

Metabolic syndrome in schizophrenia: Differences between antipsychotic-naïve and treated patients

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ABSTRACT

Metabolic syndrome (MetS) has been recognized as a risk factor for cardiovascular morbidity and mortality in general population and in patients with severe mental illnesses like schizophrenia. This paper reviews studies on MetS in schizophrenia and related psychotic disorders, and assesses the contribution of antipsychotics toward the development of MetS. Databases of Medline (PubMed), PsycINFO, and Scopus were searched for MetS, psychotic disorders, and antipsychotic drugs from inception till present. Prevalence of MetS in patients with schizophrenia was found to be ranging from 3.3% to 68.0%. Prevalence in antipsychotic-naïve and antipsychotic-treated patients ranged between 3.3-26.0% and 32.0-68.0% respectively, and was higher in younger patients, female gender and Hispanics, and lower in African-Americans and Orientals. Prevalence of metabolic abnormalities was higher in patients receiving second generation antipsychotics (SGAs), especially with clozapine, olanzapine, and risperidone, as compared to first generation antipsychotics (FGAs). Antipsychotic-induced changes on metabolic indices became evident after 2 weeks and reached maximum at 3 months of treatment. There is a need to sensitize the mental health professionals at all levels about the need of screening and monitoring for MetS in patients receiving antipsychotics.

Key words: Antipsychotic, metabolic syndrome, schizophrenia

INTRODUCTION

Metabolic syndrome (MetS) was first described by Kylin, a Swedish physician, as a cluster of cardiovascular risk factors comprising of hypertension, hyperglycemia, and gout in 1923.^[1] The syndrome has gradually evolved over time with progressively changing definitions, but the core disturbances, consisting of glucose intolerance, obesity, hypertension, and dyslipidemia remain the cornerstone of all

diagnostic criteria. All these features predispose the affected individual to increased risk of cardiovascular morbidity; a fact of paramount importance in a severe mental illness like schizophrenia which itself is associated with increased cardiovascular mortality and morbidity.^[2,3] Antipsychotics, used for the treatment of psychotic disorders, have been implicated in the development of MetS.^[4] The increasing use of second generation antipsychotics (SGAs) or 'atypicals', which currently form the primary choice pharmacotherapy for schizophrenia,^[5,6] has run parallel with the increasing recognition of MetS in psychiatric practice.^[7,8] Thus, patients suffering from schizophrenia are at the dual disadvantage of being inherently predisposed to metabolic abnormalities,^[9] which is then further worsened by the subsequent use of antipsychotics.^[10] This paper reviews MetS and related metabolic abnormalities in antipsychotic-naïve and antipsychotic-treated patients with schizophrenia and tries

Access this article online	
Quick Response Code:	Website: www.jpharmacol.com
	DOI: 10.4103/0976-500X.114596

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to delineate the role of illness vs. medication in the genesis of MetS in these patients.

SEARCH STRATEGY

Searching databases for MetS provides inconsistent results as the term itself was standardized as late as in 1998. Therefore, a list of search terms were first identified and agreed upon by authors to limit and focus the search. PubMed search queries were created using the MeSH term “MetS X” and secondary queries were created using older terms like “dysmetabolic syndrome X,” “metabolic cardiovascular syndrome,” “metabolic X syndrome,” and “insulin resistance.” Components of MetS, including dyslipidemia, hypertension, hyperglycemia, insulin resistance, increased abdominal fat, thrombosis, diabetes, and obesity were also used to generate secondary queries. Psychotic disorder search terms were limited to “schizophrenia” and “psychosis” without any consideration for any diagnostic criteria. Antipsychotic medications were searched by the MeSH term “antipsychotic agents” as well as individual drug names. The inclusion criteria for this review were all English language original articles reporting findings on adult human subjects. Reviews, systematic reviews, and meta-analysis were not included in the analysis for this article. Databases of Medline (PubMed), PsycINFO, and Scopus were searched from inception until February 2012. Due to unavoidable nonspecificity of the search terms, the initial searches returned a large number of articles (2818 results), abstracts of which were manually checked for removal of duplicates, non-English language entries, reviews, and meta-analysis. Of the remaining 167 articles, 86 research articles were found relevant to the present paper and were included for final analysis.

