

Cardiovascular disease and diabetes in people with severe mental illness: causes, consequences and pragmatic management

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The prevalence of many physical illnesses is increased in people with severe mental illness and accounts for around three quarters of all deaths; cardiovascular disease is the commonest cause of death. The level of screening for and management of diabetes and cardiovascular risk factors remains low but a straightforward yet systematic care pathway should go a long way towards reducing the health inequalities experienced by people with severe mental illness.

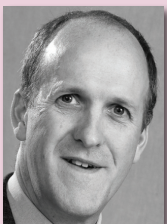
Schizophrenia and bipolar disorder are psychotic illnesses that may alter perception, thought, affect and behaviour and are characterised by intermittent loss of insight. The lifetime risk of schizophrenia is approximately 1–2% and the figure is somewhat higher for bipolar illness. Schizophrenia and bipolar disorder are often collectively known as severe and enduring mental illnesses.

Severe mental illness is associated with a three-fold increased risk of premature death and it shortens life expectancy by approximately 10–20 years.¹ Although suicide accounts for the highest relative risk of mortality, being up to 20-fold commoner than among the general population, a number of physical illnesses also occur more frequently in people with severe mental illness and cause around three-quarters of deaths, with cardiovascular disease being the commonest cause of death.¹

Primary healthcare professionals have a major role to play in reducing the burden of physical disease in people with severe mental illness. Contrary to expectation, individuals with severe mental illness attend primary care settings more frequently than the general population and are as motivated about their physical health as the rest of the population, but often lack awareness and fail to prioritise their physical well-being.² This review will examine the prevalence and aetiology of diabetes and cardiovascular disease in people with severe mental illness, and review the steps that can be taken to address this problem in a pragmatic way.

Methods

PubMed and other electronic databases were searched to identify articles that included the keywords: diabetes, cardiovascular disease, psychosis, schizophrenia, bipolar illness, antipsychotic and each individual antipsychotic drug name.



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Points for the clinic

- The prevalence of diabetes and cardiovascular disease is increased 2–3-fold in people with schizophrenia or bipolar illness
- The reasons for this include genetic and lifestyle factors as well as disease- and treatment-specific effects
- There is a need to screen people with severe mental illness systematically for diabetes and cardiovascular risk
- The principles of management are similar to those in the general population

The article draws on the author's own clinical and research experience, which included membership of three different committees whose remit was to develop pragmatic guidelines to manage diabetes and cardiovascular risk in people with severe mental illness.

Cardiovascular disease in severe mental illness

Cardiovascular morbidity and mortality are increased approximately 2–3-fold overall in people with severe mental illness.¹ This increased risk is particularly marked in younger individuals with severe mental illness, in whom the prevalence of cardiovascular disease is 3.6 times higher, compared with a 2.1-fold increase in people who are older than 50 years.³ The rates of cardiovascular disease and mortality have fallen in the general population over the last 20 years but these benefits have not been shared by people with severe mental illness and consequently, the health inequality gap has widened.

Several studies have shown that the prevalence of modifiable cardiovascular risk factors, such as obesity, smoking, diabetes and dyslipidaemia, is also increased in people with severe mental illness and explains much of the excess cardiovascular mortality (Table 1).⁴ Furthermore, the risk factors appear at younger ages: in the US Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, at baseline more than a quarter of men with schizophrenia

Table 1. Estimated prevalence of modifiable cardiovascular risk factors in people with schizophrenia and bipolar illness and relative risk compared with the general population. Adapted from De Hert *et al.*⁴

Modifiable risk factor	Schizophrenia		Bipolar illness	
	Prevalence (%)	Relative risk	Prevalence (%)	Relative risk
Smoking	50–80	2–3	54–68	2–3
Dyslipidaemia	25–69	< 5	23–38	< 3
Diabetes	10–15	2–3	8–17	1.5–3
Hypertension	19–58	2–3	35–61	2–3
Obesity	45–55	1.5–2	21–49	1–2
Metabolic syndrome	37–63	2–3	30–49	2–3

aged 20–29 years had the metabolic syndrome, compared with fewer than 10% in the general US population.⁵ The implication of this finding is that healthcare professionals need to pay attention to cardiovascular risk-factor management in people with severe mental illness from the point of diagnosis rather than waiting until they reach the age of 40 years, when they would be eligible for screening under the NHS Health Check programme.

