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The Impact of Cardiometabolic Risk in Patients with Severe Mental Illness: From Evidence to Clinical Management

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1. Introduction

People with severe mental illness have an excess burden of physical comorbidity and mortality, especially due to cardiovascular illness, compared to persons without psychiatric disorders. Individuals with schizophrenia and bipolar disorder have an increased risk for obesity, type 2 diabetes, and other cardiometabolic risk factors but they usually receive inconsistent and insufficient physical monitoring and management. There is a wide array of variables that may potentially contribute to the increased comorbidity and mortality rates associated with major mental disorders and this is partly related to lifestyle factors such as poor diet, lack of exercise and smoking.

A final important source of cardiometabolic risk in major mental disorders is treatment itself although before the introduction of the antipsychotic drugs it was acknowledged that patients with schizophrenia and bipolar disorder may be at a higher risk of abnormal glucose metabolism and metabolic disorders compared to general population. The reasons for this difference may include an inherent increased risk of diabetes associated with the illness itself and an increased metabolic risk related to behaviors having a negative impact on health.

Although the main aim of the treatment of severe mental illness is to control psychotic symptoms and enable patients to function as normally as possible it is really important to considerer in choosing a treatment the impact on physical as well as mental health. The safety and tolerability of psychotropic drugs are especially important because of the chronicity of the illnesses being treated, the need for long-term therapy and the poor insight and motivation of many of the patients. The occurrence of side effects determines not only a reduction of the physical health of patients as a whole but also a reduction of compliance and we know that sub-optimal adherence to psychotropic medication, in particular antipsychotics, greatly increases the risk of relapse and rehospitalisation.

About antipsychotics, between-drug differences in efficacy are relatively modest for the atypicals, or between atypicals and conventionals, while differences in safety and tolerability are larger and more clinically relevant. The lower risk of extrapyramidal symptoms and tardive dyskinesia with atypical antipsychotics has allowed a greater focus on other physical health risks associated with these treatment. Antipsychotic drugs have side effects such as weight gain, lipid abnormalities and disturbance of glucose regulation

that increase the risk of the metabolic syndrome, a recognized cluster of features (hypertension, central obesity, glucose intolerance / insulin resistance and dyslipidaemia) that is predictive of both type-2 diabetes and atherosclerotic vascular disease.

About the side effect of antipsychotics, in the past few years, particular attention has been paid to the ability of these drugs to prolong the corrected QT (QTc) interval, which may result in torsades de pointes and sudden cardiac death. Other factors that could lead to QTc lengthening in psychotic patients are the presence of abnormalities in glucose metabolism and comorbid cardiovascular diseases witch are increased in patients treated with antipsychotics.

These matters emphasize that cardiovascular safety of antipsychotic drugs is of paramount importance because patients diagnosed with schizophrenia, schizoaffective disorder, or bipolar disorder are at high risk to begin with.

All reviews of the association between psychotic illness, metabolic syndrome and antipsychotic medication point to the need for routine physical health screening of patients prescribed antipsychotic drugs, whatever the indication for such treatment. The maintenance of physical health is an important factor in the successful global management of these patients. For these reasons there is clearly a need for clinicians to employ multiple strategies to minimize metabolic risk in schizophrenia patients, including using metabolically more neutral medications, promoting healthier lifestyle habits, developing expertise in switching antipsychotics for metabolic reasons and, most importantly, practicing good preventive care through regular monitoring of metabolic parameters.

In recent years the importance of physical health in people with psychotic illness treated with antipsychotics has led to monitoring recommendations cosponsored by different associations (endocrinology, cardiology and psychiatry) in United States and in Europe although general health care needs in psychiatric population are commonly neglected and psychiatrists mainly focus on efficacy of treatment of psychotic symptoms.

The aim of this chapter is to evaluate the clinical importance of cardiometabolic risk factors among persons with mental disorders, addressing the contribution of antipsychotic medications to increased cardiometabolic risk, and suggesting monitoring strategies for modifiable risk factors relevant to the treatment of serious mental illness.

A Medline search was performed to examine published data from 1990 through June 2011.

The search included the following keywords: ‘diabetes’, ‘weight gain’, ‘weight management’, ‘dyslipidaemia’, ‘metabolic syndrome’, ‘QTc interval’, ‘metabolic and cardiovascular risk’, and were used interchangeably and were also combined in the search together with ‘schizophrenia’, ‘bipolar disorder’, ‘severe mental illness’ and ‘antipsychotic drugs’.

Papers were included if they were published in English, with a diagnosis of schizophrenia or bipolar disorder and treatment with antipsychotic medication.

Studies were also included if the focus was on monitoring and improvement in metabolic profile through the application of different strategies, such as psychoeducational (exercise and dietary) interventions or switching patients to less metabolically offending medications.

2. The burden of cardiometabolic illness

Individuals with major mental disorder, including schizophrenia, bipolar disorder and schizoaffective disorder, are prone to many different physical health problems (De Hert et

al., 2011). While these diseases are also prevalent in the general population, their impact on individuals with major mental disorder is significantly greater (Maj, 2009).
Subjects with major mental disorder tend to have more illnesses and a shorter lifespan than the general population, having a life expectancy that is approximately 20% shorter (Newman & Bland, 1991). Recently, a multistate study in U.S, supported by the Center for Mental Health Services in collaboration with the National Association of State Mental Health Program Directors, found that patients with serious mental illness lost an average of 25 years of potential life expectancy compared to current life expectancy in the general population. (Table 1) (Colton & Manderscheid, 2006).

Year	Arizona	Missouri	Oklahoma	Rhode Island	Texas	Utah	Virginia
1997		**26.3**	**25.1**		**28.5**		
1998		**27.3**	**25.1**		**28.8**	**29.3**	**15.5**
1999	**32.2**	**26.8**	**26.3**		**29.3**	**26.9**	**14.0**
2000	**31.8**	**27.9**		**24.9**			**13.5**

Table 1. Mean Number of Years of Potential Life Lost (YPLL) per Public Mental Health Client Who Died During a Year in Which a Service Was Received (modified from Colton & Manderscheid, 2006)

Modifiable Risk Factors	Estimated Prevalence & Relative Risk (RR)	
	Schizophrenia	Bipolar Disorder
Obesity	**45–55%, RR: 1.5-2**	**21–49%, RR: 1-2**
Smoking	**50–80%, RR: 2-3**	**54–68%, RR: 2-3**
Diabetes	**10%–15%, RR: 2**	**8–17%, RR: 1.5-2**
Hypertension	**19–58%, RR: 2-3**	**35-61%, RR: 2-3**
Dyslipidemia	**25-69%, RR: ≤5**	**23-38%, RR: ≤3**
Metabolic Syndrome	**37-63%, RR: 2-3**	**30-49% RR: 1.5-2**

Table 2. Estimated prevalence and relative risk of modifiable cardiovascular disease risk factors in patients with schizophrenia and bipolar disorder compared to the general population (modified from Correl, 2007)

This mortality gap has been noted in different study (Saha et al., 2007; Robson & Gray, 2007) even in countries where the quality of the health care system is generally acknowledged to be good (Osby et al., 2000). The excess mortality was attributable to physical illness (Saha et al., 2007; Robson & Gray, 2007), with cardiovascular disease (CVD) being the major contributor (Colton & Manderscheid, 2006). A recent cohort study of primary care patients in the UK has confirmed the increased prevalence of CVD associated with severe mental illness (Osborn, 2007) and different authors agree that cardiovascular illness may partly

explain why patients with schizophrenia die at least 10 years earlier than the general population (Heald et al., 2010; De Hert et al., 2011).