ANALYSIS

Varied syndromal definitions of MetS, proposed over time, make comparison between studies using different criteria sets difficult. One of the earliest definitions of MetS forwarded by the World Health Organization in 1998,^[11] though well-accepted, was difficult to incorporate into routine clinical practice due to its need for tests like hyper insulinemic-euglycemic clamp technique and oral glucose tolerance test (OGTT). Similar criteria proposed by the American Association of Clinical Endocrinology and later by the European Group for the Study of Insulin Resistance also required OGTT and hence were cumbersome.^[12] Currently, the criteria sets formulated by the National Cholesterol Education Program Expert Panel- Adult Treatment Panel III (NCEP ATP III) and International Diabetes Federation (IDF) are used commonly by most researchers. The NCEP ATP III definition requires the presence of at least three of the five criteria comprising of abdominal obesity,

hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol, raised blood pressure, and impaired fasting glucose.^[13] A modified NCEP ATP III definition, which uses ethnicity specific values of waist circumference (WC) to define obesity, has found better global acceptance. The IDF definition on the other hand requires central obesity (defined using ethnicity specific WC cut-offs) or body mass index (BMI) as a mandatory criterion accompanied by at least two of the other four comprising of raised triglycerides, reduced HDL cholesterol, raised blood pressure, and raised fasting plasma glucose.^[14] There are additional minor differences in the cut-off values used in the criteria of these definitions which are detailed elsewhere.^[13,14] However, irrespective of the definition used, studies show increased prevalence of MetS in schizophrenia and with antipsychotic drug use, which the rest of the paper focuses on. The paper first discusses studies done on antipsychotic-naïve patients to understand how the illness is associated with the development of MetS, followed by studies focusing on the effect of antipsychotic use on the metabolic profile of psychotic patients.

Metabolic abnormalities in antipsychotic-naïve patients

Drug-naïve patients of schizophrenia (S-DN) provide an excellent opportunity to understand the progress of illness and development of MetS, but unfortunately only a few studies have assessed the prevalence of the full spectrum of MetS in these patients. Most studies have looked into individual risk factors or components of MetS like weight, BMI, fat distribution, fasting plasma levels of glucose, insulin resistance, and lipid abnormalities in antipsychotic-naïve patients of schizophrenia which are summarized in Tables 1a and b.

There are a few studies available from the pre antipsychotic era, but problems with diagnosis and methodological issues make their interpretation difficult.^[15] In the post antipsychotic era, to circumvent the difficulty of recruiting patients with S-DN, most studies have taken outpatient sample at first diagnosis before initiation of therapy, and have defined “drug-naïve” (DN) as patients who have never received antipsychotic medication in their lifetime till the point of assessment. Some studies have also included subjects receiving antipsychotic medication for a brief period of time (lifetime cumulative exposure <10 days), or subjects who have been “drug free”(DF) for at least 3-6 months prior to the study; under the assumption that short antipsychotic exposure does not result in significant metabolic changes and the DF period possibly reverses those changes.

Metabolic abnormalities in patients with S-DN are described as below [Tables 1a and 1b].

Abnormal glucose metabolism

S-DN patients are reported to have significantly higher fasting plasma glucose levels, impaired fasting glucose tolerance, elevated insulin and cortisol levels, and insulin resistance in

Table 1a: Summary of glycemic and lipid abnormalities in antipsychotic naïve patients

Study	Sample characteristics	Study details			Glycemic abnormalities					Lipid abnormalities					Blood pressure				
		Size	Con	Age	Ethnicity	FPG	IGT	FPI	Co	IR	IGF-1	TC	HDL	LDL	TG	Le	SBP	DBP	PP
Ryan <i>et al.</i> , 2003 ^[16]	Compared drug-naïve 1 st episode schizophrenia patients with matched healthy controls	26	26	33.6	Caucasian	↑	↑	↑	↑	↑	na	↓	-	↓	-	na	na	na	na
Arranz <i>et al.</i> , 2004 ^[23]	Compared antipsychotic-free (not on current medication), antipsychotic-naïve schizophrenia patients and healthy control subjects	50+50	50	na	Caucasian	-	na	-	na	-	na	na	na	na	na	-	na	na	na
Zhang <i>et al.</i> , 2004 ^[23]	Compared untreated schizophrenia patients at first psychotic episode at baseline and after 10 weeks of antipsychotic treatment with matched controls	46	38	26.5	Chinese	-	na	-	na	na	-	-	-	-	-	-	na	na	na
Spelman <i>et al.</i> , 2007 ^[17]	Compared between first-episode drug-naïve schizophrenia patients, their first degree relatives and matched controls	38+44	38	25.2	Caucasians	-	↑	↑	↑	↑	na	-	-	-	-	-	na	na	na
Venkatasubramanian <i>et al.</i> , 2007 ^[18]	Compared antipsychotic-naïve schizophrenia patients with matched controls	44	44	33	Asian Indian	-	na	↑	↑	↑	↓	-	na	na	-	na	na	na	na
Sengupta <i>et al.</i> , 2008 ^[25]	Compared drug-naïve first episode psychosis patients (schizophrenia spectrum) and matched controls	38	36	24	Caucasian	-	-	-	na	-	na	-	-	-	-	na	na	na	na
Verma <i>et al.</i> , 2009 ^[19]	Compared drug-naïve first episode psychosis patients and matched controls	160	200	na	Caucasian	↑	-	-	na	-	na	↓	-	-	-	na	na	na	na
Fernandez-Egea <i>et al.</i> , 2009 ^[28]	Compared drug-naïve first episode psychosis patients (schizophrenia spectrum) and matched controls	41	41	29.2	Hispanic	-	-	-	-	-	na	na	na	na	na	-	na	-	↓
Fernandez-Egea <i>et al.</i> , 2009 ^[9]	Compared drug-naïve first episode psychosis patients (schizophrenia spectrum) and matched controls	50	50	29.4	Hispanic	-	↑	-	-	-	na	na	na	na	na	na	na	na	na
Padmavati <i>et al.</i> *, 2010 ^[26]	Compared patients of chronic schizophrenia never receiving treatment with healthy controls	51	51	45.8	Asian Indian	-	na	na	na	na	na	na	-	na	-	na	-	-	na