The worldwide prevalence of obesity has increased dramatically over the last three decades, largely driven by changes in diet and physical activity. These demographic changes appear to have affected people with severe mental illness to a greater extent than the general population, as studies that pre-date the 1980s did not consistently report that obesity was commoner in those with severe mental illness.⁶ By contrast, more recent studies have reported obesity rates that are approximately doubled in people with schizophrenia or bipolar illness. Body composition is also altered in people with severe mental illness: higher waist-to-hip ratios and increased visceral fat have been found even at first presentation of psychosis. Other studies have not replicated these findings, but note marked weight gain and increasing girth during treatment with antipsychotic medication.⁶

It is estimated that between 10% and 15% of people with severe mental illness have diabetes.⁴ Type 1 diabetes is not increased and so the 2–3-fold excess is explained by an increase in type 2 diabetes. It is well recognised that approximately 25% of cases of type 2 diabetes are undiagnosed in the general population but this situation is exaggerated in people with severe mental illness, among whom as many as 70% of cases are undiagnosed. This may reflect a reluctance of people with severe mental illness to volunteer their symptoms and the overlap between some symptoms of diabetes and mental illness, which may lead to reduced screening in people with severe mental illness.

The major lipid abnormalities seen in people with severe mental illness are lower levels of high-density lipoprotein (HDL) cholesterol and hypertriglyceridaemia, although not all studies have shown these abnormalities.⁷

Overall, dyslipidaemia is reported in 25–69% of people with severe mental illness.

Although some studies have reported increased rates of hypertension, this again is not a universal finding, probably reflecting the diverse action of antipsychotics on blood pressure.⁷ Smoking rates are high in people with severe mental illness, affecting 50–80%.

Antipsychotic medication and cardiovascular disease

There are concerns that antipsychotics contribute to cardiovascular risk by inducing weight gain and worsening lipid profile and blood glucose. Weight gain is a well-recognised side effect, affecting between 15 and 72% of patients.⁶

Although no antipsychotic can be viewed as weight-neutral, the risk of weight gain differs between antipsychotics: mean weight gain is highest with clozapine and olanzapine, there is an intermediate risk of weight gain with quetiapine and risperidone whereas aripiprazole, amisulpride and ziprasidone have little effect on weight. Some first-generation antipsychotics (FGAs), such as chlorpromazine, and other psychotropic medication, such as the antidepressant mirtazapine, are also associated with a high risk of inducing weight gain. Although choice of antipsychotic may be used to predict weight gain, there is marked interindividual variation in treatment-induced weight change. Other factors

associated with weight gain are younger age, lower initial body mass index, family history of obesity, concomitant cannabis use and a tendency to overeat at times of stress.⁶ The best predictor of long-term weight gain is weight change in the first 4–6 weeks of treatment, emphasising the need for regular weight measurement during the early phase of treatment.

The relationship between antipsychotics and diabetes is complex because of the long natural history of diabetes and the potential confounding effects of other diabetes risk factors in people with severe mental illness.⁸ Both genetic and lifestyle factors, such as imprudent diet and physical inactivity, may contribute to the increased prevalence of diabetes in people with severe mental illness.

Nevertheless, there are case reports of drug-induced diabetes and diabetic ketoacidosis with each of the second-generation antipsychotics; some of these report that diabetes enters remission when the drug is stopped. A large number of pharmaco-epidemiological studies have indicated that people receiving antipsychotics have a higher prevalence of diabetes and that people receiving second-generation drugs have a small but increased risk of diabetes compared with those receiving first-generation drugs. By contrast, randomised controlled trials have not demonstrated a difference in treatment-emergent diabetes between different antipsychotics or placebo, suggesting that the reasons why individuals with severe mental illness develop diabetes are much more likely to reflect their genetics, lifestyle and illness than their treatment. On the other hand, small increases in blood glucose have been reported, particularly with olanzapine and clozapine, which, if persistent over a lifetime, may translate into meaningful differences in the rates of diabetes.

