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METABOLIC COMORBIDITY IN SCHIZOPHRENIA

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ABSTRACT

People with schizophrenia are at greater risk of developing obesity, type 2 diabetes, hypertension and dyslipidemia as compared to the general population. This results in an increased incidence of cardiovascular disease, leading to greater morbidity and mortality in this vulnerable group of patients. Use of certain antipsychotic agents can compound this risk and increase the risk of developing metabolic syndrome. Appropriate identification and management of these risk factors are very important in reducing the risk and thereby improving the physical health of these patients. This review recommends a framework based on existing guidelines for the assessment, monitoring and management of patients with schizophrenia in the Indian setting.

Key words: Antipsychotics, diabetes, dyslipidemia, hypertension, metabolic syndrome, obesity, schizophrenia

INTRODUCTION

People with severe mental illness, especially schizophrenia, suffer from increased morbidity and mortality compared with the general population, having a life expectancy that is approximately 20% shorter.[1] In a meta-analysis of 18 international studies, 60% of excess mortality in schizophrenia was attributable to physical illness, with cardiovascular disease being the major contributor.[2] People with schizophrenia are reported to be twice as likely to die from cardiovascular disease than those in the general population,[3] with coronary heart disease being the leading cause of death.[4]

Several levels of evidence, from data linkage analyses to clinical trials, demonstrate that treatment-related metabolic disturbances are commonplace in this patient group and that the use of certain second-generation antipsychotics may compound the risk of developing the metabolic syndrome and cardiovascular disease. First-generation antipsychotics or typical antipsychotics have also been linked to increased risk of developing this complication.[5] In addition, smoking, poor diet, reduced physical activity and alcohol or drug abuse are prevalent in people with schizophrenia and contribute to the overall cardiovascular risk.

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Management and minimization of metabolic risk factors are thus pertinent when providing optimal care to patients with schizophrenia.

WHAT IS METABOLIC SYNDROME?

Abdominal obesity, hyperglycemia, hypertension and dyslipidemia are key components of the metabolic syndrome, a constellation of cardio-metabolic risk factors linked by their common association with insulin resistance.[6] Evidence from large clinical samples indicates a high prevalence of metabolic syndrome and all of its components in persons with serious mental illness, particularly in patients with schizophrenia. In addition, psychotropic agents, including some antipsychotic medications, are associated with substantial weight gain, as well as with adiposity-dependent and possibly adiposity-independent changes in insulin sensitivity and lipid metabolism, which increase the risk of diabetes and cardiovascular disease. Among the second-generation antipsychotics, Clozapine and Olanzapine are associated with the highest risk of substantial weight gain, similar to the weight gain potential associated with low-potency first-generation antipsychotics such as thioridazine or chlorpromazine, as well as with an increased risk of diabetes and dyslipidemia.

DEFINITION OF METABOLIC SYNDROME

Definitions of metabolic syndrome have been proposed by two bodies, and it is recommended to follow either of these [Table 1].

Epidemiology

The prevalence of metabolic syndrome in the USA is estimated to be 27%.[10] One study from India done in Chennai reported a prevalence of 11.2%.[11]

We aim to address the following clinical questions:

1. How common are metabolic risk factors in people with schizophrenia and what is their impact?
2. What is the evidence that metabolic disturbances emerge with antipsychotic treatment in this population?
3. How can metabolic risk be minimized and what are the most appropriate ways of monitoring and assessing the risk?

Table 1: Definitions of metabolic syndrome

Risk factor	NCEP/ATPIII (2002)*	WHO (1998)**
	Three or more of…	Diabetes mellitus, impaired glucose tolerance, impaired glucose or insulin resistance, plus two or more of…
Abdominal obesity	Waist circumference***	BMI >30 kg/m^2 and/or waist-to-hip ratio
Men	>102 cm (>40 in)	>0.90
Women	>88 cm (35 in)	>0.85
Triglycerides	At least 150 mg/dl or more	At least 150 mg/dl or more
HDL-cholesterol		
Men	Less than 40 mg/dl	Less than 35 mg/dl
Women	Less than 50 mg/dl	Less than 39 mg/dl
Blood pressure	More than 130/85 mmHg	At least 140/90 mmHg
Fasting glucose	>110 mg/dl	>110 mg/dl