↑=Statistically significant increase between study groups and controls, ↓=Statistically significant decrease between study groups and controls, --=No statistically significant difference between study groups and controls, na=Data not reported or data cannot be extracted from the study, *Findings are a part of main study on metabolic syndrome, Size=Sample size, Con=Size of control, Age=Mean age in years, FPG=Fasting plasma glucose, IGT=impaired glucose tolerance, FPI=Fasting plasma insulin, Co=Cortisol, IR=Insulin resistance, IGF-1=Insulin-like growth factor 1, TC=Total cholesterol, HDL=High density lipoprotein, LDL=Low density lipoprotein, TG=Triglycerides, Le=Leptin, SBP=Systolic blood pressure, DBP=Diastolic blood pressure, PP=Pulse pressure

Table 1b: Summary of obesity-related parameters in antipsychotic-naïve patients

Study	Obesity-related parameters		
	BMI	WHR	WC
Ryan <i>et al.</i> , 2003 ^[16]	–	–	–
Arranz <i>et al.</i> , 2004 ^[23]	NA	NA	NA
Zhang <i>et al.</i> , 2004 ^[22]	–	–	NA
Spelman <i>et al.</i> , 2007 ^[17]	↓	NA	–
Venkatasubramanian <i>et al.</i> , 2007 ^[18]	–	NA	–
Sengupta <i>et al.</i> , 2008 ^[25]	–	↑	–
Verma <i>et al.</i> , 2009 ^[19]	NA	NA	NA
Padmavati <i>et al.</i> *, 2010 ^[26]	↓	NA	–

↑=Statistically significant increase between study groups and controls,

↓=Statistically significant decrease between study groups and controls,

–=No statistically significant difference between study groups and controls,

NA=Data not reported or data cannot be extracted from the study,

*Findings are a part of main study on metabolic syndrome, BMI=Body mass index in kg/m², WC=Waist circumference, WHR=Waist-to-hip ratio

various studies.^[15-21] In one of the earliest studies, about 15% of the S-DN patients showed impaired fasting glucose tolerance, higher than the age-adjusted population rates (male = 11.8%, female = 5.2%).^[16]

Impaired glucose tolerance has also been reported in first degree relatives of S-DN patients, suggesting a possible genetic association between diabetes and schizophrenia. Spelman *et al.*,^[17] reported impaired glucose tolerance in 18.2% of first degree relatives compared to 10.5% in controls, while Mukherjee *et al.*,^[20] reported type II diabetes mellitus in 19% of first degree relatives of schizophrenia. Insulin-like growth factor (IGF-1) has been proposed as a possible mediator for this mechanism and S-DN patients have been found to have lower IGF-1 levels in some studies.^[18] IGF-1 is essential for optimal insulin sensitivity, and its deficiency can lead to insulin resistance.^[21] In contrast, Zhang *et al.*,^[22] failed to find any difference in fasting plasma glucose, leptin, or insulin levels between S-DN patients and healthy controls. In another study, Arranz *et al.*,^[23] compared plasma glucose, insulin, C-peptide and leptin concentrations of S-DN patients with currently noncompliant schizophrenia patients and healthy controls. S-DN subjects showed no significant changes in any parameters, whereas patients previously exposed to antipsychotics had significantly increased insulin, C-peptide, leptin concentrations, and insulin resistance, although they were currently not on antipsychotic medications. Thus, while S-DN patients may not have preexisting impairment of glucose metabolism, use of antipsychotics may have lasting effects even long after discontinuation.

