Death as a result of cardiovascular (CV) complications represents the leading natural cause of excess mortality in patients with schizophrenia.\(^1\) While lifestyle variables such as high rates of smoking, poor dietary habits, and inactivity contribute to CV disease, research has also focused on a cluster of abnormalities that define metabolic syndrome (Table 1). Although considerable debate exists about whether a diagnosis of metabolic syndrome confers added CV risk compared with that attributable to the individual criteria, there is little doubt that the syndrome captures a group of individuals at risk for both CV disease and type 2 diabetes mellitus.\(^2\)

The clinical usefulness of the metabolic syndrome concept is its ability to focus attention on a cluster of abnormalities that in isolation may not attract much clinical interest. Underlying the development of metabolic syndrome (also referred to as syndrome X or the dysmetabolic syndrome) is the finding that compensatory hyperinsulinemia, in certain abdominally obese persons, is associated with dyslipidemia, hypertension, and inflammatory markers.\(^3\) Those features distinguish patients with metabolic syndrome from overweight or obese individuals in whom hyperinsulinemia develops in the presence of decreased peripheral insulin sensitivity but without the other dysmetabolic components.

Increased diabetes mellitus prevalence has been noted in patients with schizophrenia in many countries,\(^4\) but the greater public health concern is the prevention of diabetes and preservation of b-cell function in patients who are prediabetic.\(^5\) For that reason, recent studies of patients with schizophrenia have increasingly focused on the prevalence of prediabetic states such as the metabolic syndrome. Issues in the literature revolve around the prevalence of the syndrome as a whole and that of the individual criteria, how these prevalence data compare with those in matched individuals from the general population, and the role of antipsychotic medications.

The purpose of this article is to review some of the newer findings that probe the link between metabolic syndrome and schizophrenia and to investigate whether compelling data exist to demonstrate medication-independent risk for metabolic disease in patients with schizophrenia. Recent consensus recommendations for monitoring and preventing metabolic dysfunction will be discussed, along with studies outlining comparative therapeutic options for those who meet metabolic syndrome criteria.

**Prevalence data, disease, and medication effects**

The diagnostic criteria used in many studies are based on those elaborated by the National Cholesterol Education Program (NCEP) in 2001 and subsequently updated by lowering the fasting glucose threshold to 100 mg/dL to match that established by the American Diabetes Association (ADA) for prediabetes (Table 1). Although abdominal obesity is considered a core feature of the syndrome, the NCEP definition allowed the diagnosis to be established by meeting any 3 of the 5 criteria, prompting the International Diabetes Federation (IDF) to create a newer definition that mandates abdominal obesity as a necessary criterion, combined with any 2 of the 4 remaining components.

Regardless of the definition, the past 2 years have seen the publication of multiple articles on the prevalence of metabolic syndrome, predominantly using North American or Western European samples, including several large studies that compared prevalences in patients with schizophrenia with those in matched comparison controls from the general population (Table 2). Among the recent studies, 2 recruited patients with schizophrenia or schizoaffective disorder on the basis of obesity\(^11,12\) and have limited generalizability.

The first large published estimate is from a study of 240 Canadian patients with schizophrenia or schizoaffective disorder (65% male, mean age 43.3 years). The investigators found a prevalence of...
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prospective studies (26 and 52 weeks) also indicate a benign metabolic profile comparable to that neutral.

Following early expert opinion that olanzapine and clozapine are the antipsychotic agents with the highest risk for metabolic dysfunction independent of antipsychotic exposure. Some small early studies from a group in Ireland seemed to suggest that increased visceral adiposity and glycemic abnormalities could be found in untreated and neuroleptic-naive patients with schizophrenia, but these findings have not been replicated. A larger and more rigorous study from China found no pretreatment differences in visceral fat or other metabolic parameters between patients with schizophrenia and matched controls, but marked differences emerged immediately after antipsychotic exposure.

Similarly, a Spanish study that compared 50 neuroleptic-naive subjects with schizophrenia with 50 nonadherent patients with schizophrenia and 50 control subjects found no differences in metabolic measures between the neuroleptic-naive cohort and the control subjects, arguing against a unique predisposition toward glycemic dysfunction in patients with schizophrenia.

The nonadherent patients with schizophrenia, antipsychotic-free at the time of analysis, showed significantly increased markers of insulin resistance compared with patients who were antipsychotic-naive and the control cohort, indicating the effects of earlier treatment as an important causative factor in the high prevalence of metabolic dysfunction seen in treated cohorts with schizophrenia.

