metabolic risk factors as a result of inherent vulnerability in schizophrenia and schizoaffective disorder; (3) unadjusted ORs would be higher in schizoaffective than in schizophrenia patients, following reports of a higher prevalence of diabetes, obesity, and dyslipidemia in schizoaffective patients[6,29]; and (4) differences between schizophrenia and schizoaffective patients would be reducible to differences in confounding factors.

METHOD

Subjects and Screening Routine

All patients with a DSM-IV diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorder at the University Psychiatric Center Catholic University Leuven in Kortenberg, Belgium, were asked to participate in an extensive screening and prospective follow-up of metabolic parameters. This screening routine was described extensively elsewhere.[1,30,31] In short, the study population is a dynamic, naturalistic cohort. The prospective inclusions started in November 2003 and were concluded in July 2007. Referral by the treating psychiatrist for metabolic screening and monitoring is a clinical routine in the hospital and its affiliate services. Antipsychotic drug regimens are recorded and patients are monitored using fasting laboratory tests, oral glucose tolerance tests (OGTT), and clinical examinations. Data of the most recent available evaluation were used in case of multiple OGTT assessments over time. Psychiatric diagnoses were made by experienced psychiatrists affiliated with the University Center and responsible for the patient's treatment. Bipolar disorder type I and II were not distinguished, nor were unipolar and bipolar schizoaffective disorder. There were 2 reasons why we chose not to make this differentiation between diagnostic subgroups: (1) to avoid clinician's disengagement as a result of time-expensive formal diagnostic interviews in the current, naturalistic setting and (2) because a further subdivision of different diagnostic groups would reduce the power to detect possible differences. Symptom severity was assessed by the treating psychiatrist using the Global Assessment of Functioning (GAF) score. The study was approved by the hospital ethics committee, and all patients gave written informed consent.

Metabolic Disturbances

The presence of the metabolic syndrome was assessed using the adapted ATP-III criteria. This is an update of the ATP-III criteria,[32] with a fasting glucose criterion of greater than or equal to 100 instead of greater than or equal to 110 mg/dL, plus inclusion of treatment for hypertension, lipidemia, and glycemia as criteria.[33] For the diagnosis of diabetes and prediabetic abnormalities, the criteria of the American Diabetes Association were used (impaired fasting glucose [IFG]: fasting glucose = 100–125 mg/dL and impaired glucose tolerance [IGT]: glucose = 140–199 mg/dL at 2 hours in the OGTT).[34] The homeostasis model assessment for insulin resistance (HOMA-IR) index was calculated from fasting glucose

and insulin plasma levels using the following formula: (glucose × insulin)/22.5.

Statistical Analyses

The association between psychiatric diagnosis and continuous variables was assessed by 1-way analysis of variance. The association with categorical variables was evaluated by the χ^2 test. Logistic regression unadjusted ORs for the metabolic syndrome, its individual criteria, and the presence of glucose dysregulation for the different diagnostic groups were calculated with metabolic abnormality as the dependent and psychiatric diagnosis as the independent variable. A second regression analysis controlled for known metabolic risk factors (age, gender, race), type of antipsychotic medication, use of classical mood-stabilizing medication (lithium, valproate, lamotrigine, carbamazepine), use of beta-blockers and/or thiazides, current smoking habits, current alcohol use, use of antidepressant medication, family history of diabetes, cardiovascular disease or lipid disorder, duration of illness (as a proxy of cumulative treatment exposure), and illness severity (as expressed by the GAF score) in order to determine if possible differences between diagnostic groups were reducible to these a priori–selected confounding factors.

Given the large impact of antipsychotic medication on the prevalence of metabolic abnormalities, patients who did not take antipsychotic medication or who took more than 1 antipsychotic were excluded from this analysis in order to reliably control for differences in antipsychotic medication regimens between diagnostic groups. Furthermore, analyses were carried out in patients with complete data for all the relevant variables in order to ensure comparability between equations.