Lipid abnormalities

Patients with schizophrenia frequently exhibit unhealthy lifestyle, have diet lower in fiber and higher in fat, and do lesser daily exercise, compared to the general population,^[15,24] thus expected to have abnormal lipid profile. However, the

association between dyslipidemia and S-DN has not been well-established. Two studies^[16,19] reported lower mean fasting total cholesterol and low-density lipoprotein (LDL) levels in S-DN patients, whereas several studies have failed to show any association.^[17,25,26] Spelman *et al.*, in 2007 comparing 38 S-DN patients with 44 matched healthy controls found no differences in total cholesterol, LDL, HDL, or triglycerides.^[17] Sengupta *et al.*,^[25] in a study on first episode psychosis (FEP) patients also did not find any lipid derangements except a slight trend of lower HDL levels. Further, a study on chronic patients of schizophrenia in community, who were never treated, also failed to find any significant lipid disturbances in patients compared to healthy controls.^[26]

Hypertension

Studies assessing hypertension in S-DN patients provide inconclusive results.^[26,27,28] Grover *et al.*,^[27] investigating MetS in S-DN patients, found elevated blood pressure (>135/85 mm/Hg) in 26% of the cases. In another study, Fernandez-Egea *et al.*,^[28] reported significantly higher pulse pressure but no significant difference in systolic or diastolic blood pressure while comparing S-DN patients with FEP and controls. The observed pulse pressure differences were independent of age, ethnicity, smoking, gender, and BMI, suggesting that antipsychotic-naïve patients with FEP may be inherently prone to hypertension.

Obesity

Unlike multiple studies that report antipsychotic-induced obesity, studies on S-DN patients generally show minimal or no body weight disturbance. In a study comparing 26 S-DN patients with healthy controls, Ryan *et al.*,^[16] did not find any significant difference in BMI, waist-to-hip ratio (WHR), or WC between the two groups, despite the fact the patient group had higher saturated fat content in their diet. Further, Spelman *et al.*^[17] reported lower BMI in S-DN patients when compared to healthy controls with similar dietary patterns, including low fiber intake and lower exercise levels. Lower BMI in S-DN patients has also been reported by Padmavati *et al.*^[26] in studies from India. In contrast, Sengupta *et al.*,^[25] reported an increase in WHR in their sample of S-DN patients, while Thakore *et al.*,^[29] found significantly elevated BMI and central obesity in DN and currently DF patients of schizophrenia.

Studies investigating fat deposition (subcutaneous and intraabdominal fat) in schizophrenia also provide conflicting results. While Zhang *et al.*,^[22] reported no significant difference in intraabdominal or subcutaneous fat deposition between S-DN patients and controls, Ryan *et al.*,^[30] reported a three-fold lesser intraabdominal fat in S-DN patients compared to controls, though no difference was found in subcutaneous or total body fat between the two groups. Differing ethnicity of the two study populations might explain the different findings.

Metabolic syndrome in antipsychotic-naïve individuals

Table 2 summarizes the studies on prevalence of MetS in S-DN patients. Prevalence of MetS in S-DN patients varies from as low as 3.3% to as high as 26% in various studies.^[27,31-34] While most study populations belonged to the age group of 20s or early 30s, the sample size varied widely (30-400). Methodological issues like definition of MetS used, ethnicity and inclusion criteria might explain this huge variation. For example, the study which recorded the highest prevalence of MetS (26%) had included subjects who had been previously treated with antipsychotics.^[31] Even though the authors argued that previous antipsychotic use was unlikely to affect the prevalence in a substantial manner as only 20% of the study population had received antipsychotics in past, and had been off medications for a mean period of 24.7 months, the chances of confounding cannot be ruled out.

Recently Grover *et al.*,^[27] explored the effect of changing definition sets of MetS on its prevalence. By applying the NCEP ATP III and the IDF criteria on same group of patients, the authors showed a differing prevalence of MetS at 13.0% and 10.0% respectively. Prevalence of subsyndromal MetS was found to be even higher with 30% of the subjects satisfying two out of five IDF criteria and 50% fulfilling one out of five criteria. The study highlights the fact that recognizing the underlying subsyndromal abnormalities in MetS is also important.

Metabolic syndrome in antipsychotic-treated patients

Studies reporting the prevalence of MetS in patients of schizophrenia under drug treatment (S-DT) are summarized in

Table 3. Prevalence of MetS in S-DT patients ranges from 14.7% to 68% in various studies.^[4,31,35-58] Patients with S-DT appear to have about three-fold greater risk to develop MetS than the general population, both in clinic^[39] as well as in community samples.^[35] A subset of these studies looking into patients with FEP rather than schizophrenia report a slightly lower prevalence of drug-induced MetS ranging between 10.1% to 31%.

The global prevalence of MetS in patients with S-DT varies with prevalence in the US (Clinical Antipsychotic Trials of Intervention Effectiveness, CATIE) studies having been reported around 40%, while European studies^[4,41-43] have reported slightly lesser rates of about 19-35%. Even among the subjects in the CATIE study, the White and Hispanic females had the highest (50-57%) prevalence and Black males had the lowest (22%). Other studies from the US also report similar prevalence difference, with rates being high in Hispanics (74%) when compared to non-Hispanic (41%) patients with schizophrenia.^[39] Studies from China and Taiwan have reported the lowest global prevalence of drug-induced MetS (14.7%),^[52] though other studies from the same ethnicity show prevalence ranging from 23% to 35%.^[44,56] There have also been studies from Iran,^[57] Turkey,^[49,50,58] Japan,^[37] Brazil,^[47] and Canary Islands^[48] with varying rates of MetS. Thus, although all ethnicities are predisposed to antipsychotic-induced MetS, ethnically determined protective or risk factors need to be further evaluated.

