Metabolic Complications of Schizophrenia and Antipsychotic Medications — An Updated Review

精神分裂症和抗精神病藥引發的代謝併發症：更新回顧

J Yogaratnam, N Biswas, R Vadivel, R Jacob

Abstract

Metabolic syndrome is a cluster of risk factors comprising obesity, dyslipidaemias, glucose intolerance, insulin resistance (or hyperinsulinaemia), and hypertension, and is highly predictive of type 2 diabetes mellitus and cardiovascular disease. The life expectancy of people with schizophrenia is reduced by 20%, with 60% of the excess mortality due to physical illness. Schizophrenia itself may be a risk factor for metabolic syndrome and there is also increasing concern that antipsychotic drugs, particularly second-generation antipsychotics, have metabolic consequences that contribute to the risk. Various diagnostic guidelines, updated facts with regard to epidemiology, pathophysiology, risk factors, and complications of metabolic syndrome are discussed in this review. Moreover, the impact of various antipsychotics on metabolic syndrome and their possible mechanisms are comprehensively reviewed. The authors emphasise that, while many adults with schizophrenia receive little or no medical care, such care is important given the risk of metabolic abnormalities associated not only with antipsychotic medications, but also with schizophrenia in general.

Key words: Antipsychotic agents; Metabolic syndrome X; Metabolism; Schizophrenia

Introduction

Metabolic syndrome is a cluster of risk factors comprising obesity (central and abdominal), dyslipidaemias, glucose intolerance, insulin resistance (or hyperinsulinaemia), and hypertension, and is highly predictive of type 2 diabetes mellitus and cardiovascular disease.¹ The mean age of death is 61 years for patients with schizophrenia, which is considerably younger than 76 years for the general population.² Life expectancy in people with schizophrenia is reduced by 20%,³ with 60% of the excess mortality due to physical illness.⁴

Schizophrenia itself may be a risk factor for metabolic syndrome in addition to many other factors in patients with schizophrenia, and there is also increasing concern that antipsychotic drugs, particularly second-generation antipsychotics (SGAs), have metabolic consequences that contribute to the risk.⁵ The precise relationship between antipsychotic drugs and metabolic syndrome remains uncertain, but it is clear that people with schizophrenia
treated with antipsychotic medications develop individual features of metabolic syndrome, and the syndrome itself, at a higher rate than the general population. Antipsychotic polypharmacy, which is a common practice in many psychiatric settings, as compared with monotherapy, may be independently associated with increased risk of pre-metabolic syndrome and higher rates of metabolic syndrome and lipid markers of insulin resistance, even after adjusting for patients’ lifestyle characteristics.\(^6,7\) A recent study concluded that switching to monotherapy was appropriate and reasonable as long as patients could return to polypharmacy when necessary, and switching from a higher- to a lower-risk agent or from polypharmacy to monotherapy may facilitate metabolic improvement.\(^8\)

Many reviews have concluded that there is a need for active routine physical health screening of all individuals receiving treatment with antipsychotic drugs,\(^9\) which is in keeping with the recommendations of the National Institute for Health and Clinical Excellence treatment guidelines for schizophrenia. While many adults with schizophrenia receive little or no medical care, such care is important, given the risk of metabolic abnormalities associated not only with antipsychotic medications, but also with schizophrenia in general.\(^10\)

### Diagnostic Guidelines for Metabolic Syndrome

Guidelines for diagnosis of metabolic syndrome are listed in Table 1.\(^1,11-15\) The most commonly used definitions for metabolic syndrome are in keeping with the Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program (NCEP) definition and the adapted ATP III recommendation proposed by the American Heart Association which follows the International Diabetes Federation (IDF) guideline of lowering the threshold for impaired fasting glucose to 5.56 mmol/L (100 mg/dL).\(^11\) An important difference between the NCEP / ATP III and the IDF definitions is that of the values for central obesity, which are defined as > 102 cm for men and > 88 cm for women in the NCEP / ATP III definition, the IDF values are comparatively lower at 94 cm and 80 cm, respectively, with a lower value of 80 cm for South-Asian men.\(^16\)