An important consideration was whether or not it would be useful to control for differences in body mass index (BMI) between groups, since on the one hand, BMI is a relevant metabolic outcome and highly correlated with the abnormal waist circumference criterion of the metabolic syndrome, but, on the other hand, differences in other metabolic risk factors may be determined by interdiagnostic differences in BMI. Therefore, it was decided (1) to conduct unadjusted analyses for all metabolic outcomes, (2) to conduct analyses adjusting for all relevant confounders other than BMI, and (3) to conduct an analysis with all confounders including BMI, which allowed for the separate assessment of the influence of BMI on differences between diagnostic groups. However, BMI was not included as a confounder in the analyses with the abnormal waist circumference criterion and the overall metabolic syndrome given the important overlap between BMI and the waist criterion. Furthermore, for the analyses with metabolic syndrome and the hypertension criterion as outcome, use of beta-blockers/thiazides was omitted from the model given the overlap with the "hypertension" criterion of the outcome measure (i.e., metabolic syndrome).

RESULTS

Overall Study Population

The population under study consisted of 503 patients with schizophrenia (71.2%), 112 with bipolar disorder (15.8%), and 92 with schizoaffective disorder (13.0%). Nearly all patients were white (97.7%); 62.2% of patients were men. The overall population was rather young (mean age of 37.1 years, SD = 12.0) and slightly overweight (mean BMI = 26.4 kg/m^2, SD = 4.99).

Bipolar patients were significantly older but had fewer hospitalizations and a shorter duration of illness (Table 1). Bipolar patients were more likely to live with a partner or independently in the community compared with schizoaffective and schizophrenia patients, who lived more frequently in sheltered housing or residential facilities ($\chi^2 = 42.82$, df = 6, $p < .0001$). Bipolar patients were more likely to have a job (32.1% vs. 9.8% for schizoaffective and 8.8% for schizophrenia patients).

Except for 12 bipolar patients and 1 schizoaffective patient, who were treated with mood-stabilizing and/or antidepressant medication, all patients were treated with antipsychotics (98.2%, N = 694, Table 1). There were significant differences between groups for type of antipsychotic medication ($\chi^2 = 41.2$, df = 12, $p < .0001$), with bipolar patients being more likely to receive que tiapine and less likely to receive clozapine (Table 1). Bipolar patients were most likely to receive an antidepressant, whereas schizoaffective patients were most likely to receive classical mood stabilizers (Table 1). None of the patients were taking systemic glucocorticoids.

Comparative Prevalence of Metabolic Disturbances in the Overall Sample

The prevalence of the metabolic syndrome was highest in patients with schizoaffective disorder (Table 2). Differences between groups in prevalence of the metabolic syndrome could potentially be explained by a significantly higher prevalence of increased waist circumference and triglyceride levels in schizoaffective patients as shown in Table 2. Female patients were significantly more likely to meet the waist criterion ($\chi^2 = 16.95$, $p < .001$), but there was no significant difference in prevalence of the metabolic syndrome according to gender ($\chi^2 = 1.21$, $p = .271$).

Bipolar patients had significantly higher average concentrations of high-density lipoprotein (HDL) cholesterol levels ($F = 6.47$; df = 2,704; $p = .002$) compared with schizophrenia ($p < .05$) and schizoaffective ($p < .05$) patients. There were no significant differences for total cholesterol and low-density lipoprotein cholesterol concentrations between diagnostic groups.

Table 1. Clinical and Demographic Data Among Bipolar, Schizoaffective, and Schizophrenia Patients (N = 707)

