The Moderating Impact of Ethnicity on Metabolic Outcomes During Treatment With Olanzapine and Aripiprazole in Patients With Schizophrenia

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Objective: Race is strongly associated with risk for metabolic dysfunction, but there is limited prospective data concerning the impact of race on antipsychotic metabolic outcomes among patients with schizophrenia.

Method: This study is a post hoc analysis of data from a 26-week, double-blind, randomized trial of aripiprazole (N = 155) and olanzapine (N = 159) conducted from April 2000 through June 2001 in patients aged ≥ 18 years with acute schizophrenia according to DSM-IV criteria. The data were analyzed on the basis of racial breakdown: white and black/Hispanic. Between-drug and within-drug outcomes were analyzed separately for each racial cohort across weight, lipid, and glucose parameters.

Results: For white subjects (N = 167), olanzapine significantly worsened all metabolic parameters except high-density lipoprotein (HDL) cholesterol and fasting glucose, and this was significantly different than aripiprazole for every outcome except fasting glucose. In the black/Hispanic cohort (N = 137), olanzapine treatment resulted in adverse metabolic outcomes, and these changes were significantly different from aripiprazole for adiposity, total cholesterol, and non-HDL cholesterol. Aripiprazole decreased the odds of endpoint metabolic syndrome compared with olanzapine for all subjects (OR = 0.33, 95% CI = 0.19 to 0.55), the white cohort (OR = 0.20, 95% CI = 0.10 to 0.41), and black/Hispanic subjects (OR = 0.53, 95% CI = 0.25 to 1.12), but the black/Hispanic result was not statistically significant (p = .096). Within the aripiprazole group, white subjects had significantly lower risk for metabolic syndrome, but there was no significant difference in metabolic syndrome between white and black/Hispanic subjects exposed to olanzapine.

Conclusions: Race may be an important moderator of metabolic risk during atypical antipsychotic therapy. Olanzapine treatment is associated with greater effects on adiposity and lipids than aripiprazole in both white and black/Hispanic subjects, suggesting that antipsychotic choice and intensive monitoring are important in minimizing metabolic risk, especially in nonwhite patients.

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Patients with schizophrenia experience greater mortality from natural causes, primarily due to 2-fold higher mortality rates from cardiovascular disease than the general population.[1] High smoking prevalence[2] combined with undertreatment of hypertension and dyslipidemia[3] contribute greatly to cardiovascular morbidity and mortality, but an important source of risk not captured by traditional cardiovascular risk-estimating algorithms is that attributable to insulin resistance.[4] The association between type 2 diabetes mellitus and cardiovascular disease is so strong that a diagnosis of diabetes mellitus is considered equivalent to established coronary heart disease in terms of future risk for major cardiovascular events.[5] However, diabetes mellitus represents the extreme end of the cardiovascular risk continuum, which extends from normal insulin sensitivity to prediabetic conditions such as those identified by metabolic syndrome criteria.[4]

The concept of metabolic syndrome was first elaborated 20 years ago to provide a unifying hypothesis for a cluster of clinical findings seen in a subgroup of insulin-resistant patients.[6] In these susceptible individuals, weight gain results not only in central obesity but also in compensatory hyperinsulinemia, hypertension, atherogenic dyslipidemia (decreased high-density lipoprotein

[HDL] cholesterol, elevated triglycerides), and increased levels of prothrombotic proteins and inflammatory markers.[7] The 2 commonly used clinical definitions of metabolic syndrome are those described by the National Cholesterol Education Program and the International Diabetes Federation,[8] both of which include central adiposity, hypertension, low serum HDL, high fasting triglycerides, and impaired fasting glucose (or overt diabetes mellitus).[8] Although the metabolic syndrome diagnosis is better for prediction of future diabetes mellitus risk[9] than cardiovascular risk,[10] its clinical utility derives from the ability to identify findings such as mild hypertriglyceridemia that, in isolation, might be overlooked.[11]

