Available online at ScienceDirect www.sciencedirect.com
Elsevier Masson France EM|consulte www.em-consulte.com
EUROPEAN PSYCHIATRY
European Psychiatry 24 (2009) 412–424

Review

Cardiovascular disease and diabetes in people with severe mental illness position statement from the European Psychiatric Association (EPA), supported by the European Association for the Study of Diabetes (EASD) and the European Society of Cardiology (ESC)

M. De Hert [a,*], J.M. Dekker [b], D. Wood [c], K.G. Kahl [d], R.I.G. Holt [e], H.-J. Möller [f]

[a] *University Psychiatric, Centre Catholic University, Leuven campus Kortenberg, Leuvensesteenweg 517, 3070 Kortenberg, Belgium*
[b] *Department of Epidemiology and Biostatistics and the EMGO, Institute for Health and Care Research, VU University Medical Centre, van der Boechorststraat 7, 1081 BT Amsterdam, The Netherlands*
[c] *National Heart and Lung Institute Cardiovascular Science, Imperial College, Charing Cross Campus, W6 8RP London, United Kingdom*
[d] *Department of Psychiatry, Social Psychiatry and Psychotherapy, Hannover Medical School, Carl-Neubergstrasse. 1, 30625 Hannover, Germany*
[e] *Endocrinology & Metabolism, Developmental Origins of Health and Disease, School of Medicine, University of Southampton, Southampton SO16 6YD, United Kingdom*
[f] *Department of Psychiatry, Ludwig-Maximilians-University, Nussbaumstrasse 7, 80336 Munich, Germany*

Received 22 January 2009; accepted 29 January 2009
Available online 13 August 2009

Abstract

People with severe mental illnesses, such as schizophrenia, depression or bipolar disorder, have worse physical health and reduced life expectancy compared to the general population. The excess cardiovascular mortality associated with schizophrenia and bipolar disorder is attributed in part to an increased risk of the modifiable coronary heart disease risk factors; obesity, smoking, diabetes, hypertension and dyslipidaemia. Antipsychotic medication and possibly other psychotropic medication like antidepressants can induce weight gain or worsen other metabolic cardiovascular risk factors. Patients may have limited access to general healthcare with less opportunity for cardiovascular risk screening and prevention than would be expected in a non-psychiatric population. The European Psychiatric Association (EPA), supported by the European Association for the Study of Diabetes (EASD) and the European Society of Cardiology (ESC) published this statement with the aim of improving the care of patients suffering from severe mental illness. The intention is to initiate cooperation and shared care between the different healthcare professionals and to increase the awareness of psychiatrists and primary care physicians caring for patients with severe mental illness to screen and treat cardiovascular risk factors and diabetes.

Keywords: Severe mental illness; Schizophrenia; Depression; Bipolar disorder; Physical health; Weight gain

1. Introduction

People with severe mental illnesses (SMI), such as schizophrenia, depression or bipolar disorder, have worse physical health and reduced life expectancy compared to the general population [58,82,84,124]. Evidence shows that they have a 2–3 fold increased mortality rate and that the mortality gap associated with mental illness compared to the general population has widened in recent decades [113]. This excess mortality is not only caused by increased suicide; people with SMI have an increased risk of mortality associated with physical illness, with the commonest cause of death being cardiovascular disease (CVD) [15,16,17,25,26,65,82,103,104,106,107]. The aetiology of this excess CVD is multifactorial and includes genetic and lifestyle factors as well as disease specific and treatment effects. People with SMI are more likely to be overweight, to smoke and to have diabetes, hypertension and dyslipidaemia [31,39,45,46,93,99,100,121]. They are more

* Corresponding author.
E-mail address: marc.de.hert@uc-kortenberg.be (M. De Hert).

0924-9338/$ – see front matter © 2009 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.eurpsy.2009.01.005

likely to have a family history of diabetes and the illness is associated with chronic elevations of stress hormones. Antipsychotic medication can induce weight gain or worsen other metabolic CVD risk factors [5,51,61,64,99,100,116,117,119,129,134,136]. There is emerging evidence that modifiable cardiovascular risk factors are also increased in patients with bipolar disorders and in those with a history of depression or taking drugs to treat depression [8,12,13,15,16,25,27,38,67,71,72,75,91,92,112,114,135]. The scientific literature regarding the effects of medications used in the treatments of unipolar or bipolar depression, such as antidepressants or mood stabilisers, is currently less comprehensive than for antipsychotics [11,12,15,91,92,141].

Despite the increased risk of diabetes and CVD risks, many patients with SMI have limited access to general healthcare with less opportunity for cardiovascular risk screening and prevention than would be expected in a non-psychiatric population [49,58,82,84,87]. Low rates of treatment for hypertension, dyslipidaemia and diabetes have been reported in schizophrenia patients [96]. The lack of consensus over who should take responsibility for the general healthcare needs of patients with mental illness has resulted in a continuing failure to provide appropriate services.

Psychiatrists and primary care physicians should play an active role in ensuring that patients with mental illness are not disadvantaged. Measures should include the assessment and management of cardiovascular risk factors and diabetes as part of the care of their psychiatric patients. When indicated, shared care with cardiologists, diabetologists, specialist nurses or other specialists should be established.

The aim of the joint statement of European Psychiatric Association (EPA), European Association for the Study of Diabetes (EASD) and European Society of Cardiology (ESC) is to reduce cardiovascular risk and to improve diabetes care in patients with SMI and to improve the overall health and well-being of the patients. This should reduce the burden of physical illness for patients, their families and healthcare services.

Based on a review of the evidence that patients with SMI are at increased risk of CVD and diabetes, this position statement has been developed by the EPA, in consultation with the EASD and the ESC. The statement is based upon the guidelines of ESC and EASD [59].

2. Who is at risk and why?

2.1. Cardiovascular disease

Epidemiological studies have consistently shown excess CVD mortality in patients with schizophrenia, bipolar disorder and depression [8,15,17,18,24,26,35,82,83,106,107,113,124]. In a recent meta-analysis of 37 studies carried out in 25 countries, with an estimated total of nearly 23,000 deaths, people with schizophrenia had a median all-cause standardised mortality rate (SMR) of 2.58 (90% quantiles 1.18–5.76) (2.41 for all natural causes [90% quantiles 0.99–4.10], 7.5 for all unnatural causes [90% quantiles 5.56–12.73]) [113]. The median SMR for CVD was 1.79 (90% quantiles 1.11–3.60). The median all-cause SMR for people with schizophrenia during the 1970s, 1980s and 1990s were 1.84, 2.98 and 3.20, respectively, demonstrating increasing health inequalities with an increasing mortality gap over time.

Similar findings have been reported in large studies of people with affective disorders with an overall SMR ranging from 1.23 to 2.50 [8]. In a subset of 400 patients with unipolar depression or bipolar disorder followed up for 34–38 years, the SMR for coronary heart disease (CHD) was 1.61 (confidence interval [CI] 1.31–3.54). Compared with healthy women, women with depression were particularly at risk of CHD mortality (SMR 1.7, CI 1.34–2.14), while men showed increased cerebrovascular and vascular mortality (SMR 2.21, CI 1.29–3.54). The Baltimore Maryland Epidemiological Catchment Area Study, which was a 13 years follow-up study of a representative US community sample assessed for common psychiatric illness, reported a 4.5 fold increased odds ratios for myocardial infarction in patients with depression [57,109].

The aetiology of this excess CVD is multifactorial and includes genetic and lifestyle factors as well as disease specific and treatment effects. The excess CVD mortality associated with schizophrenia, unipolar and bipolar disorder is widely attributed to the 1–5 fold relative risk of the modifiable CVD risk factors, obesity, smoking, diabetes, hypertension and dyslipidaemia, in this group of patients compared with the general public (Table 1) [5,9,13–16,33,39,41,43,47,64,65,74,88,94,99,100,116,117,119,121,129,133,135,136].

In the USA, 68% of 689 schizophrenia patients who took part in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study were smokers compared to 35% of age matched controls, 13% had diabetes versus 3% of controls and 27% versus 17% had hypertension [60]. Patients with schizophrenia also had significantly lower HDL-cholesterol (HDL-C) levels. Approximately one third of patients in CATIE had a constellation of metabolic and cardiovascular risk factors at baseline [93].

In a meta-analysis including 12 papers on hypertension and 11 on dyslipidaemia, there was a pooled risk ratio of 1.11 (0.91 to 1.35) of hypertension. Although total cholesterol was not higher in people with SMI (standardized mean difference −0.10 [−0.55 to 0.36]), some, but not all, studies reported lower levels of HDL-C and raised triglyceride levels [104].

Table 1
Estimated prevalence and relative risk of modifiable cardiovascular disease risk factors in schizophrenia and bipolar disorder compared to the general population [39,47].

Estimated prevalence and relative risk		
Modifiable risk factors	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

RR: relative risk.

An increased risk of overweight, obesity and diabetes mellitus type 2 has also been found in clinical populations with affective disorders [12,15,27,38,67,75,88,91,94].

