# Comparison of Metabolic Syndrome Incidence Among Schizophrenia Patients Treated With Aripiprazole Versus Olanzapine or Placebo

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***Background:*** Metabolic syndrome is a strong determinant of new-onset diabetes and coronary heart disease in general populations. Given the higher prevalence of metabolic syndrome among mentally ill patients, the syndrome poses a greater health risk to this population. Atypical antipsychotic treatment may exacerbate this condition. We compared both the rate and incidence of metabolic syndrome among schizophrenia patients (DSM-IV criteria) treated with the atypical antipsychotics aripiprazole or olanzapine or placebo from 4 double-blind, randomized, controlled clinical trials.

***Method:*** Metabolic syndrome was defined according to the Third Adult Treatment Panel (ATP III) Guidelines as the presence on follow-up of 3 of the following abnormalities: waist circumference > 102 cm if male and > 88 cm if female, high density lipoprotein (HDL) < 40 mg/dL if male and < 50 mg/dL if female, diastolic blood pressure ≥ 85 mm Hg or systolic blood pressure ≥ 130 mm Hg, fasting triglycerides ≥ 150 mg/dL, fasting plasma glucose ≥ 110 mg/dL. Both the rate of metabolic syndrome and the person-time incidence were computed from the on-treatment follow-up.

***Results:*** In the placebo-controlled trials, the rate of metabolic syndrome was 25.8% among 155 placebo patients and 19.9% for 267 aripiprazole patients (p = .466 by stratified log rank). The incidence of metabolic syndrome was 14.3% for 91 placebo patients versus 5.3% for 151 aripiprazole patients (p < .001). In the active comparator trials, patients treated with olanzapine (N = 373) versus aripiprazole (N = 380) exhibited rates of 41.6% and 27.9%, respectively (p = .0002). Incidence rates were 27.4% for 212 olanzapine patients versus 15.7% for 198 aripiprazole patients (p = .0055).

***Conclusion:*** Both the rate and incidence of clinically relevant metabolic syndrome differ according to the choice of antipsychotic agent. The association between metabolic syndrome and treatment warrants careful consideration in the choice of antipsychotic agents.

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In 2001, the Adult Treatment Panel (ATP) III of the National Cholesterol Education Program proposed a definition for metabolic syndrome to identify persons at risk for both coronary heart disease and type 2 diabetes.[1] The definition includes threshold levels for 5 readily measured variables linked to insulin resistance: waist circumference, triglyceride level, high-density lipoprotein (HDL) cholesterol level, fasting plasma glucose concentration, and blood pressure. This definition contrasts with the earlier World Health Organization (WHO) definition of the metabolic syndrome,[2] which is more complex in that it includes a requirement to have documented evidence of insulin resistance necessitating at least a fasting insulin measurement. As a result, the emphasis of the WHO definition is on patients with preexisting evidence of glucose dysregulation.[3] This is a weakness because by the time impaired glucose tolerance or impaired fasting glucose has developed, the risk for conversion to diabetes is high.

By contrast, the ATP III–defined metabolic syndrome classification is triggered when predefined limits of any 3 of the 5 criteria are exceeded. Thus, many persons will have other risk factors despite normal fasting glucose concentrations. A recent survey in the United States found that the prevalence of ATP III–defined metabolic syndrome was approximately 24% in white Americans and was higher in Mexican American (32%) but not African American (21%) populations.[4] On the basis of the 2000 census data, approximately 47 million U.S. adults were estimated to have the metabolic syndrome.

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Furthermore, a large number of recent epidemiologic investigations conducted on a wide variety of patient populations provide evidence for the independent prognostic impact of the ATP III–defined metabolic syndrome on new-onset diabetes and on coronary heart disease.[5–12] Indeed, the metabolic syndrome itself and its component risk factors have been linked to the development of cardiovascular and metabolic events. A recent meta-analysis by Ford[13] reported a nearly 2-fold elevated risk for cardiovascular events and a 3-fold higher diabetes rate among patients with the metabolic syndrome versus those without it. Most of these studies report an effect estimate that has been adjusted for the traditional cardiovascular risk factors such as total cholesterol, age, and smoking status when available.