Most of these studies recruited patients from outpatient settings, while few took samples from psychiatric rehabilitation services^[35] and inpatient settings.^[36,37] The sample size varied

Table 2: Summary of studies on metabolic syndrome in antipsychotic-naïve patients

Study	Country	Methodology	Sample size	Criteria for MetS	Mean age	Prevalence in drug-naïve patients (in%)	Comments
Grover <i>et al.</i> , 2012 ^[27]	India	Cross-sectional study on patients of schizophrenia without any controls	46	IDF, ATP III	31	10.0 (IDF) 13.0 (ATP III)	No controls
Pallava <i>et al.</i> , 2012 ^[31]	India	Cross-sectional comparative study on 50 antipsychotic free and 50 antipsychotic-treated patients	50	IDF	28.1	26.0	10 patients had received antipsychotics in the past
Patel <i>et al.</i> , 2009 ^[32]	USA	52 weeks follow-up of patients with early psychosis using double blind, flexible dose, multisite design	400	ATP III	24.5	4.31	Incidence of MetS 1 year post-treatment was 13.4%
Padmavati <i>et al.</i> , 2010 ^[26]	India	Compared patients of chronic schizophrenia never receiving treatment with healthy controls	51	IDF	45.8	3.8	Prevalence of MetS 7.8% in controls
De Hert <i>et al.</i> , 2008 ^[33]	Belgium	First cohort: Retrospective chart review of consecutively admitted first episode schizophrenia patients at baseline and after 3 year posttreatment with FGA	148	ATP III	22.3	4.7	Prevalence of MetS was 13.1% after 3 years ¹
		Second cohort: Prospective naturalistic follow-up study of consecutively admitted first episode schizophrenia patients at baseline and after 3 year posttreatment with SGA	148	ATP III	22.1	5.4	Prevalence of MetS was 30.6% after 3 years ¹
Saddichha <i>et al.</i> , 2007 ^[34]	India	Drug-naïve first episode schizophrenia patients were followed up prospectively for 6 week on olanzapine or risperidone with double blind design	30	IDF	26.2	3.3	Prevalence of MetS was 31.8% after 6 weeks of treatment ¹

¹Baseline assessment provided rates of MetS in drug-naïve patients, FGA=First generation antipsychotics, IDF=International diabetes federation, ATP-III=Adult treatment panel-III, SGA=Second generation antipsychotics, MetS=Metabolic syndrome

Table 3: Summary of studies on prevalence of metabolic syndrome with antipsychotic treatment

Study	Ethnicity	Samplesize	Criteria	Prevalence (%)	Males (%)	Females (%)	Population prevalence (%) ^a
Heiskanen <i>et al.</i> , 2003 ^[41]	Finnish	35	ATP III	37.0	47.0	25.0	11-20
Cohn <i>et al.</i> , 2004 ^[38]	Canadian	240	ATP III	45.0	42.6	48.5	-
Kato <i>et al.</i> , 2004 ^[39]	Hispanic	48	ATP III	63.0	-	-	22.0
McEvoy <i>et al.</i> , 2005 ^[40]	Caucasian/African American/Hispanic	1460	ATP III	40.9	36.6	54.2	23.0
Hagg <i>et al.</i> , 2006 ^[41]	Swede	269	ATP III	34.6	32.8	38.0	9.0
Saari <i>et al.</i> , 2005 ^[42]	Finland	31	ATP III	19.0	-	-	-
De Hert <i>et al.</i> , 2006 ^[43]	Belgian-Whites	430	ATP III and IDF	32.3	30.5	35.8	12.0
Lamberti <i>et al.</i> , 2006 ^[44]	Caucasian/African American/Hispanic	93	ATP III	53.8	51.6	58.1	20.7
Tirupati and Chua, 2007 ^[35]	Australian	221	IDF	68.0	70.0	59.0	29.1
Bai <i>et al.</i> , 2007 ^[45]	Taiwan	188	IDF	28.4	-	-	12.9
Bobes <i>et al.</i> , 2007 ^[46]	Spain	1452	ATP III	24.6	23.6	27.2	-
Teixeira and Rocha, 2007 ^[47]	Brazil	170	ATP III	29.4	20.8	43.6	23.7
Sánchez-Araña Moreno <i>et al.</i> , 2007 ^[48]	Canary Islands	136	ATP III	36.0	-	-	-
Boke <i>et al.</i> , 2008 ^[49]	Turkey	231	IDF	32.0	-	-	10.2
Cerit <i>et al.</i> , 2008 ^[50]	Turkey	100	ATP III/IDF	21.0/41.0	-	-	10.2
Correl <i>et al.</i> , 2008 ^[51]	Caucasian/African American/Hispanic	111	ATP III	45.9	-	-	-
Lee and Leung, 2008 ^[52]	Chinese	75	ATP III	14.7	-	-	-
Bai <i>et al.</i> , 2009 ^[53]	Taiwan	567	IDF	23.8	24.7	22.1	12.9
Brunero <i>et al.</i> , 2009 ^[54]	Australia	73	IDF	61.6	73.3	26.7	29.1
John <i>et al.</i> , 2009 ^[55]	Australia	203	ATP III/IDF	49.0/54.0	56.0	51.0	29.1
Huang <i>et al.</i> , 2009 ^[56]	Taiwanese	650	ATP III	34.9	38.9	31.5	15
Rezaei <i>et al.</i> , 2009 ^[57]	Iran	372	ATP III/IDF	27.4/38.7	-	-	-
Mattoo and Singh 2010 ^[36]	Asian Indian	90	IDF	37.8	29.8	46.5	25.0
Sugawara <i>et al.</i> , 2010 ^[37]	Japanese	1186	ATP III	27.5	29.8	25.3	14.1
Yazici <i>et al.</i> , 2011 ^[58]	Turkey	319	ATP III/IDF	34.2/41.7	27.7/42.6	39.3/41	10.2
Pallava <i>et al.</i> , 2012 ^[31]	Asian Indian	50	IDF	50.0	-	-	25-36