Risk factors for cardiovascular morbidity and mortality in the general population include those that are inherently non-modifiable (gender, age, family history) and those that are modifiable through behavioural changes and improved care (Heald et al., 2010). The differential risk for morbidity and mortality from CVD in patients with schizophrenia and bipolar disorder compared to the general population can be explained by a 1–5-fold (Tab. 2) relative risk for modifiable risk factors for CVD (Correll, 2007). These risk factors include smoking (Hennekens et al., 2005; S. Davidson et al., 2001; Goff et al., 2005; Herran et al., 2004; Ucok et al., 2004), obesity (Hennekens et al., 2005; Fagiolini et al., 2005), diabetes (Fagiolini et al., 2005; Goff et al., 2005; Kilbourne et al., 2004), arterial hypertension (Hennekens et al., 2005; Fagiolini et al., 2005; Goff et al., 2005;), dyslipidemia (Hennekens et al., 2005; Fagiolini et al., 2005; Nasrallah et al., 2006) and metabolic syndrome (Meyer et al., 2005; McEvoy et al., 2005; Cohn et al., 2004; Kato et al., 2004; Heiskanen et al., 2003; Birkenaes et al., 2007; Yumru et al., 2007).

2.1 Metabolic syndrome

With regard to cardiovascular risk in persons with severe mental illness, of most concern is the development of metabolic syndrome (Casey, 2005; Angst et al., 2002). It has also been found in 37% of patients with long-term schizophrenia (Heiskanen et al., 2003) compared with 24% in the general population and after adjusting for age, these data suggest that persons with schizophrenia have double the incidence of the metabolic syndrome compared with the general population (Ford et al., 2002). Metabolic syndrome rates in patients with bipolar disorder and schizoaffective disorder have been reported to be 30-49% (Fagiolini et al., 2005; Pacholczyk et al., 2008; De Hert et al., 2011) and 42% (Basu et al., 2004), respectively.

With the metabolic syndrome, individuals have approximately a 5-6 fold increased risk of developing diabetes and a 3-6 fold increased risk of mortality due to coronary heart disease (Grundy, 2006; Hanson et al., 2002; Laaksonen et al., 2002, Fagiolini et al., 2005; Li & Ford, 2006; Bhargava, 2003; Grundy, 2006; Pacholczyk et al., 2008). In a study of 3606 general population subjects (Isomaa et al., 2001) over a median follow-up of 6.9 years, the presence of the syndrome was associated with significantly higher all-cause mortality (18.0% versus 4.6%; $p < 0.001$) and cardiovascular mortality (12.0% versus 2.2%; $p < 0.001$).

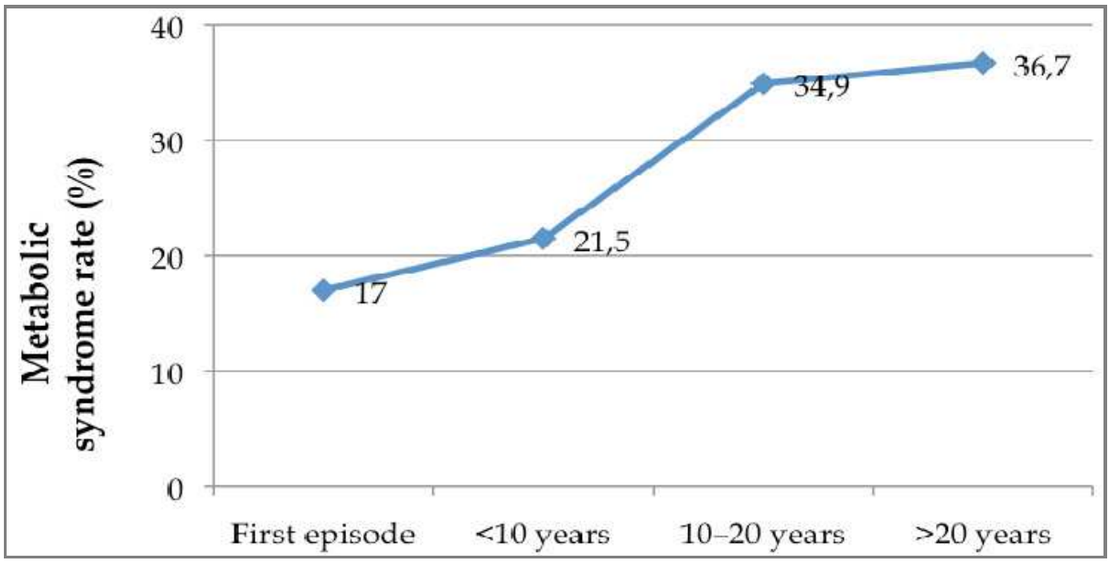
Despite several definitions of the metabolic syndrome have been proposed over the years (Tab. 3), there is agreement that the major characteristics of the syndrome include central obesity, hypertension, dyslipidemia, glucose intolerance or insulin resistance (Li and Ford, 2006; Grundy et al., 2005; De Hert et al., 2011).

Alarmingly, the metabolic syndrome risk appears to be relatively highest in younger patients, which is likely to be responsible for the dramatically reduced life expectancy (Colton and Manderscheid, 2006), with an increased risk over the course of the illness (Fig.1). In a cross-sectional study (Graph.1) metabolic syndrome rate, using NCEP ATP III definition, for first-episode patients (<1.5 years) was 17%; for recent onset patients (1.5– 10 years) it was 21.5%; for subchronic patients (10–20 years) it was 34.9%; and for chronic patients (>20 years) it was 36.7% (De Hert M et al., 2006).

