SPECIAL ARTICLE

Metabolic syndrome in people with schizophrenia: a review

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Metabolic syndrome and other cardiovascular risk factors are highly prevalent in people with schizophrenia. Patients are at risk for premature mortality and overall have limited access to physical health care. In part these cardio-metabolic risk factors are attributable to unhealthy lifestyle, including poor diet and sedentary behaviour. But over recent years it has become apparent that antipsychotic agents can have a negative impact on some of the modifiable risk factors. The psychiatrist needs to be aware of the potential metabolic side effects of antipsychotic medication and to include them in the risk/benefit assessment when choosing a specific antipsychotic. He should also be responsible for the implementation of the necessary screening assessments and referral for treatment of any physical illness. Multidisciplinary assessment of psychiatric and medical conditions is needed. The somatic treatments offered to people with severe and enduring mental illness should be at par with general health care in the non-psychiatrically ill population.

Key words: Metabolic syndrome, schizophrenia, antipsychotics

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People with severe mental illnesses (SMI), such as schizophrenia, have a reduced life expectancy compared to the general population (1-13). They have a 2-3 fold increased risk of dying, and this mortality gap associated with mental illness compared to the general population has widened in recent decades (13). People with severe mental illness have nearly twice the normal risk of dying from cardiovascular disease (CVD) (1-13).

In the psychiatric community, this has led in recent years to a growing concern about physical illness in people with SMI, specifically CVD risk (14-24). People with SMI are more likely to be overweight, to smoke and to have hyperglycaemia/diabetes, hypertension and dyslipidaemia (Table 1). With an overall increased risk of somatic comorbidities, patients with schizophrenia have poorer access and quality of physical health care (7,25-27).

In part these cardio-metabolic risk factors are attributable to unhealthy lifestyle, including poor diet and sedentary behaviour. But over recent years it has become apparent that antipsychotic agents (AP) can have a negative impact on some of the modifiable risk factors (7,14,15-42) (Table 2). Part of this negative impact can be explained by the liability of some antipsychotics to induce significant weight gain. A recent study indicates that these metabolic changes are dose independent (42).

Metabolic syndrome (MetS) brings together a series of abnormal clinical and metabolic findings which are predictive of CVD risk, though there is continuing debate around the use of the term (44-50). The causes of MetS are not fully understood, but there is a central role of visceral adiposity and insulin resistance. The most commonly used definitions for the MetS are the Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program (NCEP) (46), and the adapted ATP III-A proposed by the American Heart Association following the American Diabetes Association lowering of the threshold for impaired fasting glucose to 100 mg/dl (45,47). A more recent definition, by the International Diabetes Federation (45,49), stressed the importance of waist circumference, using both more stringent and ethnic/race specific criteria (Table 3).

In the general population, the presence of MetS is a strong predictor of CVD, CVD mortality and diabetes (50-58).

Table 1 Estimated prevalence and relative risk (RR) of modifiable cardiovascular disease risk factors in schizophrenia and bipolar disorder compared to the general population (from 16)

	Estimated prevalence, % (RR)	
Modifiable risk factors	**Schizophrenia**	**Bipolar disorder**
Obesity	45-55 (1.5-2)	21-49 (1-2)
Smoking	50-80 (2-3)	54-68 (2-3)
Diabetes	10-15 (2)	8-17 (1.5-2)
Hypertension	19-58 (2-3)	35-61 (2-3)
Dyslipidaemia	25-69 (≤5)	23-38 (≤3)
Metabolic syndrome	37-63 (2-3)	30-49 (1.5-2)

Table 2 Second generation antipsychotic agents and metabolic abnormalities (14,41,107-109)

Antipsychotic	Weight gain	Risk for diabetes	Worsening lipid profile
Clozapine	+++	+	+
Olanzapine	+++	+	+
Risperidone	++	?	?
Quetiapine	++	?	?
Aripiprazole	±	No report	No report
Ziprasidone	±	No report	No report
Amisulpride	±	No report	No report

Table 3 Definitions of metabolic syndrome (45-48)

	ATP III (3 out of 5 criteria required)	ATP III A (3 out of 5 criteria required)	IDF (waist plus 2 criteria required)
Waist (cm)	M >102, F >88	M >102, F >88	M ≥94, F ≥80
Blood pressure	≥130/85*	≥130/85*	≥130/85*
HDL (mg/dl)	M <40, F <50	M <40, F <50	M <40, F <50
Triglycerides (≥150 mg/dl)	≥150	≥150	≥150
Glucose (mg/dl)	≥110**	≥100**	≥100**

ATP – Adult Treatment Protocol; IDF – International Diabetes Federation
*or treated with antihypertensive medication; **or treated with insulin or hypoglycaemic medication.