*Third report of the National Cholesterol Education Programme (NCEP) expert panel on detection, evaluation and treatment of high blood cholesterol in adults (adult treatment Panel III)[7]; **World Health Organization[8]; ***Waist circumference for Asians is generally lower, requiring a lower cutoff of 90 cm in men (instead of 102 cm in the NCEP definition) or 80 cm in women (instead of 88 cm), when assessing the presence of central obesity[9]

4. If metabolic risk develops, how should it be managed and treated?

Schizophrenia, mortality and cardiovascular disease

It is likely that the high rates of cardiovascular disease seen in individuals with schizophrenia are connected to the increased rates of obesity,[12] lipid abnormalities,[13] diabetes,[14] hypertension[15] and smoking[16] seen in this population. The association with hypertension is a controversial issue, with some studies finding a decreased risk of hypertension in persons with schizophrenia compared with the general population.[5]

The increased risk of cardiovascular mortality may also be a result of increased prevalence of metabolic syndrome. There is a fourfold risk of metabolic syndrome in young patients with schizophrenia compared with the general population,[17] and it has been suggested that around 50% of persons with schizophrenia may be affected.[15] In general, the risk of metabolic syndrome is much higher among young patients than in the general population; but in patients aged over 55 years, the prevalence of metabolic syndrome in patients with schizophrenia may not differ from that in the general population.[5]

Obesity and schizophrenia

Overweight and obesity is a particular problem in individuals with schizophrenia compared with the general population.[17] This is probably accounted for by multitude of factors like sedentary life style, poor dietary habits, lack of exercise, use of drugs and alcohol and use of antipsychotic drugs.

Weight gain and second-generation antipsychotics (atypical antipsychotics)

Atypical antipsychotics are being increasingly used as first-line agents to treat people with schizophrenia. They are currently recommended by NICE (National Institute of Clinical Excellence, UK) as first-line agents. These agents have less risk of producing extra-pyramidal symptoms and tardive dyskinesia but, except for clozapine, do not have greater advantage in improvement of cognitive symptoms and are fairly comparable in their efficacy with first-generation antipsychotics in controlling symptoms, as shown in the CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) and CUTLASS (Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study) studies;[18,19] but existing studies show that they have a strong association with production of metabolic syndrome in patients treated with these agents [Table 2].

Treatment with Clozapine or Olanzapine is associated with the greatest weight gain, approximately 10 times the placebo-induced incidence; whereas for aripiprazole and risperidone therapy, this is only twofold.[22] Results from long-term clinical trials showed that during a 1-year period, aripiprazole and

Table 2: Weight-gain effect of second-generation antipsychotics

Authors	*Studies*	*Duration*	*Drug*	*Mean weight change from baseline*
Nemeroff[20]	4 RCT	28/52 weeks	Clozapine	10 kg/12 kg
Lieberman[21]	CATIE study	18 months	Olanzapine	4.26 kg
			Quetiapine	0.5 kg
			Risperidone	0.36 kg

ziprasidone are associated with a mean weight gain of approximately 1 kg; with quetiapine and risperidone, 2-3 kg; and with olanzapine, more than 6 kg.[23]

Diabetes and schizophrenia

Diabetes is an increasing worldwide public health problem. Rates for diabetes in patients with schizophrenia are approximately double those reported for the general population.[3]

Diabetes and antipsychotics

Both typical and atypical antipsychotics have been associated with increased risk of diabetes in patients with schizophrenia.[24,25] The volume of published literature would suggest that there is a definite link between diabetes and clozapine and olanzapine among atypical antipsychotics in particular, as well as other antipsychotics.

This is substantiated by the results from a large number of large retrospective studies using information from several different databases.