Criteria	NCEP ATP III (2001)	NCEP ATP III A (2004)	IDF (2005)	IDF & AHA/NHLBI (2009)
Required factor	None but any 3 or more of the following	None but any 3 or more of the following	Central obesity plus any 2 of the following	None but any 3 or more of the following
Additional factors				
Obesity	waist circumference ≥102 cm (men) ≥88 cm (women)	waist circumference ≥102 cm (men) ≥88 cm (women)		Elevated waist circumference and country-specific definitions as defined by the IDF and AHA/ NHLBI until more data are available
Triglycerides	≥150 mg/dL (≥1.7 mmol/L) or on elevated triglycerides Rx	≥150 mg/dL (≥1.7 mmol/L) or on elevated triglycerides Rx	≥150 mg/dL (≥1.7 mmol/L) or on lipid abnormality Rx	≥150 mg/dL (≥1.7 mmol/L) (Rx for ele- vated triglycerides is an alternate indicator)
HDL - cholesterol	<40 mg/dL (<1.03 mmol/L)(men) <50 mg/dL (<1.29 mmol/L) (women) or on reduced HDL-cholesterol Rx	<40 mg/dL (<1.03 mmol/L)(men) <50 mg/dL (<1.29 mmol/L) (women) or on reduced HDL-cholesterol Rx	<40 mg/dL (<1.03 mmol/L)(men) <50 mg/dL (<1.29 mmol/L) (women) or on lipid abnormality Rx	<40 mg/dL (<1.0 mmol/L)(men) <50 mg/dL (<1.3 mmol/L) (women) (Rx for reduced HDL-cholesterol is an alternate indicator)
Blood pressure	≥130/85 mm Hg or on hypertension Rx	≥130/85 mm Hg or on hypertension Rx	≥130/85 mmHg or on antihypertensive Rx	≥130/85 mm Hg (antihypertensive Rx in a patient with a history of hypertension is an alternate indicator)
Glucose	≥110 mg/dL (≥6.1 mmol/L) (includes diabetes mellitus) or on elevated glucose Rx	≥100 mg/dL) (≥5.6 mmol/L) (includes diabetes mellitus) or on elevated glucose Rx	≥100 mg/dL (≥5.6 mmol/L) or previously diagnosed type 2 diabetes mellitus	≥100 mg/dL (≥5.6 mmol/L) (Rx of elevated glucose is an alternate indicator)

NCEP ATP III: Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)
IDF: International Diabetes Federation
AHA/NHLBI: American Heart Association/National Heart, Lung, and Blood Institute

Table 3. Definitions of the metabolic syndrome (modified from De Hert et al., 2011)



Graphic 1. Metabolic syndrome prevalence over the disease course of schizophrenia (modified from De Hert M et al., 2006)

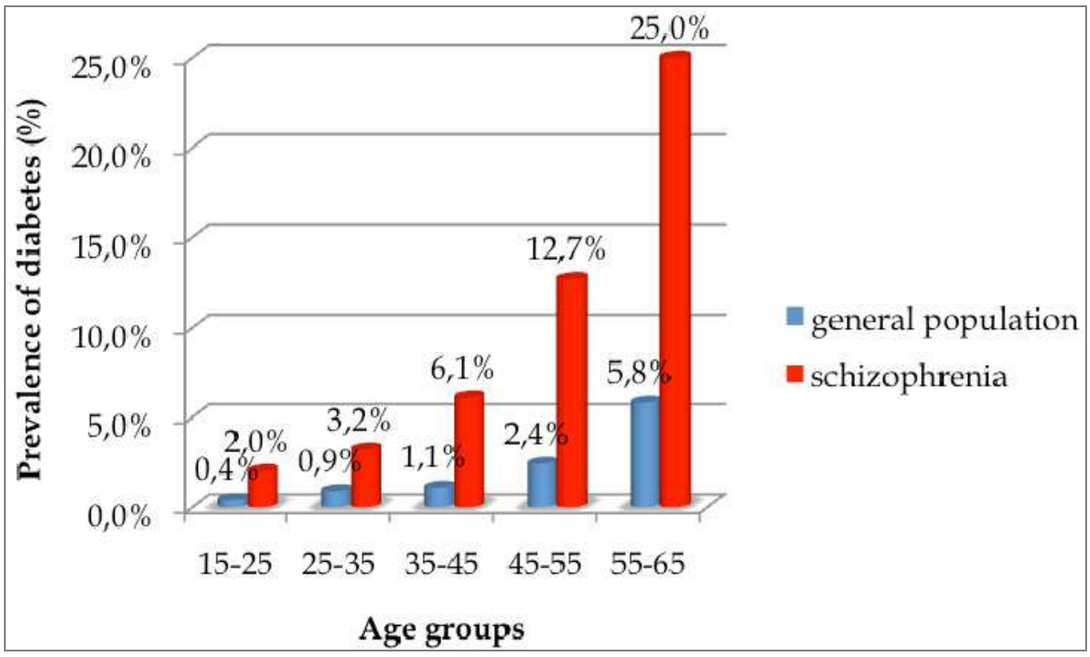
2.2 Diabetes

Currently, 70% of people with diabetes live in developing countries, and while diabetes is increasing across the world, its greatest increase will be in these countries (De Hert et al., 2011). By 2030 more than 80% of people with diabetes mellitus will live in developing countries (Whiting et al., 2010). Persons with diabetes have an increased risk of CVD, and CVD is the cause of death in 70% to 80% of these individuals (Sicree et al., 2003). Evidence suggests that the prevalence of diabetes in people with schizophrenia as well as in people with bipolar disorder and schizoaffective disorder is 2-3 fold higher compared with the general population (Bushe and Holt, 2004;).

The reason for the increased risk of diabetes mellitus in patients with major mental disorder is multifactorial and includes genetic and lifestyle factors as well as disease and treatment specific effects (Fig. 1). An increase in well-established diabetes risk factors in these patients partially accounts for much of the increased risk (De Hert et al., 2011). However, additional factors (disease, treatment) are important as well, and research suggests that, compared to the general population (De Hert M et al., 2006), the prevalence of diabetes in schizophrenia patients is 4 to 5 times higher in different age groups (Graph. 2).

In the general population two important factors that contribute to the development of diabetes are insulin resistance and obesity (Fig. 1). The link between obesity and diabetes is well established (Heald, 2010). A 10 year follow-up study has shown that people with a body mass index (BMI) of ≥35 are approximately 20 times more likely to develop diabetes than age and gender-matched subjects with a BMI of <25 (Field et al., 2001).

The reasons of an higher prevalence of diabetes in schizophrenia patients over the course of the illness is probably an effect of an increased prevalence of obesity, often attributed to antipsychotic treatment (Montejo, 2010; Mulnier et al., 2006).