^aPrevalence of MetS in the general population in the country of study, for comparison, IDF=International diabetes federation, ATP=Adult treatment panel

from as less as 31 to as large as 1460 in the CATIE study.^[40] Although, these studies generally depict a higher prevalence of MetS in S-DT patients compared with S-DN patients, their cross-sectional methodological design limits understanding of how addition of antipsychotic medications affects the occurrence or exacerbation of MetS in an already predisposed individual.

Prospective studies, on the contrary, can better assess the contribution of antipsychotics in development of MetS, by estimating its prevalence in DN patients at baseline and then prospectively following them up, while they are on medication. Such studies show a 9-28% increase in prevalence of MetS during follow-up after institution of antipsychotic medications.^[32,34,59-65] The Comparison of Atypicals for First Episode (CAFÉ) study group which assessed development of MetS in 400 FEP patients randomized to olanzapine, quetiapine, or risperidone, reported an increase in prevalence

of MetS from 4.3% at baseline to 13.4% at the end of 52 weeks with a mean period of 12.4 weeks for development of treatment-emergent MetS.^[32] Similar analysis of the CATIE trial (involving follow-up of schizophrenia patients previously exposed to antipsychotics), showed not only a high prevalence of MetS at baseline, but also an additional marginal increase at 3 months posttreatment.^[59]

Data from individual studies support the findings from these large trials. Saddichha *et al.*,^[34] reported an increase in prevalence of MetS from 3.3% at baseline to 31.8% at the end of 6-weeks treatment with olanzapine or risperidone. Later, the same group reported a 5 times higher prevalence of MetS in patients on antipsychotics, compared to healthy controls.^[64] Treatment-induced MetS was highest with olanzapine at 20-25%, followed by risperidone (9-24%) and was least with haloperidol (0-3%). Another naturalistic study from Thailand reported that around 20% of S-DT patients went

on to develop MetS at 1-year follow-up with patients having subsyndromal MetS at baseline being at a higher risk.^[65]

Other studies report metabolic abnormalities like weight gain^[60-62] and abnormal lipid profile^[63] in patients undergoing antipsychotic treatment, thereby further supporting the hypothesis that antipsychotics may alter metabolic parameters, which may be separate from those caused by the illness itself.

Factors affecting prevalence of metabolic syndrome in psychiatric patients

Sociodemographic and disorder-related factors

In contrast to the pattern seen in the general population, where prevalence of MetS is low in the young and increases with increasing age, its prevalence among patients with schizophrenia is significantly higher in younger age groups.^[38,43,66] Although prevalence of MetS increases with age,^[35] and age more than 40 years has been found a significant risk factor,^[56] the rate of rise in prevalence of MetS with increasing age in patients with schizophrenia is lesser than that seen in the general population.^[43,66] Female gender might be a risk factor for development of MetS, as in the CATIE study female patients from all the ethnicities were more vulnerable to MetS compared with males.^[40] Additionally, while females are more prone to develop central obesity, higher WC and low HDL-cholesterol, males more often develop hypertension and increased triglyceride levels.^[40,43,46,56,67] Ethnicity might also be an important risk factor for development of MetS (see above), with Hispanics and whites being more prone than the African-Americans and the Orientals.^[39,40,52]

Duration of illness is another risk factor for the development of MetS. The prevalence of MetS in patients of first episode schizophrenia treated with antipsychotics varies from 10.1% to 31% in different studies,^[34,64] which is lower than rates in patients of schizophrenia with longer duration of illness, where it has exceeded to even more than 60% in some reports.^[35,39,54] Other biological factors like IGF-1 deficiency, comorbid disorders of substance use and sedentary lifestyle with lack of exercise also contribute to the emergence of metabolic complications in these patients.