Variable	Bipolar Disorder (N = 112)	Schizoaffective Disorder (N = 92)	Schizophrenia (N = 503)	p
Age, mean ± SD, y	44.3 ± 12.2	40.7 ± 11.0	34.8 ± 11.4	< .0001
Gender (female), N (%)	67 (59.8)	49 (53.3)	151 (30.0)	< .0001
Global Assessment of Functioning score, mean ± SD	52.8 ± 12.8	58.8 ± 11.1	57.3 ± 11.8	< .001
Age at first admission, mean ± SD, y	35.9 ± 11.8	26.0 ± 8.7	24.1 ± 6.6	< .0001
No. of admissions, mean ± SD	3.1 ± 3.1	5.8 ± 3.6	4.6 ± 4.6	< .0001
Duration of illness, mean ± SD, y	8.4 ± 9.1	14.7 ± 10.7	10.7 ± 10.2	< .0001
No. of medications, mean ± SD	3.4 ± 1.5	3.8 ± 1.8	2.9 ± 1.8	< .0001
Body mass index (kg/m^2), mean ± SD	25.9 ± 4.5	28.1 ± 5.5	26.2 ± 4.9	< .01
Body mass index segmentation (kg/m^2), N (%)				.01
Normal	55 (49.1)	32 (34.8)	222 (44.1)	
Overweight	39 (34.8)	29 (31.5)	188 (37.4)	
Obese	18 (16.1)	31 (33.7)	93 (18.5)	
Family history of cardiovascular disease, N (%)	44 (39.3)	51 (55.4)	224 (44.5)	NS
Family history of diabetes, N (%)	36 (32.1)	31 (33.7)	147 (29.2)	NS
Family history of lipid disorder, N (%)	33 (29.5)	33 (35.9)	164 (32.6)	NS
Antipsychotic medication, N (%)				
No antipsychotic	12 (10.7)	1 (1.1)	0 (0.0)	< .0001
Combination of antipsychotics	6 (5.4)	15 (16.3)	64 (12.7)	.038
Antipsychotic monotherapy, N (%)				< .0001
Typical antipsychotic	2 (1.8)	3 (3.3)	18 (3.6)	
Aripiprazole	2 (1.8)	7 (7.6)	28 (5.6)	
Clozapine	4 (3.6)	7 (7.6)	66 (13.1)	
Risperidone	19 (17.0)	19 (20.7)	120 (23.9)	
Quetiapine	28 (25.0)	10 (10.9)	48 (9.5)	
Amisulpride	3 (2.7)	4 (4.3)	34 (6.8)	
Olanzapine	36 (32.1)	26 (28.3)	125 (24.9)	
Concomitant medication, N (%)				
Anticholinergic	3 (2.7)	14 (15.2)	74 (14.7)	< .01
Benzodiazepine	46 (41.1)	34 (37.0)	161 (32.0)	NS
Antidepressant	59 (52.7)	39 (42.4)	196 (39.0)	.029
Mood stabilizer	54 (48.2)	63 (68.5)	73 (14.5)	< .0001
Current smoking (cigarettes/day), mean (SD)	8.88 (11.9)	15.72 (16.3)	15.70 (16.0)	< .0001
Current alcohol use (units/day), mean (SD)	0.24 (0.96)	0.63 (1.41)	0.67 (2.2)	.049

Abbreviation: NS = nonsignificant.

Table 2. Metabolic Syndrome and Criteria Prevalence Among Bipolar, Schizoaffective, and Schizophrenia Patients (N = 707)

Variable, N (%)	Bipolar Disorder (N = 112)	Schizoaffective Disorder (N = 92)	Schizophrenia (N = 503)	p
Metabolic syndrome	26 (23.2)	46 (50.0)	145 (28.8)	< .0001
Criteria				
Waist (men: > 102 cm, women: > 88 cm)	38 (33.9)	51 (55.4)	167 (33.2)	< .001
Blood pressure (≥ 130/85 mm Hg)	57 (50.9)	54 (58.7)	249 (49.5)	NS
HDL cholesterol (men: < 40 mg/dL, women: < 50 mg/dL)	28 (25.0)	32 (34.8)	149 (29.6)	NS
Triglyceride level (≥ 150 mg/dL)	36 (32.1)	49 (53.3)	215 (42.7)	< .01
Fasting glucose (≥ 100 mg/dL)	26 (23.2)	24 (26.1)	102 (20.3)	NS

Abbreviations: HDL = high-density lipoprotein, NS = nonsignificant.

The prevalence of diabetes, IFG, and IGT did not significantly differ between diagnostic groups (Table 3). However, significant differences between diagnostic groups were found in OGTT glucose values at 30 minutes ($F = 7.65$; $df = 2,704$; $p < .001$), 60 minutes ($F = 7.62$; $df = 2,704$; $p < .001$), and 120 minutes ($F = 5.48$; $df = 2,704$; $p = .004$). Schizoaffective patients had significantly higher values than schizophrenia patients at 30, 60, and 120 minutes on the OGTT ($p < .05$), as did bipolar patients at 30 and 60 minutes ($p < .05$).

There were no significant differences between diagnostic groups for fasting glucose assessments, insulin assessments, or HOMA-IR except for OGTT insulin values at 120 minutes ($F = 5.86$; $df = 2,704$; $p = .003$), again with significantly higher values in schizoaffective than in schizophrenia ($p < .05$) or bipolar ($p < .05$) patients. Of the 12 bipolar patients not treated with antipsychotics at the time of assessment, 4 met criteria for diabetes and 1 had prediabetic abnormalities.

