METABOLIC SYNDROME IN RELATION TO PSYCHOTROPIC POLYPHARMACY

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Abstract

Objective: To assess the prevalence of metabolic syndrome (MetS) in psychiatric outpatients with a diagnosis of psychotic spectrum disorders and to investigate whether antipsychotic polypharmacy and concomitant use of mood stabilizers, antidepressants or both is associated with an increased prevalence of MetS and its parameters.

Method: Over a period of 32 months, male and female patients aged at least 18 year and receiving treatment with one or more antipsychotic agent, were consecutively recruited from the outpatient departments and classified according to DSM-IV criteria. A diagnosis of MetS was made following the NCEP-ATP-III guidelines. Apart from antipsychotics, the concomitant use of mood stabilizers and antidepressants was recorded.

Results: A total of 543 patients, mean age and duration of disease 43 and 14 years respectively, were included. The majority had a diagnosis of psychotic spectrum disorder whereas ten percent was diagnosed with affective spectrum disorder. Most patients were on antipsychotic monotherapy. Concomitant treatment with mood stabilizing agents and/or antidepressants was present in 43 percent of the patients. MetS was diagnosed in about half of the patients. No relationship with antipsychotic polypharmacy could be established, neither with the class of antipsychotic agent. Prevalence of MetS increased significantly in patients comedicated with mood stabilizing agents, antidepressants or both, especially in females.

Conclusions: MetS is present in about half of the patients treated with antipsychotics and is associated with mood stabilizing and/or antidepressant comedication. Adequate somatic treatment strategies are warranted to reduce the risk of cardiovascular diseases at relatively young age.

Key words: metabolic syndrome, mets, prevalence, antipsychotics, antidepressants, mood stabilizers, polypharmacy

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1. Introduction

It has been demonstrated that patients with severe mental illness (SMI) have a markedly reduced life expectancy as compared to the general population. Not suicide, but chronic medical disorders are major causes of death, of which cardiovascular diseases are the most important (Brown 1997, Lawrence et al. 2010). A clustering of specific risk factors for cardiovascular disease is designated as metabolic syndrome (MetS). In the beginning of the past century, two Austrian physicians originally reported about the mutual dependence of metabolic dysregulation and vascular hypertension (Hitzenberger and Richter-Quintter 1921). Many decades later, Reaven (1988) described the co-existence of the various components of the syndrome and postulated that resistance to insulin is implicated in its pathophysiology. The most commonly used definition for MetS is the Adult Treatment Panel III (ATP-III) of the National Cholesterol Education Program (NCEP) (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults 2001).

The clinical relevance of MetS is, however, still a matter of scientific debate. The American Diabetes Association and the European Association for the Study of Diabetes concluded in their joint statement that important information, especially on the exact pathophysiology, is missing to assign it as a syndrome (Kahn et al. 2005). Despite the critics, the concept of MetS is widely used in clinical practice and may be helpful to focus on the detection and early treatment of cardiovascular risk factors (De Hert et al. 2009). In the

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general population, MetS is associated with a manifest increase in diabetes mellitus and cardiovascular disease (Isomaa et al. 2001, Lakka et al. 2002, Ford et al. 2004, Hanley et al. 2007, Ford et al. 2008). As compared to the general population, a higher prevalence of MetS is demonstrated in psychiatric patients with psychotic and affective spectrum disorders (Fagiolini et al. 2005, Heiskanen et al. 2006, Garcia-Portilla et al. 2008, McIntyre et al. 2009, Mitchell et al. 2011). Additional major risk factors for MetS are use of antipsychotics (De Hert et al. 2011), mood stabilizers (Keck and McElroy 2003, Verroti et al. 2005, Livingstone and Rampes 2006) and antidepressants (McIntyre et al. 2010, van Reedt Dortland et al. 2010). Although patients with SMI are often treated with a combination of psychotropics and a differential metabolic risk between the various agents have been shown, it is unknown as yet whether polypharmacy implies an additional risk factor for MetS.

In the present observational study the prevalence of MetS is assessed in a large cohort of outpatients treated with antipsychotics for chronic relapsing disorders from the psychotic spectrum. In addition, it is investigated whether antipsychotic polypharmacy and concomitant use of antidepressants, mood stabilizers or both is associated with an increased prevalence of MetS and its parameters.