Graphic 2. Prevalence of diabetes in schizophrenia patients over the disease course compared to the general population (modified from De Hert M et al., 2006)

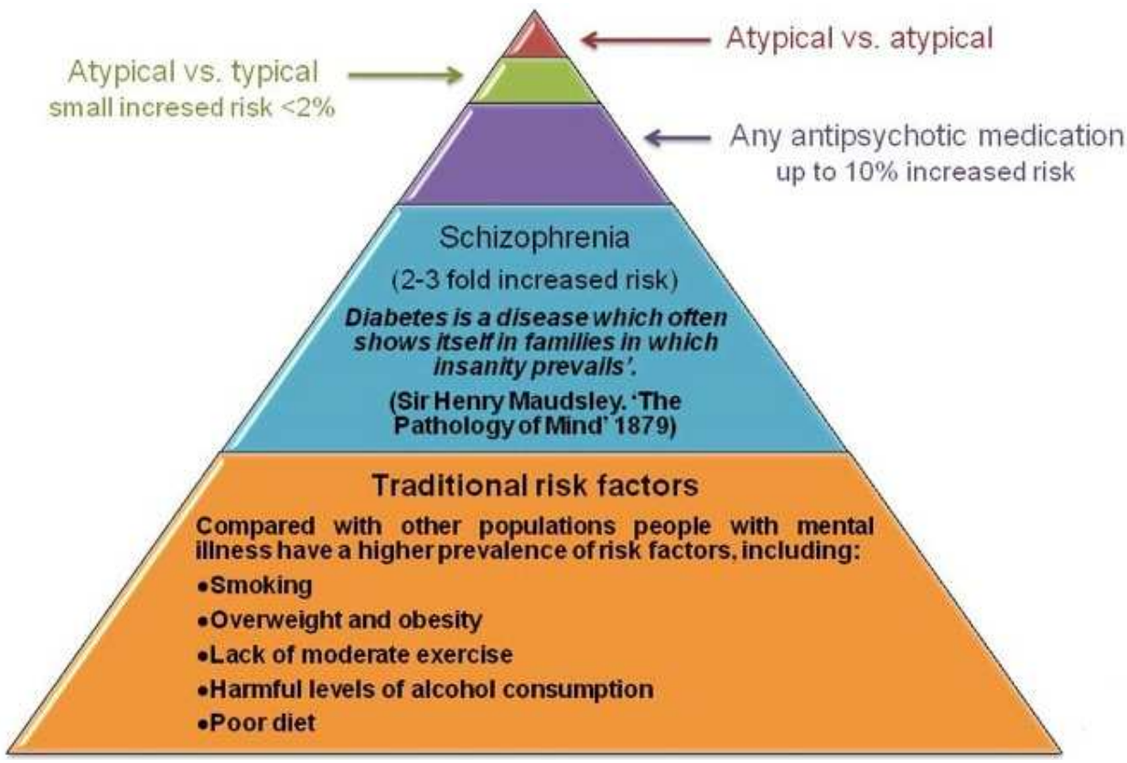
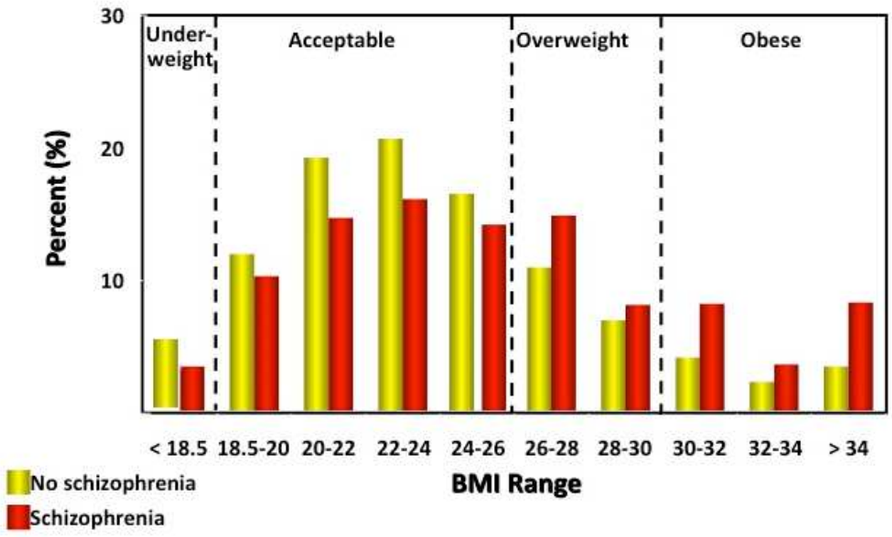


Fig. 1. Factors influencing the risk of diabetes among patients with schizophrenia (M. Smith et al., 2008)

2.3 Obesity

Obesity is becoming a significant and growing health crisis, affecting both developed and developing countries (Haslam & James, 2005; De Hert et al., 2011). People with obesity have shorter life spans and are at increased risk for a number of general medical conditions, including type 2 diabetes mellitus, diabetes mellitus (relative risk, RR >3), cardiovascular disease, CVD (RR >2-3), dyslipidemia (RR >3), hypertension (RR >2-3), respiratory difficulties (RR >3), reproductive hormone abnormalities (RR >1-2) and certain cancers (e.g., colon) (RR >1-2) (McElroy, 2009; Bray & Wilson, 2008). Levels of obesity are higher in those with schizophrenia and depression, as well as the mortality from obesity-related conditions such as coronary heart disease (Allison et al., 2009). Increasing evidence suggests that persons with major mental disorder are, compared to the general population, at increased risk for overweight and obesity (Graph. 3) (Allison et al., 1999; Dickerson et al, 2006).



Graphic 3. BMI distributions in schizophrenia patients and the general population (Allison et al., 1999)

This excess prevalence, however, has not been reported consistently in the past. Despite some early reports of obesity in the pre-antipsychotic era (Kraepelin, 1919), classical descriptions of schizophrenia refer to a thin 'neurasthenic' body habitus and many people with first-episode psychosis are not overweight (Green et al., 2006; Lieberman et al., 2003). Some recent studies show that drug-naive schizophrenia does not present with higher rates of obesity and metabolic problems than a normal population with comparable lifestyle (Padmavati et al., 2010; Verma et al., 2009). Taken together these findings suggest that other factors such as treatment or lifestyle factors may be play an important role in the development of weight gain in these patients over the course of the illness.

2.4 Dyslipidemia

Any increase in cholesterol levels has significant health implications, as a 10% increase in cholesterol levels is associated with a 20% to 30% increase in the risk of coronary heart disease (LaRosa et al., 1990).

Elevated fasting triglycerides (TG) are a direct result of insulin resistance, because insulin-dependent lipases in fat cells are normally inhibited by insulin (Stahl et al., 2009). As insulin resistance worsens, inappropriately high levels of lipolysis lead to the release of excess amounts of free fatty acids that are hepatically transformed into TG (D.A. Smith, 2007). Elevated fasting TG levels thus become a sensitive marker of insulin resistance, with fasting TG to high density lipoprotein (HDL) ratios (TG : HDL) ≥ 3.0 performing better than fasting glucose in predicting insulin resistance (McLaughlin et al., 2003).