Are Differences Between Groups Explained by Differences in Known Risk Factors?

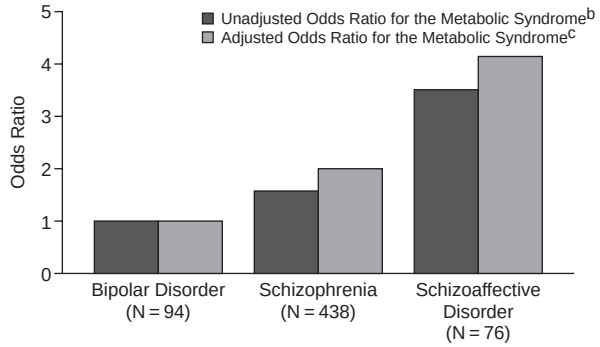
Of the overall cohort of 707 patients, 13 were not treated with antipsychotic medication, 85 were treated

Table 3. Prevalence of Glucose Abnormalities Among Bipolar, Schizoaffective, and Schizophrenia Patients (N = 707)

Variable, N (%)	Bipolar Disorder (N = 112)	Schizoaffective Disorder (N = 92)	Schizophrenia (N = 503)	p
All abnormalities	31 (27.7)	37 (40.2)	143 (28.4)	NS
IFG[a] and/or IGT[b]	19 (17.0)	27 (29.3)	111 (22.1)	
Diabetes[c]	12 (10.7)	10 (10.9)	32 (6.4)	
Fasting abnormalities	26 (23.2)	24 (26.1)	102 (20.3)	NS
IFG[a]	19 (17.0)	21 (22.8)	85 (16.9)	
Diabetes criterion fasting[c]	7 (6.3)	3 (3.3)	17 (3.4)	
OGTT abnormalities at 120 min	18 (16.1)	24 (26.1)	80 (15.9)	NS
IGT[b]	9 (8.0)	15 (16.3)	58 (11.5)	
Diabetes criterion at 120 min[c]	9 (8.0)	9 (9.8)	22 (4.4)	

[a]Fasting glucose: 100–125 mg/dL.
[b]Glucose at 2 hours on the OGTT: 140–199 mg/dL.
[c]Fasting glucose > 125 mg/dL and/or glucose at 2 hours on the OGTT > 199 mg/dL.
Abbreviations: IFG = impaired fasting glucose, IGT = impaired glucose tolerance, NS = nonsignificant, OGTT = oral glucose tolerance test.

Figure 1. Unadjusted and Adjusted[a] Odds Ratios for the Metabolic Syndrome in Different Diagnostic Groups Treated With Antipsychotic Monotherapy (N = 608) Using Bipolar Disorder as the Reference Category



[a]Adjusted for age, gender, race, type of antipsychotic medication, use of classical mood-stabilizing medication (lithium, valproate, lamotrigine, carbamazepine), current smoking habits, current alcohol use, use of antidepressant medication, family history of diabetes, family history of cardiovascular disease, family history of lipid disorder, duration of illness, and illness severity (as expressed by the Global Assessment of Functioning score).
[b]Unadjusted odds ratio; bipolar vs. schizoaffective: p < .0001,* bipolar vs. schizophrenia: p = .094, schizophrenia vs. schizoaffective: p = .002.*
[c]Adjusted odds ratio; bipolar vs. schizoaffective: p < .0001,* bipolar vs. schizophrenia: p = .046,* and schizophrenia vs. schizoaffective: p = .016.*
*Statistically significant.

with more than 1 antipsychotic, and data were incomplete for 1 patient, leaving a final sample of 608 patients for the logistic regression analysis. Psychiatric diagnosis was strongly associated with the presence of the metabolic syndrome ($\chi^2 = 14.90$, df = 2, p < .001). The unadjusted OR for the metabolic syndrome was significantly higher for schizoaffective patients (OR = 3.51, 95% CI = 1.80 to 6.85, p < .0001) compared with bipolar patients as the reference group. The OR for schizophrenia patients did not significantly differ from that of bipolar patients (OR = 1.58, 95% CI = 0.93 to 2.69, p = .094), but schizophrenia patients were significantly less likely to meet criteria for the metabolic syndrome than schizoaffective patients ($\chi^2 = 10.04$, p = .002). Adjustment did not decrease differences between diagnostic groups. Rather, the difference between bipolar and schizophrenia patients also reached statistical significance after adjustment (OR = 1.97, p = .046, Figure 1).