2. Material and Methods

2.1. Experimental design and subjects.

The study followed an open naturalistic design over a period of 32 months starting in November 2008 and was performed at the so called Function Assertive Community Treatment (FACT) program of the outpatients department of the Vincent van Gogh Institute for Psychiatry in Venray, The Netherlands. Included were male and female patients aged at least 18 years, who were treated with one ore more antipsychotic agent for psychotic symptoms belonging to the psychotic or affective cluster. The study was approved by the Institutional Review Board of the psychiatric hospital. Informed consent was obtained from all patients and their verbal approval was recorded in the individual research documents. Included were 571 consecutive patients of whom 28 had to be excluded because of missing relevant biochemical data. The study group comprised 543 patients.

Information about demographic, clinical and psychiatric classification according to DSM-IV was obtained from the medical records. Definite psychiatric diagnoses were subsequently confirmed by the psychiatrists responsible for treatment over the past years. Distribution of age and gender, diagnostic categories, duration of illness, prescribed antipsychotics and other psychotropics as well as somatic compounds used for the treatment of dyslipidemia, hypertension and diabetes mellitus are presented in **table 1**.

2.2. Psychotropic and somatic compounds.

With respect to the prescription of antipsychotics, a division was made between conventional and atypical compounds. The conventional drugs were the butyrophenones: haloperidol and pipamperone, the diphenylbutylpiperidenes: pimozide, penfluridole, fluspirilene and bromperidole, the thioxanthenes: chlorprotixene, zuclopenthixole and flupenthixol, and the phenothiazines: perphenazine and fluphenazine. As atypical antipsychotics were used: risperidone, olanzapine, quetiapine, aripiprazole, clozapine, sertindole and sulpiride. Prescribed antidepressants included the tricyclic compounds: clomipramine, imipramine, nortriptyline, doxepine and maprotiline, and the selective monoamine reuptake inhibitors: fluvoxamine, fluoxetine, paroxetine, sertraline, (es)citalopram, venlafaxine, duloxetine, trazodone, mirtazepine and bupropion. As mood stabilizers were used lithium, valproic acid, lamotrigine and carbamazepine. In addition, treatment with benzodiazepines and biperiden was recorded.

Lipid lowering medication included statins and fibrates, antidiabetic medication comprised insulin and oral antidiabetics, and antihypertensive compounds included beta-adrenergic blocking agents, calcium antagonists, diuretics, angiotensin-converting enzyme (ACE) inhibitors and angiotensin-II receptor antagonists.

2.3. Assessment of psychiatric symptom severity and evaluation of somatic parameters.

To evaluate psychiatric symptom severity and physical health condition in all patients, a so called health monitor was applied. Global assessment of functioning (GAF) was established according to DSM-IV. Severity of the psychiatric symptoms delusions, unusual thought content, hallucinatory behaviour, conceptual disorganisation, mannerisms/posturing, blunted affect, social withdrawal and lack of spontaneity was rated in order to assess whether patients with a diagnosis of schizophrenia fulfilled the criteria for symptomatic remission (Andreasen et al. 2005).

Physical examination comprised measurement of length (cm), body weight (kg), waist circumference (cm) and arterial blood pressure (mmHg). The latter was assessed with the patient in a sitting position after at least ten minutes of rest, and waist circumference was determined between the lowest rib and the iliac crest. Subsequently, body mass index (BMI, kg/m^2) was calculated. In addition, information was collected about smoking behaviour, substance use, and family history of cardiovascular diseases and diabetes mellitus.

Patients received a full-fasting laboratory screening including blood glucose (FG), glycosylated haemoglobin (A1c), triglycerides (TG), total cholesterol (TC), high density lipoprotein (HDL) cholesterol and low density lipoprotein (LDL) cholesterol. In case patients were treated with haloperidol or clozapine, plasma concentrations were determined. All biochemical analyses were performed in the same laboratory. Finally, ECG recordings were made.

All scorings were made by research nurses who had followed a special training program, whereas laboratory data and ECG recordings, including QTc interval, were evaluated by the general physician of the

psychiatric hospital. Interpretation of the data was performed by a trained investigator (first author).

2.4. Determination of metabolic syndrome.

MetS was defined according to the NCEP-ATP-III and the diagnosis was made when patients fulfilled three or more of the following five criteria: waist circumference >88/102cm (female/male), fasting blood glucose ≥6.1mmol/l and/or treatment with antidiabetic medication, HDL <1.3/1.0 mmol/l (female/male), TG ≥1.7 mmol/l, and blood pressure ≥130/85 mmHg and/or treatment with antihypertensives.