These studies, therefore, support the view that the ATP III–defined metabolic syndrome strongly predicts future risk for diabetes, information that could be used by physicians to guide clinical decision making. This point is particularly important because by the time impaired glucose tolerance is manifested, the conversion rate to diabetes is very high, and opportunities for successful interventions are possibly lessened. Thus, mechanisms to identify persons at elevated risk for diabetes in advance of glucose dysregulation are to be welcomed. Although controversy exists as to the relevance of the syndrome above and beyond that of the component risk factors,[14] the stated evidence demonstrating an independent effect seems to support its utility. Further, the syndrome has proven to be a useful screening tool for clinicians in general practice.[15] It can readily be determined from a physical examination and fasting blood laboratory results.

Given the demonstrated prognosis for morbidity of the metabolic syndrome, its potential impact on special populations has also received considerable interest. In particular, patients with schizophrenia may be susceptible to the syndrome as a consequence of sedentary lifestyle, high prevalence of smoking, and improper diet.[16] A recent systematic literature review described the prevalence of metabolic syndrome among 819 schizophrenia patients.[17] The age-adjusted pooled prevalence of metabolic syndrome (39.5%) computed from the study is double that of the general population.[18] This observation was corroborated by Correll et al.[19] and De Hert and colleagues.[20]

In addition, cardiovascular events are already recognized as the leading cause of morbidity and mortality among patients with schizophrenia.[21] Additional risks conferred by the newer, so-called atypical agents used to treat schizophrenia are of particular recent concern. Atypical antipsychotic agents, such as olanzapine, quetiapine, and clozapine, have all been linked to weight gain, glucose dysregulation/diabetes, and dyslipidemias.[22–31] Recent studies suggest that risk for weight gain and dyslipidemia were also elevated for risperidone, but not for the newer agents, aripiprazole and ziprasidone.[32,33] Although some of these effects are mediated through increased adiposity, there is evidence for an independent effect of these agents on insulin resistance and dyslipidemias.[23]

Many of the risk factor elevations associated with the use of atypical antipsychotics thus exacerbate components of the metabolic syndrome. The development of the syndrome might place a further burden of risk on patients whose cardiovascular and metabolic health may already be compromised. Lastly, a study of metabolic syndrome incidence among patients with schizophrenia might provide clinicians with an opportunity to use the results in developing guidelines for the administration of certain antipsychotic agents.

The prospective nature of the randomized clinical trial affords the opportunity to determine the incidence of metabolic syndrome according to the development of its component risk factors over the course of the trial. Applying the results of 4 randomized clinical trials, we studied both the rate and incidence of metabolic syndrome among schizophrenia patients (DSM-IV criteria) receiving olanzapine, aripiprazole, or placebo. The hypothesis for the study was (1) metabolic syndrome rates at follow-up would be similar between aripiprazole and placebo and (2) metabolic syndrome rates would be significantly greater for olanzapine versus aripiprazole at 26 weeks.

## METHOD

Data from 4 double-blind randomized controlled clinical trials designed to investigate the efficacy of aripiprazole were used for this post hoc analysis. Clinical results for 3 of these studies are described in detail elsewhere,[34–37] and for the remaining study (W. W. Fleischhacker, M.D.; R. D. McQuade, Ph.D.; R.N.M.; et al., manuscript submitted), details are available from the authors on request. Brief study descriptions are also provided in Appendix 1. The current analysis is based on available data (i.e., fasting laboratory results) from these studies. The first placebo-controlled fixed-dose trial (CN138-001) included 415 patients with acute schizophrenia. This 4-arm efficacy study tested 3 dosing levels (10, 15, and 20 mg) versus placebo for 6 weeks' duration. Among these, 154 aripiprazole patients and 47 placebo patients were evaluable for the presence of metabolic syndrome. The second placebo-controlled fixed-dose trial (CN138-047) included 306 schizophrenia patients whose condition was stabilized and who were randomly assigned to aripiprazole 15 mg/day (N = 153) or placebo (N = 153) and followed for up to 26 weeks. Among these, 113 aripiprazole patients and 108 placebo patients were evaluable for the presence of metabolic syndrome.



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**Table 1. Third Adult Treatment Panel (ATP III) Definition of Metabolic Syndrome[a]**

| ATP III Definition |
|---|
| 1. Waist circumference > 102 cm if male and > 88 cm if female |
| 2. High-density lipoprotein < 40 mg/dL if male and < 50 mg/dL if female |
| 3. Diastolic blood pressure ≥ 85 mm Hg or systolic blood pressure ≥ 130 mm Hg |
| 4. Fasting triglycerides ≥ 150 mg/dL. |
| 5. Fasting plasma glucose ≥ 110 mg/dL |

[a]Based on reference 1.

