Signs and Symptoms Associated With the Metabolic Syndrome in Psychiatric Inpatients Receiving Antipsychotics: A Retrospective Chart Review

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Objective: The metabolic syndrome has been recognized as a major health risk for patients taking atypical antipsychotics. Few studies, however, have examined large samples of psychiatric patients to explore the prevalence of the signs and symptoms associated with this condition.

Method: The investigators retrospectively identified all inpatient admissions at the study site who were treated with antipsychotics during 2003 (N = 1691) and extracted demographic and clinical data (including measures associated with the syndrome: body mass index > 30 kg/m^2, dyslipidemia, diagnosis of hypertension or diabetes). Stepwise logistic regression was used to identify variables associated with each correlate of the syndrome.

Results: In the majority of this sample (69.3%), at least 1 correlate of the metabolic syndrome was present. The odds that a patient would have 1 or more of these measures were approximately 8 times greater for those receiving clozapine than for those receiving another antipsychotic medication. These patients also had increased odds (odds ratio = 2.5) of having hypertension or diabetes. In the subsample of patients with documentation for all 5 correlates of the metabolic syndrome (N = 362), 18.8% had ≥ 3 of 5.

Conclusion: The prevalence of at least 3 correlates in psychiatric inpatients receiving antipsychotics is probably an underestimate, because diagnosis was substituted for the blood pressure and glucose measures. Nonetheless, these findings support the call for routine screening for metabolic symptoms in patients receiving antipsychotics. The risk for these symptoms may be particularly high in some subgroups identified, such as patients older than 50 years and those taking clozapine or multiple antipsychotics.

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The metabolic syndrome has recently been recognized as a major health problem, but the concept of a clustering of risk factors for cardiovascular disease (CVD) is not new, having been described at least as early as the 1920s.[1] Concern about this syndrome is particularly great for patients treated with atypical antipsychotics, and a 2004 consensus conference issued guidelines for monitoring these individuals.[2] The consequences of the metabolic syndrome have been widely discussed and include an increased risk for type 2 diabetes as well as for CVD.[1,3–6]

As recently reviewed by Eckel et al., there is continuing debate about both the criteria and the optimal measures for this syndrome.[1] The most recent consensus reports are from the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III)[7] and from the World Health Organization (WHO)[8] (Table 1).

The metabolic syndrome is common in the general population. A recent study (N = 8814) used the ATP III definition to determine the age-adjusted prevalence of each of the criteria; abdominal obesity was the most common (present in 38.6% of individuals), at least 1 criterion was present in 71.2% of the sample, and 3 or more were present (the definition of the metabolic syndrome) in nearly a quarter (23.7%).[9] Few studies, however, have examined large samples of psychiatric patients to explore the prevalence of the metabolic syndrome criteria and the variables associated with each criterion. A chart review of 208 psychiatric patients found diabetes in 17%, hypertension in 29%, and hypertriglyceridemia in 44%.[10] Another

Table 1. Criteria for the Metabolic Syndrome

National Cholesterol Education Program Adult Treatment Panel III[a]	World Health Organization[b]
≥ 3 of the following criteria:	Insulin resistance[c] plus ≥ 2 of 5 other criteria:
Fasting glucose ≥ 110 mg/dL[d]	
Abdominal obesity [e,f]	Body mass index > 30 kg/m^2 and/or
Men > 102 cm (> 40 in) waist circumference	Men > 0.90 waist/hip ratio
Women > 88 cm (> 35 in) waist circumference	Women > 0.85 waist/hip ratio
Blood pressure	Antihypertensive medication and/or high blood pressure
(≥ 130 mm Hg systolic / ≥ 85 mm Hg diastolic)	(≥ 140 mm Hg systolic or ≥ 90 mm Hg diastolic)
Triglycerides ≥ 150 mg/dL	Triglycerides ≥ 150 mg dL (≥ 1.7 mmol/L)
High-density lipoprotein cholesterol	High-density lipoprotein cholesterol
Men < 40 mg/dL	Men < 35 mg/dL (< 0.9 mmol/L)
Women < 50 mg/dL	Women < 39 mg/dL (< 1.0 mmol/L)
	Urinary albumin excretion rate ≥ 20 μg/min
	(or albumin:creatinine ratio ≥ 30 mg/g)