The Clinical Antipsychotic Trials of Intervention Effectiveness study provides randomized clinical trial evidence that supports the findings from case reports and smaller head-to-head studies.[21] Here all study drugs investigated resulted in some degree of increase in glucose metabolism measures with regards to blood glucose; the greatest increase from baseline was seen with Olanzapine (15 mg/dl), whereas Quetiapine and Risperidone demonstrated much lesser effects (6.8 mg/dl and 6.7 mg/dl respectively).

Nevertheless, the study does have limitations as not all samples for metabolic testing were fasting, and patients with preexisting diabetes were pooled with those without diabetes. Using a case-control design and a population-based UK sample, Koro *et al*. reported a significant greater risk of developing diabetes in patients on olanzapine in comparison with healthy controls (OR: 5.8; 95% CI: 2.0-16.7).[26]

There are currently no published databases analyses examining the incidence of diabetes associated with Zotepine, Amisulpiride and Aripiprazole treatment. Published data from Aripiprazole is limited because of its recent introduction, but reports from clinical trials suggest that Aripiprazole treatment is not associated with increased risks of diabetes. There were no clinically significant changes in fasting plasma glucose from baseline during 26 weeks of treatment.[27]

Dyslipidemia, schizophrenia and second-generation antipsychotics

The occurrence of dyslipidemia among patients with schizophrenia has been less well studied than the incidence of diabetes and obesity. A number of abnormal lipid profiles have been reported in the context of treatment with second-generation antipsychotics, usually in association with increased body mass.[5] Elevated fasting plasma triglyceride is an important signal for potential insulin resistance.

One of the largest studies from the UK used data from approximately 19,600 individuals with a diagnosis of schizophrenia from the general practice research database.[28] This study compared the odds ratios for developing dyslipidemia after receiving first- and second-generation antipsychotics. Dyslipidemia was

much more common with those receiving olanzapine treatment when compared with no antipsychotic treatment (OR: 4.5; $P < 0.001$) and with typical antipsychotic treatment (OR: 3.36; $P < 0.001$). In contrast, risperidone was not associated with increased risk of these complications. In one study from India published this year, there was a significant elevation in triglycerides after a 6-week trial of olanzapine and risperidone in drug-naïve patients with schizophrenia.[29] The National Cholesterol Education Programme and ATP III (Adult Treatment Panel) have identified cholesterol as the primary target for reducing risk for cardiovascular diseases.[7]

Schizophrenia as an independent risk factor for metabolic disease

Although there is clear evidence that antipsychotic drugs add to the burden of metabolic disease in patients with schizophrenia, there is increasing evidence that having the illness schizophrenia itself is a risk factor. Rates of type 2 diabetes in family members of patients with schizophrenia are between 19 and 31%, far higher than in the background population, which adds support to the hypothesis that schizophrenia and diabetes may be linked independently of medication.[30] It also has been reported that the first episode and drug-naïve schizophrenia population had higher incidence of intra-abdominal obesity as compared to healthy controls.[31]

Mechanism of antipsychotic-induced metabolic dysfunction

Mechanisms underlying antipsychotic-induced weight gain are multifactorial and may include blockade at the cholinergic, sertonergic and histamenergic sites. Studies in pre-clinical models have reported marked increases in adiposity, hepatic insulin resistance and beta cell dysfunction following olanzapine.[32] Also clozapine and olanzapine, as well as other antipsychotics, have been shown to induce insulin resistance.

RECOMMENDATIONS FOR ASSESSING, MONITORING AND MANAGING METABOLIC RISK

Initial evaluation should include a complete medical history, looking into personal and family history of obesity, diabetes, dyslipidemia, hypertension, smoking and family history of cardiovascular disease. Enquiry should also be made about diet, life style, exercise, alcohol and substance use.[33] Age, gender and ethnicity should also be noted as certain ethnic groups have increased risk of developing cardiovascular disease.

Physical examination should include checking blood pressure, measuring height and weight and calculating body mass index, as well as complete systemic examination.