An extensive body of literature has developed in the past decade documenting increased metabolic syndrome and diabetes mellitus prevalence in schizophrenia patients.[12] This increased prevalence results from a combination of elevated modifiable and nonmodifiable risk factors in this patient population,[13] with atypical antipsychotic choice emerging as an important modifiable risk factor. Numerous retrospective and prospective studies have documented the differential metabolic impact of antipsychotic medications, with clozapine and olanzapine associated with the greatest impact on weight, glycemic control, and serum lipids; quetiapine and risperidone conferring intermediate metabolic risk; and aripiprazole or ziprasidone associated with limited effects.[14] Consensus statement recommendations issued jointly by the American Diabetes Association and American Psychiatric Association[15] and guidelines for physical health monitoring in schizophrenia[16] both recommend that the relative risk of metabolic abnormalities should be taken into consideration when choosing antipsychotic therapy, recognizing that patients with schizophrenia are vulnerable to insulin resistance from modifiable lifestyle variables (e.g., smoking, poor dietary habits, inactivity) and possibly due to inherent risk conferred by the disease itself.[17]

Aside from the contribution of disease-related risk, another important nonmodifiable risk factor for insulin resistance is related to race or ethnicity. Race has a significant impact on metabolic risk, with multiple studies indicating greater visceral adiposity[18] and insulin resistance among Hispanic Americans and blacks than non-Hispanic whites.[19] The net result is higher metabolic syndrome prevalence among nonwhites[20] and increased cardiovascular disease risk.[21] The association between race and metabolic syndrome prevalence is also found among patients with schizophrenia, as seen in the baseline analysis of schizophrenia subjects (N = 689) in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE).[12] A greater proportion of black subjects met the blood pressure criterion, but fewer met the HDL criterion and the overall metabolic syndrome diagnosis than Hispanic subjects or non-Hispanic whites. Unfortunately, no information was provided on the distribution of baseline antipsychotic medications between various racial and ethnic cohorts to allow examination of these influences.

Despite the known contribution of race to cardiometabolic risk, few prospective data are available on the metabolic effects of atypical antipsychotic use in specific ethnic groups.[22] There is a significant literature focusing on racial disparities in the use of antipsychotic medications in the United States,[23,24] with non-white patients receiving greater exposure to first-generation antipsychotics. Surprisingly little data was published regarding the differential impact of race on antipsychotic metabolic adverse effects until 2002. Jin and colleagues' retrospective analysis[25] of 45 published atypical antipsychotic–associated new-onset diabetes mellitus cases noted that 47% of subjects were black, despite data indicating disproportionate use of metabolically neutral high-potency typical antipsychotics in this racial group.[23,24] The differential impact of race on antipsychotic-related metabolic outcomes has also been seen in subsequent analyses of olanzapine- or risperidone-associated diabetes mellitus cases,[26,27] clozapine-related weight gain,[28] and HDL changes during CATIE phase 1.[29] Most recently, Ader and colleagues[30] used data from a 24-week randomized, double-blind, risperidone versus olanzapine trial to examine metabolic changes in the combined cohort of black and Hispanic individuals (56% of total subjects). At baseline, the black/Hispanic cohort had similar insulin sensitivity to white subjects but had significantly higher median acute insulin response to glucose (AIR_G). Analysis of the entire subject pool revealed no significant endpoint within-drug or between-drug changes from baseline pancreatic β-cell function, as measured by disposition index calculated from an insulin-modified frequently sampled intravenous glucose tolerance test; however, a subset analysis of the black/Hispanic cohort revealed that olanzapine exposure resulted in significantly lower pancreatic β-cell function, compared with baseline disposition index, for the observed level of decreased insulin sensitivity ($p = .033$). Aside from the baseline data on insulin sensitivity and AIR_G, and this one finding, there were no other comparisons between the black/Hispanic and white cohorts.

Given the limited available data, significant gaps remain in the prospective literature analyzing racial effects on metabolic outcomes among antipsychotics with varying degrees of liability. Aripiprazole is a newer atypical antipsychotic with a novel mechanism of action based on potent partial D_2 and D_3 agonism,[31] combined with 5-HT_{2A} antagonism and 5-HT_{1A} partial agonism.[32] Aripiprazole has limited affinity for histamine H_1 receptors[31] and is associated with low potential for weight gain and other metabolic adverse effects.[14] Results from a 26-week, multicenter, randomized, double-blind trial comparing aripiprazole and olanzapine in more than 300 patients with schizophrenia showed a greater impact of olanzapine

on weight and lipid outcomes, with similar efficacy.[33] The data from this study provide an opportunity to examine the impact of race on metabolic changes for antipsychotics with disparate metabolic profiles. The aim of this post hoc analysis was to evaluate the metabolic effects of aripiprazole versus olanzapine in racial subgroups with schizophrenia.