A joint statement from the American Diabetes Association and the European Association for the Study of Diabetes concluded recently that the metabolic syndrome has been imprecisely defined, there is a lack of certainty regarding its pathogenesis, and there is considerable doubt regarding its value as a CVD risk marker. They recommended that, until further research has been carried out, clinicians should evaluate and treat all CVD risk factors whether or not patients meet the criteria for diagnosis of the MetS (59,60).

The concept of MetS has found its way into the psychiatric literature, helping psychiatric clinicians to focus more on CVD risk in patients treated with antipsychotics (34,35,61).

We conducted a systematic review on the prevalence and incidence of metabolic syndrome in patients suffering from schizophrenia. A literature search for relevant articles was carried out in two steps. First, articles published until August 1, 2008 were identified by PubMed search, using metabolic syndrome, antipsychotic(s), psychotic disorder and schizophrenia as key words. Second, a hand search was conducted based on the bibliography of the identified articles.

Since the first paper on MetS in patients with schizophrenia published in 2003, more than 30 studies have become available. Prevalence and incidence studies using different MetS criteria are shown in Tables 4 and 5 (62-99). Studies in different ethnic groups consistently show elevated prevalences of MetS in patients with schizophrenia. If population comparison data are available, the rates of MetS are 2 to 3 fold higher in patients. In studies where a comparison was possible between antipsychotic medications, a differential relative metabolic risk between agents was confirmed.

In the largest study, the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), approximately one third of patients met NCEP criteria for metabolic syndrome at baseline (82,83). A troubling finding was that 88% of patients with dyslipidaemia were not receiving treatment, as were 62% of the hypertensive patients and 38% of those with diabetes (100). Some antipsychotic agents were associated with more significant adverse effects on weight, lipids, and glucose metabolism than others (25,41,84).

A large Belgian study found similar rates of MetS, which were 2 to 3 fold higher than in an age-adjusted population sample (71,72). The prevalence of diabetes per age-band was 4-5 times higher in schizophrenia patients than in the general population.

In a recent study of metabolic syndrome in patients diagnosed with schizophrenia in 2000-2006 compared to 1984-1995, those started on second generation antipsychotics (SGA) had over twice the rate of new incident cases of metabolic syndrome after three years, compared to those treated with first generation antipsychotic agents (27.8% vs. 9.8%) (73). In patients without metabolic syndrome at baseline, the risk of developing this combination of metabolic abnormalities was significantly greater in patients started on SGA (odds ratio 3.6).

For the increased risk of MetS and other metabolic abnormalities in patients with schizophrenia, three complementary and partially overlapping causes are put forward in the literature: lifestyle factors, aspects of the psychotic disorder and antipsychotic medication. A number of recent studies explore the underlying genetic risk for the development of metabolic abnormalities (76,85,101). Future studies will need to address possible gene-environment interactions with specific antipsychotic agents (101).

People with schizophrenia on average have a lifestyle which increases their risk for the development of MetS: sedentary lifestyle, lack of regular physical activity, poor food intake, substance use and high rates of smoking (25,38,39). Part of these lifestyle factors are influenced by aspects of the illness such as negative symptoms and vulnerability to stress. Older studies have showed an increased liability 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 (21,25,39). Also, some studies have showed increased visceral adiposity, elevated glycaemia and higher cortisol levels in first-episode patients before treatment (25,40,41). A recent study showed that people with schizoaffective disorder have a higher vulnerability to develop MetS compared to people with bipolar disorder or schizophrenia (99).