The first active comparator flexible-dose trial (CN138-002) enrolled 317 patients who experienced acute episodes of schizophrenia. The severity of illness associated with this patient population required an active control, specifically olanzapine 10 to 20 mg/day (N = 156) compared with aripiprazole 15 to 30 mg/day (N = 161). Patients were followed for 52 weeks. The second 52-week flexible-dose active comparator trial (CN138-003) included 695 patients with acute schizophrenia, as in CN123-002, and 349 patients were randomized to aripiprazole and 346 to olanzapine. Among the patients in these active comparator trials, 283 olanzapine patients and 297 aripiprazole patients were evaluable for the presence of metabolic syndrome. Lastly, patients enrolled in 1 of the placebo-controlled trials (CN138-047) were rerandomized to aripiprazole or olanzapine. Of these, 90 olanzapine patients and 83 aripiprazole patients were evaluable for the presence of metabolic syndrome. Written informed consent was obtained from all patients who participated in the studies, and institutional review board approval was obtained in all 4 trials.

Appropriate vital sign and laboratory data collected at baseline and mandated office visits during the course of the trial were used to derive the metabolic syndrome case definition. Metabolic syndrome was defined according to the ATP III[1] guidelines (see Table 1). Both the rate of metabolic syndrome and the incidence were computed from the on-treatment follow-up. Only patients with complete data as to fasting laboratory results and the other metabolic syndrome measures at a single office visit were considered evaluable. Office visits were mandated at 4-week intervals for each study, and metabolic syndrome was assessed among the evaluable patients. Once metabolic syndrome was observed, patients were censored. The rate of metabolic syndrome at follow-up was compared between treatment arms using a log-rank test stratified for the presence/absence of metabolic syndrome at baseline. Further, the incidence of metabolic syndrome at follow-up was compared between treatment arms via the log-rank test. Patients exhibiting metabolic syndrome at baseline were excluded from the incidence analysis. Cox proportional hazards regression was used to estimate hazard ratios for metabolic syndrome risk adjusted for treatment and for covariates imbalanced between treatment groups at baseline.

All statistical calculations were performed using SAS version 8.1 (SAS Institute, Inc., Cary, N.C.).

## RESULTS

Table 2 provides the proportion of evaluable patients exhibiting metabolic syndrome at baseline for individual and pooled studies. The rates of metabolic syndrome did not differ between treatment arms in both the individual studies and pooled datasets. Table 3 provides the pooled baseline characteristics of all evaluable patients included in the current analysis. Among the patients enrolled in the placebo-controlled studies, only fasting serum glucose and systolic blood pressure differed between treatment arms. Among patients enrolled in the olanzapine-controlled studies, there were no observed statistically significant differences in baseline characteristics according to treatment arm.

Table 4 describes changes from baseline among individual metabolic syndrome risk factors. In the placebo-controlled studies, the only parameter for which mean change from baseline differed between groups was systolic blood pressure (p = .0207). In the olanzapine-controlled studies, mean changes in waist circumference (+2.98 cm for olanzapine vs. –0.12 cm for aripiprazole [p = .0001]) and triglyceride levels (+22.9 mg/dL for olanzapine vs. –3.4 mg/dL for aripiprazole [p = .0002]) differed significantly between the treatment arms. Mean changes in HDL cholesterol levels (+0.01 mg/dL for olanzapine vs. +2.49 mg/dL for aripiprazole) trended toward statistical significance.

Table 5 lists the rates of metabolic syndrome according to treatment arm for both the placebo-controlled and olanzapine-controlled studies. Adjusted hazard ratios (placebo/aripiprazole or olanzapine/aripiprazole ± 95% CI) derived from the Cox regression are included. Patients who exhibited metabolic syndrome at baseline are also included in this analysis. Among the placebo-controlled studies, metabolic syndrome rates were 25.8% for placebo and 19.9% for aripiprazole (p = .466) with a hazard ratio (95% CI) of 1.18 (0.77 to 1.83). For the olanzapine-controlled studies, the pooled rates were 27.9% for aripiprazole and 41.6% for olanzapine (p = .0002) with a hazard ratio (95% CI) of 1.62 (1.26 to 2.09).