[a]Data from the National Cholesterol Education Program.[7]
[b]Data from Alberti and Zimmet.[8]
[c]Insulin resistance = diabetes or impaired fasting glucose or impaired glucose tolerance or glucose uptake below the lowest quartile for background population.
[d]The American Diabetes Association has recently established a cut-point of 100 mg/dL, above which persons have either prediabetes (impaired fasting glucose) or diabetes.
[e]Overweight and obesity are associated with insulin resistance and the metabolic syndrome. Abdominal obesity is more highly correlated with the metabolic risk factors than is an elevated body mass index.
[f]Males can develop multiple metabolic risk factors when the waist circumference is only marginally increased (e.g., 94 to 102 cm [37 to 39 in]).

retrospective study (N = 166) reported dyslipidemia in 68% of the sample and obesity (BMI > 30) in 35%.[11] Sernyak et al.[12] found elevated fasting plasma glucose levels in 30.1% of outpatients taking atypical antipsychotics in a Veterans Affairs facility (N = 647). Recently published results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study document the syndrome's prevalence in a subset of subjects (N = 689), but this sample was limited to patients with schizophrenia.[13]

Guidelines such as those mentioned above[1] are useful for pretreatment screening and ongoing monitoring, but additional data are needed from psychiatric samples, since predictors in this population may be different.[14–16] This need is magnified by the fact that the atypical antipsychotics are now commonly used in the treatment of a wide variety of disorders, and previous studies have largely focused on patients with schizophrenia.[17,18]

The investigators retrospectively examined the records of all inpatient admissions at the study site during a 1-year period to determine the proportion of psychiatrically hospitalized individuals who received antipsychotics and, of these, the proportion with documented assessment of the signs and symptoms of the metabolic syndrome. They report the demographic, diagnostic, and treatment variables correlated with symptoms that have been associated with the metabolic syndrome. The treatment setting was the inpatient psychiatry service at the Institute of Living, a private, not-for-profit, urban facility serving both insured and uninsured patients, aged 5 years and older. There are approximately 3500 admissions per year, and an average length of stay is 16 days (SD 22, range: 1–462).

METHOD

All inpatients treated with antipsychotics during 2003 were retrospectively identified (N = 1691). Selection criteria excluded patients whose only exposure was p.r.n. or stat. For patients with multiple admissions, data from the first admission were used. Data collected included patient demographics, diagnoses, discharge medications, BMI, cholesterol (total, low-density lipoprotein [LDL], and high-density lipoprotein [HDL]), triglyceride, and glucose levels. Because all ATP III criteria were frequently not available, a modified ATP III definition for the metabolic syndrome was constructed based on conditions (referred to as *correlates* of metabolic syndrome) that approximate ATP III criteria. We applied the following substitutions: BMI for waist circumference, diagnosis of hypertension for actual blood pressure measurement, and diagnosis of diabetes mellitus for fasting blood sugar (FBS). Two measures were identical to ATP III criteria: triglyceride levels ≥ 150 mg/dL and HDL cholesterol levels < 40 mg/dL for males or < 50 mg/dL for women. As in the ATP III definition, the metabolic syndrome was deemed present if a patient had 3 or more of those 5 conditions.[7]

Descriptive statistics were used to characterize the sample (demographics, distribution of diagnoses). Triglyceride and cholesterol levels were not recorded for all patients. Because these measures may have been omitted nonrandomly (e.g., lipid levels ordered only in older patients or in those who appeared overweight), the groups with and without each measure were compared using logistic regression. Stepwise logistic regression was used to identify the demographic and clinical characteristics associated with (1) each correlate of the metabolic

Table 2. Independent Variables in Logistic Regressions

Age (< 50 vs ≥ 50 y)
Gender (male/female)
Race (white/black/Latino)
Psychiatric diagnosis[a]
Antipsychotic type[b]
Concurrent antipsychotics (Y/N)
Typical antipsychotic (Y/N)
Atypical antipsychotic (Y/N)
Antidepressant (Y/N)
Anticonvulsant (Y/N)
Anticonvulsant type[c]

[a]Schizoaffective disorder, schizophrenia, major depressive disorder, bipolar disorder, dementia.
[b]Aripiprazole, clozapine, olanzapine, quetiapine, risperidone, ziprasidone.
[c]Divalproex, carbamazepine.