### Epidemiology of Metabolic Syndrome

Metabolic syndrome is a burgeoning global problem, with approximately 25% of adult Europeans and Latin Americans, 22% of US adults, and 32% of Mexican Americans\(^17\) estimated to have the condition. Additionally, metabolic syndrome is considered an emerging epidemic in developing East-Asian countries, including China, Japan, and Korea, where the prevalence ranged from 8 to 13% in men and 2 to 18% in women depending on the population and definitions used.\(^18\) Even in many other countries worldwide, metabolic syndrome has been recognised as a highly prevalent health problem\(^19\) demanding attention and intervention. The exact prevalence of metabolic syndrome in patients with schizophrenia is unknown. Using baseline data from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial, the prevalence of metabolic syndrome was 40.9% and 42.7% according to the NCEP and the American Heart Association / National Heart, Lung, and Blood Institute–derived criteria, respectively.\(^20\)

### Pathophysiology of Metabolic Syndrome

Metabolic syndrome is thought to be caused by adipose tissue dysfunction and insulin resistance. Dysfunctional adipose tissue results in the release of proinflammatory cytokines such as tumour necrosis factor, adiponectin, leptin, resistin, and plasminogen activator inhibitor, which play an important role in the pathogenesis of obesity-related insulin resistance, the primary mediator of metabolic syndrome.\(^21\)

### Risk Factors for Metabolic Syndrome in Patients with Schizophrenia

People with schizophrenia on average have a sedentary lifestyle involving lack of regular physical activity, poor food intake, substance abuse, and high rates of smoking,\(^22\) which increase their risk for development of metabolic syndrome in addition to the risk from antipsychotic medications. These lifestyle factors are partly influenced by aspects of the illness such as negative symptoms and vulnerability to stress. Moreover, earlier studies have shown an increased risk for people with schizophrenia to develop metabolic abnormalities in the absence of antipsychotic medication, and there are indications of an increased risk for diabetes in first-degree relatives of patients with schizophrenia.\(^23\)

Other possibilities to explain these associations in schizophrenia include stress and abnormalities of the hypothalamic-pituitary-adrenal axis.\(^24\) A study showed that people with schizoaffective disorder are more vulnerable
to metabolic syndrome than people with schizophrenia for unexplained reasons.25

Complications of the Metabolic Syndrome

The complications of metabolic syndrome are broad. Table 26-30 shows that metabolic syndrome is a multisystem disorder involving the cardiovascular, hepatobiliary, and central nervous / psychological systems.

Antipsychotics and Metabolic Syndrome

Notwithstanding the therapeutic effectiveness of antipsychotic drugs in many illnesses such as schizophrenia, increased attention has turned to the possible deleterious side-effects of these agents. Metabolic derangements associated with antipsychotic agents have been the focus of considerable interest and debate for many years. While metabolic syndrome affects all ages of patients who take antipsychotic medications, children and adolescents receiving atypical antipsychotic medications are particularly vulnerable to these effects.31 Notably, obesity-associated metabolic disease short of type 2 diabetes mellitus (i.e. dyslipidaemia and hypertension in the absence of type 2 diabetes mellitus) may be mechanistically linked to lower academic and professional potential in adolescents, as lower cognitive performance and reduction in brain structural integrity among adolescents with metabolic syndrome has been documented in studies.32

While there appears to be a dose-dependent relationship between the dose of clozapine or olanzapine and metabolic complications, aripiprazole, quetiapine, and ziprasidone do not show a causal relationship, and risperidone has mixed results.33

Antipsychotics and Weight Gain

Interestingly, an independent association between schizophrenia and physical illnesses that have a metabolic signature, including obesity, has been proposed, with several studies reporting significantly higher (p < 0.001) prevalences of overweight (body mass index [BMI] ≥ 25 kg/m²) and obesity (BMI > 30 kg/m²) in patients with psychotic disorders than in the general population.34 Drug-naive schizophrenia patients have also been found to have more than 3 times as much intra-abdominal fat (which

Table 2. Complications of metabolic syndrome.26-30

<table>
<thead>
<tr>
<th>System</th>
<th>Complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Coronary heart disease, atrial fibrillation,26 heart failure, aortic stenosis</td>
</tr>
<tr>
<td>Hepatobiliary</td>
<td>Non-alcoholic fatty liver disease27</td>
</tr>
<tr>
<td>Central nervous system / psychological</td>
<td>Ischaemic stroke, accelerated cognitive ageing, anger, depression, hostility28</td>
</tr>
<tr>
<td>Cancer</td>
<td>Breast, colon, gall bladder, kidney, prostate gland, hepatocellular carcinoma,29 and intrahepatic cholangiocarcinoma</td>
</tr>
<tr>
<td>Other</td>
<td>Obstructive sleep apnoea, association with psoriasis30</td>
</tr>
</tbody>
</table>

Table 3. Relationship between second-generation antipsychotic medications and metabolic abnormalities.38