Table 6 lists the incidence of metabolic syndrome among the placebo- and olanzapine-controlled studies. Adjusted hazard ratios are also provided. These analyses were limited to the subset of patients without metabolic syndrome at baseline. Among the placebo-controlled studies, pooled incidence rates of 14.3% and 5.3% were seen for placebo and aripiprazole treatment arms, respectively (p = .0008), with a hazard ratio (95% CI) of 4.55 (1.76 to 11.78). Among the olanzapine-treated patients, incidence rates were 27.4% for olanzapine and

  

**Table 2. Proportion of Evaluable Schizophrenia Patients Exhibiting Metabolic Syndrome at Baseline Visit—All Studies[a]**

| Study | Olanzapine, n/N (%) | Aripiprazole, n/N (%) | Placebo, n/N (%) | Total, n/N (%) |
|---|---|---|---|---|
| CN138-001 | … | 31/154 (20.1) | 10/47 (21.3) | 41/201 (20.4) |
| CN138-047 | … | 31/113 (27.4) | 25/108 (23.1) | 56/221 (25.3) |
| Pooled | … | 62/267 (23.2) | 35/155 (22.6) | 97/422 (23.0) |
| CN138-002/003 | 55/283 (19.4) | 62/297 (20.9) | … | 117/580 (20.2) |
| CN138-047 extension | 16/90 (17.8) | 20/83 (24.1) | … | 36/173 (20.8) |
| Pooled | 71/373 (19.0) | 82/380 (21.6) | … | 153/753 (20.3) |

[a]There were no statistically significant differences between study arms (Pearson $\chi^2$).
Symbol: … = not applicable.

**Table 3. Pooled Baseline Characteristics of Patients With Schizophrenia—All Studies[a]**

| | CN138-001 and CN138-047 | | | | | | CN138-002/003 and CN138-047 Extension Phase | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Placebo | | | Aripiprazole | | | Olanzapine | | | Aripiprazole | | |
| Characteristic | No. Observed | Value[b] | SD | No. Observed | Value[b] | SD | No. Observed | Value[b] | SD | No. Observed | Value[b] | SD |
| Men | 155 | 67.7% | … | 267 | 63.3% | … | 373 | 56.0% | … | 380 | 58.2% | … |
| Race | | | | | | | | | | | | |
| White | 155 | 76.1% | … | 267 | 67.4% | … | 373 | 84.5% | … | 380 | 83.2% | … |
| Black | 155 | 13.6% | … | 267 | 16.4% | … | 373 | 9.7% | … | 380 | 7.4% | … |
| Other | 155 | 10.3% | … | 267 | 16.2% | … | 373 | 5.8% | … | 380 | 9.4% | … |
| Age, y | 155 | 41.4 | 13.1 | 267 | 40.7 | 12.5 | 373 | 37.7 | 11.6 | 380 | 37.6 | 11.3 |
| Waist circumference, cm | 151 | 93.6 | 16.1 | 262 | 93.0 | 16.5 | 363 | 91.5 | 15.3 | 370 | 92.6 | 16.5 |
| Triglycerides, fasting, mg/dL | 125 | 153.7 | 101.8 | 212 | 161.6 | 135.0 | 278 | 146.8 | 99.0 | 277 | 147.8 | 110.8 |
| HDL cholesterol, mg/dL | 125 | 44.8 | 12.5 | 212 | 47.4 | 14.5 | 278 | 44.6 | 12.7 | 276 | 43.6 | 11.6 |
| Glucose, fasting serum, mg/dL[c] | 126 | 99.6 | 24.2 | 213 | 95.2 | 18.8 | 282 | 95.6 | 23.7 | 278 | 95.3 | 17.3 |
| Systolic blood pressure, mm Hg[c] | 155 | 125.4 | 14.6 | 265 | 121.5 | 13.4 | 372 | 121.2 | 13.7 | 380 | 121.1 | 13.6 |
| Diastolic blood pressure, mm Hg | 155 | 77.8 | 10.8 | 265 | 76.5 | 9.3 | 372 | 77.2 | 9.7 | 380 | 77.0 | 9.4 |

[a]Pearson $\chi^2$ test was used to test difference in sex between the treatment groups; Wilcoxon 2-sample test was used to test difference for continuous variables.
[b]Values are expressed as means except where noted.
[c]Differences in systolic blood pressure (p = .0153) and fasting serum glucose (p = .0403) are statistically significant at the 5% significance level for the placebo-controlled studies only. The active comparator studies exhibited no differences in baseline characteristics.
Abbreviation: HDL = high-density lipoprotein.
Symbol: … = not applicable.