Despite the high prevalence of cardiovascular risk factors, there is evidence of undertreatment of these modifiable risk factors. In the CATIE study, 88% of patients with dyslipidaemia were receiving no treatment while 62% of those with hypertension and 38% of those with diabetes also received no treatment [96]. The high prevalence of undertreatment of cardiovascular risk factors was recently confirmed in a study of 2463 people with schizophrenia from 12 European countries [45]. Overall, 10.9% of patients were being treated for hypertension, 7.1% for a lipid disorder and 3.5% for type 2 diabetes. Biochemical evidence of hyperglycaemia and dyslipidaemia, however, was found in 26 and 70% of patients respectively and untreated hypertension was found in 39%.

An unhealthy lifestyle, including poor diet and sedentary behaviour, is likely to contribute to the adverse risk profile of people with SMI. Given the weight gain and other metabolic abnormalities associated with some second-generation antipsychotic agents (SGA), however it has been difficult to differentiate the contribution of psychiatric conditions and treatment per se to increased CVD risk [5,99,100,116,117,119,130].

A large, ongoing, prospective study has confirmed that many patients with first episode schizophrenia already have significant metabolic abnormalities at the time of their first episode of illness [43]. Twenty-seven percent of patients had raised total cholesterol at first episode, rising to 61% in patients with a long duration of illness. In addition, patients with first episode psychosis have been found to have altered body composition with increased intra-abdominal fat deposition as opposed to subcutaneous fat, which itself has emerged as a strong and independent risk factor for the development of CVD [77,108,126,127]. The latter findings underline the importance of possible metabolic alteration before the influence of psychopharmacological treatment and support the hypothesis that metabolic abnormalities are an inherent part of schizophrenic illness, with socioeconomic factors and possibly underlying genetic or biological factors playing a role [100,116,117,119,130].

Dysregulation of the hypothalamic-pituitary adrenal axis (HPAA) [13,15,28,66] and immunological alterations, such as altered cytokine expression, are often seen in depression and psychosis [111]. These findings may be involved in the pathogenesis of CVD and give some insight into the mechanisms by which psychiatric disease itself might contribute to the pathogenesis of increased cardiovascular risk.

In addition, there appears to be a direct effect of the antipsychotic medication on the ongoing development of CVD risk factors [97,116,117,130].

2.2. Diabetes

Several studies have shown that the prevalence of diabetes is 2–3 fold higher than people with schizophrenia compared with the general population. Several cross-sectional studies have indicated that the prevalence of diabetes among populations of people with schizophrenia is around 10–15%, or two to three times higher than in the background population [68].

Data from the Baltimore Maryland Epidemiological Catchment Area Study reported increased odds ratios for type 2 diabetes (OR = 2.2) and myocardial infarction (OR = 4.5) in depressed patients [50,57,109].

One large, ongoing, prospective study in Belgium has confirmed that a significant number of patients with schizophrenia already have diabetes at the time of their first episode of illness [43], with the prevalence of diabetes increasing from 3% in first episode and recent-onset patients (up to 2 years in treatment) to 16.5% in patients with a duration of illness of more then 20 years. In this study, the prevalence of diabetes in the age-band 15–25 years was five times more common in patients with schizophrenia compared to the general population.

Although there are fewer data, the prevalence of diabetes is also higher among people with bipolar illness. A systematic review by McIntyre and colleagues of all English language articles published between 1966–2004 found that the prevalence of diabetes in bipolar illness was up to three times greater than in the general population [91].

The reason for the increased incidence and prevalence of diabetes in people with schizophrenia and bipolar illness, like CVD risk, is multifactorial and includes genetic and lifestyle factors as well as disease and treatment specific effects. An increase in traditional diabetic risk factors such as family history of diabetes, obesity and physical inactivity probably account for much of the increased risk. It seems likely that these risk factors operate in a similar manner to the general population as illustrated by one previous study that showed that diabetes increased with age and the presence of a family history of diabetes increased the rate of diabetes in people with schizophrenia by three-fold [81]. No study, however, has examined the attributable risk of traditional diabetes risk factors in people receiving antipsychotic medication. The effects of antipsychotic drugs are discussed in the next section.

The association between depression and diabetes is complex and there is evidence that the association is bidirectional [16,67,112]. People with established diabetes have higher rates of depression than the general population, while depression has become established as a risk factor for diabetes. There are several mechanisms to explain this association from the ‘‘psychological stress’’ resulting from the diagnosis and treatment of the physical illness, through the metabolic derangement leading to mood disturbance to alterations in cytokines and stress hormones.

3. Psychopharmacological treatment and cardiovascular disease risk

Psychopharmacological treatment with antipsychotics, antidepressants and mood stabilisers is an effective and necessary component of the management of severe mental disorders like schizophrenic and affective disorders. As it is well established that people with SMI who do not take

medication have a higher risk of mortality, suicide and hospital admission than those who are on regular medication [128], any adverse metabolic effect needs to be placed within the context. Although the relationship between antidepressants and mood stabilisers and weight gain is well described, the scientific literature on the association between antidepressants or mood stabilisers and cardiovascular risk is sparse. There is, however, a considerable literature about the adverse effects of antipsychotics.

Growing evidence suggests that children and adolescents who take antipsychotic medication are at higher risk of weight gain and metabolic effects than adults who use the same drugs [32,36,79,80,103].

3.1. Weight gain

Weight gain during acute and maintenance treatment of schizophrenia and affective disorders is a well established side effect of antipsychotics affecting between 15–72% of patients [1,2,5,11,29,51,61,71,85,88,101,116,117,130]. Antidepressants and mood stabilising drugs, such as lithium and valproate, may also induce significant weight gain.

There is a marked difference in the risk of weight gain between different antipsychotic drugs. A meta-analysis of clinical trials showed that after 10 weeks of treatment, weight gain was greatest with clozapine (4.45 kg) and olanzapine (4.15 kg) while quetiapine and risperidone (2.1 kg) had an intermediate risk and aripiprazole, amisulpride and ziprasidone have little effect on weight (<1 kg). No agent, however, should be considered as truly weight-neutral as the proportion of individuals experiencing more than 7% weight gain is greater with any atypical antipsychotic than placebo [29]. It should be underlined that in the meta-analysis by Allison et al. [1], some of the first-generation antipsychotics (FGA or neuroleptics) like chlorpromazine also showed a comparably high risk of inducing weight gain. This hierarchy for risk of weight gain has been confirmed in the more recent CATIE, the European EUFEST studies and a meta-analysis [41,60,73,85,86].

There is marked inter-individual variation in weight change for each drug, which may range from dramatic weight gain to weight loss. Although weight gain is unpredictable for an individual, there are several demographic and clinical features that are associated with a greater propensity for weight gain and should aid clinical decision-making (Table 2). In particular, children and adolescents are at high risk of significant weight gain. Early weight gain (> 7% body weight within the first 6 weeks of olanzapine treatment) appears to be a good predictor of subsequent significant weight gain [76]. A comprehensive literature review, however, did not find evidence for a dose–response at the doses used to treated psychotic illnesses for most antipsychotics, except clozapine and olanzapine [118].

Among the antidepressants, tricyclic agents (most notably amitriptyline and doxepine), mitrazepine and paroxetine seem to be associated with a higher risk of weight gain [91,92,123].

The mechanisms leading to antipsychotic-induced weight gain are complex and are not fully understood. The main mechanism of weight gain appears to be through appetite stimulation but other less specific mechanisms, such as altered energy expenditure, may also be involved. Antipsychotics interact with many different brain receptors involved with appetite regulation, the most important of which are the histamine H_1 receptor, 5-HT_{2c} receptor and β3 and α1 adrenergic receptors [5,71,96,99,100,116,117,130].

Table 2
Risk factors that predict weight gain.

Clinical	Demographic
Choice of antipsychotic	Younger age
First episode psychosis	Lower initial BMI
Non-rapid cycling	Personal history of obesity
Psychotic features	Family history of obesity
	Non-white ethnic background
	Tendency to overeat in time of stress
	Cannabis use

3.2. Dyslipidaemia

Prospective studies show that the use of antipsychotics is associated with an increase in LDL cholesterol and decrease in HDL-C [41,60,69,70,93]. Furthermore some comparative studies have indicated that the effect on total and LDL cholesterol differs between antipsychotics. At present, it is uncertain whether these short-term changes will translate into clinically relevant differences in the long term [41,60,73,93,122,134,139].

The overall effect on triglycerides is more marked and here there are clear differences between drugs; those drugs associated with the most weight gain, such as clozapine and olanzapine, are associated with the largest rise in serum triglycerides [41,60,73,93,122,134,139]. The most marked differences between drugs are seen in the early phase of treatment when weight gain occurs most rapidly. In a recent study on different cardiovascular risk factors in patients diagnosed with schizophrenia from 2000–2006 compared to 1984–1995, those treated with SGA for 3 years gained twice as much weight and showed greater deterioration in triglyceride than those treated with FGA drugs for three years [46].