METHOD

Study Design

This post hoc analysis was conducted on data from a randomized, double-blind safety and tolerability study of flexible doses of aripiprazole and olanzapine in the treatment of patients with acute schizophrenia.[33] The study was conducted from April 2000 through June 2001 and enrolled patients aged ≥ 18 years with a DSM-IV diagnosis of schizophrenia in acute relapse requiring hospital inpatient treatment. Further details of the inclusion and exclusion criteria are reported elsewhere.[33] Eligible patients received flexible doses of aripiprazole (15–30 mg/day) or olanzapine (10–20 mg/day) given orally once daily for up to 26 weeks. After complete description of the study to the subjects, written informed consent was obtained. The study was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki and received institutional review board/ethics committee approval.

Metabolic Evaluations

In the original study, the primary outcome measure was the percentage of patients showing significant weight gain (≥ 7% increase in body weight) from baseline to week 26. For inclusion in the weight analysis, patients had to have both baseline and on-study weight measurements and to have taken study medication for at least 14 days. Weight and vital sign measurements were performed at baseline, day 4, and weeks 1, 2, 3, 4, 6, 8, 10, 12, 14, 18, 22, and 26. Blood samples for analysis of metabolic parameters were collected at screening and at weeks 3, 6, 12, and 26 and were analyzed for HDL cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, plasma glucose, and hemoglobin A_{1c} levels. For the purposes of this analysis, metabolic syndrome was defined using the 2001 National Cholesterol Education Program definition.[5] If no waist circumference was obtained, a body mass index ≥ 30 kg/m^2 was used as a surrogate marker for elevated central adiposity.

Statistical Methods

On the basis of the known increased risk for adiposity[18] and insulin resistance compared to white individuals,[19] black/Hispanic subjects were combined into 1 cohort (heretofore referred to as the black/Hispanic group)[30] and compared with the remaining cohort of white subjects. Descriptive statistics were performed for the overall study population and compared by race subgroups. For the characterization and comparison of patients in the different race groups, unadjusted analyses were conducted using χ^2 analyses (categorical variables) or t test analyses (continuous variables). Analyses included comparison of baseline characteristics and comparison of outcome variables. Within each race subgroup, between-treatment changes in metabolic parameters were compared using χ^2 analyses for categorical outcomes, and a repeated-measures, mixed-model analysis of covariance adjusting for baseline values and study site continuous variables. Within each treatment arm, between-race changes in metabolic parameters were compared using the same statistical tests. Predictors of metabolic syndrome were determined using generalized estimating equations (GEEs) adjusting for treatment, baseline metabolic syndrome, race, and the interaction of treatment and race, age, and gender. In addition, GEE analyses for each treatment arm were conducted to determine treatment-specific predictors of metabolic syndrome.

RESULTS

A total of 314 patients were randomly assigned to aripiprazole (N = 155) and olanzapine (N = 159), with the racial breakdown as follows: white, N = 167; black, N = 86; and Hispanic, N = 51. (The data for 10 subjects with other races was not included in this analysis.) The baseline demographic characteristics for each treatment group, by race, are shown in Table 1. There were no significant differences in the demographic or metabolic characteristics between treatment groups within each race category at baseline. Metabolic syndrome prevalence was comparable to that seen in general population data from the National Health and Nutrition Examination Survey 1999–2000 for the cohort of individuals aged 40 to 59 years.[34] Within the black/Hispanic group, subjects randomly assigned to aripiprazole had 43% higher baseline metabolic syndrome prevalence than those randomly assigned to olanzapine (32.4% vs. 22.7%, respectively), but this difference was not significantly different (p = .21).

Table 2 presents metabolic outcomes broken down by racial cohort for each medication. Six-month metabolic data were available on 46 white subjects (aripiprazole, 21; olanzapine, 26) and 45 black/Hispanic subjects (aripiprazole, 21; olanzapine, 24), although certain measures (e.g., fasting laboratory values) were available only in a subset of subjects. For white subjects, exposure to aripiprazole was associated with mean improvement in all metabolic parameters, while olanzapine treatment was associated with worsening metabolic status for all parameters except for HDL cholesterol and fasting glucose. The within-group changes from baseline were significantly different between the 2 medications, with the one exception being fasting glucose. In the black/Hispanic cohort, olanzapine

Table 1. Baseline Demographic Characteristics of Patients With Schizophrenia Randomly Assigned by Race[a]