Table 3. Diagnostic Distribution

Diagnosis	Study Sample by Primary Diagnosis, N (%)	Of All Inpatients, % Taking Antipsychotics by Primary Diagnosis, N (%)
Major depressive disorder	466 (27.6)	859 (54.2)
Schizoaffective disorder	247 (14.6)	247 (100)
Bipolar disorder	239 (14.1)	325 (73.5)
Schizophrenia	233 (13.8)	234 (99.6)
Other psychosis	128 (7.6)	132 (97.0)
Dementia	107 (6.3)	114 (93.9)
Substance abuse/ dependence	95 (5.6)	270 (35.2)
Depressive disorder NOS	56 (3.3)	171 (32.7)
Adjustment disorder	38 (2.2)	88 (43.2)
Impulse disorder	14 (0.8)	20 (70.0)
Anxiety disorder	12 (0.7)	25 (48.0)
Oppositional defiant disorder	12 (0.7)	15 (80.0)
Mood disorder NOS	10 (0.6)	18 (55.6)
Other[a]	34 (2.1)	67 (50.7)
Total N	1691	2585

[a]Other: diagnoses included delirium, eating disorder, pervasive developmental disorder, dysthymia, conduct or disruptive disorder, attention-deficit disorder, other disorders of childhood, cognitive disorder NOS.
Abbreviation: NOS = not otherwise specified.

syndrome, (2) having the metabolic syndrome (defined here as the presence of ≥ 3 of the 5 correlates noted above), and (3) having at least 1 of the 5 correlates. Models selected in the regression that included race/ethnicity variables were repeated, and all 3 of these variables were forced into the final models reported. The independent variables used in the regression are listed in Table 2.

RESULTS

For this sample of patients treated with antipsychotics, (N = 1691) the age range was 5 to 95 years (mean = 42.4, SD = 19.5, median = 41). The sample was evenly divided by gender (49% female, 51% male), but the majority of patients were white (60.3% vs. 19.8% Latino and 15.6% black). Table 3 displays the frequency of each primary diagnosis represented in the study sample (N =1691). To show the range of diagnoses for which antipsychotics were prescribed at the study site, this table also displays, by diagnosis, the proportion of all inpatients (N = 2585) treated with an antipsychotic. For example, 27.6% (N = 466) of the study sample had a diagnosis of major depressive disorder; 54.2% of all depressed inpatients (N = 859) were treated with an antipsychotic.

Table 4. Prevalence of Selected Signs and Symptoms Associated With the Metabolic Syndrome

Metabolic Syndrome Criterion	Patients Meeting Criterion,[a] N (%)	Patients With Measure Recorded,[b] N (%)
Body mass index > 30 kg/m^2	316 (28.5)	1110 (65.6)
Triglyceride levels ≥ 150 mg/dL	203 (31.7)	640 (37.8)
High-density lipoprotein cholesterol levels (Men < 40 mg/dL, Women < 50 mg/dL)	109 (18.1)	603 (35.7)
Hypertension diagnosed[d]	281 (16.6)	1691 (100)[c]
Hyperglycemia (diabetes diagnosed)[d]	188 (11.1)	1691 (100)[c]

[a]Percentage shown is percentage of the subset of patients with data for that criterion.
[b]Percentage shown is percentage of the total sample (N = 1691).
[c]Percentage shown (100%) assumes that the disorder (diabetes mellitus, hypertension), if present, was recognized and recorded on Axis III.
[d]Diagnosis used as criterion.