Most studies report lipid measurements after short periods of treatment (2–3 months) and there is a need to assess what the longer-term effects on triglyceride concentrations are once weight has stabilised.

3.3. Hypertension

The literature does not show a consistent association between SMI and hypertension. Antipsychotic drugs may worsen hypertension through weight gain but this may be offset by a hypotensive effect through adrenergic blockade.

3.4. Diabetes

An evaluation of the data regarding antipsychotic drugs is challenging because of the increased risk of diabetes among people with SMI. It is also complicated by the frequent changes

in psychotic medication made by people with SMI against the long natural history of diabetes. The sources of information range from case histories, through pharmaco-epidemiological studies to randomised controlled studies. Many of these studies have significant flaws and so it is not possible to draw firm conclusions about the risks of diabetes with antipsychotic medication [70].

Observational studies would suggest that there is an increased risk of diabetes in people receiving an antipsychotic medication. These studies, however, may be confounded by the increased risk of diabetes in people with SMI. A recent meta-analysis of the risk of diabetes in people with schizophrenia receiving antipsychotics showed that there was a 1.32 (95% CI 1.15–1.51) fold increased risk of diabetes in people taking SGA compared with conventional antipsychotics [119]. In this study, no difference was found in the risk of diabetes between different SGA. In a further systematic review of observational cohort studies, the attributable risk for individual SGA relative to FGA ranged from 53 more to 46 fewer new cases of diabetes per 1000 patients with little observable difference between the individual SGA versus FGA [30]. Furthermore, a systematic review of the 22 prospective randomised controlled trials found no consistent significant glucose abnormalities between any comparator antipsychotics or placebo in any trial [21].

Although these studies would suggest that the risk of diabetes associated with SGA medication is low, several caveats are needed. There are clearly some cases of diabetes and diabetic ketoacidosis that have occurred following treatment with antipsychotic medication, including somewhere this has occurred following re-challenge with the antipsychotic. Diabetes may also remit following the discontinuation of treatment.

Furthermore in several randomised controlled trials (RCT), differences in blood glucose have been observed. For example, in the CATIE study, there was a significantly greater increase in HbA_{1c} with olanzapine (0.4%) compared with quetiapine (0.04%), risperidone (0.07%), perphenazine (0.09%) and ziprasidone (0.11%). If these changes persisted with longer treatment, they may translate into clinically meaningful differences in the rates of diabetes between drugs [86].

The mechanism by which antipsychotic drugs induce diabetes is not clear and again is likely to involve several different systems. As well as an indirect effect on the risk of diabetes through weight gain, in vitro and animal studies have demonstrated that antipsychotics may have an effect on insulin secretion and insulin resistance [99,105,116,117,130].

Overall, the evidence is clear that the use of antipsychotics is associated with an increased risk of diabetes but this risk is small compared with other traditional diabetic risk factors. The evidence for a differential effect between different antipsychotics is less conclusive. Given our understanding in the relationship between obesity and diabetes, it is likely that that where there is significant antipsychotic induced weight gain leading to obesity over a prolonged period of treatment, this may contribute to the development of diabetes. As such there may be differences between antipsychotics in their risk for diabetes.

3.5. Cardiovascular events

A large UK study involving 46,136 people with SMI and 300,426 healthy controls demonstrated that the hazard ratios (HR) for CHD mortality in people with SMI compared with controls were 3.22 (95% CI, 1.99–5.21) for people 18 through 49 years old, 1.86 (95% CI, 1.63–2.12) for those 50 through 75 years old and 1.05 (95% CI, 0.92–1.19) for those older than 75 years. For stroke deaths, the HR were 2.53 (95% CI, 0.99–6.47) for those younger than 50 years, 1.89 (95% CI, 1.50–2.38) for those 50 through 75 years old and 1.34 (95% CI, 1.17–1.54) for those older than 75 years. Compared with healthy controls, people with SMI who were not prescribed any antipsychotics were at increased risk of CHD and stroke than controls, whereas those prescribed such agents were at even greater risk. Those receiving the higher doses were at greatest risk of death from both CHD and stroke. Exposure to atypical antipsychotics, however, was not related to CHD mortality. Compared with the non-SMI control group, the fully adjusted HR for CHD death in the SMI subgroups were as follows: 1.38 (95% CI, 1.08–1.76) for those not prescribed any antipsychotics, 0.86 (95% CI, 0.52–1.41) for those ever prescribed atypical antipsychotics and 2.12 (95% CI, 1.82–2.47) for those receiving conventional antipsychotics only [104].

A well conducted retrospective pharmaco-epidemiological cohort study involving over 90,000 people receiving antipsychotics found a 1.99–2.26 fold increased rate of sudden cardiac death in current users of typical and atypical antipsychotics [110]. The risk increased with higher doses and was not seen in former users of antipsychotics. There was no difference between typical and atypical antipsychotics. The underlying reason for this finding was not fully established in this study.

At the present time, there are no outcome data for the differences in weight gain and risk of diabetes and dyslipidaemia with each of the SGA's in terms of hard endpoints, such as non-fatal and fatal CVD and total mortality.

4. Guidelines for screening and monitoring of cardiovascular disease risk factors and diabetes

Over recent years, both national and international groups have developed screening and monitoring guidelines [5,10,22,31,34,42,48,90,115,133,137] but these are not being routinely implemented in the clinical care of patients [20,63,87,99], although they appear to be cost-effective [19]. The most recent NICE schizophrenia guidelines include the need for comprehensive physical health monitoring and involvement of general practitioners [102]. Some recent diabetes guidelines have defined a diagnosis of schizophrenia and antipsychotic use as risk factors for diabetes [4,23].

5. Assessment of cardiovascular disease risk

The European Guidelines on CVD prevention recommend that people with known CVD, type 2 diabetes or type 1 diabetes with microalbuminuria or with very high levels of individual

risk factors should automatically have all their risk factors actively managed [59].

For other people, the Guidelines recommend that risk factors should be managed according to the total CVD risk, as assessed by the Score risk charts which calculate risk according to age, sex, smoking habit, systolic blood pressure and total cholesterol, or the ratio of total to HDL-C [59]. These charts focus risk management on men over 50 and women over 55.

Recent evidence suggests that patients with SMI are typically younger, have higher blood pressure and are more likely to be smokers than the populations used to derive CVD risk scoring systems, such as Framingham and Score and there is a need to validate a risk score for this specific population of mentally ill patients [9,19,37,41,60,125].

To ensure that younger patients at high CVD risk compared to others the same age do not miss out on treatment, the European Guidelines on CVD prevention include a relative risk chart which bases the relative risk on smoking habit, systolic blood pressure and total cholesterol (Fig. 1).

In the current absence of a risk scoring system for people with SMI [125] and given the excess CVD mortality in people with SMI outlined earlier, we recommend that the decision to manage CVD risk factors in this group of patients should be based on relative risk, as shown in Fig. 1. Where individual risk factors are markedly raised, there may also be a need to manage these on an individual basis.

As obesity and metabolic abnormalities are also seen in children and adolescents who take antipsychotic medication are at particularly high risk [32,36,79,80,103], we recommend close monitoring of risk factors such as weight and lipid levels in this group, with appropriate dietary, lifestyle and therapeutic intervention, in line with recent paediatric guidance [40].

5.1. Which tests and when?

CVD risk assessment in the general population is usually carried out within a primary care setting. Many patients with serious mental health problems, however, frequently have poor access to general healthcare services. Such annual screening for CVD and metabolic disorders in patients with SMI, however, can be cost effective, owing to the reduction in costs of treating the complications of diabetes [19,59].

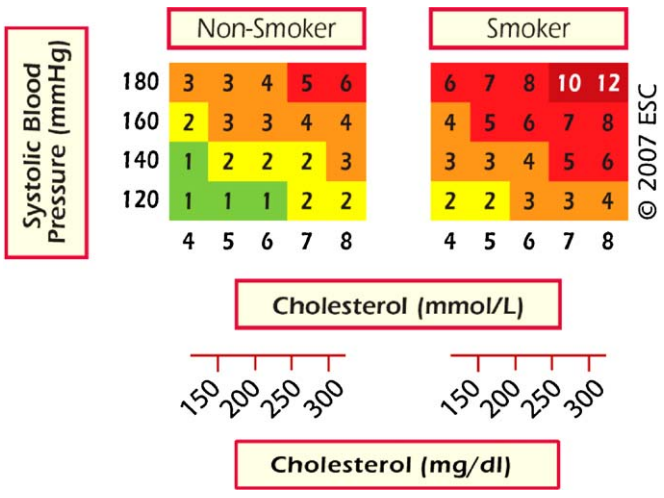

Fig. 1. Relative risk of fatal cardiovascular disease [59].

Psychiatrists are often best placed to coordinate CVD risk assessment and management, ideally as part of shared care arrangements with general and specialist healthcare services.