Antipsychotic treatment is also associated with increases in low-density lipoprotein (LDL) cholesterol and triglycerides and decreased HDL cholesterol. Again, there are differences between drugs, with greater changes generally being seen with those drugs that induce the most weight gain. There may also be other direct mechanisms as hypertriglyceridaemia may occur despite only modest weight gain.

The effect of antipsychotics on blood pressure is variable: although weight gain may lead to increased blood pressure, this may be offset by the adrenergic blockade seen with antipsychotics.⁷

Although it appears that antipsychotics have an adverse effect on several individual cardiovascular risk factors, it is important to appreciate that this may differ from their effect on cardiovascular events and mortality. A large UK study of more than 46 000 people found that while exposure to first-generation antipsychotics, particularly in high doses, was associated with excess cardiovascular mortality, this increase was not seen in people receiving second-generation antipsychotics.³ Similarly, in a large Finnish study of 66 881 people with schizophrenia, total mortality was lowest in individuals receiving clozapine and olanzapine, with no difference in cardiovascular mortality between drugs.⁹ These studies are both observational and therefore there may be other explanations or confounders underlying the results, but nevertheless the data are reassuring.

Screening for diabetes and cardiovascular risk factors

The increased prevalence of cardiovascular disease and its modifiable risk factors in people with severe mental illness provides a strong imperative to screen for diabetes and other cardiovascular risk factors. Although the case for screening does not fulfil all of the criteria laid down by the National Screening Committee, screening

is recommended by a number of national and international guidelines.^{4, 10-12}

Screening should begin prior to the commencement of treatment or as soon as is reasonably possible, 2–3 months later to assess the acute metabolic effects of the antipsychotics and thereafter on an annual basis unless significant treatment changes are contemplated (Table 2). One exception to this timetable is the measurement of weight, which should be performed weekly during the initial phase of treatment.

Cardiovascular risk assessment should include a detailed medical history to assess risk factors, physical examination to include weight and blood pressure, a blood test to assess lipids and glycaemia and an ECG.⁴ Although waist circumference may provide additional information, this measurement has proven difficult to achieve in the UK. While a fasting blood sample is required to interpret a full lipid profile, there may be merits in taking a pragmatic approach and accepting a non-fasting sample when logistical difficulties prevent the patient attending fasted. The sensitivity and specificity for diabetes, particularly if the glucose measurement is combined with measurement of glycated haemoglobin (HbA_{1c}), do not differ greatly and the 10-year cardiovascular risk assessment employs the total and HDL cholesterol, which are largely unaffected by eating. Although it may be easier to obtain a non-fasting sample, clinicians should not

assume that patients with severe mental illness are unable to attend fasted since several studies have shown that this is feasible.

The latest Quality and Outcomes Framework now includes four indicators for physical health measurements in the mental health domain; these are the recording of body mass index (MH12), blood pressure (MH13), total-to-HDL cholesterol ratio (MH14) and blood glucose (MH15).¹¹ Although MH14 and MH15 are only for those over the age of 40 years, this initiative should improve the monitoring of cardiovascular risk factors in those with psychotic illness.

Current screening practices

In the National Health Service, where to a large extent care is not offered unless requested, people with severe mental illness may be disadvantaged. The Disability Rights Commission has highlighted that, instead of receiving holistic care, many people with mental illness describe how their physical illnesses are overshadowed by the mental illness, with healthcare professionals concentrating on the latter to the detriment of the former.¹³ Consequently, many people with severe mental illness are not screened for cardiovascular risk factors. In an audit of 50 in-patients and 50 out-patients of people with severe mental illness in Hampshire, documented evidence that blood pressure had been measured was found in only 32% of case notes, while glucose (16%), lipids