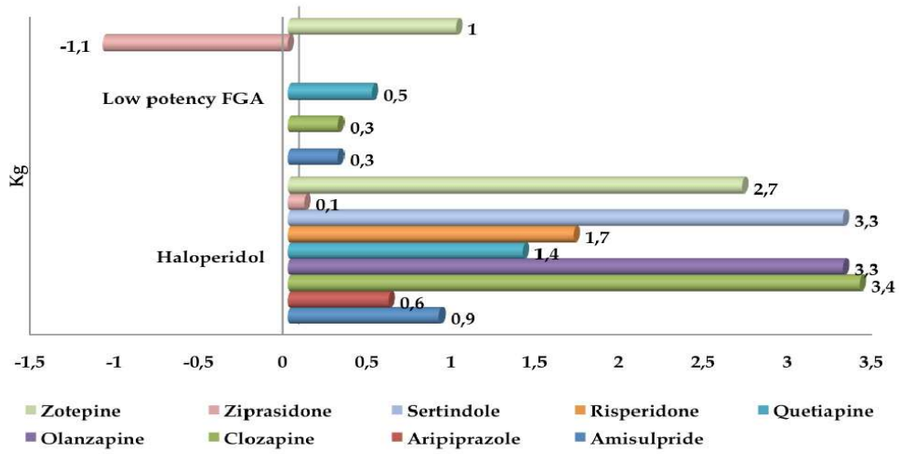
While fasting TG values provide important information on insulin resistance, fasting TG and especially non-fasting TG, also correlate with cardiovascular risk. recent studies indicate that nonfasting TG may be more important for the development of atherosclerotic arterial injury and subsequent CV risk.

The basis of this assertion lies in the concept that arterial injury may occur primarily during the postprandial period, when TG-rich particles are at their highest level and penetrate arterial intimal cells (Eberly et al., 2003). Results of a large (n = 13 981) European trial with extensive follow-up (mean 26 years), indicate a significant correlation between non-fasting TG levels and risk of major cardiovascular events (Nordestgaard et al., 2007).

3. Treatments exacerbate cardiometabolic risk factors

In addition to increased vulnerability to developing physical health problems, it has also been reported that side-effects of antipsychotic drugs have been linked to other physical health conditions such as weight gain, diabetes, and dyslipidaemia (Bobes et al., 2010). Equally, antidepressants (AD) such as paroxetine (Fava et al., 2006), and mood stabilizers, such as lithium and valproate (Bowden et al., 2000), have been associated with weight gain.

While first-generation antipsychotics (FGAs) might also lead to weight gain, especially the less frequently used low-potency FGAs, certain second-generation antipsychotics (SGAs) are now known to induce much greater weight gain (Graph. 4) and cardiometabolic changes in certain patients (Leucht et al., 2009).



Graphic 4. Effect of second generation versus first-generation antipsychotic on weight gain (modified from Leucht et al., 2009)

Of these agents, clozapine and olanzapine are generally associated with the greatest impact on body weight during both shorter- and longer-term (Leucht et al., 2009) therapy. Data suggest that risperidone has an intermediate effect on weight in the short term, and quetiapine appears to have a short-term weight gain potential similar to that of risperidone (Leucht et al., 2009). By comparison, the newer antipsychotic agents, aripiprazole and ziprasidone, are associated with minimal weight gain (Leucht et al., 2009).
The paliperidone extended release, the active metabolite of risperidone, has the same weight gain profile as its parent drug (M. Davidson et al., 2007).
No agent, however, should be considered as truly weight-neutral, as the proportion of individuals experiencing ≥7% weight gain is greater with any SGAs than with placebo (Citrome, 2007), and all antipsychotics have been found to cause significant weight gain in antipsychotics naïve or first-episode patients (Alvarez-Jiménez et al., 2008; Correll et al., 2009; Saddichha et al., 2007) (Tab. 4).
Another important issue is that the weight gain during treatment with antipsychotics occurs in the first weeks (4-6), therefore careful monitoring is necessary to start from the beginning of treatment (Jones et al., 2001; Kinon et al., 2005).

Drug	Weight gain	Glucose effects	Lipid effects	QTc prolungation
Clozapine	**+++**	**+++**	**+++**	**0**
Olanzapine	**+++**	**+++**	**+++**	**0**
Risperidone	**++**	**++**	**++**	**+**
Quetiapine	**++**	**++**	**++**	**0**
Amisulpride	**+**	**+**	**+**	**0**
Aripiprazole	**0**	**0**	**0**	**0**
Ziprasidone	**0**	**0**	**0**	**++**
Paliperidone	**++**	**0**	**0**	**0**
Sertindole	**++**	**++**	**++**	**++**
Zotepine	**+++**	**+++**	**+++**	**+**
Haloperidol	**+**	**0**	**0**	**+ (IV)**
0 = no risk or rarely causes side effects at therapeutic dose, + = mild or occasionally causes side effects at therapeutic dose, ++ = sometimes causes side effects at therapeutic dose, and +++ = frequently causes side effects at therapeutic dose.				

Table 4. Cardiometabolic side effects of antipsychotics (modified from Marder et al., 2004)

Although the mechanisms underlying weight gain are still unknown after initiation of antipsychotic treatment, a strong increase of appetite is combined with immediate substantial weight gain (Theisen et al., 2003; Gebhardt et al., 2007). The level of H1 antagonism associated with different antipsychotic medications is hypothesized to modulate feeding behavior (increased appetite and decreased sensation of satiety), based on the significant association of weight gain and the binding affinity for this receptor. Antipsychotics with minimal affinity for H1 receptors, such as aripiprazole, ziprasidone, and haloperidol, are associated with limited weight gain, while antipsychotics with a high affinity for H1 receptors, such as clozapine, olanzapine, thioridazine, and chlorpromazine, are associated with clinically significant increases in weight (Newcomer, 2005).
Serotonin 2C receptors have been another area of focus, based on data derived from mice with the 5HT2C gene "knocked out" (Stahl et al., 2009). The combined blockade of H1 and

5HT2C receptors has been especially associated with weight gain – sometimes profound – and could explain why atypical antipsychotics such as olanzapine and clozapine, which have high 5HT2C as well as H1 affinities, might have greater weight gain liabilities than an agent such as chlorpromazine, which lacks appreciable 5HT2C effects, even though it has H1 antagonist properties (Cutler et al., 2008; Kroeze et al., 2003).

The high interindividual variability in medication-induced weight gain suggests that genetic factors influence the risk to gain weight (Holt and Peveler, 2009).

Studies of genetic predictors of weight gain under antipsychotic therapy have mainly but not exclusively (Vehof et al., 2010) focused on HTR2C (Mulder et al., 2007; Opgen-Rhein et al., 2010) and LEPR (Opgen-Rhein et al., 2010; Gregoor et al., 2009) gene polymorphisms.