In the logistic model, type of antipsychotic medication was associated with the metabolic syndrome ($\chi^2 = 22.32$, df = 6, p = .001). There was a trend toward a higher risk for the metabolic syndrome in patients taking clozapine (OR = 2.53, 95% CI = 0.93 to 6.87, p = .068) compared with patients taking a typical antipsychotic. Furthermore, the known risk factors age (OR = 1.03, 95% CI = 1.00 to 1.06, p = .023) and BMI (OR = 1.31, 95% CI = 1.24 to 1.38, p < .0001) were also associated with the presence of the metabolic syndrome.

For the abnormal waist criterion, there were significant differences between diagnostic groups ($\chi^2 = 12.11$, df = 2, p = .002), again with a significantly higher OR in schizoaffective patients using bipolar disorder patients as a reference (unadjusted OR schizophrenia = 1.01, 95% CI = 0.63 to 1.62; unadjusted OR schizoaffective disorder = 2.38, 95% CI = 1.28 to 4.44). The association remained significant after adjustment for confounders ($\chi^2 = 6.80$, df = 2, p = .033; adjusted OR schizophrenia = 1.75, 95% CI = 0.93 to 3.30; adjusted OR schizoaffective disorder = 2.68, 95% CI = 1.28 to 5.63). There was also an association between diagnosis and the triglyceride criterion ($\chi^2 = 8.84$, df = 2, p = .012), with an intermediate unadjusted OR, compared with bipolar disorder patients as a reference, in schizophrenia patients (1.86, 95% CI = 1.15 to 3.00) and the highest unadjusted OR in schizoaffective patients (2.48, 95% CI = 1.32 to 4.67). The association disappeared after adjustment for confounders (BMI not included: $\chi^2 = 4.92$, df = 2, p = .085; BMI included: $\chi^2 = 2.53$, df = 2, p = .282). For the other criteria of the metabolic syndrome, no significant differences between diagnostic groups were noted.

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The association between diagnosis and the presence of glucose dysregulation reached statistical significance ($\chi^2 = 6.97$, df = 2, p = .031), with a significantly higher risk for glucose dysregulation in schizoaffective (unadjusted OR = 2.12, 95% CI = 1.11 to 4.03, p = .022) but not in schizophrenia (unadjusted OR = 1.13, 95% CI = 0.68 to 1.86, p = .640) patients compared with bipolar patients. The difference between schizophrenia and schizoaffective patients was also significant ($\chi^2 = 6.16$, p = .013). Differences remained statistically significant after including all confounders except BMI ($\chi^2 = 6.50$, df = 2, p = .039). However, after including BMI in the model, psychiatric diagnosis was no longer associated with glucose dysregulation ($\chi^2 = 4.51$, df = 2, p = .105).

Type of antipsychotic medication was strongly associated with the presence of glucose dysregulation in the logistic regression model (diabetes, IFG, and/or IGT; $\chi^2 = 28.92$, df = 5, p < .0001). Compared with patients taking typical antipsychotics, patients taking clozapine had a significantly higher risk of glucose dysfunction (OR = 4.36, 95% CI = 1.72 to 11.06, p < .01), whereas patients taking aripiprazole monotherapy were omitted from the analysis as none of the patients showed glucose dysregulation. Interestingly, use of a classical mood stabilizer was associated with a reduced risk for glucose dysregulation (OR = 0.54, 95% CI = 0.32 to 0.91, p = .021). Other confounders associated with glucose dysregulation were age (OR = 1.05, 95% CI = 1.02 to 1.07, p < .001) and BMI (OR = 1.09, 95% CI = 1.05 to 1.14, p < .0001).