**Table 4. Change From Baseline of Metabolic Syndrome Risk Factors Among Schizophrenia Patients With Metabolic Syndrome at Baseline—Pooled Studies[a]**

| | CN138-001 and CN138-047 | | | | | | CN138-002/003 and CN138-047 Extension Phase | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Placebo | | | Aripiprazole | | | Olanzapine | | | Aripiprazole | | |
| Change from baseline | No. Observed | Mean | SD | No. Observed | Mean | SD | No. Observed | Mean | SD | No. Observed | Mean | SD |
| Waist circumference, cm* | 40 | 0.21 | 4.71 | 69 | 0.05 | 4.73 | 156 | 2.98 | 6.23 | 138 | –0.12 | 6.03 |
| Triglycerides, fasting, mg/dL* | 91 | –0.57 | 72.48 | 150 | –7.99 | 58.46 | 204 | 22.91 | 76.70 | 195 | –3.37 | 77.17 |
| HDL cholesterol, mg/dL | 91 | –0.80 | 12.49 | 150 | 0.01 | 11.35 | 204 | 0.01 | 12.27 | 194 | 2.49 | 11.53 |
| Glucose, fasting serum, mg/dL | 91 | –0.22 | 24.98 | 151 | 0.64 | 13.74 | 211 | 4.57 | 65.49 | 195 | 2.27 | 20.70 |
| Systolic blood pressure, mm Hg** | 47 | –3.39 | 14.45 | 103 | 0.88 | 13.50 | 186 | 0.23 | 12.51 | 175 | 0.74 | 12.79 |
| Diastolic blood pressure, mm Hg | 47 | –1.87 | 9.00 | 103 | –0.92 | 9.98 | 186 | 0.12 | 9.24 | 175 | –0.06 | 9.69 |

[a]End of study is the last evaluable visit (with at least 3 measures of the 5 metabolic syndrome measures available).
*Olanzapine-controlled studies: Change in waist circumference (p = .0001) and triglycerides (p = .0002) are significantly different.
**Placebo-controlled studies: change in systolic blood pressure is different between the 2 groups (Wilcoxon 2-sample test, p = .0207).
Abbreviation: HDL = high-density lipoprotein.

15.7% for aripiprazole patients (p = .0055) with an adjusted hazard ratio (95% CI) of 1.88 (1.20 to 2.95).

## DISCUSSION

Patients with schizophrenia are already deemed to be at elevated risk for cardiovascular and metabolic events by virtue of their lifestyle factors, such as smoking, physical inactivity, and improper diet.[16,21] The added contribution of certain atypical antipsychotic medications to this already elevated cardiovascular and metabolic risk is also demonstrated in several epidemiologic studies.[23-33] The observation in the current study of an increased rate of metabolic syndrome among patients administered olanza-

**Table 5. Rate of Metabolic Syndrome—All Patients**

| Placebo-Controlled Studies CN138-001 and CN138-047 | | | | |
|---|---|---|---|---|
| Study | Placebo, n/N (%)[a] | Aripiprazole, n/N (%)[a] | p Value[b] | Hazard Ratio (95% CI)[c] |
| CN138-001 | 11/47 (23.4) | 28/154 (18.2) | .8756 | 1.07 (0.50 to 2.27) |
| CN138-047 | 29/108 (26.9) | 25/113 (22.1) | .0827 | 1.71 (0.96 to 3.02) |
| Pooled | 40/155 (25.8) | 53/267 (19.9) | .4660 | 1.18 (0.77 to 1.83) |
| CN138-002/003 and CN138-047 Extension Phase | | | | |
| Study | Olanzapine, n/N (%)[a] | Aripiprazole, n/N (%)[a] | p Value[b] | Hazard Ratio (95% CI)[c] |
| CN138-002/003 | 122/283 (43.1) | 85/297 (28.6) | .0015 | 1.59 (1.20 to 2.11) |
| CN138-047 extension | 33/90 (36.7) | 21/83 (25.3) | .0339 | 1.86 (1.05 to 3.29) |
| Pooled | 155/373 (41.6) | 106/380 (27.9) | .0002 | 1.62 (1.26 to 2.09) |

[a]n = number of patients meeting Third Adult Treatment Panel (ATP-III) criteria for metabolic syndrome; N = number of patients evaluable for metabolic syndrome (i.e., at least 3 measures available at the same visit).
[b]p Value based on a log-rank test stratified by baseline metabolic syndrome status (i.e., metabolic syndrome yes/no/unassessable).
[c]The parametric estimate and 95% CI for hazard ratio (placebo/aripiprazole, olanzapine/aripiprazole) was obtained from the Cox regression model with treatment as a covariate and the same strata as the log-rank test.