Table 2. Recommended screening based on currently available guidelines

	Baseline	2–3 months	Annual	Target
Medical history, to include family history, ethnicity, smoking, alcohol, diet, exercise	✓	✓	✓	
Height	✓			
Weight ^a	✓	Every week during first 6–8 weeks of treatment and at every clinic visit thereafter but at least quarterly	✓	BMI < 25 kg/m ²
Blood pressure	✓	✓	✓	< 140/90 mmHg
Glucose ^b	✓	✓	✓	<ul style="list-style-type: none"> • Fasting glucose < 6.0 mmol/l • Non-fasting glucose < 7.8 mmol/l
Glycated haemoglobin ^c	✓	✓	✓	< 6.0% (42 mmol/mol) if no history of diabetes; target should be individualised for people with diabetes but likely 6.5–7.5% (47–58 mmol/mol)
Lipid profile ^d	✓	✓	✓	<ul style="list-style-type: none"> • Total cholesterol < 5.0 mmol/l or < 4.0 mmol/l if established CVD or diabetes • LDL cholesterol < 3.0 mmol/l or < 2.0 mmol/l if established CVD or diabetes • 30% reduction in patient starting statins
ECG	✓	✓	✓	To assess QTc interval

^aAdditional information can be obtained by measuring waist circumference: target in men < 94 cm, in women < 80 cm. Lower values should be sought in people from non-European descendance;

^bEither a fasting or non-fasting sample can be used. Fasting samples are more reproducible but may be logistically more difficult to obtain. A formal 75-g OGTT is needed only rarely;

^cNote HbA_{1c} may be normal in situations where there is a rapid onset of diabetes;

^dEither a fasting or non-fasting sample can be used. Fasting samples are needed to assess LDL cholesterol and triglycerides but cardiovascular risk can be calculated using total:HDL cholesterol ratio which is largely unaffected by eating. BMI = body mass index; CVD = cardiovascular disease; LDL = low-density lipoprotein; HbA_{1c} = glycated haemoglobin; OGTT = oral glucose tolerance test; HDL = high-density lipoprotein.

Table 3. National Institute for Health and Clinical Excellence (NICE) recommendations regarding management of physical illness in people with schizophrenia¹⁰

11.4	Promoting recovery
11.4.1	Primary care
11.4.1.1	Develop and use practice case registers to monitor the physical and mental health of people with schizophrenia in primary care.
11.4.1.2	GPs and other primary healthcare professionals should monitor the physical health of people with schizophrenia at least once a year. Focus on cardiovascular disease risk assessment as described in 'Lipid modification' (NICE clinical guideline 67) but bear in mind that people with schizophrenia are at higher risk of cardiovascular disease than the general population. A copy of the results should be sent to the care coordinator and/or psychiatrist, and put in the secondary care notes.
11.4.1.3	People with schizophrenia at increased risk of developing cardiovascular disease and/or diabetes (for example, with elevated blood pressure, raised lipid levels, smokers, increased waist measurement) should be identified at the earliest opportunity. Their care should be managed using the appropriate NICE guidance for prevention of these conditions.
11.4.1.4	Treat people with schizophrenia who have diabetes and/or cardiovascular disease in primary care according to the appropriate NICE guidance.
11.4.1.5	Healthcare professionals in secondary care should ensure, as part of the Care Programme Approach, that people with schizophrenia receive physical healthcare from primary care as described in recommendations.

(9%) and weight (2%) were assessed even less frequently.¹⁴ This was despite a high prevalence of the metabolic syndrome in these patients and a significant number with a 10-year cardiovascular risk of greater than 20%.

The National Institute for Health and Clinical Excellence (NICE) guidance places the responsibility for screening for physical health problems within primary care (Table 3).¹⁰ Despite this, there is a lack of clarity among mental healthcare professionals about whose responsibility physical health screening is.¹⁵ Mental healthcare professionals have also expressed concern about their lack of understanding about what should be measured and when and how to interpret the results. Lack of access to necessary equipment may be a further barrier. Although some people with severe mental illness may never attend their general practice, many do and are willing to undergo screening.¹⁶ For those who are seen only within mental health settings, the psychiatry team should ensure that physical health screening is undertaken. Furthermore, there is a responsibility for psychiatry teams to ensure that people with severe mental illness receive physical healthcare from primary care and this should form part of the clinical care plan.¹⁰ In order to ensure that patients are not missed, clear communication between primary care and mental health teams is essential.