	White[b]		Black/Hispanic[b]	
Variable	Aripiprazole (N = 76)	Olanzapine (N = 91)	Aripiprazole (N = 71)	Olanzapine (N = 66)
Age, y	39.8 (10.7)	38.9 (11.3)	38.5 (10.5)	37.0 (10.8)
Male gender, N (%)	58 (76.3)	68 (74.7)	50 (70.4)	44 (66.7)
Weight, kg	80.5 (22.4)	80.2 (20.0)	82.3 (22.4)	83.8 (22.8)
BMI, kg/m^2	27.0 (6.3)	26.9 (6.3)	28.4 (6.9)	28.9 (8.8)
Waist circumference, cm	95.7 (18.2)	96.0 (15.6)	97.9 (18.1)	97.2 (18.5)
Systolic blood pressure, mm Hg	120.8 (14.1)	120.0 (14.7)	122.6 (15.6)	123.2 (14.2)
Diastolic blood pressure, mm Hg	75.1 (9.1)	76.2 (9.2)	78.0 (8.0)	77.6 (8.8)
Fasting triglycerides, mg/dL	174.0 (103.5)	160.4 (101.8)	147.5 (107.3)	157.4 (132.6)
Cholesterol, mg/dL	190.3 (37.2)	183.6 (42.5)	176.6 (47.8)	185.0 (39.5)
HDL cholesterol, mg/dL	42.2 (10.5)	42.7 (12.7)	44.2 (12.5)	46.4 (13.9)
Non-HDL cholesterol, mg/dL	148.1 (38.7)	141.1 (42.1)	132.6 (49.0)	138.7 (39.7)
Fasting LDL cholesterol, mg/dL	110.3 (36.8)	108.3 (36.6)	107.4 (39.9)	113.6 (31.5)
Fasting glucose, mg/dL	87.9 (18.7)	91.9 (22.9)	92.0 (23.3)	91.5 (17.5)
Hemoglobin A_{1c}, %	5.4 (0.6)	5.6 (0.9)	5.6 (0.6)	5.5 (0.5)
Metabolic syndrome, N (%)	22 (28.9)	30 (33.3)	23 (32.4)	15 (22.7)

[a]All values are mean (SD) except where noted.
[b]All between-group comparisons were nonsignificant ($p > .05$).
Abbreviations: BMI = body mass index, HDL = high-density lipoprotein, LDL = low-density lipoprotein.

Table 2. Mixed-Model Results of Baseline to Endpoint Changes From Observed Case Data in White and Black/Hispanic Subjects

	White								Black/Hispanic							
	Aripiprazole			Olanzapine			Difference		Aripiprazole			Olanzapine			Difference	
Outcome Measure	N[a]	LS Mean	SE	N[a]	LS Mean	SE	Estimate	p Value	N[a]	LS Mean	SE	N[a]	LS Mean	SE	Estimate	p Value
Weight, kg	20	–1.44	0.36	26	3.37	0.32	–4.81	.000	21	0.99	0.36	23	4.57	0.38	–3.58	.000
Waist circumference, cm	16	–0.62	0.88	22	2.38	0.77	–3.00	.002	18	1.30	0.88	23	3.84	0.86	–2.54	.015
Systolic blood pressure, mm Hg	20	–2.62	1.28	26	1.20	1.11	–3.82	.024	21	0.64	1.24	23	0.49	1.26	0.14	.925
Diastolic blood pressure, mm Hg	20	–3.10	0.98	26	2.21	0.85	–5.30	.000	21	1.51	0.81	23	0.45	0.83	1.06	.280
Fasting triglycerides, mg/dL	7	–26.87	14.32	8	8.52	12.92	–35.39	.009	15	31.92	22.54	14	56.89	24.32	–24.97	.370
Cholesterol, mg/dL	16	–15.72	4.40	25	4.78	4.00	–20.50	.000	21	–2.49	4.83	24	13.60	4.85	–16.09	.005
HDL cholesterol, mg/dL	16	3.04	1.14	23	0.18	1.05	2.86	.015	21	1.83	1.20	24	–0.13	1.19	1.96	.146
Non-HDL cholesterol, mg/dL	16	–19.26	4.15	23	4.33	3.80	–23.58	.000	21	–3.47	4.55	24	13.60	4.57	–17.07	.002
Fasting LDL cholesterol, mg/dL	7	–16.68	5.61	8	2.34	4.87	–19.03	.001	15	–1.85	4.98	14	6.23	5.21	–8.07	.153
Fasting glucose, mg/dL	7	–0.69	3.31	8	–3.69	2.91	3.01	.485	14	7.93	3.73	15	6.64	3.72	1.29	.759
Hemoglobin A_{1c}, %	15	–0.26	0.12	23	0.14	0.10	–0.40	.015	20	0.11	0.13	23	0.24	0.12	–0.13	.365