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, LDL-cholesterol (by calculation) and HDL-C;
- blood pressure (measured twice and average taken), heart rate, heart and lung auscultation, foot pulses;
- ECG.

Normal and abnormal values for fasting blood glucose, fasting blood lipids and blood pressure are provided in Table 3.

It is recommended that measurements should be taken at the initial presentation and before the first prescription of antipsychotic medication (Fig. 2). 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 HbA_{1c} should be made regularly (approximately every 3 months) [6].

6. Management of cardiovascular disease risk factors

The recommended interventions for management of CVD risk factors are summarised in Fig. 2.

6.1. Smoking habit

Smokers should be encouraged to stop smoking all forms of tobacco. Those who demonstrate a readiness to quit can be referred to a smoking cessation service which can offer behavioural counselling, nicotine replacement therapy or other pharmacological intervention.

Table 3
Abnormal values for major measurable cardiovascular disease risk factors [59,138].

	Abnormal value
Fasting blood glucose	Impaired fasting glucose: between 6.1 and 7 mmol/l (110–125 mg/dl) Diabetes: $\geq$ 7.0 mmol/l (126 mg/dl)
Lipids	
Total cholesterol	Without diabetes: $>$ 5 mmol/l (190 mg/dl) With diabetes: $>$ 4.5 mmol/l (175 mg/dl)
LDL-cholesterol	Without diabetes: $>$ 3 mmol/l (115 mg/dl) With diabetes: $>$ 2.5 mmol/l (100 mg/dl)
Blood pressure	Without diabetes: $>$ 140/90 mmHg With diabetes: $>$ 130/80 mmHg

Practical experience has shown that discouraging patients and healthcare staff from smoking on psychiatric wards and at clinics is a useful first step towards smoking cessation [56,120,132].

6.2. Body weight

Maintaining a healthy body weight and shape by healthy eating and regular physical activity is the a key component of lowering CVD risk and prompt action is needed in patients who are overweight at initial assessment or who show signs of early weight gain with antipsychotic medication.

Patients should be advised to lose weight if they have:

- BMI $>$ 25 kg/m^2 (especially if it is greater than 30 kg/m^2);
- waist circumference greater than 88 cm in women or greater than 102 cm in men.

A recent meta-analysis of 10 randomised trials involving 482 patients receiving antipsychotics was undertaken to assess the effectiveness of lifestyle modification. The trials, which lasted for 2–6 months and included studies that described the prevention of treatment emergent weight gain as well as the treatment of established obesity, found a statistically significant reduction in mean body weight of around 2.5 kg with lifestyle modification compared with usual treatment [3].

Referral to a nutritionist/dietician/personal trainer or lifestyle programme should be considered [53,54–56]. Lifestyle advice/support should include information about the importance of healthy eating and regular exercise [59]. Patients should be advised to take 30 minutes of moderately vigorous activity — at least a brisk walk — on most days of the week

Lifestyle advice/support must include information about the importance of healthy eating and regular exercise [59]. Patients should be advised to take 30 minutes of moderately vigorous activity — at least a brisk walk — on most days of the week. Referral to a nutritionist/dietician/personal trainer or lifestyle programme could be considered.

Consideration should be given to switching antipsychotic when an individual gains significant amount of weight, particularly when the therapeutic response has been limited.

Several pharmacological agents have been tried to reverse or prevent antipsychotic-induced weight gain. No drug has been found to be particularly effective but a recent systematic review showed that there was preliminary evidence that metformin may attenuate weight gain in both adult and adolescent patients taking atypical antipsychotics [95,140]. While larger trials of longer duration are needed, metformin may be considered in patients with additional risk factors, such as a personal or family history of metabolic dysfunction.

6.3. Diabetes and fasting blood glucose

The World Health Organisation (WHO) defined diabetes as a fasting plasma glucose of 7 mmol/L or more (126 mg/dL) [7,23,52,138]. In an asymptomatic individual, the diagnosis should be confirmed with a second fasting measurement on another day. The measurement of HbA_{1c} may be used in the future for diagnosing diabetes [129].

In all forms of diabetes, inadequate control of glycaemia will result in complications of diabetes. These complications include diabetic neuropathy, diabetic retinopathy, diabetic kidney disease and an increased risk of infection. The goal of metabolic control should be to achieve HbA_{1c} levels below 7% of total haemoglobin.

Patients with type 2 diabetes are likely to require additional pharmacological management, but this should be no different from the general population, for which guidelines are available from the EASD and the American Diabetes Association (ADA) [6].

Psychiatric centres should cooperate with diabetes centres to establish shared care of patients with mental illness and diabetes. For patients who require insulin treatment a diabetes nurse educator from a diabetes centre should be available upon request for patients in psychiatry units.

Patients with diagnosed diabetes should be seen by a physician and/or a diabetes nurse regularly and as required depending on the therapy used. Fasting blood glucose and HbA_{1c} should be measured regularly (approximately every 3–6 months). An annual examination should include measurement of CVD risk factors, urinary albumin excretion and serum creatinine, an eye examination, ideally including fundus photography, and foot examination to diagnose early signs of complications [6].

Insulin treatment should be initiated and monitored by healthcare professionals with expertise in the management of diabetes. Special attention should be given to the prevention of hypoglycaemia in patients on insulin treatment. Avoidance of hypoglycaemia is best achieved by involving the patient's family and cares in the education process about the risks and consequences of hypoglycaemia. Education of the patients on insulin should include blood glucose monitoring and the adaptation of the insulin doses based upon the values.

Patients with impaired fasting glucose, defined by the WHO as fasting glucose between 6.1 and 7 mmol/l (110–125 mg/dl), have high risk of diabetes and increased risk of CVD and so particular care is needed to ensure that these individuals undergo annual monitoring of glucose level and CVD risk

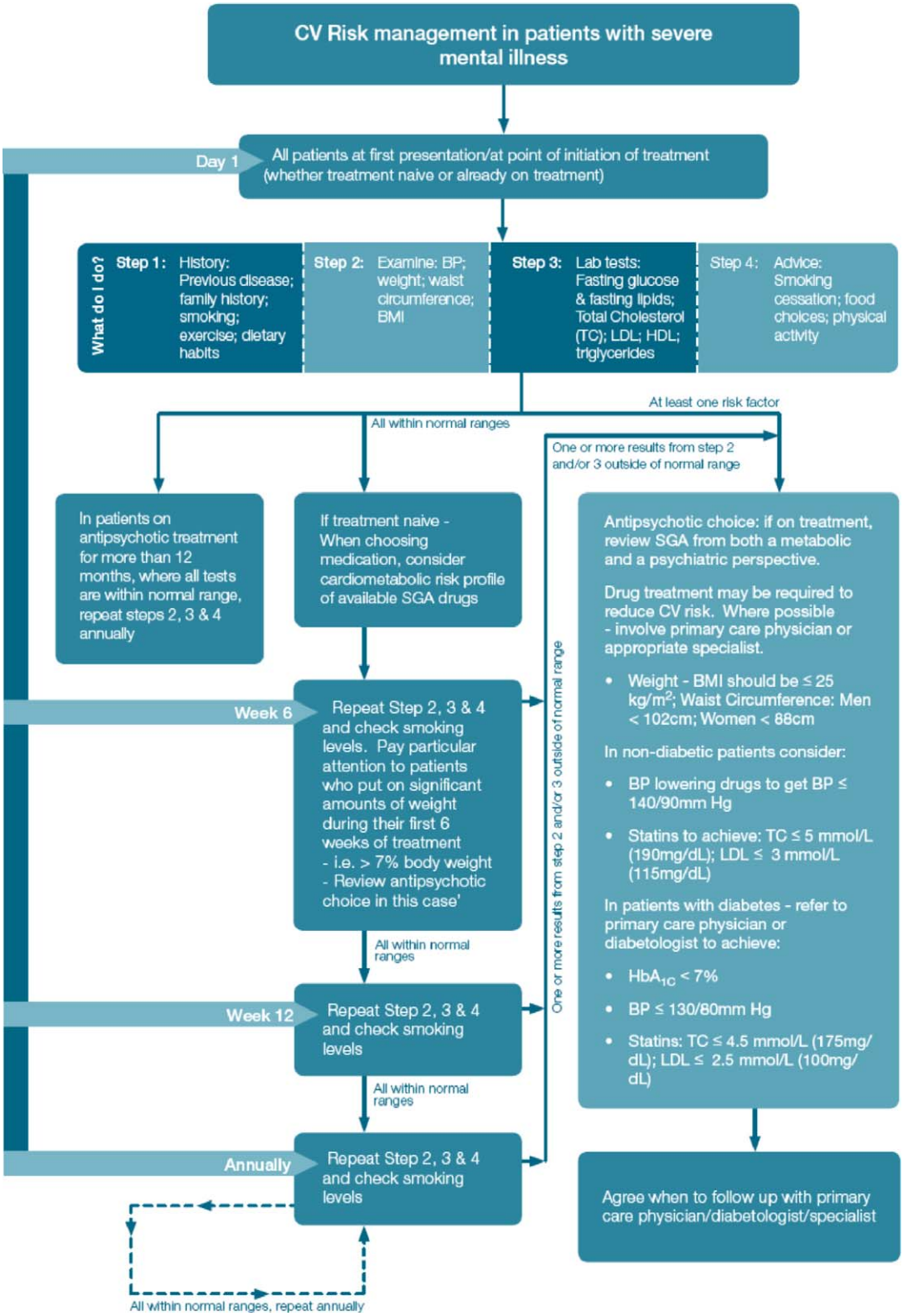

Fig. 2. Cardiovascular risk management in people with severe mental illness.

profile [6,52,138]. In the presence of different CVD risk factors in people, with SMI closer monitoring should be considered.