The increased risk to develop MetS under antipsychotic agents is in part related to their propensity to induce weight gain. Although all antipsychotics can induce weight changes, the relative risk to induce clinically relevant weight changes (>7% increase) is clearly different between antipsychotic agents (25,29,31). In up to 25% of cases of MetS under antipsychotic treatment, no weight gain or increased abdominal adiposity was present, suggesting a direct link between

Table 4 Prevalence of metabolic syndrome (MetS) in people with schizophrenia

Study	Country	N	Design	Mean age	% MetS	Criteria
Heiskanen et al (78)	Finland	35		44.5	37.1	ATP III
Almeras et al (62)	Canada	42	Olanzapine	31.7	33.0	ATP III
	Canada	45	Risperidone	28.4	11.0	ATP III
Basu et al (65)	USA	33	Schizoaffective disorder	44.5	42.4	ATP III
Cohn et al (68)	Canada	240		42.7	44.6	ATP III
Kato et al (80)	USA	48		40.3	63.0	ATP III
Straker et al (96)	USA	89		39.8	29.2	ATP III
Meyer et al (83)	USA	1231		42.8	35.8	ATP III
McEvoy et al (82)	USA	342	White males	39.8	40.9	ATP III
		92	White females	44.2	56.2	ATP III
Saari et al (88)	Finland	31		31.0	19.4	ATP III
Correll et al (69)	USA	367		42.9	37.3	ATP III
De Hert et al (71)	Belgium	430		36.5	32.3	ATP III-A
De Hert et al (72)	Belgium	415		37.7	33.3	IDF
		100	First episode (maximal duration 2 year illness)	25.7	17.0	IDF
		130	Duration illness <10 years	29.0	28.5	IDF
		106	Duration illness 10 to 20 years	39.0	42.4	IDF
		79	Duration illness >20 years	49.8	49.4	IDF
Hagg et al (77)	Sweden	269		46.0	34.6	ATP III
Lamberti et al (81)	USA	93	Clozapine	34.4	53.8	ATP III
Meyer et al (84)	USA	80		49.0	51.2	ATP III
Bobes et al (66)	Spain	1452		40.7	24.6	ATP III
Correll et al (70)	USA	294	Antipsychotic monotherapy	43.6	34.3	ATP III
De Hert et al (73)	Belgium	208	3 months after start antipsychotics	33.7	27.9	ATP III-A
		23	3 months after start amisulpride	33.7	13.0	ATP III-A
		31	3 months after start aripiprazole	33.7	9.7	ATP III-A
		25	3 months after start clozapine	33.7	56.0	ATP III-A
		54	3 months after start olanzapine	33.7	33.3	ATP III-A
		25	3 months after start quetiapine	33.7	32.0	ATP III-A
		50	3 months after start risperidone	33.7	24.0	ATP III-A
L'Italien et al (79)	USA	155	Placebo trials, placebo endpoint	41.4	25.8	ATP III
		267	Placebo trials, aripiprazole endpoint	40.7	19.9	ATP III
		373	Active comparator trials, olanzapine endpoint	37.7	41.6	ATP III
		380	Active comparator trials, aripiprazole endpoint	37.6	27.9	ATP III
Mulder et al (85)	Netherlands	112		36.0	25.0	ATP III
Sicras-Mainar et al (94)	Spain	742	Different diagnosis treated with antipsychotics	55.1	27.0	ATP III
		57		37.5	35.0	IDF
Srisurapanont et al (95)	Thailand	38		53.7	36.2	ATP III
		44		44.3	31.8	ATP III-A
Suvisaari et al (97)	Finland	108		34.6	34.0	ATP III-A
Teixeira and Rocha (98)	Brazil	122	First episode, before treatment with FGA	23.1	5.7	ATP III-A
		122	First episode, 3 year FGA	26.8	13.1	ATP III-A
Cerit et al (67)	Turkey	108	First episode, before treatment with SGA	21.9	5.6	ATP III-A
De Hert et al (74)	Belgium	108	First episode, 3 year SGA	25.1	31.6	ATP III-A
		2270		41.0	33.9	ATP III-A
De Hert et al (75)	Europe	58		36.3	40.0	ATP III-A
Ellingrod et al (76)	USA	99	First episode after treatment	26.1	18.2	IDF
Saddichha et al (90)	India	433		38.0	34.0	ATP III
Schorr et al (91)	Netherlands	53		35.0	45.0	ATP III
Schorr et al (92)	Netherlands	260		28.0	35.0	ATP III
Schorr et al (93)	Netherlands	503	Schizophrenia	34.8	28.8	ATP III-A
van Winkel et al (99)	Belgium	92	Schizoaffective disorder	40.7	50.0	ATP III-A