Treatment and medication-related factors

The most consistent finding in all studies on patients with schizophrenia is that the development of MetS is associated with antipsychotic treatment. Irrespective of the antipsychotic agent used, duration of treatment, total cumulative dose and polypharmacy have been identified as major determinants for higher prevalence of MetS in patients of schizophrenia. Polypharmacy with both multiple antipsychotics or antipsychotics and mood stabilizers has been shown to increase the risk.^[35] Comparative studies have reported prevalence of MetS as high as 50% in patients on polypharmacy compared to 34% in those on monotherapy.^[68]

As a group, FGAs appear to have a lower risk for causing MetS than SGAs. The multicentric CATIE study, which used perphenazine as a representative of the FGA group, reported no change in prevalence of MetS in perphenazine group at 3 months follow-up. In contrast, a significant increase in prevalence of MetS (34.8-43.9%) was seen in the olanzapine arm.^[69] A recent study from France^[70] on a large sample of 2270 patients of schizophrenia on FGAs and SGAs confirmed higher prevalence of MetS (36.7% vs. 30.7%) in patients on SGAs as compared with those on FGAs. Furthermore, patients on SGAs had higher prevalence of dysglycemia (28.5% vs. 22.0%) and low HDL cholesterol (35.3% vs. 29.7%), compared with those on FGAs. Similarly, De Hert *et al.*,^[33] reported prevalence of MetS to be three times in SGA-treated group than in the FGA-treated patients. In one of the earliest studies, Lindenmayer *et al.*,^[8] had reported higher prevalence of diabetes in clozapine-treated patients, higher postload glucose levels on glucose tolerance test, higher weight gain, and elevated cholesterol in clozapine and olanzapine-treated patients, compared with haloperidol-treated group.

In absence of systematic studies comparing different FGAs in their propensity to cause MetS, it becomes difficult to argue the advantage of any one FGA over another. However, the fact that FGAs have a relatively less propensity to cause MetS, should not be interpreted as FGAs to be metabolically safe and therefore the treatment of choice. Enough studies are available that document metabolic abnormalities associated with the use of various FGAs. Chlorpromazine and thiothixene have been associated with significant weight gain in as many as 80% of the treated sample (compared to weight gain in 46.6% of the controls).^[71,72] Chlorpromazine and other phenothiazines have been reported to cause hyperglycemia and glycosuria in nearly 25% of the treated patients by 1 year of use,^[73] and haloperidol has been associated with higher glucose levels and insulin resistance in patients of schizophrenia.^[74,75] Clinical vigilance, therefore, needs to be maintained for detecting metabolic abnormalities even when treating patients with FGAs.

There has been a strong research initiative over the last decade to compare the relative contribution of various SGAs in the causation of MetS. Although metabolic abnormalities are associated with almost all SGAs, clozapine and olanzapine appear to be most consistently associated with the development of MetS. Even in the very first study which reported increased prevalence of MetS in schizophrenia, over half of the patients were on clozapine.^[4] In the retrospective-prospective cohort comparison study by De Hert *et al.*,^[33] the difference between FGA- and SGA-treated patients disappeared when patients on clozapine and olanzapine were removed from the analysis. Two other studies comparing clozapine, olanzapine, and haloperidol similarly reported worsening of glycemic profiles with a significant increase in triglyceride levels in clozapine and olanzapine group, compared with the haloperidol group.^[8,76]

A number of studies have reported clozapine to be more frequently associated with MetS than other antipsychotics.^[35,56,67] One study has estimated this risk to be two and half times higher in clozapine-treated patients than in those treated with other antipsychotics.^[44] Other studies have reported isolated metabolic abnormalities like impaired glucose tolerance and diabetes mellitus,^[67] and elevated insulin levels^[77] suggesting peripheral insulin resistance with clozapine treatment. There are also reports of elevation of cholesterol levels^[81] and increased levels of serum triglycerides with clozapine treatment in comparison to haloperidol, quetiapine, and other FGAs or SGAs.^[78-82] Clozapine-treated patients have also reported more weight gain compared with other antipsychotics,^[83] an effect that becomes maximum in the first 12 months but may continue for as long as 46 months despite being on active weight-loss programs involving diet and exercise.^[80]