Most patients (96.0%, N = 1623) received an atypical antipsychotic. While conventional agents continued to be prescribed (N = 298, 17.6%), it was rare for these drugs not to be used in conjunction with an atypical agent (N = 68, 4.0%). Among the atypical antipsychotics, risperidone was the most commonly prescribed (40.9%, N = 692); olanzapine (37.1%, N = 627) and quetiapine (21.6%, N = 366) were the next most frequently used, with aripiprazole, ziprasidone, and clozapine each given to less than 10% of the sample. More than 1 atypical antipsychotic was given concurrently to 18.6% of patients (N = 314).

Table 4 displays, for each correlate of the metabolic syndrome, the proportion of patients with the relevant measures present in the medical record; also shown is the proportion with an abnormal value for each correlate. HDL cholesterol and triglyceride levels were not obtained in nearly two thirds of patients, and all 5 measures were present in the medical records of only 362 (21.4%). For the sample as a whole (N = 1691), 45.3% (N = 766) met at least 1 criterion for the syndrome, 184 (10.9%) met 2 criteria, and 108 (6.4%) met 3 or more criteria. For the subset of patients with complete data (N = 362), 251 (69.3%) met 1 criterion, 65 (18.0%) met 2 criteria, and 68 (18.8%) met 3 or more criteria. FBS, ordered in 93.3% of the sample, was > 110 mg/dL in 23.6% of this subset.

Table 5. Variables Associated With the Metabolic Syndrome Criteria

Dependent Variable	Patients With the Variable Recorded, N	Independent Variable[a]	Odds Ratio (95% CI)	p Value
Metabolic syndrome	362	Olanzapine prescribed	0.441 (0.237 to 0.818)	.009
≥ 1 criterion	362	Clozapine prescribed	8.208 (1.055 to 63.837)	.044
		Any antidepressant prescribed	2.189 (1.313 to 3.651)	.003
Triglycerides > 150 mg/dL	640	White	0.742 (0.307 to 1.793)	.507
		Black	0.039 (0.147 to 1.036)	.059
		Latino	0.623 (0.244 to 1.593)	.323
		Dementia	0.521 (0.279 to 0.974)	.041
		> 1 antipsychotic prescribed concurrently	1.449 (1.033 to 2.033)	.032
High-density lipoprotein cholesterol < 40 mg/dL men, < 50 mg/dL women	603	White	0.474 (0.185 to 1.212)	.119
		Black	0.536 (0.196 to 1.469)	.225
		Latino	0.989 (0.369 to 2.652)	.983
		> 1 antipsychotic prescribed concurrently	1.566 (1.046 to 2.346)	.030
		Antidepressant prescribed	1.678 (1.122 to 2.508)	.012
Diabetes mellitus diagnosed	1691	Age ≥ 50 y	5.886 (4.139 to 8.368)	< .001
		White	0.438 (0.214 to 0.895)	.024
		Black	1.039 (0.473 to 2.285)	.924
		Latino	1.616 (0.761 to 3.434)	.212
		Clozapine prescribed	2.555 (1.157 to 5.639)	.020
		Olanzapine prescribed	0.583 (0.408 to 0.833)	.003
		> 1 antipsychotic prescribed concurrently	1.767 (1.186 to 2.632)	.005
		Any anticonvulsant prescribed	1.682 (1.207 to 2.345)	.002
		Carbamazepine prescribed	0.224 (0.051 to 0.980)	.047
Hypertension diagnosed	1691	Age ≥ 50 y	8.290 (5.972 to 11.508)	< .001
		White	0.888 (0.438 to 1.800)	.741
		Black	2.247 (1.040 to 4.857)	.040
		Latino	1.536 (0.714 to 3.307)	.272
		Dementia	1.887 (1.288 to 2.764)	.001
		Clozapine prescribed	2.510 (1.156 to 5.450)	.020
Body mass index > 30 kg/m^2	1110	Male	0.613 (0.466 to 0.807)	< .001
		White	0.581 (0.305 to 1.106)	.098
		Black	0.911 (0.452 to 1.837)	.795
		Latino	0.859 (0.434 to 1.700)	.663
		Schizoaffective disorder diagnosed	1.422 (0.999 to 2.025)	.050
		Olanzapine prescribed	0.535 (0.388 to 0.738)	< .001
		Risperidone prescribed	0.725 (0.537 to 0.979)	.036
		> 1 antipsychotic prescribed concurrently	1.742 (1.220 to 2.488)	.002
		Any antidepressant prescribed	1.457 (1.053 to 2.016)	.023
		Any anticonvulsant prescribed	1.534 (1.161 to 2.026)	.003