[a]N represents endpoint sample. Mixed-model results are derived from all time points.
Abbreviations: HDL = high-density lipoprotein, LDL = low-density lipoprotein, LS = least squares.

treatment also resulted in deleterious changes in each metabolic outcome, but these changes from baseline were significantly different from the aripiprazole subjects only for weight-related outcomes (weight and waist circumference), total cholesterol, and non-HDL cholesterol. As shown in Table 3, significantly greater improvements with aripiprazole treatment were observed in white subjects than in black/Hispanic subjects on most metabolic measures. A nearly identical pattern was seen for olanzapine-treated subjects, but the differences between racial cohorts were smaller for most parameters and were statistically significant only for weight. A subanalysis comparing the metabolic outcomes between black/Hispanic cohorts found similar trends in metabolic changes across nearly all outcomes, with no significant between-group difference on glycemic parameters, central adiposity, fasting triglycerides, or the odds of developing metabolic syndrome.

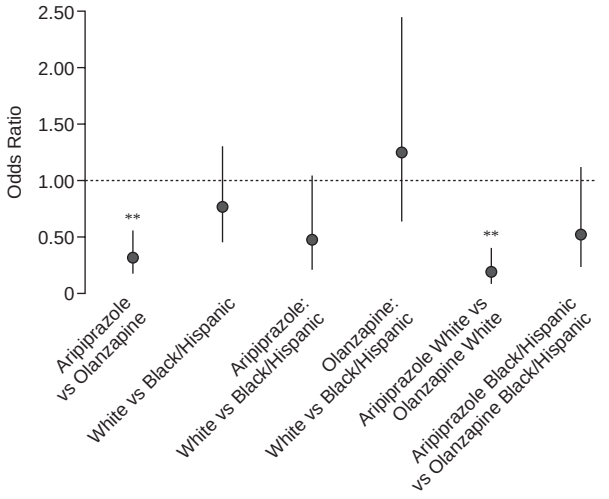
The impact of baseline metabolic syndrome diagnosis, drug exposure, and race on the presence of endpoint metabolic syndrome status can be seen in the results of logistic regression models. Across all subjects, a baseline diagnosis of metabolic syndrome was the single greatest predictor of endpoint metabolic syndrome (OR = 13.43, 95% CI = 8.03 to 22.47). The OR was similarly high and nearly identical for both medication groups (aripiprazole, OR = 13.78, 95% CI = 6.21 to 30.59; olanzapine, OR = 12.83, 95% CI = 6.58 to 25.05). The effect of medication and race on metabolic syndrome rates is illustrated in Figure 1. Aripiprazole treatment significantly decreased the

Table 3. Mixed-Model Results of Baseline to Endpoint Changes From Observed Case Data Between White and Black/Hispanic Cohorts by Treatment Arm

	Aripiprazole Difference[a]		Olanzapine Difference[a]	
Outcome Measure	Estimate	p Value	Estimate	p Value
Weight, kg	–2.48	.000	–1.24	.012
Waist circumference, cm	–1.82	.044	–1.06	.310
Systolic blood pressure, mm Hg	–4.39	.023	–0.00	.997
Diastolic blood pressure, mm Hg	–5.45	.000	–0.02	.983
Fasting triglycerides, mg/dL	–41.39	.049	–32.22	.139
Cholesterol, mg/dL	–13.91	.007	–8.63	.094
HDL cholesterol, mg/dL	–1.13	.356	–1.86	.146
Non-HDL cholesterol, mg/dL	–13.00	.008	–5.95	.224
Fasting LDL cholesterol, mg/dL	–11.35	.038	–0.38	.944
Fasting glucose, mg/dL	0.81	.785	–4.80	.282
Hemoglobin A_{1c}, %	–0.36	.010	–0.14	.336

[a]Difference calculated as white – black/Hispanic for each variable.
Abbreviations: HDL = high-density lipoprotein, LDL = low-density lipoprotein.