Assessment of cardiovascular risk

Cardiovascular risk is usually assessed by the use of locally relevant risk engines. These have not been validated in people with severe mental illness, who are typically younger, have higher blood pressure and are more likely to smoke than the populations used to derive cardiovascular disease risk scoring systems such as Framingham and QRISK. As traditional risk factors only partially explain the excess cardiovascular disease seen in people with severe mental illness, it seems likely that these traditional risk engines will

underestimate cardiovascular risk in people with severe mental illness and so general practitioners should have confidence to treat those identified as at high risk. Pending further research, there is also an argument to consider primary cardiovascular prevention in individuals at intermediate levels of cardiovascular risk who would not routinely reach the National Service Framework or NICE thresholds for treatment.

Managing cardiovascular risk factors

Diabetes and cardiovascular risk factors in people with severe mental illness should be managed along similar lines to the general population despite the additional challenges to ensure that the patient understands the need for lifestyle modification and medication.

Smoking

Healthcare professionals should provide smokers with information about the risks of smoking and encourage them to quit. Behavioural counselling and pharmacological approaches, such as nicotine replacement, are suitable for people with severe mental illness.

Obesity

The nihilism that surrounds obesity management has been challenged recently by a number of observational studies and randomised controlled trials in people with severe mental illness.^{17,18} Trials have shown that non-pharmacological lifestyle interventions lead to ~2.5-kg reductions in mean body weight over 2–6 months,¹⁷ while longer observational studies have demonstrated that further weight loss is achievable with on-going support.¹⁹

A range of unlicensed pharmacological treatments have been tried to treat or prevent antipsychotic-induced weight gain, with limited benefit.¹⁷ There is, however, preliminary evidence from short-term studies that metformin may attenuate weight gain or promote weight loss. While longer definitive trials are needed, the joint European Associations' position statement recommends that metformin may be considered as a second-line treatment in patients with additional risk factors, such as a personal or family history of metabolic dysfunction.

Dyslipidaemia

Target levels of total cholesterol and LDL cholesterol are the same as those for the general population (< 5.0 mmol/l and < 3.0 mmol/l, respectively) but tighter goals of < 4.0 mmol/l and < 2.0 mmol/l may be appropriate for individuals with established cardiovascular disease or diabetes. No cardiovascular disease outcome trials with statins have been performed specifically in people with severe mental illness but these drugs are as effective in lowering total and LDL cholesterol in this population as in the general population.²⁰ Furthermore, there is no evidence that lipid-lowering medication is associated with suicide or traumatic deaths in people with severe mental illness.

Diabetes

The treatment of diabetes in people with severe mental illness should follow currently available treatment algorithms, although oral anti-diabetes agents that induce less weight gain may have advantages, given the high prevalence of obesity in people with severe mental illness. The additional challenges of managing co-morbid diabetes

and mental illness, however, require close collaboration between mental and physical health services.

Attention must also be paid to preventing diabetes; recent trials have shown that lifestyle intervention programmes involving dietary modification, weight-loss and increased physical activity reduce the incidence of type 2 diabetes. As these programmes share many features with lifestyle weight-loss programmes used in people with severe mental illness, it is hoped that the programmes may also lead to diabetes prevention although this has not been formally assessed. Metformin treatment may also be considered.⁴

Hypertension

The management of hypertension in severe mental illness should follow the same treatment algorithm as in the general population, with target blood pressure levels of < 140/90 mmHg being recommended. Patients should be advised to reduce smoking and salt intake. European and UK guidelines emphasise the need to choose antihypertensive agents best suited to the individual patient's needs as the achieved blood pressure is more important than the agent used to achieve it.

Conclusion

The increased rates of diabetes and cardiovascular disease in people with severe mental illness provide a clinical imperative to screen and manage cardiovascular disease using a systematic approach. In the past, the physical health needs of people with severe mental illness have largely been ignored, creating significant health inequalities. Although there are additional challenges in the treatment of people with severe mental illness, doing the simple things well is likely to have a significant impact on cardiovascular disease in severe mental illness.

Conflicts of interest

Professor Holt has undertaken lectures for Astra Zeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Novo Nordisk and Otsuka Pharmaceuticals. He has served on advisory boards for Astra Zeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline and Novo Nordisk. He has received funding to attend conferences from Astra Zeneca, Eli Lilly, GlaxoSmithKline, Novo Nordisk.