Second generation antipsychotics seem also to have a stronger diabetogenic risk than first generation antipsychicotics (Scheen and De Hert, 2007; Okumura et al., 2010; Citrome et al., 2007), the risk being 1.3 fold higher in people with schizophrenia taking SGAs compared with those receiving FGAs (M. Smith et al., 2008). However, the risk of diabetes-related adverse events differs between SGAs. specifically olanzapine (Ramaswamy et al., 2006; Yood et al., 2008; Koller & Doraiswamy, 2002; Starrenburg & Bogers, 2009) and clozapine (Yood et al., 2008; Starrenburg &Bogers, 2009; Koller et al., 2001) and, to a lesser extent, quetiapina (Koller et al., 2004) and risperidone (Koller et al., 2003), are associated with an increased risk of diabetes (Strassnig et al., 2003) in people who have schizophrenia or bipolar disorder (Guo et al., 2007; Guo et al., 2006). A recent large-scale pharmacoepidemiologic study (including 345.937 patients) found low to moderate, but significantly increased rates of incident DM compared with the general population for clozapine (RR=1.45), olanzapine (RR=1.29) and risperidone (RR=1.23). Rates increased two or more times with ziprasidone and sertindole. Aripiprazole, amisulpride and quetiapina did not have a significantly increased rate (Kessing et al., 2010).

Other psychotropic drugs such as antidepressants may also increase the risk of diabetes mellitus, probably partly due to side effects such as sedation, increased appetite, and weight gain (Sussman et al., 2001; L.C. Brown et al., 2008). Given the heterogeneity and small sample sizes of the few currently available studies, it is unclear whether or not specific antidepressants themselves may increase the risk of diabetes mellitus. Nevertheless, it seems that an increased risk of diabetes is associated with the concurrent use of tricyclic antidepressants and serotonin reuptake inhibitors (SSRIs) (OR=1.89) (L.C. Brown et al., 2008), the long-term use of both tricyclic antidepressants (incidence rate ratio, IRR=1.77) and SSRIs (IRR=2.06) in at least moderate daily doses (Andersohn et al., 2009), as well as the use of antidepressant medication in high-risk patients (Rubi net al., 2008). Furthermore, although understudied, certain mood stabilizers, especially valproate, have been associated with an elevated risk for the development of insulin resistance (Verrotti et al., 2009; Pylvänen et al., 2006), conferring a risk for diabetes mellitus, which is possibly related to weight gain (Masuccio et al., 2010), and/or fatty liver infiltration (Luef et al., 2004), but also to valproate itself (Pylvänen et al., 2002).

Additionally to weight gain and diabetes, some SGAs cause hypertriglyceridaemia, which is an independent risk factor of coronary arteriosclerosis (Tschoner et al., 2007). A prospective study comparing the effects of the SGAs clozapine, olanzapine, risperidone and the FGA sulpiride on glucose and lipid metabolism in first-episode schizophrenia at baseline and 8 weeks after inclusion showed that besides higher C-peptide, fasting insulin and insulin resistance index (IRI), cholesterol and triglyceride levels were significantly increased in the clozapine and olanzapine groups (Wu et al., 2006). Because of these results the authors

recommend that baseline and 6-month monitoring of fasting blood glucose, fasting cholesterol and triglyceride levels should be obtained in routine clinical practice with all antipsychotics to monitor the risk for development of hyperglycaemia and hypercholesterolaemia. Another study described a negative effect of olanzapine administration on total cholesterol and triglycerides, whereas favourable metabolic effects were observed in ziprasidone-treated patients with regard to total cholesterol, LDL and HDL (R.R. Brown & Estoup, 2005). These results were confirmed in different studies (Lieberman et al., 2005; Rettenbacher et al., 2006) and the authors suggest ziprasidone as a favourable alternative treatment for already overweight patients.

In the assessment of cardiometabolic risk, in recent years, particular attention has been paid to the ability of psychotropic drugs to prolong the corrected QT (QTc) interval, which may result in torsades de pointes and sudden cardiac death (Glassman, 2005; Zareba, 2007). An increasing number of psychotropic drugs, are known to delay cardiac repolarization and to induce torsade de pointes. Antipsychotic drugs have a dose-dependent effect on the myocardial repolarization by inhibiting the delayed potassium rectifier current (IKr) (Yap & Camm, 2003). There is a consensus that QTc values >500 msec, or an absolute increase of 60 msec compared with drug-free baseline, puts a patient at significant risk of torsade de pointes, ventricular fibrillation and sudden cardiac death (Haddad and Sharma, 2007; Pies, 2001; Elbe & Savage, 2010). Most antipsychotics and some antidepressants may be associated with QTc prolongation (Glassman, 2005). Patients using AP have higher rates of cardiac arrest or ventricular arrhythmias than controls, with ratios ranging from 1.7 to 5.3 (Ray et al., 2001; Hennessy et al., 2002; Reilly et al., 2002). Antipsychotics associated with a greater risk of QTc prolongation include pimozide, thioridazine and mesoridazine among the FGAs (Vieweg, 2002; Reilly et al., 2002) and sertindole and ziprasidone among the SGAs (Thomas et al., 2010). However, the largest randomized study to date (n=18,154) did not find a statistically significant difference in the risk of sudden cardiac death between ziprasidone and olanzapine treated patients with schizophrenia (Strom et al., 2011).

3.1 The time of monitoring

The maintenance of physical health is an important factor in the successful global management of schizophrenia patients. Research studies have continued to draw attention to monitoring the physical health of patients with schizophrenia in order to successfully enhance these individuals' quality of life (Nasrallah, 2005). In the past decades physical health monitoring of patients with severe mental disorder looked for the extrapyramidal symptoms and tardive dyskinesia often associated with conventional antipsychotics. Atypical antipsychotics were developed to overcome extrapyramidal side effects associated with the use of typical antipsychotics at clinically effective doses, and this has led to widespread use since their introduction over a decade ago (Balf et al., 2008). Despite these benefits, the use of second generation antipsychotics has also been associated with reports of dramatic weight gain, diabetes and atherogenic lipid profiles (Newcomer et al., 2002).

Over recent years, both national and international groups have developed screening and monitoring guidelines (ADA, 2004; De Hert et al., 2009). These guidelines are based on the principle that it is particularly important to establish baseline CVD risk at initial presentation so that any subsequent change during treatment can be monitored. The medical history and examination should therefore include: history of previous CVD, diabetes or other related disease; family history of premature CVD, diabetes or other related

disease; smoking habit; weight and height in order to calculate body mass index (BMI) and waist circumference; fasting blood glucose; fasting blood lipids: total cholesterol, triglycerides, LDLcholesterol (by calculation) and HDL-C; blood pressure (measured twice and average taken), heart rate, heart and lung auscultation, foot pulses; ECG (De Hert et al., 2009).