2.5. Analyses of data

All patients were treated with one or more antipsychotic agent (AP). For analysis of the data, patients were grouped according to the use of one antipsychotic drug, i.e. antipsychotic monotherapy (AMT) and two or more different antipsychotic compounds, i.e. antipsychotic polytherapy (APT). Patients who were on AMT were dichotomized by the use of typical or atypical compounds. In addition, patients with either haloperidol monotherapy (AMT-Hal) or clozapine monotherapy (AMT-Cloz) were clustered. In case patients were prescribed concomitantly antidepressants (AD), mood stabilizers (MS) or both (AD + MS), they were categorized separately. Finally, patients on antihypertensives, lipid lowering agents and antidiabetics were grouped.

2.6. Statistics

Means and standard deviations were calculated for the continuous variables. Chi-square and independent samples t-tests were used to evaluate the associations between (parameters of) MetS and demographic and clinical variables. Prevalence of MetS and its parameters was compared between the following subgroups: AMT vs. APT, conventional vs. atypical agents, AP without vs. with concomitant prescription of AD and/or MS. Pearson's correlation test and independent samples t-test were applied to calculate associations between MetS-parameters and plasma concentrations of clozapine, desmethylclozapine and haloperidol. Discriminant analysis was used to assess which MetS-parameters were the most contributing factors to a diagnosis of MetS. All data were analysed using SPSS 16.0 for Windows. Statistical significance was considered at the level of $p<0.05$.

3. Results

3.1. Demographic and clinical characteristics.

The study group comprised a total of 543 patients (mean age ± SD: 43.0 ± 12.5; age range: 18-81 years; female: n=230 (42%); male: n=313 (58%); GAF-score: mean ± SD: 56 ± 10; range: 10-80). According to the medical records, psychotic symptoms had become manifest approximately twelve years (median) prior to present examination (mean duration of illness: ± SD: 14.1 ± 9.8 years). A total of 243 patients had a diagnosis of schizophrenia of whom 39% fulfilled the symptomatic remission criteria.

As can be inferred from **table 1**, 439 patients (81%) were diagnosed with schizophrenia spectrum disorders (schizophrenia, schizoaffective disorder or another psychotic disorder) while 56 (10%) fulfilled the criteria for affective spectrum disorders (bipolar disorder or depressive disorder). In 48 patients (9%) other psychiatric diagnoses were made for which symptomatic treatment with antipsychotics was prescribed by the psychiatrist responsible for treatment.

3.2. Pharmacological treatment regimens.

The majority of patients used antipsychotic monotherapy (n=479; 88%). Conventional antipsychotics were prescribed to 140 patients (29%) (butyrophenones: n=61; diphenylbutylpiperidines: n=27; thioxanthenes: n=50 and phenothiazines: n=2). A total of 339 patients (71%) received atypical antipsychotics (risperidon: n=129, olanzapine: n=54, quetiapine: n=58, aripiprazole: n=24, clozapine: n=72, sertindole: n=1 and sulpiride: n=1). Sixty patients (11%)

Table 1. *Characteristics of the total patient group*

Demographics	*N=543*
Mean age (SD)	43.0 (12.6)
Male/female	313/230 (58/42%)
Caucasian	429 (79%)
DSM-IV classification:	
Schizophrenia	243 (45%)
Schizo-affective disorder	64 (12%)
Other psychotic disorder	132 (24%)
Bipolar disorder	28 (5%)
Depressive disorder	28 (5%)
Others	48 (9%)
GAF-score (SD)	56.1 (10.4)
Mean duration of illness (SD)	14.1 (9.8)
Number of antipsychotic agents:	
1 Antipsychotic	479 (88%)
≥ 2 Antipsychotics	64 (12%)
Other psychotropics:	
Antidepressants	156 (29%)
Mood stabilizers	107 (20%)
Benzodiazepines	224 (41%)
Anticholinergics	87 (16%)
Somatic treatments:	
Antihypertensives	70 (13%)
Lipid lowering agents	76 (14%)
Antidiabetics	36 (7%)

were treated with two antipsychotics (conventional only: n=6; atypical only: n=22; conventional + atypical: n=32). The remaining 4 patients (1%) used more than two antipsychotics in various combinations.