[a]All independent variables were binary; df = 1.

The first stepwise logistic regression identified variables associated with the presence of the metabolic syndrome and of each correlate individually (Table 5). For the full syndrome, only treatment with olanzapine was retained in the regression; the odds of having ≥ 3 correlates were approximately 56% lower in patients receiving this drug compared with the remainder of the sample. Among olanzapine-treated patients, 11.5% had the metabolic syndrome versus 22.8% of those not taking this drug ($\chi^2 = 6.98$, df = 1, p = .008). For patients taking clozapine, the odds of having at least 1 of the 5 correlates were approximately 8 times greater compared with the remainder of the sample (after controlling for antidepressant use). Nearly all clozapine patients (93.8%) had at least 1 condition associated with metabolic syndrome, a finding significantly less common, although still frequent (68.2%), in nonclozapine patients ($\chi^2 = 4.69$, df = 1, p = .030). The odds of having a diagnosis of diabetes or a diagnosis of hypertension were approximately 2.5 times greater for patients taking clozapine compared with the remainder of the sample. For both conditions, age ≥ 50 was the dominant variable, with older patients having odds ratios (ORs) of 5.8 and 8.2 for diabetes and hypertension, respectively.

The second stepwise logistic regression identified variables associated with having an assessment for dyslipidemia (Table 6). Neither age nor race variables affected the odds of having HDL or triglyceride levels ordered. However, for patients with schizophrenia, the odds that these tests were ordered were more than twice that for all other patients.

DISCUSSION

Among patients with complete data available, the metabolic syndrome was present in 68 (18.8%) of the sample, and at least 1 abnormality was present in 251 (69.3%),

Table 6. Assessment of High-Density Lipoprotein and Triglyceride Levels

Independent Variable[a]	Odds Ratio (95% CI)	p Value
Any anticonvulsant prescribed	1.312 (1.068 to 1.613)	.010
> 1 antipsychotic prescribed concurrently	1.356 (1.037 to 1.772)	.026
Dementia diagnosed	1.414 (1.007 to 1.986)	.045
Major depressive disorder diagnosed	1.841 (1.446 to 2.345)	< .001
Schizoaffective disorder diagnosed	1.531 (1.149 to 2.040)	.004
Schizophrenia diagnosed	2.195 (1.308 to 3.685)	.003

[a]All independent variables were binary; df = 1.

based on the conditions associated with ATP III criteria (as specified for this study). These proportions are probably underestimates. Many subjects were not assessed on all measures, and the study used a recorded diagnosis of diabetes and hypertension rather than elevated FBS and blood pressure. The prevalence of the metabolic syndrome among subjects in the CATIE study was approximately 40%, with about 85% of the sample meeting at least 1 of the ATP III criteria.[13] Because the mean length of stay was 16 days, and information on antipsychotic use prior to admission was incomplete, some patients' exposure to antipsychotics may have been short-term. Nonetheless, these findings further support the conclusion that a large number of patients taking antipsychotics are at increased risk for the health problems associated with metabolic syndrome.[13,19–29] As noted by Kahn et al., the clinical focus in screening for metabolic abnormalities is to identify patients who meet any of the criteria, not only those with the full syndrome.[30] Thus, among psychiatric patients, the number of individuals at risk may be 2 to 3 times the estimates based on the presence of the metabolic syndrome per se. In addition, as shown in this and previous reports, atypical antipsychotics are increasingly used for a wide variety of conditions.[18,31,32] More than 40% of the patients in this study had a mood disorder diagnosis.