DISCUSSION

Findings

This study aimed to test 4 specific hypotheses. The first hypothesis was that unadjusted ORs for metabolic disturbances would be higher in schizophrenia and schizoaffective patients than in bipolar patients. This was true for schizoaffective patients but not for schizophrenia patients, who had a similar risk for the metabolic syndrome and glucose dysregulation as bipolar patients. Our second hypothesis was that differences between bipolar patients on the one hand and schizophrenia and schizoaffective patients on the other would not be reducible to known metabolic risk factors given the evidence for inherent vulnerability in schizophrenia and schizoaffective disorder. This hypothesis was confirmed for schizoaffective patients, for whom ORs were not decreased after controlling for known confounders. Interestingly, for schizophrenia patients, it was only after adjustment for confounders that a significant difference with bipolar patients for the metabolic syndrome (but not glucose dysregulation) was found.

Third, it was confirmed that unadjusted ORs for the metabolic syndrome and glucose dysregulation were higher in schizoaffective than in schizophrenia patients. However, these risk differences were not reducible to known confounders, which disproved our fourth hypothesis, although for glucose dysregulation, differences between schizophrenia and schizoaffective patients were in part mediated by BMI.

Are These Findings Consistent With Existing Literature, and How Can They Be Explained?

A recent study in 110 bipolar and 160 schizophrenia patients (of whom 32 were diagnosed with schizoaffective disorder) found rates of diabetes and the metabolic syndrome to be equal in schizophrenia and bipolar disorder,[35] but this study failed to control for all possibly relevant confounders other than age.

A recent study in male veterans[29] found an increased risk of dyslipidemia, coronary artery disease, and diabetes in bipolar patients compared with patients with schizophrenia and an increased risk for dyslipidemia and obesity in patients with schizoaffective disorder compared with schizophrenia patients, adjusting for age, race, and tobacco use. However, this study relied completely on database diagnoses from the Veterans Affairs (VA) database. This is problematic because of established underuse of medical facilities in the VA system, especially in patients with schizophrenia,[36] and underdiagnosis of important health conditions such as hyperglycemia and diabetes in antipsychotic-treated patients followed up within the VA system.[37] Since half of all antipsychotic-treated patients within the VA system are diagnosed with schizophrenia,[38] it is likely that prevalence rates of metabolic disturbances were particularly underestimated in the schizophrenia and schizoaffective groups.[29] Furthermore, this study in male veterans[29] did not control for the confounding influence of gender, antipsychotic medication, and other relevant medicines. Findings from the current study indicate the necessity of controlling for confounders in order to reliably evaluate differences between diagnostic groups.

A third, methodologically more rigorous study investigated the prevalence of diabetes in a sample of 243 50- to 75-year-old inpatients with diagnoses of schizophrenia, schizoaffective disorder, bipolar I disorder, major depression, and dementia.[6] The authors found an increased risk for diabetes in patients with schizoaffective disorder and, to a lesser extent, in patients with bipolar disorder when controlling for age, gender, race, BMI, and antipsychotic medication.

Compared with earlier work, the current study is the first with high diagnostic validity for both psychiatric diagnosis and metabolic outcomes in a well-characterized, large sample. Overall, findings from the current study and earlier studies[6,29,35] suggest that, contrary to the initial hypothesis, bipolar patients do not have a lower unadjusted risk for metabolic disturbances compared with schizophrenia patients. When controlled for confounders, however, results from the current study indeed suggest a

higher intrinsic vulnerability in patients with schizophrenia for the metabolic syndrome as an overall indicator of metabolic risk but not for glucose dysregulation.

Furthermore, those studies investigating schizoaffective disorder as a separate entity[6,29] consistently found evidence for increased metabolic risk in schizoaffective patients compared with schizophrenia patients, although the exact type of metabolic disturbance differed between studies. This finding is consistent with those of the current study, as we found that risk for the metabolic syndrome as a metabolic symptom cluster, rather than differences in individual metabolic outcomes, is higher in schizoaffective disorder, even after controlling for a range of possible confounders. Furthermore, all 3 studies found a higher BMI in schizoaffective patients, which was statistically significant in the current study and in the study by Kilbourne and colleagues.[29] Remarkably, an increased risk for type 1 diabetes was also recently reported in patients with schizoaffective disorder.[39]

The possible mechanism underlying differences in metabolic risk in different diagnostic categories is as of yet unclear. A potential gene of interest could be the brain-derived neurotrophic factor gene (BDNF), which contains a Val66Met single nucleotide polymorphism. This polymorphism was recently associated with antipsychotic-induced weight gain in patients with chronic schizophrenia[40] and also with sensitivity to stress in a general population female twin sample.[41] Since sensitivity to stress is a well-established trait in severe mental illness,[42] these findings with regard to BDNF could provide an interesting putative link between metabolic outcomes and phenotypic expression of broadly defined psychosis.