Of the total group, 124 patients (23%) were on co-treatment with antidepressants (tricyclic compounds: n=14, selective monoamine reuptake inhibitors: n=107, combination of the two classes: n=3), whereas 75 (14%) used mood stabilizers as co-medication (lithium: n=28, valproic acid: n=33, carbamazepine: n=1, lamotrigine: n=1, combination of different agents: n=12). In 32 patients (6%) an antidepressant in combination with a mood stabilizer was prescribed. With respect to somatic treatment regimens, 70 patients (13%) took antihypertensives, 76 (14%) were on lipid lowering agents and 36 (7%) used antidiabetic medications.

3.3. Metabolic syndrome in relation to antipsychotic treatment.

Key features of the total group concerning individual or family risk factors for the development of cardiovascular or metabolic disorders, like abdominal obesity, hypertension, smoking and alcohol use as well as family history of cardiovascular diseases and diabetes mellitus, are depicted in **table 2**.

From the total group of patients, 259 (48%) were diagnosed with MetS. Waist circumference, triglycerides and blood pressure were the most contributing factors. Patients with MetS were on average older than those without (44 vs. 42 years), but the difference did not reach the level of significance . No relationship between MetS and gender, smoking, ethnicity or remission status could be demonstrated. Concerning the MetS-parameters, males were more likely than females to meet the criteria for high blood pressure (63 vs. 48% [χ^2=13,0; p<0.001]) and high TG (59 vs. 46% [χ^2=8,5; p=0.004]), whereas abdominal obesity was more prevalent in females (80 vs. 48% [χ^2=55,0; p<0.001]). The rate of MetS and its parameters did not differ significantly between the AMT-group (58% out of n=479) and the APT-group (50% out of n=64). In the AMT group no numeric difference in MetS could be demonstrated between patients receiving conventional and atypical antipsychotics (46% and 48% respectively) neither for any of the MetS-parameters. Concerning atypical antipsychotics, percentages of MetS for clozapine, quetiapine, risperidone, aripiprazole and olanzapine were 54, 52, 49, 38 and 37% respectively. Rates of MetS for the conventional antipsychotics ranged from 39% for the butyrophenones to 52% for the thioxanthenes. No association could be demonstrated between plasma concentrations of haloperidol or (desmethyl)clozapine and MetS-parameters in the AMT-Hal and AMT-Cloz groups.

Table 2. *Frequency of cardiovascular risk factors*

Risk factors:	**Total group (n=543)**
Metabolic syndrome parameters	
Abdominal obesity	62%
Hypertension	57%
Hyperglycemia	23%
Low HDL-cholesterol	39%
High Triglycerides	53%
Metabolic Syndrome	48%
Other parameters	
Obesity (BMI≥30)	32%
Family history of DM[1] (first degree relative)	9%
High LDL-cholesterol (≥2.5 mmol/l)	73%
High total cholesterol (≥ 5.0 mmol/l)	57%
Smoking	62%
Daily alcohol use	42%
Daily substance use	10%
Family history of CVD[2]	11%
Long QTc interval (men>450, women>470 msec)	1%

1= diabetes mellitus; 2= cardiovascular diseases

3.4. Metabolic syndrome in relation to concomitant treatment with antidepressants and/or mood stabilizers.

Of the total group (n=543), 231 patients (43%) were on co-treatment with antidepressants and/or mood stabilizers (AD: n=124, MS: n=75, MS + AD: n=32). Prevalence of MetS was significantly higher in the group on co-treatment with AD and/or MS, as compared to that without AD and/or MS (57 vs. 41% [χ^2=14,4; p<0.001]). Rates of MetS increased significantly in the groups on co-treatment with MS, AD or a combination of MS and AD (53, 57 and 66% respectively [χ^2=15,74, df=3; p=0.001]) (**Figure 1**). No significant associations were found between (parameters of) MetS and type of antidepressant or mood stabilizing agent.

As compared to male patients, female patients had more frequently a diagnosis from the affective spectrum (31 vs. 16% [χ^2=17,8; p<0.001]) and received more often co-medication with AD and/or MS (51 vs. 36% [χ^2=12,5; p<0.001]). As can be inferred from **table 3**, female patients on AD and/or MS co-medication had significantly more frequent a diagnosis of MetS (60% vs. 37%). Prevalence of MetS and its parameters did not differ in male patients with or without AD and/or MS co-medication.