Figure 1. Predictors of Endpoint Metabolic Syndrome Status



Effect	Odds Ratio	95% CI	p Value
Aripiprazole vs Olanzapine	0.33	0.19 to 0.55	.000
White vs Black/Hispanic	0.78	0.47 to 1.30	.337
Aripiprazole: White vs Black/Hispanic	0.48	0.22 to 1.04	.064
Olanzapine: White vs Black/Hispanic	1.26	0.65 to 2.43	.492
Aripiprazole White vs Olanzapine White	0.20	0.10 to 0.41	.000
Aripiprazole Black/Hispanic vs Olanzapine Black/Hispanic	0.53	0.25 to 1.12	.096

**p < .0001.

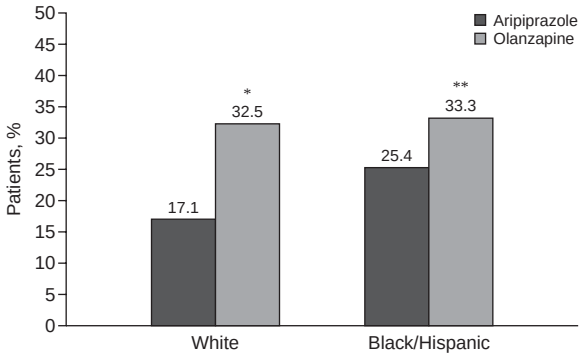
odds of endpoint metabolic syndrome compared with olanzapine treatment (OR = 0.33, 95% CI = 0.19 to 0.55). For both medication arms combined, white subjects were somewhat less likely than the black/Hispanic cohort to have metabolic syndrome at endpoint, but the effect was not statistically significant. For white subjects treated with aripiprazole, there was 5-fold lower risk of metabolic syndrome than for white subjects treated with olanzapine (OR = 0.20, 95% CI = 0.10 to 0.41). For black/Hispanic subjects, the likelihood of metabolic syndrome was decreased by nearly half for aripiprazole versus olanzapine, but the effect was not statistically significant. The effect of race within drugs showed a lower likelihood of metabolic syndrome among white subjects treated with aripiprazole than among black/Hispanic subjects (OR = 0.48, 95% CI = 0.22 to 1.04) and a numerically higher likelihood of metabolic syndrome among white subjects treated with olanzapine than black/Hispanic subjects, but the differences were not significant. Figure 2 provides week-26 metabolic syndrome prevalence by race, illustrating a significant disparity for white subjects between aripiprazole (17.1%) and olanzapine (32.5%) (p = .013) and a numerical difference for black/Hispanic subjects (aripiprazole, 25.4% vs. olanzapine, 33.3%) that did not reach statistical significance.

DISCUSSION

Psychopharmacology is slowly entering the age of personalized medicine, as investigators strive to find predictors of positive treatment outcomes[35] and medication adverse effects.[36] That ethnicity may relate to antipsychotic response has recently been suggested by genetic data from the CATIE schizophrenia trial,[37] but these results require replication. In the absence of firmly established genetic markers for the prediction of antipsychotic treatment outcome, psychiatrists must rely on clinical variables. The association between ethnicity and both cardiovascular and metabolic risk is widely described in the general medical literature, but many atypical antipsychotic studies have failed to report ethnicity data.[22] Nonetheless, this is an area of intense clinical and regulatory interest, given the retrospective data indicating greater risk of antipsychotic metabolic adverse effects among black[26,38] and Hispanic patients,[39] combined with recent findings from CATIE phase 1[29] and the Ader study.[30]

Presented here is one of the few prospective data sets to specifically examine the modifying impact of race on antipsychotic metabolic outcomes, using 2 agents with very different risk profiles. Aripiprazole is associated with markedly less metabolic liability than olanzapine,[14] and this finding is replicated within each racial grouping. Regardless of race, olanzapine use consistently generated greater metabolic adverse effects than aripiprazole, although the differential metabolic effects of olanzapine and aripiprazole may not be applied equally across all metabolic parameters. Insulin resistance correlates much more strongly with serum triglyceride values among

Figure 2. Percentage of Patients Meeting Criteria for Metabolic Syndrome at Week 26 by Race



*Cochran–Mantel-Haenszel, p = .013.
**Cochran–Mantel-Haenszel, p = .117.

whites than among African Americans[40]; moreover, data from this study and those from a retrospective analysis of clozapine treatment[28] suggest an impact of race on vulnerability toward antipsychotic-induced weight gain. Conversely, the data from CATIE phase 1 reveal limited antipsychotic effects on blood pressure across all racial groups.[29]