There have been several studies that have shown that lifestyle intervention is effective in the prevention of type 2 diabetes [78,131]. These programmes have involved dietary modification, weight loss and increased physical activity. The principles of these programmes are similar to those used in the lifestyle modification programmes in people with SMI

described above. Consequently, these programmes are expected to have benefits, in terms of diabetes prevention although this has not been formally tested in people with SMI.

The Diabetes Prevention Program also demonstrated that metformin is associated with a reduction in incident diabetes. For diabetes prevention, a Consensus Development Panel recommended metformin use only for very-high-risk individuals (those with combined impaired fasting glucose and impaired glucose tolerance, who are obese and under 60 years of age with at least one other risk factor for diabetes). In addition, the panel highlighted that in the Diabetes Prevention Program, metformin was most effective compared to lifestyle in those with BMI of at least 35 kg/m^2 and those under age 60 years [98].

There is preliminary evidence that metformin improves insulin sensitivity, glucose and HbA_{1c} in people with SMI [95,140]. In the absence of long-term studies of combined antipsychotic and metformin therapy, consideration may be given to the use of metformin in high-risk patients.

6.4. Fasting blood lipids

Management of elevated fasting lipid levels should be carried out in the context of total CVD risk assessment (Fig. 1).

Target levels of total cholesterol and LDL-cholesterol are less than 5 mmol/l (190 mg/dL) and less than 3 mmol/l (115 mg/dL) respectively. More rigorous goals of less than 4.5 mmol/L (175 mg/dL) and less than 2.5 mmol/L (100 mg/dL) are recommended for patients with established CVD or diabetes (Table 3).

Patients should be encouraged to eat lean meat, fish and low fat dairy products and to replace saturated fat with monounsaturated and polyunsaturated fats from vegetable and marine sources [59]. Those with mildly elevated cholesterol levels may be able to reach target levels through diet alone, while others are likely to require lipid lowering therapy, usually with statins.

Statin treatment has been demonstrated to be effective in the management of dyslipidaemia in patients with SMI [44,62]. Psychiatrists who are involved in ongoing lipid management should be aware of the need for liver function and creatinine kinase tests.

If total CVD risk is high (Score $\geq$ 5% over 10 years for fatal CVD) then total cholesterol should be reduced to less than 5.0 mmol/l or less than 4.5 mmol/l in those with established CVD or diabetes.

6.5. Blood pressure

High blood pressure in severely mentally ill patients is often missed. Target blood pressure levels of less than 140/90 mmHg are recommended.

Lifestyle changes, such as stopping smoking, reducing salt intake, weight reduction and increased exercise, may be sufficient to reduce mildly elevated blood pressure, although some patients are likely to require pharmacological therapy. Recently updated European guidelines stress the importance of choosing antihypertensive agents best suited to individual patient's needs [59,89].

6.6. Management of adverse drug-related effects on cardiovascular disease risk factors

Choice of psychotropic medication should take account of potential effects of different agents on CVD risk factors, such as weight and glucose levels and lipid profiles, especially in patients who are overweight or have diabetes or are at high total CVD risk factors. Clinical decision-making is always complex and has to consider efficacy aspects as well. A dilemma may arise with clozapine which is recommended by many guidelines as the antipsychotic of choice for those with refractory schizophrenia as clozapine is associated with the highest risk of weight gain and related CVD risk factors.

7. Summary and conclusion

The EPA, supported by the EASD and the ESC, published this statement with the aim of improving the care of patients suffering from SMI. The intention is to initiate cooperation and shared care between the different healthcare professionals and to increase the awareness amongst psychiatrists and primary care physicians caring for patients with SMI of the need to screen and treat increased cardiovascular risk factors and diabetes.

In addition, the academic associations involved with this statement point out that more research is required concerning the cardiovascular problems of people with SMI and their treatment.

8. Conflicts of Interest – Financial Disclosure Statement

This position statement was written without funding of pharmaceutical companies.

Prof. Dr. De Hert has been a consultant for, received grant/research support and honoraria from and been on the speakers/advisory boards of Astra Zeneca, Bristol-Myers Squibb, Eli Lilly, Janssen-Cilag, Lundbeck JA, Pfizer and Sanofi-Aventis.

Prof Dekker has received grants and honoraria from Astra Zeneca, Bayer, Merck & Co Inc, Novartis, Novo Nordisk and Pfizer.

Dr. Kahl received honoraria from Astra Zeneca, Bristol-Myers Squibb, Eli Lilly, Janssen-Cilag, Bristol-Myers Squibb, Otsuka and Wyeth.

Professor Wood has received unrestricted educational grants from, served on advisory boards of or/and given invited lectures for Astra Zeneca, Bristol-Myers Squibb, GlaxoSmithKline, Merck Sharp & Dohme, Pfizer, Sanofi-Aventis, Schering Plough, Servier Laboratories and Sun Pharma, India.

Prof. Holt has been a consultant for, has received funding to attend conferences and/or has served as a speaker or on advisory boards for Astra Zeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Novo Nordisk.

Prof. Dr. Möller has received grants or is a consultant for and on the speakership bureaus of Astra Zeneca, Bristol-Myers

Squibb, Eisai, Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Lundbeck, Merck, Novartis, Organon, Pfizer, Sanofi-Aventis, Sepracor, Servier and Wyeth.

Acknowledgement

The authors would like to thank all members and staff of the EPA, the EASD and the ESC who contributed to the development of this position statement.