The odds of having the metabolic syndrome, a diagnosis of diabetes, or a BMI > 30 kg/m^2 were reduced in olanzapine-treated patients compared with patients not taking this drug. These findings contradict many earlier studies and may reflect differences in patient populations and treatment (e.g., olanzapine dosage and duration) or variability in individual susceptibility to these side effects.[26,27,33–35] Another possible explanation is that the prescribers for the patients in this study selected an alternative antipsychotic for patients who were overweight, had an elevated FBS, or had a diagnosis of diabetes, an interpretation of the findings that is consistent with other research.[33] By contrast, the odds that clozapine patients would have at least 1 criterion for the metabolic syndrome were greatly increased (OR = 8.208). Clozapine is generally reserved for patients who have failed to respond to other antipsychotics, and for these individuals, there may be no alternative medication, which is not the case for patients taking olanzapine. Patients taking clozapine also had increased odds for a diagnosis of diabetes (OR = 2.555), an association previously reported, but other important associations may exist that were not identified because of inadequate power in the clozapine subgroup (N = 46).[26] For example, we did not find that clozapine-treated patients had increased odds for elevated triglyceride or reduced HDL cholesterol levels, but both outcomes have been associated with clozapine in prior reports.[36,37]

There was a statistically significant association between 1 or more of the correlates of the metabolic syndrome and several of the independent variables, but most of the ORs were modest. (See Table 5.) It was expected that age (≥ 50 vs. < 50 years) would be associated with the diagnoses of diabetes and hypertension; it has long been known that hypertension is more common in African Americans than in other racial/ethnic groups and that dementia and hypertension are associated.[26,34] Patients taking multiple antipsychotics had modestly increased ORs for obesity, dyslipidemias, and diabetes mellitus, a finding consistent with another recent study.[35] This prescribing practice was much more common in patients with schizophrenia/schizoaffective disorder than in individuals with other diagnoses (39.4% vs. 9.0%, df = 1, χ^2 = 222.254, p ≤ .001). It is possible that the association found for use of multiple antipsychotics is explained by an independent association between diabetes and schizophrenia.[38–47] It should also be noted that weight gain and diabetes have been associated with a variety of psychotropic medications. Valproic acid, often used in both schizoaffective and bipolar disorders, commonly causes weight gain, as do some antidepressants; both agents were significantly associated with BMI > 30 in the present study.[48–50]

Limitations of the study include its examination of prevalence data and the missing clinical information. Using diagnosed disease obviously misses all patients with previously undetected elevations in glucose levels or blood pressure. The sample, while large, did not have a sufficient number of subjects taking each antipsychotic to allow for all comparisons of interest. Patients at the study site may not be representative of those at other facilities. Potentially important variables that could not be evaluated include eating habits, level of physical activity, family history, and length of exposure to the index medications. It should also be noted that stepwise logistic regression can produce models that exclude variables of interest. For example, factors that do not meet the statistical significance criterion for inclusion may, in combination with other variables, account for substantial confounding.[51]

The results of this study underscore the need for monitoring general health status, perhaps especially in identifiable subgroups of psychiatric patients, and may guide choice of antipsychotic. There was considerable off-label

use of antipsychotics for diagnoses with few or no efficacy studies, raising questions about the risk-benefit profile for patients with these diagnoses. The relevant demographic, clinical, and treatment variables identified form a mixed picture, and further research is needed to characterize the individuals at greatest risk. Almost all patients (93.8%) taking clozapine, for example, were positive on at least 1 of the measures of concern, strongly supporting the need for ongoing monitoring and intervention in at least this subgroup. However, periodic screening may be needed in all patients receiving atypical antipsychotics, given that a majority of patients in this and other samples have abnormal values on 1 or more dimension of the metabolic syndrome.[13] Also, as shown here and elsewhere, assessment for metabolic conditions is not now routine, even in hospitalized patients.[10,11,52]

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

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