Fasting blood glucose, serum lipids should also be measured before initiating the patient on an antipsychotic.[34]

Choice of the antipsychotic should be made considering previous response, metabolic parameters of the patient, side-effect profile of the drug, as well as patient preference. Studies have shown that all antipsychotics are comparable in their efficacy, so choice of a drug should be based primarily looking at the side-effect profile and propensity to cause metabolic syndrome. Education and advice

should be given about life style changes such as healthy diet, moderate exercise, weight control measures and cutting down smoking and alcohol. Interventions may include closer monitoring of weight, engagement in a weight management program, use of an adjunctive treatment to reduce weight or changes in a patient's antipsychotic medication. If a patient is taking a medication that is associated with a higher risk for weight gain, the mental health care provider should consider switching the medication to one with less weight gain liability.

Ongoing monitoring of patients receiving second-generation antipsychotics

Several guidelines have been published for the ongoing monitoring of patients on antipsychotics, e.g., Expert Consensus Guidelines 2003, guidelines by the American Diabetes Association and other agencies. We would suggest the following guidelines [Table 3].[35]

BMI should be calculated by measuring height and weight, and WHO classification should be used. Ethnicity should be considered when determining weight classification, particularly in the South Asian population, for whom the definition of overweight varies from >23 kg/m^2 and obesity from 25 kg/m^2. Measurement of waist circumference is ideal, but we feel it is intrusive and may be less practical in a psychiatric setting.

Management of metabolic risk factors in individuals with schizophrenia already maintained on antipsychotics

If there is weight gain corresponding to 1 BMI unit or more than 5% increase in weight, we recommend switching to a drug with lesser metabolic side effect profile. Cross-titration is advised rather than abrupt withdrawal.

Management of high blood pressure

Appropriate antihypertensive medication should be started if the patient shows consistently high blood pressure readings - more than 160/100 mmHg or more than 140/90 mmHg with diabetes. Certain antipsychotic medications may contribute directly to cardiovascular risk with occurrence of arrhythmias and sudden death,[36,37] and recommendations for cardiovascular monitoring have been made.[34]

Management of dyslipidemias

Appropriate medication for elevated lipids should be started as per accepted guidelines for managing patients with these disorders.

Relevance to Indian setting

Indians in particular are more prone to develop metabolic side effects such as diabetes mellitus, dyslipidemias and cardiovascular disease.[38]

Table 3: Monitoring protocol for metabolic syndrome

	Base line	*1st month*	*2nd month*	*3rd month*	*6th month*	*9th month*	*12th month*
WT	*	*	*	*	*	*	*
BMI	*	*	*	*	*	*	*
BP	*			*			*
Fasting blood sugar (AC)	*			*			*
Serum Cholesterol	*			*			*
Triglycerides	*			*			*
HDL	*			*			*
LDL	*			*			*

Asian Indians have a high prevalence of insulin resistance syndrome that may underlie their greater-than-normal tendency to develop diabetes mellitus and early atherosclerosis. Important reasons could be their excess body fat and adverse body fat patterning, including abdominal obesity, even when the body mass index is within the currently defined limits. Underlying genetic tendency or early life adverse events may contribute to such a phenotype, but life style factors or modulated inherited factors appear to play an important role because obesity and dyslipidemia become worse with urbanization and migration.[39] A recent prospective study done in India in previously drug-naïve patients with schizophrenia revealed an increased incidence of metabolic syndrome, of 31.81% cases, after 6 weeks of therapy with a single antipsychotic drug in comparison of an incidence of 3.33% at baseline.[29]

Routine screening for these conditions does not happen as regularly, especially in large psychiatric units and hospitals. Death rates among psychiatric inpatients in mental hospitals across India are still high, with a high proportion having unexplained deaths.

There is an urgent need for carrying out well-designed studies to identify prevalence and incidence of these disorders in patients with schizophrenia, promoting more awareness among colleagues and health-care professionals, as well as to identify and treat risk factors associated with these conditions. Consistency in monitoring and measuring metabolic parameters is paramount - so that treatable high-risk patients can be identified and managed, thereby reducing morbidity and mortality. We would recommend the monitoring scheme recommended above to be used uniformly across the country so that overall physical health of these patients can be improved.

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