**Table 6. Incidence of Metabolic Syndrome in Patients Without Metabolic Syndrome at Baseline**

| Placebo-Controlled Studies CN138-001 and CN138-047 | | | | |
|---|---|---|---|---|
| Study | Placebo, n/N (%)[a] | Aripiprazole, n/N (%)[a] | p Value[b] | Hazard Ratio (95% CI)[c] |
| CN138-001 | 6/24 (25.0) | 6/89 (6.7) | .0098 | 4.35 (1.31 to 14.5) |
| CN138-047 | 7/67 (10.4) | 2/62 (3.2) | .0304 | 4.92 (1.01 to 24.0) |
| Pooled | 13/91 (14.3) | 8/151 (5.3) | .0008 | 4.55 (1.76 to 11.78) |
| CN138-002/003 and CN138-047 Extension Phase | | | | |
| Study | Olanzapine, n/N (%)[a] | Aripiprazole, n/N (%)[a] | p Value[b] | Hazard Ratio (95% CI)[c] |
| CN138-002/003 | 44/144 (30.6) | 26/142 (18.3) | .0247 | 1.78 (1.07 to 2.94) |
| CN138-047 extension | 14/68 (20.6) | 5/56 (8.9) | .0898 | 2.37 (0.85 to 6.60) |
| Pooled | 58/212 (27.4) | 31/198 (15.7) | .0055 | 1.88 (1.20 to 2.95) |

[a]n = number of patients meeting Third Adult Treatment Panel (ATP-III) criteria for metabolic syndrome; N = number of patients evaluable for metabolic syndrome (i.e., at least 3 measures available at the same visit) who did not have metabolic syndrome at baseline.
[b]p Value based on a log-rank test stratified by protocol.
[c]The parametric estimate and 95% CI for hazard ratio (placebo/aripiprazole, olanzapine/aripiprazole) was obtained from the Cox model with treatment as a covariate and the same strata as the log-rank test.

pine is consistent with the findings from these previous studies.[19,20] Patients administered aripiprazole, by contrast, exhibited a metabolic syndrome rate and incidence comparable to or less than that of placebo in both the individual trials and in pooled analysis. An examination of the changes to specific risk factors over the follow-up period provides insight as to the observed metabolic syndrome results. In the placebo-controlled studies, weight, triglycerides, and HDL cholesterol levels have improved among the aripiprazole patients relative to the placebo-controlled patients. In the olanzapine-controlled studies, weight, triglycerides, and HDL cholesterol changes appear to account for the observed differences in metabolic syndrome rate and incidence between olanzapine and aripiprazole. This finding is consistent with both epidemiologic data and other clinical trial studies.[32,33,35]

Several important limitations to the current study must be considered. First, the conducted analysis was post hoc and not prespecified at the time of development of the study. Another limitation is that the estimation of metabolic syndrome was limited to those patients with fasting laboratory results and complete information on metabolic syndrome risk factors from a single visit. Nonfasting laboratory values can greatly increase the variability of triglyceride and glucose determinations. Therefore, it was deemed necessary to restrict the analyses to patients with fasting lab results. This restriction may have resulted in differential distributions of metabolic syndrome risk factors between treatment arms, a difference that is also indicated by examining the proportion of evaluable patients exhibiting metabolic syndrome at the baseline visit (see Table 2). Imbalances were noted for certain variables (e.g., systolic blood pressure and fasting serum glucose) between some of the treatment groups, particularly for the placebo-controlled studies. For this reason, the statistical analysis was stratified by the presence or absence of metabolic syndrome at baseline, and Cox regression was further applied to adjust for these covariates. Another limitation to the analysis was that patients who first exhibited metabolic syndrome on follow-up in a single visit were censored from further observation. Some of these may have reverted to normal status, although studies suggest that this is unlikely without a change in treatment regimen or lifestyle.[38,39]

  

Although the analysis might have been limited to patients with incident metabolic syndrome only, we considered it important to include patients with prevalent metabolic syndrome at baseline. It was possible that some patients with prevalent metabolic syndrome at baseline would revert to normal status on treatment or on placebo.