In the present analysis, there were significant metabolic differences between aripiprazole and olanzapine for multiple parameters, particularly among whites, but the absence of significant between-drug differences in serum glucose for either racial cohort is not entirely unexpected. Much of the antipsychotic metabolic literature has focused on hyperglycemia and new-onset diabetes mellitus, but in general, the development of diabetes mellitus is the end result of a long-term process spanning 10 or more years. For many years, pancreatic β-cells can compensate for peripheral insulin resistance by increased insulin output, yet genetically susceptible individuals cannot maintain this output indefinitely and sustain progressive β-cell loss—resulting initially in postprandial hyperglycemia and eventually in fasting hyperglycemia.[41] The antipsychotics olanzapine and clozapine may have adiposity-independent effects on insulin sensitivity,[42] but most schizophrenia patients retain sufficient β-cell reserve over short periods of time (e.g., less than 1 year) to maintain glycemic control. Even in large data sets, such as that from the CATIE schizophrenia trial, olanzapine treatment is associated with deleterious changes in central adiposity and other markers of insulin sensitivity (e.g., serum triglycerides), but significant differences in mean fasting glucose changes compared with other antipsychotics are not evident.[29] Tracking serum glucose remains important in identifying patients who have progressed from normoglycemia to prediabetes or overt diabetes mellitus, but the present data echo the findings from CATIE and reinforce the value of the metabolic syndrome concept in highlighting insulin-resistant patients for early intervention to preserve β-cell function and forestall the development of diabetes mellitus.

The most interesting and novel finding of this analysis relates to the within-drug outcomes based on race. When the metabolic impact of an antipsychotic is small, as in the case of aripiprazole, the effect of race is clearly evident. When examined across each individual metabolic parameter or with the more aggregate assessment based on metabolic syndrome status, white patients experienced metabolic improvement with aripiprazole, whereas black/Hispanic aripiprazole-treated subjects experienced less consistent improvement but ultimately more favorable outcomes than black/Hispanic subjects taking olanzapine. For olanzapine-treated patients, the effect of the medication itself is so large that it overwhelms the effect of race, although black/Hispanic subjects exhibited numerically worse metabolic outcomes than white subjects, effects that may become more apparent over time. The 47% reduction in risk (OR = 0.53) of developing metabolic syndrome for black/Hispanic subjects taking aripiprazole versus olanzapine is likely clinically relevant in spite of the lack of statistical separation and may inform future study designs with race as a variable.

Limitations of the present analysis rest in the fact that this is a post hoc examination of a study not designed or powered to demonstrate between-race differences in metabolic outcomes for either treatment. As noted previously, the failure to find between-drug differences for the black/Hispanic cohort on several measures, including metabolic syndrome prevalence, was likely the result of type II error and possibly the result of insufficient time to fully manifest the metabolic changes for each medication. While black/Hispanic individuals do have higher cardiometabolic risk than whites, larger studies would analyze the black/Hispanic cohorts separately, since the patterns of risk do vary between these 2 groups.

Patients with schizophrenia are a high-risk group for the development of metabolic disorders, with antipsychotics playing an important role through mechanisms that are not entirely understood. To minimize antipsychotic-related metabolic risks among racial and ethnic subgroups with increased vulnerability necessitates an ability to unravel the specific physiologic interactions between the genetic determinants of race-based metabolic risk and the as yet unknown specific metabolic actions of antipsychotics. The greater propensity for black/Hispanic patients to develop treatment-emergent metabolic effects highlights the importance of mitigating risk, and underscores the need for monitoring of all patients treated with atypical antipsychotics. Unfortunately, the rates of metabolic monitoring are disturbingly low even after publication of consensus guidelines,[3,43] indicating that renewed efforts must be undertaken by the psychiatric profession to be responsible

for basic health assessment and to advocate for greater access to health care in patients with identified health problems. For the present, important interventions to minimize metabolic and cardiovascular risk during antipsychotic treatment include the choice of metabolically more favorable antipsychotics combined with diligent monitoring for all patients. Clinicians should also be well versed in both pharmacologic and behavioral means to promote weight loss in antipsychotic-treated patients,[44–46] as well as the health improvements that can be achieved by switching antipsychotics.[47–49] As advocates for the severely mentally ill, the psychiatric community must set an example by attending to the total health of these metabolically high risk patients.

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

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