	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 12
History of previous CVD or other related disease	X							
Smoking habit	X							
Weight	X	X	X	X	X	X	X	X
Heigh	X							
Waist circumference	X	X						
Fasting blood glucose	X						X	X
Total cholesterol	X						X	X
Triglycerides	X						X	X
LDL-C	X						X	X
HDL-C	X						X	X
Blood pressure	X							
ECG	X		X					

Table 5. Screening and monitoring of cardiovascular disease risk factors (modified from De Hert et al., 2009).

It is recommended that measurements should be taken at the initial presentation and before the first prescription of antipsychotic medication (Tab. 5). The frequency of testing will depend on the patient's medical history and the prevalence of baseline risk factors. For patients with normal baseline tests, it is recommended that biochemical measurements are repeated at 6 weeks and 12 weeks after initiation of treatment and at least annually thereafter. The frequency of testing will depend on the presence of risk factors and detected abnormalities. During the initial phase of treatment, it is important to measure weight weekly to identify those individuals who gain weight rapidly with psychotropic treatment. In patients with diabetes, an assessment of glycaemia control by HbA1c should be made regularly (approximately every 3 months).

The huge amount of data on cardiometabolic side effects of antipsychotics have shifted over the years the attention of the clinicians to a greater perception of cardiometabolic diseases in patient with severe mental illness (Fig. 2) although still several studies indicate that mentally ill patients receive substandard care regarding routine metabolic monitoring (Haupt et al., 2009).

Since the publication of monitoring guidelines in 2004 (ADA 2004) the following recommendations have been generally accepted as the standard of care: assessment of CVD risk factors and all five components of the metabolic syndrome (ie, weight and waist circumference, blood pressure, and fasting glucose and lipids) prior to antipsychotic initiation; weight assessments at each visit (or monthly for the first 3 months and then

quarterly); and assessment of all components of the metabolic syndrome at 3 months and annually. However a retrospective study which evaluated plasma lipid and glucose testing rates in patients receiving second-generation antipsychotics before and after guidelines were published revealed monitoring for plasma lipids and glucose in this population remains low (Haupt et al., 2009).

Reasons are complex and involve patient nonadherence with medical appointments and interventions, suboptimal monitoring and management behaviors of mental and medical health care providers, and systems issues of fragmented care and poor access to care.

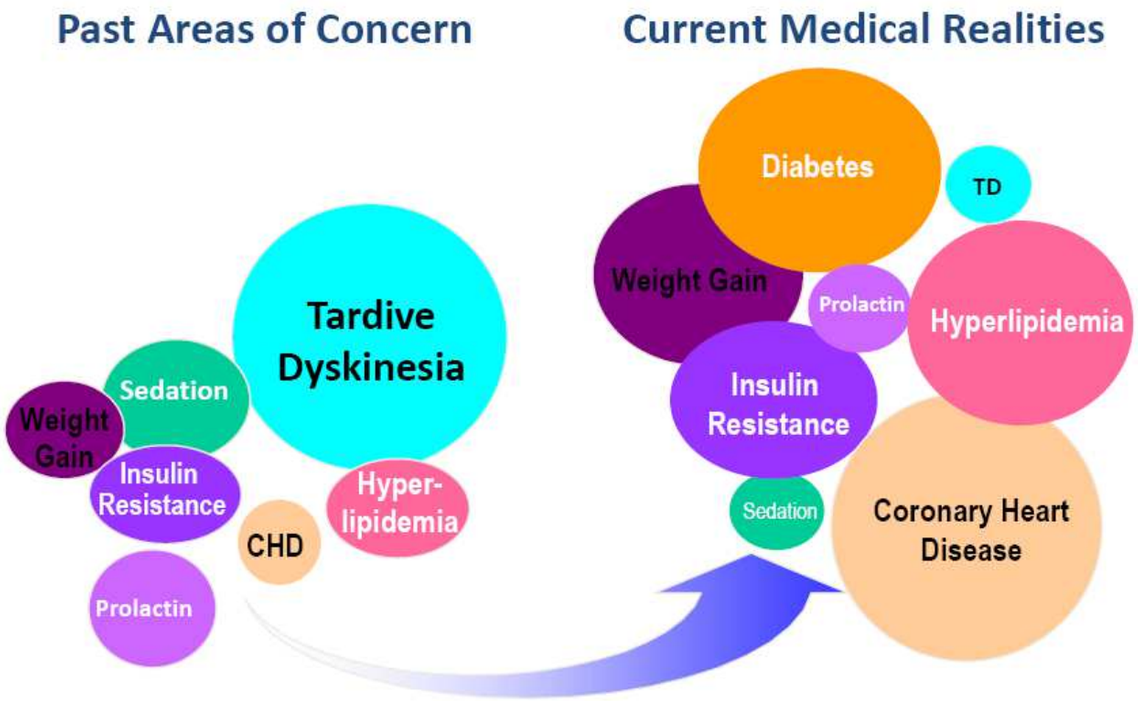


Fig. 2. Shift in risk perception of antipsychotics

3.2 Practical issue to reduce cardiometabolic risk

Given the increased incidence of CVD mortality in people with schizophrenia and bipolar disorder, efforts should be made to lower the modifiable risk factors in this population. A reduction in the prevalence of metabolic syndrome is an important target to improve the physical health of patients with severe mental illness (Heald, 2010). If the patient has central obesity, hypertensive blood pressure (≥130/85 mm Hg), pre-diabetes (fasting plasma glucose =100-125 mg/dL or hemoglobin A1C =5.7-6.4%) or DM (fasting plasma glucose ≥126 mg/dL or hemoglobin A1C >6.4%), or marked dyslipidemia (total cholesterol >350 mg/dL; LDLcholesterol >160 mg/dL; triglycerides >300 mg/dL), he/she should be referred

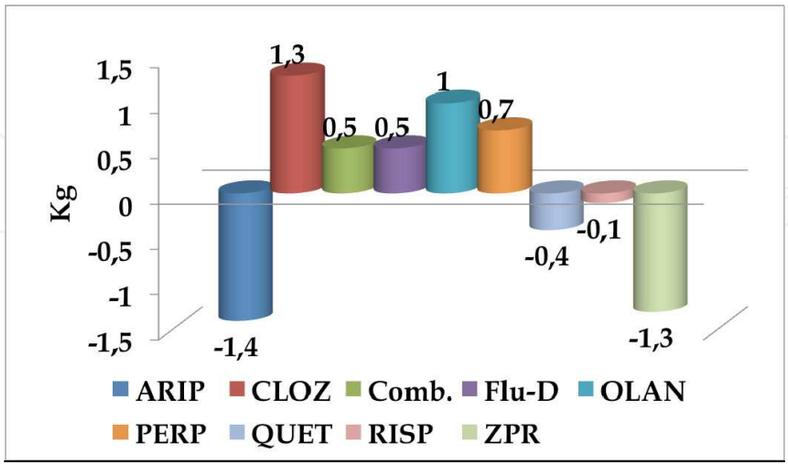
to primary care provider to treat these conditions, unless simple healthy lifestyle guidance or behavioural adjustment and/or switching to a lower cardiometabolic risk medication can address these medical conditions adequately (De Hert et al., 2009).