<table>
<thead>
<tr>
<th>Drug</th>
<th>Weight gain</th>
<th>Risk for type 2 diabetes mellitus</th>
<th>Worsening lipid profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Risperidone</td>
<td>++</td>
<td>++ / +</td>
<td>+</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>++</td>
<td>++</td>
<td>++ / +</td>
</tr>
<tr>
<td>Aripiprazole*</td>
<td>+ / –</td>
<td>+ / –</td>
<td>+</td>
</tr>
<tr>
<td>Ziprasidone*</td>
<td>+ / –</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Amisulpride*</td>
<td>+ / –</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Paliperidone*</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Asenapine*</td>
<td>++ / +</td>
<td>+</td>
<td>D</td>
</tr>
<tr>
<td>Iloperidone*</td>
<td>++ / +</td>
<td>+</td>
<td>D</td>
</tr>
<tr>
<td>Bifeprunox*</td>
<td>+ / –</td>
<td>+ / –</td>
<td>D</td>
</tr>
</tbody>
</table>

Abbreviations: + = increased effect; – = no effect; D = discrepant results.
* Newer drugs with limited long-term data.
is correlated with insulin resistance) as age- and BMI-matched control participants, supporting the independent association between psychosis and weight gain. Additionally, weight gain typically occurs within the first 4 to 12 weeks of treatment and may not reach a plateau.

While the prevalence of obesity in the medicated schizophrenic population is currently estimated to range from 40 to 60% versus 30% of the general adult population, the differences between typical and atypical agents with regard to the risk for weight gain and disorders of carbohydrate and lipid metabolism remain unclear, although weight gain and carbohydrate and lipid metabolism disorders may be more common in patients taking atypical agents. Several studies have supported the claim that treatment with atypical antipsychotics was associated with more weight gain than treatment with typical antipsychotics.

Of the typical antipsychotics, lower potency agents (chlorpromazine and thioridazine) induce greater weight gain than higher potency drugs (fluphenazine and haloperidol). Typical antipsychotic-associated weight gain appears to be comparable for oral and depot formulations of the same drug. Of those atypical antipsychotics (SGAs), clozapine and olanzapine appear to have the greatest propensity to induce weight gain, quetiapine and risperidone have intermediate risk, followed by aripiprazole, ziprasidone, and amisulpride which carry the least risk (Table 3). Weight gain associated with risperidone and quetiapine does appear to correlate with dose, and newer antipsychotics such as bifeprunox, asenapine, iloperidone, and paliperidone are known to cause low weight gain.

The mechanism of antipsychotic-induced weight gain is undetermined, but several neurotransmitter systems have been implicated (Table 4). Olanzapine, which has the highest affinity for histaminic receptors, is associated with high rates of weight gain, while ziprasidone and aripiprazole, with lower affinities for histamine receptors, are associated with lower rates of weight gain. A genetic predisposition for aberrant folate metabolism and hyperhomocysteinaemia and genetic markers, such as 5-hydroxytryptamine (5-HT) 2C receptor and brain-derived neurotrophic factor, and blockade of the serotonin receptor 5-HT2C have also been linked to risk for weight gain.

### Antipsychotics and Diabetes Mellitus

Additional studies have found the prevalence of both diabetes and obesity to be 2 to 4 times higher in people with schizophrenia than in the general population, with overall prevalence estimates for diabetes among patients with schizophrenia ranging from 16 to 25%. Poor outcomes for diabetes in patients with schizophrenia are due to the reasons that their high rates of smoking (up to 75%) worsens the prognosis of diabetes and increases non-adherence to treatment for diabetes, which is estimated to be about 50%. Most cases of new-onset type 2 diabetes caused by antipsychotic medications occur within the first 6 months of treatment and are often, although not always, associated with significant weight gain or obesity. A family history of diabetes is also associated with an increased risk in this population.

A large population-based case-control study found the risk of diabetes associated with antipsychotic agents to be quite variable. Olanzapine and risperidone had 4.2 and 1.6 times the risk associated with conventional agents, and 5.8 and 2.2 times the risk associated with no treatment, respectively. Several large retrospective population studies have found that olanzapine and clozapine are associated with a significantly higher rate of diabetes than the other agents, with a particular risk for younger patients. Quetiapine appears to be more likely than conventional drugs to be associated with diabetes, but may ameliorate clozapine-related diabetes when given in conjunction with