Both the rate and incidence of clinically relevant metabolic syndrome differ according to the choice of antipsychotic agent. Fortunately, the emergence of clinical guidelines for treatment of metabolic abnormalities offers direction to clinicians as to interventions, including lifestyle change, pharmacologic treatment, and possible alteration of antipsychotic regimen.[40,41] Application of the metabolic syndrome definition in clinical practice provides clinicians both with a measure of its prognostic impact for diabetes and cardiovascular disease and with a useful screening tool.

*Drug names:* aripiprazole (Abilify), clozapine (Clozaril, FazaClo, and others), olanzapine (Zyprexa), quetiapine (Seroquel), ziprasidone (Geodon).

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**Appendix 1. Description of Studies Included in the Analysis of Metabolic Syndrome Incidence Among Schizophrenia Patients Treated With Aripiprazole Versus Olanzapine or Placebo**

| Trial # (Study) | Design | Population | Treatment Arms |
|---|---|---|---|
| CN138-001 (McEvoy et al[36]) | Randomized, double-blind, placebo-controlled, fixed-dose, multicenter<br>Comparison of efficacy and safety<br>USA and Canada<br>6 weeks | 420 hospitalized schizophrenic patients (DSM-IV criteria) in acute relapse<br>326 men, 94 women<br>18–76 years old<br>Baseline PANSS score, mean:<br>Placebo: 92.6<br>Aripiprazole 10 mg: 92.9<br>Aripiprazole 15 mg: 92.4<br>Aripiprazole 20 mg: 91.9 | Aripiprazole 10 mg/d (N = 70)<br>Aripiprazole 15 mg/d (N = 70)<br>Aripiprazole 20 mg/d (N = 70)<br>Placebo (N = 210) |
| CN138-047 (Pigott et al[34]) | Randomized, double-blind, placebo-controlled, multicenter study (31 sites)<br>Czech Republic, Poland, Russia, Ukraine, and USA<br>26 weeks | 310 patients with chronic stable schizophrenia (DSM-IV) taking other antipsychotic medications for at least 3 months, PANSS total score ≥ 60, PANSS hostility/uncooperativeness subscale score ≤ 4 (moderate), and CGI-S score ≤ 4<br>174 men, 136 women<br>18–77 years old | Aripiprazole 15 mg/d (N = 155)<br>Placebo (N = 155) |
| CN138-047 (Chzanowski et al[37]) open-label extension | Randomized, open-label<br>International<br>52 weeks | 214 stabilized patients with chronic schizophrenia, PANSS total score ≥ 60, PANSS hostility/uncooperativeness subscale score ≤ 4 (moderate)<br>112 had completed CN138-047<br>102 had relapsed after ≥ 2 weeks of treatment<br>116 men, 98 women<br>18–77 years old | Aripiprazole 15–30 mg/d (N = 107)<br>Olanzapine 10–20 mg/d (N = 107) |
| CN138-002 (McQuade et al[35]) | Randomized, double-blind, flexible-dose, multicenter study<br>USA, Argentina, Brazil, Canada, and Mexico<br>12-week study plus 40-week extension for total of up to 52 weeks | 317 hospitalized schizophrenic patients in acute relapse with PANSS score ≥ 60 (moderate)<br>229 men, 88 women<br>18–75 years old | Aripiprazole 15 mg/d up to 30 mg/d (N = 159)<br>Olanzapine 10 mg/d up to 20 mg/d (N = 158) |
| CN138-003 (Fleischhacker et al[a]) | Multicenter, randomized, double-blind, comparative study of inpatients who were having an acute relapse of schizophrenia<br>Europe<br>52 weeks | 703 inpatients and outpatients who were hospitalized for acute relapse of schizophrenia with PANSS score ≥ 60 (moderate)<br>399 men, 304 women<br>18–65 years old | Aripiprazole 15–30 mg/d (N = 355)<br>Olanzapine 10–20 mg/d (N = 348) |

[a]W. W. Fleischhacker, M.D.; R. D. McQuade, Ph.D.; R.N.M.; et al., manuscript submitted. Details are available from the authors on request.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale; DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition; PANSS = Positive and Negative Syndrome Scale.

  