FGA – first-generation antipsychotic; SGA – second generation antipsychotic; ATP - Adult Treatment Panel; IDF - International Diabetes Federation

the antipsychotic agent and the development of metabolic abnormalities (25). Some authors link the receptor profile of antipsychotics to their differential liability to induce weight gain and other metabolic changes (25,29,33,41). Antagonism for muscarinergic receptors could lead to more pronounced weight gain. Antipsychotics can lead to increased appetite by interfering with the dopamine reward system (32). There is emerging data that glucose abnormalities can occur soon after initiation of treatment and that these can be reversible after discontinuation of medication, indicating a direct effect on pancreatic function (25,38, 39,42).

Growing evidence suggests that children and adolescents who take antipsychotic medication are at higher risk of weight gain and metabolic effects than adults who use the same drugs (102-104).

Table 5 Incidence of metabolic syndrome (MetS) in people with schizophrenia

Study	Country	N	Design	Mean age	% MetS	Criteria
De Hert et al (71)	Belgium	31	Baseline aripiprazole	36.7	61.3	ATP III-A
			Endpoint aripiprazole	36.7	29.0	ATP III-A
Attux et al (64)	Brazil	44	First episode 6 months	26.3	6.8	ATP III
De Hert et al (73)	Belgium	155	After 3 months SGA	33.7	18.7	ATP III-A
		16	After 3 months amisulpride	33.7	6.3	ATP III-A
		16	After 3 months aripiprazole	33.7	0.0	ATP III-A
		20	After 3 months clozapine	33.7	45.0	ATP III-A
		45	After 3 months olanzapine	33.7	24.4	ATP III-A
		21	After 3 months quetiapine	33.7	19.1	ATP III-A
		37	After 3 months risperidone	33.7	10.8	ATP III-A
L'Italien et al (79)	USA	91	Placebo trials, placebo	41.4	14.3	ATP III
		151	Placebo trials, aripiprazole	40.7	5.3	ATP III
		212	Active comparator trials, olanzapine	37.7	27.4	ATP III
		198	Active comparator trials, aripiprazole	37.6	15.7	ATP III
Saddichha et al (89)	India	30	First episode 6 weeks	26.9	27.5	IDF
Srisurapanont et al (95)	Thailand	35	Naturalistic 1 year follow-up	34.7	20.0	IDF
De Hert et al (74)	Belgium	122	First episode, 3 year FGA	26.8	9.8	ATP III-A
		108	First episode, 3 year SGA	25.1	27.8	ATP III-A
		8	First episode, 3 year amisulpride	25.1	12.5	ATP III-A
		10	First episode, 3 year aripiprazole	25.1	0.0	ATP III-A
		12	First episode, 3 year clozapine	25.1	50.0	ATP III-A
		34	First episode, 3 year olanzapine	25.1	41.3	ATP III-A
		24	First episode, 3 year quetiapine	25.1	12.6	ATP III-A
		20	First episode, 3 year risperidone	25.1	10.2	ATP III-A
Meyer et al (84)	USA	164	Baseline olanzapine	40.9	34.8	ATP III-A
			After 3 months olanzapine	40.9	43.9	ATP III-A
		147	Baseline risperidone	40.9	30.6	ATP III-A
			After 3 months risperidone	40.9	30.6	ATP III-A
		143	Baseline quetiapine	40.9	37.8	ATP III-A
			After 3 months quetiapine	40.9	37.1	ATP III-A
		77	Baseline ziprasidone	40.9	37.7	ATP III-A
			After 3 months ziprasidone	40.9	29.9	ATP III-A
		129	Baseline perphenazine	40.9	37.2	ATP III-A
			After 3 months perphenazine	40.9	38.0	ATP III-A
Schorr et al (93)	Netherlands	260	12 months incidence	41.0	14.0	ATP III
			12 months reversibility	37.0	33.0	ATP III

FGA – first-generation antipsychotic; SGA – second generation antipsychotic; ATP - Adult Treatment Panel; IDF - International Diabetes Federation

GUIDELINES FOR SCREENING AND MONITORING

Prevention should be key. Clinicians should take into account both the present CVD risk as well as the metabolic risk profile of the antipsychotic chosen. To avoid weight gain, diet and lifestyle interventions should be started early after treatment initiation.