### Table 4. Mechanisms of metabolic complications of antipsychotic medications

<table>
<thead>
<tr>
<th>Metabolic complication</th>
<th>Possible mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight gain</td>
<td>· Histamine receptor blockade</td>
</tr>
<tr>
<td></td>
<td>· Blockade of the serotonin receptor 5-HT2C</td>
</tr>
<tr>
<td></td>
<td>· Aberrant folate metabolism and hyperhomocysteinaemia</td>
</tr>
<tr>
<td></td>
<td>· Genetic markers, such as 5-HT2C receptors</td>
</tr>
<tr>
<td></td>
<td>· Brain-derived neurotrophic factor levels</td>
</tr>
<tr>
<td>Diabetes mellitus / hyperlipidaemia</td>
<td>· Weight gain</td>
</tr>
<tr>
<td></td>
<td>· Disruption of hypothalamic regulation of glucose serum levels</td>
</tr>
<tr>
<td></td>
<td>· Potent anticholinergic activity</td>
</tr>
<tr>
<td></td>
<td>· Hyperprolactinaemia</td>
</tr>
<tr>
<td></td>
<td>· Others:</td>
</tr>
<tr>
<td></td>
<td>· 5-HT2A / 5-HT2C antagonism</td>
</tr>
<tr>
<td></td>
<td>· Weight gain</td>
</tr>
<tr>
<td></td>
<td>· Leptin resistance</td>
</tr>
</tbody>
</table>

Abbreviation: 5-HT = 5-hydroxytryptamine.
clozapine. Data for aripiprazole and ziprasidone suggested that neither drug alters glucose homeostasis. Aripiprazole may even reverse diabetes caused by other drugs, although ketoacidosis has been reported with aripiprazole. Among the traditional neuroleptics, chlorpromazine and thioridazine are the agents most closely associated with diabetes mellitus, although the associations are weaker than those with olanzapine or clozapine. The prevalence of impaired glucose tolerance seems to be higher with aliphatic phenothiazines than with fluphenazine or haloperidol, although haloperidol has been reported to increase insulin resistance and to be associated with higher fasting glucose levels in obese women compared with control participants.

Interestingly, some studies have suggested that first-generation antipsychotics are no different from SGAs in their propensity to cause diabetes, whereas others have suggested a modest, but statistically significant excess incidence of diabetes with SGAs.

A number of mechanisms for antipsychotic medication–induced diabetes mellitus have been suggested, although none has been proven with certainty (Table 4). While drug-induced weight gain has been highly associated with diabetes, diabetes has occurred in the absence of weight gain, and hypothalamic dopamine antagonism by antipsychotic medications or disruption of hypothalamic regulation of glucose serum levels have been suggested, along with potent anticholinergic-induced inhibition of insulin secretion. Other mechanisms suggested include increased insulin resistance in peripheral tissues caused by hyperprolactinaemia, 5-HT2A / 5-HT2C antagonism, increased lipids, weight gain, and leptin resistance.

Antipsychotics and Hyperlipidaemia

Phenothiazines are known to be associated with increased levels of triglycerides and low-density lipoprotein cholesterol and a decreased level of high-density lipoprotein cholesterol. Higher cholesterol levels have been reported with chlorpromazine-treated patients than those receiving haloperidol. The CATIE study showed that of the atypical antipsychotic agents, olanzapine and quetiapine are associated with increases in total cholesterol levels and triglyceride levels. Notably, risperidone and ziprasidone are associated with decreases in cholesterol and triglyceride levels, and patients treated with clozapine have triglyceride levels that are almost double those treated with typical antipsychotic agents. Aripiprazole and ziprasidone have minimal adverse effects on blood lipids and may even reverse dyslipidaemias associated with previous antipsychotic use.

Although the exact mechanism of causation of hyperlipidaemia is unknown, one or more of the mechanisms described above as causes for antipsychotic medication–induced diabetes mellitus (Table 3) may be involved in the pathogenesis.

Typical versus Atypical Antipsychotic Medications in Metabolic Syndrome

Although most of the emphasis on metabolic syndrome is aimed at SGAs, several studies have failed to detect differences in the prevalences of metabolic syndrome between patients taking SGAs and those taking conventional antipsychotic agents. It may be possible that the effects of conventional antipsychotic agents on metabolic symptoms have been underestimated. Support for this possibility comes from a study that compared olanzapine and haloperidol in patients with first-episode psychosis—a group of patients who were comparatively free of previous treatment and symptom chronicity. After 2 years, patients taking olanzapine had gained a mean of 33.9 lb (15.4 kg), and those taking haloperidol had gained 16.5 lb (7.5 kg) — a considerable weight gain indicating that typical antipsychotic agents are associated with weight gain and related metabolic abnormalities. A recent systematic review compared the metabolic effects among the different SGAs and showed that clozapine and olanzapine had the highest incidences.