While the debate over disease effects awaits more studies of neuroleptic-naive patients with schizophrenia, the relative contribution of various antipsychotics has become firmly established. Following early expert opinion that olanzapine and clozapine are the antipsychotic agents with the highest risk for metabolic dysfunction, the large CATIE schizophrenia trial (n = 1460) provided sound confirmation of this conclusion while noting that ziprasidone appears to be metabolically neutral.

Aripiprazole was not included in the first 2 phases of CATIE, but data from long-term prospective studies (26 and 52 weeks) also indicate a benign metabolic profile comparable to that for ziprasidone.

Obesity increases risk for metabolic dysfunction, but reports of type 2 diabetes mellitus and ketoacidosis occurring in patients with schizophrenia without marked weight gain raised the issue of weight-independent drug effects on glucose/insulin homeostasis. Aside from clinical data provided by these case reports, compelling biologic findings have emerged from animal studies, which indicate that olanzapine not only increases weight but appears to preferentially induce increases in visceral adiposity.

Moreover, exposure to single doses of clozapine and olanzapine is associated with decreased
peripheral insulin sensitivity in a dose-dependent manner in laboratory animals.\textsuperscript{30} Insulin normally acts to suppress hepatic gluconeogenesis, but clozapine and olanzapine appear to interfere with this process immediately after exposure, resulting in abnormal hepatic glucose output from the liver. This presents the most compelling argument for weight-independent effects of these medications on metabolic function, although confirmation of this effect in human studies with larger samples is required.

**Monitoring and treatment**

In response to the obvious public health impact of the high prevalence of metabolic syndrome, several expert and consensus panels have convened in the United States,\textsuperscript{22,31} Canada, and Belgium\textsuperscript{32-34} to support aggressive monitoring of metabolic parameters in all patients exposed to antipsychotics. At the minimum, those prescribing antipsychotics should obtain baseline and annual measures of all variables that encompass metabolic syndrome criteria—including waist circumference—with more frequent monitoring suggested for weight (typically at each visit), lipids, and glucose related to aggregate risk from the antipsychotic agent itself (Table 4). In addition, patient variables including age, personal or family history, and ethnicity should be recorded. The ADA consensus panel did not provide clear guidelines for treatment of all antipsychotic-related metabolic problems, but the parameters that define the metabolic syndrome provide useful markers for determining when to intervene. The sole exception is weight gain, for which the ADA consensus panel recommended intervention when the patient experiences a 5% weight gain,\textsuperscript{22} since most individuals have difficulty in losing more than 5% on their own. Once abnormalities have been identified, both the ADA consensus panel\textsuperscript{22} and NCEP suggest a trial of lifestyle modification for up to 3 months.\textsuperscript{6} The clinical difficulty rests in the fact that these programs are not widely available to patients with schizophrenia, and even those targeted for weight reduction in this population often fail to achieve clinical goals.\textsuperscript{35} Nonetheless, when available they should be offered, but the interventions must be reassessed for effectiveness after 3 months. If no progress toward metabolic goals has occurred, other strategies must be pursued, including pharmacotherapy for hyperlipidemia, hypertension, or mild type 2 diabetes or switching from metabolically offending antipsychotic medications.

The conundrum facing many practitioners is whether to treat metabolic problems as they arise, or attempt to switch patients from metabolically offending medications and thus obviate the need for referral and additional medications. For patients with refractory schizophrenia who are being treated with clozapine, the absence of other viable medication choices precludes switching, but extensive data from industry switch studies,\textsuperscript{12,36,37} other switch data,\textsuperscript{38} and the CATIE schizophrenia trial\textsuperscript{23} demonstrate that many patients can be switched to metabolically more benign antipsychotics without loss of effectiveness. A reanalysis of the CATIE phase 1 data showed that the patients who were randomized to the same antipsychotic medication taken at study entry (in essence, nonswitchers) continued to take their medication longer than those who were switched to a new medication, arguing for attempts at behavioral or other management of metabolic problems as the first step before medication changes.\textsuperscript{39} For those patients for whom switching is not feasible or initially preferred, establishment of relationships with primary care providers is paramount to ensure that the patient receives appropriate follow-up and treatment. Further research will help clarify the risks and benefits of switching for metabolic purposes and elucidate the biologic mechanisms for drug-related metabolic effects (and disease-related effects if they exist), but minimization of CV risk remains a major clinical goal during antipsychotic therapy of schizophrenia.

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**Drugs Mentioned in This Article**

Aripiprazole (Abilify)
Clozapine (Clozaril)
Olanzapine (Zyprexa)
Topiramate (Topamax)
Ziprasidone (Geodon)

**References**


Evidence-Based References

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