Despite the risks, many patients with SMI have limited access to general healthcare, with less opportunity for cardiovascular risk screening and prevention than would be expected in a non-psychiatric population (7,25-27). There is a lack of consensus over who should take responsibility for the general healthcare needs of mental health patients, which has resulted in a continuing failure to provide appropriate services. General health care needs in this population are commonly neglected and psychiatrists mainly focus on efficacy of treatment of psychotic symptoms.

Over recent years, both national and international groups have developed screening and monitoring guidelines (14,105-112), but these have not made their way to routine clinical care for patients (113,114).

Before start of treatment, the cardio-metabolic risk profile of a patient should be assessed. At the start of treatment, patients should be closely monitored for the relevant metabolic parameters. An easy screening tool for MetS is the measurement of waist circumference in combination with fasting glucose (sensitivity 100%) (96).

Lifestyle interventions, with diet, increased physical activity and smoking cessation, are the first-line treatments to decrease the risk for CVD in people with MetS (8). The Adult Treatment Panel guidelines recommend a reduced intake of saturated fat and cholesterol, increased intake of fibres and increased physical activity (46). A reduction of 10% of cholesterol levels results in a 30% reduction of CVD risk. A lowering of blood pressure of 4 to 6% decreases CVD risk 15%. Smoking cessation would result in a 50 to 70% lowering of CVD prevalence. Maintaining a body mass index below 25 lowers CVD risk 35 to 55%, and having active lifestyle (20 minutes brisk walk a day) results in a similar decrease of risk (8). These data also apply for people with severe mental illness, but no studies are available that confirm that short-term beneficial effects of lifestyle interventions result in long-term

changes (115,116). However, there is growing evidence that lifestyle interventions can be effective for groups of patients with schizophrenia.

There is a general consensus that physical activity has a mild to moderate favorable effect on many metabolic and cardiovascular risk factors that constitute or are related to the MetS (117). Regular physical activity is effective in prevention and treatment of hypertension (118,119), obesity (120), impaired glucose tolerance and diabetes (121) and dyslipidaemia (122). Therefore, it should be an important component in multidisciplinary programs for people with schizophrenia. At the moment, identifying an optimal dose or intervention strategy for physical activity programs in people who have schizophrenia is not possible (123). The current guidelines for the general population of accumulating 30 min of moderate lifestyle physical activity, five days a week (124) should also be applied to people who have schizophrenia. Compliance with these guidelines appears to markedly decrease the likelihood of MetS especially in high risk groups (117). In physical activity related treatment programs for people who have schizophrenia, special attention could be given to the specific cardio-metabolic comorbidities by using the physical activity recommendations for chronic somatic diseases (125). A physical activity program should be adapted to the patients' previous experiences, their attitude towards physical activity, their personal preferences and objectives.

If a patient develops metabolic abnormalities (e.g., weight gain, increased blood pressure, glucose or lipid levels) following initiation of antipsychotic therapy, consideration should be given to switching the patients to an SGA which has not been associated with significant weight gain or diabetes. Initiation of appropriate blood pressure, glucose or lipid lowering therapy should also be considered, in consultation with the patient's general practitioner when that is possible, or with a specialist physician when this is considered appropriate. Until recently, there was no data on the safety and efficacy of statins in patients also exposed to antipsychotics. In patients with schizophrenia, statins were an effective and safe treatment for severe dyslipidaemia but they did not succeed in reversing MetS (126, 127).

A European current update of screening and monitoring guidance is being produced (128,129) and an update of the ADA/APA 2004 consensus document is expected to be published this year (14).

CONCLUSIONS

MetS and other CVD risk factors are highly prevalent in people with SMI. The psychiatrist needs to be aware of the potential metabolic side effects of antipsychotic medication and to include them in the risk/benefit assessment when choosing a specific antipsychotic. He should also be responsible for the implementation of the necessary screening assessments and referral for treatment of any physical illness. Multidisciplinary assessment of psychiatric and medical conditions is needed. Psychiatric treatment facilities should offer and promote healthy lifestyle interventions. The somatic treatments offered to people with severe and enduring mental illness should be at par with general health care in the non-psychiatrically ill population.

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