4. Discussion

In the present study the prevalence of MetS was investigated in a large group of Dutch outpatients with a mean age of 43 years, diagnosed with psychotic spectrum disorders, and receiving maintenance treatment with antipsychotics. MetS was found to be present in about half of the patients receiving antipsychotics, an about threefold higher number than the general population of the Netherlands (Dekker et al. 2005, Bos et al. 2007) and of the Western world in general (Ford et al. 2004, Bo et al. 2007, Jeppesen et al. 2007). No relationship could be demonstrated between MetS and age, gender, smoking, ethnicity and remission status. Similar to the findings by other investigators, waist circumference and triglycerides appeared to be the major contributing factors for the identification of MetS (Jin et al 2010, Mitchell et al. 2011).

The here observed prevalence of MetS is comparable to the percentages found in almost all studies published during the past decade (Mitchell et al. 2011). Albeit that few studies found that polypharmacy with antipsychotics is associated with an increased risk for MetS (Heiskanen et al. 2003, Cerit et al. 2010), our observation that antipsychotic polypharmacy is not associated with MetS is in line with the reports by several other investigators (Correll et al. 2007, Krane-Gartiser et al. 2011, Misawa et al. 2011). Concerning symptomatic reduction of psychopathology, more than one third of the patients with a diagnosis of schizophrenia met the remission criteria. Although this number is in agreement with the literature on naturalistic studies with schizophrenia (De Hert et al. 2007, Lambert et al. 2010), it does not reflect adequate social and/or vocational functioning (San et al. 2007, Tuinier et al. 2008, Shrivastava et al. 2010, Gorwood et al. 2011).

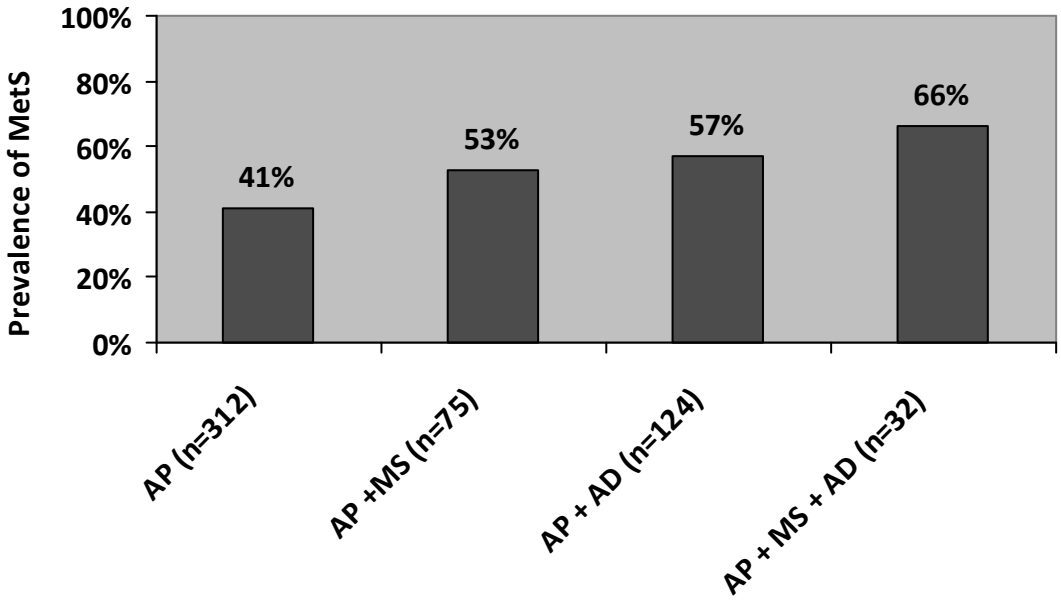
With respect to the differential risk of conventional and atypical antipsychotics for MetS, the results of the present study did not show differences between the

Table 3. *Metabolic syndrome and its parameters in male and female patients with antidepressive and/or mood stabilizing co-medication*

	Men		Women	
	AP without co-medication N=200	AP with co-medication N=113	AP without co-medication N=112	AP with co-medication N=118
Metabolic syndrome	43%	54%	37%	60%*
Abdominal Obesity	45%	54%	74%	85%*
Hypertension	60%	69%	46%	49%
High Triglycerides	58%	60%	37%	55%*
Low HDL cholesterol	36%	38%	38%	50%
Hyperglycemia	24%	23%	17%	25%

*Significant differences (p<0.05; χ^2-tests) between the two groups of female patients