References

[1] Allison DB, Mentore JL, Heo M, Chandler LP, Cappelleri JC, Infante MC, et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. Am J Psychiatry 1999;156(11):1686–96.
[2] Allison DB, Newcomer JW, Dunn AL, Blumenthal JA, Fabricatore AN, Daumit GL, et al. Obesity among those with mental disorders: a National Institute of Mental Health meeting report. Am J Prev Med 2009;36(4):341–50.
[3] Álvarez-Jiménez M, Hetrick S, González-Blanch C, Gleeson J, McGorry P. Non-pharmacological management of antipsychotic-induced weight gain: systematic review and meta-analysis of randomised controlled trials. Br J Psychiatry 2008;193:101–7.
[4] American Association of Clinical Endocrinologists 2007. Medical Guidelines for Clinical Practice for the Management of Diabetes Mellitus. AACE Diabetes Mellitus Guidelines. Endocr Pract 2007;13(Suppl. 1):3–68.
[5] American Diabetes Association. Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes. Diabetes Care 2004;27:596–601.
[6] American Diabetes Association. Standards of medical care in diabetes - 2009. Diabetes Care 2009;32(Suppl. 1):S13–61.
[7] American Diabetes Association. Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 2009;32(Suppl. 1):S63–7.
[8] Angst F, Stassen HH, Clayton PJ, Angst J. Mortality of patients with mood disorders: follow-up over 34-38 years. J Affect Disord 2002;68(2-3):167–81.
[9] Arango C, Bobes J, Aranda P, Carmena R, Garcia-Garcia M, Rejas J, et al. A comparison of schizophrenia outpatients treated with antipsychotics with and without metabolic syndrome: Findings from the CLAMORS study. Schizophr Res 2008;104(1-3):1–12.
[10] Barnett AH, Mackin P, Chaudhry I, Farooqi A, Gadsby R, Heald A, et al. Minimising metabolic and cardiovascular risk in schizophrenia. J Psychopharmacol 2007;21(4):357–73.
[11] Bech P, Vendsborg PJ, Rafaelson OJ. Lithium maintenance treatment of manic-melancholic patients: its role in the daily routine. Acta Psychiatr Scand 1976;53:70–81.
[12] Berken GH, Weinstein DO, Stern WC. Weight gain: a side effect of tricyclic antidepressants. J Affect Disord 1984;7:133–8.
[13] Bjorntorp P. Stress and cardiovascular disease. Acta Physiol Scand Suppl 1997;640:144–8.
[14] Bobes J, Arango C, Aranda P, Carmena R, Garcia-Garcia M, Rejas J, et al. Cardiovascular and metabolic risk in outpatients with schizophrenia treated with antipsychotics: results of the CLAMORS Study. Schizophr Res 2007;90(1-3):162–73.
[15] Brown AD, Barton DA, Lambert GW. Cardiovascular abnormalities in patients with major depressive disorder: autonomic mechanisms and implications for treatment. CNS Drugs 2009;23(7):583–602.
[16] Brown LC, Majumdar SR, Newman SC, Johnson JA. History of depression increases risk of type 2 diabetes in younger adults. Diabetes Care 2005;28:1063–7.
[17] Brown S. Excess mortality of schizophrenia. A meta-analysis. Br J Psychiatry 1997;171:502–8.
[18] Brown S, Inskip H, Barraclough B. Causes of the excess mortality of schizophrenia. Br J Psychiatry 2000;177:212–7.
[19] Bruggeman R, Schorr S, Van der Elst K, Postma M, Taxis K. Cost-effectiveness of screening for diabetes in a cohort of patients with schizophrenia. Schizophr Res 2008;102(1-3):161–2.
[20] Buckley PF, Miller DD, Singer B. Clinicians' recognition of the metabolic adverse effects of antipsychotic medications. Schizophr Res 2005;79:281–8.
[21] Bushe CJ, Leonard BE. Blood glucose and schizophrenia: a systematic review of prospective randomized clinical trials. J Clin Psychiatry 2007;68(11):1682–90.
[22] Cahn W, Ramlal D, Bruggeman R, de Haan L, Scheepers FE, van Soest MM, et al. Prevention and treatment of somatic complications arising from the use of antipsychotics. Tijdschr Psychiatr 2008;50(9):579–91.
[23] Canadian Diabetes Association. Clinical Practice Guidelines for the prevention and management of diabetes in Canada. Can J Diabetes 2008;32(Suppl. 1):S1–20.
[24] Capasso RM, Lineberry TW, Bostwick JM, Decker PA, St Sauver J. Mortality in schizophrenia and schizoaffective disorder: An Olmsted County, Minnesota cohort: 1950-2005. Schizophr Res 2008;98(1-3):287–94.
[25] Carnethon MR, Biggs ML, Barzilay JI, Smith NL, Vaccarino V, Bertoni AG, et al. Longitudinal Association Between Depressive Symptoms and Incident Type 2 Diabetes Mellitus in Older Adults. The Cardiovascular Health Study. Arch Intern Med 2007;167:801–8.
[26] Casey DE, Haupt DW, Newcomer JW, Henderson DC, Sernyak MJ, Davidson M, et al. Antipsychotic-Induced Weight Gain and Metabolic Abnormalities: Implications for Increased Mortality in Patients With Schizophrenia. J Clin Psychiatry 2004;65(Suppl. 7):4–18.
[27] Cassidy F, Ahearn E, Carroll BJ. Elevated frequency of diabetes mellitus in hospitalized manic-depressive patients. Am J Psychiatry 1999;156:1417–20.
[28] Chrousos GP. The role of stress and the hypothalamic-pituitary-adrenal axis in the pathogenesis of the metabolic syndrome: neuroendocrine and target tissue-related causes. Int J Obes 2000;24:S50–55.
[29] Citrome L. Risk-Benefit Analysis of Available Treatments for Schizophrenia. Psychiatric Times 2007;1:27–30.
[30] Citrome L, Holt RIG, Zachry WM, Clewell JD, Orth PA, Karagianis JL, et al. Risk of treatment-emergent diabetes mellitus in patients receiving antipsychotics. Ann Pharmacother 2007;41:1593–603.
[31] Citrome L, Yeomans D. Do guidelines for severe mental illness promote physical health and well-being? J Psychopharmacol 2005;19(6):102–9.
[32] Cohen D, Huinink S. Atypical antipsychotic-induced diabetes mellitus in child and adolescent psychiatry. CNS Drugs 2007;21(12):1035–8.
[33] Cohen D, Stolk RP, Grobbee DE, Gispen-de Wied CC. Hyperglycemia and diabetes in patients with schizophrenia or schizoaffective disorders. Diabetes Care 2006;29(4):786–91.
[34] Cohn TA, Sernyak MJ. Metabolic monitoring for patients treated with antipsychotic medications. Can J Psychiatry 2006;51:492–501.
[35] Colton CW, Manderscheid RW. Congruencies in increased mortality rates, years of potential life lost, and causes of death among public mental health clients in eight states. Prev Chronic Dis 2006;3:A42.
[36] Correll CU. Assessing and maximizing the safety and tolerability of antipsychotics used in the treatment of children and adolescents. J Clin Psychiatry 2008;69(Suppl. 4):26–36.
[37] Correll CU. Balancing efficacy and safety in the treatment with antipsychotics. CNS Spectr 2007;12(Suppl. 17):12–20.
[38] Correll CU, Frederickson AM, Kane JM, Manu P. Equally increased risk for metabolic syndrome in patients with bipolar disorder and schizophrenia treated with second-generation antipsychotics. Bipolar Disord 2008;10:788–97.
[39] Correll CU, Frederickson AM, Kane JM, Manu P. Metabolic syndrome and the risk of coronary heart disease in 367 patients treated with second-generation antipsychotic drugs. J Clin Psychiatry 2006;67(4):575–83.
[40] Daniels SR, Greer FR, the Committee on Nutrition. Lipid Screening and Cardiovascular Health in Childhood. Pediatrics 2008;122:198–208.
[41] Daumit GL, Goff DC, Meyer JM, Davis VG, Nasrallah HA, McEvoy JP, et al. Antipsychotic effects on estimated 10-year coronary heart disease risk in the CATIE schizophrenia study. Schizophr Res 2008;105:175–87.