This putative link is especially interesting because the pattern of metabolic disturbances found in the current study has similarities with the expression of stress sensitivity in severe mental illness: (1) schizophrenia patients were reported to be more sensitive to stress than bipolar patients[42] and (2) within the schizophrenia spectrum disorders, female patients were found to display the largest sensitivity to stress and to suffer from a schizoaffective expression of the disorder more often than male patients.[43] Furthermore, hormones implicated in the response to stress such as cortisol are also known to have effects on body weight, insulin resistance, and glucose regulation, which strengthens the biological plausibility of a possible link between metabolic outcomes and phenotypic expression of psychosis in terms of stress sensitivity. Future research should specifically investigate whether differences in metabolic outcomes between diagnostic groups are indeed mediated by BDNF genotype or by peripheral BDNF levels.

Limitations

The current findings need to be interpreted in light of some limitations. A first limitation is the lack of a formal diagnostic interview to establish psychiatric diagnosis, leading to the possibility of clinicians' misdiagnosis and the lack of further subdivision of bipolar and schizoaffective patients. For example, given the range of symptoms and differences in functional impairment between bipolar I and II patients, it would have been interesting to see how differences between bipolar subtypes may impact the risk for metabolic disturbances. A second limitation is the lack of detailed information on lifestyle, exercise, dietary habits, and other psychosocial and behavioral factors, which could have given more insight into a possible disease-specific, nongenetic contribution to metabolic disturbances, since these factors may be related to diagnosis through degree of functional impairment.

A third limitation is that although metabolic monitoring is intended for all patients with severe mental illness in the University Center, it is possible that bipolar patients not taking antipsychotic drugs at the time of assessment were less likely to be referred for metabolic screening. This could have led to an underrepresentation of these patients in the current sample. Given the influence of antipsychotic medication on metabolic outcomes, the absolute prevalence of metabolic abnormalities in the bipolar patients of the study sample therefore could be an overestimation. However, this possible referral bias cannot explain interdiagnostic differences in reported ORs, since the current approach of only including antipsychotic-treated patients in the logistic regression analysis is more likely to reduce interdiagnostic differences to the null than to create spurious results. A fourth limitation is that the current study is a cross-sectional study that disallows establishing causality. Therefore, longitudinal studies, although difficult to perform, are necessary to confirm these observations.

Finally, although we adjusted for a range of confounding factors, including duration of illness as a proxy of cumulative treatment effects, there may have been residual confounding for those variables for which exposure-time relationships are important, for example, how long a particular medication had been prescribed or how long current alcohol and smoking habits had been present. This is especially relevant for antipsychotic treatment effects, since a presentation of cross-sectional treatment may reflect everyday clinical practice in which clinicians tend to avoid medications with a high metabolic risk profile in patients they consider to be at risk for metabolic syndrome, as suggested recently in the context of the current naturalistic follow-up protocol.[44] The results may therefore underestimate the influence of antipsychotics on the findings. Furthermore, cumulative exposure to antipsychotics with and without a risk to induce metabolic disturbances instead of duration of illness could have given a better control for cumulative treatment effects in the regression analysis, but it was not possible to reliably determine treatment history retrospectively (which

medications, for how long) in these patients with an average illness duration of 10.9 years. Controlling for present medication effects combined with controlling for duration of illness as a proxy of cumulative treatment exposure therefore was considered the best option with the data at hand.

These limitations pinpoint the necessity to interpret the current results with caution, however, since other factors may underlie the association between psychiatric diagnosis and metabolic disturbances. Prospective follow-up studies aimed specifically at assessing a possible relation between diagnosis and metabolic outcomes are therefore necessary to confirm or refute the current results.

Drug names: aripiprazole (Abilify), carbamazepine (Carbatrol, Equetro, and others), clozapine (Clozaril, FazaClo, and others), lamotrigine (Lamictal and others), lithium (Eskalith, Lithobid, and others), quetiapine (Seroquel), risperidone (Risperdal), valproate (Depacon and others).

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