Management Strategies for Metabolic Syndrome

The following strategies have been suggested for directly caused adverse effects of antipsychotic agents on glucose–insulin homeostasis and lipid metabolism:

1. Patients with previously diagnosed diabetes mellitus and / or hyperlipidaemia should be given conventional antipsychotic agents or atypical agents such as aripiprazole, which have no or few effects on glucose-insulin homeostasis and lipid metabolism.

2. For patients who develop hyperinsulinaemia and / or hyperlipidaemia during treatment with clozapine, olanzapine, or structurally related agents, a change to an antipsychotic drug with no or minimal capability to induce such adverse metabolic effects should be considered, or maintenance therapy with the lowest effective dose possible, together with regular follow-up of metabolic parameters and appropriate treatment whenever necessary, is advised.

3. For patients who develop diabetes mellitus during therapy with antipsychotic agents, a change to an antipsychotic agent with no or little propensity to cause the condition is the first recommendation. For patients taking clozapine, the lowest effective dose possible should be given, with clinical evaluation and determination of serum antipsychotic concentration, along with concomitant therapy for hyperlipidaemia / hyperglycaemia.

General Advice for Prevention of the Development of Metabolic Syndrome

1. All patients who are going to start treatment with, or
are already using an antipsychotic drug with high or intermediate propensity to induce weight gain should undergo regular monitoring of weight and lifestyle modifications / therapy such as dietary adjustments, weight reduction, and physical training, if necessary.

2. If such a patient gains a considerable amount of weight or has become overweight or obese already, a change of the antipsychotic agent to a less weight-inducing drug should be considered. Another possibility to decrease antipsychotic-induced weight gain may be dose reduction. In the general population, controlled clinical trials have established modest efficacy for obesity drugs in combination with lifestyle therapy.\(^{63}\) Orlistat (a lipase inhibitor) and sibutramine (a serotonin-dopamine-norepinephrine reuptake inhibitor) are the only drugs currently approved for long-term weight loss.

3. Interventions to stop cigarette smoking and to reduce physical inactivity are also of great importance in decreasing the risk of insulin resistance and type 2 diabetes mellitus in patients treated with antipsychotic agents.\(^{63}\)

4. In order to further decrease the risk for development of insulin resistance and type 2 diabetes mellitus in antipsychotic medication–treated patients, daytime sedation caused by these drugs, leading to physical inactivity, has to be recognised and handled properly.\(^{63}\)

5. Psychiatrists also have to be aware of those antipsychotic medication–treated patients who are older, have a family history of type 2 diabetes mellitus, and/or are of an ethnic group with high genetic susceptibility to type 2 diabetes mellitus (e.g. American Indians, Mexican Americans, and Hispanics) and, therefore, have an increased risk of developing insulin resistance and type 2 diabetes mellitus.\(^{63}\)

Screening and Monitoring during the Use of Antipsychotic Medications

In view of the evidence for an increased prevalence of metabolic syndrome in schizophrenia, individuals presenting with a first episode of psychosis should be screened using the appropriate diagnostic criteria.\(^{15}\) According to the Maudsley guidelines,\(^{40}\) metabolic parameters should be measured with the frequency as described below:

1. Plasma glucose (fasting blood sample, if possible) should be done at baseline, at 4 to 6 months, and then yearly. Ideally, all patients should have oral glucose tolerance tests performed as this is the most sensitive method of detection of diabetes mellitus. Fasting plasma glucose tests are less sensitive but are still recommended.

2. Blood pressure should be measured at the baseline and frequently during dose titration.

3. Fasting blood lipids (cholesterol and triglycerides) should be measured at baseline, at 3 months, and then yearly. Patients prescribed clozapine, olanzapine, quetiapine, or phenothiazines should ideally have their serum lipids measured every 3 months for the first year of treatment.

4. Weight (including waist circumference and BMI, if possible) should be measured at baseline, frequently for 3 months, and then yearly.

Conclusion

In summary, while many adults with schizophrenia receive little or no medical care, such care is important given the risk of metabolic abnormalities and metabolic syndrome associated with schizophrenia and with the antipsychotic medications used to treat the condition. There is a need for active routine physical health screening of all individuals receiving treatment with antipsychotic drugs. The implementation of such guidelines can substantially improve the health of patients with schizophrenia. However, adopting the guidelines in clinical practice can be challenging.

References


12. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and...