[42] De Hert M, van Eyck D, De Nayer A. Metabolic abnormalities associated with second generation antipsychotics: fact or fiction? Development of guidelines for screening and monitoring. Int Clin Psychopharmacol 2006;21(Suppl. 2):11–5.
[43] De Hert M, van Winkel R, Van Eyck D, Hanssens L, Wampers M, Scheen A, et al. Prevalence of diabetes, metabolic syndrome and metabolic abnormalities in schizophrenia over the course of the illness: a cross-sectional study. Clin Pract Epidemiol Ment Health 2006;2:14. doi: 10.1186/1745-0179-2-14.online.
[44] De Hert M, Kalnicka D, van Winkel RM, Hanssens L, Van Eyck D, Wampers M, et al. Treatment with rosuvastatin for severe dyslipidemia in patients with schizophrenia and schizoaffective disorder. J Clin Psychiatry 2006;67(12):1889–96.
[45] De Hert M, Falissard B, Mauri M, Shaw K, Wetterling T. Epidemiological study for the evaluation of metabolic disorders in patients with schizophrenia: The METEOR Study. Eur Neuropsychopharmacol 2008;18(Suppl. 4):S444.
[46] De Hert M, Schreurs V, Sweers K, Van Eyck D, Hanssens L, Šinko S, et al. Typical and atypical antipsychotics differentially affect long-term incidence rates of the metabolic syndrome in first-episode patients with schizophrenia: a retrospective chart review. Schizophr Res 2008;101(1-3):295–303.
[47] De Hert M, Schreurs V, Vancampfort D, van Winkel R. Metabolic syndrome in people with schizophrenia: a review. World Psychiatry 2009;8(1):15–22.
[48] De Nayer A, De Hert M, Scheen A, Van Gaal L, Peuskens J. Belgian consensus on metabolic problems associated with atypical antipsychotics. Int J Clin Pract 2005;9:130–7.
[49] Druss BG. Improving medical care for persons with serious mental illness: challenges and solutions. J Clin Psych 2007;68(Suppl. 4):40–4.
[50] Eaton WW, Armenian H, Gallo J, Pratt L, Ford DE. Depression and risk for onset of type II diabetes. A prospective population-based study. Diabetes Care 1996;19(10):1097–102.
[51] Falkai P, Wobrock T, Lieberman J, Glenthoj B, Gattaz WF, Möller HJ, et al. Guidelines for Biological Treatment of Schizophrenia. Part 1: Acute treatment of Schizophrenia. World J Biol Psychiatry 2005;6(3): 132–91.
[52] Farouhi NG, Balkau B, Borch-Johnsen K, Dekker J, Glumer C, Qiao Q, et al. The threshold for diagnosing impaired fasting glucose: a position statement by the European Diabetes Epidemiology Group. Diabetologia 2006;49:822–7.
[53] Faulkner G, Soundy AA, Lloyd K. Schizophrenia and weight management: a systematic review of interventions to control weight. Acta Psychiatrica Scandinavica 2003;108:324–32.
[54] Faulkner G, Cohn TA. Pharmacologic and nonpharmacologic strategies for weight gain and metabolic disturbance in patients treated with antipsychotic medications. Can J Psychiatry 2006;51(8):502–11.
[55] Faulkner G, Cohn T, Remington G. Interventions to reduce weight gain in schizophrenia. Schizophr Bull 2007;33(3):654–6.
[56] Faulkner G, Taylor A, Munro S, Selby P, Gee C. The acceptability of physical activity programming within a smoking cessation service for individuals with severe mental illness. Patient Educ Couns 2007;66(1): 123–6.
[57] Fenton WS, Stover ES. Mood disorders: cardiovascular and diabetes comorbidity. Curr Opin Psychiatry 2006;19:421–7.
[58] Fleischhacker WW, Cetkovich-Bakmas M, De Hert M, Hennekens C, Lambert M, Leucht S, et al. Cormorbid somatic illnesses in patients with severe mental disorders: clinical, policy and research challenges. J Clin Psychiatry 2008;69:514–9.
[59] Fourth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. European guidelines on cardiovascular disease prevention in clinical practice: executive summary. Eur J Cardiovasc Prevent Rehabil 2007;14(Suppl. 2):E1–40.
[60] Goff DC, Sullivan LM, McEvoy JP, Meyer J, Nasrallah H, Daumit G, et al. A comparison of ten-year cardiac risk estimates in schizophrenia patients from the CATIE study and matched controls. Schizophr Res 2005;80(1):45–53.
[61] Haddad PM, Sharma SG. Adverse effects of atypical antipsychotics; Differential Risk and Clinical Implications. CNS Drugs 2007;21:911–36.
[62] Hanssens L, De Hert M, Kalnicka D, van Winkel R, Wampers M, Van Eyck D, et al. Pharmacological treatment of severe dyslipidaemia in patients with schizophrenia. Int Clin Psychopharmacol 2007;22:43–9.
[63] Haupt DW, Rosenblatt LC, Kim E, Baker RA, Whitehead R, Newcomer JW. Prevalence and predictors of lipid and glucose monitoring in commercially insured patients treated with second-generation antipsychotic agents. Am J Psychiatry 2009;166(3):345–53.
[64] Henderson DC. Schizophrenia and comorbid metabolic disorders. J Clin Psychiatry 2005;66(Suppl. 6):11–20.
[65] Hennekens CH. Schizophrenia and increased risks of cardiovascular disease. Am Heart J 2005;151(3):598–603.
[66] Heuser I. The hypothalamic-pituitary-adrenal system in depression. Pharmacopsychiatry 1998;31:10–3.
[67] Hill Golden S, Lazo M, Carnethon M, Bertoni AG, Schreiner PJ, Dieze Roux A, et al. Examining a Bidirectional Association Between Depressive Symptoms and Diabetes. JAMA 2008;299(23):2751–9.
[68] Holt RIG, Bushe C, Citrome L. Diabetes and schizophrenia 2005: are we any closer to understanding the link? J Psychopharmacol 2005;19(6):56–65.
[69] Holt RIG. Severe mental illness, antipsychotic drugs and the metabolic syndrome. Br J Diab Vasc Disease 2006;6(5):199–204.
[70] Holt RIG, Peveler RC. Antipsychotic drugs and diabetes - an application of the Austin Bradford Hill criteria. Diabetologia 2006;49(7): 1467–76.
[71] Holt R, Peveler R. Obesity, serious mental illness and antipsychotic drugs. Diabetes Obes Metab 2009;11(7):665–79.
[72] Kahl KG, Bester M, Greggersen W, Rudolf S, Dibbelt L, Stoeckelhuber BM, et al. Visceral fat disposition and insulin sensitivity in depressed women with and without borderline personality disorder. Psychosom Med 2005;67:407–12.
[73] Kahn RS, Fleischhacker WW, Boter H, Davidson M, Vergouwe Y, Keet I, et al. Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial. Lancet 2008;371:1085–97.
[74] Katon WJ. The comorbidity of diabetes and depression. Am J Med 2008;121(11 Suppl. 2):S8–15.
[75] Kinder LS, Carnethon MR, Palaniappan LP, King AC, Fortmann SP. Depression and the metabolic syndrome in young adults: Findings from the Third National Health and nutrition Examination Survey. Psychosom Med 2004;66:316–22.
[76] Kinon BJ, Kaiser CJ, Ahmed S, Roteli M, Kolloack-Walker S. Association between early and rapid weight gain and change in weight over one year of olanzapine therapy in patients with schizophrenia and related disorders. J Clin Psychopharmacol 2005;25(3):255–8.
[77] Kissebah AH. Intra-abdominal fat: is it a major factor in developing diabetes and coronary artery disease? Diab Res Clin Pract 1996;30: 25–30.
[78] Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346(6):393–403.
[79] Kryzhanovskaya LA, Robertson-Plouch CK, Xu W, Carlson JL, Merida KM, Dittmann RW. The safety of olanzapine in adolescents with schizophrenia or bipolar I disorder: a pooled analysis of 4 clinical trials. J Clin Psychiatry 2009;70(2):247–58.
[80] Kumra S, Oberstar JV, Sikich L, Findling R, McClellan J, Vinogradoc S, et al. Efficacy and Tolerability of Second-Generation Antipsychotics in Children and Adolescents With Schizophrenia. Schizophr Bull 2008;34:60–71.
[81] Lamberti JS, Crilly JF, Maharaj K, Olson D, Wiener K, Dvorin S, et al. Prevalence of diabetes mellitus among outpatients with severe mental disorders receiving atypical antipsychotic drugs. J Clin Psychiatry 2004;65:702–6.
[82] Laursen TM, Munk-Olsen T, Agerbo E, Gasse C, Mortensen PB. Somatic hospital contacts, invasive cardiac procedures, and mortality from heart disease in patients with severe mental disorder. Arch Gen Psychiatry 2009;66(7):713–20.