Olanzapine has also been associated with significant weight gain. In the CATIE study, patients in the olanzapine group gained more weight than with any other drug (mean weight gain was 0.9 kg monthly), and 30% of patients in the olanzapine group gained 7% or more of their baseline body weight (compared with 7-16% in the other groups).^[84] The CAFÉ study also found the highest weight gain among olanzapine-treated patients at 52-weeks follow-up.^[32] Eighty percent of olanzapine-treated patients, compared with 57.6% of risperidone and 50.0% of quetiapine-treated patients recorded weight gain of more than 7% from baseline. Similarly, other studies have reported significant increase in body weight, serum leptin levels, and percentage of body fat,^[85] and new onset diabetes^[86] in patients treated with olanzapine. Olanzapine induced weight gain has also been associated with both elevated triglycerides and total cholesterol,^[87,88] though some studies have failed to find this association.^[89]

Treatment with other SGAs has also been reported to produce an increase in body weight ranging from <1 kg to >4 kg.^[90] Long-term use of aripiprazole^[91] and ziprasidone^[92] is associated with a mean weight gain of about 1 kg over a year, amisulpiride with a gain of about 1.5 kg over 1 year,^[93] and quetiapine and risperidone with a gain of 2-3 kg over 1 year.^[94] Quetiapine has also been associated with increased triglycerides and total cholesterol levels.^[32] In comparison, olanzapine and clozapine, the drugs with highest propensity for MetS, cause weight gain of around 4-5 kg over 1 year.^[95,96,97]

Although the major bulk of research have tried to differentiate between various antipsychotic medications in their tendency to cause MetS, some large scale multicentric trials, like the Cardiovascular, Lipid and Metabolic Outcomes Research in Schizophrenia study, do report no statistically significant differences between patients with and without MetS in relation to the mean duration or type of antipsychotic treatment,^[96]

and; therefore, all current trends need to be considered with clinical pragmatism.

DISCUSSION

The present review estimates the prevalence of MetS as ranging from 3.3% to 68% in patients with schizophrenia. Prevalence ranges from 3.3% to 26% in DN patients, and 14.7-68% in patients on antipsychotics, is higher in younger patients, female gender and Hispanics, and lower in African-Americans and Orientals. Use of both SGAs as well as the FGAs increases the risk, though the prevalence of MetS and its different components appears higher with SGAs as compared with FGAs. Effect of antipsychotic treatment on metabolic indices is evident after 2 weeks^[32] and reaches maximum at around 3 months of treatment^[61,63]

A large number of the prevalence studies currently available are cross-sectional. While such studies alert us about the phenomenon, it limits understanding of the drug-disease interaction. A large number of studies, due to limitations in design, or feasibility, have focused on select metabolic abnormalities or specific components of the syndrome. Heterogeneity in these studies not only limits comparability but also restricts understanding of how derangement of certain components of MetS affects others. Use of multiple different diagnostic criteria also compromises comparability but is expected to happen given the recent nature of the issue.

Systematic analysis of different medications in their propensity to cause MetS is also a rarity. Currently, no study is available that tries to assess which among the FGAs cause the least metabolic derangement. Similarly for SGAs, while a multitude of studies focus on the metabolic abnormalities caused by clozapine, olanzapine, and risperidone; studies need to be done comparing the relative merits and demerits of the apparently metabolic safe SGAs like quetiapine, aripiprazole, and ziprasidone which will be immensely helpful for developing clinical guidelines. Studies that look into the etiology of drug-induced MetS are also few and far between and causation hypothesis are generally presented as opinions or deductive reasoning by authors. Certain clinically relevant questions like, whether metabolic abnormalities remit or keep progressing after antipsychotic discontinuation, and scope of changing the antipsychotic agent in cases of drug-induced MetS are currently unexplored and provide future directions for research.

CONCLUSION

The review suggests that antipsychotics have a major contribution in increasing the prevalence of MetS in schizophrenia and related disorders, although some metabolic abnormalities might occur in antipsychotic-naïve patients. SGAs especially clozapine and olanzapine are associated

with higher risk of MetS and subthreshold MetS. With the FGAs, though weight gain and abnormalities in the glucose metabolism have been reported, prevalence of MetS has not been investigated in detail.

These findings have important public health implications. Two out of the five IDF and NCEP ATP III criteria for detecting MetS viz. BMI/WC and blood pressure are part of routine clinical examination, while the other three, which are blood tests, are also commonly available. Despite the ease of measurement of these parameters, MetS is not monitored and addressed regularly. This review provides a further impetus for mental health professionals to be cognizant of the risk of development of MetS in patients on treatment with antipsychotics. The screening for MetS should be incorporated in routine clinical care in all patients on treatment with antipsychotics, particularly the SGAs.

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How to cite this article: Chadda RK, Ramshankar P, Deb KS, Sood M. Metabolic syndrome in schizophrenia: Differences between antipsychotic-naïve and treated patients. *J Pharmacol Pharmacother* 2013;4:176-86.
Source of Support: Nil, **Conflict of Interest:** None declared.

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