References

- Brown S, Kim M, Mitchell C, Inskip H. Twenty-five year mortality of a community cohort with schizophrenia. *Br J Psychiatry* 2010; **196**: 116–21.
- Buhagiar K, Parsonage L, Osborn DP. Physical health behaviours and health locus of control in people with schizophrenia-spectrum disorder and bipolar disorder: a cross-sectional comparative study with people with non-psychotic mental illness. *BMC Psychiatry* 2011; **11**: 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 Research Database. *Arch Gen Psychiatry* 2007; **64**: 242–9.
- De Hert M, Dekker JM, Wood D, Kahl KG, Holt RI, Moller HJ. 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). *Eur Psychiatry* 2009; **24**: 412–24.
- McEvoy JP, Meyer JM, Goff DC, et al. Prevalence of the metabolic syndrome in patients with schizophrenia: Baseline results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial and comparison with national estimates from NHANES III. *Schizophr Res* 2005; **80**: 19–32.
- Holt RI, Peveler RC. Obesity, serious mental illness and antipsychotic drugs. *Diabetes Obes Metab* 2009; **11**: 665–79.
- 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 metaanalysis. *BMC Psychiatry* 2008; **8**: 84.
- Holt RI, Peveler RC. Antipsychotic drugs and diabetes—an application of the Austin Bradford Hill criteria. *Diabetologia* 2006; **49**: 1467–76.
- Tiihonen J, Lonnqvist J, Wahlbeck K et al. 11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). *Lancet* 2009; **374**: 620–7.
- National Collaborating Centre for Mental Health. The NICE guideline on core interventions in the treatment and management of schizophrenia in adults in primary and secondary care CG82. London: The British Psychological Society and The Royal College of Psychiatrists; 2010.
- NHS Employers. Quality and Outcomes Framework guidance for GMS contract 2011/12: Delivering investment in general practice. http://www.nhsemployers.org/Aboutus/Publications/Documents/QOF_guidance_GMS_contract_2011_12.pdf. 2011. Accessed 8-11-0011.
- Citrome L, Yeomans D. Do guidelines for severe mental illness promote physical health and well-being? *J Psychopharmacol* 2005; **19**(6 Suppl): 102–09.
- Disability Rights Commission. Equal Treatment: Closing the gap. A formal investigation into physical health inequalities experienced by people with learning difficulties and mental health problems. London: Disability Rights Commission; 2006.
- Holt RI, Abdelrahman T, Hirsch M, et al. The prevalence of undiagnosed metabolic abnormalities in people with serious mental illness. *J Psychopharmacol* 2010; **24**: 867–73.
- Barnes TR, Paton C, Cavanagh MR, Hancock E, Taylor DM. A UK audit of screening for the metabolic side effects of antipsychotics in community patients. *Schizophr Bull* 2007; **33**: 1397–403.
- Osborn DP, King MB, Nazareth I. Participation in screening for cardiovascular risk by people with schizophrenia or similar mental illnesses: cross sectional study in general practice. *Br Med J* 2003; **326**: 1122–3.
- Baptista T, ElFakih Y, Uzategui E et al. Pharmacological management of atypical antipsychotic-induced weight gain. *CNS Drugs* 2008; **22**: 477–95.
- Alvarez-Jimenez M, Hetrick SE, Gonzalez-Blanch C, Gleeson JF, McGorry PD. Non-pharmacological management of antipsychotic-induced weight gain: systematic review and meta-analysis of randomised controlled trials. *Br J Psychiatry* 2008; **193**: 101–07.
- Holt RI, Pendlebury J, Wildgust HJ, Bushe CJ. Intentional weight loss in overweight and obese patients with severe mental illness: 8-year experience of a behavioral treatment program. *J Clin Psychiatry* 2010; **7**: 800–05.
- Hanssens L, De Hert M, Kalnicka D, et al. Pharmacological treatment of severe dyslipidaemia in patients with schizophrenia. *Int Clin Psychopharmacol* 2007; **22**: 43–9.