[83] Lawrence DM, Holman CD, Jablensky AV, Hobbs MS. Death rate from ischemic heart disease in Western Australian psychiatric patients 1980-1998. Br J Psychiatry 2003;182:31–6.
[84] Leucht S, Burkard T, Henderson J, Maj M, Sartorius N. Physical illness and schizophrenia. Acta Psychiatr Scand 2007;116(5):317–33.
[85] Leucht S, Corves C, Arbter D, Engel RR, Li C, Davis JM. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. Lancet 2009;373(9657):31–41.
[86] Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 2005;353(12):1209–23.
[87] Mackin P, Bishop D, Watkinson H. A prospective study of monitoring practices for metabolic disease in antipsychotic-treated community psychiatric patients. BMC Psychiatry 2007;25:7–28.
[88] Maina G, Salvi V, Vitalucci A, D'Ambrosio V, Bogetto F. Prevalence and correlates of overweight in drug-naive patients with bipolar disorders. J Affect Disord 2008;110:149–55.
[89] Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germono G, et al. Guidelines for the management of arterial hypertension. Eur Heart J 2007;28:1462–536.
[90] Marder SR, Essock SM, Miller AL, Buchanan RW, Casey DE, Davis JM, et al. Physical health monitoring of patients with schizophrenia. Am J Psychiatry 2004;161:1334–49.
[91] McIntyre RS, Konarski JZ, Misener VL, Kennedy SH. Bipolar disorder and diabetes mellitus: epidemiology, etiology, and treatment implications. Ann Clin Psychiatry 2005;17(2):83–93.
[92] McIntyre RS, Sozcynska JK, Konarski JZ, Kennedy SH. The effect of antidepressants on glucose homeostasis and insulin sensitivity: synthesis and mechanisms. Expert Opin Drug Saf 2006;5:157–68.
[93] Meyer JM, Davis VG, Goff DC, McEvoy J, Nasrallah H, Davis S, et al. Change in metabolic syndrome parameters with antipsychotic treatment in the CATIE Schizophrenia Trial: Prospective data from phase 1. Schizophr Res 2008;101(1-3):273–86.
[94] Meyer JM, Stahl SM. The metabolic syndrome and schizophrenia. Acta Psychiatr Scand 2009;119(1):4–14.
[95] Miller LJ. Management of Atypical Antipsychotic Drug–Induced Weight Gain Focus on Metformin Pharmacotherapy 2009;29(6):725–35.
[96] Nasrallah HA, Meyer JM, Goff DC, McEvoy JP, Davis SM, Stroup TS, et al. Low rates of treatment for hypertension, dyslipidemia and diabetes in schizophrenia: data from the CATIE schizophrenia trial sample at baseline. Schizophr Res 2006;86(1-3):15–22.
[97] Nasrallah HA. Atypical antipsychotic-induced metabolic side effects: insights from receptor-binding profiles. Mol Psychiatry 2008;13:27–35.
[98] Nathan DM, Davidson MB, DeFronzo RA, Heine RJ, Henry RR, et al. Impaired fasting glucose and impaired glucose tolerance: implications for care. Diabetes Care 2007;30:753–9.
[99] Newcomer JW, Nasrallah HA, Loebel AD. The atypical antipsychotic therapy and metabolic issues national survey. J Clin Psychopharmacol 2004;24:1–6.
[100] Newcomer JW. Second-Generation (Atypical) Antipsychotics and Metabolic Effects. A Comprehensive Literature Review. CNS Drugs 2005;19(Suppl. 1):1–93.
[101] Newcomer JW. Antipsychotic medications: metabolic and cardiovascular risk. J Clin Psychiatry 2007;68(Suppl. 4):8–13.
[102] NICE. Schizophrenia Core interventions in the treatment and management of schizophrenia in adults in primary and secondary care. 2008; online: http://www.nice.org.uk/guidance/index.jsp?action=download&o=42139 (site consulted on 1st July 2009).
[103] Nicol G, Haupt D, Flavin K, Schweiger J, Hessler M, Hessler E, et al. Preliminary results of the MEAC study: metabolic effects of antipsychotics in children. Schizophr Bull 2009;35(Suppl. 1):32.
[104] Osborn DP, Levy G, Nazareth I, Petersen I, Islam A, King MB. Relative risk of cardiovascular and cancer mortality in people with severe mental illness from the United Kingdom's General Practice Rsearch Database. Arch Gen Psychiatry 2007;64(2):242–9.
[105] Osborn DP, Wright CA, Levy G, King MB, Deo R, Nazareth I. Relative risk of diabetes, dyslipidaemia, hypertension and the metabolic syndrome in people with severe mental illnesses: systematic review and meta-analysis. BMC Psychiatry 2008;8:84. 25.
[106] Ösby U, Correia N, Brandt L, Ekbom A, Sparen P. Mortality and causes of death in schizophrenia in Stockholm county, Sweden. Schizophr Res 2000;45(1-2):21–8.
[107] Ösby U, Correia N, Brandt L, Ekbom A, Sparen P. Time trends in schizophrenia mortality in Stockholm County, Sweden: cohort study. BMJ 2000;321(7259):483–4.
[108] Peiris AN, Sothmann MS, Hoffmana RG, Hennes MI, Wilson CR. Adiposity, fat distribution, and cardiovascular risk. Ann Int Med 1989;110:867–72.
[109] Pratt L, Ford D, Crum R, Armenian H, Gallo J, Eaton W. Depression, Psychotropic Medication, and Risk of Myocardial Infarction. Circulation 1996;94:3123–9.
[110] Ray WA, Chung CP, Murray KT, Hall K, Stein CM. Atypical antipsychotic drugs and the risk of sudden cardiac death. N Engl J Med 2009;360(3):225–35.
[111] Rozanski A, Blumenthal JA, Kaplan J. Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. Circulation 1999;99:2192–217.
[112] Rubin RR, Ma Y, Marrero DG, Peyrot M, Barret-Conner EL, Kahn SE, et al. Elevated depression symptoms, antidepressant medicine use, and risk of developing diabetes during the diabetes prevention program. Diabetes Care 2008;31:420–6.
[113] Saha S, Chant D, McGrath J. A Systematic Review of Mortality in Schizophrenia. Arch Gen Psychiatry 2007;64:1123–31.
[114] Sahota DP, Knowler W, Looker H. Depression, diabetes and glycemic control in an American Indian Community. J Clin Psychiatry 2008;69(5):800–9.
[115] Sáiz Ruiz J, Bobes García J, Vallejo Ruiloba J, Giner Ubago J, García-Portilla González MP. Consensus on physical health of patients with schizophrenia from the Spanish Societies of Psychiatry and Biological Psychiatry. Actas Esp Psiquiatr 2008;36(5):251–64.
[116] Scheen AJ, De Hert MA. Abnormal glucose metabolism in patients treated with antipsychotics. Diabetes Metab 2007;33:169–75.
[117] Scheen A, van Winkel R, De Hert M. Traitement neuroleptique et troubles metabolic. Med Mal Metabol 2008;2(6):593–9.
[118] Simon V, van Winkel R, De Hert M. Are weight gain and metabolic side-effects of atypical antipsychotics dose-dependent? A Literature review. J Clin Psychiatry 2009;70(7):1041–50.
[119] Smith M, Hokins D, Peveler R, Holt R, Woodward M, Ismail K. First- versus second generation antipsychotics and risk for diabetes in schizophrenia: systematic review and meta-analysis. Br J Psychiatry 2008;192(6): 406–11.
[120] Smith RC, Lindenmayer JP, Davis JM, Cornwell J, Noth K, Gupta S, et al. Cognitive and antismoking effects of varenicline in patients with schizophrenia or schizoaffective disorder. Schizophr Res 2009;110(1-3):149–55.
[121] Stahl SM, Mignon L, Meyer JM. Which comes first: atypical antipsychotic treatment or cardiometabolic risk? Acta Psychiatr Scand 2009;119(3):171–9.
[122] Stroup TS, Lieberman JA, McEvoy JP, Swartz MS, Davis SM, Rosenheck RA, et al. Effectiveness of olanzapine, quetiapine, risperidone, and ziprasidone in patients with chronic schizophrenia following discontinuation of a previous atypical antipsychotic. Am J Psychiatry 2006;163(4):611–22.
[123] Stunkard AJ, Myles MS, Allison KC. Depression and obesity. Biol Psychiatry 2003;54:330–7.
[124] Surtees PG, Wainwright NWJ, Luben RN, Wareham NJ, Bingham SA, Khaw S. Depression and ischemic Heart Disease Mortality: Evidence From the EPIC-Norfolk United Kingdom Prospective Cohort Study. Am J Psychiatry 2008;165:515–23.
[125] Taxis K, Schorr S, Fouchier M, Slooff C, Bruggeman R. Is it appropriate to use cardiovascular risk scores in patients with psychotic disorders? Schizophr Res 2008;102(1-3):169.
[126] Thakore JH, Richards PJ, Reznek RH, Martin A, Dinan TG. Increased intra-abdominal fat deposition in patients with major depressive illness as measured by computer tomography. Biol Psychiatry 1997;41:1140–2.

[127] Thakore JH, Mann JN, Vlahos I, Martin A, Reznek RH. Increased visceral fat distribution in drug-naive and drug-free patients with schizophrenia. Int J Obes 2002;26:137–41.
[128] Tiihonen J, Wahlbeck K, Lönnqvist J, Klaukka T, Ioannidis JP, Volavka J, et al. Effectiveness of antipsychotic treatments in a nationwide cohort of patients in community care after first hospitalisation due to schizophrenia and schizoaffective disorder: observational follow-up study. BMJ 2006;333(7561):224 [Epub 2006 Jul 6].
[129] The international expert committee. International Expert Committee Report on the Role of the A1C Assay in the Diagnosis of Diabetes. Diabetes Care 2009;32:1327-L1334. doi: 10.2337/dc09-9033.
[130] Tschoner A, Engl J, Laimer MS, Rettenbacher M, Fleischhacker W, et al. Metabolic side effects of antipsychotic medication. Int J Clin Pract 2007;61(8):1356–70.
[131] Tuomilehto J, Lindström J, Eriksson JG, Valle TT, Hämäläinen H, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med 2001;344(18): 1343–50.
[132] Ussher MH, Taylor A, Faulkner G. Exercise interventions for smoking cessation. Cochrane Database Syst Rev 2008;4:CD002295.
[133] van Winkel R, De Hert M, Van Eyck D, Hanssens L, Wampers M, Scheen A, et al. Screening for diabetes and other metabolic abnormalities in patients with schizophrenia and schizoaffective disorder: evaluation of incidence and screening methods. J Clin Psychiatry 2006;67(10):1493–500.
[134] van Winkel R, De Hert M, Wampers M, Van Eyck D, Hanssens L, Scheen A, et al. Major changes in glucose metabolism including new-onset diabetes within 3 months after initiation or switch of atypical antipsychotic medication in patients with schizophrenia and schizoaffective disorder. J Clin Psychiatry 2008;69:472–9.
[135] van Winkel R, De Hert M, Van Eyck D. Prevalence of diabetes and the metabolic syndrome in a sample of patients with bipolar disorder. Bipolar Disord 2008;10:342–8.
[136] van Winkel R, van Os J, Celic I, Van Eyck D, Wampers M, Scheen A, et al. Psychiatric diagnosis as an independent risk factor for metabolic disturbance. Results from a comprehensive, naturalistic screening program. J Clin Psychiatry 2008;69(8):1319–27.
[137] Waterreus AJ, Laugharne JD. Screening for the metabolic syndrome in patients receiving antipsychotic treatment: a proposed algorithm. Med J Aust 2009;190(4):185–9.
[138] World Health Organisation: Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia – Report of a WHO/IDF Consultation, 2006.
[139] Wu RR, Zhao JP, Liu ZN, Zhai JG, Guo XF, Guo WB, et al. Effects of typical and atypical antipsychotics on glucose-insulin homeostasis and lipid metabolism in first-episode schizophrenia. Psychopharmacology 2006;186(4):572–8.
[140] Wu RR, Zhao JP, Jin H, Shao P, Fang MS, Guo XF, et al. Lifestyle intervention and metformin for treatment of antipsychotic-induced weight gain: a randomized controlled trial. JAMA 2008;299(2): 185–93.
[141] Zimmermann U, Kraus T, Himmerich H, Schuld A, Pollmächer T. Epidemiology, implications and mechanisms underlying drug-induced weight gain in psychiatric patients. J Psychiatr Res 2003;37:193–220.