Non-pharmacological interventions, incorporating dietary and physical activity modifications, demonstrated promise in terms of preventing weight gain in schizophrenia (De Nayer et al., 2005; Sáiz Ruiz et al., 2008; Buckley et al., 2005; Haupt et al., 2009; Vreeland, 2007; Faulkner et al., 2007; Alvarez-Jiménez et al., 2008). The impact on one's overall health, even with simple life style changes, is considerable. A healthy diet, regular physical activity and quitting smoking are the key components of lowering the prevalence and impact of modifiable risk factors. However, if lifestyle interventions do not succeed, medication, including statins, anti-hypertensive therapy or antidiabetic agents, may be indicated. These drugs should be prescribed and managed as for the general population and are generally well tolerated (Cormac, 2009; Laurent & Simons, 2009). Moreover, pharmacologic treatments added to reduce antipsychotic-related weight can be tried. To date, most evidence exists for metformin (500 to 1000 mg bid with meals) or topiramate (50-200 mg in divided doses) (Maayan & Correll, 2010).

If these strategies fail, the clinician should consider switching from a medication with a higher weight-gain liability to one with a lower weight gain liability. Ziprasidone and perphenazine treatments in the CATIE trial (Lieberman et al., 2005) were associated with mean weight loss, most likely related to the switch from a previous antipsychotic treatment. Of those patients who had gained > 7% of their body weight in initial phase of the CATIE who were then randomly assigned to ziprasidone in the second phase of the trial (Stroup et al., 2006), 42% lost more than 7% of their body weight; 20% of those randomly assigned to risperidone lost more than 7% of their body weight; and 7% of patients randomly assigned to quetiapina lost 7% of their body weight. None of the patients who gained >7% of their body weight in the initial phase of the study and were then randomly assigned to olanzapine in the subsequent phase lost more than 7% of their body weight. In phase 3 (Stroup et al., 2009), participants selected openly from the following nine possible treatment regimens: antipsychotic monotherapy with oral aripiprazole (ARIP), clozapine (CLOZ), olanzapine (OLAN), perphenazine (PERP), quetiapine (QUET), risperidone (RISP), or ziprasidone (ZPR); long-acting injectable fluphenazine decanoate (Flu-D); or a combination of any two of these treatments (Comb). If the selected treatment was not discontinued because of inadequate efficacy, intolerability, or any other reason, patients could continue taking this regimen until the completion of 18 months of study treatment. Of the common choices, those who selected aripiprazole and ziprasidone had the highest body mass index and the most monthly weight loss was associated with aripiprazole and ziprasidone (Graph. 5).

Clinicians should consider switching antipsychotics when there is a clear relationship between antipsychotic exposure and change in healthrisk category (i.e., obesity, diabetes, sleep apnea), the patient is about to stop or has stopped antipsychotic use because of weight gain, the patient has bulimia or the patient is abusing weight loss drugs due to newly developed weight gain on antipsychotic treatment. Current evidence (Weiden, 2007) indicates that switching is an effective strategy primarily in patients whose weight gain is attributable to preswitch antipsychotic and in whom long-term monotherapy with a weight-neutral agent can be maintained. In this population, the effectiveness of switching appears to be related to a reversal of the weight-increasing effects of a prior antipsychotic medication.

Regarding the effect of antipsychotics on the QTc interval, the use of lower doses and monotherapy may represent an effective strategy in reducing the risk of QTc lengthening (Di Sciascio et al., 2011).



Graphic 5. Weight change among the commonly selected treatments in Phase 3 of CATIE (Stroup et al., 2009)

4. Conclusion

The mortality gap between patients with severe mental illness and the general population has substantially widened in recent decades, warranting close attention to the cardiovascular health of this patient population. Reasons for the increased prevalence rates of CHD risk factors are complex, but include effects of mental illness, poor lifestyle behaviors, weight gain, and metabolic abnormalities conferred by psychiatric treatments, particularly by SGAs. While the mechanisms for weight gain are still unclear and direct, weight-independent mechanisms for at least some SGAs regarding glucose and lipid abnormalities have been discussed, it is clear that antipsychotics differ in their risk for adverse changes in body weight and metabolic dysregulation (Correll, 2007).

As individuals with mental illness are more likely to be overweight or obese than the general population, weight should be routinely monitored in all patients, especially in those receiving treatment with atypical antipsychotic medications associated with weight gain (Balf et al., 2008).

Routine adverse-effect monitoring should be part of any pharmacologic treatment. For antipsychotics, this should include baseline assessments of EPS and abnormal involuntary movements, sleep duration and quality, daytime sedation, sexual and reproductive dysfunction, and risk factors for cardiovascular disease, including unhealthy lifestyle (Correll, 2007).

By using the charts and tables in this article, clinicians will be better informed to educate the patient in a variety of interventions that will diminish the potential for medication side effects, promote better pharmacologic efficacy from prescribed medications, and improve the overall quality of life.

In conclusion, the management of patients at risk of cardiometabolic disease can be complex, but if performed systematically and in conjunction with healthcare professionals

who can address the metabolic complications in a complementary fashion, it can provide a clinical outcome that will be potentially very beneficial to the individual patient. The reintegration of psychiatric care and general somatic services seems to represent one of the most important challenges for psychiatric care today.

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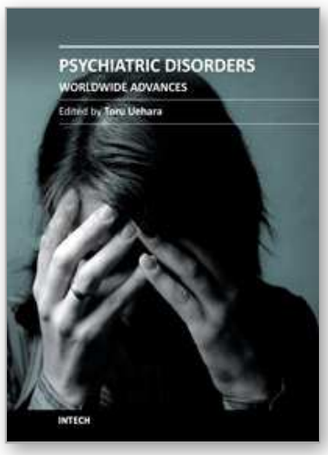

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A psychiatric disorder is defined as any complex condition that involves the impairment of cognitive, emotional, or behavioral functioning. Aside from knowing the physical organic factors, its causal pathology has remained a mystery. Regarding recent advances in psychiatry and neurosciences, psychiatric disorders have been closely associated with socio-cultural, psychological, biochemical, epigenetic or neural-networking factors. A need for diverse approaches or support strategies is present, which should serve as common knowledge, empathetic views or useful skills for specialists in the filed. This book contains multifarious and powerful papers from all over the world, addressing themes such as the neurosciences, psychosocial interventions, medical factors, possible vulnerability and traumatic events. Doubtlessly, this book will be fruitful for future development and collaboration in â€œworld psychiatryâ€.

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