Figure 1. *Effect of co-medication with antidepressants (AD) and/or mood stabilizers (MS) on the prevalence of metabolic syndrome in patients receiving antipsychotics (AP)**



* Concomitant prescription of AD and/or MS increased the prevalence of MetS significantly (χ^2=15,74, df=3; p=0.001)

two classes of compounds. Most other studies, however, have demonstrated that MetS-components are more often present in patients treated with atypical antipsychotics (Perez-Iglesias et al. 2007, Sikich et al. 2008, Smith et al. 2008, Falissard et al. 2011, Gautam and Meena 2011), an effect that is most probably related to their receptor binding profile (Newcomer 2005, Nasrallah 2008, De Hert et al. 2011).

No relationship between metabolic parameters and plasma concentrations of haloperidol and (desmethyl)clozapine was found. Until now, the associations between daily dose or plasma concentrations of antipsychotics and metabolic parameters are not clear albeit that clozapine plasma concentration, independent of daily dose, may be associated with metabolic dysregulations (Simon et al. 2009). With respect to haloperidol, no data are available about a potential relationship between plasma concentration and metabolic parameters.

Although the prevalence of MetS was not influenced by either antipsychotic polypharmacy or class of antipsychotic agent, concomitant treatment with mood stabilizing agents, antidepressants or both did increase the rate of MetS considerably, especially in females. No relationship between (parameters of) MetS and type of antidepressant or mood stabilizing agents could be demonstrated. As described by other investigators, each class of antidepressant and mood stabilizing medication is associated with various aspects of MetS (Keck and McElroy 2003, McIntyre et al. 2010).

To date, almost all studies on the prevalence of MetS in patients with psychiatric disorders do not distinguish between patients treated with different classes and combinations of psychotropic drugs. The results of one study, aimed to investigate the relationship between treatment with atypical antipsychotics, mood stabilizers or both, and the presence of MetS in bipolar patients, suggest that treatment with atypical antipsychotic agents is associated with higher MetS rates than treatment with a combination of mood stabilizers and atypical antipsychotics (Yumru et al. 2007). Since this study deals with relatively young bipolar patients only and information about the distribution of the different antipsychotics and comedication with other psychotropics, such as antidepressants, is not mentioned, no comparison with the results of the present study is possible.

The finding that there is a sex-specific difference in the metabolic effects of psychotropic polypharmacy is in accordance with studies that found MetS to be more frequently present in female patients treated with antipsychotic drugs as compared to male patients (McEvoy et al. 2005, De Hert et al. 2006, Bobes et al. 2007). In contrast, in the general population MetS is more prevalent among males (Dekker et al. 2005, Bo et al. 2007, Jeppesen et al. 2007). These findings are suggestive for a gender-specific vulnerability for disease and/or psychotropic induced metabolic effects (Haack et al. 2009). Further research is required to explore this hypothesis and its putative pathophysiological mechanisms.

Apart from medication effects, other factors may be involved in the susceptibility for MetS, such as a biological vulnerability associated with the mental disorder itself (Thakore et al. 2002, Ryan et al. 2003) and life style factors such as unhealthy diet and lack of physical exercise (Osborn et al. 2007, Chuang et al. 2008). Since these factors were not evaluated in the present study, it can not be excluded a priori that they have influenced the outcomes. Other limitations of this study

are that diagnoses were not made according to an assessment instrument but in accordance with the information from the medical records with subsequent confirmation by the at that moment responsible psychiatrist. Also, compliance to and duration of psychotropic treatment regimens could not be assessed since most patients had been treated with various antipsychotics and other psychotropics in the course of their disease with a mean duration of more than 10 years. Moreover, its cross sectional design is not appropriate to determine the exact treatment duration of the various psychotropics patients had been prescribed over the past decade.

The results of this naturalistic cohort study demonstrate that MetS develops in about half of the patients treated with antipsychotics for psychoses within the schizophrenia or affective spectrum. Since female patients are more frequently diagnosed with a psychotic disorder from the affective spectrum and are therefore receiving co-treatment with antidepressive or mood stabilizing compounds, their risk of MetS is substantially higher. It should be stressed, however, that not MetS per se, but its separate components are the main targets for somatic treatment. Therefore, future studies should focus primarily on prevention and adequate somatic treatment of the individual MetS-parameters in order to avoid cardiovascular complications at a relatively young age. Such a strategy is hampered by the poor access and quality of physical health care for psychiatric patients, even in the Western world.

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